

## **ABSTRACT**

### **Study of mechanisms influencing inflammatory and neurodegenerative processes and their subsequent treatment in models of ALS and spinal cord injury**

The mechanisms of neurodegeneration during spinal cord injury (SCI) and amyotrophic lateral sclerosis (ALS) are complex and poorly understood, which is why it's troublesome to counteract them with effective therapies. This thesis explores the pathways of autophagy, endoplasmic reticulum (ER) stress, and the mammalian target of rapamycin (mTOR) pathway that regulates these mechanisms in models of both SCI and ALS. Upregulation of autophagy and the mTOR pathway in an *in vivo* contusion SCI injury model was confirmed. The mTOR inhibition led to upregulation of autophagy, reduction of inflammation, and recovery in acute SCI. Upregulated autophagy was discovered in the SOD1G93A rat model of ALS. By treating the ALS rats with human mesenchymal stem cells, prolonged survival of the animals and preservation of motor neurons (MNs) possibly occurred through modulation of autophagy. The involvement of the mTOR pathway in the degeneration of MNs was further explored in the context of astrocytes. Pleckstrin homology like domain family A member 3 (PHLDA3), a newly discovered repressor of the mTOR pathway, was found to lead to ER stress if overexpressed in astrocytes and can lead to the death of MNs *in vitro*. Finally, the mTOR pathway was shown to be involved in the maturation of a newly developed model of primary spinal cord neurons. Primary neurons isolated from embryonic mice mature *in vitro* and lose their regenerative ability, making the model useful for further exploration of mechanisms involved in degeneration and regeneration of the spinal cord neurons. Together these results broaden the knowledge of the complex processes that take place in the spinal cord during the pathology and treatment of SCI and ALS.

### **Keywords**

spinal cord injury, amyotrophic lateral sclerosis, neurodegeneration, inflammation, autophagy, ER stress, mTOR, PHLDA3, *in vitro* model