CHAPTER 8

Summary

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The aim of thesis was to increase our insight into the pathological mechanisms behind LCH by studying different aspects of healthy DCs, LCH cells, and a mouse model of histiocytosis. Furthermore, we initiated a study to evaluate a human monoclonal antibody directed against the cell surface protein CD1a in order to find a rational therapy for LCH.

In LCH, the pathological LCs appear to be in an immature, activated state. The recently described involvement of the Wnt/beta-catenin signaling pathway in the differentiation and maturation of human hematopoietic progenitor cells towards DCs and mouse bone marrow derived DCs, led us to investigate a putative role for beta-catenin in LCH cells and in the differentiation and maturation of monocytes to moDCs, as described in **Chapter 3**. The finding that the presence of transcriptionally active beta-catenin is crucial in the early stages of monocyte differentiation and that its absence leads to an inhibition in maturation marker expression led us to conclude that the absence of this form of beta-catenin in LCH cells might be an important factor responsible for the immature phenotype of these pathological cells. We, therefore, propose to study the possibility to activate transcriptionally active beta-catenin in LCH cells by stimulation of the Wnt-pathway to determine whether the maturation block can be overcome. In **Chapter 4** a mouse model of malignant histiocytosis, which was created in the 1980s, is re-evaluated. This model was made by infecting BALB/c and DDD mice with Malignant Histiocytosis Sarcoma Virus (MHSV). The reason for evaluation was the increased knowledge on the mononuclear phagocytic system in combination with the increased insights in histiocytic disorders. The initial description of the MHSV model reported on the viral transformation of mature macrophages. Our phenotypical analysis of the affected cells and derived cell lines showed, however, that $CD8\alpha^{+}Langerin^{+}$ DCs located in the spleen were infected together with other myeloid subsets, including precursor cells, and Mφ. Reintroduction of primary tumor-derived cell lines into healthy mice showed the capability of these tumor cells to home to different organs and to adapt their phenotype to the microenvironment by up and downregulation of DC and Mφ cell surface markers. The conclusion of our re-evaluation is that the MHSV model represents a heterogeneous neoplastic disease with characteristics of Mφ/DC sarcomas.

LCH is a heterogeneous disorder which can present as one lesion at a single site which requires minimal to no intervention to a widespread disease which can be life-threatening if not treated with multiple chemotherapeutic agents. The medications used are not specific for the disease process in LCH, but rather to limit general pathways such as immune responses and proliferation of cells, with the potential consequences of serious side effects. Finding targeted therapies for LCH is therefore required. In **Chapter 5**, the evaluation of a completely human anti-human anti-CD1a monoclonal antibody CR2113 is described. CD1a is a cell surface marker which is expressed on LCH cells and would therefore be a very specific agent for the treatment of LCH. The anti-CD1a antibody has been tested for its affinity and specificity for the CD1a molecule. Furthermore, the cytotoxic potency on CD1a expressing cells was determined. CR2113 has proven to bind specifically to CD1a and effectively kill CD1a expressing cells. This anti-CD1a monoclonal antibody should, therefore, be further investigated in a pre-clinical setting for its usefulness as a therapeutic agent for LCH.

Shortened telomeres are a characteristic of premalignant disorders and cancers. In **Chapter 6**, telomere lengths of LCH cells isolated from local, multisystem and systemic LCH lesions were analyzed and compared to telomere lengths in healthy skin LCs and LCs found in reactive lymph nodes. LCH cells were found to have significant telomere length shortening in all the manifestations of disease compared with the control cells. This suggests that a possible intrinsic and fundamental alteration, similar to neoplastic disorders, might play a role in the etiology and/or pathogenesis of LCH.