2. Summary

Plasmacytoid dendritic cells (pDCs) have been implicated as regulators of infectious diseases, autoimmune disorders and cancer. pDCs can promote immune responses against viral infections leading to viral clearance and resolution of infection. However, pDCs may also support chronic inflammatory diseases, and interfere with anti-tumor activity. The capability of activated pDCs to produce large amounts of type I interferons and other proinflammatory mediators is thought to be responsible for their actions. Many questions concerning the precise contributions of pDCs to disease have remained unanswered, as their unequivocal identification *in vivo* requires several phenotypic markers. In the present study, we have made use of a novel mouse strain, DPE^{GFP}, in which pDCs are transgenically modified to express the green fluorescent protein (GFP). The GFP-tag enables their identification and purification *ex vivo* at levels that had not been achieved in the past. In the first chapter, we investigated how differential activation of pDCs by TLR ligands modulates their functions. In the second chapter, we determined the migratory behavior of pDCs to sites of inflammation. In the third chapter, we assessed the role of pDCs in the immune response against influenza virus infection.

In order to address the first question, we studied the effects of two model ligands, influenza virus A/PR/8 and CpG 1826 oligonucleotide, on the phenotype and the functions of pDCs. Upon activation, pDCs differentiated into two distinct subsets, one that produced large amounts of type I interferons after treatment with PR/8 virus, while the other one induced by CpG 1826 was characterized by higher levels of costimulatory molecules and pro-inflammatory cytokines and chemokines. Microarray analysis and investigation of intracellular signaling pathways allowed for the discovery of a distinct activation program that helps to understand pDCs' versatile functions in antimicrobial defense and inflammation.

In the second chapter, we extended previous observations that pDCs express a distinct panel of adhesion molecules and chemokine receptors. In homing assays we demonstrated

that blood-borne pDCs can enter various tissues, including lymphoid and peripheral organs. In a peritonitis model, we found that pDCs preferentially accumulate at sites of inflammation. Finally, we deciphered the molecules involved in pDC migration into the inflamed peritoneum.

In the final study, we asked whether the absence of pDCs alters immune responses to infection with influenza virus A/PR/8. Surprisingly, we found that Ikaros$^{L/L}$ mice, which lack peripheral pDCs, appeared to have a similar course of disease and viral clearance, as well as comparable levels of neutralizing antibodies. However, we observed a delayed recruitment of T cells into infected airways, which could be overcome by reconstitution of Ikaros$^{L/L}$ mice with wild-type pDCs. We showed that activation and differentiation of effector/memory CD8$^+$ T cells was not impaired in Ikaros$^{L/L}$ mice.

In conclusion, this study provides novel insights into the functional and migratory properties of pDCs, and suggests that pDCs are dispensable for the resolution of primary influenza virus infections.