1. Objectives of this study

Plasmacytoid dendritic cells (pDCs) have recently been identified as sentinels for viral pathogens in humans and mice. They are best known for producing high amounts of type I interferons. Accumulating evidence suggests that besides their production of IFNs, activated pDCs are able to release a panel of immunomodulatory mediators that impact several other cell types of the immune system. In addition to their benevolent role in antimicrobial defense, pDCs have also been implicated in the pathogenesis of certain diseases. This is based on findings that pDCs accumulate in target tissues of several autoimmune diseases where they may serve as a source of pro-inflammatory cytokines. However, the precise function of pDCs in inflammatory reactions, including antiviral immunity, remains poorly understood. The encompassing goal of this dissertation was to determine how pDCs contribute to the orchestration of an antiviral immune response using influenza virus infection in mice as a model. The rationale for this study is to better understand the induction and regulation of pDC functions and to provide the basis for optimizing antiviral and anti-inflammatory treatment strategies.

The following three specific aims were addressed:

Aim 1. To determine the activation/differentiation pathways of pDCs using the prototypic Toll-like receptor (TLR) agonists influenza virus and CpG 1826

In this aim, we asked the question whether differential activation of pDCs could result in the modulation of their differentiation. PDCs were activated by the TLR7 ligand influenza virus A/PR/8 and by the TLR9 ligand CpG 1826 oligonucleotide *in vitro* and *in vivo,* and characterized for their phenotype and functions. As a part of the experimental approach, micro array gene expression profiles were generated in order to identify a possible stimulus-specific transcriptome. We also tested whether the kinetics and the quality of intracellular signaling pathways in pDCs could provide a possible mechanistic explanation of the distinct effects observed with those two TLR ligands.

Aim 2. To characterize pDC migration pathways in the steady-state and into sites of inflammation

We hypothesized that pDCs take part in a broad immunosurveillance program of the entire body that is mediated by distinct trafficking routes. We analyzed which organs pDCs reside in, and what molecules guide their migration routes throughout the organism. To this end, we performed homing assays under homeostatic and inflammatory conditions. The underlying molecular mechanism and the specific involvement of adhesion molecules and chemokine receptors was determined by the use of blocking reagents.

Aim 3. To investigate the role of pDCs during the immune response to influenza virus infection

In this aim, the functional contributions of pDCs to anti-influenza immunity were determined. In order to address this question, we made use of a newly described mouse strain, Ikaros$^{L/L}$, which harbors a mutation in the Ikaros gene locus that results in a lack of peripheral pDCs. We established a murine influenza infection model, and monitored the course of disease in Ikaros$^{L/L}$ mice as compared to wild-type mice. In particular, we determined the generation of anti-influenza B and T cell responses. We asked whether T cell recruitment is impaired in infected Ikaros$^{L/L}$ mice. Finally, we analyzed whether pDC-deficiency results in altered generation of antigen-specific effector and memory T cells.