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Resolving inflammation – Analysis of mechanisms in relation to Alzheimer pathology and aging

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Karolinska Institutet

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-295-1
Cover: Brain by Igor Morski (igormorski.pl)

Resolving inflammation – Analysis of mechanisms in relation to Alzheimer pathology and aging

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public in Ulf von Euler J3:06, Bioclinicum, Karolinska University Hospital, Solna, Friday the 3rd of September at 15:00.

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To my family

ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia, and its clinical symptoms are the reflections of pathological changes in the brain. The main pathological features of AD are intracellular aggregates of hyper-phosphorylated tau protein and extracellular deposits of amyloid β (Aβ) peptide in amyloid plaques. Chronic inflammation in the central nervous system (CNS) appears as a crucial hallmark of AD. The excessive presence of Aβ causes a chronic inflammatory response as an outcome of protective host response, and inflammation drives production of Aβ. In return, inflammatory cytokines induce Aβ peptide formation resulting in a vicious circle. Resolution of inflammation has been revealed as an end phase of inflammation for restoring and healing tissue. This process is mediated by pro-resolving lipid mediators (LMs) that are derived from omega-3 and omega-6 essential fatty acids. Previous studies reported reduced levels of pro-resolving LMs in human CSF and brain of AD patients. Many studies demonstrated the beneficial effects of the bioactive pro-resolving LMs in *in vitro* and *in vivo* models for chronic inflammatory diseases. Thus, detailed analysis of the inflammatory and pro-resolving LM production, their synthetic enzymes and receptors is necessary for using these potent LMs as treatment strategy at the appropriate disease stage for AD.

The current studies focused on markers involved in the resolution process and their association to Alzheimer pathology. We showed that receptors activated by pro-resolving LMs and mediating resolution were increased in *post mortem* human AD brains, indicating compensation for low levels of pro-resolving LMs (**Paper I**). In the second study, we investigated the changes in the levels of LMs, phospholipids, free fatty acids and inflammatory proteins at different ages in an AD mouse model in order to pinpoint the disruption occurring in the resolution process during disease progression. This study revealed that alterations in the resolution of inflammation could be observed when the Aβ burden was dominant, *i.e.* at older ages. However, changes in phospholipids in terms of membrane composition occurred earlier in the AD mice compared to wild-type (WT) mice (**Paper II**). This study led us to test pro-resolving LMs for therapeutic purposes in **Paper III**. We treated mice with AD pathology by intranasal administration of pro-resolving LMs and performed behavioral tests, electrophysiology and biochemical experiments. We found that pro-resolving LMs recovered both memory and gamma oscillation impairments, as well as decreased neuroinflammation. Based on these results, the molecular and cellular mechanisms affected upon LM treatment can be utilized for a treatment approach in clinical studies.

In conclusion, alterations observed in the synthesis of pro-resolving LMs may occur with healthy aging and at the later stages of disease pathology as shown with human and mouse brains with AD pathology. Pro-resolving LMs can rescue memory impairments by Aβ peptide pathology.

LIST OF SCIENTIFIC PAPERS

I. **Ceren Emre**, Erik Hjorth, Krishna Bharani, Steven Carroll, Ann-Charlotte Granholm, Marianne Schultzberg

Receptors for pro-resolving mediators are increased in Alzheimer's disease brain

Brain Pathology, 2020; 30(3):614-640

II. **Ceren Emre**, Khanh V. Do, Bokkyoo Jun, Erik Hjorth, Silvia Gómez Alcalde, Marie-Audrey I. Kautzmann, William C. Gordon, Per Nilsson, Nicolas G. Bazan, Marianne Schultzberg

Age-related changes in brain phospholipids and bioactive lipids in the *App* knock-in mouse model of Alzheimer's disease

Acta Neuropathologica Communications, 2021; 9(1):116

III. **Ceren Emre**, Luis Arroyo-Garcia, Khanh V. Do, Bokkyoo Jun, Silvia Gómez Alcalde, Silvia Maioli, Per Nilsson, Erik Hjorth, André Fisahn, Nicolas G. Bazan, Marianne Schultzberg

Intranasal delivery of pro-resolving lipid mediators rescued memory and gamma oscillation impairment in *App* KI mice

Manuscript

LIST OF SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Hazal Haytural, Georgios Mermelekas, **Ceren Emre**, Saket Milind Nigam, Steven L. Carroll, Bengt Winblad, Nenad Bogdanovic, Gaël Barthet, Ann-Charlotte Granholm, Lukas M. Orre, Lars O. Tjernberg, Susanne Frykman

The proteome of the dentate terminal zone of the perforant path indicates presynaptic impairment in Alzheimer's disease

Molecular and Cellular Proteomics, 2020; 19(1):128-141

II. Ying Wang, **Ceren Emre**, Helena Gyllenhammar-Schill, Karin Fjellman, Helga Eyjolfsdottir, Maria Eriksdotter, Marianne Schultzberg, Erik Hjorth

Cerebrospinal fluid inflammatory markers in Alzheimer's disease: Influence of comorbidities

Current Alzheimer Research, 2021; 18(2):157-170

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LIST OF ABBREVIATIONS

AA	arachidonic acid
Ach	acetylcholine
ACSF	artificial cerebrospinal fluid
AD	Alzheimer's disease
AnxA1	annexin 1
ApoE	apolipoprotein *E*
APP	amyloid β precursor protein
AT	aspirin-triggered
Aβ	amyloid β-peptide
BA46	Brodmann area 46
BARK1	β-adrenergic receptor kinase
Bax9	Bcl-2-associated X protein
BBB	blood-brain barrier
Bcl-2	B-cell lymphoma 2
Bcl-xl	B-cell lymphoma xl
BF	basal forebrain
Bfl-1	Bcl-2-related protein A1
Bik	Bcl-2-interacting killer
BLT1	leukotriene B4 receptor
camp	cyclic adenosine monophosphate
CaSR	calcium-sensing receptor
CB	cerebellum
CDK5	cyclin dependent kinase 5
CDP-DAG	cytidine diphosphate diacylglycerol
CG	cingulate gyrus
ChemR23	chemokine-like receptor-1
CNS	central nervous system
cPLA2	cytosolic PLA2
CSF	cerebrospinal fluid
CX3CL1	C-X3-C motif chemokine ligand 1
CX3CR1	C-X3-C motif chemokine receptor 1
Cyc-LT	cysteinyl-leukotriene
DHA	docosahexaenoic acid
DS	Down Syndrome
ECE-2	endothelin-converting enzyme 2
ECL	electrochemiluminescence
ENFTs	extraneuronal NFTs
ENT	entorhinal cortex
EOAD	early-onset AD
EPA	eicosapentaenoic acid
EPHA-1	ephrin type-A receptor 1
EPM	elevated plus maze
EPSC	excitatory post-synaptic current
ER	endoplasmic reticulum
FA	fatty acid
FAD	familial AD

FC	fear conditioning
FSN	fast spiking interneurons
Gas-6	growth arrest-specific 6
GFAP	glial fibrillary acidic protein
GM-CSF	granulocyte macrophage colony-stimulating factor
GPCR	G protein-coupled receptor
GPL	glycerophospholipids
GPR37	parkin-associated endothelin-like receptor/Pael-R
GWAS	genome-wide association study
HDL	high-density lipoprotein
HIPP	hippocampus
HSPG	heparin sulphate proteoglycans
IDE	insulin-degrading enzyme
IF	immunofluorescence
IHC	immunohistochemistry
IL	interleukin
INFTs	intraneuronal neurofibrillary tangles
iNOS	inducible nitric oxide synthase
iPLA2	calcium-independent PLA2
KA	kainic acid
LC-MS/MS	liquid chromatography–tandem mass spectrometry
LFP	local field potential
LGR6	leucine-rich repeat containing G protein-coupled receptor 6
LM	lipid mediator
LOAD	late-onset AD
LOX	lipoxygenase
LRP1	low-density lipoprotein receptor 1
LT	leukotriene
LX	lipoxin
MALDI-IMS	matrix-assisted laser desorption/ionization-imaging mass spectrometry
MAPK	mitogen-activated protein kinase
MaR	maresin
MCI	mild cognitive impairment
MCP-1	monocyte chemoattractant protein-1
MIP-1	macrophage inflammatory protein-1
miRNA	microRNA
MMSE	mini-mental state examination
Nagly	N-arachidonoylglycine
NASH	nonalcoholic steatohepatitis
NEP	neprilysin
NF-κB	nuclear factor κ-light chain enhancer of activated B cells
NFTs	neurofibrillary tangles
NIA-AA	National Institute on Aging and the Alzheimer's Association
NOR	novel object recognition
NPD1	neuroprotectin D1
NSAID	nonsteroidal anti-inflammatory drug
OF	open field
PA	phosphatidic acid
PAMP	pathogen-associated molecular pattern
PC	phosphatidylcholine

PE	phosphatidylethanolamine
PET	positron emission tomography
PG	prostaglandin
PI	phosphatidylinositol
PKA	protein kinase A
PLA	phospholipase
PMN	polymorphonuclear leukocyte
PPP	pattern recognition receptor
PS	phosphatidylserine
PSEN1	presenilin 1
PSEN2	presenilin 2
PUFA	polyunsaturated fatty acid
RA	rheumatoid arthritis
RAGE	advanced glycosylation end products
RORα	retinoic acid-related orphan receptor α
ROS	reactive oxygen species
RvD	resolvin D
SAD	sporadic AD
SAMP8	senescence-accelerated prone mouse 8
SCI	subjective cognitive impairment
SM	sphingomyelin
sPLA2	secreted PLA
TG	triacylglycerol
TLR	toll-like receptor
TNF	tumor necrosis factor
TREM2	triggering receptor expressed on myeloid cells 2
WHO	World Health Organization
WT	wild-type
YKL-40	chitinase 3-like 1
15S-HpETE	15S-hydroperoxy eicosatetraenoic
17-HDHA	17S-hydroxy-DHA
3xTg-AD	triple transgenic AD mouse
5XFAD	five FAD mutations mouse

1 INTRODUCTION

1.1 Dementia and its implications for public health

Dementia is a condition characterized by a progressive decline in cognitive function and the ability to perform daily activities. The impairment in memory is commonly accompanied by changes in behavior, loss in motivation and depression. Age is the strongest known risk factor for dementia, but it is not healthy aging. As life expectancy is increasing worldwide, the risk for developing dementia is rising dramatically. There are over 50 million people affected by dementia and every year approximately 10 million people are diagnosed with dementia, estimated to reach 82 million worldwide by 2030. Dementia is caused by loss of neurons and their connections in brain regions that are involved in memory and thinking. Alzheimer's disease (AD), vascular dementia and Lewy body dementia are types of dementia that are chronic and not reversible. AD is the most common type of dementia, accounting for over 50 percent of dementia cases. The global cost of care for individuals with AD or other dementias was US $1 trillion in 2018 [80, 244]. Considering its large economic impact, the World Health Organization (WHO) has adopted a global action plan which aims to improve recognition and awareness, to decrease risk factors for dementia, to improve diagnosis, care and treatment, and to support research [226].

1.2 Alzheimer's disease

AD is a neurodegenerative disorder with clinical symptoms due to progressive neurodegeneration in regions of the brain involved in memory and learning. As the disease progresses, disruption in neuronal networks and loss of neurons spread throughout the brain and eventually result in impaired basic physiological functions such as eating, swallowing, walking and bathing. The lifespan after diagnosis of AD is less than 10 years. Patients with AD not only suffer themselves from disease symptoms but they become a burden to their family, caregivers and healthcare system. AD can be either hereditary, *i.e.* familial AD (FAD), or without known genetic cause, so called sporadic AD (SAD). Approximately 5% of AD cases are early-onset AD (EOAD), with the first symptoms appearing before 65 years of age. About 10% of EOAD cases have an FAD defined as a rare autosomal dominant disorder [134] with known mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) [292, 305]. SAD is the most common form, accounts for 95% of all AD cases and mainly have a late onset (LOAD), with the first symptoms appearing after 65 years of age. The *E4 allele* of apolipoprotein (APOE4) is the most important genetic factor for developing AD [63]. The etiology of SAD includes combinations of genetic variants and environmental factors, such as diet, education and toxic exposures.

The main pathological hallmarks of AD are extracellular plaques of aggregated β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) of hyper-phosphorylated microtubule-

associated tau proteins in neurons. These pathological characteristics are accompanied by neuroinflammation, synaptic degeneration and neuronal cell death [31].
Studies show that AD pathophysiology starts decades before the clinical symptoms [31] and it is crucial to identify the earliest signs of disease pathology with the development of new techniques, biomarkers and imaging. Being diagnosed with subjective cognitive impairment (SCI), not uncommon in elderly people with cognitive complaints, carries an increased risk for dementia [250]. PET-imaging studies showed a smaller hippocampus volume in an SCI group compared to a healthy group [318], and based on a biomarker study, the cerebrospinal fluid (CSF) sample profile of SCI patients was more similar to that of AD than to the profile of healthy individuals [323]. Mild cognitive impairment (MCI) is a prodromal state of dementia and can be considered as an intermediary state between SCI and AD. MCI patients show mild difficulties with memory and thinking, without affecting their daily activities. The yearly conversion rate from MCI to probable AD is 10 to 15% compared to 1-2% in the general population [239]. Given these findings, patients with SCI and MCI who represent the very early stages of cognitive deterioration should be selected for early diagnosis of AD and to provide effective treatment.

1.2.1 Pathophysiology of AD

1.2.1.1 Aβ and tau

In autopsied brains of patients with dementia, Dr. Alois Alzheimer observed amyloid plaques and NFTs, suggesting that these pathologies caused the symptoms. Various hypotheses have been put forward regarding the causative factors for AD including Aβ, tau, inflammation and cholinergic dysfunction [106]. According to the amyloid cascade hypothesis, APP is cleaved aberrantly by β- and γ-secretases yielding excess amounts of Aβ peptides, especially the more hydrophobic and aggregation-prone $A\beta_{42}$, which results in inadequate clearance and aggregation [259]. The classical view was that Aβ peptides are deposited extracellularly forming senile plaques, however, there is accumulating evidence that Aβ peptide can also be produced and accumulated intraneuronally, contributing to synaptic dysfunction and neurodegeneration [159]. Aβ polymerization occurs in sequential phases, first Aβ monomers aggregate into soluble oligomers, then to insoluble oligomers, generating protofibrils and fibrils [128]. Amyloid plaques are morphologically classified in diffuse and neuritic plaques. Neuritic plaques are dense core fibrillar deposits which consist of dystrophic neurites, activated astrocytes and microglia, and are associated with neuronal death. Scoring of plaque density is performed for pathological assessment of AD and used as part of staging of the disease. Diffuse plaques contain degenerating neuronal processes with paired helical filaments of tau and are not considered for pathological diagnosis of AD because they are commonly found in brains of elderly with healthy aging. Amyloid plaques mainly present in the isocortex, while entorhinal cortex, hippocampus, basal ganglia and cerebellum are affected to a lesser extent [283].

Compared to NFTs, amyloid plaques are less useful in terms of predicting the pattern of progression, however, Thal et al. proposed a scoring system in five stages: assessment of Aβ deposit distribution starting from isocortex (Stage 1); entorhinal cortex, hippocampus, amygdala, insular cortex (Stage 2); basal forebrain, thalamus, hypothalamus (Stage 3); brainstem structures (Stage 4); molecular layer of cerebellum and pons (Stage 5) [312] (Fig. 1).

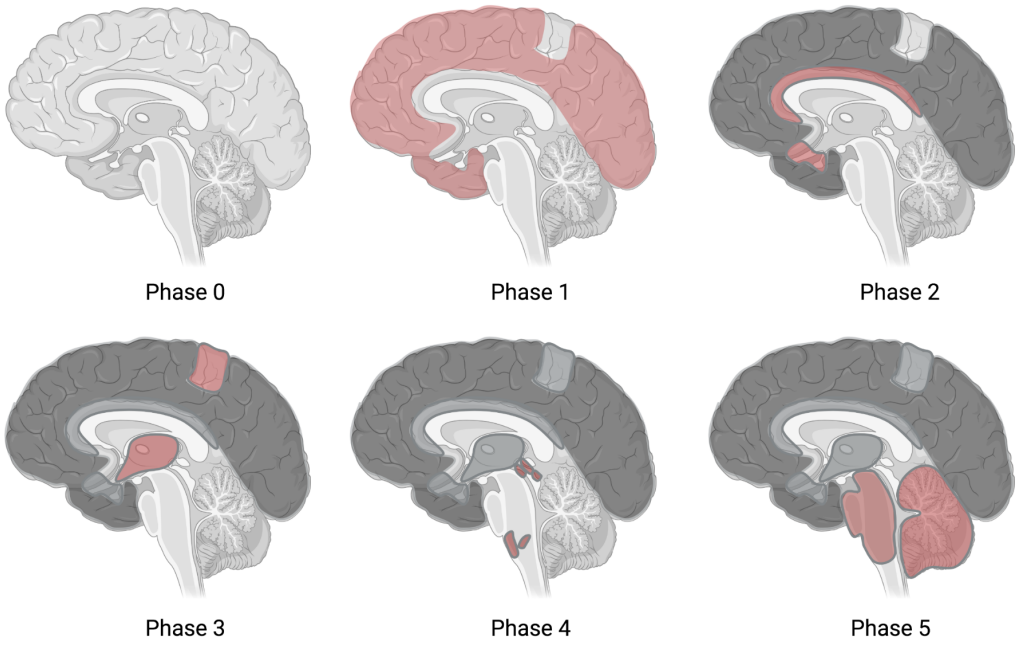

Figure 1: Different regions of brain develop amyloid deposits in a hierarchical order: in the first phase, sparse amyloid deposits are found in neocortical areas (red); in the second phase allocortex, hippocampus and entorhinal cortex start to exhibit amyloid deposits; in phase 3 striatum and subpial structures display Aβ deposits; in phase 4 midbrain, substantia nigra and medulla oblongata start to exhibit Aβ deposits, and in phase 5 cerebellum and the reticular formation of pons show Aβ deposits. This image is created in BioRender.com.

