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THESIS OUTLINE

It is generally accepted that macrophages play an important role during the pathogenesis of multiple sclerosis (MS), which may be both beneficial and detrimental. Different subtypes of macrophages exist, the two extremes are classically activated (CA/M1), proinflammatory, macrophages and alternatively activated (AA/M2), growth promoting, macrophages. These two types of macrophages could be involved in different stages, damage and repair, of lesion formation in MS. In the central nervous system (CNS) and specifically in MS relatively little research has been done focusing on the divergent effects of the different subtypes of macrophages. In this thesis the aim was to determine the effects of differently activated macrophages on axonal damage and repair.

Chapter 2 describes a specific model for de- and remyelination we set-up in whole brain spheroid cultures. In spheroid cultures all CNS cells are present in a three dimensional conformation and multilayered myelin is formed. Axons are myelinated in spheroids, in contrast to MS lesions where the myelin sheath is damaged. Therefore, in order to mimic the demyelinated state in the spheroid model we developed a model to induce demyelination in the spheroids. Using lysophosphatidylcholine demyelination was induced, without effects on other CNS cell types.

In **chapter 3** we determined the migratory characteristics of differently activated macrophages in the context of the CNS. We studied the migration of AA and CA macrophages towards conditioned medium from different CNS cell types, motility and adhesion. CA macrophages were attracted towards astrocytes. AA macrophages were attracted towards neurons. CA macrophages were less motile and adhered more compared to AA macrophages.

Next, we addressed the question how the AA phenotype is induced in MS lesions. It has been suggested that in MS lesions foamy macrophages have a AA phenotype, since they expressed little pro-inflammatory cytokines and iNOS. In vitro, myelin ingestion was found to inhibit the lipopolysaccharide (LPS) response. We hypothesized that activation of liver X receptor (LXR) by myelin ingestion could lead to the AA phenotype and reduction in LPS response due to the blocking effect of LXR on NF- κ B. In **chapter 4** we investigated whether knock-down of LXR could inhibit the repression of the LPS response seen after myelin ingestion. LXR knock-down restored the LPS response in foamy macrophages.

However, during this study we observed differences between myelin preparations in cytokine induction. One preparation did induce the expression of IL-10 and TNF- α and LPS insensitivity, while another did not. We questioned whether LPS contamination in one of the preparations was responsible for induction of both the high anti-inflammatory cytokine levels and the LPS insensitivity (**chapter 5**).

Chapters 6 focuses on the phagocytosis and degradation of neurons and neuronal fragments by the different subtypes of macrophages. CA macrophages phagocytosed more neuronal fragments and neurons compared to AA macrophages. The degradation of neuronal antigens proceeded at a similar pace in the differently activated macrophages.

Appendix

We next investigated whether the differently activated macrophages could have divergent effects on neuronal cultures. We exposed neuronal cultures directly to differently activated macrophages or their conditioned medium. We found that CA macrophages are damaging to neurons, due to the release of cytotoxic agents. The AA macrophages are not neurotoxic and release nerve growth factors (**chapter 7**).

In **Chapter 8** we focus on the presence of CA and AA macrophages in MS lesions. In the course of this thesis we found that CA and AA macrophages have divergent effects on neurons. CA macrophages were found to induce damage, while AA macrophages did not and even expressed neuronal growth factors (**chapter 7**). We therefore wanted to determine whether these divergent phenotypes actually occurred in MS lesions (**chapter 8**). Indications that differently activated macrophages were present in MS lesions had been found, but until now nobody had ever performed a systematic study of markers for both CA and AA macrophages in MS lesions. We selected a panel of markers based on literature that should be differently expressed on human AA versus CA macrophages and determined their expression in lesions. In MS lesions the expression of markers for the CA phenotype was much higher compared to the AA phenotype, indicating that macrophages in MS lesions have a more CA phenotype.