The effect of tumor microenvironment on efficiency of melanoma targeted therapy

Although malignant melanoma covers only 4% of skin cancers, it is responsible for over 80% of deaths associated with this organ's disease, and for that reason it is considered as the one of the most life-threatening type of cancer. This low survival rate is associated with high variability and diversity among melanomas, what results in difficulties in its treatment. That is why more and more research is being carried out to verify the influence of a new anticancer drugs based on therapies targeting the molecules responsible for the metastasis of melanoma. Moreover, an important component that determines the effectiveness of the therapy is the tumor niche (microenvironment), which is a complex and multicomponent system, specific for each type of cancer. In addition to the various types of cells which accompany melanoma (such as keratinocytes, fibroblasts, adipocytes, endothelial cells and cells of the immune system), it also includes a whole range of macromolecules and growth factors produced by both normal and cancer cells. All these elements may affect the bioavailability of drugs and regulate the resistance of melanoma cells, and thus affect the effectiveness of the treatment.

Therefore, the aim of this project is to determine the impact of various cell types present in the tumor environment and the proteins they produce on the efficiency of targeted melanoma therapy. Our research will use pairs of inhibitors that block the activity of c-Met receptor (hepatocyte growth factor receptor; foretinib) and EGFR (epidermal growth factor receptor; lapatinib, gefitinib). It has been shown that elevated levels of these proteins is often observed in melanoma. In addition, our previous studies have demonstrated that application of pairs of these drugs, and inhibiting the activity of both receptors simultaneously (EGFR and c-Met), results in reduction of melanoma cells growth and its invasive capacity, which is crucial in the process of metastasis.

In the first stage of the study, after characterizing the factors secreted by non-cancerous cells present in melanoma environment, we will check whether selected EGFR and c-Met inhibitors are able to limit the growth and mobility of these cells. In the next stage, using co-cultures (culture of different types of cells together), we will examine the effect of adjacent cells on the sensitivity of melanoma cells to the selected inhibitors. Additionally, we will investigate the influence of hypoxia as well as various extracellular matrix components on the effectiveness of foretinib with lapatinib or gefitinib on melanoma cells growth in mono- and co-cultures. In the last stage of the study, we will analyze cells as well as proteins that form the melanoma microenvironment and are present in biopsy samples taken from patients.

The conducted research will allow us to further our knowledge concerning the influence of cancer cell surroundings on the effectiveness of targeted therapies. In addition, they will facilitate understanding of the molecular basis of drug resistance, which is associated not only with melanoma cells, but also can be modulated by its microenvironment. The proposed project may also lead to the development of new therapeutic strategies specifically targeted not only against cancer cells, but also affecting the environment in which it is located, and thus inhibiting the spreading of tumor.