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Abstract

**Regulation of spatial distribution of the fibroblast growth factor receptor 1 by multimeric ligands based on coiled-coil motifs and oligomeric variants of GFP**

FGFR1 is a membrane receptor involved in transmission signals through the plasma membrane. FGFR1 signaling is precisely regulated because aberrant activity of this receptor is associated with the development of numerous cancers and metabolic diseases. Although the number of signaling pathways under the control of FGFR1 is limited, there is a great diversity of elicited cellular responses triggered by the FGF-FGFR1 signaling complexes. This is due to the presence of number of regulatory mechanisms of FGFR1 signaling. The specificity and duration of the transmitted signals are determined by the stability of FGF-FGFR1 complexes, interactions with other plasma membrane proteins, endocytosis and intracellular sorting of the receptor.

In this doctoral dissertation, we identified previously unknown regulatory mechanism of FGF-FGFR signaling in which the spatial organization of FGFR1 in the plasma membrane modulated by extracellular lectins (galectin-1 and -3) determines the activity and intracellular transport of the receptor. We demonstrated that although both galectins bind to the same sites on FGFR1, due to their different oligomeric state, differentially influence function and cellular trafficking of FGFR1. The obtained data suggested a potential possibility to control the activity and endocytosis of FGFR1 by oligomerization of the receptor on the cell surface. Based on these observations, I developed a novel system for generation of oligomeric FGFR1 ligands of distinct architectures, which I used for controlled oligomerization of receptor and determine the effect of these ligands on endocytosis and activation of FGFR1 and receptor-dependent signaling pathways. I determined that the spatial organization of FGFR1 in the plasma membrane determines the specificity of cellular responses to the transmitted signals and receptor endocytosis. The oligomeric ligands were efficiently internalized into cells producing FGFR1 on the surface, suggesting that they can be used as a cytotoxic drug carriers in targeted therapy. Based on obtained results, I designed a novel strategy for the generation of oligomeric

cytotoxic conjugates with intrinsic fluorescence and I confirmed the high cytotoxicity of the conjugates against FGFR1-overproducing cancer cells.