The role of Diaph1 signaling in diabetic neuropathy pathogenesis

In our project, we plan to determine the role of mammalian Diaphanous 1 (Diaph1) signaling in diabetic neuropathy – one of the most prominent neurological complications of diabetes, affecting from 30 to 70% of all diabetic patients worldwide. Diabetic neuropathy is the single most common reason for foot ulcerations and amputation and is responsible for severe sensory abnormalities and reduced quality of life in thousands of diabetic patients worldwide. The total annual costs incurred by all payers in treating people with diabetes and related complications in the EU alone were estimated to be €90 billion in 2011, and the trend is upward. So far, despite intensive studies, efforts have failed to establish a coherent image of the causes of this disease. It is currently believed that the neurodegenerative changes that occur in the diabetic nerve arise from a number of overlapping processes such as increased inflammation, increased oxidative stress, protein glycation and axonal transport alteration and point to Diaph1 and RAGE as potential molecular contributors and therapeutic targets in the disease.

Diaph1, Diaphanous1-related protein, belongs to the family of Rho-GTPase formins and is involved in actin structure modification and modulation of microtubulin dynamics. Diaph1 was first described as an intracellular RAGE ligand in 2008 and since then intensive efforts have been made in revealing the role of Diaph1-RAGE signaling in the nervous system. To date, the detailed mechanisms of RAGE and Diaph1 contribution to neurodegeneration remain unclear, however studies indicate that Diaph1 expression might be tightly correlated with RAGE-triggered excessive protein glycation and inflammation, affecting axonal transport and contributing to the development of neuropathological changes in the diabetic peripheral nerve (Fig.1).

Here, in this proposal, based on literature and compelling data from of our own laboratories we hypothesize that long-term, sustained hyperglycemia triggers increased RAGE-driven neuroinflammation and increased cellular stress concomitant with downregulation of Diaph1, increased cytoskeleton protein glycation, their malfunction and impaired binding to Diaph1 leading to impaired axonal transport and long-term neuronal dysfunction resulting in the development of diabetic neuropathy. We predict that the deletion of the Diaph1 encoding gene alone will affect the pathogenesis of diabetic neuropathy, accelerating the onset of the disease that might be alleviated in Diaph1-RAGE double knockout. In order to test this hypothesis, we will employ a translational approach and examine both samples from diabetic patients as well as from streptozotocin induced mouse model of diabetes. In the first phase of the project we will study expression levels of Diaph1, RAGE, cytoskeleton proteins and inflammatory and oxidative stress markers at the tissue level at set time points over the course of the disease and in the second phase, we will test our hypothesis in primary cell cultures obtained from diabetic mice and observe changes in neuronal morphology and function over the course of the experiment. We believe that the dual role of Diaph1 – as a cytoskeleton protein modulator and RAGE binding partner, makes this molecule of special interest in the studies of diabetes related neuronal changes. Deciphering the exact role of Diaph1 signaling in diabetic neuropathy may become a milestone in our basic understanding of mechanisms governing neurodegeneration, helping us delineate previously unknown molecular links between complex signaling pathways involved in neuronal dysfunction in diabetic patients and forming the first step towards successful prevention and treatment of this and similar neurodegenerative disorders.

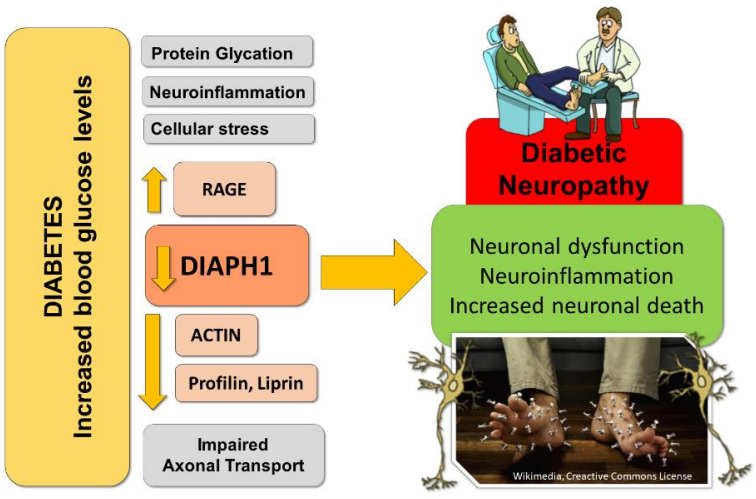

Figure 1. Long term increase in blood sugar, the hallmark of diabetes, leads to numerous physiological changes, affecting a number of tissues in our bodies and if not treated leading to their malfunction. Peripheral nerves are among the most susceptible structures, affected by long-term diabetes. Symptoms of peripheral nerve dysfunctions include tingling, numbness, loss of sensation, pain and in most severe cases movement disability. On a molecular level, simultaneous increase in expression of certain proinflammatory and cellular stress factors such as RAGE and decrease in physiological regulators such as Diaph1 and related cytoskeleton proteins have been reported. Over a period of time, the accumulation of pathological changes leads to irreversible nerve damage and diabetic neuropathy.