The molecular basis of prion toxicity: Transcriptomics in an organotypic slice model

Summary / Zusammenfassung

Prion diseases are inevitably fatal neurodegenerative diseases where the proteinaceous infectious particle, the prion, is the disease-causing agent. The current hypothesis is that the endogenous prion protein (PrPC) misfolds into the disease-associated conformation (PrPSc). PrPSc can then act as a template for further oligomerization and aggregation. However, it is not known how these aggregated proteins lead to neurotoxicity.

Our lab has established a method that allows for ex vivo prion infection of living brain slices prepared from mice (the “prion model”). In addition, it was observed that treatment of cerebellar slices with PrP antibodies induces neurotoxicity in a time-, dose- and PrP-dependent manner (the “antibody model”).

We have performed a timecourse analysis of these two ex vivo models of prion-mediated neurotoxicity in terms of cell proliferation, cell death (propidium iodide incorporation) and cell loss over time.

Corresponding microarray analyses for each timepoint have also been performed in both models. In addition, a microarray analysis was performed to identify prion-altered gene expression programs that are returned to normal upon treatment with neuroprotective compounds. Through pharmacological inhibitors of receptors, enzymes and channels we interfere with different pathways and try to find pathways that are crucial in mediating PrP dependent neurotoxicity.

Keywords / Suchbegriffe

Prion disease, Neurotoxicity, mechanism, POSCA, Microarray

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