Thesis summary (English)

The primary aim of the thesis "***Microglia priming in the aging brain: Implications for neurodegeneration"*** was to understand microglia phenotypes associated with brain aging and the potential mechanisms for this age-associated change. Microglia in the aging brain assume a hypersensitive proinflammatory phenotype termed as "priming". Brain aging is the degenerative result of multiple cellular insults. DNA damage accumulation and critical shortening of the ends of chromosomes in cells called telomeres are two well-studied mechanisms that cause organismal aging. In addition to aging mice, we utilized transgenic mouse models in which the above mentioned aging mechanisms are triggered artificially to accelerate aging.

For this purpose, we utilized the ERCC1$^{\Delta/-}$ mice, a mouse model of DNA damage accumulation previously shown to suffer cognitive impairment and known to model a human progeroid disorder to understand microglia phenotype and functionality. In addition to aging mice, ERCC1$^{\Delta/-}$ proved to be a good mouse model to study age associated phenotypic changes in microglia. In the ERCC1$^{\Delta/-}$ mice, age associated microglia priming was shown to be a response to neuronal dysfunction as a result of genotoxic stress. The prominence of microglia priming in the white matter tracts of the brain suggests that the axons might be primarily affected by the accumulation of DNA damage. The exact mechanism by which DNA damage accumulation affects axonal function is yet to be worked out. However, a possible mechanism could be transcriptional blockage as a consequence of DNA damage accumulation inducing metabolic stress and axonal dystrophy in neurons.

On the other hand, in a mouse model of telomere shortening, the most prominent change observed in microglia was the increased cytokine response to peripheral inflammation due to alterations in the blood brain barrier. The results show that telomere shortening occurs in microglia with brain aging. However, critical telomere shortening is not the reason for microglia priming in the aging brain. Brain endothelium particularly in the white matter are more susceptible to telomere attrition than microglia as a cell type. These studies together highlight two possible mechanisms that make the white matter of the aging brain a particularly vulnerable target in the aging brain.

The thesis also highlights regional differences between gray and white matter in microglia priming in the aging mouse and human brain. Surprisingly, microglia priming in the white matter already begins at middle age in humans. The increased and persistent white matter microglia priming draws attention to the role of white matter changes particularly in axons in brain aging and explores the possible use of white matter priming as a predictive factor to envisage the progression of cognitive aging and onset of neurodegeneration. It is well known that other clinical parameters such as Aβ plaque pathology, tau accumulation do not linearly correlate to cognitive impairments in the elderly. Microglia-mediated neuroinflammation in the white matter together with functional assessment of white matter function using non-invasive approaches such as Diffusion Tensor Imaging (DTI) and pathological markers of axonal dystrophy could yield powerful predictive tools for the assessment of cognitive impairment and pathological progression of neurodegeneration in the elderly.