

Objective of the project

The *WWOX* gene is located in a chromosomal fragile site FRA16D. It is one of the largest known human genes, its size is over 1 million bp. The protein that it encodes is relatively small. It contains two WW protein-interaction domains and dehydrogenase/oxydoreductase SDR domain. The disturbance in *WWOX* gene expression is commonly found in various cancers and it correlates with worse prognosis and resistance to treatment. Therefore, soon after its discovery *WWOX* was classified as a tumor suppressor gene, a gene that is meant to suppress neoplastic transformation of cells by controlling the cell cycle progression and maintaining the stability of the genome. Nevertheless, it was impossible to find any mechanism by which *WWOX* protein could participate in those processes. The growing number of evidence shows that *WWOX* is not a classical tumor suppressor but rather plays a role of one of the pivotal regulators cell differentiation, metabolism and programmed cell death (apoptosis). In the presented project we are planning to investigate the role of *WWOX* gene in neural differentiation of human neural stem cells and the sensitivity of neurons to apoptosis.

The basic research to be carried out

In the human neural stem cell line we will silence the *WWOX* gene expression. Next, by analyzing transcriptome, we will investigate how it influences the activity of all the other genes. The data from the experiment will be subjected to an advanced bioinformatics analysis aiming to identification of transcription factors regulated by *WWOX*. Then we will examine how *WWOX* depletion impacts on neurons differentiation. We will induce differentiation of the hNSC with silenced *WWOX* and analyze their transcriptome, analogically as previously, in order to define what cellular pathways and a specific gene activity is changed. The last goal is to investigate how silencing of *WWOX* gene will influence neuron sensitivity to induced apoptosis.

Reasons for choosing the research topic

Most of the research on *WWOX* molecular function has been so far conducted on cancerous tissues and cell lines, what was justifiable by its putative tumor suppressor role. The knowledge on physiological *WWOX* role in normal cells and tissues is still very poor. Our preliminary studies, conducted on brain tumors and human neural stem cells, show that *WWOX* might be significantly involved in differentiation and proper functioning of central nervous system. Recently, it was reported that inherited mutations of *WWOX* effect with severe neuronal disorders and mental retardation. Moreover, there are good prerequisite to claim that improper *WWOX* functioning lays in the ground of neurodegenerative diseases such as Alzheimer and Parkinson disease. The proposed study will allow for determining the molecular function of *WWOX* protein in neuronal differentiation and functioning, as well as provide new insight into molecular basis of neural system development and pathology.