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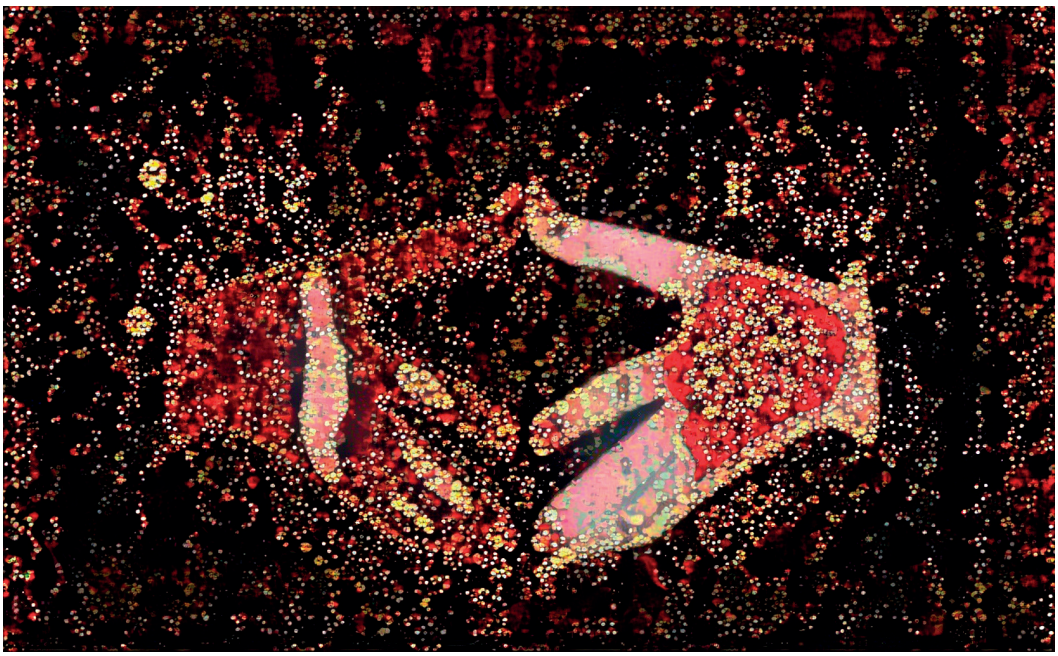
Mechanisms of Resident T cell-driven Tissue Responses during the Onset and Recurrence of Human Skin Inflammation



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月下白梅図 White Plum Blossoms and Moon
Itō Jakuchū, 1755, ink and color on silk

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MECHANISMS OF RESIDENT T CELL-DRIVEN TISSUE RESPONSES DURING THE ONSET AND RECURRENCE OF HUMAN SKIN INFLAMMATION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the patients

“You have to learn to say no to shit”

Papa Emeritus – Ghost

Stockholm, September 29th, 2017

ABSTRACT

Long-lived tissue-resident memory T cells (T_{RM}) reside in nonlymphoid organs and can drive direct cytotoxicity, focal cytokine release and potent tissue-wide anti-infectious responses upon antigenic challenge. T_{RM} cells poised to pathogenic responses have been identified in active and resolved psoriasis and mice models of allergic contact dermatitis (ACD). It is challenging to investigate the interactions between T_{RM} cells and the local microenvironment in human tissues, and whether these cells promote disease in the absence of circulating T cells is less studied. This thesis focuses on the functional consequences of T_{RM} cell activation inside the skin.

PAPER I: T_{RM} cells can provide protection from infections. The retention marker CD49a was correlated to both the epidermal location of skin T_{RM} cells and their cytotoxicity. IL-15 unleashed the killing capacities of $CD8^+CD103^+CD49a^+$ T cells. The expression of CD49a in $CD8^+CD103^+$ skin T cells was associated with more IFN-γ release compared to $CD8^+CD103^+CD49a^-$, which were conversely better IL-17 producers. CD49a expression delineated a $CD8^+$ T_{RM} cell specialization that was conserved in two inflammatory skin diseases psoriasis and vitiligo that were respectively enriched for $CD8^+CD103^+CD49a^-$ and $CD8^+CD103^+CD49a^+$ T_{RM} cells.

PAPER II: Psoriasis is linked to overproduction of IL-17 and Type 1 interferon is implicated as a disease trigger in the early events transforming never-lesional psoriasis (NLP) into full-blown psoriasis. $CCR6^+CD49a^-$ T_{RM} cells poised towards IL-17 production were enriched in NLP, possibly due to microbe-induced epidermal chemotaxis. Activation of skin-resident T cells in NLP skin triggered Type 1 interferon tissue responses, potentially via IFN-γ-induced release of IFN-α in keratinocytes. As IFN-γ-potent T_{RM} cells accumulate in NLP epidermis, our findings suggest that Type 1 interferon release in NLP could be driven by T_{RM} cells.

PAPER III: T_{RM} cells poised to IL-17 and IL-22 production are retained in the epidermis in resolved psoriasis. In healthy and diseased skin, the activation of T cells within skin explants using the pan-T cell-activating antibody OKT-3 led to interferon-driven core-response *CXCL10* and *CXCL9* expression. Additionally, IL-17-specific transcriptional signature was induced in resolved and active psoriasis sample, and the magnitude of this response was correlated with relapse shortly upon withdrawal of UVB treatment.

PAPER IV: An upregulation of *S100As* transcripts persisted in the long-term in the epidermis of patients with resolved allergic contact dermatitis (ACD), indicating a disease scar. While inflammatory transcripts *CXCL10*, *GZMB*, and *MMP12* were normalized after antigen exclusion for two months and two years, they were quickly induced in resolved epidermis upon exposure to the allergen. *MMP12* was specifically upregulated in the epidermal compartment and codes for a protein capable of degrading the collagen IV that is a constituent of the skin basement membrane.

In conclusion, the T_{RM}-driven tissue responses in human healthy and inflamed skin are highly compartmentalized and disease-specific. This concords with the functional heterogeneity of T_{RM} cells themselves but also relies on their interplay with the stromal cells, which can help unveil pathogenic mechanisms in these relapsing-remitting inflammatory skin diseases. Preventing the T_{RM} cell establishment or favoring their displacing by topical treatments could lead to significant improvements in the care of patients suffering from inflammatory diseases.

PLAIN LANGUAGE SUMMARY

The skin separates the human body from the environment. The epidermis is the very external layer of the skin. Specialized cells can differentiate aggressions that should trigger a reaction from harmless microbes and chemicals. However, this system can become defective, which leads to the development of inflammation, like the autoimmune disease psoriasis and the allergic disease allergic contact dermatitis.

T cells are cells that can remember previously encountered dangers and mount disease-driving immune responses. Psoriasis and allergic contact dermatitis are both relapsing-remitting diseases in which T cells are present in the active phase of the disease and are targeted in current successful therapies.

In psoriasis patients, T cells predisposed to the disease are present in skin areas that have never developed lesions so far. They can produce IL-17, a harmful protein blocked nowadays in biological therapies against psoriasis. The cells may be attracted to the normal-looking skin of psoriasis patients because of patient's abnormal tissue-reaction to microbes. In active psoriasis, T cells accumulate in the skin and part of them remain after the inflammation disappears. Activating these dwelling T cells in patients' biopsies led to molecular changes reminiscent of the active disease. The tissue-changes induced by the T cells could correlate to the remission time, from the moment a treatment is discontinued until a new one is started again. This finding is promising but needs to be confirmed in clinical trials.

In allergic contact dermatitis, allergen avoidance is the only cure. Patient skin was sampled during the active allergy, then 2 months and finally 2 years after the disappearance of symptoms. Even after 2 years, the molecular state of the skin was not back to normal, indicating a "disease scar". The T cells retained in the skin are likely to contribute to this scar. Molecular changes evocative of the active allergy and capable of disrupting the barrier between epidermis and the underlying dermis were observed in the skin upon T cell-activation. This would enable blood cells to invade the upper layer and the skin and create symptoms.

In sum, we have added arguments for the relevance of skin T cells in the development and recurrence of inflammatory skin diseases, by proposing mechanisms explaining how T cells can colonize the skin and start the inflammatory chain-reaction. Residing T cells could be used as predictors of relapse in the coming years. In the future, one aim is to be capable of displacing the disease-driving resident T cells thanks to topical treatments.

SAMMANFATTNING PA SVENSKA

Huden är kroppens barriär mot omvärlden och skyddar mot omgivningens mikrober och kemikalier. I epidermis, den yttersta delen av huden, hittas flera olika sorters immunceller, bland annat T-celler, insprängda mellan keratinocyter. I huden kan immunceller utlösa en vävnadsreaktion för att skydda kroppen från mikrobiell invasion och skador. Vid kroniska inflammatoriska sjukdomar överreagerar hudens immunsystem mot ämnen/mikrober och skapar en lokal obalans i huden vilket i sin tur kan leda till sjukdomar som psoriasis eller allergisk kontakt-dermatit. Denna avhandling fokuserar på T-celler i huden som driver patologiska immunsvar. Psoriasis och kontakteksem är båda sjukdomar där T-celler ansamlas lokalt i huden och där patologi återkommer på samma ställen på huden upprepade gånger. Vid psoriasis är huden koloniserade av T-celler som producerar cytokinen IL-17 som kan driva inflammation och därmed patologi. Keratinocyter hos psoriasispatienter reagerar på svamp med att producera cytokiner som attraherar IL-17-producerande celler till epidermis. Vid aktiv psoriasis ackumuleras T-celler lokalt i huden och en del av dem blir kvar efter att inflammationen läkt, trots att huden ser helt normal ut. Vid reaktivering svarar dessa kvarvarande T celler med IL-17 och kan på så sätt starta vävnadsinflammation igen. Studierna som presenteras i denna avhandling visar att reaktiverade T-celler som har kraftigt IL-17 svar, med *SPRR2* och *DEFB4A*, korrelerar med snabbt återfall av psoriasis. Detta fynd kan testas i prospektiva kliniska studier och skulle kunna leda till en förbättring av nuvarande behandlingsstrategi.

Vid kontekteksem är det enda sättet att bli symptomfri genom att undvika ämnet som orsakar allergin. Vi undersökte huden från patienter med aktiv sjukdom, efter två månader och slutligen två år efter aktiv sjukdom. I tidigare drabbad hud var genuttryck inte normaliserat efter två år, vilket indikerar att ett "sjukdomsärr" finns kvar i huden hos patienter med kontakteksem. T-cellerna som fanns kvar i huden kunde aktiveras när hudbiopsier stimulerades i kultur. De molekylära förändringar som sågs efter aktivering påminde om svaret man kan se i överhuden vid en aktiv allergisk reaktion. Det immunsvar som observerades har potential att öppna upp basalmembranet mellan överhuden och underliggande dermis. Således kan de långlivade T-cellerna i huden starta vävnads-förändringar som gör att blodceller kan penetrera till epidermis och orsaka patologi. Dessa resultat öppnar upp för att använda målinriktade lokalbehandlingar vid behandling av eksem. I framtiden, hoppas vi kunna urskilja olika T-cells typer i huden, och hitta behandlingar där vi kan ersätta de skadliga cellerna med skyddande.

RESUME EN FRANCAIS

La peau sépare le corps humain de son environnement. L'épiderme est la couche la plus externe de la peau où des cellules spécialisées peuvent différencier les agressions des expositions inoffensives. Quand ce système est défectueux, une inflammation survient, comment dans le psoriasis, une maladie auto-immune, ou l'eczéma de contact allergique (ECA), toutes deux des maladies récidivantes localement. Les lymphocytes T sont des cellules qui gardent en mémoire les dangers déjà rencontrés.

Chez les patients atteints de psoriasis, des lymphocytes T prédisposés à la maladie sont présents dans les zones cutanées naïve, qui n'ont jamais encore développé de lésions (non-lésionnelle). Ils peuvent produire de l'IL-17, une protéine nocive bloquée actuellement dans les thérapies biologiques contre le psoriasis. Ces lymphocytes résidents dans la peau non-lésionnelle seraient attirés par une réaction tissulaire anormale aux microbes de la peau.

Dans le psoriasis actif, les cellules T s'accumulent dans la peau puis diminuent en parallèle l'amélioration des symptômes. L'activation de ces lymphocytes T dans les biopsies de peau normalisée après une poussée conduit à des altérations moléculaires rappelant la maladie active. Cette signature moléculaire pourrait permettre de prévoir le temps de rémission, jusqu'à la mise en place d'un nouveau traitement. Cette découverte est prometteuse et doit être confirmée par des essais cliniques.

Dans l'ECA, le seul remède consiste à éviter l'allergène. Nous avons examiné la peau des patients pendant l'allergie active, puis 2 mois et enfin 2 ans après la disparition des symptômes. Même après 2 ans, l'état moléculaire de la peau n'était pas revenu à la normale, indiquant une "cicatrice de la maladie". Des modifications moléculaires évocatrices de l'allergie active et susceptibles de rompre la barrière entre l'épiderme et le derme sous-jacent ont été observées dans la peau lors de l'activation des lymphocytes T. Cela permettrait aux cellules sanguines d'envahir la couche supérieure de la peau et entrainer des symptômes.

Les travaux de cette thèse argumentent en faveur de la pertinence des lymphocytes T cutanés dans le développement et la récurrence des affections cutanées inflammatoires, en proposant des mécanismes expliquant comment les lymphocytes T colonisent la peau et déclenchent une réaction en chaine aboutissant à l'inflammation. Les lymphocytes T résidents pourraient être utilisées comme prédicteurs de rechute dans les années à venir. A l'avenir, nous espérons pouvoir remplacer les lymphocytes T résidents responsables pathologiques grâce à des traitements topiques.

LIST OF SCIENTIFIC PAPERS

I. **CD49a Expression Defines Tissue-Resident CD8 + T Cells Poised for Cytotoxic Function in Human Skin**

Stanley Cheuk, Heinrich Schlums, Irène Gallais Sérézal, Elisa Martini, Samuel Chiang, Nicole Marquardt, Anna Gibbs, Ebba Deltofsson, Andrea Introini, Marianne Forkel, Charlotte Högg, Annelie Tjernlund, Jakob Michaelsson, Lasse Folkersson, Jenny Mjösberg, Lennart Blomqvist, Marcus Ehrström, Mona Ståhle, Yenan Bryceson*, Liv Eidsmo*

Immunity, 2017 Feb, 46(2):287-300

II. **A skewed pool of resident T cells triggers psoriasis-associated tissue responses in never-lesional psoriasis skin**

Irène Gallais Sérézal, Elena Hoffer, Borislav Ignatov, Elisa Martini, Beatrice Zitti, Marcus Ehrström, Liv Eidsmo

Journal of Allergy and Clinical Immunology, 2019 Apr, 143(4):1444-1454

III. **Resident T Cells in Resolved Psoriasis Steer Tissue Responses that Stratify Clinical Outcome**

Irène Gallais Sérézal, Cajsa Classon, Stanley Cheuk, Mauricio Barrientos-Somarribas, Emma Wadman, Elisa Martini, David Chang, Ning Xu-Landen, Marcus Ehrström, Susanne Nylén, Liv Eidsmo

Journal of Investigative Dermatology, 2018 Aug, 138(8):1754-1763

IV. **A long-term T cell-driven disease memory in allergic contact dermatitis initiates tissue responses with matrix-degrading capacities**

Irène Gallais Sérézal, Poojabahen Tajpara, Elena Hoffer, Marcus Ehrström, Mihaly Matura, Liv Eidsmo

Manuscript

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACD	Allergic Contact Dermatitis
APC	Antigen-Presenting Cells
CC	Chemokine C-C Motif
CCR	Chemokine-Receptor
CCR	Receptor of Chemokine with C-C Motif
CD	Cluster of Differentiation
cDNA	Complementary DNA
CLA	Cutaneous Lymphocyte Antigen
CLR	C-Type Lectin Receptors
CTLA4	Cytotoxic T Lymphocyte Antigen 4
CXC	Chemokine C-X-C Motif
CXCR	Receptor of Chemokine with C-X-C Motif
DAMPS	Damage-Associated Molecular Patterns
DMEM	Dulbecco's Modified Eagle Medium
DNA	Deoxyribonucleic Acid
DRESS	Drug Reaction with Eosinophils and Systemic Symptoms
FBS	Foetal Bovine Serum
FDE	Fixed Drug Eruption
FKPM	Fragment Per Kilobase Million
GFP	Green Fluorescent Protein
GO	Gene Ontology
GSEA	Gene Set Enrichment Analysis
GWAS	Genome-Wide Association Study
HC	Healthy Control
HKCA	Heat Killed *Candida albicans*
HLA	Human Leucocyte Antigen
HSV	Herpes Simplex Virus
IFN	Interferon
IL	Interkeukine
ILC	Innate Lymphoid Cells
JAK	Janus Kinase
LC	Langerhans Cells
LCE	Late Cornified Enveloppe
MAIT	Mucosal-Associated T Cells
MCI	Methylchloroisothiaozolinone
MF	*Malassezia furfur*
MHC	Major Histocompatibility Complex
MI	Methylisothiazolinone

MMP	Metalloprotease
mRNA	Messenger RNA
NK	Natural Killer
NLP	Never-Lesional Psoriasis
PBMC	Peripheral Blood Monocellular Cell
PD1	Programmed Cell Death 1
pDC	Plasmacytoid Dendritic Cells
PCR	Polymerase chain reaction
PMA	Phorbol 12-myristate 13-acetate
PP	Plaque (lesional) psoriasis
PRR	Pattern Recognition Receptors
QC	Quality control
RNA	Ribonucleic Acid
RP	Resolved Psoriaiss
RT-qPCR	Reverse Transcription Quantitative PCR
SC	*Saccharomyces cerevisiae*
SNP	Single nucleotide polymorphism
SPF	Specific Pathogen Free
SPRR	Small Proline-Rich Region
t-SNE	T- Distributed Stochastic Neighbour Embedding
T	T cell
Tc	CD8+ T cell
T_{CM}	Central memory T cell
TCR	T Cell Receptor
T_{EM}	Effector Memory T Cell
TEN	Toxic Epidermal Necrosis
TGF	Tumour Growth Factor
Th	CD4+ T cell
TLR	Toll-Like Receptors
T_{MM}	Migratory Memory T cells
TNF	Tumour Necrosis Factor
T_{PM}	Peripheral Memory T Cell
TPM	Transcripts Per Kilobase Million
TR	*Trichophyton rubrum*
TRAIL	TNF-related apoptosis-inducing ligand
Tregs	Regulatory T cells
T_{RM}	Tissue-resident Memory T cells
UV	Ultraviolet

1 INTRODUCTION

For the **human skin** to fulfill its many functions, the local immune system has to constantly balance between tolerance and inflammatory responses. At the cellular level, barrier immunology orchestrates many actors, including stromal cells. Among the resident immune cells in the skin, T cells are involved in the tissue response to infections and also in the pathogenesis of several inflammatory diseases. This thesis focuses on **tissue-resident memory T cells** (T_{RM} cells) in the skin, and their function in common chronic T cell-driven dermatoses.

1.1 THE HUMAN HEALTHY SKIN AND ITS IMMUNE SYSTEM

1.1.1 The structure of the human skin

The skin is one of the largest human organs and an essential barrier (Proksch *et al.,* 2008), ensuring its own homeostasis and the protection of the internal tissues. It has to constantly sense the environment and elicit regulated tissue responses to ensure protection while safeguarding the tissue.

The skin is formed by the epidermis and the dermis, which are separated by the basement membrane. The epidermis is an epithelium that lacks blood vessels and relies on the underlying dermis for nutrition. The predominant cell type is the keratinocyte. The thickness of the epidermis depends on the body site, and each layer has particular structural properties and shape (Figure 1) (Kolarsick *et al.,* 2007). The basal layer is home to epidermal stem cells that allow for the constant regeneration of the epidermis. The further up from the basement membrane, the more differentiated keratinocytes are. Protruding between the keratinocytes, melanocytes are placed at the basement membrane and produce the pigment melanin. Hair follicles are epidermal structures diving into the dermis. They are important structures for tissue homeostasis that facilitate wound healing and interactions with the microbiota. The basement membrane is the lower frontier of the epidermis (Vidal, 2013). It is not a porous membrane but an interlacement of anchoring molecules of collagens, glycoproteins, and proteoglycans produced mainly by the keratinocytes, attaching the epithelium to the underlying dermis (Figure 2).

The dermis is a highly vascularized fibrous tissue populated by fibroblasts, containing matrix proteins such as collagens. It contains skin appendages, such as the sebaceous glands, sweat glands. Skin nerve endings are present in the dermis and up to the epidermis, and sense pain and temperature. The hypodermis lies under the dermis and contains the subcutaneous fat and larger blood vessels.

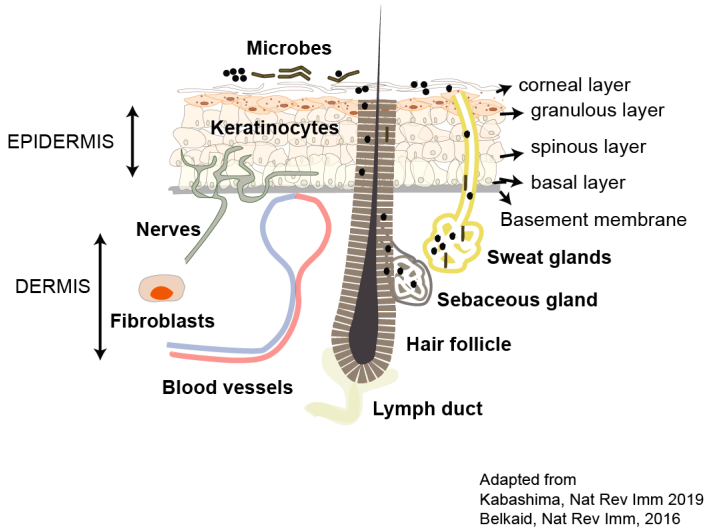


Figure 1 The human skin structure

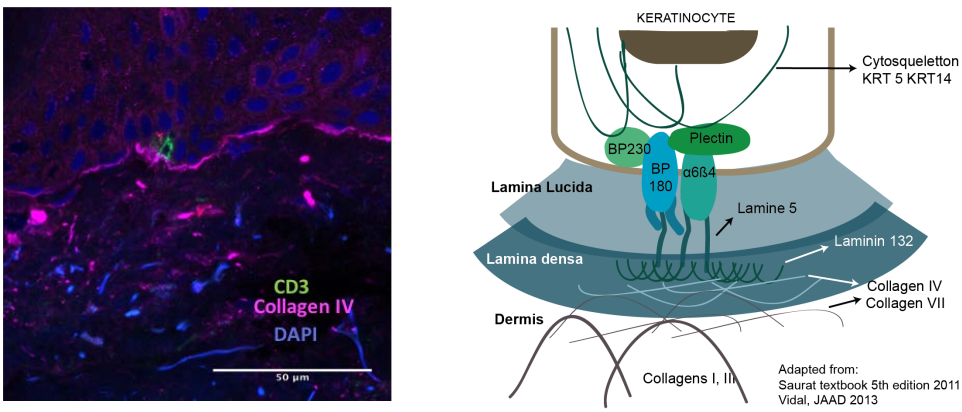


Figure 2 The skin basement membrane

On the left, confocal microscopy was performed after cryosection of healthy human skin. On the right, schematic illustrating the composition of the basement membrane.

1.1.2 The skin external environment

The skin is exposed to ultraviolet (**UV)** radiation daily, allowing for the production of Vitamin D that impacts the interplay between the skin and the microbiota (Agak *et al.,* 2014) and locally the proliferation and differentiation of the keratinocytes (Svendsen *et al.,* 1997). Furthermore, UV radiation affects melanocytes production of melanin that protects the skin from burns and cancers. However, UV radiation also has mutagenic effects and is involved in the generation of most of the skin cancers (Marrot *et al.,* 2008; Reichrath, 2013).

The last centuries with the era of industrialization present another challenge for the skin with steadily increasing contacts with chemicals and pollutants (Cetta *et al.,* 1991; Rovira *et al.,* 2019; Goldsmith 1996). The daily use of household and cosmetic products, and body hygiene products in modern society has also introduced repetitive contacts with many chemicals that may lead to irritant contact dermatitis, one of the most common occupational diseases (Carøe *et al.,* 2014; Mowad *et al.,* 2016).

