Research Interests – Prof. Dr. Veit Hornung

Innate immunity – a question of self or non-self and beyond

The physical integrity of every living organism is at constant risk of being attacked by micro-organisms of its environment or pathologically transformed cells of its own body. The main function of the cells, molecules and mechanisms that we refer to as the 'immune system' is to maintain the individual integrity of our body against these threats. In this context, the innate branch of the immune system serves as the first line of defence that has the intricate task to detect molecules and organisms that are of potential danger to the organism. Central to this complex task is a repertoire of so called pattern recognition receptors (PRRs) that are expressed by cells of the innate immune system. In the course of evolution, these PRRs have evolved to detect molecules that are characteristic for microorganisms, but not present within the host. As such, the ligands or targets of these PRRs are commonly referred to as microbe-associated molecular patterns (MAMPs).

While the innate immune system plays an important role in initiating and orchestrating adaptive immune responses (T and B cell activation), it can also trigger immediate antimicrobial effector functions at the cellular and systemic level, perceived as an inflammatory response. While inflammation constitutes a beneficial response pattern of the organism to fight microbial infection and to restore tissue homeostasis, inflammation can also lead to disease if abnormal in magnitude, duration, localisation or cause. It is now well appreciated that many chronic inflammatory diseases are initiated or perpetuated by a misguided innate immune system that responds to endogenous damage signals as if microbial infection was at play. To this end, PRRs of the innate immune system misinterpret molecules of its own organism as dangerous and trigger inflammatory responses. In analogy to the MAMP terminology, these signals are commonly referred to as damage associated molecular patterns (DAMPs).

PRRs sense MAMPs and initiate effector mechanisms that are geared to eliminate the microbial pathogen. Highlighted are areas of interest of my research group.

In our research projects, we are trying to understand what mechanisms are employed by the innate immune system to distinguish self from non-self or harmless from dangerous, respectively. To this end, (i) we are trying to decipher relevant MAMP or DAMP molecules during infection or sterile inflammation, (ii) we aim at the identification of novel PRRs, signalling cascades and their functional roles, and (iii) we develop strategies to manipulate this interface for therapeutic application. Specifically, in the past years, research in my group has mainly focused on two topics in innate immunity that approach the fascinating question of non-self recognition from two different perspectives:

From the 'ligand perspective', we have extensively studied **how nucleic acids are sensed by PRRs** of the innate immune system and what effector functions are initiated by these sensing modalities. Since most microbial pathogens expose some type of nucleic acid or degradation products thereof during their life cycle (e.g. genomic DNA/RNA, replication products or RNA transcripts), nucleic acid detection plays a paramount role in innate immune surveillance. While classic MAMP structures can be present in microbial nucleic acids (e.g. 5' triphosphate dsRNA being sensed by RIG-I), microbe-derived nucleic acids often lack characteristic features that label them as non-self to the host (e.g. dsDNA). Here, the host employs the strategy to interpret nucleic acids as non-self or dangerous, if they arise in compartments that are usually devoid of this class of nucleic acid (e.g. detection of double stranded DNA by the cGAS-STING axis in the cytosol).

Nucleic acid detection is tightly connected to the type I IFN system that serves as a powerful branch to trigger antiviral and adaptive immune responses. As such, insight into nucleic acid sensing PRR systems also opens new avenues for the development of therapeutic approaches that are geared at activating the immune system (e.g. therapeutic vaccines against cancer cells). At the same time, dissecting these pathways also helps to understand certain disease entities, in which an overactive immune system is triggered by erroneous recognition of endogenous nucleic acids (e.g. the autoimmune disease systemic lupus erythematosus, SLE).

Conversely, from the 'PRR perspective' we have been specifically interested in the family of so-called **inflammasome sensors** that are coupled to the proteolytic activation of caspase-1, which results in the maturation and secretion of IL-1β. IL-1β is a highly pro-inflammatory cytokine with pleiotropic activities and its activity has been implicated in many sterile inflammatory diseases. Intriguingly, inflammasome-driven IL-1 activation is not only at play in diseases where inflammation is the predominant symptom (e.g. gout), but also in diseases such

as type II diabetes, atherosclerosis or Alzheimer's disease, where a chronic, smouldering inflammatory response perpetuates or even initiates disease pathology. These conditions pose a big health care burden to our modern societies with yet unmet therapeutic needs. While we have a fairly good understanding that inflammasomes are involved in these diseases, we know relatively little about their molecular modes of action. Here, our focus is to explore basic principles of inflammasome activation at the molecular and cellular level. We believe that these studies will not only provide us with novel insights into basic biology, but also allow us to identify targets for the future development of therapeutic applications.