NFTs are intraneuronal filamentous inclusions within the cell soma of pyramidal neurons and were first observed by Dr. Alois Alzheimer. Under pathological conditions, the microtubule associated protein tau is hyperphosphorylated, causing microtubules to disassemble and tau molecules to aggregate into paired helical filaments, resulting in impairment of axonal transport and in dendrite breakdown (Fig. 2). Also NFTs have been distinguished according to their morphological stages: pre-NFTs (diffuse NFTs) are located in the cytoplasm of neurons with normal morphology and well preserved dendrites; mature intraneuronal NFTs (iNFTs) are filamentous tau aggregates that push the nucleus to the cell periphery in neurons with signs of distorted dendrites; extraneuronal (ghost) NFTs (eNFTs) are found in dead, tangle-bearing, neurons remaining after disintegration of the cell nucleus and dendrites [30, 296]. The

spatiotemporal progression pattern of NFTs is more predictable compared to amyloid plaques. They begin to develop in the entorhinal cortex and hippocampus (the allocortex of the medial temporal lobe) and spread to the primary sensory cortex, both motor and visual areas. Braak and Braak [31] defined six stages in which NFTs appear: Stage I - in the transentorhinal region, Stage II - in the CA1 of hippocampus, Stage III - in the subiculum of the hippocampal formation, Stage IV – in the amygdala and thalamus, Stage V - progressively spreading to isocortical regions, and Stage VI - spreading to the primary sensory, motor and visual areas [32](Fig.2).

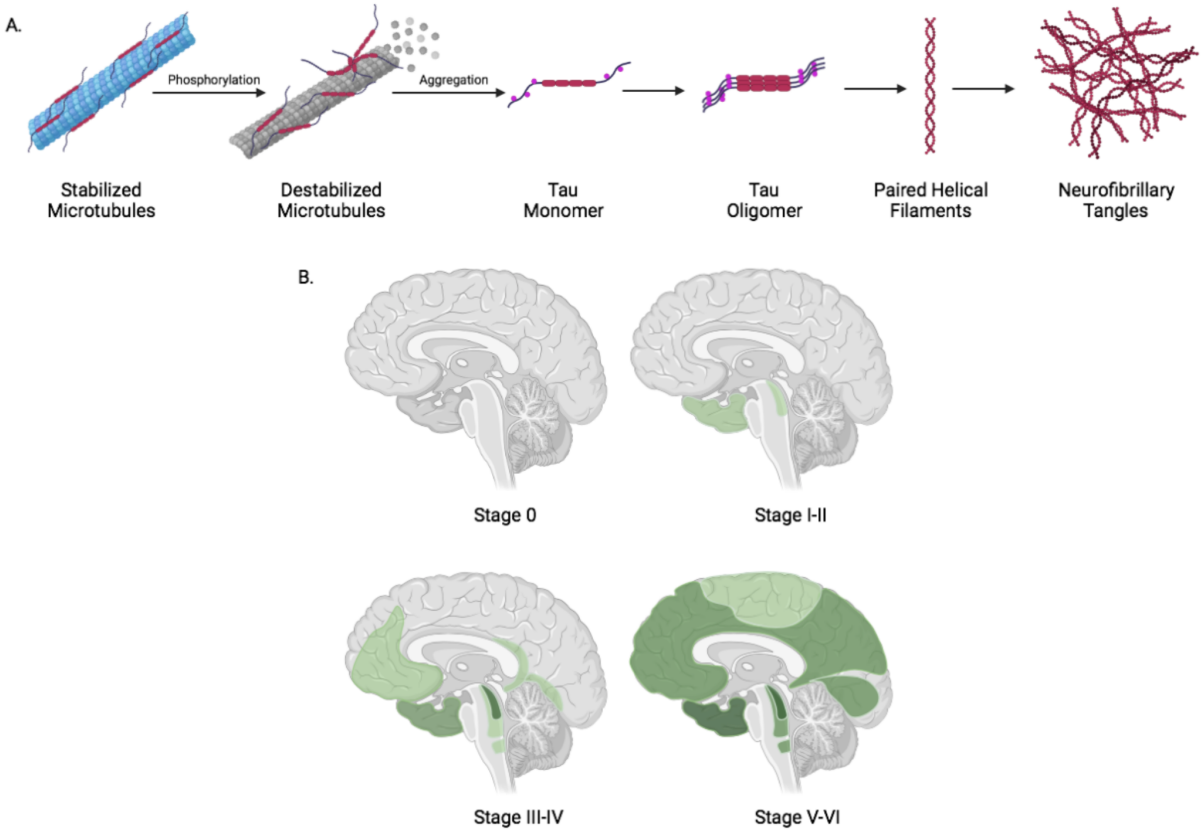

Figure 2: (A) Development of tau neurofibrillary tangles (NFTs) (B) NFTs start to appear in the locus coeruleus, transentorhinal cortex and entorhinal cortex at stages I-II. Hippocampus, amygdala, basal temporal cortex, insular cortex and basal frontal cortex exhibit NFTs at stage II-IV. Sparing the cerebellum, NFTs spread through neocortical regions at stage V-VI. This image is created in BioRender.com.

Several clinicopathological studies have determined that the density and distribution of NFTs correlate with clinical features of dementia [25, 93]. A committee set up by The National Institute on Aging and the Alzheimer's Association (NIA-AA) in 2012 published revised guidelines for the neuropathological assessment of AD by adapting Braak's and Thal's staging systems to a new scoring system that transforms amyloid plaque (A), NFT (B) and CERAD neuritic plaque (C) scores into a shorter scale (0-3) [203]. The new guidelines separate the clinical and pathological aspects of the disease by using three morphological hallmarks of the disease without cognitive status.

1.3 Inflammation

Over the last decade, the importance of inflammation in AD has been gaining interest. For the first time in 1910 Oskar Fischer stated that extracellular amyloid deposition induces an inflammatory reaction followed by a regenerative response of surrounding nerve fibers. However, with the methods available at the time Fischer could not identify this inflammatory process around the plaques by histopathology. In 1982, the inflammatory response in the *post mortem* AD brain was shown by Eikelenboom and Stam, demonstrating that dense core plaques are surrounded by immunoglobulins and complement factors [79]. Later on, the resident immune cells of the brain, microglia, were found in a reactive phenotype in the grey matter within the cortical regions of AD brains and concentrating particularly in the areas of senile plaques [189]. Accumulating studies from different groups showed that together with the two core pathologies of AD, NFTs and Aβ plaques, the inflammatory process is consistently activated and that its contribution to AD pathogenesis is fundamental [64, 95, 317].

Acute inflammation is a well-controlled defence mechanism against injury, infections and toxins when the pro-inflammatory and anti-inflammatory signalling pathways are in balance, eventually leading to repair of the damaged area. However, as seen in AD, a sustained inflammatory response due to excessive Aβ production and cytokine release results in chronic inflammation, which can cause cumulative damage over time [293]. Neuroinflammation is not exclusive to AD, and other neurodegenerative disorders such as Parkinson's disease [112], multiple sclerosis [49], traumatic brain injury [35], stroke [5] and amyotrophic lateral sclerosis [179] also demonstrate elevated levels of inflammatory markers. In all of these disorders, there is increasing evidence that inflammatory responses can occur prior to neuronal cell loss. Recent findings have shifted our understanding of the timing of the inflammatory reactions in the course of AD, previously thought to be more active due to neurodegeneration occurring during the disease progression. However, correlative analysis from clinical studies have shown that inflammatory markers are present in the CSF already at early stages of AD, and that they may facilitate both Aβ and NFT pathologies, indicating a much earlier involvement in the disease [37, 306]. Furthermore, one group demonstrated that tau pathology, amyloid plaques and gliosis can be triggered with a viral infection using wild-type (WT) mice, suggesting that immune responses can stimulate AD-like pathology [155]. In the beginning of the 1990s, epidemiological studies showed that patients with rheumatoid arthritis displayed a lower prevalence of AD, suggested to be due to treatment with anti-inflammatory drugs [190]. McGeer put forward the hypothesis that this treatment could be a strategy to protect against developing AD [190]. These results lead researchers to use nonsteroidal anti-inflammatory drugs (NSAIDs) in transgenic animal models of AD, resulting in reduced AD-like pathology [192]. However, despite the link between the use of NSAIDs and decreased risk for developing AD, human trials with NSAID treatment have failed to demonstrate conclusive outcomes with no or only minor benefits in treating AD, even causing gastrointestinal side effects [198, 254].

Preventing the beginning of an inflammatory response can mean losing the innate immune functions which are beneficial and necessary against infection or pathology. A study showed the beneficial effects of low-dose curcumin for inducing resolution and phagocytosis of amyloid with increased expression of triggering receptor expressed on myeloid cells 2 (TREM2). However, the same study also demonstrated that a high dose of curcumin caused suppression of inflammation, supporting the notion that intervention in different phases of inflammation can either cause immunomodulation or immunosuppression [311]. Another study supporting the importance of the beginning of inflammation showed that treatment with a non-steroidal anti-inflammatory drug (NSAID) blocked exercise-induced elevation of pro-inflammatory lipid mediators (LMs) and pro-resolving LM synthesis, while the vehicle group had increased levels for both pro-inflammatory and pro-resolving LM production. That is, acute pro-inflammatory signals are necessary to stimulate resolution of inflammation [187]. These observations imply that instead of inhibiting inflammatory pathways, stimulating the resolution of inflammation can be a treatment strategy. Pro-resolving LMs are endogenously produced mediators of resolution which provides homeostasis at the end of an inflammatory response. This new concept, resolution of inflammation, was introduced by Dr. Charles Serhan [272] and will be discussed further in sections below.

1.3.1 The role of inflammation in AD

The primary function of inflammation is protection against a harmful stimulus, but it can be detrimental when the immune response becomes chronic. Persistent activation of immune cells causes the release of various pro-inflammatory and toxic molecules, including cytokines and reactive oxygen species (ROS). In the central nervous system (CNS), microglia are resident myeloid cells and considered as immune cells in view of their ability to release inflammatory and cytotoxic factors, perform phagocytosis and present antigens [105]. They are widely distributed and continuously survey the brain for pathogens, providing homeostasis and plasticity by remodeling synapses [245]. In a healthy brain, microglia display a so called ‘resting’ state, having small cell somata and long processes that extend and retract for the surveillance of the environment to detect danger signals and communicate with neurons and other glial cells. This type of detection is achieved *via* various receptors for neurotransmitters, cytokines and chemokines, such as toll-like receptors (TLRs), receptor for advanced glycosylation end products (RAGE), CD14 and CD36 [182]. When a threat is recognized by microglia, they undergo morphological changes by shortening their processes and enlarging the cell soma and migrate to the site of the ‘danger’.

Astrocytes are large glial cells, abundant in the CNS, that contribute to formation of the blood-brain barrier (BBB) and support neurons by synapse generation, uptake of neurotransmitters and providing ion homeostasis [4, 202, 314]. Recent reports with bulk and single-cell RNA-seq demonstrated the heterogeneity of astrocytes in terms of subpopulation and activation

phenotypes. Many different astrocyte populations have been defined within different regions of the brain, making them diverse in functional and molecular aspects [137]. Like microglia, astrocytes express many pattern recognition receptors (PRRs) as a response to pathogen-associated molecular patterns (PAMPS), such as activation of TLR3 by a virus RNA induces activation of nuclear factor κ-light chain enhancer of activated B cells (NF-κB) and production of pro-inflammatory cytokines [284]. Involvement of microglia and astrocytes in AD pathogenesis will be discussed further below.

1.3.1.1 Inflammation and Aβ

In AD, it is thought that the initial activation of microglia is the presence of Aβ. Soluble oligomers and fibrils of Aβ peptides bind to receptors expressed by microglia resulting in production of inflammatory cytokines such as interleukin (IL) -1 [96, 234], IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF) [234] and tumor necrosis factor (TNF)-α [82], as well as chemokines such as monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 (MIP-1) [191]. These downstream pathways are activated after Aβ peptide is taken up and degraded by several mechanisms. The lysosomal system is one of these and executes several metabolic tasks. Shortly, endocytosed Aβ is delivered to early endosomes where it is sorted and sent to late endosomes destined for a degradation pathway. In the meantime, the Golgi apparatus provides lysosomes with hydrolytic enzymes from the endoplasmic reticulum (ER) and these lysosomes fuse with late endosomes where proteolysis occurs. After degradation, molecules are disposed either to the cytosol or to other organelles. Lysosomal peptidases are cathepsin-B and endothelin-converting enzyme 2 (ECE-2), shown to be involved in Aβ degradation [100].

Another clearance process is the autophagy pathway which is important for the turnover of cellular organelles and degradation of Aβ. A study demonstrated that microglia degrade Aβ with autophagic processes, and when autophagy is disrupted activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome becomes excessive, causing neuronal death [56]. Similar to macrophages, microglia express a variety of receptors for the recognition and phagocytosis of apoptotic cells, pathogens and aggregated proteins. Axl and Mer are cell surface receptor tyrosine kinases and known to recognize so called “eat me” signals. Briefly, apoptotic cells have externalized phosphatidylserine (PS) on their plasma membrane and PSs are tagged with growth arrest-specific 6 (Gas6) for binding to Axl and Mer in an indirect binding fashion, resulting in engulfment and enzymatic degradation of apoptotic cells [167]. Another mechanism includes complement proteins, C1q, C3b and C4, which are found on the apoptotic cell membrane to take care of the cell or on synapses for synaptic pruning, and bind to complement receptors CR1, CR3 and CR4 expressed on microglia [307]. Interestingly, a study showed that Aβ also contains PSs, explaining how microglia can engage with Aβ using the Gas6-PS bridge [127]. Activated microglia migrate to the sites of plaques and initiate

phagocytosis of Aβ in early AD as shown in animal models [196]. However, long-lasting microglial activation leads to exhausted microglia due to excessive APP processing and Aβ production [294]. A study suggested the impairment in microglial function by showing decreased levels of Aβ-binding scavenger receptors and Aβ-degrading enzymes [114]. Another hypothesis is that Aβ oligomers, due to their protein structure and hydrophobic nature, are more likely to bind to the phospholipid bilayer and create pores which disrupt the cell membrane of glial and neuronal cells. In early stages of AD, Aβ species binding to microglial cell membranes could explain dysfunctions in microglia [321]. Fibrillary Aβ taken up by microglia may not perform a successful degradation [59] and may accumulate within the lysosomes due to the acidic environment, causing formation of compact dense core Aβ and microglial death [12], contributing to the plaque expansion. A recent study showed that loss of Axl and Mer receptors in an AD mouse model significantly decreased the ability of microglia to recognize and take up amyloid plaques, resulting in fewer dense core plaques, suggesting the role of microglia in dense core plaque formation [127]. Altogether these studies demonstrate the complex and contrasting roles of microglia in AD pathogenesis, showing both beneficial and detrimental actions of microglia (Fig. 3). Several genome-wide association studies (GWAS) identified common risk factors that are enriched in myeloid cells such as CR1, TREM2, CD33 and ephrin type-A receptor 1 (EPHA1), indicating a role of microglia in development of sporadic AD [213].

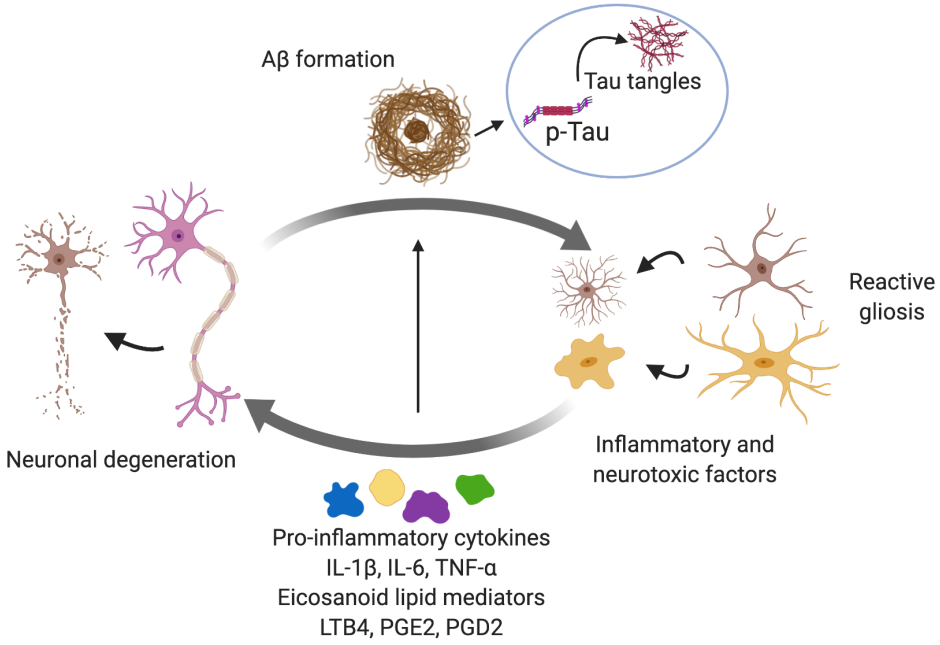

Figure 3: A vicious circle connects neuroinflammation, neurodegeneration and plaque formation in Alzheimer's disease. Presence of Aβ peptides induces activation of microglia and astrocyte resulting in increased production and secretion of pro-inflammatory protein and lipid mediators. In return, further glial activation causes release of toxic radicals which damage neurons and cause neuronal death. Eventually, cellular damage aggravates inflammation by recruiting more immune cells, eventually leading to Aβ and tau tangle formation. This image is created in BioRender.com.