After birth, the skin is rapidly colonized by **micro-organisms**, in parallel to the arrival of additional immune cells (Scharschmidt *et al.,* 2015). The composition of the skin microbiota is highly dependent on the body site and is well characterized when it comes to bacteria (Grice and Segre 2011; Grice *et al.,* 2009). Increasing information on the fungal microbiota or mycobiota is now available (Belkaid and Segre 2014) but the viruses and archaea composition in normal skin remains obscure. Their interactions with the human body (Findley *et al.,* 2013; Takemoto *et al.,* 2014), and with other components of the biotas (Hannigan *et al.,* 2015) is an area of intense work. Despite some major technical improvements, refined information about the strains and the potential inter-domain microbial interferences are yet challenging to obtain. With tight links to the innate and adaptive immune system (Thaiss *et al.,* 2016), the skin microbiota could be considered as the most outer part of our immune system.

1.1.3 Barrier immunology

To safeguard the skin against infections and avoid excessive immunopathology, several cell-types can start an immune response and regulate inflammation, to fulfill the complex contextual functions of the skin. The focal communication system between cells in the skin relies on signaling molecules.

Cytokines are soluble proteins that can mediate immune and inflammatory signals. The term **interleukins** initially referred to proteins mediating a signal between lymphocytes but they can also be detected by other cell types (Abbas *et al.,* 2014). Cytokines that initiate chemotaxis have been named **chemokines** and are responsible for leukocytes migrating, both in homeostasis and to the sites of inflammation. Cytokines and chemokines can be produced by innate or adaptive immune cells and stromal cells. Some cytokines are blocked or activated to treat diseases, exemplified by TNF blockers in rheumatoid arthritis and interferons in C hepatitis. Damage-associated molecular patterns (DAMPS) or **alarmins** are additional signals comprised by small proteins or nucleic acids that are recognized by pattern recognition receptors (PRR). Several of the DAMPS proteins have cytokine-like functions and share common receptors.

There is no strict delimitation between cytokines, chemokines, alarmins, and antimicrobial peptides. For example, β-defensin 2 is an **anti-microbial peptide** with direct killing activity, produced in response to cytokines such as IL-17 or IL-6, it can bind to the chemokine receptor CCR6 and induce cell attraction. In Table 1, a subjective selection of signaling molecules relevant for this thesis is presented based on the following references: (Yang *et al.,* 2017; Sebastiani *et al.,* 2002; Griffith *et al.,* 2014; Bromley *et al.,* 2008).

NAME	SIZE (kDa)	ALT. NAME	RECEPTOR	FUNCTIONS (NON EXHAUSTIVE)
CXCL-9	14	Mig	CXCR3	Attracts Th1, Th17, CD8, NK T cells
CXCL-10	10	IP-10	CXCR3	Attracts Th1, Th17, CD8, NK T cells
CXCL-8	11	IL-8	CXCR1 CXCR2	Attracts Neutrophils
CCL-20	10	MIP-3α, LARC	CCR6	Attracts Th17 cells. B cell and DC homing, antimicrobial
CCL-4	10	MIP-1β	CCR5	Attracts Macrophage and NK cell, guides encounter with DCs in lymph nodes
IL-17	35		IL-17RA (5 IL-17R)	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment and activation of neutrophils
IFN-γ	40-60		IFNGR1/IFNGR2	Cytotoxic activity and TH1 differentiation; upregulation of MHC class I and II, induction of epithelial apoptosis in skin and mucosa
IFN-α	15–21		IFNAR	Defense against viral infection, activation of naive T cells
TNF	25	TNF-α	TNFR1, TNFR2	Proinflammatory mediator and immunosuppressive mediator
IL-15	18.6			T-cell activation; proliferation and activation of NK cells
IL-22	23		IL-22R	Pathogen defense; wound healing; tissue reorganization
IL-13	10		IL-13R1a1 and IL-13R1a2	Ig class switching, upregulation of MHC class II, activation of eosinophils and mast cells; defense against parasite infections
IL-10	18		IL-10R1/IL-10R2	Immunosuppressive effect through APCs or direct effects on Tcell subsets
IL-9	14		IL-9R	T and mast cell growth factor; inhibition of TH1-cytokines; proliferation of CD81 T cells and mast cells; chemokine
DEFB2	7	BD-2	CCR2, CCR6, TLR4	Antimicrobial
S100As	10-13	7: Psoriasin	RAGE, TLR4	Leukocyte recruitment, pro-apoptotic
LL-37	19	Cathelicidin	FPRL1, TLR7,8,9, P2X7, EGFR, MrgX2, CXCR2	Leukocyte recruitment

Table 1 Interleukins (IL), chemokines (CXCL, CCL) and other signalling molecules

In vertebrates, the immune system is classically divided into innate and adaptive. The **innate immune system** is the most ancient, representing the first line of defence against aggressions at the body's boundaries.

The main cell types in the skin innate immune system are mast cells, eosinophils, basophils, neutrophils, innate lymphoid cells (ILCs), natural killer (NK) cells, macrophages and dendritic cells (Nestle *et al.,* 2009; Artis and Spits 2015). Many cells from the innate immune systems are found in the skin at a steady state (Figure 3), in the dermis (Nestle *et al.,* 2009), such as dendritic cells (DC): $CD1c^+$, $CD141^+$, myeloid DCs and plasmacytoid DCs (pDCs), as well as macrophages and $CD14^+$ monocytes (Kashem *et al.,* 2017). The dermis is vascularized and prone to a higher turnover of cells than the epidermis. Langerhans cells (LCs) are APCs seeded into the epidermis during the fetal stage and self-renew locally during rodent life (Merad *et al.,* 2002). When the skin gets attacked, LCs in the epidermis and DCs in the dermis are activated and migrate to lymph nodes to present the antigen to T cells.

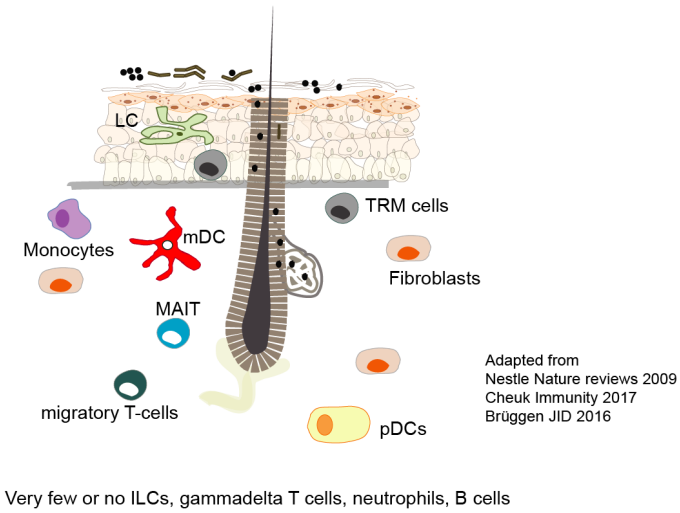


Figure 3 Immune cells in human skin

Innate immune cells can recognize pathogens. At the cellular level, the recognition occurs through PPRs such as Toll Like Receptors (TLRs) and C-type lectin Receptors (CLRs), recognizing specific structures like bacterial flagella or chemical compound such as mannan, RNA, DNA (Murphy *et al.,* 2012). The PRR expression decides what pathogens innate immune cells recognize. Extracellular pathogens can be recognized directly by macrophages and be degraded through **phagocytosis**. An important function of the innate immune system is the antigen presentation to the cells of the adaptive immune system, contributing also to the body defense (Owen *et al.,*, 2013). Antigen presentation relies on

the expression of the loading molecules MHC (Major histocompatibility complex). **MHC I** is expressed by nucleated human healthy cells and can present short, intracellular peptides after an intracellular protein has gone through degradation in the proteasome. Cells that are infected or cancerous will then be detected and undergo apoptosis. **MHC II** is expressed by APCs and will present longer peptides after a protein has been phagocytosed and degraded in a lysosome. The MHC I aims at a direct killing of the presenting cell by $CD8^+$ T cells and NK cells, while the APCs will migrate to the lymph node to present the peptide loaded on MHC II to $CD4^+$ T cells. Exceptions exist and cross-presentation of extracellular MHC I-loaded peptide to $CD8^+$ T cells is also possible (Abbas *et al.,* 2014). Different skin APCs can promote diverse functions in the activated T cell (Kashem *et al.,* 2016). Albeit highly efficient and powerful, the innate immune system lacks pathogen specificity and the classic definition of long-term memory.

The canonical division between innate and adaptive immunology was questioned by the **"trained memory"** concept that originates from the observation that plants with no adaptive immune system and that had been exposed to attenuated microorganisms were protected for long periods against reinfections (Netea *et al.,* 2011; Pereira *et al.,* 2016). This "immune training" rather than immune memory relies partly on an enhanced recognition system with an increase of TLR expression leading to a state of alert in that given cell, but not a specific refined memory (Netea *et al.,* 2011). These **epigenetic changes** can lead to cellular plasticity where exposure will trigger transcriptional profiling in a cell to optimize its function, (Alculumbre *et al.,* 2018; Feinberg, 2007). In addition to this temporary cellular adaptation, epigenetic changes can be stable in a given cell for its entire life and even transmits to its progeny (Bonasio *et al.,* 2010). Thus, although innate cells have no "memory" machinery, they can participate in the optimization of tissue protection.

The **adaptive immune system** allows for the recollection of previous foreign encounters and improves immune response upon new challenges. T cells provide cellular immunity and B cells antibody-driven humoral immunity, together contributing to a defence system with specific recognition of antigens followed by quick killing or production of antigen-specific antibodies. Both B and T cells have developed an advanced process of receptor generation, allowing for antigen-specificity.

Many cell types and many molecular mechanisms take part in skin immunity and immunology. One challenge when studying skin immunology is the extraction of immune cells from their environment to phenotypically and functionally characterize them. The skin is a highly compartmentalized organ, 3D structure is essential and cell-to-cell interactions are tightly regulated (Mitsui *et al.,* 2012; Shirshin *et al.,* 2017). Thus, separating the cells from their environment can alter their characteristics and functions. Another sensitive issue is the identification of migratory vs resident immune cells that requires longitudinal information difficult to achieve in human research. Whole tissue analysis is complementary to the refined cellular characterizations and there is a need for techniques capable to get detailed cellular and molecular information inside the human skin itself, preferably *in vivo*.

1.2 SKIN T CELLS

1.2.1 Introducing T cells

In recent years, several new T cell subsets (Godfrey *et al.,* 2015) have been characterized. Gamma-delta (γδ) T cells and MAIT (mucosal-associated T cells) are of particular interest in the barrier organs. However, as these T cell types represent a minority of the human skin T cells this thesis focused on αβ T cells (Cheuk *et al.,* 2017; Toulon *et al.,* 2009).

1.2.1.1 Formation and activation of T cells

Early T cell progenitors are generated in the bone marrow and maturate into T cells in the thymus. Each T cell harbors a **T cell receptor** (TCR), composed by heterodimers of either αβ or γδ chains. The αβ TCR is dominant in humans (Haas 1993). The generation of the chains relies on the random rearrangement of V (variable), D (diversity, only for β chain) and J (joining), at the *TRA* locus for α chains and at the *TRB* locus for the β chain. The additional random deletion of nucleotides at the regions' junctions leads to an almost endless diversity of specific TCR (Abbas *et al.,* 2014; C. Y. Wang *et al.,* 2016). The TCR is fixed for a given T cell during its whole life and transmits to its progeny.
In the **thymus**, the progenitors are exposed to specific APCs named cortical thymic epithelial cells harboring self-peptides loaded on MHC I and II. This positive selection is ensuring that the T cells recognize a peptide-MHC complex. The second step takes place in the medulla, where medullary thymic epithelial cells will present antigens that are otherwise tissue-restricted, regulated by the transcription factor autoimmune regulator AIRE (Klein *et al.,* 2014). The cells that recognize the MHC-self antigen complex with a high affinity will undergo apoptosis to avoid autoimmunity. The TCR associates with an additional CD247 protein, or ζ-chain and CD3 to form the **TCR complex**. At the end of the selection and maturation processes, T cells will carry a functional TCR and express either CD4 or CD8.
CD4 is a glycoprotein of the immunoglobulin (Ig) superfamily. It is expressed on the surface of T cells, macrophages and DCs. CD4 interacts with the MHC II through one of its Ig domains (Abbas *et al.,* 2014). T cells harboring CD4 are referred to as MHC II-restricted. The binding of CD4 allows for closer contact between the TCR and the MHC II and a subsequent stronger intracellular signal mediated by CD3 (Barber *et al.,* 2006). **CD8** is the molecule equivalent to CD4 for MHC I-restricted cells. It can also be expressed by Natural Killer (NK) cells and DCs.

Moving forward, the mature, yet **naive T cell** leaves the thymus. If it encounters an APC presenting its cognate antigen in a secondary lymphoid organ, the TCR complex will bind to the MHC. The intracellular tail of CD3 has an immunoreceptor tyrosine-based activation motif (ITAM) that will be phosphorylated upon activation of the TCR complex and starts a cascade of signaling. To achieve activation, the naive T cell has to receive **three signals**. Signal 1 is the TCR-MHC recognition, signal 2 is the involvement of co-stimulatory molecules and signal 3 is the exposure to a favorable cytokine environment (Abbas *et al.,* 2014; Chen *et al.,* 2013). In the absence of signal 2 and signal 3, anergy is likely to be the functional fate of the T cell. In rare cases, naïve T cells can be activated independently of a TCR-MHC interaction (Clement *et al.,* 2011). A known case of this is the superagonist

monoclonal antibody against CD28 that triggered a life-threatening cytokine storm during a clinical trial (Hünig, 2012). A myriad of **co-stimulatory and co-inhibitory** molecules have been uncovered during the last decades (Chen *et al.,* 2013). Co-stimulatory molecules deliver positive signals to T cells; co-inhibitory molecules deliver negative signals. For instance, when co-stimulatory CD28 expressed on T cell binds to CD80/CD86 (B7-1/B7-2) on a DC, it leads to T cell priming and DCs' activation. To limit tissue damage and the inflammation, the co-inhibitory cytotoxic T lymphocyte antigen 4 (CTLA4) is expressed on the T cell and CD28 is downregulated.

After activation, the T cell undergoes clonal expansion and drives an antigen-specific immune response. To study the T cell capacity to produce cytokines, a widely used proxy is based on Phorbol 12-myristate 13-acetate (PMA) that activates the protein kinase C, a protein activated downstream of the second signal (Figure 4). Ionomycin is often combined with PMA and also activates PKC (Chatila *et al.,* 1989). It thus bypasses the TCR complex and triggers the T-cell activation.

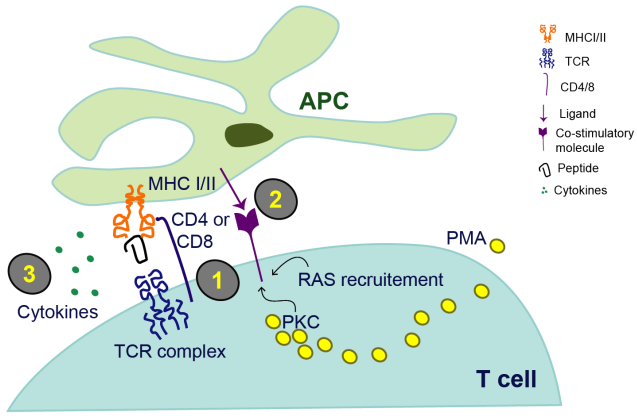
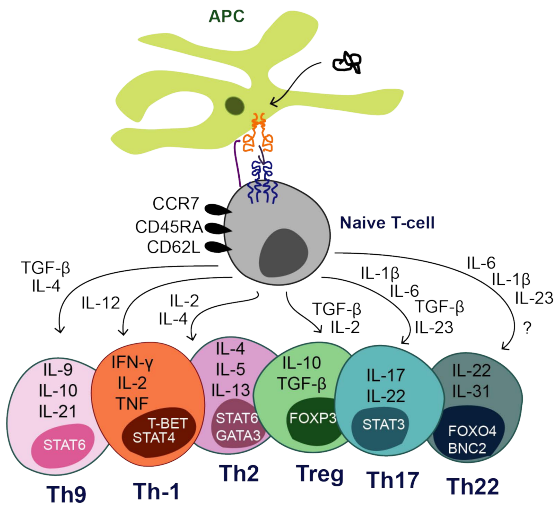


Figure 4 The three signals of naive T cell activation

1.2.1.2 CD4⁺ and CD8⁺ T cells

The classification of "helper" **CD4** subsets is based on the cytokines they produce (page 19). The differentiation is influenced by the cytokines present in the environment (Figure 5) and on the expression of co-signaling molecules (Chen *et al.,* 2013). Apart from cytokine production, $CD4^+$ T cells support the maturation of B cells into plasma cells and memory B cells. They recognize extracellular antigens presented by APCs on MHC II (Abbas *et al.,* 2014). An important subtype of $CD4^+$ T cells is regulatory T cells (Tregs). They are instrumental in the control of inflammation. They classically express the transcription factor FOXP3 and produce IL-10 and TGF-β, but these characteristics are not fixed and FOXP3 can be lost, with the cytokine production switching to pro-inflammatory ones (Zhou *et al.,* 2009). The differentiation into Tregs will be controlled by the expression of certain co-inhibitory molecules. When expressed in conventional T cells, PD1 can promote the differentiation into induced Tregs (Chen *et al.,* 2013).

The classification of different CD4$^+$ T cell subsets is useful for *in vitro*-based studies but the system allows plasticity. Tissue inflammation can for instance modify their cytokine production (Cosmi *et al.,* 2014). Thus, depending on the tissue state, overlap can be observed between Th2 and Th17 (Harrison *et al.,* 2018), and *FOXP3* can be induced in Th17 cells (Bovenschen *et al.,* 2011; Huber *et al.,* 2010).



Adapted from
Zou, Nat Imm Rev 2010
Van de Broek, Nat Imm Rev 2018
Kaplan, Nat Imm Rev 2015
Eyerich, JCI 2009
Plank, JI 2017

Figure 5 CD4$^+$ T cell subsets

The classical function of **CD8$^+$** T cells is the cytotoxicity. They recognize an intracellular antigen processed and presented on the MHC I and in certain situations, MHC I-loaded peptides from extracellular material that are cross-presented (Bevan 2006; Wehr *et al.,* 2019). CD8$^+$ T cells kill target cells through the immune synapse, forming a hole in the membrane with Perforin and releasing Granzymes into the target cell that will undergo apoptosis (Talanian *et al.,* 1997). They can as well produce cytokines such as IFN-γ, IL-2, TNF and TNF-related apoptosis-inducing ligand (TRAIL) among others. In nonlymphoid tissues, this can start potent antiviral tissue responses (Murphy *et al.,* 2012; Ariotti *et al.,* 2014; Schenkel *et al.,* 2013; Vassina *et al.,* 2005).

1.2.1.3 T cell recruitment to the site of inflammation

Both the APC's organ of origin and the type of APC responsible for the T cell activation will determine the subsequent homing and functional fate of that T cell (Kashem *et al.,* 2017). The induction of tissue-specific chemokine receptors and **homing** molecules will guide T cells to the inflamed site (Campbell *et al.,* 2002). For instance, the cutaneous lymphocyte antigen (CLA) is induced on T cells that will home to the skin (Clark *et al.,* 2006). Several other receptors are relevant for skin attraction such as CCR4, CCR10, CCR6 and CCR8 (Homey *et al.,* 2002; Campbell *et al.,* 2007; Xia *et al.,* 2014; Homey *et al.,* 2000; Islam *et al.,* 2011). The ligands of homing molecules can be expressed at a steady state, or produced by the tissue during inflammation, such as the chemokines CXCL-10 and CXCL-9 that are produced by keratinocytes during viral infections and attract $CXCR3^+$ T cells (Hickman *et al.,* 2015; Iijima *et al.,* 2015).

1.2.1.4 Memory T cells subsets

When the acute infection and inflammation subside, most of the effector T cells die off. Some will evolve into memory cells that trigger a quick and efficient immune response when the antigen is next encountered. In contrast to naïve T cells, the activation of memory T cells does not require three signals, as cell activation has been reported by single TCR-MHC engagement or even by co-stimulatory signals without TCR commitment (Barski *et al.,* 2017; Chen *et al.,* 013).

How the various subsets of T cells are generated during inflammation is only partly understood, and most of the current knowledge springs from mice (Akondy *et al.,* 2017; Henning *et al.,* 2018; Eidsmo *et al.,* 2018). The different subsets of circulating memory cells consist classically of effector memory T cells (T_{EM} $CD45RA^-CCR7^-$), central memory T cells (T_{CM} $CD45RA^-CCR7^+$) that are capable of producing cytokines, and stem cell memory (T_{SCM} $CD45RA^+CCR7^+CD95^+CD122^+$) that have no effector function but proliferate and self-renew (Kumar *et al.,* 2018; Sallusto *et al.,* 1999). A list of the T cells markers relevant in this thesis is presented in Table 2, based on the work of (Beura *et al.,* 2014; Wong *et al.,* 2016; Owen *et al.,* 2013; Groom *et al.,* 2011). Of note, these markers were described according to bulk analysis of T cells, and single-cell techniques will allow the further division into functionally relevant subsets (Hughes *et al.,* 2019).

The subset considered responsible for the long-term memory were T_{CM} as they persisted in the blood. A durable persistence in nonlymphoid tissues was later shown for T_{EM} (Masopust 2001; Lanzavecchia and Sallusto 2005; Sallusto *et al.,* 1999) and even occasionally for T_{CM} (Gehad *et al.,* 2018; Clark *et al.,* 2012). The population of T_{EM} found in the nonlymphoid tissues may also overlap with a more recently described subset of circulating T cells, peripheral memory cells (T_{PM}) that go back and forth between the circulation and the nonlymphoid tissues (Gerlach *et al.,* 2016) as shown in Figure 6. Migratory memory T cells (T_{MM}) are $CCR7^+$L-selectin$^-$ T cells identified in humans, that have an intermediary phenotype between T_{CM} and T_{EM} and can also enter peripheral tissues (Watanabe *et al.,* 2015). The next part will focus on the T cells that are found in the skin.

Marker	Function	Naive	Effector	T_{CM}	T_{EM}	T_{RM}
L-selectin	Homing to LN	++	-	++	-	-
CCR7	Migration of naive T cells to LN	++	-	++	+/-	-
CD44	cell adhesion and migration	-	+++	+++	+++	++
CD69	S1PR1 inhibition	-	-/+	-	-	++
CD103/αeβ7	Integrin	+	-	-	-	+++
S1P1	lymphocyte egress from lymphoid organs.	++	++	++	++	-
CD45RA	Receptor-mediated signaling	++	-	-	-	-
CD45RO	Receptor-mediated signaling	-	++	++	++	++
CXCR3	Chemokine receptor for CXCL-9, CXCL-10	-	++	++	+	++
CD62L	C-type lectin adhesion molecule	++	+	++	+/-	-

Table 2 T cell markers

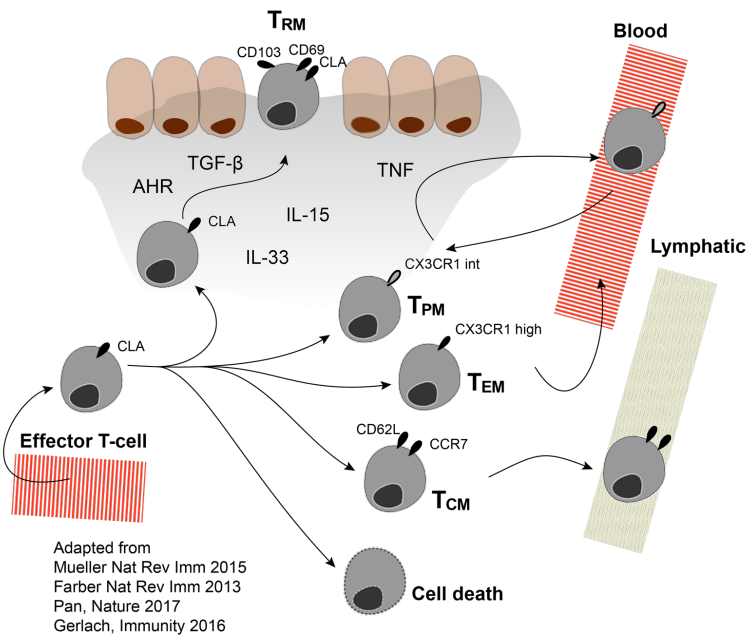


Figure 6 Memory T cell-subsets

1.2.2 Tissue resident memory (T_{RM}) T cells

1.2.2.1 T cells in the skin

A localized tissue memory was suspected since the early 1900s, based on for instance the protection obtained from repeated superficial inoculations of fungi in the skin (De Lamater *et al.,* 1938). The cells involved in this tissue memory remained unknown. Some 40 years ago, Bos *et al.,* identified **T lymphocytes in human skin** and proposed the existence of a skin immune system (Bos *et al.,* 1987). Skin mainly harbors αβTCR T cells (Foster *et al.,* 1990), and their TCRs are not in balance with circulating T cells (Clark *et al.,* 2006; Dunn *et al.,* 2006). Microscopy and later on flow cytometry analysis showed that the vast majority of skin T cells are either $CD4^+$ or $CD8^+$ but $CD4^-CD8^-$ αβTCR T cells exist in human skin (Groh *et al.,* 1989). Among the estimated 1 million T cells per cm^2 that populate human skin (Clark *et al.,* 2006), most are found in the dermis around the vessels and skin appendages (Bos *et al.,* 1987). Epidermal T cells encounter for less than 10% of the skin T cells, with a memory/effector phenotype observed already in 1996 (Spetz, Strominger, and Groh-Spies 1996). **Tregs** are found in the human dermis, close to hair follicles. Few Tregs have shared TCR with other skin memory T cells (Rodriguez *et al.,* 2014), and their establishment is influenced by the skin microbiota (Naik 2012; Scharschmidt *et al.,* 2017, 2015).

