„FGFR2 importance in luminal breast cancer progression and therapy"
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Luminal breast cancers, representing approximately 70% of all diagnosed breast cancer (BCa) cases, are characterised by high expression of estrogen receptor (ER). In recent years it has been proven that the presence of progesterone receptor (PR) is a good prognostic factor (luminal A subtype (ER+, PR+)), while PR-negative tumours are more aggressive and respond much worse to applied treatment (luminal B (ER+, PR-)). Moreover, in the presence of specific ligands, estrogens and progesterone, PR directly interacts with ER, resulting in a unique gene expression programme that is associated with tumour growth inhibition and patients' better response to the treatment.

The tumour microenvironment is an important factor promoting BCa progression. Intercellular communication between stromal and cancer cells is based on paracrine signalling with the engagement of different growth factors (including FGFs), which can regulate the activity of steroid hormone receptors, leading to hormone-independence. Fibroblast growth factor receptor 2 (FGFR2) is actively involved in the transduction of signals from the microenvironment. In our recent work, we have shown that FGFR2 signalling activates ER and PR independently, leading to worse cell response to therapy and the degradation of PR, characteristic for disease progression. The doctoral thesis aims to analyse the involvement of FGFR2-dependent signalling in the regulation of ER-PR cross-talk in the context of luminal breast cancer progression and therapy.

The experiments carried out in the course of the doctoral dissertation included extensive *in vitro* studies using luminal breast cancer model cell lines and the analysis of clinical material. Using PLA (Proximity Ligation Assay) it was possible to demonstrate that FGFR2-dependent signalling inhibits the formation of ER-PR complex. Moreover, applied FGF7 stimulations abolished the inhibitory effect of progesterone on cell growth in three-dimensional Matrigel cultures. FGF7 also reduced the effect of tamoxifen (ER-targeting drug) on luminal breast cancer cells. FGF7/FGFR2 signalling regulated both, phosphorylation and the expression level of ER and PR, in the presence of steroid hormones. In addition, analysis of the expression of the ER-dependent gene panel showed that FGF7/FGFR2 signalling inhibited progesterone-mediated ER-dependent gene expression. The last stage of work was a clinical analysis of material collected from 226 ER+/PR+ patients. Correlation between FGFR2 level with the expression profile of ER-dependent gene panel showed several significant positive correlations within the analysed groups of patients. Moreover, in the group of postmenopausal patients, FGFR2 is a good prognostic factor, which is not observed in younger patients.

The described project, combining *in vitro* studies with clinical analyses, for the first time describes and characterises the role of FGFR2 in the regulation of steroid hormone receptors in the context of luminal breast cancer progression and therapy. Taking into account the fact that therapies targeting FGFR family are gaining more and more interest in oncology, I believe that specific FGFR inhibitors may find application in the treatment of patients with hormone-dependent breast cancer.