Description for the public

A stroke is a medical condition in which poor blood supply to the brain results in cells death. Stroke was the second, after heart disease and before cancer, reason of death worldwide in 2017 affecting in total 6.2 million individuals. The dysfunction of the brain vary widely depending on the size and location of the lesion, but usually corresponds to the area of injury. Disability affects 75% of stroke survivors and it can be physical, mental, emotional or combination of these three. Among survivals, 30 to 50% will develop post-stroke depression, which is characterized by sleep disturbances, lower self-esteem, lethargy and social withdrawal, and is often drug-resistance. This project deals with ischemic optic neuropathy, which is poorly understood type of central nervous system white matter stroke. It is primary reason of permanent blindness due to retinal ganglion cell axon damage and cell death. Although such white matter ischemia comprises an important source of human disability, the molecular mechanisms contributing to neuronal dysfunction and death remain poorly understood, and there exist few effective therapies to prevent or restore loss of vision. Despite intensive research, it is still unclear why neurons die when the brain tissue suffers ischemia, and why they lose the ability to regenerate even if the blood flow in the brain is restored. The neuroscientists agree that the most plausible reason of this phenomenon is deprivation of neurons and supportive cells from essential blood-supplied trophic factors or losing the responsiveness to the external stimulation. This initiates ischemic cascades making neurons to execute programmed cell death. One of the most important mediator of neuronal survival is nuclear factor of activated T-cells (NFAT). Together with its upstream activator and several inhibitors, it binds the scaffold A-kinase anchoring protein α (mAKAP). It is believed that mAKAP forms a highly specialized center of signal integration, which can serve as a target for regulation of NFAT activity. We hypothesize that mAKAPα may be a critical node in the neuronal signal transduction network by orchestrating NFAT activation in neuroprotection and axon growth. In this project, we would like to test this hypothesis. The experiments proposed by us are complementary. In Aim1, we will dissect *in vitro* how NFAT might be regulated by a multimolecular signaling complex, obtaining new mechanistic data regarding the localized regulation of a transcription factor by multiple upstream signaling pathways that act in concert to control gene expression. In Aims 2 and 3, we will test whether inhibition of NFAT transcriptional activity is necessary and sufficient to promote retinal ganglion cell survival *in vivo.* To achieve it, we will use NFAT knockout mice and examine how manipulating the pathways hypothesized to regulate NFAT can be effective in modulating the ischemic outcome. Based on these data we plan to use virus-based gene therapy to attempt if our adenoviruses could be helpful to minimize optic nerve injury and restore vision in progressive ischemic optic neuropathy. Our experiments should provide new insights into both retinal disease and white matter stroke in general, inspiring new therapeutic approaches to a problem of great clinical significance. This would be a significant step forward in the understanding of molecular mechanisms of stroke neuropathology and should reveal a pre-clinical potential of NFAT signaling modulators in developing a new treatment strategy.