1.2.2.2 Skin residency – CD8 T cells

The idea of **T cells dwelling** in the skin progressed since early 2000. The hypothesis was first that the T cells detected in the skin were T_{EM}, thus coming into the skin from blood vessels and leaving to scan lymph nodes for their cognate antigen (Von Andrian *et al.,* 2003). The observed absence of CCR7 expression prevented them to subsequently leave for the lymph nodes and suggested that these memory T cells could instead reside in the nonlymphoid tissues (Schenkel *et al.,* 2014). The proof of residency was achieved in nonlymphoid organs in mice in 2001, and later on in skin (Gebhardt *et al.,* 2009), using several imaginative methods (Figure 7).

In parabiotic mice, the blood circulations of two mice are joined, the circulating cell-subsets equilibrate but the resident cells are retained in their original animal (Gaide *et al.,* 2015). Other methods use skin grafts to compare which skin T cells equilibrate with the circulation and which remain in the skin (Glennie *et al.,* 2015). Circulating cells can be depleted using female T cells transferred with male T cells before infection. The male circulating T cells will be rejected within 2 weeks but the epidermal skin-resident T cells are protected from eradication (Gebhardt *et al.,* 2011b). Furthermore, cells crawling out of the skin were considered as resident and analyzed (Clark *et al.,* 2006). In graft of human hands, long-lived donor T cells persisted years after the graft (Eljaafari *et al.,* 2006). In certain cases, T_{RM} cells from the donor can be differentiated from the host through their expression of HLA (Lian *et al.,* 2014). The duration of T_{RM} persistence in human skin is not known.

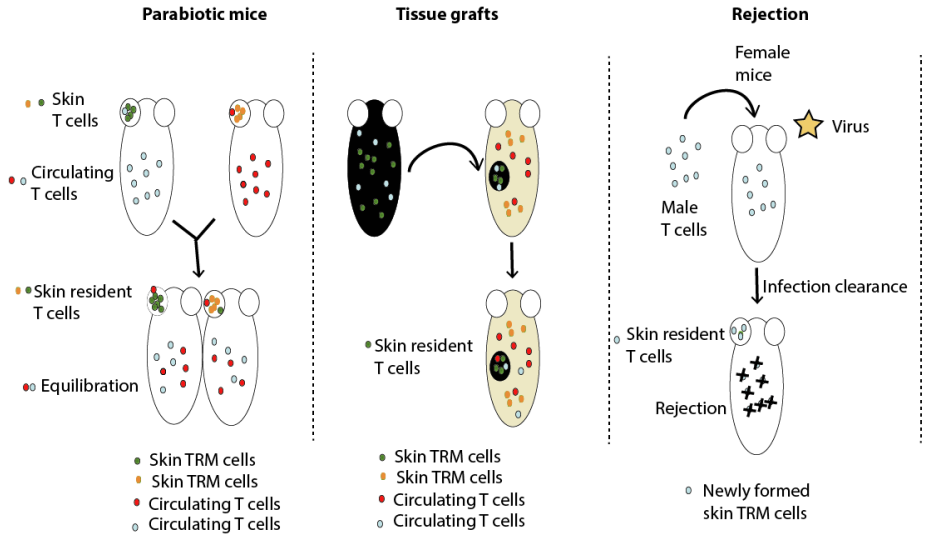


Figure 7 Mice models of skin T_{RM} cells

The mice models allowed the **characterization** of $CD8^+$ T_{RM} cells as memory T cells establishing in nonlymphoid organs after infections or inflammation, and subsequently parked in tissues. Upon a new encounter of the antigen, they slow down their tissue crawling and proliferate locally. This was shown in mice in a contact hypersensitivity model, where T cells in skin were exposed externally to UV converted from GFP by violet during an antigenic challenge. They did proliferate locally but stayed absent from LN 5 days after the challenge (Park *et al.,* 2018). Conversely, a recent report using mice bought from pet stores or co-housed with them showed that $CD8^+$ T_{RM} cells could leave the skin after activation and populate secondary lymphoid organs (Beura *et al.,* 2018), inviting to caution when extrapolating results obtained from mice with a controlled microbial environment. In 2019, new technological feat allowed the visualization of human $CD8^+$ T_{RM} cells within biopsies of human skin. This technical *tour de force* could confirm the crawling behavior and the localization of T cells under LCs and in the papillary dermis (Dijkgraaf *et al.,* 2019).

Several surface markers have been correlated to long-term skin dwelling in mice, and have been used for the identification of T_{RM} cells in humans. First, most of the $CD8^+$ T_{RM} cells identified using parabiotic experiments express CD69. **CD69** is expressed on both $CD4^+$ and $CD8^+$ T_{RM} cells. CD69 down-regulates S1PR1 and mediates tissue retention (Skon *et al.,* 2013; Shiow *et al.,* 2006). Mediators like interferons can promote T cells retention through the upregulation of CD69, indicating that during viral challenges, the retention of cells in the tissue where they reside is prioritized (Shiow *et al.,* 2006). Although it is a

useful residency marker for $CD8^+$ T_{RM} cells in the epidermis, its use in dermis requires caution (Watanabe *et al.,* 2015; Collins *et al.,* 2016). Other markers include the integrins **CD103** and CD49a. CD103 is the α-chain of the αEβ7 integrin and **CD49a** is the α1 unit of the α1β1 integrin (Linda M Wakim *et al.,* 2012; Gebhardt *et al.,* 2009); they bind respectively to e-cadherin and collagen IV. In human skin, most T cells express either/or CD103 and CD69 (Watanabe *et al.,* 2015). In $CD8^+$ T_{RM} cells of mice skin, the expression of CD69 is rather specific for the residency as skin $CD8^+CD69^-$ T_{RM} cells do recirculate (Hirai *et al.,* 2019).

1.2.2.3 $CD4^+$ T_{RM} cells in the skin

Blood memory $CD8^+$ T cells are a major antiviral player, and they can persist life-long while $CD4^+$ T cell-memory slowly fades (Homann *et al.,* 2001). Although the focus was first on $CD8^+$ T_{RM} cells, $CD4^+$ T cells represent the majority of T cells in both human and mice skin, often located in clusters with DCs in the dermis (Collins *et al.,* 2016; Cheuk *et al.,* 2014). Additionally, in mice skin before any challenge, $CD8^+$ T cells are virtually absent, and most $CD4^+$ T cells were **recirculating**. More research started to focus on $CD4^+$ T_{RM} cells and showed that they are generated upon infectious challenges in mice after *Candida albicans*, protecting against subsequent challenges, and in human skin exposed to *Leishmania major* (Park *et al.,* 2018; Glennie *et al.,* 2015). After skin injection with herpes simplex virus (HSV) in mice, they accumulate in the **dermis** around hair follicles but not in the epidermis (Gebhardt *et al.,* 2011b). $CD4^+$ T_{RM} cells also express the residency markers CD69 and CD103 but in human skin, a smaller proportion of $CD4^+$ T cells express CD69 and/or CD103 than $CD8^+$ T cells (Boniface *et al.,* 2018). This suggests that the $CD4^+$ T_{RM} cells might be more prone to recirculation. Indeed, despite the expression of T_{RM} markers while in the skin, half of $CD4^+$ T_{RM} cells can lose the CD69 marker and recirculate, as shown with parabiotic setups and follow-up of cells after photo-conversion in the skin (Collins *et al.,* 2016). In a humanized setup, recent work showed that $CD4^+$ skin T_{RM} cells from grafted human skin onto mice could downregulate CD69, migrate out of the skin and populate an artificial skin matrix that had been grafted elsewhere onto the mice, and where they could restore their initial phenotype (Klicznik *et al.,* 2019).

1.2.2.4 Compartmentalization

An additional level of complication when studying T_{RM} cells in human skin is the **compartmentalization** of skin. Mice skin differs from human skin in the density of hair follicles, the thinness of epidermis and a high proportion of γδ T cells, to cite the most challenging differences. Mice skin is most often analyzed as a whole, without separating epidermis from dermis, even though the migratory properties of dermal T_{RM} cells and epidermal T_{RM} cells are likely to differ. The T_{RM} **phenotype** in the dermis is less reliable than in the epidermis, with fewer cells expressing CD69 and CD103, both among $CD4^+$ and $CD8^+$ T cells (Watanabe *et al.,* 2015). In 2013, Mackay *et al.,* showed that in order to express CD103, $CD8^+$ T cells had to first migrate to the epidermis, as the blockade of their migration upward to the epidermis decreased the number of $CD103^+$ T_{RM} cells (Mackay *et al.,* 2013). The expression of residency marker correlates with the actual persistence, as dermal $CD4^+$ T_{RM} cells that express fewer markers equilibrate with the circulating

populations in long-term parabiotic mice experiments (Collins *et al.,* 2016). In mice, $CD8^+$ T_{RM} cells are most often studied in the epidermis and $CD4^+$ T_{RM} cells in the dermis. This creates a confusion between the differences shown in $CD8^+$ vs $CD4^+$ T_{RM} cells and the ones in epidermal vs dermal T_{RM} cells in the literature.

Table 3 exposes some of the differences between epidermal and dermal T_{RM} cells, but does not consider variations between CD4 and CD8 subpopulations. **Motility** of epidermal and dermal T_{RM} cells differ (Park *et al.,* 2018), possibly depending on whether the stroma is tight or loose, and what cells are present. In that regard, the skin can be divided into three compartments: epidermis, papillary dermis and deeper dermis. T cells in the epidermis are the slowest. In the study by Park *et al.,* the $CD4^+$ T cells in the papillary dermis interacted more with DCs than their deep-dermis counterparts (Park *et al.,* 2018).

		Epi - T_{RM}	Derm - T_{RM}
L-selectin	Homing to LN	-	-
CCR4	Homing to skin	++	++
CCR7	Migration of naive T cells to LN	-	-
CD69	Tissue retention	+++	+
CD103/aeb7	Integrin	+++	+
CD45RO	Memory T cells	+++	+++
CD45RA	Naïve T cells	-	-
CLA	Homing	+++	+++
CCR6	Homing	++	++

Table 3 T_{RM} cell-markers

1.2.3 The functions of skin T_{RM} cells

1.2.3.1 Skin protection against infections

Protective functions of T_{RM} cells **against infections** have been demonstrated in mice and strongly suggested in humans. T_{RM} cells locally patrol the skin (Ariotti *et al.,* 2012; S. L. Park, Zaid, *et al.,* 2018). Upon new encounter of their antigen, they trigger strong tissue-responses, as shown against **viruses** (Gebhardt *et al.,* 2009) and place the tissue into a state of alertness (Ariotti *et al.,* 2014), amplified by the stroma. T_{RM} cells have been extensively studied using models of HSV infection in mice where HSV-specific $CD8^+$ T_{RM} cells colonized preferentially the epidermis (Gebhardt *et al.,* 2009; Ariotti *et al.,* 2012). Skin re-infected by HSV could clear the infection, even without recruitment or circulating counterparts (as schematically represented in Figure 8). In humans, elegant HSV studies recruited subjects with recurrent genital herpes, and biopsies were taken at different timepoints on the genital mucosa. Using multimer staining, they could show the persistence of HSV-specific $CD8^+$ T cells two months after a recurrence, close to the basement membrane (Zhu *et al.,* 2007). These cells expressed *GZMB*, *TNF* and *IFNG* (Zhu *et al.,* 2013). Data indicated that the local number of $CD8^+$ T cells could predict whether an asymptomatic shedding or a clinical lesion would appear (Schiffer *et al.,* 2010). Additionally, asymptomatic HSV shedding was associated with an increased number of these specific T cells locally. Although this setting could not assess residency of the cells, it reinforced the idea that resident T cells could play an essential role in the peripheral immunity.

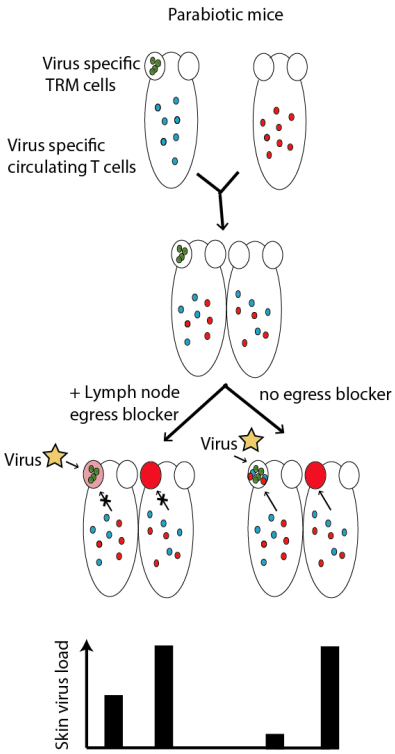


Figure 8 Virus-based T_{RM} studies

T_{RM} cells are less studied in non-viral microorganisms. Another type of microorganism infecting and/or colonizing the human skin is **fungi**. A resistance to reinfection could be obtained after a transcutaneous "lymphocyte sensitization" to dermatophytes in guinea pigs (Poulain *et al.,* 1980). In humans, a similar phenomenon was also described by Greenbaum in 1924 (Greenbaum, 1924). Dermatophytes most often create superficial lesions in human subjects, but in case of deeper dermal infections, several immunological reactions are described. First, they can trigger distant lesions,

"psoriasis-like" inflammatory papules named dermatophytids in non-infected skin sites (Gianni *et al.,* 1996). Dermatophytes can also create a Type IV hypersensitivity in case of persistent or recurrent infections and the intradermal inoculation of the preparation based on fungal products "trichophytin" then creates a delayed inflammation in the skin (Woodfolk *et al.,* 1996; Chakrabarti *et al.,* 1995). This reaction was used as an indicator of recent on ongoing infection with a dermatophyte some decades ago and was not species-specific (Grappel *et al.,* 1974). The "trichophytin" reaction persisted up to three years after the infection cleared. These findings strongly suggest the implication of memory T cells ensuring a long-term memory in the skin, although T_{RM} cells have not been described yet in this setting. Additionally, it was shown that $CD4^+$ T_{RM} cells can provide tissue protection against the opportunistic pathogen *C. albicans* (Park *et al.,* 2018; Roth *et al.,* 1988). T_{RM} cells are thus implicated in skin reaction to a wide range of microorganisms.

1.2.3.2 Protection against cancerous cells

T_{RM} cells are perfectly placed in the epidermis to be major player in the control of skin neoplasms, both melanoma but also basal cell carcinoma and squamous cell carcinoma. It is sound immunological planning that T_{RM} cells preferentially localize at the basement membrane, since access to the vessels is critical to the tumor egress. T_{RM} cells have been implicated in the **prevention** of melanoma in a mice model of vitiligo where the skin T_{RM} cells specific for melanocytes procured protection against subsequent melanoma development (Malik *et al.,* 2017). Additionally, the induction of T_{RM} cells in the skin of mice upon vaccination was shown to inhibit melanoma growth locally (Gálvez-Cancino *et al.,* 2018). In the **early stage** of the tumor as well, T_{RM} cells were identified as critical epidermal players to limit the development of invasive tumor (Park *et al.,* 2018). This study provided an explanation to clinical observation of melanoma relapsing sometimes decades after the first tumor was excised (Shen *et al.,* 2000). In **established cancers**, T_{RM} cells infiltrating the tumors is a booming area, and in melanoma T cells with T_{RM} phenotype were identified in 2016 in human tissue (Boddupalli *et al.,* 2016).

1.2.3.3 Effector functions

So how do the T_{RM} cells provide local protection? In 2008, Wakim *et al.,* proved the concept of T cell local proliferation in nonlymphoid tissue. The **proliferation** of $CD8^+$ tissue-resident T cells was shown possible in tissues upon encounter of their cognate antigen, with the participation of recruited $CD4^+$ T cells and DCs (Wakim *et al.,* 2008). Additionally, they showed that newly-recruited $CD8^+$ T cells could also proliferate on-site (Wakim *et al.,* 2014). Not strictly physiological, these proof-of-concept experiments were done on dorsal root ganglia grafted on kidneys and strongly suggested that resident T cells were capable of unleashing a T cell-driven response in their homing tissue. At the molecular level, **cytokine** production and **cytotoxicity** are key functions of T cells. Flow cytometry and later on transcriptome studies showed that both $CD4^+$ and $CD8^+$ T_{RM} cells in human and mice skin are potent producers of cytokines like IFN-γ, IL-2 granzymes and TNF, among others (Watanabe *et al.,* 2015; Beura *et al.,* 2019). Additionally, the production of cytokines differs depending on the CD103 marker expression with CD103 associated to increased IL-17 an IL-22 production in human skin (Watanabe *et al.,* 2015;

Kurihara *et al.,* 2019). The **transcriptome** of human skin T_{RM} cells, both $CD8^+$ and $CD4^+$ has been published in recent years and emphasized the differences between circulating and skin T cells (Li *et al.,* 2016; Mackay *et al.,* 2013), as well as between epidermal and dermal cells (Cheuk *et al.,* 2017). $CD4^+$ and $CD8^+$ subsets of T_{RM} cells are often studied as if they were homogeneous subsets but single-cell omics are bringing a well-needed level of complexity to identify new functional subsets (Hughes *et al.,* 2019).

1.2.3.4 Tissue responses

$CD8^+$ and $CD4^+$ T_{RM} cells can trigger quick **tissue-wide** responses when they reencounter their antigen in epithelia (Ariotti *et al.,* 2014; Schenkel *et al.,* 2013; Beura *et al.,* 2019). For instance, upon reactivation of herpes-specific $CD8^+$ T_{RM} in the skin of mice, or exposure to herpes peptide, the full-thickness skin transcriptome shows upregulation of pro-inflammatory signals as early as 3 hours after the challenge (Ariotti *et al.,* 2014). The signal from cytokines directly produced by the $CD8^+$ T_{RM} cells is amplified by other skin cells, driving the recruitment of circulating immune cells. When an antigen-specific T_{RM} cell population is triggered, it can protect against an **antigenically unrelated pathogen** (Schenkel *et al.,* 2013). The *in vitro* amplification of cytokine signals by keratinocytes has been thoroughly characterized using transcriptomic analyses and shows strong upregulation and release of chemokines and antimicrobial peptides (Swindell *et al.,* 2015; Swindell, *et al.,* 2013; Nograles *et al.,* 2008). Apart from stromal cells, T_{RM} cells are likely to influence other cells. For instance, mice devoid of $CD4^+$ T_{RM} cells have impaired DC maturation compared to mice with $CD4^+$ T_{RM} cells (Beura *et al.,* 2019).

In conclusion, T_{RM} cells in the skin are more numerous than T cells in the blood circulation (Clark *et al.,* 2006), and are capable of providing a first line of defense with quick responses directed toward a tissue challenge. Upon local recall, T_{RM} cells engage in focal interactions with the tissue's other immune and stromal cells, providing anti-infectious and anti-cancerous defenses (Park *et al.,* 2018; Gebhardt *et al.,* 2009).

1.2.4 T_{RM} cells subsets, establishment and survival in the tissue

The cellular origin of T_{RM} cells in humans is not known, but several reports in mice indicate that these cells derive from effector cells that enter the tissue after the encounter of their antigen (Jiang *et al.,* 2012; Mackay *et al.,* 2013; Ariotti *et al.,* 2012). Here the current knowledge regarding T_{RM} homing, development and persistence in the skin is introduced.

1.2.4.1 Recruitment and differentiation

Skin T_{RM} cells can be attracted to the skin by non-specific local inflammation as bystander T cells (Gebhardt *et al.,* 2012). This finding has been used in a "prime and pull" vaccination setting where mice were vaccinated using a herpes virus peptide and circulating activated T cells were attracted to the skin with a pro-inflammatory topical treatment. At that site, the mice were protected against the actual HSV (Shin *et al.,* 2012). Locally, the expression of CXCR3 by T cells is required to guide them to virally infected cells (Hickman *et al.,* 2015), independently of whether their cognate antigen was present or not. On the other hand, **antigenic exposure** improves the establishment of T_{RM} cells in the skin with enhanced

expression of CD103 and CD69 and potentializes their capacities to further recruit immune cells upon new antigenic challenge (Schenkel *et al.,* 2013). Additionally, an antigen-dependent competition in the inflamed tissue shapes the T_{RM} cell pool (Muschaweckh *et al.,* 2016). Overall, the antigen-dependence or -independence of T_{RM} cell-development and maintenance seems site-specific and what is valid for the skin may differ in other organs (Maru *et al.,* 2017; Thom *et al.,* 2015; Casey *et al.,* 2012), and can vary from epidermis to dermis.

The **differentiation** into T_{RM} cells in the skin and the subsequent persistence depends on environmental factors such as **IL-15** and **TGF-**β (Schenkel *et al.,* 2016; Shane *et al.,* 2014; Zhang *et al.,* 2013; Mackay *et al.,* 2013). The TGF-β produced by several cell types in the skin will increase the expression of retention markers (Gebhardt *et al.,* 2012; Travis *et al.,* 2014). In 2013, a seminal study provided a characterization of the *in situ* development of T_{RM} cells in mice (Mackay *et al.,* 2013). Mackay *et al.,* showed that *IL15*$^{-/-}$ and *TGFB*$^{-/-}$ mice developed less skin $CD8^+CD103^+$ T_{RM} cells. They could also show that the absence of **CXCR3** on T cells led to fewer T_{RM} cells and that the expression of IL-15 by other epidermal cells than T cells was instrumental to the establishment of epidermal T cells, indicating that the stromal microenvironment is essential to T_{RM} cell development. In 2015, the same team showed that the downregulation of T-box transcription factors and *EOMES* were essential to the T_{RM} cell formation in the epidermis, via their effect on TGF-β (Mackay *et al.,* 2015). The presence of $CD4^+$ T cells is as well crucial for $CD8^+$ T_{RM} cells to correctly express CD103 and localize within another barrier organ, the lungs (Laidlaw *et al.,* 2014) but this is not as clear regarding the skin.

1.2.4.2 Seeding

Besides establishing in inflamed areas deprived of their cognate antigens, T_{RM} cells can **seed to distant skin** sites at the time of the effector response, and shape a more global memory in other sites of the same organ (Gaide *et al.,* 2015). The factors underlying global seeding are not well understood. Experimental models of viral infections suggest that several antigenic exposures facilitate the seeding to distant sites and that the recall response is weaker than at the initially infected site (Davies *et al.,* 2017). Transposed to inflammatory diseases, this suggests that early-treatment strategies may limit the diffusion of pathogenic T_{RM} cells. In addition to seeding at the time of acute infections, established skin $CD4^+CD103^+$ T_{RM} cells can recirculate and seed to distant skin site in a model of mice xenotransplanted with human skin (Klicznik *et al.,* 2019).

