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Impact of Genetic Variability on Early Immune Reactions following Nerve Injury

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ABSTRACT

Injury to the central nervous system (CNS) is frequently associated with significant morbidity, in worst case mortality. This in turn leads to considerable disease burden for the individual and also for society. The spectrum of conditions that cause damage to the CNS is wide and highly diverse, ranging from acute trauma to degenerative diseases that progress over decades. But in spite of the heterogeneity, there exist common aspects. For instance, there is often interplay between the immune and nervous systems in one stage or another of disease. Also, the genetic background of the individual influences both susceptibility to and severity of the disease. This thesis focuses on the early immune reactions that occur after CNS injury in rodents, based on the hypothesis that early immune reactions affect important downstream events, not least nerve cell death.

In **study I** a large rat experimental cross F2(DAxPVG) was created from the inbred strains DA and PVG. The global transcriptome in the spinal cord was screened using microarrays five days after ventral root avulsion (VRA), a reproducible nerve injury model. In parallel, whole genome mapping was performed. The expression and genetic data was co-analyzed to identify gene regions regulating components of the complement system, in turn associated with loss of synapses. Lastly, we identified a link between the cholinergic and complement systems, which was confirmed *in vitro*.

In **study II**, data from the F2(DAxPVG) cross was used to analyze regulation of complement receptors following injury. We found a strong cis-regulatory influence acting on the expression of complement receptor 2 (CR2), a receptor mostly associated with B cell functions, but with unknown role in the adult CNS. CR2 was up regulated on astrocytes and protected from injury induced synapse loss in rodents. Levels of CR2 were increased in the cerebrospinal fluid (CSF) of rats following injury, but also in the CSF of patients with multiple sclerosis as compared to controls, implicating a possible role for CR2 also in context of human disease.

Traumatic brain injury (TBI) is one of the leading causes of death in the young population. Secondary events following initial injury contribute to the damage, but are not fully understood. In **study III** TBI was performed on DA and PVG rats and the ensuing injury processes analyzed at both the molecular and cellular levels using microarrays and flow cytometry. Large strain differences in complement activation and the size and composition of multiple immune cell populations were found. Complement was also found to label axons of injured neurons and the degree of complement expression correlated with the levels of neurofilament-light in CSF, a marker of axonal injury.

C-type lectins (CLECs) are a group of immune molecules structurally similar to members of the complement family. Study I demonstrated several loci co-regulating the expression of complement and CLEC transcripts, thus providing a link between the two families. In **study IV** we examined the properties of a congenic rat strain, Aplec, which onto DA background has a very small genomic insert from PVG consisting of 7 CLEC genes. The Aplec rat displayed improved survival of motor neurons following VRA compared to DA, which in turn was associated with increased infiltration of T cells. This demonstrates that CLECs convey neuroprotection after nerve root injury, potentially through T cell pathways.

These results provide insights into the molecular pathways regulating inflammation after mechanical nerve injuries, in turn of relevance for nerve injury-induced synaptic remodeling and neurodegeneration.