Similar to microglia, astrocytes surround, take up and degrade Aβ plaques. They are the most abundant CNS-resident cells of neuro-ectodermal origin and involved in several functions in the brain. The increased levels of Aβ in the brain results in functional and morphological changes of astrocytes including the calcium signalling, glutamate uptake and Aβ clearance. Different proteases such as neprilysin (NEP), insulin-degrading enzyme (IDE), ECE-1 and ECE-2 have been reported to contribute to the enzymatic cleavage of monomeric and oligomeric forms of Aβ, and in LOAD these enzymes displayed an inactive form making them dysfunctional [76]. Furthermore, surface receptors (for acetylcholine (ACh) and glutamate) expressed by astrocytes can bind to Aβ and increase inflammatory mediators which can result in elevated intracellular calcium levels and disrupt neuron-glia signal transmission [166]. ApoE is produced in the liver peripherally and by astrocytes in the CNS. The main roles of ApoE include to provide repair in the brain, regulate glucose metabolism and to transport lipids. A study on mice lacking ApoE in astrocytes showed a failure to clear Aβ [151], indicating that release of ApoE due to astrocyte activation stimulates microglial phagocytosis of Aβ. Another study demonstrated less effective elimination of Aβ plaques by astrocytes expressing the *ApoE4* allele compared to astrocytes expressing the *ApoE3* allele [288].

1.3.1.2 Inflammation and tau

The role of inflammation in tau pathology should not be forgotten since NFTs represent the second pathological hallmark of AD. Similar to Aβ, tau can induce an immune response in the brain and inflammation has been shown to modulate tau pathology [164]. In a mouse model, increased levels of IL-1β stimulate the production of other cytokines, such as IL-6 which in turn stimulates the activation of cyclin-dependent kinase 5 (CDK5), involved in hyperphosphorylation of tau [247]. In addition, binding of Aβ to the calcium-sensing receptor (CaSR) in human astrocytes resulted in altered intracellular signalling and induction of tau hyperphosphorylation [55]. Under physiological conditions, there is a balance in tau homeostasis where phosphorylation and hyperphosphorylation are controlled. In human *post mortem* AD brains, the activities of CDK5 and p38/mitogen activated protein kinase (p38/MAPK) were elevated and tau dephosphorylating phosphatases were decreased [104]. Contribution of microglia to tau pathology has been shown in a tauopathy mouse model, in which an immunosuppressant resulted in reduced microgliosis and tau propagation [339]. Also, tau was shown to induce NLRP3 inflammasome activation similar to Aβ, leading to IL-1β and IL-8 production [131]. IL-8 stimulates kinases that are involved in tau hyperphosphorylation [224]. However, during tau propagation, as an early phenomenon, neurons try to cope with tau by increasing the interaction of the C-X3-C motif chemokine ligand 1 (CX3CL1) with the C-X3-C motif chemokine receptor 1 (CX3CR1) expressed on microglia in order to limit excessive activation of microglia [162]. Supporting this, CX3CL1 - CX3CR1 signalling is decreased in microglia upon aging and AD pathology [144].

Initially, tau oligomers are formed intracellularly and upon hyperphosphorylation misfolded tau fails to stabilize the microtubules, resulting in self-aggregation and NFT formation. One of the mechanisms involved in tau release is exosomes mediating tau release and synaptic tau transmission [328]. When tau is not degraded fully into a non-toxic form by microglia, they can be released within exosomes and promote tau seeding in other cells [121]. Similar to Aβ, tau can be taken up by astrocytes, involving heparin sulphate proteoglycans (HSPGs) and low-density lipoprotein receptor 1 (LRP1) that are expressed on the cell surface of astrocytes for lysosomal degradation. However, the uptake of tau can contribute to its spreading and to disruption of astrocyte functions by affecting Ca^{2+} signalling and ATP release, which eventually alters the support for neurons and maintenance of several other functions [241]. A recent study reported that induction of tau accumulation in astrocytes located in the hilus region of the hippocampus, caused mitochondrial dysfunction, neuronal cell death and memory deficits, highlighting the functional consequences of astrocytic tau pathology [252]. Another recent article reported that tau aggregates in the form of exosomes enter cells by the endo-lysosomal system. Due to the high acidity and lysosomes aiming to digest exosomes, both exosome and lysosome membranes are ruptured, and tau is released into the cytosol, causing more tau deposition [243]. These studies further indicate the critical role of glial cells during the uptake of protein aggregates that is initiated for clearance purposes but instead aggravates protein accumulation (Fig. 3).

1.4 Resolution of inflammation

Inflammation is a protective process to fight harmful stimuli, providing homeostasis and repair. However, when its magnitude or duration is dysregulated, it can contribute to several different pathologies (Fig. 4). Inflammation needs to be terminated and drugs have been designed to reduce pro-inflammatory mediators, such as NSAIDs and glucocorticoids. The concept of resolution in inflammation is not new [225] and recent studies have changed our understanding in that resolution of inflammation is an active process which involves biosynthesis of active mediators that promote homeostasis [272]. The resolution process is explained to consist of *i)* termination of immune cell infiltration to the site of injury/infection, *ii)* switch to an anti-inflammatory phenotype, *iii)* phagocytosis of cell debris, inflammatory cells and harmful stimuli, *iv)* upregulation of pro-resolving LMs and *v)* regeneration/repair of affected tissue [39]. Owing to the importance of this stage of inflammation, new drugs that can promote endogenous pro-resolving pathways can be developed, representing a novel strategy to regulate inflammation and restore function without suppressing beneficial effects of inflammation.

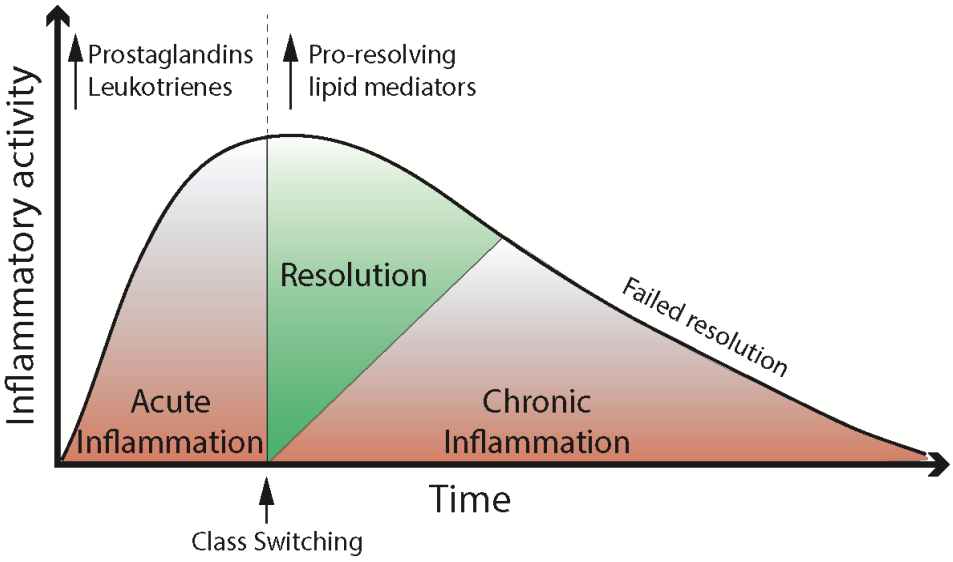

Figure 4: Acute inflammation is a self-limiting inflammatory response: the ideal outcome is resolution of inflammation. From the beginning till resolution, immune cells start with synthesis of pro-inflammatory factors and switch to pro-resolving mediators. Failure of resolution leads to chronic inflammation.

1.4.1 Phospholipids

Phospholipids are important sources for polyunsaturated fatty acids (PUFAs) that are used for the generation of potent bioactive LMs. Phospholipids are polar lipids containing hydrophobic hydrocarbon residues and hydrophilic head group. Glycerophospholipids (GPL) consist of two fatty acids (FAs) that are esterified at the sn-1 and sn-2 positions of the glycerol backbone, making this portion hydrophobic. The sn-3 site contains a phosphate group that is modified with an alcohol, making this portion hydrophilic. GPLs are named according to the hydrophilic group attached to the phosphate group and to date four main groups have been identified: ethanolamine, inositol, serine and choline. Phosphatidylethanolamine (PE), phosphatidylinositol (PI), PS and phosphatidylcholine (PC) are the most studied phospholipids. There are also lysophospholipids whose FA chain has been cleaved from the sn-1 or the sn-2 site. Sphingolipids have the long-chain amino alcohol sphingosine, instead of a glycerol backbone, and this is esterified to a FA and a phosphate group. Sphingomyelin (SM) as a sphingolipid, contains choline attached to its head group [2]. Phospholipids form the lipid bilayer of cell membranes and intracellular organelles, rendering the membranes selective and permeable barriers. Biological membranes are also embedded with cholesterol, proteins and glycolipids. The function and integrity of membranes rely on their phospholipid composition. Phospholipids mostly contain unsaturated FAs at sn-2 site, such as AA, linoleic acid, α-linolenic acid or EPA, while the sn-1 site contains saturated FAs, such as palmitic acid [340]. Besides being structural lipids in the cellular membranes, phospholipids can act as LMs such as platelet-activating factor that induces inflammation [315], PUFAs are substrates for pro- and anti-inflammatory LMs in inflammation and its resolution [310], and diacylglycerols are

secondary messengers in cell signalling [57]. Synthesis of PC and PE is observed within the cytosol after addition of choline or ethanolamine head groups to the phosphatidic acid [320]. Synthesis of PS occurs in ER by exchanging the head groups from choline or ethanolamine to serine in the presence of PC and PE, using PS synthase I or synthase II, respectively [319]. Biosynthesis of PI occurs in the ER, where cytidine diphosphate diacylglycerol (CDP-DAG) is attached to inositol with CDP-DAG phosphatidyl transferase [91]. SM synthesis starts in ER first and is finished in the Golgi apparatus by a series of enzymatic reactions involving ceramide and PC as substrates [180]. In brain, the membranes have distinct and stable phospholipid composition, exhibiting high concentration of PE and PS in organelle membranes and high concentrations of PC and SM in the plasma membranes [88]. For the biosynthesis of phospholipids, the majority of PUFAs are transported from the gastrointestinal tract, either from the diet or via the liver which produces PUFAs from linoleic and α-linolenic acid [122].

It has been shown that PUFAs esterified to phospholipids are highly susceptible to modification by ROS [28]. ROS can cause non-enzymatic lipid peroxidation, generating oxidized phospholipids that can stimulate both pro- and anti-inflammatory mechanisms [24]. In fact, peroxidised phospholipids are more exposed and a better substrate than native phospholipids for phospholipase 2 (PLA2) hydrolysis [194].

1.4.2 Phospholipases

PLAs are either membrane-associated, present in the cytosol or secreted. They hydrolyze phospholipids at specific ester bonds. There are two main PLAs, phosphodiesterases and acylhydrolases. The structure of a GPL contains a glycerol backbone with two nonpolar FAs are at the sn-1 and sn-2 positions (R_1 and R_2), and the phosphoryl group is attached to a polar head group such as choline, inositol or ethanolamine. Phosphodiesterases catalyze the hydrolysis of the phosphoryl group bond (*e.g.* PLC and PLD), while acylhydrolases, as the name suggests, hydrolyze the ester bonds (*e.g.* PLA1, PLA2 and PLB). PLA1 and PLA2 were named because of hydrolyzing the sn-1 and sn-2 positions yielding FAs and 2-acyl or 1-acyl-lysophospholipids, respectively. PLB on the other hand can hydrolyze both sn-1 and sn-2 positions together [29, 72].

The activity of PLA1 has been found in many cells and tissue such as the brain, muscles, testis and immune cells [115, 117, 235, 263]. There are two different families of PLA1s, the extracellular and intracellular PLA1s. Extracellular PLA1s are found in the blood stream and involved in regulation of high density lipoprotein (HDL) levels by catalyzing hydrolysis of phospholipids and triacylglycerol (TG) [136]. Membrane associated extracellular PLA1s are known for producing lysophosphatidylserine and lysophosphatidic acid which are potent bioactive LMs and act by growth factor-like lipid inducing activation of mast cells, neurite growth, cell proliferation and brain development [143, 269, 336]. The function of intracellular PLA1s, on the other hand, are currently not well known. They may be involved in the

remodeling of phospholipids due to their catalysis activity at the sn-1 position and consecutive acylation of the same lysophospholipids. Intracellular PLA1s have a preference for certain phospholipids (PE and phosphatidic acid (PA)) over others (PS and PC) [214].

PLA2 catalyzes hydrolysis of the ester bond of phospholipids at the sn-2 position, i.e. the position where PUFAs are mainly found. Six different PLA2s have been defined: cytosolic PLA2 (cPLA2), calcium-independent PLA2 (iPLA2), lysosomal PLA2, platelet-activating PLA2, adipose PLA2 and secreted PLA2 (sPLA2). Each of these PLA2s are involved in variety of lipid metabolism and disease progression depending on their expression pattern in different cells and tissues [210]. To this date, 11 sPLA2 have been identified in mammals, and they are highly stable due to their disulphide bonds and contain a Ca^{2+} binding site. In the extracellular space, these secreted enzymes catalyze phospholipids in the presence of Ca^{2+} and release PUFAs and lysophospholipids. In addition to cellular phospholipids, they act on microvesicles, lipoproteins and membranes of microbes [209]. Each isoform of sPLA2s has specific preference for sn-2 FAs and polar head groups, resulting in synthesis of pro- and anti-inflammatory LMs, membrane remodeling and alterations in extracellular phospholipids [211]. Even though they are secreted enzymes, before their release to the outer space they can also hydrolyze sn-2 sites intracellularly and release PUFAs [206]. Some sPLA2s cannot hydrolyze the cell membrane phospholipids but act on bacterial phospholipids as a host defence [150].

There are six members of the cPLA2 family that have distinct enzymatic properties and tissue expression [92, 168]. Among these isoforms, cPLA2α is a well-established form that is widely expressed in mammalian cells and tightly regulated by transcriptional and posttranslational processes [169, 221]. Its activity depends on intracellular calcium levels and phosphorylation by protein kinases upon cell stimulation [171]. When intracellular Ca^{2+} is elevated, cPLA2α is translocated from the cytosol to the intracellular membrane, and Ca^{2+} binding increases its hydrophobicity and facilitates penetration of the enzyme into the membrane bilayer [116, 216]. However, Ca^{2+} alone is not sufficient for the catalytic activity of cPLA2α which is regulated by phosphorylation of the Ser residues at 505, 515 and 727 by protein kinases [71, 316]. There is accumulating evidence that cPLA2α has a preference for the hydrolysis of AA at the sn-2 position and for the production AA-derived LMs [62, 170]. Due to different PUFAs released by cPLA2α activity, it is difficult to predict the physiological function of cPLA2α that can yield downstream of both pro- and pro-resolving LMs [168].

iPLA2 is found in the cytosol, ER, mitochondrial membrane or the inner part of the cell membrane and does not require Ca^{2+} for its activity [248]. iPLA2s don't show substrate specificity and can hydrolyze sn-1 acyl chains as well [173]. They are involved in phospholipid acyl remodeling, PUFA release for signalling and Ca^{2+} homeostasis [14, 169, 248]. Under physiological conditions iPLA2 located in cytosol is translocated to the intracellular membranes of organelles upon stimulation [268]. During oxidative stress, iPLA2 found in ER

and the mitochondrial membrane is involved in repair of lipid peroxidation and prevention of cell death [66].

1.4.3 Pro-resolving lipid mediators

In recent years, several pro-resolving LMs have been discovered and with lipidomics analysis their molecular structure and origin (PUFAs) have been identified [270]. Resolution begins with an eicosanoid signalling pathway that switches the conditions from a pro-inflammatory to a pro-resolution state by distinct mediator synthesis. At the beginning of an acute inflammatory response, arachidonic acid (AA)-derived mediators (prostaglandins and leukotrienes) are upregulated, affecting vascular permeability and stimulating polymorphonuclear (PMN) cell recruitment [172] [280]. The increase in the production of these pro-inflammatory lipids is ultimately stopped, and the production of pro-resolving LMs such as lipoxins starts. This is viewed as a "class-switching" mechanism (see below). The pro-resolving LMs include the resolvins, neuroprotectins, lipoxins and maresins. The resolvin D (RvD) series mediators, neuroprotectins and maresins are biosynthesized from docosahexaenoic acid (DHA), and the RvE series mediators are derived from eicosapentaenoic acid (EPA) [271]. Lipoxins are derived from AA [261].