1.2.4.3 Persistence

The factors permitting the sustainability of T_{RM} populations in the skin and other organs are the focus of much work. It can be arduous experimentally to differentiate the factors that influence the *in situ* development from the ones affecting the persistence. Again, most of what is known come from $CD8^+$ T_{RM} cells in mice. T_{RM} cell-survival requires no further contact with their antigens (Mackay *et al.,* 2012). A residual **T-bet** expression was necessary for the $CD8^+$ T_{RM} cell persistence in the skin (Mackay *et al.,* 2015).

Their survival depends on exogenous **lipid uptake** (Pan *et al.,* 2017). T_{RM} cells express many cytokine receptors, and the absence of IL-15 and IL-7 inhibits the persistence of some T_{RM} subsets in the epidermis (Adachi *et al.,* 2015; Schenkel *et al.,* 2016) (Figure 9).

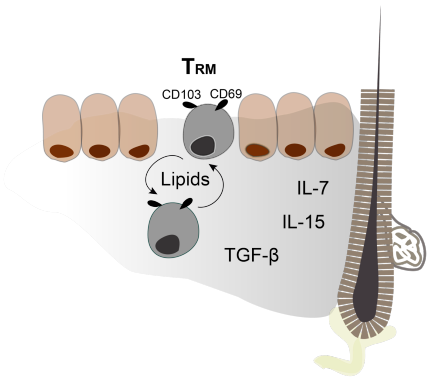


Figure 9 T_{RM} persistence

Keratinocytes also participate in the retention of T_{RM} cells through the expression of the integrins αvβ6 and αvβ8 that activate latent TGF-β (Mohammed *et al.,* 2016). The factors regulating retention in the epidermis is likely to differ from the dermis. Epidermal T_{RM} cells are suggested to be more sequestered in the epidermis than dermal ones, and less likely to recirculate, although this has not been formally demonstrated. In a model of viral skin infection, the depletion of cells accessible to the bloodstream led to the preferential disappearance of $CD4^+$ T_{RM} cells over epidermal $CD8^+$ T_{RM} cells (Gebhardt *et al.,* 2011a), indicating that the only T cells secluded from the circulation were in the epidermis, and were $CD8^+$.

1.2.4.4 Replacement

In mice bred isolated from common pathogens (specific pathogen-free SPF), the majority of epidermal T cells are δγ. Upon infection, αβ T_{RM} cells do **displace** the epidermal γδ T cells that were present from birth, leading to a higher proportion of αβ T cells than γδ T cells. Human fetal and neonatal T cells harbor very few epidermal T cells compared to adult skin (Di Nuzzo *et al.,* 2009; Watanabe *et al.,* 2015) and, to the best of our knowledge, their γδ TCR assessment is lacking. Whether a displacement similar to mice occurs at birth in humans is not known. Fetal dermal T cells exist, both FOXP3 negative and positive, but the epidermal description is lacking as well as the characterization of their TCR (Schuster *et al.,* 2012). This shift from γδ T cells to αβ T cells in mice suggested than the replacement of older T_{RM} cell-populations with new skin T_{RM} cells was a general mechanism of T_{RM}-mediated immunity (Zaid *et al.,* 2014). However, recent work highlighted that new T_{RM} cells in the skin could implement the old T_{RM} population, without displacing them (Park *et al.,* 2018). How T_{RM} niches jugulate their populations remains to elucidate. A hypothesis proposed in the literature is that in the event of tissue damage, extracellular nucleotides detected by T_{RM} could trigger the **death** of T_{RM} cells, and thereby give some free space for new cells to get installed as shown in mice liver T_{RM} cells (Stark *et al.,* 2018).

In conclusion, T_{RM} cells are subject to much attention (Figure 10). Many questions are still unanswered regarding the dynamics or replacement of the cells and their survival in tissues, that are particularly relevant inflammatory skin diseases in T_{RM} cells might be pathogenic.

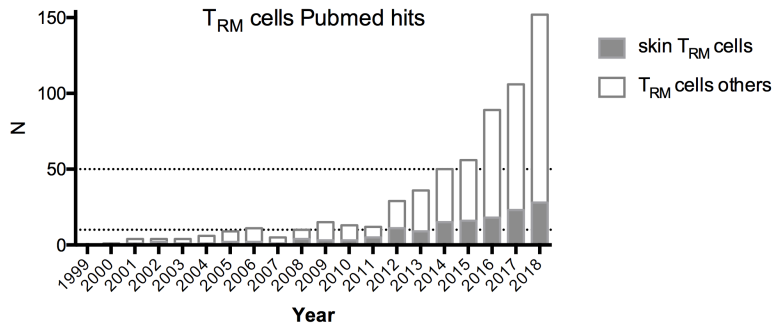


Figure 10 Popularity of T_{RM} cells over 20 years

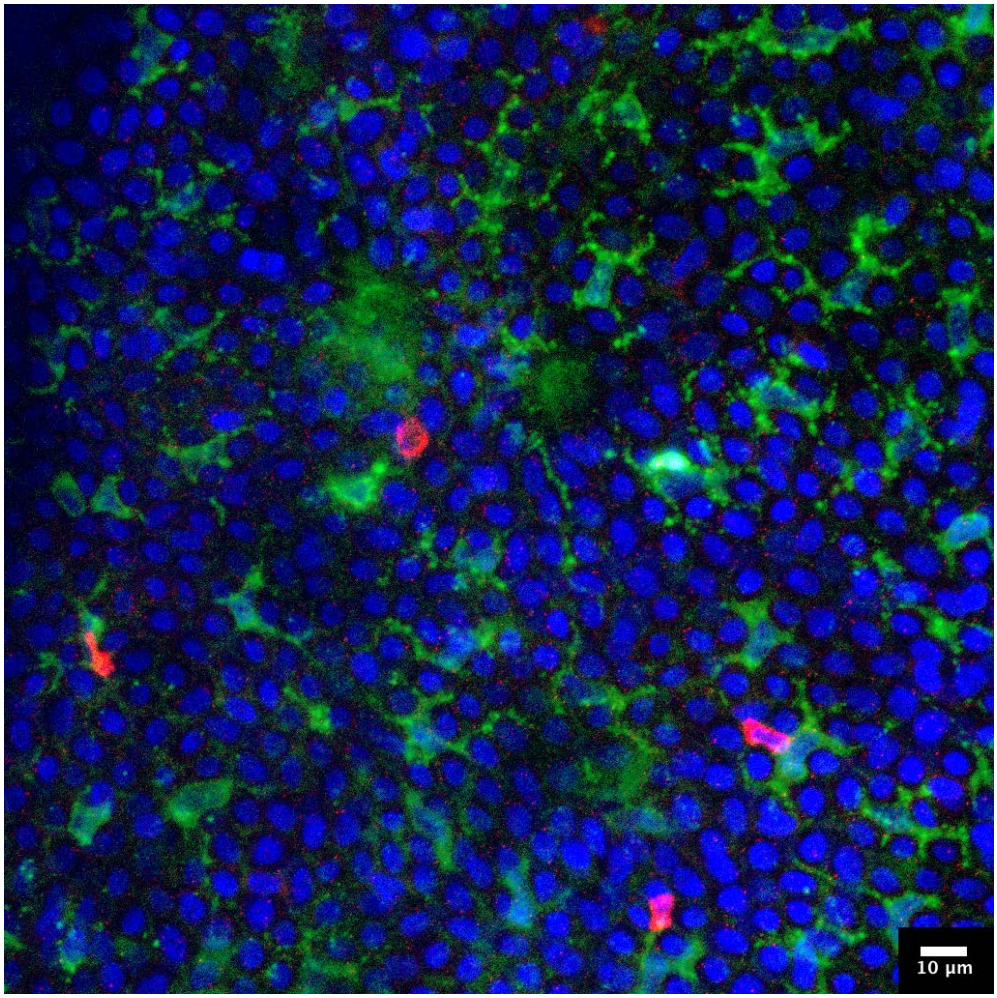


Figure 11 The skin upper layer

Confocal microscopy was performed on an epidermal sheet from healthy donor, showing in blue the cell nuclei with DAPI, in red CD3 marking T cells and in green langerin marking LCs. Courtesy of Dr. Cheuk.

1.3 THE INFLAMED SKIN

Inflammatory skin diseases are common and their consequences in term of quality of life can be dramatic for patients, with social isolation and working difficulties. The esthetic modifications are usually the first concern of patients, but the physical symptoms are not negligible: pruritus and pain can occur and be extremely difficult to live with (Balieva *et al.,* 2016). The financial burden for patients and health care is also increasing rapidly (Rosenberg and Rosenberg 2015). Schematically, an inflammatory disease is named autoimmune when the pathophysiology involves adaptive immunity with reactivity to self-proteins and antigens; autoinflammatory when the innate immune system is responsible. Classifying a disease into one or the other category can prove challenging (Peckham *et al.,* 2016). The three diseases studied in this Ph.D. thesis cover different aspect of the interplay between resident T cells and the skin microenvironment: **psoriasis** is IL-17-driven and has a dynamic between chronic lesions, **resolution and relapse** that makes it a good model to study the role of T_{RM} cells in relapse; **contact dermatitis** is an **antigen-specific** response to external factors and allows local T cell trigger with a known antigen. **Vitiligo** is an **autoimmune disease** with dominance of IFN-γ and cytotoxic T cell activity targeting the melanocyte.

1.3.1 Psoriasis

Psoriasis affects two to four percent of the population in Sweden. The genetic background is inherited (Squire, 1873), and environmental triggering factors start off the symptoms (Yin *et al.,* 2015; Fry *et al.,* 2013; Farkas *et al.,* 2010; Leung *et al.,* 1993). Patients often report stress such as mourning, problems at work and childbirth as a first triggering event. Infections are other common triggering factors and bacterial throat infections often start guttate psoriasis (Leung *et al.,* 1995). Psoriasis is also a systemic disease that can involve the joints, with a detectable imbalance in circulating cytokines and subsets of T cells (Bai *et al.,* 2018; Arican *et al.,* 2005; Sigmundsdóttir *et al.,* 2001). Its association with an increased cardiovascular morbidity stems in this chronic inflammation (Boehncke *et al.,* 2015).

Clinically, psoriasis lesions are red, infiltrated, well demarcated and scaly (Boehncke and Schön 2015). They might itch. Several topographical subtypes are described. The most common is psoriasis vulgaris or plaque psoriasis that account for 90% of cases. In that form, the plaques are several centimeters in diameter, can cover large areas of the body and typically predominate on elbows, knees, and the lower back (Boehncke *et al.,* 2015). The patients sampled for this Ph.D. were exclusively suffering from psoriasis vulgaris. Histological hallmarks of the pathology include the thickness of the epidermis corresponding to the keratinocyte proliferation; modification of the maturation stages of those keratinocytes; infiltration by immune cells such as neutrophils and infiltrating DCs (Kim *et al.,* 2015).

1.3.1.1 Skinomics: from genetics to proteomics

Already in early medical literature, familial forms of psoriasis were described (Squire, 1873). Antigen testing of lymphocytes could uncover that the HLA type was associated with psoriasis in a polygenic manner, except for patients where psoriasis outbreak was

induced by streptococcus (Russell *et al.,* 1972). **PSORS1** locus was later identified, containing HLA-C but also ten other genes, and sequencing could be performed thanks to technological developments. HLA-Cw6 was identified as a preeminent risk-allele for early-onset psoriasis. Later on, thanks to the increasing size of patient cohorts, genome-wide association studies (**GWAS**) could uncover that more than 60 loci are associated to psoriasis, but HLA remains the strongest association (Yin *et al.,* 2015; Liang *et al.,* 2017).

Beyond DNA sequence, analysis of **mRNA** with RT-qPCR showed upregulated transcripts in psoriasis skin compared to healthy skin (Elder *et al.,* 1989). Microarrays were later developed with panels allowing a high throughput analysis. The non-coding genomic expression was explored, and several dysregulations in microRNAs were identified (Meisgen *et al.,* 2012; Srivastava *et al.,* 2017). Finally, mRNA sequencing permitted a global transcriptome analysis with *de novo* identification of transcripts of interest. As cells taken out of their microenvironment rapidly change characteristics, bulk analysis of skin tissue is preferred but raises a challenge as many cell types are present in the tissue. An elegant though time-consuming alternative is the use of laser capture on frozen tissue to select a small area with given cell types before purifying the RNA (Mitsui *et al.,* 2012).

Techniques allowing bioinformatical "dissection" analysis of the RNA obtained from bulk tissues were therefore developed concomitantly. In order to better understand the transcriptome output, the dysregulated transcripts can get labelled as belonging to modules of genes associated to given biological functions (B. Li *et al.,* 2014). These clusters of genes can be defined based on the behavior of transcripts in many different types of samples acquired with different techniques. The pathway analysis is widely used, the most common being the gene ontology (GO). Another technique is the gene set enrichment analysis (GSEA) that runs with ranked lists instead of on an arbitrarily selected number of dysregulated transcripts. For instance, transcripts "set" from keratinocytes exposed to certain cytokine can be searched for in the transcriptome of whole tissue samples to detect the presence of this cytokine indirectly. Repetition of this analysis based on different cytokines can help estimate what was the predominant cytokine influencing a tissue at the time of sampling.

Proteomics show the actual protein content of the tissue. Of note, comparison of proteomic and transcriptomic data in lesional psoriasis could identify substantial variations. For instance, in the study by Swindell *et al*, specific ribosomal proteins appeared strongly upregulated by mass spectrometry but not overexpressed at the RNA level. Opposite trends also existed, and only 209 differentially expressed transcripts were consistent with proteins changes in total (Swindell *et al.,* 2015). The quantity of data generated by omics techniques is overwhelming, but it nevertheless allowed the field of psoriasis to gain knowledge on the physiopathology and will be reviewed in the following corresponding parts of the thesis.

Lipidomic and metabolomic analysis of psoriasis skin may hopefully complement the knowledge brought by the gene/transcript/protein triad in the search for useful biomarkers and treatment targets in the coming years (Kang *et al.,* 2017).

1.3.1.2 Immunological pathways of psoriasis

Clinical observations added strong arguments for the implication of the immune system in psoriasis. For instance, a female patient developed psoriasis after receiving a bone marrow transplant from her brother (Gardembas-Pain *et al.,* 1990). Before the 1970s, the interest was concentrated on humoral immunology, with the description of immunoglobins in the epidermis of psoriasis. The focus progressively shifted to T cells (Bjerke, Krogh, and Matre 1978; Thiers 1980). Apart from their presence in skin lesions, arguments for the role of T cells were reinforced by psoriasis treatments. Several efficient strategies against psoriasis such as cyclosporine and antimetabolites have effects on T cells, although not exclusively (Murphy *et al.,* 2003; Gottlieb *et al.,* 1992). The maintenance of the plaques was shown to depend on the APC/T cells crosstalk, but not on E-selectin that is supposed to block the migration of T cells in the skin (Ellis *et al.,* 2001; Bhushan *et al.,* 2002). The importance of T cells progressively settled and psoriasis was long considered as a Th1 disease with. **TNF and IL-17** were subsequently proven critical for psoriasis development and chronicity (Lowes *et al.,* 2007), as proven by the efficiency of the TNF blockers as psoriasis treatments, and more recently by the blocking of IL-17 pathway, either directly with IL-17 blockers (Langley *et al.,* 2014; Lebwohl *et al.,* 2015) or indirectly (anti-IL12/23 ustekinumab). IFN-γ also participates to this pathway as it programs myeloid APCs to induce human IL-17$^+$ T cells through the cytokines IL-1 and IL-23 (Kryczek *et al.,* 2008). The currently accepted pathophysiology of active psoriasis is summarized in Figure 12.

Importantly, there are hints that other cell types less studied could also play a role. Macrophages can produce IFN-α in draining lymph nodes of psoriasis in a mice model, and increase T cell infiltration (Stockenhuber *et al.,* 2018). The integration of data from GWAS and transcriptome could identify in what cell types the candidate genes near susceptibility loci were susceptible to be expressed. Surprisingly, neutrophils came out as the primary cell type in this analysis (Swindell *et al.,* 2014). Although T cells are critical to psoriasis pathology, the constitutive or circumstantial coexistence of many immune cell types in the skin calls for caution in focusing all efforts on one cell type.

1.3.1.3 The development of psoriasis – the keratinocytes

The fact that keratinocytes from non-lesional skin differ from healthy ones suggests a "priming" for the development of psoriasis (Kragballe *et al.,* 1985). Keratinocytes from non-lesional skin of psoriasis patients exhibit several particularities. First, a decreased triggering of IRF-1 and STAT1 in response to IFN-γ exposure (Jackson *et al.,* 1999). Second, a better integrin-dependent adhesion (Chen *et al.,* 2001). Third, proliferation upon the exposure to supernatants from activated lesional T cells, which is not the case of healthy keratinocytes (Bata-csorgo *et al.,* 1995). Fourth, upregulated anti-apoptotic genes and higher resistance to apoptosis upon UVB exposure (Bivik *et al.,* 2017). Fifth, a modified gene expression analyzed by microarrays and RNA compared to healthy keratinocytes, with the decrease of differentiation markers (Swindell *et al.,* 2017; Pasquali *et al.,* 2019). Last, a different DNA methylation profile, including for several psoriasis candidate genes (Verma *et al.,* 2018).

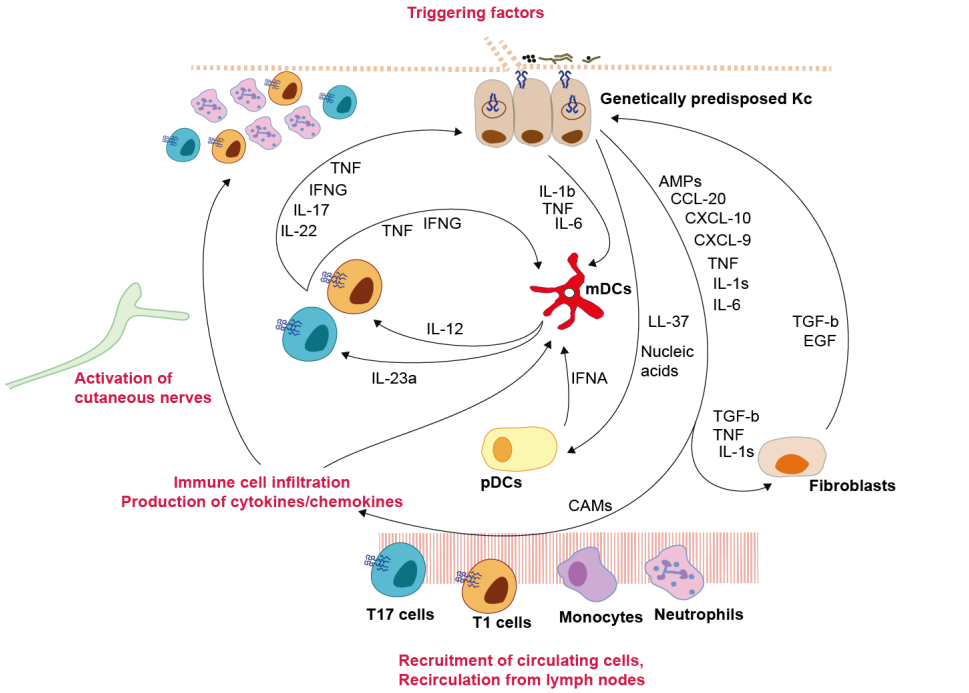


Figure 12 The current physiopathology of psoriasis

1.3.1.4 The development of psoriasis - a role for Type 1 interferon?

Several findings indicate that Type 1 interferons are involved in the early events of plaque formation. First, Type 1 interferons administrated for their antiviral properties can trigger psoriasis flare-ups or development (Kuzel *et al.,* 1990; Funk *et al.,* 1991). Second, plasmacytoid dendritic cells (pDCs) accumulate and produce a high quantity of Type 1 interferon in prepsoriatic skin engrafted to mice (perilesional skin > 0,5cm from the lesion) and can trigger psoriasis in a Type 1 interferon-dependent manner (Nestle *et al.,* 2005). Thus, Type 1 interferon could activate the myeloid DC that subsequently stimulates T cells, further amplifying the recruitment of more immune cells to the skin in a positive feedback loop. Two other findings shadowed the latter interesting discovery. The first is the spontaneous development of psoriasis upon engraftment of non-lesional skin onto mice, despite these mice's lack of Type 1 and Type 2 interferon receptors (Boyman *et al.,* 2004). The second is the inefficacy of clinical trials targeting interferons in psoriasis (Bissonnette *et al.,* 2010). Nevertheless, if Type 1 interferon plays a significant role in the development but not in the sustainability of psoriasis, a blocking could be worth testing in a preventive setting and not on stable disease.

1.3.1.5 The development of psoriasis – T cells

What drives the initial lesion on never previously involved skin is not known. Non-involved skin of patients with psoriasis expresses more genes of the IL-17 pathway (Chiricozzi *et al.,* 2016), and epidermal genes involved in keratinocytes differentiation such as SPRR2B, LCE3D and S100A7 (Gudjonsson *et al.,* 2009). The suspicion of a **subclinical infiltration** of pro-inflammatory immune cells led several groups to test whether grafting of non-lesional skin on mice would trigger psoriasis development. Initially, the grafting of non-lesional 0,4mm thick skin onto nude mice did not trigger the development of histological psoriasis on the grafts (Fraki *et al.,* 1981), although it developed markers of a lesion such as a higher plasminogen activator activity. Another group, proceeding to a similar experiment on nude mice, could witness the development of psoriasis from **non-lesional skin grafted to the mice** after six weeks (Krueger *et al.,* 1981). Two decades later, Boyman *et al.,* repeated the experiment on AGR129 mice and observed the spontaneous development of psoriasis macroscopically and microscopically (Boyman *et al.,* 2004). Additionally, the administration of high doses of the anti-CD3 antibody OKT-3 to block or deplete the T cells led to the blockade of psoriasis development on the grafts.

A noticeable difference between the characteristics of the nude and the AGR129 mice models is the presence of NK cells in the nude mice model (Gudjonsson *et al.,* 2007) that may have managed to regulate "better" the triggering of the inflammation. That no psoriasis was observed in the study by Fraki *et al.,* could depend on the size of the graft, the distance from the lesion where the non-lesional skin was sampled, the PASI of the patients, and other information that did not appear in the paper. This spontaneous development might be driven by the enrichment of epidermal **$CD8^+$ T cells** observed in non-lesional skin (Cheuk *et al.,* 2014; Barbara S. Baker *et al.,* 1984). Indeed, in non-lesional skin with few epidermal T cells, the blockade of T-cell migration to the epidermis through an $\alpha 1\beta 1$ inhibitor was enough to arrest the development of psoriasis. However, if the non-lesional skin was more "active", as defined by the presence of epidermal T cells in the graft, this blocking was less efficient (Conrad *et al.,* 2007), emphasizing the role of **epidermal** T cells. These seminal studies clarified that skin T cells in non-lesional skin are critical for psoriasis development.

1.3.1.6 Psoriasis as a disease of the MHC presentation?

Psoriasis is too frequent to be aimless. Much energy and skills were deployed in looking for the antigen(s) of psoriasis T cells. The principal argument for an antigen-dependent process came from the description of HLA-C as the dominant genetic risk factor for the development of psoriasis (Nair *et al.,* 2006). A defect in the regular TCR-MHC interaction in patients with the HLA*06:02 epitope would explain the creation of multiples autoreactive T cells clones in the skin. **Molecular mimicry** refers to the recognition of a harmless self-peptide by immune cell receptor due to its molecular similarity to a pathogenic antigen. Streptococcal throat infections trigger psoriasis guttate. The existence of T cell clones reacting to both the streptococcal M protein and skin keratins expressed in psoriasis suggested that psoriasis might arise from T cells directed against the skin (Valdimarsson *et al.,* 2009; Prinz, 2004; Diluvio *et al.,* 2014). M protein-specific T cells are generated after a throat infection and homes preferentially to the skin (Johnston *et al.,* 2004). There, the T cells recognize keratin antigens expressed either constitutionally or

upon skin trauma and mistake them for a bacterial antigen. In cases with streptococcal-associated psoriasis exacerbations, the decrease of keratin-reactive T cells correlates to the response to treatment and tonsillectomy could even improve patient's quality of life (Thorleifsdottir *et al.,* 2016).

