BCR-ABL-containing leukemic extracellular vesicles as a novel, immunosuppressive factor controlling function of regulatory T cells

Research conducted in the past few decades has clearly demonstrated a crucial role of immune system in eradication, but also development of different cancers. In healthy people immune system cells kill tumour cells, preventing the disease. However, as cancer progresses, it shuts down the antitumor arm of the immune system, leading to a state of immunosuppression. Immunosuppression is largely driven by regulatory T cells – a subset of T cells that in healthy people maintains balance and homeostasis. Regulatory T cells (Treg) are characterized by expression of Foxp3 transcription factor, which drives their suppressive function.

Development of immunosuppression also seems crucial in chronic myeloid leukemia (CML) – a blood cancer that arises in the bone marrow due to a chromosomal translocation, formation of Philadelphia chromosome and *BCR-ABL1* fusion gene. This gene encodes BCR-ABL protein with kinase activity, which induces robust, uncontrolled proliferation of immature blood cells. BCR-ABL can activate various signalling proteins and thereby regulates multiple biological processes in leukemic cells. CML cells very potently interact with cells inside the bone marrow, but also, upon disease spreading, in other tissues. These interactions can be cell-contact dependent or through factors released outside the cell. Recent research presents increasing evidence for the role of extracellular vesicles (EVs) in intercellular communication. Such EVs, containing proteins, RNAs and other factors, are also released by leukemic cells.

Our preliminary data have shown that EVs released by chronic myeloid leukemia cells (CML-derived EVs) can induce immunosuppression, which can facilitate disease progression. We have also observed that leukemic extracellular vesicles contain the BCR-ABL protein. Our preliminary findings suggest that BCR-ABL, contained in leukemic extracellular vesicles, controls crucial pathways in regulatory T cells and contributes to widespread immunosuppression in leukemia.

The aim of proposed studies is to precisely analyse how regulatory T cells are influenced by chronic myeloid leukemia-derived extracellular vesicles and BCR-ABL in these EVs. We also want to observe these processes in a wider biological context, conducting experiments on *in vivo* mouse model and analysing material from chronic myeloid leukemia patients. To perform proposed studies, we will apply modern approaches and techniques used in cell biology and leukemia studies, such as high-resolution imaging (confocal and electron microscopy), multicolor flow cytometry and cell sorting.

Collectively, our proposed research will potentially contribute to understanding mechanisms driving progression and development of chronic myeloid leukemia. Prospectively, it may also pinpoint a novel biomarker of leukemia development or relapse, as well as implicate regulatory T cells as a novel immunotherapeutic target in CML.