# Abstract of the Doctoral Dissertation

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## The Role of FGF1 and FGF Receptors in the Response of Cancer Cells to Cytotoxic Agents

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The problem of cancer cells developing drug resistance to current therapies is a common phenomenon affecting cancer patients worldwide. Despite intensive research into new therapeutic strategies, the complex mechanisms of drug resistance pose a challenge to science and medicine. reason for the decreased sensitivity of cancer cells to the drugs used is the activity of growth factors and their receptors, including proteins from the fibroblast growth factor (FGF) family. Belonging to this family, FGF1 protein together with FGF receptor 1 (FGFR1) are involved in many biological processes, i.e. control of the cell cycle and cell division, cell differentiation and migration, angiogenesis or stress response. Elevated expression and activity of FGF1 and FGFR1 are associated with the development of various cancers, including breast, lung and bone cancers. However, their role in the emergence of drug resistance is still poorly understood.

In my thesis, which is a collection of four scientific publications, I have investigated the role of FGF1 and FGFR1 proteins in the protection of cancer cells against anticancer drugs. In a review paper, I presented the existing knowledge on the involvement of FGF and FGFR family proteins in the acquisition of drug resistance by tumors and its possible applications in the development of more effective anticancer therapies. In two subsequent papers, I focused on investigating the role of FGF1 and FGFR1 in protecting cancer cells from compounds that disrupt tubulin polymerization, such as taltobulin, paclitaxel and vincristine. My findings confirmed that FGF1 activity in FGFR1-positive cancer cells reduces the cytotoxicity of these drugs, which is dependent on receptor activation and downstream cell signaling pathways. I demonstrated that FGF1 can protect cancer cells by inhibiting apoptosis, promoting cell migration, and activating membrane transporters. Additionally, I identified the cell signaling pathways responsible for the protective effects of the FGF1/FGFR1 complex. The key protein was AKT kinase, whose activity in protecting against drugs in osteosarcoma and small cell lung cancer cells was controlled by two independent pathways: a canonical, PI3K protein-dependent pathway, and an alternative, mTOR kinase-dependent pathway. In the case of hormone

receptor-positive breast cancer cells, the FGF1/FGFR1-dependent MEK/ERK pathway was also involved in protection against taltobulin. My most recent work addresses the inhibition of the FGF1/FGFR1 activation loop and explored the potential to reverse the acquisition of drug resistance by cancer cells. I have identified a novel FGFR1 inhibitor, honokiol, which, by directly interacting with the kinase domain of receptor, blocks its activation and thus downstream cell signaling pathways. I demonstrated that honokiol blocks the protective effects of FGF1 in osteosarcoma cells stably transfected with FGFR1 and small cell lung cancer cells. In this study, I also employed another strategy to block FGFR1 activation, the so-called ligand trap, which is a recombinant extracellular FGFR1 fragment in fusion with an Fc. By using tumor cell lines I derived that were resistant to drugs targeting tubulin polymerization, I showed that the use of the FGF ligand trap prevents the development of long-term drug resistance in osteosarcoma cells.

The results of my study extend the knowledge of the role of FGF1 and FGFR1 proteins in the acquisition of drug resistance, which may be of great importance for the development of new, more effective therapeutic strategies targeting cancer.