

The aim of the proposed project is to characterize the role of Dynamin-2 protein in Diffuse large B cell lymphoma (DLBCL) pathogenesis and to identify mechanisms leading to DLBCL cells death after Dynamin-2 inhibition.

DLBCL is aggressive and the most common lymphoid malignancy in adults. The most widely used treatment for DLBCL presently is the combination of chemotherapy and the monoclonal antibody rituximab. The prognosis of patients with DLBCL has certainly improved when rituximab was added to the standard chemotherapy, however, about 40% of the patients still relapse or have refractory disease. Therefore, development of new targeted therapeutic agents are urgently needed.

We identified Dynamin-2 gene (DNM2) as a one of the most crucial for DLBCL cells survival. Our preliminary experiments show that Dynamin-2 inhibition impairs many mechanisms supporting cancer cell survival. It dampens crucial for DLBCL cells signaling emanating from B cell receptor (BCR) and autophagy process, which is used by malignant cell to survive chemotherapy. Moreover, Dynamin-2 inhibition blocks internalization of molecule therapeutic monoclonal antibody-rituximab, therefore likely leading to increased efficacy of this therapy. Since Dynamin-2 can be inhibited by phenothiazine-derived antipsychotic drugs (APDs), widely used for decades to treat patients with schizophrenia and other psychotic disorders, detailed characterization of the role of this protein in pathogenesis of DLBCL might yield a clinically applicable targeted therapeutic strategy.

In the proposed project we plan to use cell models with genetically and pharmacologically inhibited Dynamin-2 to characterize the role of this protein in pathogenesis of DLBCL. At first we will assess influence of Dynamin-2 inhibition on cell signaling using high-throughput technologies like RNA-seq. Next we will determine consequences of Dynamin-2 inhibition on characteristic for lymphoma signaling emanating from B cell receptor. Since Dynamin-2 inhibition affects autophagy and rituximab internalization, we will elucidate its effects on these processes in the immuno-chemotherapy (R-CHOP) context used in DLBCL.

The proposed project will allow for better understanding of the pathological mechanisms leading to DLBCL. Beside the cognitive character of the project, it also possess high clinical significance. Precise and detailed understanding of Dynamin-2 functions in DLBCL will likely lead to an evaluation of this protein as a potential therapeutic target. This may translate to further personalize anticancer therapy, which highly impact clinical efficacy.