Linking Innate and Adaptive Immunity to \textit{Streptococcus pneumoniae}

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av

Marie Olliver

Huvudhandledare:
Professor Birgitta Henriques-Normark
Institutionen för Mikrobiologi, Tumör- och Cellbiologi, Karolinska Institutet,
Institutionen för Laboratoriemedicin,
Karolinska Universitetssjukhuset och
Smittskyddsinstitutet

Bihandledare:
MD, PhD Peter Bergman
Institutionen för Laboratoriemedicin,
Karolinska Institutet och Karolinska
Universitetssjukhuset

Assistant Professor Laura Plant
Institutionen för Mikrobiologi,
Tumör- och Cellbiologi,
Karolinska Institutet

Professor Staffan Normark
Institutionen för Mikrobiologi,
Tumör- och Cellbiologi,
Karolinska Institutet

Fakultetsopponent:
Professor Ingileif Jónsdóttir
Landspitali - The National University
Hospital of Iceland
Division of Infectious and Inflammatory Diseases, deCODE genetetics
Reykjavik, Island

Betygsnämnd:
Professor Hans-Gustaf Ljunggren
Institutionen för medicin,
Karolinska Institutet

Professor Jan-Ingmar Flock
Institutionen för laboratoriemedicin,
Karolinska Institutet

Professor Olle Stendahl
Institutionen för klinisk och
experimentell medicin,
Linköpings Universitet

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ABSTRACT

*Streptococcus pneumoniae* (the pneumococcus) most commonly colonizes the human nasopharyngeal mucosa without causing any symptoms. However, this organism has the potential to spread to normally sterile sites and cause pneumonia, meningitis or sepsis; diseases which are characterized by excessive inflammation. Despite the large burden of pneumococcal disease, relatively little is known about the mechanisms behind development of natural immunity to the pneumococcus. The purpose of this thesis was to study the role of human dendritic cells (DCs) in linking innate and adaptive immune responses to pneumococci. The immunological events in which DC-mediated T helper (Th) cell responses are generated were also investigated, as well as possible ways to modulate these responses.

As a first part of this work, a novel role of the pneumococcal toxin pneumolysin in the evasion of DC-mediated immunosurveillance was described. Pneumolysin inhibited DC maturation, production of inflammatory cytokines and inflammasome activation, and induced caspase-dependent apoptosis of infected cells. Interestingly, murine DCs differed in their response to pneumolysin, emphasizing the need to study human responses to this human-specific pathogen.

In the second part of this work, we demonstrated that pneumococcus-infected monocytes and DCs efficiently promote the production of inflammatory Th1 and Th17 cytokines from autologous co-cultured memory cells. Live pneumococci and pneumococcal peptidoglycan triggered activation of DCs, which in turn induced the generation of Th cytokines via cell-to-cell contact and soluble components. Our work further revealed that the inflammatory response could be modulated with exogenous substances, such as recombinant cytokines, and cytokine- and receptor-blocking antibodies. Moreover, exposure of DCs to vitamin D skewed the response from an inflammatory Th1/Th17 phenotype towards a regulatory T cell phenotype.

In the last part of this work, we focused on patients with primary immunodeficiencies (PIDs), suffering from frequent respiratory tract infections. The mechanisms behind the infectious susceptibility among these patients remain elusive and we hypothesized that it may be due to defects in the production of antimicrobial peptides (AMPs) in the nasal mucosa. We found that two patient groups, namely common variable immunodeficiency (CVID) and Hyper-IgE syndrome (HIES), had a dysregulated AMP response to bacteria in the upper respiratory tract. In addition, cells from these patients exhibited an impaired Th17 cytokine response.

In order to improve management of patients with pneumococcal infections there is a need to elucidate the role of DC-mediated cytokine responses in the delicate balance between protective immunity and immunopathology. An increased understanding of these processes is also essential for the development of pneumococcal vaccines, designed to elicit cell-mediated immunity. The work presented in this thesis contributes to our understanding of the dynamic interplay between pneumococci and host cells, and provides the opportunity to explore the potential role of vitamin D in limiting the inflammatory response in pneumococcal disease.