Theme: Mucosal Immunity

Time: Tuesday 19 June 2018
Location: Conference room 7.15.92, Blegdamsvej 3, 2200 Copenhagen N
Organizer: Graduate School of Immunology and Infectious Diseases
Chairman: Hanne Frøkiær

Afternoon

13.00	Welcome Hanne Frøkiær
13.10	Thomas T MacDonald, Queen Mary University of London, UK: Homeostasis of intestinal immunology
13.50	Andrew R Williams, University of Copenhagen: Modulation of mucosal immune function by intestinal parasites
14.30	Esther C de Jong, University of Amsterdam: Mucosal DC and retinoic acid – homing/tolerance
Break	
15.30	Michael U Martin, University of Giessen: IL-33 and barrier protection
16.10	Alessandra Geremia, University of Oxford, UK: Innate and adaptive immunity in inflammatory bowel disease
17.00	Closing remarks

Abstracts: Mucosal Immunity

Modulation of mucosal immune function by intestinal parasites

Andrew R Williams,
University of Copenhagen

Parasitic worms of the intestine (helminths) infect over one billion people worldwide, making them one of the most successful and ubiquitous classes of human pathogens. Helminths strongly modulate host mucosal immune function by inducing highly polarized T-helper (Th2) responses, as well as secreting a battery of regulatory and anti-inflammatory molecules which suppress host immune responses and promote chronic infections. Whilst helminths cause much morbidity in developing countries, their rapid elimination in developed countries is thought to contribute to rising rates of allergies and autoimmune diseases in these areas, and indeed controlled inoculation with helminths has shown clinical promise as a novel treatment for autoimmunity and inflammatory disorders.

Micosal DC and retinoic acid – homing/tolerance

Ester C de Jong,
Amsterdam UMC, Dept. Experimental Immunology, Amsterdam, Netherlands

My research is focussed on the role of dendritic cells (DCs) in the initiation of immune responses. My ongoing fascination is how various micro-organisms prime human DCs for the induction of specific types of T cell responses. My initial studies have developed in several different research lines that are all supporting the concept that T cells are programmed by DCs depending on the type of micro-organism they encountered. Moreover, I have demonstrated that DC function is also imprinted by their resident tissue. In this respect, is the vitamin A metabolite all-trans retinoic acid (RA) an important determinant of intestinal immunity. RA primes dendritic cells to express CD103 and produce RA themselves, which induces gut-homing receptors α4β7 and CCR9 and amplifies TGF-β-mediated development of Foxp3+ regulatory T (Treg) cells in mice. We investigated the effect of RA on human DCs and subsequent development of T cells. We report a novel role of RA in immune regulation by showing that RA-conditioned human DCs did not substantially enhance Foxp3 but induced α4β7(+) CCR9(+) T cells expressing high levels of interleukin (IL)-10, which were functional suppressive Treg cells. IL-10 production was dependent on DC-derived RA. The data postulates a novel mechanism for IL-10 in maintaining tolerance to the intestinal microbiome. Moreover, upon infection of the lamina propria this tolerogenic response is converted to an inflammatory response. Immunoglobulin A (IgA) immune complexes (IgA-IC), which are present after bacterial infection of the lamina propria, are important for the induction of inflammation by the human $CD103^{+}$DC subset. IgA-IC, by recognition through FcαRI, selectively amplify the production of proinflammatory cytokines TNF, IL-1β and IL-23 by human $CD103^{+}$ DCs and enhanced DC-driven Th17 cell responses. The maturation and development of the intestinal immune system are highly influenced by microbiota. However, the characterization of fetal intestinal DCs, which has not yet been exposed to microbiota, is lacking. We have investigated DC

subsets in fetal gut. The fetal intestines contained three different DC subsets: CD103-SIRPα-, CD103-SIRPα+ and CD103+SIRPα+ DCs. Interestingly, CD103+SIRPα- DCs, a cross presenting subset in adult gut, were almost absent in fetal gut, whereas CD103-SIRPα- DCs were present. All fetal intestinal DCs only produced cytokines in response to PGN, but not to LPS and Poly (I:C). Unlike the DC subsets in adult gut which have distinct functions of inducing T cell polarization, these DC subsets had equivalent capacity to drive allogeneic naïve CD4+ T cell polarization.
During my lecture I will discuss these data.

Interleukin-33 and barrier protection or The two lives of Interleukin-33: In- and outside of cells

Michael U Martin,
Immunology, Justus-Liebig-University Giessen, Germany

Interleukin-33 (IL-33) is a member of the IL-1 family of pro-inflammatory cytokines of the innate and adaptive immune systems that plays a prominent role in orchestrating inflammatory responses. IL-33 is constitutively produced by epithelial cells (skin and mucosa) and endothelial cells (blood vessels). Intracellular IL-33 translocates to the nucleus due to the presence of a nuclear localization sequence in its N-terminus where it is stored and may be involved in gene regulation. Upon injury and destruction of cells, but not after apoptosis, intracellular IL-33 is released and functions as a classical cytokine by binding to the IL-33 receptor α-chain (IL-1R4) expressed on a wide variety of tissue and immune cells. Biologically active full-length IL-33 can be proteolytically processed extracellularly by inflammatory proteases in its N-terminus to increase its biological activity by 10 – 30 times locally and temporarily before the core IL-1 structure is affected and cytokine activity is lost. The functional IL-33 receptor complex is a heterodimer consisting of IL-33 receptor α-chain (IL-1R4) and IL-1 receptor accessory protein (IL-1RAcP also called IL-1R3) that activates a common signaling module employing MyD88, IRAK molecules and TRAF6 to activate different signalling pathways most importantly the NF-κB pathway. Upon breaching of barriers, e.g. by helminths or also by some types of allergens, stored IL-33 is released and participates in the organization of immediate local inflammatory responses with the aims to control possible intruders, to repair wounds, and to skew the beginning adaptive immune response in the direction required (normally a Th2-dominated T-cell answer).

Innate and adaptive immunity in inflammatory bowel disease

Alessandra Geremia,
University of oxford, UK

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the intestine that encompasses Crohn's disease (CD) and ulcerative colitis (UC). The exact cause of IBD remains unknown. Available evidence suggests that an abnormal immune response against the microorganisms of the intestinal flora is responsible for the disease in genetically susceptible individuals. The adaptive immune response has classically been considered to play a major role in the pathogenesis of IBD. While CD has long been considered to be driven by a Th1 response, UC has been rather associated with a non-conventional Th2 response. Beside classical Th1 and Th2 responses, a role for Th17 cells, a subpopulation of inflammatory T cells, which expand in response

to interleukin (IL)-23, has also emerged. IL-23 promotes expansion and maintenance of Th17 cells, which secrete the proinflammatory cytokine IL-17 and have been implicated in the pathogenesis of many chronic inflammatory disorders. Recent studies have shown that IL-23 also acts on a population of innate lymphocytes, called innate lymphoid cells (ILC) that can contribute to inflammatory cytokine production and tissue inflammation. A role for ILC in the pathogenesis of colitis-associated cancer is also emerging.

Studying the interactions between various constituents of the innate and adaptive immune systems will certainly open new horizons in the knowledge about the immunologic mechanisms implicated in gut inflammation