ENDOCYTOSIS OF AXL RECEPTOR AND ITS ROLE IN AXL-MEDIATED SIGNALING

Endocytosis is a process by which cells take up substances important for their proper functioning, e.g. nutrients, from the surrounding environment. During endocytosis the plasma membrane invaginates and forms intermediate vesicles containing the internalized material. These intermediate structures further transport cargo to the special network of vesicles called endosomes, which are responsible for subsequent delivery of internalized substances to various cell organelles.

By endocytosis cells also internalize specialized proteins which regulate their functions and are responsible for signal transduction between cells or between cells and their surroundings. An important group of such regulatory proteins are receptors located on the cell surface. They sense changes in the cellular environment by binding specific messenger molecules, which are secreted by different cells. This binding promotes receptor activation, which subsequently induces the activation of other proteins. The induced proteins cause further activation of other proteins, etc. This cascade of activation allows delivery of signals through the whole cell and triggers an appropriate cellular response, e.g. cell division. Additionally, an activated receptor is taken up into the cell by endocytosis, and it is eventually transported to special organelles called lysosomes, where it is degraded. The receptor degradation terminates the signaling cascade. Alternatively, an internalized receptor can be also directed back to the plasma membrane and such recycling leads to sustained signal transduction, as the receptor can continue to activate the signaling cascade. Nowadays, multiple studies showed that endocytosis regulates not only the duration of signal transduction activated by the receptor but it also affects the cell response to the signal. Moreover, endosomes are also important organelles where the specific proteins associated with them can be activated.

One of the receptors which attracts increasing interest of scientists and pharmaceutical companies due to its role in tumorigenesis is AXL receptor. AXL regulates many essential processes of the cell such as survival and growth. Its overactivation is implicated in development of different cancers and in increased ability of cancer cells to form a metastatic tumor. Unfortunately, processes that regulate AXL signaling are poorly characterized. Moreover, data concerning AXL endocytosis and its involvement in AXL-mediated signal transduction are almost completely lacking. Therefore, **the general objective of the proposed project is to characterize AXL endocytosis and to establish its role in signaling activated by AXL**. Specifically, the detailed aims of this proposal are to:

1) generate tools to visualize endocytosis of AXL and study its signaling;
2) characterize in detail AXL endocytic trafficking;
3) identify proteins, genes and cellular response activated by AXL;
4) evaluate the influence of AXL endocytosis on its signaling.

The experiments will be performed in cancer (glioblastoma) and normal cells.

Most of our knowledge about receptor endocytosis relies on the results obtained for only one receptor – epidermal growth factor receptor (EGFR), while AXL endocytosis has not been investigated in detail so far. This project **will provide for the first time comprehensive data about endocytosis of AXL receptor, and it will shed light on the mechanisms by which endocytosis may regulate AXL signaling**. Since one of the models used in this project will be glioblastoma cells, the obtained results may contribute to our understanding of the role of AXL signaling in development of cancer. Additionally, the project will provide also **comprehensive data about genes activated by AXL**, thus it can potentially lead to identification of cancer-related genes in glioblastoma cells. It is worth noting that **such global analysis will be performed for the first time**. Taken together, this proposal **will bring new discoveries in the field of endocytosis, signal transduction as well as cancer cell biology.**