1.4.3.1 Lipoxins

Lipoxins are anti-inflammatory and pro-resolving LMs which were identified for the first time using human leukocytes in the 1980s by Serhan et al [277]. They are derived from AA which yields crucial metabolites important for inflammation, such as prostaglandins (PGs) and leukotrienes (LTs). There are two types of lipoxins, LXA_4 and LXB_4, and there are two main pathways for their production utilizing lipoxygenases (LOXs) [278] (Fig. 5). The first route of synthesis involves 15-lipoxygenase (LOX)-1 and -2 which oxygenize AA into 15S-hydroperoxy eicosatetraenoic (15S-HpETE), which is further converted to 5S, 15S-diHpETE by 5-LOX and finally into lipoxins by epoxidation and hydrolysis. The second pathway involves catalysis of AA by 5-LOX into LTA_4, which is converted into lipoxins by 12/15-LOX [277]. There is 3rd route that is dependent on aspirin and generates 15-epi-LXA_4 by the activities of cyclooxygenase-2 (COX-2) and 5-LOX [61] (Fig. 5). Lipoxins are synthesized at the site of inflammation and exert their pro-resolving effects by binding to a G protein-coupled lipoxin A4 receptor (ALX)/formyl peptide receptor 2 (FPR2) [281]. When lipoxins interact with ALX/FPR2, the receptor is internalized to the perinuclear region which initiates anti-inflammatory actions [13]. Lipoxins stimulate internalization of ALX/FPR2 from cell surface to endosomes and to lipid rafts which is critical for phagocytosis of apoptotic cells through actin

rearrangement [181, 251]. Lipoxins also terminate neutrophil infiltration [54], downregulate CD11b expression [83], decrease NK-κB activation and suppress IL-8 secretion upon binding to ALX/FPR2 [138]. The 'class-switching' mechanism is one of the most important processes and occurs prior to the beginning of resolution, when the pro-inflammatory phenotype switches to a pro-resolving phenotype of the immune cells. In a murine-pouch model, the levels of different LMs were assessed at different time points after injection of TNF-α [172]. First, the levels of the pro-inflammatory LM LTB_4 were elevated and then PGE_2 followed. Thereafter, a marked increase in LXA_4 was observed and persisted at high levels, while PGE_2, LTB_4 and neutrophil numbers dropped. This study indicated PGE_2 as the inducer of pro-resolving pathways. Also, these data defined resolution of inflammation as an active process and acute inflammation is self-controlled system [172].

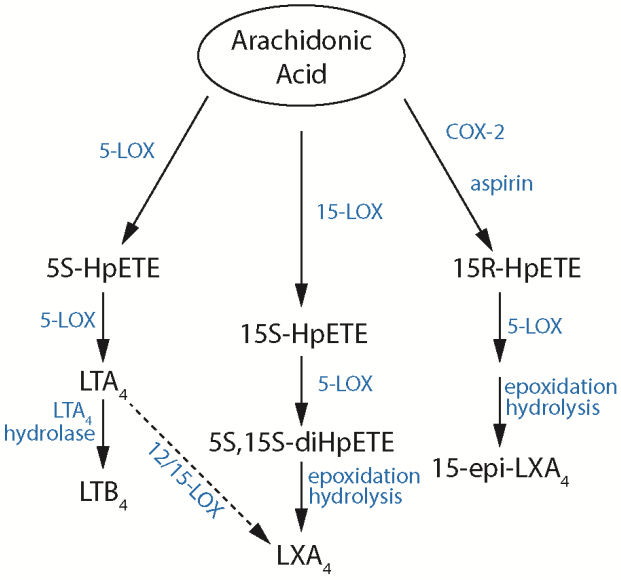

Figure 5: Biosynthesis of lipoxins and other AA metabolites.

1.4.3.2 Resolvins

Resolvins are categorized as D-series and E-series due their parent substrates DHA and EPA, respectively. Similar to lipoxins, resolvins have potent immunoregulatory actions which are protective [279].

Resolvin D-series: The synthesis of RvD1 (Fig. 6) begins with oxygenation of DHA by 15-LOX-1 into 17S-hydroxy-DHA (17S-HpDHA) which is oxygenated by 5-LOX and the following enzymatic epoxidation and hydrolysis yields RvD1. There are also RvD epimers (AT-RvDs) which are synthesized in the presence of aspirin by the enzymatic activity of COX-2 and 5-LOX [301]. GPR32 and ALX/FPR2 mediates the activities of RvD1. In an LPS-induced acute lung injury model, RvD1 down-regulated the activation of signalling pathways including NK-κB and MAPKs that regulate the release of pro-

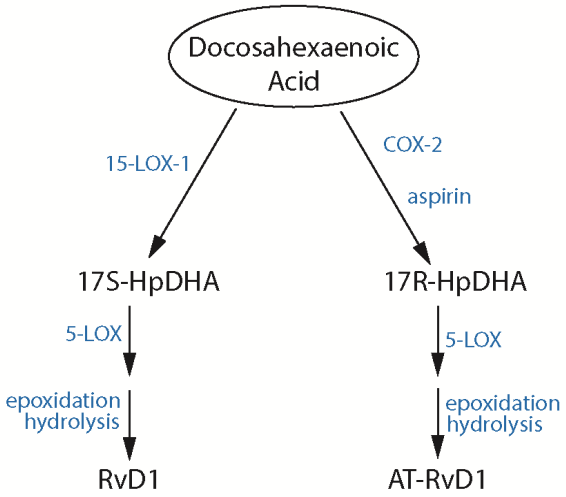

Figure 6: Biosynthesis of RvD1 and AT-RvD1

inflammatory cytokines and the expression of inducible nitric oxide synthase (iNOS). A protective role of RvD1 in lung injury was shown to be mediated by binding to ALX/FPR2 [324]. Interaction of RvD1 with GPR32 demonstrated changes in specific microRNAs (miRNAs) that are involved inflammation and resolution [249, 285]. Potent pro-resolving actions of RvD1 include the induction of phagocytosis, production of IL-10, and reduction of ROS and pro-inflammatory cytokines [39]. A study on rheumatic arthritis demonstrated increased production of LXA_4 upon treatment with RvD1 [220].

Resolvin E-series: RvE1 is synthesized from EPA by the enzymatic activity of cytochrome P450 (CYP450), or acetylated COX-2 in the presence of aspirin, yielding 18R-HEPE which is further catalyzed by 5-LOX [7] (Fig. 7). Similar to other pro-resolving LMs, RvE1 stops neutrophil infiltration [274], decreases dendritic cell migration, reduces IL-12 production [6], inhibits NF-κB activation [39] and increases phagocytosis by macrophages [120]. Chemokine-like receptor-1 (ChemR23) and leukotriene B4 receptor (BLT1) (also known as LTB_4 receptor) were identified as mediators of RvE1 induced activities [6, 8]. RvE1 binds to BLT1 as a partial agonist and inhibits LTB_4-induced pro-inflammatory signals such as immobilization of Ca^{2+} and NF-κB activation [8]. In addition, administration of RvE1 increased LXA_4 production in a model of allergic airway inflammation [108].

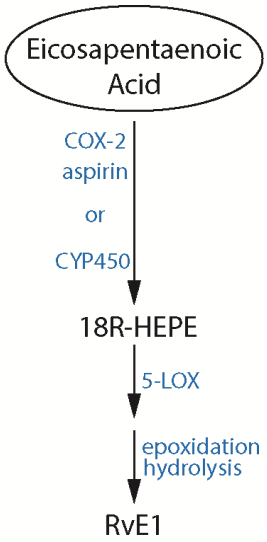

Figure 7: Biosynthesis of RvE1

1.4.3.3 Maresins

Maresins are derived from DHA, with a synthetic route where 12-LOX oxygenates DHA into 14S-HpHDHA followed by epoxidation and hydrolysis [282] (Fig. 8). Maresin 1 (MaR1) was the first maresin to be identified and its actions involve down-regulation of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) [218], inhibition of NF-κB gene expression [186], limiting neutrophil infiltration, stimulation of tissue regeneration and uptake of debris [304]. Recently, leucine-rich repeat containing G protein-coupled receptor 6 (LGR6) was reported as the receptor for MaR1 in human phagocytes by Chiang et al. after screening approximately 200 GPCRs [53]. Unlike other GPCRs (the typical ligand receptor interaction), LGR6 domains do not signal alone but require interaction with other domains [325]. MaR1 induces efferocytosis and phagocytosis in an LGR6-dependent manner. Also, MaR1 decreased IL-8 levels, resulting in reduced

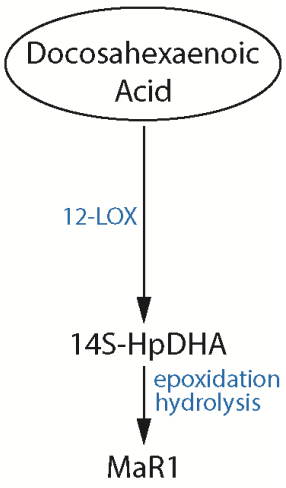

Figure 8: Biosynthesis of MaR1

neutrophil chemotaxis [53]. In the same year, Han et al. identified another receptor for MaR1, retinoic acid-related orphan receptor α (RORα), which is an important modulator for polarization of macrophages in non-alcoholic steatohepatitis (NASH) pathogenesis. RORα is a nuclear receptor and crucial for switching the macrophage phenotype from a pro-inflammatory to an anti-inflammatory state. The beneficial effects of DHA on NASH had been shown previously and after testing metabolites of DHA, Han et al. showed that MaR1 was a specific endogenous ligand for RORα. Interestingly, the interaction of MaR1 with RORα increased 12-LOX expression which also elevated the MaR1 production, indicating an autoregulatory circuit in the liver [103].

1.4.3.4 Neuroprotectins

Neuroprotectin D1 (NPD1) was the first LM to be identified as neuroprotective and shown to be derived from DHA [21, 208]. Its synthesis (Fig. 9) involves two pathways, where the first route includes oxygenation of DHA to 17R-HpDHA by COX-2 in the presence of aspirin, followed by epoxidation and hydrolysis yielding AT-NPD1 [20]. The second pathway consists of oxygenation of DHA by 15-LOX-1 into 17S-HpDHA followed by epoxidation and hydrolysis [208]. NPD1 was shown already in 2005 to provide neuroprotection in a brain ischemia-reperfusion model [185]. In both the experimental stroke model and *in vitro*, NPD1 reduced leukocyte infiltration, COX-2 expression, and IL-1β-induced NF-κB activation [185]. In an *in vitro* model of AD, NPD1 also upregulated expression of B-cell lymphoma xl (Bcl-xl), 2 (Bcl-2) and Bcl-2-related protein A1(Bfl-1), which are neuroprotective and anti-apoptotic Bcl-2 family proteins, and downregulated pro-apoptotic Bcl-2-associated X protein (Bax) and Bcl-2-interacting killer (Bik) [177]. The receptor for NPD1 was identified recently as the parkin-associated endothelin-like receptor/Pael-R (GPR37) by Bang et al [15]. Binding of NPD1 to GPR37 induced an increase in intracellular Ca^{2+} levels, which is required for macrophage phagocytosis, and also reduced the levels of IL-1β levels while increasing IL-10 and TGF-β levels, thus favoring an anti-inflammatory phenotype [15].

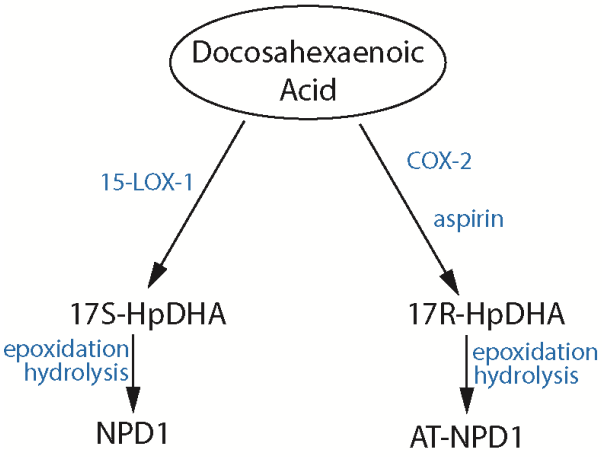

Figure 9: Biosynthesis of NPD1 and AT-NPD1

1.4.4 Leukotrienes and prostaglandins

1.4.4.1 Leukotrienes

Leukotrienes (LTs), as the name indicates, are produced by leukocytes and exert their functions on different target cell types [99]. There are two types of LTs: LTB_4 and cysteinyl-LTs (cys-LTs) which include LTC_4, LTD_4 and LTE_4. Their synthesis (Fig. 10) starts with catalysis of AA into 5-hyroperoxyeicosatetraenoic acid (5-HETE) by 5-LOX and the accessory 5-lipoxygenase-activating protein (FLAP) and further into LTA_4. LTA_4 is an unstable metabolite which can be catalyzed either into LTB_4 by LTA_4 hydrolase or into cys-LTs by LTC_4 synthase [87, 199, 238]. LTB_4 signals through BLT1 and BLT2, while cys-LTs bind to CysLT1, CysLT2 and CysLTE receptors [215]. GPR17 [60], GPR99 [139], PPAR [232] and P2Y12 [233] can also mediate activities of cys-LTs. Cys-LTs stimulate eosinophil recruitment during inflammation, induce chemotaxis and smooth muscle contraction, and increase vascular leakage [45, 77]. Due to their role in pro-inflammatory pathways, to prevent their actions inhibitors of 5-LOX or CysLT receptors are commonly used in clinical practice [3, 132].

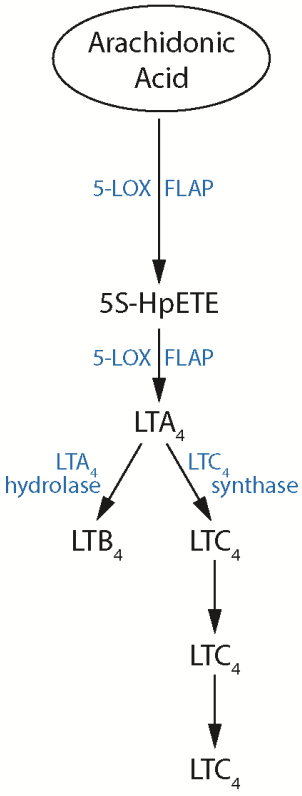

Figure 10: Biosynthesis of leukotrienes

LTB_4 is a potent chemoattractant and one of the first signals that attract immune cells to the site of inflammation. The main cellular sources of LTB_4 are immune cells but non-immune cells can also produce LTB_4 without the presence of the enzymes. This process is called transcellular biosynthesis where intermediate metabolites of LTs are released to the extracellular space and taken up by other cells to produce LTB_4 [257]. The LTB_4-BLT1 signalling axis is crucial for neutrophil migration [1, 160], phagocytosis, secretion of lysosomal enzymes and neutrophil granulation [149]. LTB_4 enhances NF-κB activation and contributes to release of cytokines such as IL-1β, IL-6 and TNF-α, and chemokines such as CXCL1, CCL2 and MCP-1 [125, 256]. LTB_4 *via* BLT1 and BLT2 receptors also increases intracellular Ca^{2+} flux and activation of phospholipases that further stimulate LTB_4 production [74]. Continuous LTB_4 synthesis can be detrimental for the host defence.

1.4.4.2 Prostaglandins

Prostaglandins (PGs) are formed by sequential oxygenation of AA by COX-1 and COX-2 to PGG_2 and PGH_2 intermediate products, which are further catalysed to PGE_2, $PGF_{2\alpha}$, PGD_2 and PGI_2, by PGE, PGF, PGD and prostacyclin synthases, respectively [290] (Fig. 11). PGs exert their actions *via* the PGD receptor (DP), PGE receptors (EP1, EP2, EP3 and EP4), PGF receptor

(FP) and the PGI receptor (IP) [217]. These receptors are coupled to a variety of intracellular signalling pathways, and therefore, PGs have multiple functions that in one context may stimulate and in another context, inhibit cellular mechanisms.

PGE_2 is the most abundant PG, and its actions are limited to the microenvironment where the cells produce it due to the rapid conversion into an inactive form (15-keto PGE_2) [341]. PGE_2 is involved in the initiation of acute inflammation, binding to EP2 and EP4 which induces an increase in cyclic adenosine monophosphate (cAMP) levels, and vasodilation resulting in neutrophil infiltration [119, 142]. The PGE_2-EP3 interaction activates the phosphoinositide 3-kinase (PI3K) pathway resulting in release of IL-6 that promotes neutrophil recruitment [205]. These events indicate the role of PGE_2 in acute inflammation, however, it has also anti-inflammatory functions which makes PGE_2 important for regulation of the inflammatory process [46]. Both PGE_2 and PGD_2 induce the switch in AA catalysis from LTB_4 to LXA_4 production and thereby initiating the synthesis of pro-resolving LMs [273].