Several antigenic candidates have thereafter been described such as the antimicrobial peptide **LL-37, skin lipids, melanocytes** antigens (Lande *et al.,* 2014; Kim *et al.,* 2016; Arakawa *et al.,* 2015; Morizane *et al.,* 2012; Cheung *et al.,* 2016). In most of the patients, however, a link with an external antigen such as bacterial infection is not clinically obvious. Stable psoriasis skin indeed hosts many antigen-experienced T cells, but their actual role in the disease development and relapse is challenging to prove as they can be attracted to the tissue by the local inflammation without driving the disease. Targeting these non-specific T cells is unlikely to improve the disease outcome.

Psoriasis may be too frequent to be useless. The molecular mimicry that could explain the disease development in a category of patients may represent an evolutionary-driven capacity to develop strong antimicrobial responses that were useful in other human contexts. In order to exert such a strong selection, an infectious disease would have to be particularly harmful. One tempting hypothesis is that the "psoriasis genotype" has been progressively selected in the middle-age in response to leprosy, as these two diseases seem mutually exclusive, indicating that a psoriasis genotype might protect against leprosy (Wahba *et al.,* 1980; Bassukas *et al.,* 2012). Following this hypothesis, anything (self or non-self) resembling specific *Mycobacterium leprae* antigens would unleash psoriasis in individuals genetically predisposed.

1.3.1.7 The recurrence of psoriasis and T_{RM} cells

Although effective systemic treatments are available and efficient in controlling the disease, the relapses are frequent upon treatment discontinuation, preferentially at the site of previous lesions. At the molecular level, the presence of a **"molecular scar"** has been shown in healed skin under TNF blockers treatment, with transcript dysregulation in resolved psoriasis compared to non-lesional skin (Suárez-Fariñas *et al.,* 2011). Notably, this analysis was done on whole skin biopsies and did not allow to conclude on the epidermal versus dermal signal. Part of the dysregulated transcripts related directly to T cells metabolism but many related to stromal cells, thus emphasizing that T cells are most likely not the only dysregulated cell type in resolved skin. An example is LCs in resolved psoriasis that are more prone to produce IL-23 upon TLR activation (Martini *et al.,* 2017).

The hypothesis of a **T cell-related local cellular memory** in the healed skin became one focus of the attention, supported by several findings. The T cell clonality exhibits similarities between resolved skin and lesional skin, more than with non-lesional skin (Vollmer *et al.*, 2001; Matos *et al.*, 2017). Focusing on T cells, the cell composition of the healed skin is indeed different: $CD4^+$ T cells producing IL-22 and $CD8^+$ T cells producing IL-17 are retained in the resolved epidermis after treatment (Cheuk *et al.,* 2014). A causal role of the resident T cells in the local relapse remains to be proven**.** The antigens recognized by the retained T cells in healed psoriasis skin are unknown. Despite the oligoclonality of T_{RM} cells in resolved psoriasis, the hope to find a limited number of antigens responsible for the disease subsists, based on the observation that resolved skins of

different patients shared TCR-α and TCR-β antigen receptor sequences that were absent from healthy samples (Matos *et al.*, 2017). These antigens could be from the self or part of a microorganism. Judging by patients reported clinical information, however, finding a single exogenic antigen explaining psoriasis relapses in unlikely, as triggering factors has wide inter- and intra-individual variability. Nevertheless, TCR identifications could prove useful to stratify patients according to their resident clones and hopefully identify subsets of patients where at least one known factor triggering the relapse could be avoided.

1.3.1.8 The skin microorganisms in psoriasis

Reports on dysbalanced bacterial microbiota in psoriasis skin are published, with no clear association between disease gravity and one skin bacterium (Gao *et al.,* 2008; Fahlén *et al.,* 2012; Alekseyenko *et al.,* 2013; Tett *et al.,* 2017). This raises the question of whether research should focus more on other microorganisms like viruses or fungi. The first argument for studying fungi is the clinical similarities existing between fungal infections and various forms of psoriasis (Atzori *et al.,* 2012). This observation has baffled dermatologists and a "parasitic origin" of psoriasis was suggested in the past, reinforced by the efficacy of some antimicrobial treatments (Heaney, 1927). The second argument is that IL-17 is involved in the immune responses towards fungal infections (Hau *et al.,* 2015). The third is that fungal products can drive psoriasis arthritis in mice, and delayed hypersensitivity in human (Woodfolk *et al.,* 2000, 1996; Khmaladze *et al.,* 2014). The possibility and frequency of co-occurrence of psoriasis and fungal presence in psoriasis have been debated in the literature, with no definite answer given (Alteras *et al.,* 1986; Henseler *et al.,* 1997). Two exciting tracks can be named here. First, microbial coexistence between bacteria and fungi species are different in psoriasis and in healthy skin (Stehlikova *et al.,* 2019). Inter-species interactions could create additional antigens susceptible to act on T cells. Second, the high frequency and diversity of malassezia in psoriasis skin (Takemoto *et al.,* 2014). In experimental settings, circulating T cells of psoriasis patients react to *Malassezia furfur* with increased production of IFN-γ (Kanda *et al.,* 2002). Malassezia is more commonly found in the scalp of patients with psoriasis than the controls (Rudramurthy *et al.,* 2014). This field might bring answers regarding frequent antigenic exposure of psoriasis skin in the coming years, but technical challenges remain as many detected microbial sequences in the skin remain difficult to link to known microorganisms.

1.3.1.9 Treatments

Psoriasis severity is very variable, and the majority of patients with a relatively limited disease will not need systemic oral treatments. Sea bath and sun is known to improve psoriasis since ancient times, and it is not altogether impossible that the inheritable leprosy "as white as snow" from Bible's Neeman that improved after six baths in the Jordan was psoriasis (Squire, 1873; Vora, 2015). In **UV** therapy, both UVA and UVB can be used. Narrow-band UVB is the modern treatment of choice, and the current regiment in Sweden involves UVB exposure (313nm) three times a week, for a total of 25 to 30 times. This treatment can be repeated once a year during several years without increasing the risk of skin cancer. UVB and UVA decrease the density of immune cell in the skin, both dendritic cell and T cells, and even have systemic effects (Sigmundsdottir *et al.,* 2005; Pearse *et al.,*

1987; Ozawa *et al.,* 1999). UVA penetrates deeper into the skin than UVB (Meinhardt *et al.,* 2008) and can cause more DNA damage. The use of PUVA therapy is limited since it promotes skin malignancies (Archier *et al.,* 2012; Lindelöf *et al.,* 1992). It reaches deeply-rooted immune cells in the epidermis, and modify the cell populations in the dermis. Modification of epidermal composition of T cells in the skin under PUVA treatment has been shown to precede the clinical improvement, but not the dermal composition or the APC composition, underlining again the importance of the epidermal compartment in psoriasis (Baker *et al.,* 1985). UVA is usually associated with a photosensitizer extracted from the Psoralea plant. Skin is exposed to psoralen either orally or locally with bath-PUVA.

The treatment of psoriasis builds on **local treatments** such as steroids, vitamin D, or tar. Several therapeutic revolutions occurred in the past decades. First, non-targeted **systemic therapies** appeared such as retinoids, cyclosporine and methotrexate, which remains the first line of systemic therapy. Therapies targeting cytokines were introduced more recently, following the lead of rheumatoid arthritis. TNF blockers, anti-IL12/23, anti-IL-17 are the main categories (Boehncke *et al.,* 2015; Hueber *et al.,* 2010). The clinical response to biologics has recently been linked to single nucleotide polymorphisms (SNP), with patients expressing variants related to high levels of IFN-γ to be more likely to respond to anti-IL12/23 (Loft *et al.,* 2018).

1.3.2 Allergic Contact Dermatitis

1.3.2.1 Clinics, diagnosis and genetics

Allergic contact dermatitis (ACD) is the clinical manifestation of contact allergy upon re-exposure to the causative hapten. Contact allergy is a very common pathological reaction pattern with an estimated prevalence of 20% in Europe (Alinaghi *et al.,* 2019). It has significant occupational consequences as the allergy often is the result of a work-related exposure. The chronic inflammation is directed against a hapten (Girolomoni *et al.,* 2004) and very often affects the hands which are the most often exposed body surfaces to chemicals. The most well-known and common hapten causing ACD is nickel.

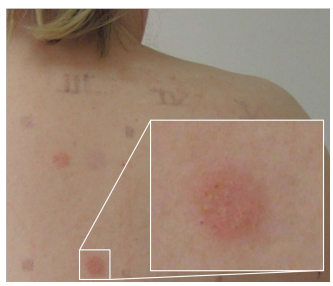


Figure 13 Clinical picture of positive patch-testing for ACD

Clinically, ACD lesions are often eczematous but many other clinical manifestations can occur, such as granulomatous and mucous membrane lesions. When affecting the hands, the

clinical presentation might differ and make the diagnosis challenging. Upon diagnostic patch testing, the skin is exposed to a panel of chemicals in a controlled way, usually as occlusion patch tests on the back of the patients (Mowad *et al.,* 2016). The reading of the test is preferably done twice: first after two days when the exposure ceases and then at day five to seven (Figure 13). A positive test consists of an eczematous lesion confined to the exposure site on the back but in some cases even previously affected skin sites flare up. A biopsy is usually not necessary. When performed, it shows spongiosis, intraepidermal vesicles, moderate epidermal and perivascular lymphocytic infiltrate and papillary dermal edema. Various treatment strategies are possible, but the only cure is allergen avoidance, as local persistence of the antigen in the skin leads to an extended duration of disease (Rashid *et al.,* 2016; Kaidbey *et al.,* 1984). Avoidance is challenging for the patients since the source of the exposure is not seldomly hidden for the patient and can be linked to his/her occupation.

Genetic predisposition has been described in rodent equivalent of ACD named cutaneous hypersensitivity (CHS). Breeders observed that different strains had a variable probability of developing CHS despite using similar protocols (Chase *et al.,* 1941; Turk, 1968). In humans, first degree relatives of patients with nickel ACD have a 2,83 RR to develop the disease (Fleming *et al.,* 1999). GWAS identified loci associated with nickel ACD (Kim *et al.,* 2013). Variation in TNF, its promoter region, and deletion of late cornified envelope antigens (LCE) 3B and 3C among others have been associated to ACD (Ertam *et al.,* 2009; Dittmar *et al.,* 2017; Molin *et al.,* 2011; Schnuch *et al.,* 2011). Interestingly, neither HLA nor filaggrin mutations are major genetic factors associated to the development of ACD (Landeck *et al.,* 2014; Silvennoinen-Kassinen *et al.,* 1979), but it associates to an earlier onset (Carlsen, *et al.,* 2010). Patients suffering from ACD have an insufficient generation of bulk ceramides that, together with a facilitating local factor such as an occupation with frequently humid skin, could facilitate the development of ACD (Kim *et al.,* 2017; Jakasa *et al.,* 2018).

1.3.2.2 Sensitization and elicitation

ACD is a model of Type IV allergy. A T cell-dependent skin allergy is named Type IV in opposition to the three other types in which antibodies and mast cells are responsible for the symptoms (Warrington *et al.,* 2018). It refers to a T cell-dependent mechanism where the first contact with a substance will lead to sensitization with the development of memory T cells. This first step can be totally. The next exposure – or challenge will trigger a robust immune response and symptoms. Several categories can be differentiated among Type IV allergies. In each case the antigen activates T cells but the effect in the tissue differs. In IVa, the production of IFN-γ will lead to macrophage activation, as in tuberculin reaction or in ACD. In IVb, IL-4 and IL-5 will be released from Th2 cells, leading to the recruitment of eosinophils, as in drug reaction with eosinophils and systemic symptoms (DRESS) syndrome. In IVc, cytotoxic T cells will be responsible for direct cytotoxicity, as in toxic epidermal necrosis (TEN) and fixed drug eruption (FDE) (Phillips *et al.,* 2018).

The **sensitization** to an allergen in ACD starts with the penetration of a hapten in the skin. A molecule can in some cases become a hapten by oxydation prior to the entrance in the skin (pre-hapten), after metabolisation in the skin (pro-hapten), or by UV exposure as in

photoallergic contact dermatitis (Kerr *et al.,* 2010; Kaplan *et al.,* 2012). Haptens are small molecules that can easily penetrate in the skin contrarily to protein antigens (Kabashima *et al.,* 2018). The presence of the hapten in the skin will trigger the innate immune system with effects on keratinocytes and mast cells via TLR activation (Kaplan *et al.,* 2012) and then be internalized by an APC. The APC will get activated and leave the skin to present its content in a draining lymph node. Both LCs and dermal DCs can fulfil this function (Streilein, 1989; Bennett *et al.,* 2007; Fukunaga *et al.,* 1990) although it seems LCs are more prone to trigger regulatory responses. In the presence of the right co-activation signals in the lymph nodes, naïve T cells will become activated and move back to the site of inflammation (Saint-Mezard *et al.,* 2003). It is noticeable that $CD8^+$ T cells are the quickest to be on site and the most responsible for the effector events in ACD (Vocanson *et al.,* 2006; Hennino *et al.,* 2011).

After resolution of the infection, the next encounter of the hapten will lead again to the presentation by APCs to memory T cells. These T cells are either present in the skin or recruited, leading to the **elicitation** of ACD. The accumulation of LCs is a classical sign of the ACD pathology in the skin, stressing their participation in the disease (Rosa *et al.,* 2016). Since APCs, T cells, and the hapten are present in the same location during elicitation, there are several ways for the hapten to get involved in the MHC-TCR relationship (Moulon *et al.,* 1995). The hapten can bind to a protein before entering an APC, and stay attached until MHC presentation, bind to the peptide after it was loaded on an MHC, or bind to the TCR directly and get in contact in the peptide there (Figure 14).

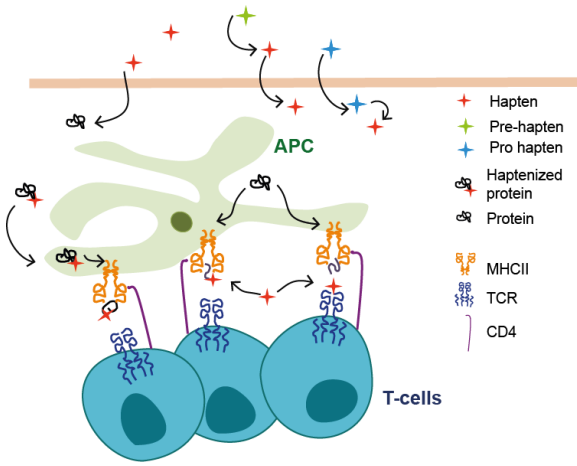


Figure 14 Hapten presentation in ACD

1.3.2.3 Disrupting the basement membrane

Contact dermatitis exhibits histological findings similar to atopic dermatitis where T cells transmigrate from the vessels to the dermis and will relocate to the epidermis. Atopic dermatitis is associated to a lower expression of collagen IV at the basement membrane that is correlated to the presence of IL-13 (Kim *et al.,* 2018; Shin *et al.,* 2015). Decreased collagen IV is believed to ease the penetration of immune cells into the epidermis.

Metalloproteases (MMPs) are enzymes that can degrade different collagens and blocking MMPs can impair the T cell migration through vessels' basement membrane through the action on collagen IV (Gschwandtner *et al.,* 2008). Different cell types can produce MMPs (Swindell *et al.,* 2013), including keratinocytes (Tewari *et al.,* 2014; Manetti *et al.,* 2012). MMP-12 can degrade both collagen IV and dermal collagens and its transcript can be induced in keratinocytes upon exposure to cytokines (Swindell *et al.,* 2013 2012). The proteolytic functions of MMPs can also target chemokines and cytokines (McQuibban *et al.,* 2000) with, for instance, MMP-12 truncating IFN-γ on its receptor binding sequence (Dufour *et al.,* 2018). Metalloproteinases can thus superimpose several tissue-relevant functions. Factors arising directly from T cells can also help attack the basement membrane. For instance, Granzyme B produced by $CD8^+$ T cells can increase the transmigration of T cells and remodel the extracellular matrix (Prakash *et al.,* 2014).

1.3.2.4 T_{RM} cells in T-cell mediated allergies

An elegant human example of T_{RM} cells in Type IV skin allergy is the almost exclusively epidermal disease **fixed drug eruption** (FDE), where the sensitization to a medication will trigger an accumulation of medication-specific T cells in given skin areas. T_{RM} cells migrate to the skin (Mizukawa *et al.,* 2002), and then persist at the dermal-epidermal junction in healed lesions. These cells lie in the epidermis and are for 90% $CD8^+$ (Mizukawa *et al.,* 2008). The areas involved are usually limited and the lesion can be unique, first erythematous and later hyperpigmented. Exceptions to that are the disseminated FDE and more severe bullous forms. One characteristic of FDE is the lifelong persistence of the reactivation of the lesion if the substance is administrated again. Upon challenge, they produce high level of IFN-γ and granzymes (Teraki *et al.,* 2003). $CD4^+$ cells are also present in smaller number and are composed primarily of Tregs in the lesion (Mizukawa *et al.,* 2008). Upon rechallenge, the same sites will develop the lesions, but it is not unusual that subsequent challenges will involve progressively larger skin zones, but seldom new areas. It is puzzling to consider that FDE is clinically little susceptible to the seeding phenomena of T_{RM} cells, whereas ACD is. Indeed, to diagnose FDE, a patch-test has to be positive on the healed skin and negative on the non-lesional skin, whereas the patch-test can be applied to any skin site for ACD and still trigger inflammation within a couple of days, reflecting the presence of skin memory T cells. The specific homing of $CD8^+$ T_{RM} cells in the epidermal compartment in FDE versus a more shared epidermal and dermal residency of both $CD4^+$ and $CD8^+$ T_{RM} cells in ACD could be an explanation and underlines the relevance of learning from both epidermal and dermal compartments in human T_{RM} cell biology. Very interestingly, cases of successful desensitization are described where the repetitive and gradually increasing exposure reinforced the $CD4^+$ T cell-population in the epidermis as well as the presence of $CD25^+$ T cells, indicating the presence of Tregs (Teraki *et al.,* 2004). Patients were then able to re-take the medication. Thus, control of the disease could be achieved by artificially modifying the skin T cells composition poising it toward an improved regulatory balance. The observation that Japanese patients got FDE on the site of recent HSV infections led to a hypothesis that HSV-specific cross-reactive skin T cells would react to drug-modified keratinocytes (Shiohara *et al.,* 2012). This form of drug-induced molecular mimicry would trigger FDE.

In **TEN**, the skin reaction is stronger, with separation of epidermis and dermis and mucosal involvement leading to intense pain and high risks of infection and death. Some severe cases of FDE can mimic TEN (Mitre *et al.,* 2017). They differ in their pathology by a higher infiltrate of $CD4^+$ dermal T cells, including $FOXP3^+$ ones and less intraepidermal cytotoxic T cells (Cho *et al.,* 2014). The causal factor is most often a drug, but viral and bacterial infections can be involved as well (Merot and Saurat 1985). $CD8^+$ T cells are also present in the lesions (Miyauchi *et al.,* 1992). Skin allergy could be triggered in immunocompromised mice upon injection of PBMCs from an allergic human and graft of its skin onto the mice. This effect disappeared with the depletion of $CD8^+$ T cells – indicating the essential role of this subset in the disease (Saito *et al.,* 2013). T_{RM} cells have so far not been characterized in TEN.

In **ACD**, the exposure to the hapten takes place in the skin usually both at sensitization and at elicitation. The first one is considered as a prerequisite, although elicitation (challenge) can occur after systemic administration as well. The immune response varies depending on the hapten. Transcriptomic analysis showed that only a few genes are commonly dysregulated by common allergens such as nickel, rubber and fragrance altogether, but the type of response is common, mainly Th1 and Th2 but also Th17/Th22 (Dhingra *et al.,* 2014). The kinetics deciphering of the immune response upon skin-challenge with haptens showed that gene expression at day 3 involved all major T cell subsets, and was more regulatory at day 14 (Gulati *et al.,* 2014). The skin persistence of allergen-primed T cells after challenge was suspected long before their identification in guinea pigs (Rustemeyer *et al.,* 2002; Scheper *et al.,* 1983) and more recently, the generation of T_{RM} cells in the skin was demonstrated both in CHS and in ACD. The hapten triggers a quicker inflammation in previously exposed skin, illustrating the expansion of antigen-specific T_{RM} cells (Gaide *et al.,* 2015). In term of function, T_{RM} cells in CHS can quickly produce IFN-γ and very little IL-17 upon challenge with PMA/ionomycin (Schmidt *et al.,* 2016). How long these cells remain present in the human skin after a challenge is still unknown, at least for several months in mice according to a recent study that also emphasized the pathogenic role or epidermal allergen-specific resident cells in this disease as $CD8^+$ T_{RM} cells were 10 times more frequent in the epidermis than in the dermis. Additionally, $CD8^+$ T_{RM} cells could trigger a flare by themselves without the participation of blood T cells and their elimination abrogated the allergen-induced flares (Gamradt *et al.,* 2019).

1.3.2.5 Methylisothiazolinone

Methylisothiazolinone (MI) is a potent skin sensitizer used as a preservative in many cosmetic, household, and industrial products such as paints. In 2005, it was introduced on the market in 25 times higher concentration than its previous use, as a mixture of Methylchloroisothiaozolinone (MCI) and Methylisothiazolinone. Soon an epidemic of ACD was observed due the presence of MI in personal care products and water-based paints (Venables *et al.,* 2016). The incidence peak seems to have passed, probably due to regulation of the EU and the self-regulation of the cosmetic industries who have started to replace MI by other conservatives (Uter *et al*., 2019).
As mentioned above, MI and MCI have long been used together as a preservation mixture and many patients who sensitized primarily to the more potent hapten MCI developed ACD to products containing MI due to cross-reactivity (Stingeni *et al.,* 2018). MI binds to

epidermal cysteine thiols residues in order to become antigenic in the reconstituted human epidermis (Debeuckelaere *et al.,* 2016). It leads to T cell proliferation in ACD patients and creates a Th1 and Th2 reaction in PBMCs (Masjedi *et al.,* 2003; Popple *et al.,* 2016).

1.3.3 Vitiligo

Vitiligo is an autoimmune skin disease. Several genetic loci have been identified and many are shared with rheumatoid arthritis, type-1 diabetes and celiac disease (Jin *et al.,* 2016). Vitiligo is the whitening of the skin by the absence of melanin produced by the melanocytes (Figure 15). The most common body parts involved are the hands, the knees, but any part of the skin can be involved. Skin areas exposed to frictions and trauma are more prone to develop vitiligo.

1.3.3.1 Treatment and physiopathology

The disease pathophysiology is not straightforward and involves oxidative stress, autoantibodies and cytotoxic T cells. Melanocytes are absent of the inter-follicular epidermis in vitiligo lesions but remain in hair follicles, and start to proliferate during treatment (Cui *et al.,* 1991; Ortonne *et al.,* 1980). Melanocyte-derived auto-antigens have been identified, such as Melan-A and gp100 proteins (Palermo *et al.,* 2005; Oyarbide-Valencia *et al.,* 2006). Infiltration of $CD8^+$ T cells capable of killing melanocytes is present in perilesional of patients with vitiligo (Wu *et al.,* 2013). The causal role of T cells in vitiligo is supported by the occurrence of vitiligo in 12% of the melanoma patients treated with the anti-CTLA4 Ipilimumab, and the development of vitiligo during immunotherapy is proposed as a good prognosis factor (Hodi *et al.,* 2010; Hua *et al.,* 2015).

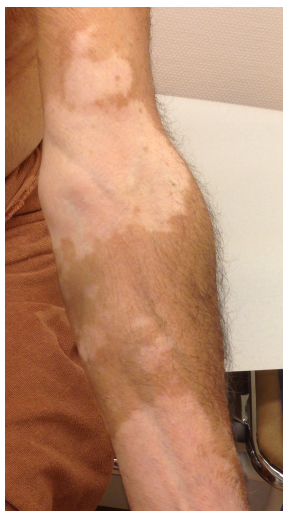


Figure 15 Vitiligo clinical presentation

Treatments include topical steroids and UV therapy with limited efficacy. Surgical interventions are sometimes proposed in case of stable vitiligo, such as the transplantation mixtures of epidermal and dermal cells from non-lesional skin onto involved areas (Thakur *et al.,* 2019). Systemic pulses of steroids can also help to stop disease progress (Tovar-Garza *et al.,* 2019).

