AXL RECEPTOR SIGNALING IN CANCER CELL GROWTH AND DRUG RESISTANCE

One of main causes of anti-cancer therapy failures is the acquisition of resistance to drugs by cancer cells, so-called cancer drug resistance. This phenomenon causes anti-cancer drugs to stop working, which leads to disease relapse and progression. Cancer drug resistance is caused by several different cellular and biochemical mechanisms, thus understanding them is extremely important for the development of therapeutic strategies to overcome the resistance of cancer cells.

Standard chemotherapeutic drugs work by blocking the metabolic pathways of the cell. Recent studies have shown that one of the mechanisms increasing resistance of cancer cells to such drugs is uptake of fragments of dead cells, present within the tumor mass, by living cancer cells. After degradation inside the cell, these fragments constitute an alternative source of nutrients needed for the growth of cancer cells which were nutrient-deprived due to the action of a chemotherapeutic agent. Such uptake of cellular debris occurs by macropinocytosis. This is a specific form of membrane transport that allows cells to take up significant volumes of extracellular fluid and particles into large vesicles called macropinosomes. Digested proteins and other macromolecules taken up by macropinocytosis can then fuel the growth of cancer cells. Given this, macropinocytosis may increase the survival of cancer cells under conditions of nutrient deficiency. Importantly, macropinocytosis can be activated by special proteins present on the cell surface called receptors, which regulate different cell functions and transmit signals between the cell and its external environment, and also between cells.

The aim of the proposed project is to investigate how receptors activate and regulate macropinocytic uptake of different types of nutrients from the environment and to study if and how this phenomenon contributes to drug resistance of cancer cells and, subsequently, to the growth of tumors despite the applied therapy. We will use AXL as a model receptor for our studies. Our preliminary data indicate that the AXL receptor stimulates macropinocytosis, which may contribute to increase survival of cancer cells grown under nutrient deficiency conditions. It is known that excessive activation of AXL is associated with the development of drug resistance to multiple anti-cancer therapies, including modern targeted therapies. These properties distinguish it from other receptors, and although the first AXL inhibitors are in clinical trials, **the biological processes, molecular and cellular mechanisms underlying drug resistance activated by this receptor remain unknown**.

The project has **two specific objectives** aimed at: 1) revealing the molecular mechanisms and effectors of AXL signaling that drive nutrient uptake by macropinocytosis, 2) clarifying whether AXL-activated nutrient uptake is involved in cancer drug resistance and tumor growth in cellular and animal models.

Knowledge acquired during the project implementation will be of both basic and translational significance. On the one hand, it will broaden our understanding of the molecular mechanisms regulating cancer drug resistance. On the other hand, such knowledge constitutes an indispensable basis for the development of targeted therapies limiting growth and drug resistance of cancer cells, which so far are highly insufficient.