Theme: Chronic Inflammation

Time: Wednesday 30 May 2018
Location: Conference room 7.15.92, Blegdamsvej 3, 2200 Copenhagen N
Organizer: Graduate School of Immunology and Infectious Diseases
Chairman: Thomas Bjarnsholt

13.00	Welcome Thomas Bjarnsholt
13.15	Mihaela Gadjeva (Gerald Pier), USA: Chronic inflammation and bacteria.
14.00	Flemming Bendtsen, Hvidovre Hospital: Chronic liver infections
14.45	Claus Henrik Nielsen, University of Copenhagen: Chronic inflammation in general
15.30	Coffee Break
16.00	Jennifer Elisseeff, John Hopkins: Immune Response to Biomaterials
16.45	Lea Klingenberg Barfod, University of Copenhagen: Chronic Malaria infection
17.30	Closing remarks

Abstracts: Chronic Inflammation

Chronic inflammation and bacteria

Mihaela Gadjeva,
Harvard, USA

It has long been considered that neutrophil responses to various infectious challenges is innately pre-determined. Here, we provide data that demonstrates that neutrophil transcriptomes and proteomes are modulated by the microbiota. Using RNAseq and quantitative proteomic approaches we defined mature neutrophil transcriptome and proteome signatures at steady state and during infection with *Pseudomonas aeruginosa*. We found that the proteomic signatures of mature neutrophils derived from the germ free (GF) and specific pathogen free (SPF) mice were significantly different. GF-serum exposed neutrophil progenitors did not mature efficiently and had compromised bactericidal properties when compared to progenitors matured in SPF-derived serum. To identify molecular pathways, we set-up an *in vitro* system where neutrophil progenitors were transduced with lenti-guides to knock-down key microbiota-driven pathway gene targets. Our data suggest that microbiota epigenetically alters neutrophil functions. During infection with *P. aeruginosa*, GF-derived neutrophils responded with alterations in transcriptional regulation, ncRNA processing, rRNA metabolic processes, mRNA processing, and splicing, while the SPF-derived neutrophils responded with alterations in acetylation. Consistently, GF mice were more susceptible to *P. aeruginosa*-induced infection compared to SPF controls. Cumulatively, the data support the concept that microbiota affects neutrophil maturation by defining not only the quantity, but also the quality of mature neutrophils.

We predict that neutrophil responses can be specifically tailored to pathogens. Neutrophil responses, although innately determined, are adapted and molded by the commensal presence. There are significant implications from these conclusions with regard to chronic infections exemplified with significant alterations in gut microbiota. Namely, failure to respond to pathogen insult may be not only a result of pathogen evasion strategies, but also inability of the host to mount protective response due to altered neutrophil priming.

Equipped with this concept in mind, we will discuss strategies to optimize innate responses to *P. aeruginosa* to improve clearance. We will examine the strengths and challenges of strategies that aim to boost immunity such as use of monospecific or bispecific mAbs targeting *P. aeruginosa* extracellular polysaccharides or enzymes that could alter biofilm formation.

Chronic liver infections

Nina Kimer,
Amager-Hvidovre Hospital**,** Copenhagen, Denmark

This talk will take offset in chronic liver infections and their impact on liver function and morbidity, and move on the impact of infections in chronic liver disease which often precipitates complications to liver disease and worsens prognosis and survival.

Moreover, this talk will address the aspects of gut microbiome imbalance and bacterial translocation in chronic liver disease and cirrhosis and the possible influence of systemic inflammation in liver disease and the perspectives of treatment or prophylaxis in patients with cirrhosis.

Chronic inflammation in autoimmune disease

Claus Henrik Nielsen,
Institute for Inflammation Research, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital Rigshospital, Copenhagen, Denmark

After a brief introduction to autoimmune diseases, representative examples of autoimmune diseases will be detailed: Autoimmune thyroid disease, comprising Graves' disease and Hashimoto's thyroiditis are organ-specific autoimmune disease involving a few, well-described self-antigens. Rheumatoid arthritis (RA), on the other hand, is a systemic autoimmune disease in which many autoantigens may be involved. The majority of RA patients show immune responses to citrullinated self-proteins, exemplifying how post-translational modification (PTMs) of proteins may generate neo-antigens that elicit autoimmune responses. PTM, in general, and citrullination, in particular, will be described, and the possibility of targeting citrullination therapeutically will be discussed in the context of therapies already in use.

Lessons from Translation: Engineering a pro-regenerative immune environment with biomaterials

Jennifer Elisseeff,
Johns Hopkins University School of Medicine, Baltimore, Maryland

The immune system is the first responder to trauma and foreign bodies such as biomaterials, yet this response and its capacity to orchestrate tissue repair has been largely ignored. Today, biomaterials can be engineered with exquisite control over physical (mechanical and geometric) properties and can present an array of spatially controlled biological cues in the form of peptides, proteins, or sugars. Until now, these scaffolds have directly targeted stem cells, vascular development, and differentiated cells to stimulate tissue formation or wound healing. Unfortunately stem cells have not proven to be the panacea for rebuilding tissues. Translating tissue engineering technologies to the clinic, we discovered cells from adaptive immune system responded to the biomaterials. We profiled in depth the immunological response to the wound environment in combination with biological scaffolds. The adaptive immune system, specifically Th2 T cells, is required for the scaffold stimulation of wound repair. We are now investigating in detail the innate and adaptive immune response to synthetic and biological scaffolds. In parallel we are exploiting these discoveries to design immunomodulatory materials for tissue repair. Ultimately, targeting the immune system represents a paradigm shift for the field and will bring to fruition, at least in part, the promise of regenerative medicine.

Persisting viral infection and the T-cell response

Alan Randrup Thomsen,
University of Copenhagen

Persisting viral infections is a fact of human life. Most of these infections are not associated with clinical disease. On the other hand, some persisting viruses induce ongoing tissue damage primarily or to a large extent due to chronic activation of the immune system, e.g. hepatitis B and C. For this reason it is important to understand the complex interplay between persisting virus and the antiviral immune response. Studies primarily in murine models of chronic infections have made it clear that persiting virus markedly impact the quality of the induced T cell response. In the context of chronic antigen stimulation, CD8 T cells differentiate into a more or less dysfunctional phenotype often called “exhausted” cells. These cells differ in several ways from “normal” CD8 memory T cells generated when antigen is eliminated. Regarding the CD4 T cells, these also acquire a different functional status from what dominates following acute infection. Thus, in the context of chronic antigen stimulation IL-21 producing follicular T helper cells dominate the virus-specific CD4 T cell population. The underlying mechanisms and functional consequences of these differences will be discussed.