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Summary of the doctoral thesis

Modulation of fibroblast growth factor receptor 1 activity by controlling its distribution on the cell surface

FGFR1 is an integral membrane protein with tyrosine kinase activity, which interacts with extracellular ligands and transmits signals through the plasma membrane, regulating pivotal cellular processes. FGFR1-related aberrations are associated with the progression of various cancers, therefore FGFR1 consists a good molecular target in the anti-cancer targeted therapy.

There are many mechanisms that regulate the activity of FGFR1, one on them is endocytosis. Despite expanding knowledge about the cellular transport of FGFR1, the molecular mechanism that initiates internalization of this receptor is still unknown. Endocytosis of FGFR1 is important for cell biology, but this mechanism can be also used as a tool for efficient and highly selective delivery of drugs into FGFR1- positive tumor cells in targeted anti-cancer approach. Anti-cancer targeted therapy involves cytotoxic conjugates consisting of antibodies or ligands combined with a highly potent anti-cancer drug. Targeted molecule recognizes a cell surface biomarker specific for cancer cells, then, using the receptor-mediated endocytosis, introduces cytotoxic molecule to the cell interior, leading to cell death. Despite the great development of targeted therapies in recent years, the search for new therapeutic modalities that will increase the precision and efficiency of selective anticancer treatment is still ongoing.

In the present study I investigated the effect of modulation of the oligomeric state of FGFR1 on the efficiency of receptor endocytosis. I created a set of multimeric FGFR1 ligands with different architecture and receptor binding site, that cluster FGFR1 on the cell surface. I have shown that the tetramerization of FGFR1 stimulates rapid and highly efficient receptor uptake by involving various endocytic mechanisms. Moreover, I have observed that the clustering of FGFR1 into larger oligomeric structures inhibits the internalization of the receptor, leading to its accumulation on the cell surface. The obtained data formed the basis for the development of tetravalent, cytotoxic targeting molecule that specifically recognizes FGFR1. Due to the increased efficiency of internalization and precise delivery of cytotoxic drug to FGFR1-positive cells, the obtained data highlighted a high potential of oligomeric conjugates

as efficient targeting molecules in selective anti-cancer therapy. Based on this discovery, I have constructed a modular system for ligand oligomerization and development of highly cytotoxic multimeric conjugates directed against various cell surface markers of tumors.