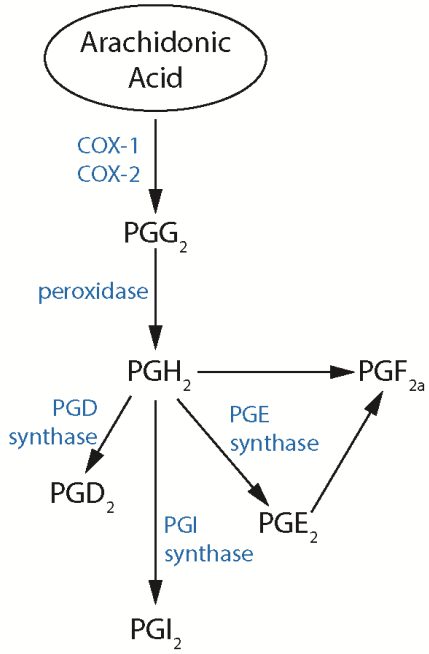

Figure 11: Biosynthesis of prostaglandins

PGD_2 is a ligand for two receptors, DP1 and DP2 [287]. The function of PGD_2 is complex since it can either promote or suppress the inflammatory response depending on which receptor it binds to in each context. Similar to PGE_2, PGD_2 is also involved in the initiation and progression of inflammation by inducing leukocyte migration, production of pro-inflammatory cytokines, causing oedema and increase the local blood flow [85, 240]. However, PGD_2 also exerts anti-inflammatory effects *via* DP receptors by decreasing neutrophil infiltration and dendritic cell migration [102], indicating that PGD_2 is important for both the beginning of inflammation and the resolution of inflammation [94].

$PGF_{2\alpha}$ is one of the most abundantly produced PG at the sites of inflammation [264]. It has two identified receptors, FPA and FPB [242] and is involved in female reproduction [298], brain injury [258] and pain [157]. Elevated levels of $PGF_{2\alpha}$ have been described in cardiovascular disease, obesity, diabetes, rheumatic disease and brain ischemia, triggering production of pro-inflammatory cytokines [18, 110, 111, 258]. The interaction of $PGF_{2\alpha}$ with its receptors induces IL-1β production *via* NF-κB activation and the production of IL-6 *via* ERK, PI3K and p38, indicating that $PGF_{2\alpha}$ modulates various signalling pathways as a pro-inflammatory LM [332].

1.4.5 Receptors for lipid mediators

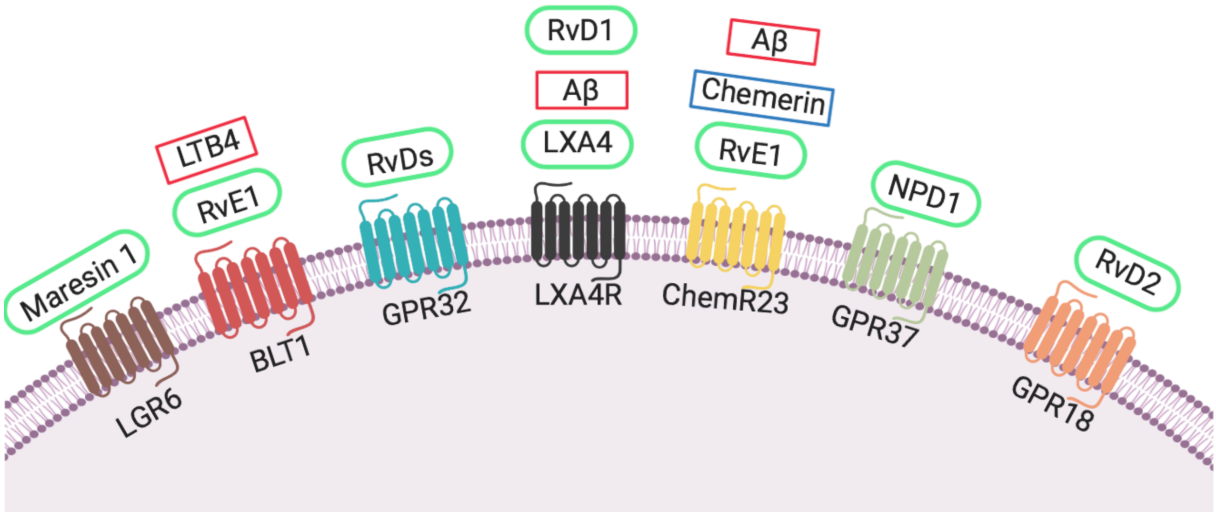

Figure 12: G-protein-coupled receptors with their corresponding ligands i.e. pro-resolving lipid mediators, leukotriene B4, Aβ and chemerin

1.4.5.1 ALX/FPR2

ALX/FPR2 is a type of GPCR expressed by neutrophils, lymphocytes, monocytes, macrophages, epithelial cells, neurons and glia [175, 197]. It interacts with LXA_4, 15-epi-LXA_4, RvD1, AT-RvD1, RvD3 and Annexin 1 (AnxA1) to transmit pro-resolving intracellular signals [11, 51, 109, 153, 154]. The activities mediated by ALX/FPR2 include decreased leukocyte migration, induced efferocytosis, apoptosis of granulocytes, reduced phosphorylation of MAPKs and inhibition of PLA2 activity [17, 98, 181, 230]. However, ALX/FPR2 signalling also involves pro-inflammatory activities due to certain ligands *i.e.* $A\beta_{42}$, mitochondrial peptides, prion protein and microbial peptides [44]. Interaction of these peptides with ALX/FPR2 promotes phosphorylation of MAPK signalling, Ca^{2+} mobilization, synthesis of cytokines (*i.e.* IL-8, IL-6 and TNF-α), chemotaxis, NF-κB activation and superoxide production [33, 165, 267]. These latter ligands are chemotactic agonists for the receptor and their binding to ALX/FPR2 followed by internalization of the receptor-peptide complex leads to activation of the immune cell [65]. Receptor-mediated uptake of peptides is followed with endocytosis and recycling of the receptor back to the cell surface. This process at early phases of inflammation is beneficial, but prolonged exposure causes accumulation of the receptor-peptide complex within the cell contributing to protein aggregation [335].

1.4.5.2 ChemR23

ChemR23 is a GPCR with two identified ligands, the peptide chemerin [331] and RvE1 [274]. It is expressed on endothelial cells, monocytes, macrophages, natural killer cells, dendritic cells, neurons and glial cells [141, 231, 260, 327]. As a chemoattractant, chemerin modulates

chemotaxis and infiltration of immune cells to the site of inflammation *via* ChemR23 during the early stage of inflammation [322]. However, the pro-inflammatory chemerin can be cleaved by serine or cysteine proteases generating anti-inflammatory chemerin fragments. These proteases are released from macrophages and apoptotic cells at the end of an inflammatory response in order to induce pro-resolving functions [253], demonstrating both pro- and anti-inflammatory roles of chemerin. On the other hand, the interaction between RvE1 and ChemR23 is known to trigger only pro-resolving actions, such as intracellular Ca^{2+} release, reduction of cAMP levels, limiting pro-inflammatory cytokine production, down-regulation of NF-κB, phosphorylation of Akt signalling and increased phagocytosis [130].

1.4.5.3 BLT1

BLT1 has two ligands with high affinity, LTB_4 and RvE1 [8, 338]. It is expressed in the spleen, heart, bone marrow, brain, muscle and liver, with the highest expression in leukocytes, macrophages, neutrophils, neurons and glial cells [81, 337]. The major activities of LTB_4 are mediated by BLT1. Using $BLT1^{-/-}$ mouse models, the LTB_4-BLT1 axis was found to stimulate iCa^{2+} flux, neutrophil chemotaxis and recruitment [303]. LTB_4-BLT1 signalling is important for protection of the host against invasion by activating and recruiting immune cells [204, 237]. However, this interaction also has pathological roles in inflammatory diseases. Macrophages expressing BLT1 accelerate plaque formation in arteries as well as NF-κB activation and cytokine production [297]. In murine models of peritonitis and bronchial asthma, BLT1 deficient mice showed reduced infiltration of immune cells and attenuated symptoms of disease [303, 308]. In dermatitis, psoriasis and arthritis, both BLT1 deficiency and BLT1 antagonists resulted in beneficial effects by reducing an excessive inflammatory response [145, 228, 299], indicating the involvement of LTB_4-BLT1 axis in neutrophil accumulation that causes lesions. In 2007, Arita et al. showed that RvE1 as partial agonist, binds to BLT1 and blocks LTB_4-induced actions such as Ca^{2+} mobilization and NF-κB activation [8]. RvE1 decreases neutrophil trafficking and superoxide release in *in vitro* and *in vivo* models [9, 107]. Interestingly, recent work by Yang et al. showed that RvE1-ChemR23 interaction resulted in phosphorylation of BLT1 by β-adrenergic receptor kinase (BARK1) and internalization that and prevention of LTB_4-induced actions [334].

1.4.5.4 GPR18

GPR18 is expressed in the spleen, testis, bone marrow, lymph nodes, brain and immune system, with expression on leukocytes, monocytes, macrophages and microglia [50, 90, 193]. RvD2 activates GPR18 and exerts pro-resolving actions by inducing phagocytosis of apoptotic cells and microbes. The RvD2-GPR18 interaction also alters the phenotype of macrophages from a pro-inflammatory phenotype to an anti-inflammatory by elevating the expression of anti-inflammatory proteins CD206 and CD173. This signalling also decreases neutrophil infiltration

and induces efferocytosis [50]. In a model of peritonitis, RvD2-GPR18 interaction showed decreased NLRP3 inflammasome activation [176]. N-arachidonoylglycine (NAgly) is another ligand for GPR18 which triggers pro-resolving pathways such as reduction of leukocyte migration and apoptosis of immune cells [40].

1.4.5.5 GPR32

GPR32 was identified together with ALX/FPR2 as receptors for RvD1 in human macrophages [153]. Binding of RvD1 to GPR32 stimulates phagocytosis and clearance of cell debris [154]. RvD1 also protects endothelial cell integrity *via* GPR32 [48]. GPR32 is expressed by neutrophils, macrophages, epithelial cells, lymphocytes, neurons and microglia [123, 219, 266, 313, 342]. Not only RvD1 but also RvD3, RvD5 and AT-RvD1 can signal through GPR32, exerting pro-resolving actions [52, 69, 227].

1.4.5.6 LGR6

LGR6 is known as a Wnt signalling mediator along with LGR4 and LGR5 that are found in different types of adult stem cells [16]. LGR4-6 receptors bind to secreted protein R-spondins (Rspo1-4) to induce Wnt/β-catenin signalling, resulting in increased cell proliferation and cell migration, important for metastasis [43]. Also, LGR6 was shown to be expressed in tumor-initiating cells in a mouse skin cancer model [126], and can thereby serve as a diagnostic and prognostic marker. LGR6 is expressed by many cell types such as bone marrow cells, stem cells, skin cells, hair cells, neurons and astrocytes [86, 200, 291]. Recently, Chiang et al. reported that LGR6 acts as a receptor for MaR1 in human macrophages and that MaR1-LGR6 interaction increased cAMP levels and induced phagocytosis, chemotaxis and efferocytosis [53].

1.4.5.7 GPR37

GPR37 is highly expressed in the brain by oligodendrocytes, neurons and astrocytes [184, 333], as well as by macrophages [15]. GPR37 is well known as a substrate for parkin, an E3 ubiquitin ligase which is involved in ubiquitination and clearance of misfolded proteins [129]. Mutations in parkin causes loss of function of parkin ligase which results in insoluble intracellular aggregates of GPR37, indicating an association of GPR37 with Parkinson's disease (PD) [146]. GPR37 accumulation has been demonstrated in Lewy bodies in the brains of PD patients [147, 212]. However, GPR37 also has neuroprotective roles where the interaction with neuropeptides, prosaposin and prosaptide, results in protection against oxidative stress and provides cell survival [195]. In 2018, Bang et al. reported that GPR37 can mediate activities of NPD1. Interestingly, GPR37 was not expressed in microglia but in macrophages. The NPD1-GPR37 axis was shown to increase iCa^{2+} flux, induce macrophage phagocytosis, suppress IL-1β expression and stimulate IL-10 and TGF-β production [15].

1.4.6 Enzymes for lipid mediators

1.4.6.1 Lipoxygenases

LOXs catalyze the oxygenation of PUFAs into conjugated hydroperoxides. They are found in mammals and plants and are highly expressed in many cell types due to synthesizing signalling molecules with crucial metabolic and structural roles [156]. There are different LOX isozymes which add a hydroperoxy group at 5, 12 or 15 carbons, explaining their names 5-, 12- and 15-LOX [34]. In both human and rodents, 12- and 15-LOX catalyze AA and yield 12-(S)-HpETE and 15-(S)-HpETE metabolites with different ratios. Therefore, they are commonly called 12/15-LOX [75]. The major substrates for 12/15-LOX are omega-6 PUFAs due their abundance in cells compared to omage-3 PUFAs [42]. 12/15-LOX forms 15-HETE and 12-HETE from AA in a 9:1 ratio [38]. These lipids can induce both pro- and anti-inflammatory signalling pathways. Their binding to PPARγ induces neuroprotective effects [300], and the binding to GPR31 results in activation of ERK1/2 and NF-κB, in turn inducing IL-6 and IL-12 production [97, 124]. Using DHA as substrate, 12/15-LOX yields 17-HDHA and 14-HDHA in equal amounts. The biological functions of these intermediate omega-3 monohydroxy FAs are limited [158]. 12/15-LOX not only oxygenate free PUFAs but also catalyze the esterified PUFAs found in membranes [22]. A study in 2012 showed that 30% of the generated 15-HETE comes from 12/15-LOX oxidation of intact phospholipids in membranes [223]. The products of this enzyme activity are still incorporated in the phospholipid bilayer, and not secreted. They exhibit their effects by protein interactions [222]. 12/15-LOX reside in the cytosol but are also bound to intracellular membranes. iCa^{2+} flux increases the amount of membrane-bound 12/15-LOX by stimulating its translocation and this event elevates the oxygenase activity of PUFAs [36].

5-LOX catalyzes oxygenation of AA into LTs. In a resting cell, 5-LOX is located either in the nuclear membrane or in the cytosol. When cells expressing 5-LOX are stimulated, AA is liberated from the nuclear membrane by cytosolic (c) PLA_2 and membrane-bound FLAP forms a complex with the released AA, facilitating the 5-LOX activity by transferring AA to 5-LOX resulting in LT production [236]. Phosphorylation of 5-LOX modulates export and activity of 5-LOX which is shown to be phosphorylated by p38, ERK2 and protein kinase A (PKA) on Ser-271, Ser-633 and Ser-523, respectively [178, 329, 330]. Elevation of cAMP leads to phosphorylation of Ser-523 which suppresses 5-LOX activity and prevents LT synthesis [84, 178]. Another cellular event affecting the activity of 5-LOX is iCa^{2+}-induced translocation of 5-LOX from the cytosol to the nucleus. However, a study showed that 5-LOX activity is not dependent on iCa^{2+} if there are high levels of AA present [289]. In contrast to 15-LOX, 5-LOX preferentially catalyzes free PUFAs rather than esterified ones [265]. The combined activity of 5-LOX and 12/15-LOX yields lipoxins. This coordinated activity of LOX enzymes may require transcellular interaction of many cell types to exchange intermediate LMs since not all cell types express these LOX combinations required to produce lipoxins [229].

1.4.6.2 Cyclooxygenases

COX enzymes are involved in the synthesis of important LMs, such as PGs, AT-RvD1, AT-NPD1 and RvE1. Although both COX-1 and -2 produce PGs, they are regulated differently. COX-1 is constitutively expressed in mammalian cells, while COX-2 is present at very low levels in mammalian cells and is inducible by different stimuli such as cytokines [113]. COX enzymes are mainly located in the ER membrane, but also found in vesicles, mitochondria and the nucleus [174]. COXs have two different catalytic activities; cyclooxygenase activity and peroxidase activity, which are sequential during the synthesis of PGs. AA is oxygenated by cyclooxygenase activity to PGG2 and then peroxidase activity reduces PGG2 to PGH2 [73]. PGH2 is further catalysed into different PGs by tissue and cell specific synthases. Aspirin inhibits COX activity in a time-dependent manner by acetylating the Ser-530 residue [27]. Covalent modification of the active site by acetylation prevents substrate-enzyme alignment for oxygenation. COX-1 acetylation prevents PGG2 and thereby all PG production. Acetylated COX-2 *via* aspirin is different from COX-1, due to its larger oxygenase active site. COX-2 remains active in the production of oxygenated products but instead of PGG2 production, oxygen insertion occurs in the R rather than S configuration and yields AT-LXA4, AT-RvD1 and AT-NPD1 from AA and DHA substrates that resist inactivation longer [275, 276, 301].

1.4.7 Resolution of inflammation and AD

Aging is a major risk for developing AD and is associated with increased inflammation which may propagate AD pathogenesis. Arnardottir et al. demonstrated that a BalbC mouse model displaying delayed resolution had elevated PMN cell infiltration, failed in clearance of recruited PMNs, and showed a constant increase in pro-inflammatory cytokines and a disturbed production of pro-resolving LMs [10]. In a study by our group on the senescence-accelerated mouse-prone 8 (SAMP8) model, displaying tau hyperphosphorylation, Aβ aggregation, oxidative stress and cognitive impairment [326], there was an upregulation of the receptor, ALX/FPR2, for LXA_4 and RvD1, compared to the senescence-accelerated mouse resistant 1 (SAMR1), whereas the levels of LXA_4 and RvD1 were not altered. Moreover, the levels of L12-LOX, the enzyme involved in LXA_4 and RvD1 synthesis, was lower in the brain of SAMP8 mice and co-localized with Aβ plaques in the hippocampus. These results showed that even though there was an increased pro-inflammatory state in SAMP8 mice the pro-resolving LMs were not increased [326].

