

Research Project Summary

Myelin is an insulating, lipid-rich material that is produced by oligodendrocytes in the central nervous system. It forms the myelin sheath around the axons of the neuronal cells and is essential for the proper nerve function. Canavan disease is a rare recessive autosomal white matter leukodystrophy that is caused by mutations of the aspartoacylase gene (*ASPA*), leading to myelin sheath degeneration and severe neurological impairment. *ASPA* is highly expressed in oligodendrocytes after birth, during the formation of the myelin sheath around the axons (myelination). *ASPA* is an enzyme that catalyzes the conversion of the most abundant amino acid in the brain, N-acetylaspartate (NAA) to acetate and aspartic acid. In Canavan disease there is loss of the *ASPA* activity in oligodendrocytes, which leads to elevation of the NAA levels in the central nervous system of the Canavan disease patients. Nevertheless, the mechanism of the Canavan disease pathogenesis remains unknown. We have previously developed a genetic animal model of Canavan disease, the *nur7* mouse, which carries a mutation in the *ASPA* gene and shows symptoms that strikingly resemble the human disease. We recently used the *nur7* mouse to establish cultures of oligodendrocytes in order to investigate the molecular mechanisms of the Canavan disease pathogenesis. Our studies showed that loss of *ASPA* function does not cause death of oligodendrocytes or myelination defects, indicating that *ASPA* might have a role outside of myelination. Furthermore, we found that high levels of NAA observed in the central nervous system of the Canavan disease patients have no toxic effect on oligodendrocytes. To determine the molecular pathways for Canavan disease pathogenesis, we performed a high-throughput analysis of the gene expression changes in oligodendrocytes isolated from the *nur7* mutant mice, which lack *ASPA* activity. This approach has revealed a number of genes that are affected in the *nur7* mutant oligodendrocytes. As a next step, we will evaluate the importance of these genes in Canavan disease pathogenesis using a sophisticated myelinating cell culture system. This approach could help us identify new molecular pathways and therapeutic targets for Canavan disease.