1.3.3.2 T_{RM} cells in Vitiligo

Vitiligo has clinically a tendency to come back in selected areas of the body, suggesting the implication of T_{RM} cells in the pathogenesis. Several studies investigated the mechanistic basis of T_{RM} cells implication in vitiligo. Perilesional skin of vitiligo patients exhibited an accumulation of cytotoxic T_{RM} cells and high expression of CXCR3 (Boniface *et al.,* 2018). At the tissue level, keratinocytes responses to IFN-γ were necessary to the induction of vitiligo in a mouse model in which the inhibition of IFN-γ production by T cells was later shown to induce re-pigmentation (Richmond *et al.,* 2018). These findings, together with ours (Cheuk *et al.,* 2017),

collectively established T_{RM} cells as a likely mechanism of vitiligo development. The dermal localization of the infiltrate, however, might complicate topical treatments aiming at T cell population remodeling, as they will be less easily reached than in ACD or psoriasis. Current therapeutic perspectives include tofacitinib, a pan-JAK inhibitor that suppresses IL-15 signaling that has been reported effective against vitiligo (Craiglow *et al.,* 2015). Additionally, the blocking of the receptor subunit that allows IL-15 binding to its receptor efficient on mice vitiligo (Richmond *et al.,* 2018).

In conclusion, the skin is a complex organ that is particularly suitable for T_{RM} study by its relatively easy sampling with minimal scarring and risks for patients. Additionally, if a remodeling of epidermal T_{RM} cells is achievable through external treatments, it could prove very useful in skin inflammatory diseases. With the current techniques used in immunology, improved knowledge about human biology can be reached by studying the skin, and will hopefully open new perspectives of treatments for other inflammatory diseases.

2 AIM AND RESEARCH QUESTIONS

The Ph.D. thesis aimed to increase our understanding of how T_{RM} cells impact on the skin microenvironment during the onset and relapse of **common inflammatory skin diseases.**

This thesis is divided in four research questions:

Question 1: In human skin, are functionally distinct T_{RM} cell subsets altered in inflammatory skin diseases?

Question 2: In skin that has never been affected by psoriasis, do T_{RM} cells differ in composition and functionality?

Question 3: Are T_{RM} cells from resolved psoriasis skin capable of initiating clinically relevant tissue responses?

Question 4: How do allergen-specific T_{RM} cells provoke disease-driving tissue responses in resolved allergic contact dermatitis?

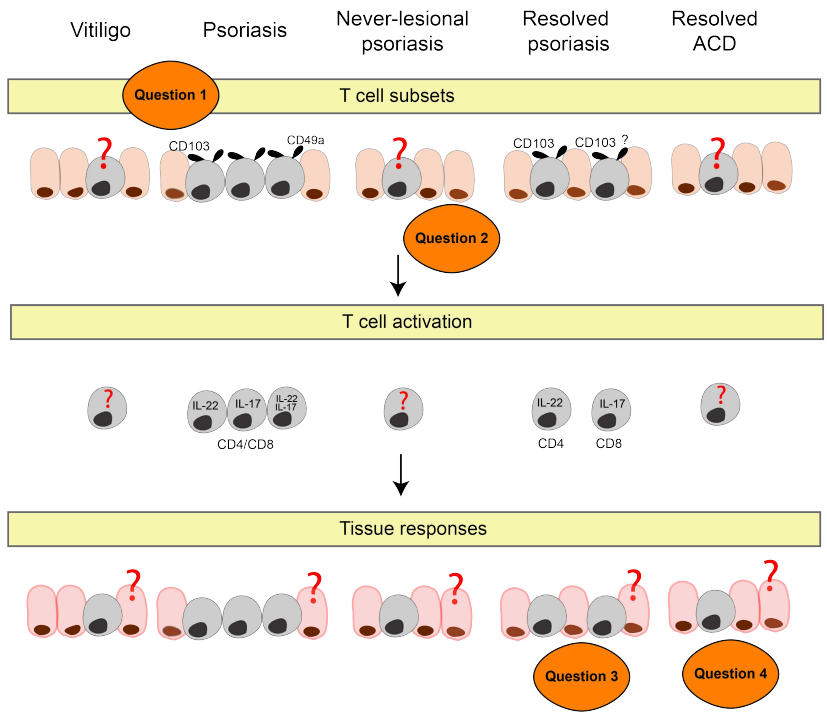


Figure 16 Research questions

3 METHODS

3.1 SKIN

Biopsies (PAPERS I, II, III, IV)

Skin from healthy patients lacking history or symptoms of inflammatory skin diseases was obtained through the plastic surgery department. Skin from patients with the following conditions was sampled: 1/ Vitiligo (**PAPER I**) both lesional and non-lesional; 2/ Allergic Contact dermatitis (**PAPER IV**), lesional and non-lesional, at diagnosis and after two months or after two years after the resolution of symptoms; 3/ Psoriasis, both lesional, never-lesional, resolved after UVA, UVB, biologics treatments (**PAPER II, III**). Skin biopsies were collected and processed (within 4 hours) or immediately cryopreserved at -80°C. Untreated psoriasis skin was collected at least one centimeter inside the edge of the lesion. Resolved lesions in psoriasis were identified with help of photographs, hyperpigmentation or reliable patient history. All tissue samples were collected according to the Declaration of Helsinki Principles and approved by the regional ethical committee of Stockholm, reference no: 2012/50-31/2, 2015/0041-32, 2013/976-31/4, 2017/1774-32. Signed consent forms were collected.

Confocal microscopy (PAPER I, II, III)

Cryopreserved skin biopsies were sectioned (10 µm) at -20°C, fixed and permeabilized using Transcription Factor Staining Buffer Set (00-5523-00, eBioscience) and incubated with antibodies overnight at 4°C. Amplification using streptavidin-conjugated antibodies (anti-mouse, Vector) in **PAPER III** was followed by fluorochrome labelling. Images were acquired in a laser scanning confocal microscopy and analyzed in Fiji. Antibodies used were: MMP-12 (ab137444 from abcam and 703D10 from movus bio), Collagen IV (clone COL-94, Abcam), CD8 (AB4055, AbCAM), CD3 (clone CD3-12, Abcam), MelanA (clone EP1422Y, Abcam), keratin 5/6 (cloneD516, DAKO), CD49a (clone 550594, BD Bioscience).

Stimulation of skin biopsies

In **PAPER II, III, IV,** full-thickness skin biopsies were incubated in Dulbecco's Modified Eagle Medium (DMEM, Gibco) supplemented with fetal bovine serum (FBS Hyclone) 10% and PEST (penicillin 100 units/ml and streptomycin 100 mg/ml; Gibco by LifeTech, Waltham, MA) in the presence of different products. To simulate an antigenic ligation, αCD3 antibody OKT-3 (CD3ε) 1µg/mL was compared to a control IgG2a control 1µg/mL (both both Biolegend, Ultra LEAF). Exposure to cytokines was also performed to study tissue responses: rhIL-17A 100ng/mL, rhIFN-γ 100ng/mL (all from R&D Systems, Minneapolis, Minn) for 16 hours. In **PAPER III,** Mannans from *Saccharomyces cerevisiae* or *Malassezia furfur,* Heat killed *Candida albicans* (in **PAPER II**) were used to mimic contact with common fungi. The peptides P5 (YIIDTGIDID) and P24 (LSGTSMASPH) from *Trichophyton rubrum* were custom-made and ordered from Sigma Aldrich. Methylisothiazolinone (100ppm) (Sigma Aldrich 725765-5g) was used in **PAPER IV** to perform an antigen-specific stimulation of memoy T cells. For the various stimulations, skin explants were incubated for 16-48 hours at 37°C. When collected, supernatants were immediately cryopreserved at -80°C.

ELISA and Collagenase assay

Thawed supernatants were analysed using ProcartaPlex™ (eBioscience) in **PAPER III**; ELISA and the CCL-20 ELISA (Quantikine ELISA Kit Human CCL-20/MIP-3 alpha, R&D systems) in **PAPER II** according to the manufacturer's protocol and read using Bio-Rad Bio-Plex 200 System (Bio-Rad Laboratories). Cut-off for detection was set at 10pg/mL. In **PAPER IV**, the properties of rhMMP-12 and rhMMP-1 (RnD systems) were tested at 2 to 2000ng/mL, on collagen IV and collagen I using the EnzChek® Gelatinase/Collagenase Assay Kit (Thermofisher) together with DQ™ collagen type I and DQ™ collagen type IV from Thermofisher. After 2-7 days of incubation, the plate was read using a fluorescence reader.

3.2 RNA

Purification of RNA from biopsies (PAPER II, III, IV) and q-PCR

After incubation at 37°C, epidermis and dermis were separated after incubation in 5 U/ml Dispase in PBS overnight at 4°C, and cryopreserved in Qiazol at -80°C until tissue homogenization using a TissueLyser (Qiagen) for 4 min at 50Hz. Total mRNA was purified with miRNeasy kit (Qiagen) according to manufacturer's protocol. RNA quality and quantity were checked using either Nanodrop or Bioanalyser RNA Nano Kit (Agilent). RNA was conserved in RNase free water at -80°C until analysis. RNA was converted to cDNA using the HighCapacity cDNA Reverse Transcription Kits (Applied Biosystems). Reverse transcription Quantitative PCR (RT-qPCR) was performed using TaqMan PreAmp Master Mix Kit (Applied Bioscience) and the TaqMan Gene Expression Master Mix (Applied Bioscience) following the manufacturers' protocols. Gene expression was normalized to the house-keeping gene *b2-microglobulin* (*B2M*).

RNA sequencing (PAPER I, III, IV)

mRNA was first enriched with oligo(dT) beads, then fragmented randomly. cDNA is synthetized using random hexamers and reverse transcriptase. The synthesis buffer containing dNTPs (illumina) is added together with RNase H and E. coli polymerase I to generate the second strand. The final library is ready after A-tailing, adapter ligation, PCR enrichment. The library concentration is quantified using Qubit 2.0 fluoromer (life technologies), then diluted to 1ng/uL before checking the insert size on Agilent 2100 and quantifying by RT-qPCR. For all samples, the sequencing was performed on HiSeqTN 2000 (Illumina) and the reference genome for alignment was hg19. In **PAPER I and III,** the library construction was done using SMARTSeq v4 Ultra Low Input RNA Kit (ClonTech) and sequenced on Illumina HiSeqTM 2000, at Beijing Genomic Institute, (BGI, Hong Kong). The analysis was performed by BGI using the pipeline in Figure 17. Alignment was performed with Bowtie and data are available at www.ncbi.nlm.nih.gov/geo/query/acc.cgi, GSE103489 for **PAPER III**, GSE83637 for **PAPER I**. In **PAPER IV,** RNA was sequenced by Novogene. Genevia Technologies (Tampere, Finland) performed the analysis using a similar pipeline. TopHat2 (also using Bowtie) was used for the alignment. Aligned reads per gene were counted with htseq-counts using the genome fasta and annotation gtf files as references. After counting, normalized gene expression estimates were computed using TPM (transcripts per kilobases per million reads) method which first normalizes for gene length, and then for sequencing depth. Data are not yet deposited.

Nanostring Technologies (PAPER II, III, IV)

Nanostring is a quantitative method counting RNA copies and was performed according to manufacturer's protocol (NanoString Technologies, Inc. Custom CodeSet). One custom panel of 119 genes was used for **PAPER II** and **III** and a second larger panel of 200 transcripts was used for **PAPER IV**, including the same 5 house-keeping genes (G6PD, GUSB, HPRT1, SF3A3, ZC3H14) in both panels. NOL7 was not used as a HKG as it showed too much variability in between samples. RNA counts were generated in nSolver software (NanoString Technologies, Inc.). Analysis were performed with JMP 12 and with the company Genevia Technologies (Tampere, Finland) for the generation of differentially expressed genes and time-series analysis.

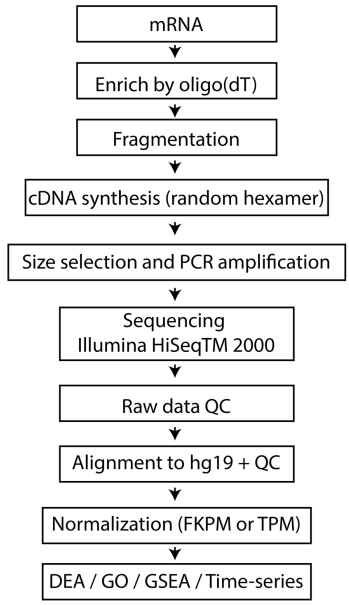


Figure 17 mRNA sequencing and analysis pipeline

Hg = human genome, QC = quality control, TPM =Transcripts Per Kilobase Million, FKPM = Fragment Per Kilobase Million, DEA = differential expression analysis, GO = gene ontology, GSEA = gene-set enrichment analysis.

3.3 CELLS

Keratinocytes culture

Punch biopsies were placed in dispase as described above. The following day, the epidermis was separated from the dermis and treated with 0.05% Trypsin/EDTA (Gibco) for 30 minutes at 37°C. DMEM and FBS were used to interrupt the reaction. The epidermal cell suspension was cultured in a flask coated with collagen I (Gibco) in EpiLife medium (Gibco) supplemented with human keratinocyte growth supplement (Gibco), 100 U/ml PEST and Fungizone (Gibco). Keratinocytes were then frozen for later use. Ten thousand thawed keratinocytes (passage 3) were plated in 48 well plates, and exposed to

recombinant(r) human cytokines in PAPER III during 16 hrs after they reached a 100% confluence: rhIL-17A 5 ng/mL, rhIFN-γ 5 ng/mL, rhIL-22 (5 ng/mL), rhTNF (5 ng/mL), rhIFN-α (5 U/mL) (all from R&D Systems, Minneapolis, Minn) for 16 hours.

Preparation of skin cell suspension from biopsies

Patients biopsies (4mm) or healthy skin biopsies (6mm) were incubated in 5U Dispase (Life technologies, Carlsbad, CA) overnight at 4°C. Smaller biopsies or cut biopsies were incubated a shorter time, 4-6 hours leading to similar effect. Epidermis and dermis were manually separated and incubated with 4.5 mg/mL Collagenase III (Worthington, Lakewood, NJ) and 5µg/ml DNAse (Roche, Basel, Switzerland) for 90 minutes at 37°C. A cell suspension was obtained after mechanical disruption of the tissue by pipetting up and down for several 4-7 minutes (for 6mm dermis and for the epidermis) or using Medicon (for 4mm dermis) and filtration was done through a 100 µm first and then 70µm cell strainer (BD Bioscience). The preparation of cervix and gut samples was done similarly and detailed in **PAPER I.**

Cell sorting

Freshly isolated cell suspensions were stained and kept on ice before sorting. In **PAPER II**, Cell sorting into QIAzol Lysis Reagent (Qiagen) was performed using MoFlo XDP (Beckman Coulter) cell sorted, by CD45 and CD3 markers. In **PAPER I** and in the results part, skin cell suspensions were stained for CD45 CD4, γδTCR, CD3, CD103 and CD49a and PBMCs for CD3, CD4, γδTCR, CD45RA, CD62L and CLA and then sorted into Qiazol later RNA extraction, or Cell lysis Solution from Qiagen Puregene Kit (Qiagen) for DNA extraction. Sorted Qiazol-cell lysate were kept at -80 °C before extraction while lysate for DNA extraction were kept at 4 °C. Sorted cells were maintained in complete medium overnight before further experiments for the cytotoxicity experiments. T_{EM} were defined as T cells negatives for CD45RA and CD62L.

TCR sequencing (PAPER I)

DNA Extraction and TCR Sequencing DNA was extracted (Puregene, QIAGEN) and the TCR-β CDR3 regions were sequenced and mapped (ImmunoSEQ, Adaptive Biotech). Data from productive reads were extracted from ImmunoSEQ platform for further analysis. Raw data were uploaded on the immuneACCESS platform provided by Adaptive- Biotech (doi.org/10.21417/B76K56). Details

PMBCs isolation (PAPER I, II, III)

Peripheral blood mononuclear cells (PBMCs) were prepared from 10-20 ml of peripheral blood using Ficoll Paque Plus (GE Healthcare) according to the manufacturer's protocol. PBMCs were then either frozen in 1/1 volume of freezing medium (FBS with 20% DMSO) or cultured in Roswell Park Memorial Institute medium (RPMI) supplemented with 10% FBS and PEST for further experiments within 4 days.

Cytotoxicity Assay (PAPER I)

In brief, sorted and rested cell populations were used as effector cells against 51Cr-labeled P815 target cells supplemented with 0.5 mg/ml of anti-CD3 antibody (clone S4.1, Invitrogen) with effector-to- target ratios between 10 and 0.3. Samples were run in duplicates for 4hours at 37°C. 51Cr release in supernatant was measured on a g-counter (Wizard2, PerkinElmer) and specific lysis was calculated.

Flow cytometry
Freshly prepared cells were put in complete medium (RPMI supplemented with 10% FBS and PEST. Cell suspensions were stimulated same day or the day after with PMA (50ng/ml, Sigma for **PAPER I, III,** 200ng/ml in **PAPER II**) and ionomycin (1 μg/ml, Sigma) for 4 hours in the presence of brefeldin A (Golgiplug, BD Biosciences) and stained at 4°C. Intracellular cytokine staining was performed after permeabilization, following the manufacturer's protocol (BD Cytofix/Cytoperm). The entire sample was acquired using LSR II.

Additional ethical permits were used for the **PAPER I:** 2012/1900-31/1, 2013/1377-31 with updates 2015/1078-32 and 2015/2124-32. Extensive methods are available at openarchive.ki.se/xmlui/handle/10616/45045.

3.4 STATISTICAL ANALYSIS

In **PAPER I, II, III, IV, s**tatistical analyses and graphical illustration were performed with PRISM (v6, GraphPad) or JMP 12 (SAS). Heatmaps were generated by MeV: Multi Experiment Viewer (www.tm4.org/mev.html). Mann–Whitney U test or Wilcoxon matched-pairs signed rank test were used for testing independent or paired data. Linear regression was performed with PRISM. Correlations were determined using Pearson's test. FlowJo V9.9 was used to analyse flow cytometry data. In **PAPER II**, Barnes-Hut t-distributed stochastic neighbour embedding (t-SNE) analysis of 13-parametric data was performed on live $CD3^+$ T cells as described in (Schlums *et al.,* 2018). For data analyses and graphical visualizations, the R packages Rtsne, plyr, Hmisc, gplots, MASS, ggplot2, grid and RColorBrewer were used (Wickham, 2011). Time-series analysis were performed for **PAPER IV** using the calculated log2-fold changes between lesional (or healed) samples compared to all non-lesional samples from each given timepoint. The fold-changes were averaged in the case where several comparisons were involved at a specific time point. Then, the log2 fold changes comparing that time point value to the previous time point, were obtained by using the formula log2(median(Fold change of comparisons at time 2)) - log2(median(Fold change of comparisons at time 1)). The values for the first time point (Day 7) were set to zero to emphasize the changes in time. The genes were then clustered into clusters with the k-means clustering method based on their timecourse behavior. Visualisation of the calculated log2 fold changes across the time points were created using the ggplot2 R package (Wickham, 2016), with genes colored according to their associated cluster. To study the biological schemes of genes in each cluster, over-representation analyses were performed using R package clusterProfiler (Yu *et al.,* 2012), with adjusted p-value cutoff of 0.05 and minimum gene set size of 5. The analyses determined whether any of the gene sets were associated to a cluster at a frequency greater than what would be expected by chance. The enrichment p-values were computed using the hypergeometric distribution and listed for each cluster.

For the enrichment analysis presented in the results part, PARTEK Partek Genomics Suite software (Partek, St. Louis, MO) was used. For the three time-points Day 7, Month 2 and Year 2 of the ACD study, baseline samples were aligned with bowtie 2. One sample was excluded because of low alignment quality. The quantification was done with PARTEK E/M, normalization to TPM was done and annotation was performed using RefSeq. Lists of

DEGs were generated comparing lesional (or healed) to NL samples. Transcripts with p-value <0,1 were subsequently used for enrichment analysis using gene lists previously published by Swindell et al (Swindell *et al.,* 2016). These cytokine activity signatures were based on the identification of cytokine-responsive transcripts comparing exposed keratinocytes to non-exposed keratinocytes to cytokines *in vitro*, ranked by the p-value obtained comparing the stimulation to the control. The top 100 cytokine-induced or the top 100 cytokine-repressed were used. Results were considered further usable if p-value <0.05.
An additional dataset was used for enrichment analysis. RNAseq of T cell-subsets was generated after sorting of different subsets of circulating $CD4^+$ and $CD8^+$, CLA^+ or CLA^-. In the dermis, CD4 and CD8 T cells were sorted according to the presence of CD103 and CD69 on their surface, and in the epidermis according to their CD69, CD103 and CD49a status. Gene lists of the top 100 genes expressed in each subset were generated and used with the enrichment analysis function of PARTEK.

4 RESULTS AND DISCUSSION

4.1 T_{RM} FUNCTIONALITY

4.1.1 CD49a defines a subset of $CD8^+$ T_{RM} cells poised to cytotoxicity

Results: The expression of CD103 in $CD69^+$ T_{RM} cells is associated with a higher production of IFN-γ in epidermis and IL-22 in the dermis in human (Watanabe *et al.,* 2015). Using flow cytometry, **PAPER I** identified that the presence of the CD49a integrin on $CD8^+$ T_{RM} cells in the human epidermis was linked to stronger effector functions in terms of cytotoxicity and IFN-γ production. In Fig. 2, RNA sequencing showed that epidermal $CD8^+CD103^+CD49a^+$ T cells expressed more *GZMB* and *IFNG* and less *CCR6* in comparison to $CD8^+CD103^+CD49a^-$ T cells. $CD49a^+$ T_{RM} cells required the presence of IL-15 to swiftly produce Granzyme B and perforin (Fig. 3), and perform actual cell-killing (Fig. 5). Finally, functional dichotomy according to the CD49a expression was conserved in T cells extracted from vitiligo and psoriasis lesions, with $CD8^+CD103^+CD49a^+$ cells poised to more IFN-γ production than $CD8^+CD103^+CD49^-$ cells and *vice versa* regarding the IL-17 production. In never-lesional psoriasis (NLP) and active psoriasis, $CD49a^-$ T_{RM} cells accumulated in the epidermis and were more prone to IL-17 than $CD49a^+$ epidermal cells (**PAPER II,** S. Fig. 4).

Discussion: These data indicate that CD49a is a phenotypic marker of functional relevance in both healthy and diseased human skin. Of note, epidermal and dermal compartments are not exposed to the same dangers and may need different T cell protection. In healthy skin, the $CD8^+CD103^+CD49a^+$ cells are primarily present in the epidermis. Several findings underscore that these cells could play a role in controlling skin malignancies. First, $CD49a^+$ T_{RM} cells that recognize melanocytes are enriched and activated in vitiligo, a disease that is correlated to a reduced risk as well as to good treatment response in melanoma (Hua *et al.,* 2015; Richmond, Strassner, Rashighi, *et al.,* 2018). Second, $CD49a^+$ T_{RM} cells are situated close to their ligand collagen IV located at the basement membrane of both skin and blood vessels. This represents the optimal location for potential gatekeepers of the dermo-epidermal zone and the venules, limiting the dissemination of the malignant cells. Third, their cytotoxicity would make these cells excel at eradicating tumor cells. In patients with disseminated melanoma subcutaneously vaccinated with a melanocyte-derived antigen recognized by T cells (Melan-A), the ratio of circulating $CD8^+$ T cells expressing CD49a was correlated with better survival (Murray *et al.,* 2016). To better understand the role of the CD49a T cells in the early steps of melanoma, the characterization of the CD49a status of T cells located close to *in situ* melanoma compared to invasive melanoma would be useful.