Studies on mouse models with AD-like pathology show evidence supporting an impaired resolution and its role in disease pathology. In the transgenic mouse model harboring five FAD mutations (5xFAD), treatment with a combination of LXA_4 and RvE1 significantly decreased several pro-inflammatory cytokines and chemokines (M-CSF, IFN-γ, IL-1β, IL-6, IL-10, TNF-α) and the number of activated microglia [140]. Studies on the triple transgenic AD (3xTg-AD) mice showed reduced levels of LXA_4 in the brain, and treatment for 2 months with AT-LXA_4

was shown to rescue cognitive decline and reduced tau phosphorylation and Aβ levels [78]. In a recent study on a Down Syndrome (DS) mouse model, displaying AD-like pathology, RvE1-treated animals showed improved cognitive function and normalized ChemR23 levels compared to the untreated group [101]. Furthermore, RvE1 has been demonstrated to have a role in regulating synaptic transmission and excitotoxic signalling [135]. Combinatory treatment of RvD1 and aspirin revealed prevention of neuronal dysfunction and cognitive decline after orthopedic surgery in mice through regulation of astrocyte activation and long-term potentiation [309].

Clinical evidence supporting deficient resolution of inflammation in humans was shown initially by demonstrating a ratio of LXA_4 to pro-inflammatory cysteinyl leukotrienes favoring the latter in urine samples from older age groups compared to young persons, in a cohort of healthy people with age ranging from 43 to 102 years [89]. This study suggests that with age, the arachidonic cascade is more directed towards the production of pro-inflammatory mediators than LX synthesis and supports impact of aging on resolution [89]. Wang et al. showed failed resolution of inflammation by investigating resolution markers. CSF samples from AD, MCI and SCI individuals and hippocampal tissues from a different cohort revealed lower levels of LXA_4 in AD compared to MCI and SCI, whereas there was no group difference for RvD1 levels neither in the CSF nor in hippocampal tissue. Immunohistochemical analysis of ALX/FPR2 and ChemR23, receptor for RvE1, displayed stronger staining intensity in the hippocampus of AD cases compared to control individuals which may suggest a compensatory response due to decreased pro-resolving LMs. This work also showed elevated levels of 15-LOX-2, an enzyme involved in the biosynthesis of LXA_4 and reduced levels of the anti-inflammatory cytokine, IL-10 in AD [327]. Since the LMs are synthesized from omega-3 and -6 FAs, their impact on inflammation and AD has been investigated too. The study by Lukiw et al. showed decreased levels of NPD1 and DHA in the CA1 region of hippocampus, of *post mortem* human AD brains compared to controls. The group also indicated protective and anti-inflammatory effects of NPD1 on neuronal/glial co-cultures by altered expression of apoptotic genes [177]. *In vitro* studies performed in our group showed increased Aβ phagocytosis by DHA treatment of human CHME3 microglial cells and by MaR1 in differentiated human THP-1 macrophages [118]. The studies on human samples (see above) indicated that resolution of inflammation is disrupted in AD and this change may contribute to the exacerbation of AD pathogenesis. However, several questions regarding mechanisms need to be answered. On the other hand, accumulating evidence shows that PUFAs and their pro-resolving derivatives have beneficial effects on resolution. Further studies on clinical materials and animal models as well as clinical trials are necessary to understand the molecular mechanisms and the potential therapeutic effects of pro-resolving LMs and other LMs.

With the recent advances in methodology, lipidomics research became a powerful tool to screen various lipid classes, utilizing human samples such as blood, CSF and *post mortem* tissues

toward identifying changes and biomarkers for early diagnosis of AD and other neurodegenerative diseases. Liquid chromatography–tandem mass spectrometry (LC-MS/MS) is a technique that combines physical separation (liquid chromatography) with mass analysis (mass spectrometry) in order to detect and quantify small organic molecules, providing extra precision and higher sensitivity (MS/MS). By utilizing LC-MS/MS, information on head group of lipids, length of carbon chains and degree of saturation/unsaturation of FAs can be obtained [26].

In addition to Aβ and tau pathology, Alois Alzheimer also reported accumulated fatty deposits when describing the disease. The association between lipid metabolism and neurodegeneration in AD has been demonstrated later by several studies [47, 161, 188]. Unlike proteins, the production of lipids is not strictly dependent on genetic translation, and they are metabolized by enzymes and obtained through the diet. There are approximately 100,000 lipid species in the human lipidome which is greater than the number of identified proteins [286]. Lipids are defined according to their head group, molecular weight, number of carbons, single and double bonds, and the overall structure. Lipids fall into eight main categories: fatty acyls, GPLs, sphingolipids, saccharolipids, polyketides, isoprenols and sterols. In brain there are only cholesterol, phospholipids and sphingolipids, which are found in neuronal membranes and myelin [133]. Lipids are fundamental for their use in energy storage, cell membrane formation, cellular transport and as signalling molecules. Besides their structural roles, lipids form membrane micro-domains called lipid rafts which contain receptors and ion channels and their function is modulated depending on lipid content [70]. There is accumulating evidence from both animal models and human studies that lipid metabolism is altered with AD pathology. Mainly cholesterol, phospholipids and glycerolipids are affected. Studies on *post mortem* brain tissue showed changes in sphingolipids both at early and late stages of AD. Sphingolipids are enriched in myelin and lipid rafts together with cholesterol. There is an endogenous production in the brain of cholesterol which is abundant in myelin sheaths, and there is evidence that neuronal dysfunction occurs due to alterations in cholesterol [68, 302]. Phospholipids constitute the fundamental membrane-forming lipids and various classes of phospholipids (PC, PI, PE) have been found to be reduced in AD brains as compared to control brains [152]. Signalling molecules derived from phospholipids through the activity of phospholipases can also be altered in AD due to the observed phospholipid changes. Bioactive messengers (such as LMs) synthesized from AA, DHA and EPA are involved in important inflammatory pathways and decrease in phospholipids containing these PUFAs may contribute to unresolved inflammation, synaptic dysfunction and neuronal loss [23].

2 RESEARCH AIMS

The aim of this project was to study neuroinflammation and resolution of inflammation in Alzheimer's disease (AD) by analyzing human *post mortem* brains (***Paper I***), characterizing the alterations in bioactive lipid mediators (LMs) and phospholipids with aging in an AD mouse model (***Paper II***) and investigating the effects of pro-resolving LMs as treatment strategy in an AD mouse model (***Paper III***).

Specific aims for each paper:

Paper I: To characterize the receptors for pro-resolving LMs within different brain regions of human AD brain and healthy control brain, and perform correlations between resolution markers and AD neuropathology

Paper II: To investigate the alterations in bioactive LMs and phospholipids, and analyze glial cell activation and inflammatory proteins upon normal and pathological aging in a mouse model for AD in order to further understand molecular mechanisms involved in dysregulation of lipid metabolism in AD

Paper III: To test therapeutic the potential of pro-resolving LMs in reversing AD-like pathology and behavior by intranasal administration of pro-resolving LMs and explore the effects on neuroinflammation, cognitive function and oscillatory activity in a mouse model for AD

3 MATERIALS AND METHODS

3.1 Human and animal models

3.1.1 Human *post mortem* brain samples

Post mortem human brain tissue is a valuable source of material for studying pathophysiology of diseases such as AD and to explore new diagnostic targets. It is also important to know the limitations, suitability and correct handling of the tissue when performing protein, lipid, DNA and RNA analysis. Many factors can affect the outcome of the study such as the *post mortem* time interval (PMI), age, gender, cause of death, temperature of storage and procedure for processing tissue. Therefore, it is important to have cohorts consisting of age- and gender-matched cohorts and that the difference in PMI between the diagnostic groups is minimal. Studies on proteins and lipids must be carried out carefully since protein levels can be affected by post-translational modifications and degraded over time and lipids can undergo lipid peroxidation, influencing the analytes of interest. *Post mortem* brain samples in **Paper I** were obtained from the Brain Bank at the Medical University of South Carolina. The cohort contained 9 AD, 3 early AD, 1 MCI and 9 healthy cases. They were age- and gender-matched, and PMI did not differ between the AD and control group. Six different brain regions were investigated, *i.e.* basal forebrain, hippocampus, entorhinal cortex, Brodmann area 46, cingulate gyrus and cerebellum. In order to evaluate the pathology for Aβ and tau, sections were stained with Bielschowsky silver stain. According to the NIA/AA staging protocol, stained sections were given scores for Braak stages (0-VI), Thal phase (0-5) and neuritic plaque load (0-3).

3.1.2 $App^{NL-G-F/NL-G-F}$ knock-in mice

Several mouse models for AD have been generated in order to investigate the pathological mechanisms. Since the discovery of mutations found in FAD (*i.e.* APP and PSEN), transgenic mouse models were engineered to overexpress APP and promote Aβ pathology [148]. However, overexpression of mutations can cause other artificial phenotypes in mouse. To overcome this problem, Saito and coworkers generated a mouse model ($App^{NL-G-F/NL-G-F}$) using a knock-in strategy expressing APP containing a humanized Aβ sequence with three mutations, the Swedish "NL", Iberian "F" and Arctic "G" mutation [255]. In contrast to transgenic APP models, this mouse model expresses APP at endogenous levels. At 2 months of age, Aβ deposition starts and at 6 months, impairments in cognition are detected [255]. The $App^{NL-G-F/NL-G-F}$ mouse (here called *App* KI) also exhibits glial activation. This mouse model does not exhibit neuronal loss and NFTs, which is a limitation. Only Aβ-induced memory deficit is not sufficient to explore all the AD pathology and symptoms. Therefore, it was suggested by Takashi Saito that this model should be considered as a preclinical AD model [262].

In **Paper II**, 2, 4, 8 and 18 months-old male *App* KI and age-matched wild-type (WT) mice were used. In **Paper III,** 6 months old male *App* KI and age-matched WT mice were used. For biochemical analysis, the mice were anaesthetized with isoflurane and perfused intracardially

with 0.9% physiological saline. Brains harvested for Western blot, Meso Scale multi-immunoassay and LC-MS/MS analysis were freshly frozen in dry ice and kept in -80 °C. Brains for immunohistochemistry were fixed with paraformaldehyde (PF) and either embedded in paraffin or sectioned and stored in cryoprotectant.

3.2 Analytical techniques

3.2.1 Multiplex immunoassay

In **Paper II** and **Paper III**, cytokines and chemokines were analyzed in the cortex and hippocampus using multiplex immunoassays (Meso Scale Discovery, MD, USA). The advantage of using Meso Scale Discovery (MSD) is smaller sample volume consumption compared to ELISA and providing a multiple detection system by using microplates where each well contains up to 10 spots for detecting different protein markers. MSD plates are already coated with high binding carbon electrodes at the bottom which facilitates easy attachment of biological samples during the incubation step. As detection system, MSD utilizes electrochemiluminescence (ECL) labels that are conjugated to detection antibodies. After incubation with detection antibodies, electricity is applied to the bottom of the plate and emitted light is read as intensity for each analyte-antibody complex. MSD with ECL system provides high sensitivity, better dynamic range and less matrix effects compared to traditional colorimetric reactions used by ELISA. In **Paper II** and **Paper III**, concentrations of 19 cytokines and chemokines were determined in brain homogenates of *App* KI mice. In **Paper II** and **III**, samples used for MSD were homogenates processed according to the protocol mentioned in Western blot methods (see below). In **Paper III**, $A\beta_{40}$ and $A\beta_{42}$ levels were analyzed using MSD $A\beta_{42}$ peptide kit. In order to have soluble and insoluble protein fractions, harvested fresh frozen brains were homogenized using a 3-step extraction protocol. This procedure enables analysis of different Aβ species with WB and immunoassays. The soluble fraction obtained by the first mechanical homogenization step in Tris-buffered saline (TBS) contains no or very low levels of soluble Aβ forms. Addition of detergent to the TBS allows extraction of soluble Aβ species, whereas extraction of insoluble Aβ requires homogenization with formic acid.

3.2.2 Western blot

In **Paper I - III** Western blot (WB) was used to investigate protein markers for inflammation and resolution. WB is an analytical technique utilized to detect and quantify a specific protein in a given sample. The method involves separation of proteins according to their molecular weight using gel electrophoresis, transfer to nitrocellulose membranes and probing with antibodies. Detection of proteins was performed by fluorescence-labelled secondary antibodies. The signals were visualized using the Odyssey CLx Imaging System (LI-COR) and proteins of interest were quantified using Image Studio Lite v5.2 (LI-COR). The Revert Total protein stain

kit (LI-COR) was used to detect total proteins which were used to normalize the levels of proteins of interest. Despite the versatility of WB, the method can give false-positive results by antibodies reacting to different proteins other than the protein of interest. Small and large proteins require different protocols to achieve proper transfers. In order to test the specificity of antibodies, peptides or immunogens used for the production of antibodies should be utilized in blocking experiments to help eliminating non-specific bands. Another limitation of WB is that densitometric analysis of the bands can be subjective and also gives information about the level of protein in the entire brain tissue sample, *i.e.* including neurons, glial cells and blood vessels. The results should therefore be interpreted with caution and the combination with other methods such as immunohistochemistry will provide further information.

3.2.3 Immunohistochemistry

Immunohistochemistry was performed in **Paper I - III** to investigate amyloid pathology, neuroinflammation and resolution of inflammation. The detection of the staining was performed using immunofluorescence or using enzyme-substrate based immunohistochemistry, such as with horse radish peroxidase and diaminobenzidine (DAB). In **Paper I** and **Paper II**, paraffin-embedded sections were used for the immunohistochemistry. In **Paper III**, we used free-floating brains sections. In order to label Aβ plaques, we used Thioflavin-S staining combined with immunohistochemistry for Aβ-peptide. In **Paper I**, we analyzed the staining intensity of markers using semi-quantitative densitometry by assessment of the mean pixel intensities in the region of interest using NIH Image J software. Also, we used the cell counter plugin in the software for counting glial cells (**Paper I** and **Paper II**). In order to quantify the area positive for antibody staining, we applied the thresholding tool in NIH Image J (**Paper II** and **Paper III**). Images were acquired with Nikon Eclipse E800 light microscope, Zeiss 710 confocal microscope and Leica epifluorescence microscope. Immunohistochemistry allows regional and cellular localization of proteins (and other molecules) of interest. With advanced technology, this method also allows demonstration of organelle interactions and movements at a cellular level. Immunohistochemistry, similar to WB, also requires proper optimization of each antibody to prevent non-specific signals. Comparison of the staining intensity gives only semi-quantitative data, whereas estimation of numbers of positive cells by stereological methods can give more accurate information. When using chromogens such as DAB, it is crucial to consider the non-linearity of antibody binding and perform methods that avoid batch to batch differences with consistent protocol and evaluation. Sample preparation such as fixation time and sectioning are important factors influencing the staining intensity. When performing quantitative analysis, from the beginning of tissue preparation to staining protocol and imaging, samples should be subjected to the same protocol. There should be also controls such as antigen blocking to achieve correct interpretation of positive signals.

3.2.4 LC-MS/MS

Lipidomics, which is the analysis of lipids by spectrometric methods, gives information about the structure, quantity and their biological functions. LC-MS/MS provides accuracy and precision with better selectivity, especially for low-abundant bioactive lipid molecules that we focused on in this thesis. Compared to LC-MS/MS, enzyme immunoassays (EIA) and ELISAs suffer from cross-reactivity between isomeric lipid species which have the same molecular weight but different structural configuration, leading to false positive results. LC-MS/MS also allows separation of several lipid species based on their chain lengths and number of double bonds, revealing the acyl chain combinations for glycerophospholipids. We used LC-MS/MS in **Paper II** and **Paper III** for analysis of bioactive LMs and phospholipids, and the spatial organization of phospholipids (MALDI-IMS) in mouse brain homogenates and fresh frozen sections from the cortex and hippocampus. For lipid extraction, brain tissues were homogenized mechanically, and an internal standard mixture of deuterium-labelled lipids was added to each sample before sonication and storage at −80°C overnight. The samples were centrifuged and the supernatants collected. The pellets were washed and centrifuged, and the supernatants from both centrifugations were combined. Distilled water with a low pH was added, and the samples vortexed and centrifuged. The pH of the upper phase was adjusted with HCl and the lower phase was dried under N_2-gas and then resuspended either in MeOH or in acetonitrile chloroform/MeOH to analyze FA derivatives or phospholipids, respectively. LC-MS/MS analysis was performed using a Xevo TQ UPLC (Waters, Milford, MA, USA). The level of each phospholipid species was calculated as % of the total amount in each sample.

3.2.5 MALDI-IMS

Matrix-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS) is a label-free method that allows detection of several lipid species simultaneously in the same tissue. Phospholipids are the major structural lipids and also have several biological functions. Therefore, it is crucial to investigate changes in phospholipid metabolism in relation to disease pathology. This method enables us to identify regional differences in specific lipid molecules, for instance providing information within regions of the brain where cell layers and projections have different functions. MALDI-IMS was used in **Paper II** to investigate the spatial distribution of phospholipid content in the brain of *App* KI and WT mice at different ages,. Frozen mouse sections were covered with a matrix in a sublimation chamber. MALDI was performed in a Synapt G2-Si (Waters, Milford, MA) with positive ion mode data collection. HD Imaging software (Waters, Milford, MA) was utilized to design the pattern of tissue scanning (15 μm spatial resolution for both horizontal and vertical movement) and data analysis. Each image spot consisted of a collection of 1 sec data acquisition. The data processed with HD Imaging were converted with an in-house program, and BioMap software (Novartis) was used to generate images.

