OPTINEURIN DYSFUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is the fastest progressing adult neurodegenerative disorder affecting motor neurons in the brain, brainstem and spinal cord. Mutations in a multifunctional ubiquitin-binding adaptor protein optineurin have recently been found in a subset of ALS patients. Optineurin has been shown to regulate numerous cellular processes including inflammatory signaling, autophagy, vesicular trafficking and cell death, but its role in ALS pathogenesis remains unclear. Two main ALS hallmarks - proteinopathy and chronic neuroinflammation - are common to all ALS patients, despite their unusually wide genetic and clinical heterogeneity. Neuroinflammation triggers neuronal damage and death by enhancing glutamate toxicity, protein aggregation and/or oxidative stress. Nevertheless, various anti-inflammatory approaches have failed to stop or slow down disease progression. For this reason, it is imperative to redefine the role of the immune system in neurodegeneration. Here I will describe our optineurin loss of function mouse model in which we found diminished Tank binding kinase 1 (TBK1) activation in microglia and neurons. Diminished TBK1 activation led to a decreased production of immunomodulatory cytokine IFN-beta in microglia and neurons. This in turn led to a subsequent disbalance of proinflammatory and anti-inflammatory factors. Understanding the role of immunity in ALS is important for designing targeted approaches, which will hopefully be able to support the protective functions of the immune system while suppressing toxic neuroinflammation.