CD49a is required for T cells to enter the epidermis, as exposed in 1.3.1.5. It is unclear whether $CD8^+CD103^+$ cells not harboring CD49a did not need this marker to penetrate the epidermis of if they have lost it after their entry. Whether the functional dichotomy between $CD49a^{+/-}$ T_{RM} cells is acquired before or after the entry into the epidermis is also unknown. Determining the role of cytokine exposure or other local tissue factors in the expression of

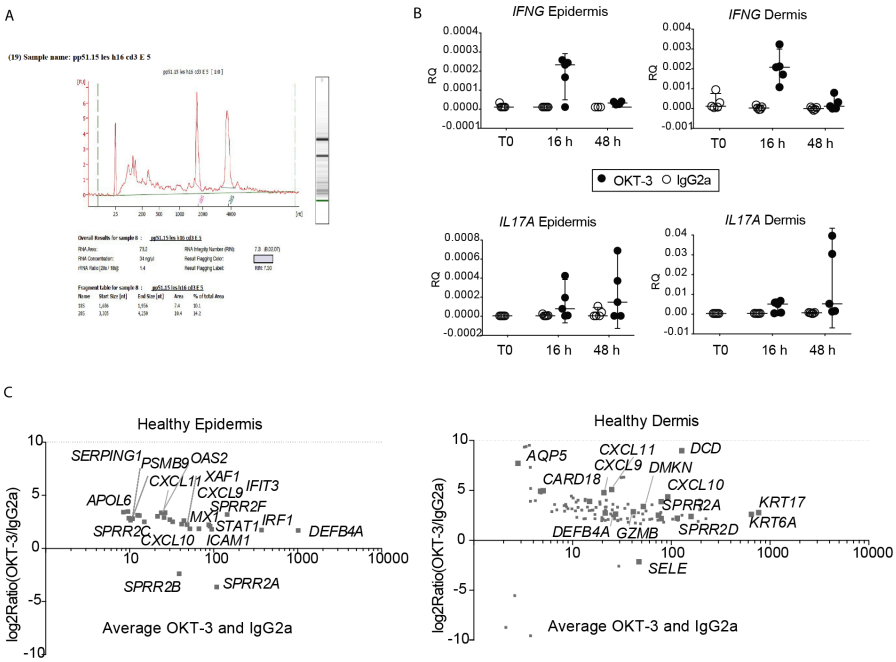
T_{RM} markers is an active field of research. Indeed, when the factors influencing the expression of the functional markers on T_{RM} cells are known, it could open the way to marker-modifying interventions and hopefully permit to alter T cell function in the upper layer of the skin, to potentially control skin protective functions.

4.1.2 *Ex vivo* activation of T cells in skin explants is a reliable method to study T cell-related tissue responses

Results: To characterize the functional consequences of T_{RM} cell-activation in human tissue, a method inspired by DiMeglio *et al.,* was set-up (Di Meglio *et al.,* 2014). One day after *ex vivo* TCR stimulation with the anti-CD3 OKT-3 in skin biopsies, the antibody was detectable on T cells in the skin (**PAPER III,** Fig. 1). An increase in IL-17 and IFN-γ production was noted in T cells then extracted from the skin. This effect was maximal after one day and decreased progressively during the following days (not shown). After 72 hours, the tissue architecture started to be degraded in *ex vivo* cultures. Following 16-48 hours of culture and 4-8 hours of incubation in dispase, the purified mRNA was of reasonable quality (Result Figure 1A). Rapid upregulation of mRNA levels of chemokines and cytokines was obvious in OKT-3 stimulated tissues. To limit the tissue damage due to the incubation, the 16 hours timepoint was chosen for the following experiments (Result Figure 1B). Many transcripts were up- or downregulated by OKT-3 exposure, as determined by mRNA sequencing, both in epidermis and dermis (Result Figure 1C). Those genes were taken into consideration in designing a custom panel of genes for RNA copy counting with Nanostring Technologies. The expression of classically epidermal genes (*keratins*, *defensin*) in the dermal activated samples after OKT-3 emphasized the difficulty to interpret dermal data since the hair follicles stay in that skin compartment during the dispase-driven separation of the epidermis from the dermis.

Discussion: Likewise the tissue-wide transcriptomic changes observed in mice upon reactivation of virus-specific T_{RM} cells (Ariotti *et al.,* 2014), clear interferon-driven tissue responses were observed in human skin explants. This reflected the known production of IFN-γ by epidermal and dermal T cells (Watanabe *et al.,* 2015). This was clear in both epidermis and dermis despite the seclusion from the blood circulation. Three mRNA analysis methods, RT-qPCR, nanostring, and RNA-sequencing could confirm the main differentially expressed transcripts.

In this thesis, the focus was on epidermal tissue responses instead of responses in the dermis that is richer in T cells. This has four explanations. The first is the few cell types present in the epidermis, namely keratinocytes, LCs, T cells, melanocytes that facilitate results extrapolation. Second, to ensure that the cells analyzed were not circulating, the non-vascularized epidermis was preferred to avoid blood contamination. Third, since residency cannot be directly tested in *ex vivo* samples, focusing the analysis on epidermis made it more probable that the cells observed were resident ones. The last additional technical reason lies in the anatomy of the skin. When separating epidermis and dermis, the hair follicle stays in the dermis. Thus, the dermal samples are a mix of dermis and hair follicles cells, while the epidermal sample is plain interfollicular epidermis.



Result Figure 1 Method development

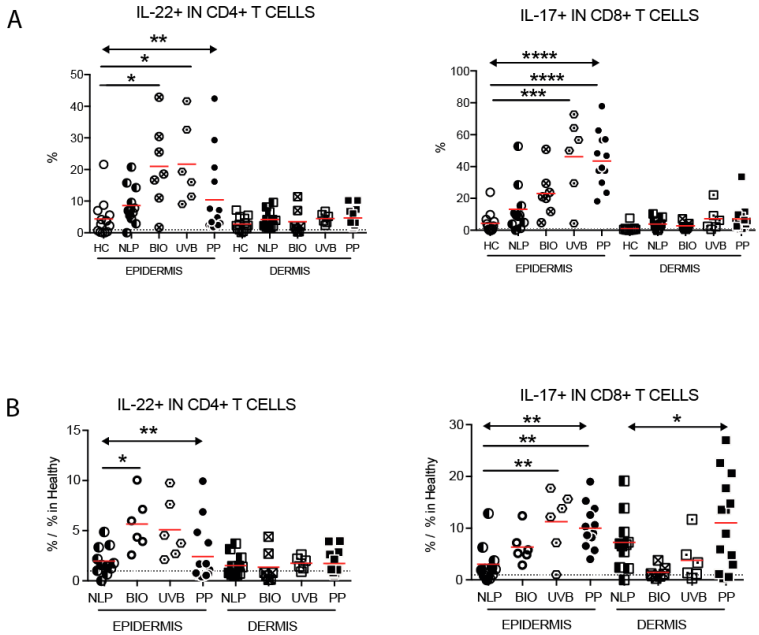
(A) Example of bioanalyzer output of one sample of mRNA from epidermis after the incubation of skin explants 16 hours with OKT-3 and thereafter separation of epidermis and dermis with dispase. (B) RT-qPCR of epidermal and dermal samples after incubation with OKT-3 or IgG2a, showing 2 timepoints. Housekeeping gene is beta2microglobuline, dot plot of the data visualized with the 2^-deltaCT method. (C) Dot plots of the RNA sequencing data, showing results from three healthy samples. 16h is 16 hours, 48h is 48 hours.

4.2 RESIDENT T CELLS IN PSORIASIS

4.2.1 Epidermal T_{RM} cells in Never-lesional psoriasis differ from healthy skin

Results: Psoriasis is a multifactorial disease with a genetic predisposition. The normal-looking skin of psoriasis patients differs from healthy skin (Swindell *et al.,* 2017; Chiricozzi *et al.,* 2016). Whether the skin T_{RM} cell population also differed remained to be shown. As circulating cytokines are modified in severe disease and might influence the skin cell compositions (Arican *et al.,* 2005), we set up to characterize skin T_{RM} cells in patients with mild disease. Confocal imaging identified a higher epidermal thickness and more numerous $CD8^+$ T cells than in healthy skin (**PAPER II**, Fig. 3). Next, flow cytometry helped characterize the T cell subsets and their cytokine production. Two subsets prone to IL-17 production, namely $CD8^+CD103^+CD49^-$ cells and $CD4^+CCR6^+$ cells were more abundant in NLP compared to the healthy epidermis (Fig. 3G-H). Indeed, $CCR6^+IL17^+$ cells were more abundant in NLP epidermis, but not dermis, and around 10% of $CCR6^+$ T cells co-produced IL17 and IFN-γ (Fig. 4). An imbalance of $IL\text{-}17^+$ and $IL\text{-}22^+$ T cells in resolved psoriasis lesions had been described by the group (Cheuk *et al.,* 2014), with Tc17 and Th22 T cells retained in resolved skin after both biologics and light treatments. The cytokine production of resolved skin and NLP skin were compared. Cytokine-producing T cells were more abundant in the epidermis than in the dermis for both RP and NLP. Ratios of the cytokine production in NLP with RP to healthy skin showed that the percentages of $IL\text{-}22^+$ cells among $CD4^+$ and $IL17^+$ cells among $CD8^+$ T_{RM} cells in NLP were intermediate between healthy and RP skin (Result Figure 2).

Discussion: The non-lesional skin from psoriasis patients has long been suspected to be in a "pre-psoriatic" state and the T cells from NL skin are sufficient to develop lesional skin as presented in 1.3.1.5. In **PAPER II**, I added a functional description of those T cells in the NLP skin that can be incriminated in disease development with an increase in T cells producing IL-22 and IL-17 in NLP compared to HC epidermis. When a factor is increased in inflamed tissue, pathogenicity is often suspected but causality can be complicated to assess. Both IL-17 and IL-22 are considered pathogenic in psoriasis and the pathogenicity of IL-17 has been proven through the use of its inhibition as a treatment. However, the role of IL-22 is less clear (Le *et al.,* 2019). In vitro, IL-22 drives proliferation of keratinocyte but IL-22 has homeostatic functions in barrier tissues (Eyerich *et al.,* 2010) and in the gut, the lack of IL-22 from ILCs lead to the dissemination of gut bacteria. In conclusion in psoriasis, it is not yet clear whether the presence of IL-22 is a consequence of the tissue disruption by IL-17 or if it is actively aggravating the tissue pathology.



Result Figure 2 Differences in cytokine production between psoriasis and healthy skin T cells

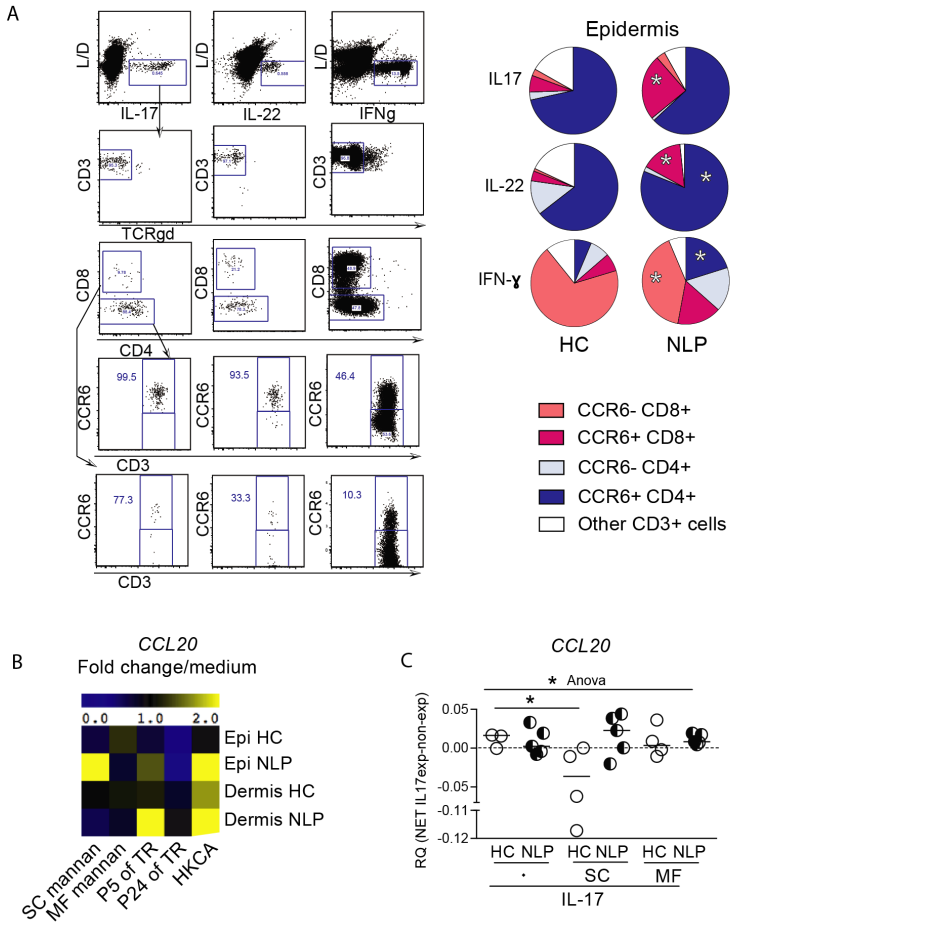
*Skin biopsies were taken from patients untreated on lesional and never-lesional skin, in treated patients on healed skin, and on healthy donors. Epidermis and dermis were separated and skin cell suspensions were prepared. After both extra- and intracellular stainings, flow cytometry analysis was performed. (A) Dot plots of the percentage of live, $CD3^+$, $\gamma\delta TCR^-$ cells $CD4^+$ T cells producing IL-22 (left) and $CD8^+$ T cells producing IL-17 (right). (B) Same samples but dot plots of the ratio of the percentage of cytokine-producing cells in diseased skin over the percentage in healthy skin. * if $p<0.05$, ** if $p<0.01$, *** if $p<0.001$, **** if $p<0.0001$. NLP = never-lesional skin, BIO = treated with biologics (anti-TNF or anti-IL-12/23), UVB = treated by UVB, PP = lesional psoriasis.*

4.2.2 Recruitment of CCR6+ T cells to the skin might be influenced by microbial exposures

Results: Why certain subsets of T_{RM} cells are preferentially recruited and stay in the NLP epidermis is not known. The vast majority of IL-17 and IL-22 producing T cells in NLP epidermis were $CCR6^+$ (Result Figure 3A). As $CCR6^+$ Tregs have been reported (Yamazaki *et al.,* 2008; Voo *et al.,* 2009), 3 donors and 3 NLP skin samples were stained with Foxp3 but could not detect $Foxp3^+$ T cells in either healthy or NLP epidermis (not shown). Microbes participate in the regulation of local immunity, and whether the exposure to certain microbial antigens could trigger the production of the CCR6 ligand CCL-20 in NLP skin was tested. Taken that IL-17 is a major anti-fungal defense system, focus was put on fungal products : *Candida albicans* (HKCA), Mannan from *Saccharomyces cerevisiae* (SC) and from *Malassezia furfur* (MF) as well as peptides P5 and P24 from *Trichophyton rubrum* (TR) that had been involved in skin delayed hypersensitivity in humans (Woodfolk *et al.,* 2000, 1996) were added to skin explants overnight. RNA was purified from the epidermis and dermis. *CCL20* expression was increased in NLP epidermis after exposure to HKCA and SC, but not MF and TR (**PAPER II** and Result Figure 3B). IL-17 induced a moderate upregulation of *CCL20* in healthy and NLP epidermis, but the exposure of healthy epidermis to SC prevented the IL-17-driven upregulation of *CCL20*, while no such an effect could be observed in NLP (Result Figure 3C).

Discussion: The enrichment of epidermal NLP in $CCR6^+$ T cells is striking, as is the increased cytokine production by this subset. Incriminating skin's previous antigen experiences in the development of the resident T cell subsets is tempting, and that includes the microbiota. Previous work showed that bacteria on the skin can modulate its T cell population and shed light on the mechanisms involved (Naik 2012; Naik *et al.,* 2015). Trying to understand the recruitment of $CCR6^+$ T cells to the NLP epidermis, a difference in the response of NLP epidermis to fungal antigens compared to healthy skin was identified at the RNA level. The cell type producing CCL-20 could, however, not be determined. A modification of the Dectin or TLR expression by keratinocytes is possible, as well as the participation of LCs. Less probable, direct TLR-driven detection of SC by the T cells might also be possible. Independently of the molecular mechanisms, the global skin sensing system to common antigens seems modified in psoriasis. Additionally, our data suggested an immunomodulatory effect of SC on the healthy epidermis. Other antigens implicated previously in psoriasis pathogenesis could be tested in a similar setting, such as peptides containing the ALEEAN amino-acids found in the streptococcal M protein, Melan-A or LL-37 (Valdimarsson *et al.,* 2009; Prinz 2004; Morizane and Gallo 2012; Arakawa *et al.,* 2015).

A recent report showed that the accumulation of $CD8^+IL\text{-}17^+$ T_{RM} over $CD8^+IFN\text{-}\gamma^+$ T_{RM} cells in the NLP epidermis was correlated with disease duration (Vo *et al.,* 2019). These findings and ours suggest a progressive accumulation of cells with disease-triggering capacities that could be driven by an inadequate response to skin commensals.



Result Figure 3 Fungal antigens trigger a *CCL20* epidermal signal that could participate in the attraction of CCR6$^+$ T cells to the skin

*(A) Flow cytometry analysis of skin T cells based on the cytokine-positivity. On the right, pie charts of the contribution of CCR6$^+$ T cells to the cytokine production. Stars highlight the population statistically different between HC and NLP. (B) Heat map of the fold change of gene expression (RT-qPCR) after exposure to different fungal products, mean per group is used, 4-8 patients per group. No Log2 transformation. (C) Dot plot of the expression of CCL20 (RT-qPCR) after exposure of skin to IL-17 +/- SC or MF. Net changes are expression changes compared to samples not exposed to IL-17. HC is healthy controls, NLP is never-lesional psoriasis. SC, MF, HKCA, P5 and P24 refer to fungal antigens explained in text. For RT-qPCR, housekeeping gene is beta2microglobuline, dot plot of the 2^-deltaCT method. * if $p<0.05$.*

4.2.3 T cell-activation In NLP triggers Type 1 interferon responses, potentially through the effect of Type 2 interferon on keratinocytes

Results: In **PAPER II**, NLP keratinocytes overexpressed *Myxovirus 1 (MX1)*, a proxy used for the presence of Type 1 interferon, compared to healthy cells (Fig. 2B-D). The activation of T cells in biopsies using OKT-3 further increased *MX1* in NLP epidermis and in resolved psoriasis epidermis during treatment with biologics. *MX1* was upregulated by both Type 1 and Type 2 interferons (Fig. 2D) and IFN-α could be detected in keratinocytes supernatants after exposure to IFN-γ. NLP epidermis contained a higher density of $CD4^+$ $IFN\gamma^+$ T cells than in healthy epidermis, and a higher proportion of $CD4^+CCR6^+$ T cells produced IFN-γ in NLP epidermis (Result Figure 3A above).

Discussion: IFN-α has been involved in the early development of psoriasis lesion, based on arguments developed in the introduction page 42. No increased population of pDCs in the NLP skin was found (**PAPER II** Fig. 2C). This might be due to the low inflammatory state of our never-lesional skin that was sampled from patients with mild disease, far from the lesion whereas Nestle *et al* took samples immediately outside the clinical edge. The data presented in the thesis add an alternative mechanism that could explain the early presence of keratinocyte-derived IFN-α in the psoriasis skin, induced by IFN-γ from T_{RM} cells. Additionally, Tregs were recently proposed in a mouse model of psoriasis as another biological pathway of IFN-α control, as their absence led to an unabated release from macrophages (Stockenhuber *et al.,* 2018).

OKT-3 activation triggered strong pro-inflammatory signals in NLP explants. It raises the question of the underlying regulation that prevents disease development despite the pro-inflammatory poising. Contrary to the dermis where many immune cell-types can reside, few are found in the epidermis, and it is conceivable that this control would come from T cells themselves. The techniques that were used to activate T cells might have shut off regulatory mechanisms. PMA bypasses co-stimulatory mechanisms and OKT-3 stimulation might overrule the effect of for instance PD1 that can be expressed on both human and mouse T_{RM} cells (Gamradt *et al.,* 2019; Kumar *et al.,* 2017; Z. Wang *et al.,* 2019). One clinical argument for the role of PD1 in psoriasis control is the development of psoriasis in patients treated with anti-PD1 (Bonigen *et al.,* 2017). Overall, the genetically or epigenetically-driven peculiarities of keratinocytes from psoriasis patients combined to a different T cell balance in the skin have together the capacity to poise the tissue toward psoriasiform responses.

4.2.4 The tissue responses to T cell-activation in resolved psoriasis indicates the time before relapse

Results: Both NLP and resolved psoriasis (RP) differ from healthy skin in terms of T_{RM} cell subsets and functions. In **PAPER III**, T cell activation in skin biopsies collected from patients after different treatments for psoriasis was performed. A common feature RP skin was IL-17-related epidermal tissue-responses to T cell activation (Fig. 3, Fig. 4), whereas the IFN-related responses *CXCL9* or *CXCL10* were upregulated in healthy skin, active, or resolved psoriasis. Next, the balance between IFN-γ and IL-17 responses upon T cell activation was assessed to test if such analysis could help predict the clinical outcome in patients. Resolved skin was sampled at the end of a UVB regimen, and T cells were activated in the biopsies using OKT-3. The balance between IFN-γ-related responses (*CXCL10*) and IL-17-related responses (*DEFB4A, SPRR2A, SPRR2B*) correlated to the time before relapse as defined by the need to start UVB again or other systemic therapies.

Discussion: The findings show that the interplay between the resident T cells and the surrounding stroma could have clinical use. To this day, the skin transcriptome was often offered as a potential predictor of treatment-response, but not as a relapse-predictor. One tool that was reported as capable to predict the disease relapse is Koebner phenomena, which refers to the formation of a psoriasis lesion at the site of skin injury. The reverse phenomenon is also observed, in which an injury on a psoriasis plaque results in a healed spot on the skin (Eyre *et al.,* 1982). Patients not experiencing Koebner and patients experiencing the reverse Koebner experienced an improvement of psoriasis over a 6-month follow-up (Eyre *et al.,* 1982). Skin trauma might impair the usual tolerogenic mechanisms. This interesting observation could also be due to a high systemic inflammation as the psoriasis area severity index (PASI) is correlated to the increase of certain circulating subsets of immune cells (Luan *et al.,* 2014; Eysteinsdóttir *et al.,* 2013). Hence, a tissue disruption could be enough to recruit T_{EM} to the skin, especially if circulating clones recognized skin local antigens (Muschaweckh *et al.,* 2016). If confirmed in future studies, this tool to predict disease flares could be a valuable addition in clinical practice for dermatologists.

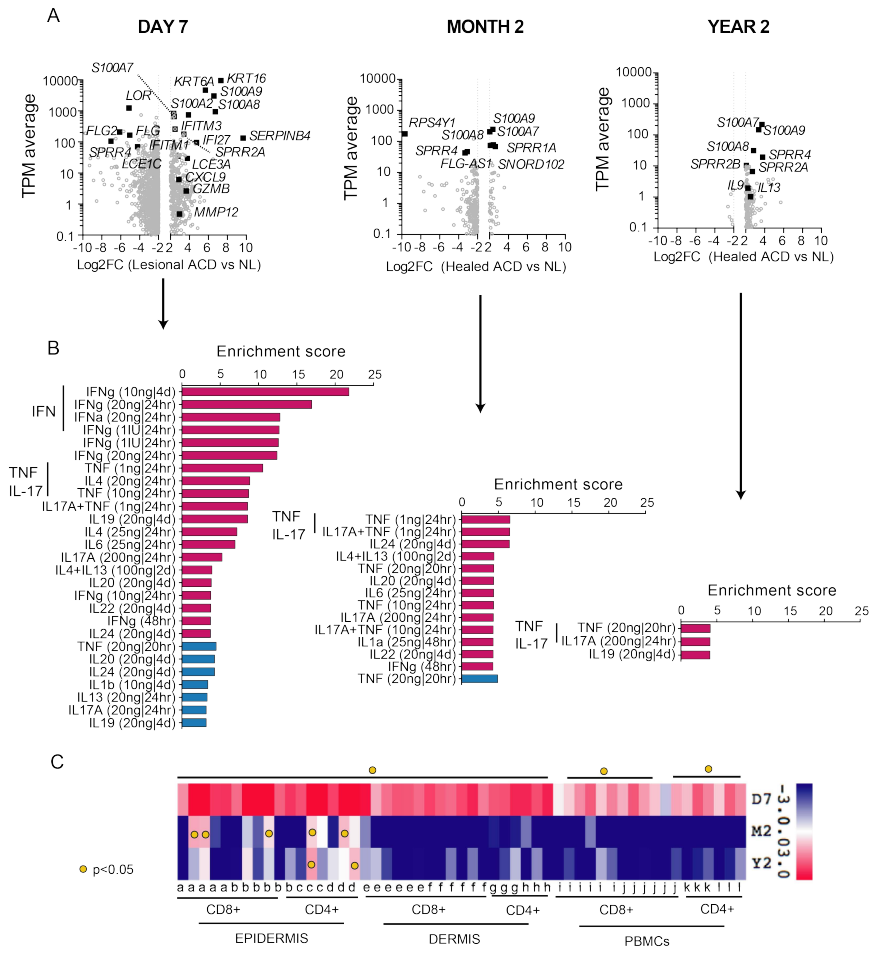
Previous work from the laboratory showed that T_{RM} cells producing IL-22 and IL-17 were retained in healed epidermis from psoriasis patients (Cheuk *et al.,* 2014). Here, activating T cells in healed skin led to a stronger IL-17 signal than in healthy skin, which was expected from the T_{RM} population. This indicates that the functionality of the cellular infiltrate correlates to its effect on the surrounding tissue upon activation.