3.3 Behavioral tests

Behavioral tests were used to analyze the effects of pro-resolving LMs on anxiety-like behavior, memory and learning. The mixture of the LMs RvD1, RvD2, RvE1, MaR1 and NPD1 (Cayman Chemicals, USA) (200 ng in 10 µl/mouse) was administered into the nostrils by a pipette to the *App* KI mice (n = 13). Vehicle (0.9% saline) was administered to *App* KI mice (n = 15) and WT mice (n = 15). Two *App* KI mice were treated with a mixture of deuterium-labelled LMs (RvD1-d_5, RvD2-d_5 RvE1-d_5 and MaR1-d_5 (Cayman Chemicals, USA)). Intranasal administration of LMs was performed 3 times a week for 9 weeks. Behavioral tests were performed during weeks 7-9 while the treatment was ongoing. Between the behavioral tests the mice were allowed to rest for one full day.

3.3.1 Open field

The open field (OF) test is used to test anxiety, exploratory behavior, and locomotor activity. OF consists of a box (45 cm x 45 cm, 40 cm height) with a black bottom and surrounded by clear walls. The mice are placed in the arena and allowed to explore for 20 min. The activity is recorded by a video-tracking system above the box to monitor distance travelled, rearing activity, time spent in divided areas (central and peripheral), and velocity of movement. The rational for using variables such as time spent in a central and peripheral part is to assess the motivation to explore these areas voluntarily. Normal behavior in mice would be to seek protection by the wall and displaying more explorative activity when the distance travelled is longer. Animals that are less anxious are expected to spend more time in the center.

3.3.2 Elevated plus maze

The elevated plus maze (EPM) test is used to assess anxiety, consisting of two open and two closed arms at 90 degrees angle, each arm 35 cm long, 8 cm wide and height 50 cm from the floor. The closed arms have side walls. The mice were placed in the center of the maze and allowed to explore for 5 min. The sessions were recorded with Ethovision XT (Noldus) software to analyze the number of entries to the arms and the time spent in each area (center, open and closed arm). Mice usually prefer to stay in closed arms, avoiding the open arms, and the time spent in open arms is used as an indication of less anxiety.

3.3.3 Novel object recognition

The novel object recognition (NOR) test is used to study short- and long-term memory, by analyzing the time spent with the objects presented. The test consists of an open field chamber (45 cm x 45 cm, 40 cm height) with 3 days of testing including habituation (day 1), familiarization (day 2) and test (day 3). On day 1, animals are allowed to explore the open field arena freely for 10 min without presentation of objects. On day 2 the animals are allowed to explore two identical objects in the same arena for 10 min and returned to the home cage for

24 h. On day 3, one of the training objects is replaced with a novel object and the animals are allowed to explore these two objects for 10 min. The discrimination index (DI) is used as a metric for recognition memory by comparing the preferential exploration of the new object to the old object. DI was calculated as follows: (time spent exploring novel object - time spent exploring familiar object) / (time spent exploring novel object + time spent exploring familiar object). DI varies between +1 and -1, where a positive score indicates more time spent with the novel object and negative score indicates more time spent with the familiar object, and score 0 indicates a null preference. The behavior of normal (or control) mice would be an innate preference for novelty, and mice remembering the familiar object will spend more time with the novel object.

3.3.4 Fear conditioning

The fear conditioning (FC) test is used to assess the ability of mice to learn and remember by making association between environmental cues and aversive experiences. The test is based on conditioning the mice with a stimulus and later observing the innate fear response by measuring the freezing behavior. The FC test included 3 days of testing. On day 1 as the training phase, the mice were placed in an arena (20 cm x 20 cm, black box) to explore freely for 2 min and exposed to a 30 sec sound stimulus (55 dB, 5000 Hz) followed by a 2 sec electric shock (0.3 mA). Both the sound and shock stimuli were repeated 3 times in the same session to strengthen the association. After a 24 h delay (day 2) , the context-dependent fear was evaluated by placing the mice into the same arena and observing the freezing behavior without the sound and shock during the 3 min. On both day 1 and 2, the arena was cleaned with 70% ethanol and distilled water between the sessions. On day 3 (after 24 h), cued-dependent fear was assessed by measuring freezing in response to the sound stimulus after 2 min of exploration freely in a new chamber (round, clear, 20 cm diameter). The arena was cleaned with hypo-chlorous water (50% diluted) after every session to provide a different environment with a different odor. The test was recorded with a camera and infrared sensors to detect the motion in 3 dimensions using a Multi Conditioning System (TSE Systems GmbH, Bad-Homburg, Germany). Cognitively healthy mice are expected to freeze in the contextual and cued chamber, showing the impact of shock on intact memory formation. The FC test is a sensitive test providing information on associative learning, and short- and long-term memory without requiring food deprivation. Tasks in the test require different brain area connectivity. Therefore, it allows assessing memory dependent on prefrontal cortex, hippocampus and amygdala with contextual and cued FC. However, the test is stressful due to the foot shocks. Fear and anxiety can affect the freezing response in mice.

3.4 Electrophysiology

We performed *in vitro* electrophysiological recordings in **Paper III** to understand the effects of pro-resolving LMs on electrical activities. In order to analyze the network functions, we used brain slices from the mice providing intact neural circuitry.

3.4.1 Tissue collection and hippocampal slices

After behavioral tests, the mice were anesthetized with isoflurane and decapitated for brain dissection. The whole brain was placed into an ice-cold artificial cerebrospinal fluid (ACSF) and sectioned horizontally into 350 μm thick slices using a vibratome. The slices were placed into a chamber containing ACSF and supplied with humidified carbogen gas for 1 h before recording.

3.4.2 Local field potential recordings and whole-cell experiments

The slices were placed in a submerged chamber and continuously superfused with ACSF bubbled with carbogen gas. Local field potentials (LFPs) were recorded in the CA3 *stratum pyramidale* of the hippocampus. In order to induce gamma oscillations, kainic acid (KA) (Tocris Bioscience, Bristol, UK) was added to the bath keeping 34°C. Oscillations were recorded after 20 min allowing stabilization. Whole cell recordings were carried out in fast spiking interneurons (FSN). In order to measure the action potential and excitatory post-synaptic currents (EPSCs), potassium-based intracellular solution was used. LFP recordings and patch-clamp recordings were performed using a Multiclamp 700B (Molecular Devices, CA, USA).

3.5 Statistics

3.5.1 Univariate analysis

Univariate analyses were performed using Statistica (**Paper I**) and GraphPad Prism software (**Paper II** and **Paper III**). Kruskal-Wallis ANOVA was used to test for group differences, with the Dunn *post hoc* test. Mann-Whitney U test was used for two group comparisons. Correlations were analyzed by the Spearman Rank Order test. $P < 0.05$ was considered statistically significant.

3.5.2 Multivariate analysis

Multivariate analysis (MVA) methods, principal component analysis (PCA) and orthogonal projections to latent structure (OPLS), were utilized in **Paper I and Paper II**. Multiple variables such as LM receptors, inflammatory proteins (cytokines and chemokines), bioactive LMs, and phospholipids were analyzed together to assess a pattern for inflammation and resolution in human and mouse brain. MVA can identify a pattern of the data, showing group separation and clusters when the study contains many variables. The advantage with MVA

method is integrating multiple independent variables, to uncover relationships and variability of dependent variables that univariate analyses cannot describe with a single factor.

3 ETHICAL ASPECTS

This thesis contains research that used *post mortem* human brain tissue (**Paper I)** as an explorative study to investigate changes in resolution markers in AD. To be able to carry out the analyses, the *post mortem* consent, brain collection, fixation and standardized neuropathological assessments were performed according to the protocol of the Alzheimer's Disease Neuroimaging Initiative (ADNI) [41] and according to standard operating procedures (SOP) of the Carroll A. Campbell Jr. Neuropathology Laboratory (CCNL) Brain Bank at the Medical University of South Carolina (MUSC). The brain tissues were dissected in the CCNL Brain Bank in Charleston, SC.

In **Paper II** and **Paper III,** we used the laboratory animals which were handled according to the Karolinska Institutet guidelines and Swedish National guidelines. The breeding, behavioral tests, drug administration and tissue collection were approved by ethical committees in Sweden (S6/14 and 12370-2019).

4 RESULTS AND DISCUSSION

Paper I: Receptors for pro-resolving mediators are increased in Alzheimer's disease brain

It has been shown that pro-resolving LMs are decreased in the brain and CSF of AD patients indicating disrupted resolution of inflammation in AD [177, 327]. Pro-resolving LMs exert their actions *via* receptors that are still being identified [201], and so far, only some have been described in the brain. In Paper I, the aim was to investigate receptors for RVE1, ChemR23 and BLT1, in different regions of AD and healthy human brain. Six brain regions were analyzed, the hippocampus, entorhinal cortex (ENT), basal forebrain (BF), cingulate gyrus (CG), Brodmann area 46 (BA46) and cerebellum (CB). In the hippocampus, the subregions Cornu Ammonis (CA) 1, CA2 and dentate gyrus (DG) were studied. The receptors were assessed by densitometry after immunohistochemistry as well as WB. Densitometry showed a marked increase in BLT1 in CA2, ENT, BF, BA46 and CG in AD cases as compared to controls and these results were supported by double-blind scoring of BLT1 staining. Analysis of the relationship between BLT1 and the progression of pathology demonstrated that high staining intensity for BLT1 coincided with high Braak scoring. However, the relationship between BLT1 staining intensity and amyloid pathology was not linear and instead showed clustering of AD cases with highest Aβ score and clustering of non-AD cases with lowest Aβ score.

Western blot results did not show any changes for BLT1 expression in hippocampus, BF, BA46 nor CG. An explanation for the discrepancy between the results from immunohistochemistry and WB may be that WB data are obtained from several different cell types, blood vessels and extracellular matrix, while the immunohistochemical technique allows assessment at the higher levels of resolution, *i.e.* at the cellular or cell layer level. Lastly, the studies on BLT1 revealed that this protein responding to LMs is expressed by microglia and astrocytes, in addition to neurons.

The staining for ChemR23 was markedly higher in AD than in control brains in the same regions as BLT1 except for the BA46. In addition, the ChemR23 levels were increased in the CA1 region. Subjective scorings for ChemR23 supported the densitometry data. The relation between ChemR23 and Braak stages displayed a gradual increase for both NFTs and ChemR23, indicating that ChemR23 levels increased with the disease progress. However, similar to BLT1, the cases with high staining intensity for ChemR23 were clustered at the later stages of amyloid plaque pathology, and cases with lower ChemR23 levels were clustered at the lowest amyloid scoring. Similar to BLT1, the WB data for ChemR23 did not show changes that corresponded with the data from immunohistochemistry.

The state of inflammation was analyzed using markers for microglia, HLA-DR, and astrocytes, YKL-40. Counting of total microglia numbers and subpopulations differentiated according to morphology supported previous studies on glial cell numbers and activation [295], in that the

AD cases had significantly higher total numbers of microglia and of activated microglia in the CA1, CA2, ENT, BF, CG and BA46, compared to controls. However, there was no difference in the CB. Analysis of an astrocyte marker, YKL-40 [246], by WB showed higher levels of YKL-40 in the hippocampus and BF of AD brains compared to control individuals.

In summary, we showed that BLT1 and ChemR23 levels were higher in AD brains in a region-specific manner. This was the first study demonstrating the distribution of BLT1 within the human brain and we showed that BLT1 is expressed by neurons, microglia and astrocytes. Decreased levels of pro-resolving LMs and increased levels of RvE1 receptors can suggest a compensatory reaction and this can be utilized in the future as a therapeutic intervention to stimulate resolution in AD.

Paper II: Age-related changes in brain phospholipids and bioactive lipids in the *App* knock-in mouse model of Alzheimer's disease

Studies on lipid dysfunction have shown that PUFAs, particularly omage-3 DHA, phospholipids (PE and PI) and pro-resolving LMs are decreased in AD patients compared to controls [67]. Increased pro-resolving LM receptors and enhanced activity of enzymes (COXs and LOXs) involved in pro-inflammatory LM production have been reported by several groups [183]. Although there is accumulating evidence of these alterations in lipid metabolism, it remains unclear how the phospholipids and their acyl chain composition, pro-resolving LMs, their receptors and enzymes are affected with aging and AD pathology. We addressed these questions and also investigated neuroinflammation and downstream intracellular signalling molecules in this study using the App knock-in mouse model $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ (*App* KI) at 2, 4, 8 and 18 months of age in comparison with age-matched WT mice.

The amyloid plaque load was analyzed in cerebral cortex and hippocampus with the 6E10 Aβ peptide antibody in order to demonstrate the relation of amyloid pathogenesis with lipids, their biosynthetic pathways and inflammatory markers. Aβ deposition was seen at 2 months and increased with age [163]. Inflammatory and pro-resolving LMs were investigated next, showing elevated levels for both types of LMs in *App* KI mice compared to WT mice at 18 months of age. Interestingly, together with elevated levels of PGE2 and LTB_4, LXA_4 levels were also higher, supporting a class-switch mechanism [172]. Regarding the effect of age on LMs, we observed a similar age-dependent change in the hippocampus of WT and *App* KI mice, showing a peak at 8 months age and lower levels at 18 months. In the cortex, however, the levels of LMs in *App* KI mice were higher at 18 months compared to WT mice after the peak at 8 months. Analysis of biosynthetic enzymes showed higher levels of COX-1 and 15-LOX-1, and lower levels of p-5-LOX at 18 months in the *App* KI mice than the WT mice. The lower levels of p-5-LOX supported the high levels of LTB_4 and LXA_4 levels. Elevated COX-1 levels confirmed the high levels of PGs.

Analysis of the protein levels for BLT1, ChemR23, LGR6, ALX/FPR2 and GPR18, showed lower levels for ChemR23 and ALX/FPR2, and higher levels of LGR6 and GPR18 in 18 months old *App* KI mice compared to WT mice. Previously we hypothesized that higher levels of receptors could be a compensatory mechanism for reduced levels of pre-resolving LMs. However, it is crucial to consider that these GPCRs are not only activated by pro-resolving lipids but also by other ligands. Due to the dynamic structure of this process, changes in the receptors for pro-resolving LMs cannot be attributed only to the levels of these pro-resolving LMs but could be targeted to stimulate pro-resolving mechanisms based on the observations in human AD where increased LM receptors and reduced levels of LMs were observed [81].

We continued by investigating the phospholipid acyl chain composition of the phospholipids and found that the DHA-containing PCs, PE and PS were seen in lower levels in the *App* KI compared to WT mice at 18 months. On the other hand, AA-containing PC and PE were higher in *App* KI than in WT mice at 18 months age. Changes in AA-containing phospholipids were supported by decreased levels of phosphorylated cPLA2 (p-cPLA2) levels, indicating reduced hydrolysis of AA at the sn-2 site [19]. We also found that signalling molecules such as MAPKs, which are involved in phosphorylation of many proteins including cPLA2, had a lower phosphorylation rate in 18 months old *App* KI mice.

The phospholipid composition was also investigated spatially by MALDI-IMS using fresh frozen brain sections. The high spatial resolution (15 μm) revealed that the levels of AA-containing PC were higher in WT mice than in *App* KI at 8 and 18 months of age, particularly in the *stratum radiatum*. DHA-containing PC was higher in WT mice at 8 months of age in *stratum radiatum*. This information and further investigation on different subregions of the hippocampus can provide information regarding the effects of progression in AD pathology on variations in lipid composition, and regarding the availability of PUFAs in phospholipids for the regional production of LMs.

Characterization of inflammatory markers in the *App* KI mouse model demonstrated that most of the inflammatory cytokines and chemokines were elevated at 18 months of age in the *App* KI mice compared to WT mice. Microglial markers for phagocytic and resident phenotypes were also altered, showing increased levels of TREM2 and GAL-3 levels at 8 and 18 months of age. However, the TMEM119 levels were higher at 2 and 4 months of age, indicating a transformation of microglia from resident to an activated phenotype depending on the disease pathology. We also observed lower levels of C3 at 18 months of age in the *App* KI mice, suggesting activation of the complement system and cleavage of C3 into fragments for exerting their actions.

Finally, we investigated the activation of microglia and astrocytes using Iba1, GFAP, and S100β as markers, and performed cell counting within the subregions of hippocampus (DG and CA1) and cortex. We found that Iba1-positive microglia increased in numbers starting from 4 months of age in the *App* KI mice compared to WT mice, while GFAP and S100β

immunostaining showed an increase in the number of labelled astrocytes only at a later age, 18 months, in *App* KI mice compared to controls.

In summary, for the first-time alterations in phospholipids, bioactive LMs, their receptors and biosynthetic enzymes were evaluated in the same study to understand the timeline of an inflammatory response and its resolution. We demonstrated that both pro-inflammatory and pro-resolving LMs were higher in 18 months old *App* KI mice than WT mice. However, aging had the same effect on LM and phospholipid levels in both WT and *App* KI mice, showing a similar trend in lipid changes. The data also showed the highest levels of cytokines and chemokines in 18 months old *App* KI mice. This study highlights that changes in inflammatory factors do not occur until the Aβ pathology is advanced in this mouse model. Exploring the effects of aging and AD pathology on the dynamics of resolution can help us to design studies that are effective for terminating chronic inflammation and stimulating the resolution in inflammatory diseases.

