NON-CANONICAL ESTROGEN RECEPTOR (ER) SIGNALLING IN BREAST CANCER PROGRESSION

Breast cancer (BCa) is the most prevalent cancer worldwide. The majority of diagnoses comprise the luminal subtype which is characterized by the presence of estrogen receptor (ER+) in cells and therefore the progression of the disease depends on estrogens. For this reason, it is routinely treated with agents that inhibit ER activity (endocrine therapy). Although this strategy has greatly improved patients' survival, resistance to the treatment eventually develops in a majority of patients posing a significant clinical problem. Fibroblast growth factor receptor 2 (FGFR2) present on the cellular membrane of BCa cells was shown to activate ER *in vitro* and contribute to resistance to ER-targeting drugs. On the other hand, high expression of FGFR2 was identified as a good prognostic factor in ER+ disease. Further stratification of these patients revealed that there are subgroups where FGFR2 promotes BCa progression. Hence it can be concluded that the role of FGFR2 depends on other molecular factors.

When activated by its ligand, ER functions as a transcription factor - binds to specific DNA sequences and regulates gene expression. The receptor activity may be modulated by other cellular components, including the AP-1 complex composed of various Jun and Fos proteins. The exact composition of the complex determines its activity and DNA-binding abilities. Through a tethering mechanism, AP-1 can induce ER binding to AP-1-specific genomic sequences. This ER displacement results in the regulation of genes expression not controlled by estrogen, which may be an important hallmark of steroid hormone-independent BCa - resistant to anti-ER drugs. Our group have demonstrated that the expression of FGFR2 correlates with the expression of individual proteins from the Jun family, which may result in regulation of the composition and, therefore, the activity of the AP-1 complex and its interaction with ER. The project aims to determine the role of FGFR2 signalling cascade in the regulation of AP-1-ER interaction in the context of BCa resistance to endocrine therapy.

In this project we will investigate the impact of FGFR2 activity on the protein composition of the AP-1 complex, the involvement of FGFR2 signalling in the regulation of ER and AP-1 binding to DNA. The role of the ER/AP-1 pathway in the response of breast cancer cells to anti-ER therapy will be established *in vitro* and in animal model. Moreover, the prognostic value of the FGFR2-AP-1 interplay in ER+ BCa patients will be determined. Due to the comprehensive approach employing a broad array of research techniques, the project is expected to address the question about the role of FGFR2 in ER+ breast cancer. Moreover, it has a high potential to identify a subgroup of patients who may benefit from the introduction of therapeutic strategies based on FGFR-targeting agents.