4.3 RESIDENT T CELLS IN ALLERGIC CONTACT DERMATITIS

4.3.1 Transcriptomic analysis of ACD epidermis shows the persistence of a discrete disease signature up to two years after the resolution

Results: In ACD, exposure to the allergen leads to a clinical relapse within days. Skin samples were collected at day seven after epicutaneous testing and after a 2-month exclusion of the allergen. Four patients were included from an additional cohort that had been exposed to the allergen for another study two years ago (Yazar *et al.,* 2015). All patients had ACD to methylisothiazolinone (MI) (MI-ACD). Lesional or healed skin were compared to NL skin from the same patients taken simultaneously. RNA sequencing illustrated in Result Figure 4A showed that the number of transcripts up or downregulated progressively decreased with time. Two years after the cessation of symptoms, there was nevertheless several dysregulated transcripts. Enrichment analysis was performed using data from previously published studies in which keratinocytes were exposed to various cytokines mixes. Looking for which cytokine-signatures were embedded in the transcriptome and were most likely to explain the observed changes in our samples, the number-one driver of the transcriptional changes was IFN-γ at day 7, replaced by TNF and IL-17 after 2 months after resolution (Result Figure 4B). Enough skin material was not available for flow cytometry characterization of T_{RM} cell-subsets in the skin. Instead, "in silico dissection" using enrichment analysis based on previous RNAseq data of T_{RM} cells subsets from healthy skin was performed using the ranked transcripts expressed in different T_{RM} cell-subsets. Neither circulating cell nor dermal T_{RM} cell-signatures appeared after 2 years of disease resolution. Instead, the signature from $CD4^+$ epidermal T cells seemed to faintly persist (Result Figure 4C).

Discussion: The characterization of T_{RM} subsets is lacking in human ACD. Although TCR analysis shows the long-term persistence of clonal T cells (Gaide *et al.,* 2015) in healed ACD, the transcriptome is normalized 4-8 months after the active disease was resolved (Gulati *et al.,* 2014). ACD is not clinically known to disappear fast, however, it is conceivable that T_{RM} cell attrition happens to such an extent that their clinical relevance is uncertain, as shown in mice (Gamradt *et al.,* 2019). Our data suggest that the epidermal transcriptome is not fully normalized two years after the withdrawal of the antigen, with persistent upregulation of S100As transcripts. However, the small sample size in this study warrants caution. Our setting differs from Gulati et al, as epidermis was separated from dermis before snap freezing. The findings may, therefore, illustrate differences in wounding-reactions between healed and non-lesional skin rather than a baseline expression. Indeed, the epidermis has an "inflammatory memory" that participates in subsequent wound repair independently of T_{RM} cells (Naik *et al.,* 2017). This epidermal memory was associated with epigenetic changes in epidermal stem cells. Therefore, the molecular scar identified in ACD could only partly be due to the T cells generated during ACD two years earlier and a disease memory might also lie in keratinocytes themselves.



Result Figure 4 Transcriptomic analysis in ACD up to 2 years after the cessation of exposure

Biopsies were taken at day 7 (second reading of patch-test), 2 months and 2 years after the diagnosis and the eviction of the allergen methylisothiazolinone. Epidermis was separated from dermis and mRNA was purified, and sequenced. (A) Volcano plots of the Transcripts Per Kilobase Million (TPM) of dysregulated transcripts between lesional vs non-lesional or healed vs non-lesional (Log2FC <-2 or >2). (B) Enrichment analysis generated with PARTEK, using gene sets previously published where keratinocytes were exposed to cytokines and gene lists from upregulated or downregulated genes by these cytokines were generated (Swindell et al., 2016). The top 100 upregulated were used to generate the red bars and the top 100 downregulated genes to generate the blue bars. Red bars show the enriched cytokine signature present in upregulated genes from our data. Blue bars show the enriched cytokine signature present in downregulated genes from our data (C) Heatmap generated with MeV, from enrichment analysis generated with PARTEK, where -log10 (p-value) is plotted, using gene set from T_{RM} RNA sequencing data from the group, partly published in Cheuk et al., (Cheuk et al., 2017). 3-6 donors per group. a-EPI-CD8CD103$^+$CD49a$^+$; b-EPI-CD8 CD103$^+$CD49a$^-$; c-EPI-CD4CD103$^+$CD49a$^-$; d-EPI-CD4 CD103$^-$CD49a$^-$; e-DER-CD8 CD103$^+$CD49a$^-$; f-DER-CD8 CD103$^-$CD49a$^-$; g-DER-CD4 CD103$^+$CD49a$^-$; h-DER-CD4CD103$^-$CD49a$^-$; i-CD8CLA$^+$TEM ; j-CD8CLA$^-$TEM; k-CD4CLA$^+$TEM ;l-CD4CLA$^-$TEM.

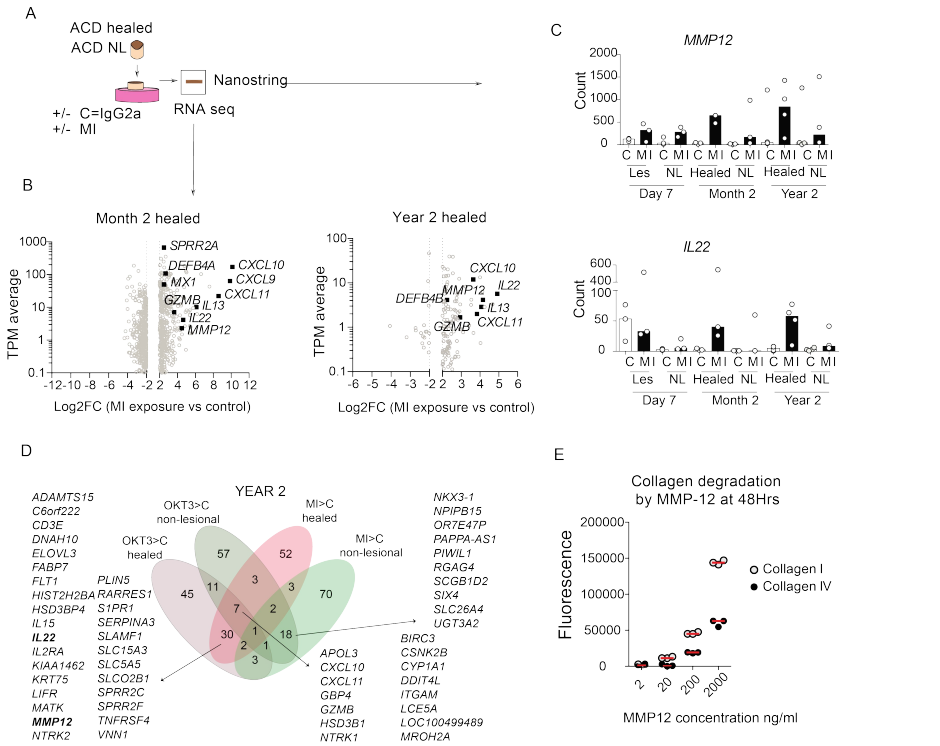
4.3.2 The elicitation of ACD in skin explants two years after disease resolution triggers responses capable of matrix-disruption

Results: The role of skin T cells in the ACD relapses is discussed in humans, and shown in mice (Gaide *et al.,* 2015; Gamradt *et al.,* 2019). In **PAPER IV**, using both RNA sequencing and Nanostring Technologies, the exposure to the allergen could elicit potent tissue-responses up to two years after resolution (Result Figure 5A-B). Transcript dysregulations were absent or much milder in NL skin than in healed skin (Result Figure 5C). Among the top 100 genes upregulated in each group of samples, 30 were common between MI or OKT-3 exposure and specific to the healed epidermis, indicating an overlap between the allergen-specific responses and the effect of bulk T cell activation (Result Figure 5D). Among these genes, *MMP12* was one that was also detected in lesional skin (Result Figure 5B). MMP-12 from macrophages has been associated with disease severity in a mice model of hypersensitivity, as *mmp12*$^{-/-}$ mice were protected from the development of symptomatic skin allergy (Meguro *et al.,* 2016; Nakagomi *et al.,* 2015). When testing MMP-12 activity on collagen IV and I, the collagen was degraded in a dose-dependent and time-dependent manner (Result Figure 5E and data not shown) (Taddese *et al.,* 2010; Gronski *et al.,* 1997). Thus, the allergen-specific skin memory had the potential to trigger matrix-degradation, both at the basement membrane with collagen IV and in the dermis with collagen I.

Discussion: The in-depth analysis of a small patient group in which ACD was elicitated in skin biopsies uncovered mechanisms of disease memory. Part of the MI signature was specific to healed skin (*MMP12*, *IL22*), but others overlapped with non-lesional skin (*CXCL10*, *CXCL11*). The upregulation of *CXCL10* and *CXCL11* was expected after OKT-3 as part of the core response to T cell activation as shown in **PAPER III**. The upregulation of these same transcripts by MI in non-lesional skin at month 2 was more intriguing and could reflect that T_{RM} cells had seeded to other sites of the skin, a phenomenon that is known in mice, especially in case of repeated exposures and minor local trauma (Muschaweckh *et al.,* 2016b; Davies *et al.,* 2017). The differences observed between the Month 2 and Year 2 disease memory might depend on several things. First, the T_{RM} cells might progressively disappear. Second, the antigen might still be present in the skin at month 2, perpetuating the T cell settlement locally, but not at year 2. It was shown in mice that allergens could persist in the skin more than a month after the exposure (Gamradt *et al.,* 2019). Third, the type of exposure to the allergen differed substantially, as one group was sampled on healed skin after a patch-test (high concentration, 48h under occlusion) and the other after a weeks-long rinse-off study. I tried to control for these differences by intraindividual sampling of healed and non-lesional skin.

Exposure of resolved skin to MI did not totally phenocopy active ACD. *MMP12* was one of the transcripts that were both upregulated in the lesional ACD skin and after elicitation in healed skin. *MMP12* expression could help discriminate eczema from psoriasis (Quaranta *et al.,* 2014), and the protein has primarily been detected in macrophages but can also be expressed in keratinocytes (Kulig *et al.,* 2016), like in lupus skin examined with microscopy (Manetti *et al.,* 2012). The increase of *MMP12* could relate to IL-13 and IFN-γ exposure in keratinocytes but it is not part of the top upregulated genes upon exposure of healthy keratinocytes to common cytokines (Ramalingam *et al.,* 2016; Swindell *et al.,*

2016). From these data, it is arduous to conclude on the pathogenicity of MMP-12. Degradation of collagen can favor the entry of inflammatory cells, thus increasing the inflammatory infiltrate. But MMP-12 could also be fulfilling other functions such as cytokine cleavage or promoting fibrosis (Dufour *et al.,* 2018; England *et al.,* 2011). A more thorough characterization of its role in the skin is needed.



Result Figure 5 Tissue responses to *ex vivo* elicitation of CD in skin explants

(A) Experimental setting. (B) RNA was purified and sequenced from epidermal samples after incubation of whole skin biopsies in MI, OKT-3 or the control. Volcano plots of Transcripts Per Kilobase Million (TPM) of dysregulated transcripts between MI-exposed and control (IgG2a). (C) Bars of the quantitative validation of RNA sequencing finding, using Nanostring Technologies. (D) Venn diagrams generated with JMP, of top 100 upregulated transcripts between MI or OKT-3-exposed and non-exposed healed and non-lesional samples, using RNA sequencing data, for each group stated in the figure. (D) Dot plot of the collagen degradation after exposure to MMP-12 at different concentration during 48 hours. MI = Methylisothiazolinone, NL = Non-lesional, FC = Fold change, Les = lesional, control = IgG2a

4.4 ETHICAL CONSIDERATIONS

- The experiments performed for this thesis involved human sampling. The patients don't directly benefit from the research and are exposed to potential side-effects after the sampling, such as skin infection, thus restricting the number of patients included and the number of biopsies taken for each patient.
- Another consideration is the relationship with the patient while sampling as patients may agree to participate in the research also because it grants them quick access to a dermatologist. It is a problem as the dermatologist taking research samples is usually not the one in charge of the patients' follow-up. This lack of continuity might lead to suboptimal care. We tried to consider that when meeting the patients and choosing a medication.
- One last problem relates to the number of patients that are sampled. Competing interests are at play: the first is to use as few samples as possible to decrease the risk of side-effects and not waste human material; the second is to make sure that data collected are enough to lead to new medical knowledge. This point is always considered when choosing the number of patients to samples for a given project and we tried to make sure all samples were used wisely and in the best possible way.

4.5 MAIN LIMITATIONS

- Skin explants permitted a compartmentalized analysis of the skin, with respect to its 3D microenvironment, but the live visualization of the cellular interplay could not be visualized. We used confocal microscopy in complement to assess the cellular contacts.
- The healthy donors underwent surgery, were more often women and were younger than the psoriasis patients that were recruited, thus making our control group imperfect. We tried to use non-lesional skin from the same patients as control. Ongoing studies focus on the relationship between age and T_{RM} cell-subsets.
- The techniques used in the generation and analysis of mRNA sequencing data were not part of the established competences in the laboratory. We chose to outsource analysis to the external companies to ensure a high level of expertise.
- Over the years, dozens of patients were sampled, but only a few samples were used for each experiment, leading to a lack of power, and sometimes the absence of meaningful statistical comparisons. Whenever possible, we have tried to collect enough samples to ensure relevant statistical comparisons.

5 CONCLUSIONS AND FUTURE PERSPECTIVES

In human skin, functionally distinct T_{RM} cell-subsets are altered during inflammatory skin diseases.

The functional dichotomy uncovered in **PAPER I** was based on the surface marker CD49a. It was conserved in common inflammatory skin diseases as $CD8^+CD103^+CD49a^-$ that are prone to IL-17 production were enriched in lesional and non-lesional psoriasis. Together with the work of other research teams, the data exposed in this thesis proposes $CD49a^+$ T_{RM} cells as a good target for further pharmaceutical development in the field of vitiligo. The cytotoxic capacities of $CD8^+CD103^+CD49a^+$ T_{RM} cells suggest a potential use in dermato-oncology. The blossoming single-cell techniques will most likely help identify further disease-relevant functional subsets.

In skin that has never been affected by psoriasis, T_{RM} cells differ in composition and functionality.

In addition to the genetic predisposition of NLP keratinocytes, an imbalance in skin T_{RM} subsets poises NLP skin to psoriasis development. As shown in **PAPER II**, a microbe-driven mechanism could participate in the accumulation of $CCR6^+$ T cells in the epidermis. This calls first for a deepened study of factors allowing T_{RM} survival and replacement in non-lymphoid tissues, and later on to microbe-based local treatments, reshuffling the T_{RM} cell subsets in NLP and preventing disease development. However, a better knowledge of skin microbiota has to be reached first. A major question remains. If the whole skin of psoriasis patients is predisposed to the disease, how are plaques arising only in certain spots and not on the entire body surface? There, I hope that a joint effort of the psoriasis research community will uncover skin regulatory mechanisms in never-lesional skin that will help explain the focal control of psoriasis development.

In resolved psoriasis skin T_{RM} cells are capable to initiate tissue-responses relevant to clinical practice.

T_{RM} cells retained in resolved psoriasis can release cytokines that are amplified by stromal cells into potent tissue-responses in both skin compartments, although they correlated to the disease outcome only in epidermis. If validated in further studies, the findings of **PAPER III** pave the way for the development of a relapse predictor applicable to clinical practice. This also opens perspectives for other chronic inflammatory diseases. For instance, in patients with successfully treated inflammatory bowel diseases, the question about treatment withdrawal is arising. When to stop–and when to restart–a treatment are highly relevant questions for clinicians and patients, and tools deciphering the stroma—T_{RM} interplay could be translated to chronic inflammatory diseases in several organs.

In resolved allergic contact dermatitis, allergen-specific T_{RM} cells provoke tissue responses with matrix-degrading capacities

The data presented in **PAPER IV** show the existence of a long-lasting disease memory that is capable of rapid tissue responses upon allergen exposure, with the release of immune cell recruitment signals and a matrix-degrading potential. There is still a lot to uncover in ACD

compared to psoriasis and direct translation into clinics are more difficult to foresee. In particular, the characterization of the cellular functions of T_{RM} cells in ACD is lacking. In situations where the avoidance of the allergen is impossible, strategies limiting the establishment of T_{RM} cells or the tissue protein-licensing could be of interest. Whether our findings of matrix-degrading potential upon ACD elicitation can be translated to atopic dermatitis relapses remain to determine. In that case, early blockade of metalloproteinases might be of use in the early phases of local flares in moderate forms of atopic dermatitis, to limit symptoms.

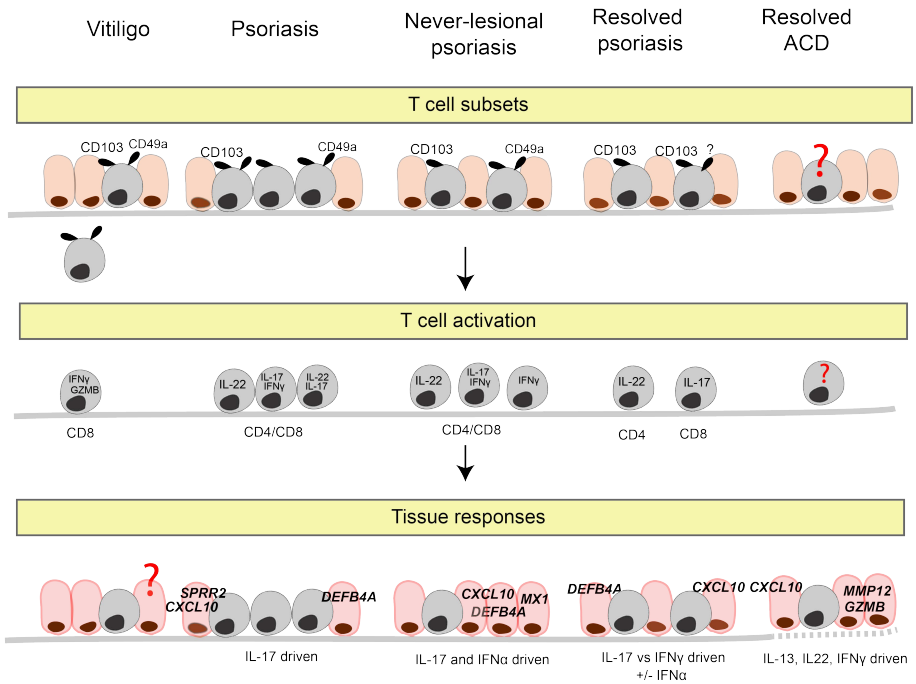


Figure 18 Answers to the research questions

In conclusion, functional subsets of T_{RM} cells that were identified in human skin were imbalanced in T cell-driven inflammatory skin diseases. Their interaction with stromal cells inside the skin microenvironment created disease-specific tissue-responses (Figure 19). Epidermal tissue responses appeared more pathogenic than dermal ones, echoing the preferential epidermal enrichment of T_{RM} cells with pathogenic potential. Local treatments displacing the pathogenic skin T_{RM} cells could improve the T cell-driven disease evolution hopefully by limiting local relapses and the development of focal inflammation. The last decade brought great technological advances and it is nowadays possible to perform multi-omics analyses on a few square-millimeters of human tissues and observe human cell crawling in skin biopsies. I am confident that major discoveries can be done using human samples, in collaboration with patients.

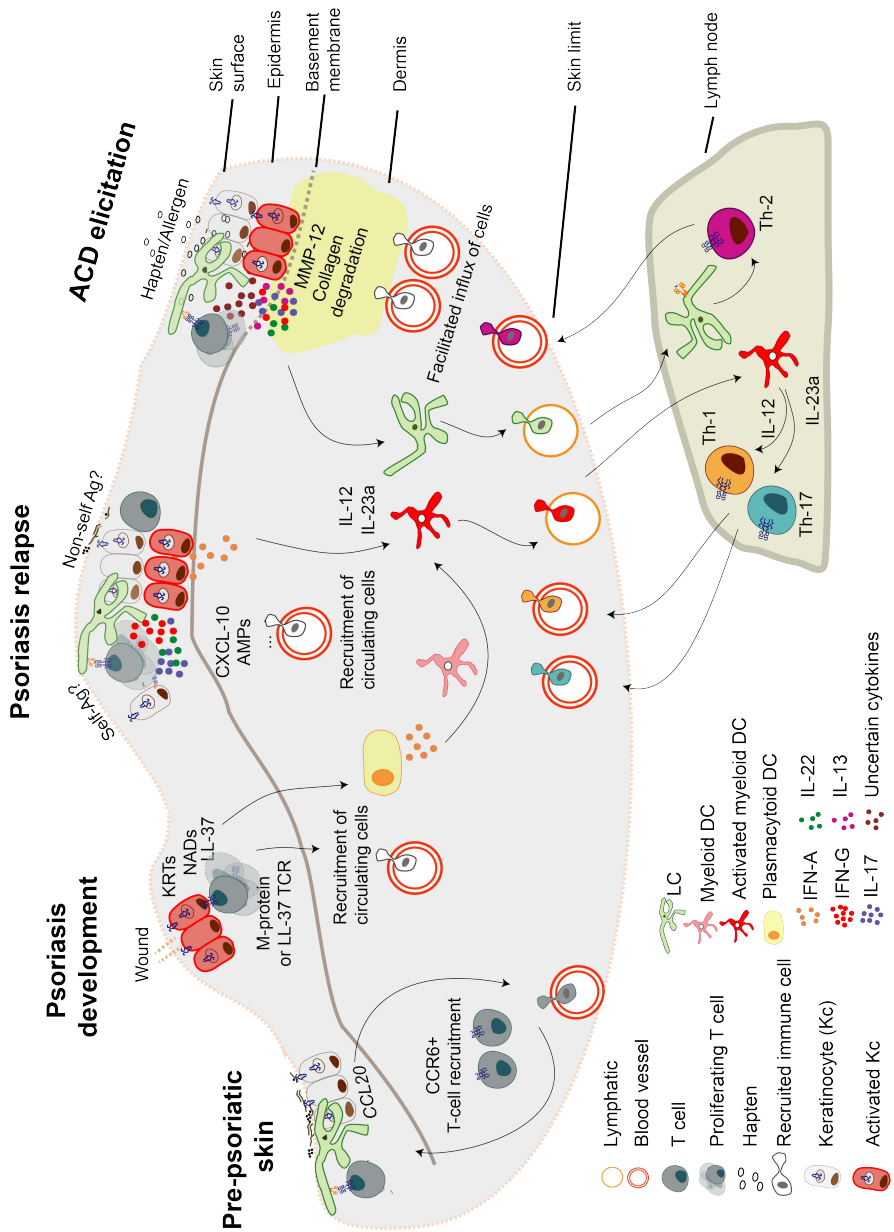


Figure 19 Proposed inclusion of the thesis findings in the physiopathology of psoriasis and allergic contact dermatitis

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This is just something we live with."

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*Except the South of France.

7 FIGURES AND TABLES

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• References especially relevant to the background of the Ph.D. thesis

“C'est pas parce qu'on comprend rien qu'il faut faire n'importe quoi”
(*Understanding nothing is no excuse to do nonsense*)

Pr Benoît Funalot quoting Pr Arnold Munnich quoting Pr Jean Frézal,
Trans-generational wisdom from French geneticists