Paper III: Intranasal delivery of pro-resolving lipid mediators rescued memory and gamma oscillation impairment in App KI mice

AD suffers from chronic inflammation due to excessive Aβ production and tangle formation which cause persistent glial cell activation and neurodegeneration. Recently, neuroinflammation is appreciated as a possible disease mechanism for AD due to the findings with epidemiological studies showing that anti-inflammatory drugs can spare RA patients from AD. Stimulating resolution to terminate inflammation rather than blocking an inflammatory response which is a necessary process for the host defense, could be more effective and natural. In this study, we treated 6 months old *App* KI mice with pro-resolving LMs by intranasal administration to investigate whether cognition, behavior and inflammation could be improved. We included five different pro-resolving LMs: RvE1, RvD1, RvD2, NPD1 and MaR1. The treatment lasted for two months with administration every second day. We performed behavioral tests, including explorative and locomotor activity, anxiety-like behavior, learning and memory. There was no effect of the treatment observed in the EPM and open field tests in terms of total distance travelled and time spent in open arms. However, treatment of the *App* KI mice with LMs resulted in a significantly longer time spent with the novel object in the NOR test, indicating their improved memory for familiar object compared to *App* KI mice receiving vehicle. We also found that *App* KI mice treated with LMs displayed a longer freezing time in the FC test compared to *App* KI mice given vehicle, suggesting improvement in memory function after receiving LMs.

We next investigated the effects of LMs on network rhythmicity due to the recovery in memory. Electrophysiological analysis showed a decrease in *in vitro* gamma oscillations in the *App* KI mice compared to WT mice. The treatment of *App* KI mice with pro-resolving LMs resulted in

recovery in the gamma oscillation power, whereas the effect on gamma oscillation frequency did not reach statistical significance. However, the reduction in excitatory postsynaptic current (EPSC) charge transfer in fast spiking neurons (FSN) observed in *App* KI mice compared to WT mice was recovered by treatment with pro-resolving LMs.

Interestingly, the treatment with LMs did not result in a reduction for Aβ-positive plaque area. This was also supported by analysis of $A\beta_{42}$ levels in brain homogenates using immunoassays, showing no difference between *App* KI mice receiving LMs or vehicle. An explanation could be that plaques are formed for protection and that they are less toxic than oligomeric Aβ peptides [127]. Pro-resolving LMs did not change the plaque load but may have affected other forms of Aβ before fibrillation, which will require further studies. Although there was no reduction in Aβ plaque load, we can claim that treatment with pro-resolving LMs did not allow for more plaque formation since the data showed a slight decrease that did not reach statistical significance. Furthermore, we investigated the extent of gliosis by staining the brain sections with Iba1 and GFAP antibodies and analyzed the area occupied by the cells, indicating their phenotype and activation state. The quantitative assessment showed that treatment with pro-resolving LMs reduced the area covered by microglia in the *App* KI mice compared to treatment with vehicle. However, there was no treatment effect on astrocyte activation.

Examination of receptors for pro-resolving LM, synaptic markers and the phagocytic microglia marker TREM2, by WB did not show a treatment effect. A possible explanation for a lack of effect on the expression of receptor levels may be the short half-life and rapid elimination of pro-resolving LMs.

Analysis of the glutamate receptors, GLUR1 and GLUR4 in the cortex did not reveal a treatment effect, nor of the postsynaptic marker PSD95. However, the GABA A1α receptor was significantly reduced by the treatment of *App* KI mice with pro-resolving LMs. Studies on AD have suggested alterations in the excitatory and inhibitory balance and showed that the glutamatergic system is more affected than the GABAergic system [57, 204]. Only mild changes have been observed in the GABAergic system, *i.e*. reduction in GABA receptor subunits, loss of GABA as neurotransmitter or a decrease in GABA binding [57, 204]. Therefore, the reduction in GABA A1α levels upon treatment with LMs could indicate recovery of the excitatory and inhibitory balance.

The levels of TREM2 were elevated in *App* KI compared to WT mice, but there was no effect by treatment with LM, although a tendency for decrease could be seen. We also investigated the effect of treatment with LMs on the levels of pro- and anti-inflammatory cytokines and chemokines. The data showed no statistically significant effects, only a tendency for lower pro-inflammatory markers by the treatment. Finally, we looked at the levels of free PUFAs, bioactive LMs and phospholipid content in the brain by LC-MS/MS analysis. There was no effect on the levels of PUFAs or LM, but two DHA-containing PSs (16:0/22:6 and 22:6/22:6) were significantly elevated by the treatment with LMs.

We continued examination of markers for resolution and neurotransmission, such as pro-resolving LM receptors, synaptic markers and TREM2, phagocytic microglia marker using western blot analysis. However, treatment with LMs did not change the levels of the LGR6, BLT1, ChemR23, GPR18 and ALX/FPR2 receptors. Why pro-resolving LM treatment did not affect expression of receptor levels could be reasoned due to the short life and their rapid elimination of pro-resolving LMs under physiological conditions. Among the glutamate receptors, GLUR1 and GLUR4; GABA receptor GABA A1α; postsynaptic marker PSD95 investigated within the cortex, only GABA A1α was significantly reduced in *App* KI LM group compared to *App* KI vehicle. Studies suggested the alterations in excitatory and inhibitory balance in AD and showed that mostly glutamatergic system is affected rather than the GABAergic system. There are only mild changes observed for GABAergic in terms of reductions in GABA receptor subunits, loss of GABA as neurotransmitter or decrease in GABA binding [58, 207]. Therefore, significantly reduced GABA A1α levels after LM treatment in this study can be explained as the actions pro-resolving LMs which might have helped with the recovery of excitatory and inhibitory balance. Elevated TREM2 levels in *App* KI vehicle compared to WT, wasn't altered in *App* KI LM group but there was a decreased tendency. We also investigated the levels of pro- and anti-inflammatory cytokines and chemokines whether pro-resolving LM has an effect and showed no significant changes. However, there were non-significant tendencies for lower pro-inflammatory markers in App KI Lm group compared to vehicle group. Finally, we looked at the levels of free PUFAs, bioactive LMs and phospholipid content in the brain. LC-MS/MS analysis did not show any changes in PUFA and LM levels, but two DHA-containing PSs (16:0/22:6 and 22:6/22:6) were significantly elevated with LM treatment.

In summary, our study showed recovery of cognition and gamma activity, as well reduced microglial activation in an AD mouse model, highlighting the use of pro-resolving LM as treatment approach.

5 CONCLUDING REMARKS

The main aim of this thesis was to assess the state of resolution of inflammation with aging and AD pathology in order to understand the mechanisms and pinpoint the alterations during resolution for therapeutic interventions with pro-resolving LMs. The results showed elevated levels of receptors for pro-resolving LMs in different regions of human *post mortem* brains from AD patients. The thesis also describes changes with aging in bioactive LMs and phospholipids in the CNS of an AD mouse model, but also in WT mice. Moreover, five major pro-resolving LMs were administered intranasally to an AD mouse model in order to analyze biochemical, behavioral and electrophysiological parameters.

- BLT1 and ChemR23 were increased in the AD brain and they were correlated with AD pathology. HLA-DR positive microglia were higher in the AD brain. YKL-40 protein levels were elevated in the AD brain.

- Both inflammatory and pro-resolving LMs were elevated in the AD mouse brain at older age. ChemR23 and ALX/FPR2 were decreased, LGR6 and GPR18 were increased in AD mouse brain at older age.

- DHA-containing phospholipids were decreased and AA-containing phospholipids were increased in AD mouse brain at older age. cPLA2 activity was decreased in AD mouse brain at older age.

- Pro- and anti-inflammatory cytokines and chemokines were increased in AD mouse brain at older age. TREM2 and GAL-3 were elevated in AD mouse brain.

- Pro-resolving LM mediator treatment recovered cognitive and gamma oscillation impairments and decreased microglial activation.

- DHA-containing phospholipids were elevated after pro-resolving LM treatment in AD mouse brain.

6 FUTURE PERSPECTIVES

Resolution is a newly discovered process within the inflammation response and more in-depth studies are necessary to decode resolution mediators and the time-course for their production and activities. Considering the urgent need for disease-modifying drugs in AD treatment at early stages, it is crucial to assess the interactions between pro-resolving LMs and their receptors, as well as to investigate the enzymatic synthesis of LMs in order to utilize them as potential targets for therapeutic approaches.

- The effects of pro-resolving LMs on functional networks related to cognitive mechanisms is important to investigate in terms of their actions on excitatory and inhibitory neurons.

- PUFAs are precursors for pro-resolving LMs whose production depends on the availability of these free PUFAs, phospholipid content and activity of the enzymes. These factors should be investigated in a controlled experimental set-up with both cell and animal models to understand the dynamics of resolution of inflammation.

- Analogues of pro-resolving LMs with a longer half-life and resistance to oxidation should be studied in animal models in order to investigate their potential for use in human clinical studies in the near future.

- Further studies should be carried out in a mouse model with more advanced AD pathology in order to reveal whether pro-resolving LMs are sufficient to rescue cognition.

8 ACKNOWLEDGEMENTS

I would like to thank people who contributed to my thesis and supported me during my PhD studies.

To my main supervisor, **Marianne**, thank you for your support and guidance during the past 5 years. I always appreciated you being open-minded and supportive to the new ideas and approaches coming from your group members. You give value and recognize everyone's contribution for the work done. Your thorough feedbacks always helped me to improve. Thank you for the opportunities to work in different labs with our collaborators, which allowed me to broaden my knowledge and skill sets. I am grateful for being part of your research group which helped me reach where I am today.

To my co-supervisors: **Erik**, thank you for all the help and time you provided when teaching new methods and discussing results. You have always been very patient to your students. I enjoyed discussions with you to hear your opinions and ideas. I admire that you encourage students to contribute science with honesty and hard work. **Lotta,** thank you for the support, guidance, inspiration and the positive energy you bring in. I appreciate the time we spent together during aging study, you taught me a lot about human brain anatomy and made it fun working for hours by the microscope. Also, thanks for having me in Denver and giving me the chance to meet with your group members. I learnt a lot from you and appreciate your feedback during my PhD studies. **Dr. Bazan**, thanks for having me in your lab. It was a memorable moment arriving to New Orleans for the first time with your and Dr. Haydee's warm welcome. Under your supervision, I gained a lot of knowledge and experience with hardworking people at Neuroscience Center. You have always been supportive and excited for the work I have done during our collaboration. I am thankful for having the chance to work with you and your group at LSU. **Silvia**, thank you for your help during the first years of my PhD. I had so little experience with mice but your patience and knowledge with animal behavior helped me very much.

To the MS group members: **Ying**, thank you for everything. In our small group, we were lucky to start together to this journey. Although we had different projects during our studies, you were always very interested and eager to discuss about findings. You have been a supporting colleague and friend. I hope we will meet again in China and visit the places we planned. I will miss the sweet treats you bring from your home country. Wishing you luck in your future endeavors. **Silvia**, you are a dedicated, hardworking and self-motivated person. You always have a positive attitude with a smile on your face. We worked on many projects together in such a short time but you learnt a lot. I am sure you will achieve greater things in your PhD studies, good luck! Thanks to all former students who worked with us and contributed to the work we have done in our group: **Zaki**, **Hümeyra**, **Lisanne**, **Elin**, **Bram**, **Sara**, **Tuuli** and **Lea**. Thank you **Veronica**, for all the help with new methodologies at the beginning of my PhD. Thank you, **Eric Hamlett**, for visiting us and bringing your positive energy to the group.

To my co-workers: **Hazal**, canim arkadasim, I will never forget the first time we met on a Friday night at Tango. I am so glad that I have a friend I can always talk to. You have been a great support for both work and life matters. We shared some unforgettable moments together, I will always cherish those times. I will miss both you and Jonas**. Giacomo**, kuzu, I cannot say how much I appreciate your friendship during the time we spent together at NVS. You have been a great listener and a big support. I thank you for all the good times both in and out of work. I will miss our lunch breaks and remember the fun times we had celebrating midsummer. Thank you **Chenhong** for everything we got to do together during our studies. I will never forget our fun trips to Norway during Ski conferences. I am always up for exploring new food destinations with you. **Nuno**, thank you for all the fun times we had together. I appreciate your friendship and honest opinion in and outside the lab. I hope that we will meet again in Sweden or plan a trip to Turkey! My dear friend **Médoune**, who made the time pass faster by the microscope when working side by side. I always enjoyed your short visits to our office to chat at Novum. Thank you for the fun times at work and outside the work. **Raul**, you were like a mentor to me and other students at NVS. You motivated me as well as amazed me with your passion for science. You were also a great friend outside of work. Your future students will be very lucky to have you. **Luis**, I always appreciated your willingness to help people and the motivation you have for your work. It was a pleasure to collaborate with you, I learnt a lot. I am sure you will achieve great success in your career. **Dani**, I will never forget the day we both presented our work for admission to KI as PhD students. You were the chill person who actually calmed me down before the stage. You have been a person I enjoyed talking to. I always looked forward to you coming back from Portugal so we can have those delicious pastéis de nata. Thank you for everything! **Maria**, my first and last roommate in Stockholm, who made living in Stuvsta more fun. We could just talk hours after a long day at work. We did have some fun times together. I wish you the best in your career. **Francesca**, thank you for all the help and advise you have given me on animal work. Wishing you good luck in your PhD studies. **Julen**, thank you for all the fun time together. You have been a friend who brings positivity to work, also helpful and easy to talk to. You are passionate about what you do, which also motivates others around you. I am confident that you will achieve greater things in your career. Good luck! **Laetitia**, thank you for the all fun times together at NVS events, picnics and dinners. I appreciate you taking time when I needed your advice on work matters. **Luana,** thanks for all the nice chats we had during the lunch breaks. You have been a great example to me for the hard work and motivation you have for your work. I wish you the best in your future career. **Axel**, thank you for the nice time while sharing offices at Novum. **Amit,** thank you for the fun times we had at NVS events and Friday nights. I would also like to thank **Patricia, Cristina, Catarina, Arturo, Märta, Emilia, Ipsit, Juraj, Simone, Jiang, Makoto, Erika, Lorena, Konstantinos, Una, Kirsten, Joana, Berni**, **Agus, Mona-Lisa and Tamer.**

To all PIs, researchers and administrators at NVS: **Bengt, Gunilla, Lars, Sophia, Helena, Erik S., Elisabet, Homira, Janne, Angel, Anna M., Mia L. and Maria A.,** thank you for providing a friendly and productive working environment. **Eva** and **Maria R.**, thank you for being available whenever we needed help and taking care of us.

To our collaborators: **Per**, thank you for your input and hard work for providing the animals and contribution to the projects. **André Fisahn**, for your insights and help on our projects. **Khanh, Bokkyoo, Marie-Audrey, Zevie, William Gordon and Aram,** thank you for your efforts, hard work and help. I am thankful for the time I worked with you all and other researchers at the LSU Neuroscience Center.

To my former supervisor, **Luis Miguel Garcia-Segura**, thank you for your guidance and help during my master studies. I learnt several methods and also was given freedom to run projects myself as a master student. My mentor, **Pelin Kelicen,** I am very grateful for your guidance which helped me at the beginning of my career. I always admired your hard work and motivation to contribute science.

To my family and friends: Canim **annecim, babacım** ve **Eren**'im, sizin desteğiniz olmadan bu zorlu süreci nasıl atlatırdım düşünemiyorum. Sevincimde ve üzüntümde hep yanımda oldunuz. Aldığım kararları hep desteklediniz ve bulunduğum yere gelmemde sizin katkınız çok büyük. Aramızdaki mesafeye rağmen hiçbir zaman yalnız hissetmedim ve bana bir telefon uzaklıkta oldunuz. Sizleri çok seviyorum, iyi ki varsınız canlarım benim! **Mehmet** dedem, anneannem **Kiraz**, babaannem **Güllü** ve rahmetli **Aliseydi** dedem, sizlerin duaları hiç eksik olmadı, ellerinizden öpüyorum. Ayrıca ismini yazamadığım diğer tüm aile bireylerine bu süreçteki destekleri için teşekkür ederim, hep yanımda olduğunuz ve bana inandığınız için. **Sebastian,** jag uppskattar djupt ditt stöd och tålamod under min doktorsexamen. Du lyssnade alltid och hjälpte mig att övervinna de tuffa tiderna. Tack älskling, för att du var där för mig. **Pelle, Birgitta, Kalle, Ilse, Leila, Marie and Gunilla,** er vänlighet och varma personligheter fick mig att aldrig känna mig ensam i Sverige. Tack så mycket för allt stöd. Biricik lise arkadaşlarım **Yasemin, Kubilay, Arın** ve **Çağıl**; ilkokul arkadaşlarım **Didem, Kübra, Gizem, Pelin ve Aydin**; üniversite arkadaşlarım **Merve** ve **Alper**; Madrid'deki dostum **Deniz**; hepinize teşekkür ediyorum desteğiniz için. Last but not least my dearest friends **Jackie** and **Kristelle,** who always supported and praised me for the research I am doing.

Finally, I would like to thank the Swedish Research Council, Alzheimerfonden, Gamla Tjänarinnor and Gun och Bertil Stohnes Foundation for funding the projects in this thesis.

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