FGFR2/NRF-2 AXIS IN LUMINAL BREAST CANCER AND THE EFFECTS ON CELL GROWTH AND RESPONSE TO ANTI-ER DRUGS

Breast cancer (BCa) is the most common cancer in women with approximately 1.7 million new cases diagnosed every year. Approximately 50-60% of diagnosed cases are positive for both estrogen and progesterone receptor (ER+/PR+) which is a feature of luminal A subtype. Application of personalized therapy targeting ER activity revolutionized the treatment of BCa. Despite the success of such an approach, most patients eventually develop acquired resistance to anti-ER drug. It is widely accepted that tumour microenvironment (TME) plays a critical role in cancer progression and contributes to the failure of therapies. Cancer-associated fibroblasts are the most prominent components of TME. They secrete a variety of cytokines and growth factors, including FGFs (fibroblast growth factors), which are specific ligands for **fibroblast growth factor receptors (FGFRs)**. FGF/FGFR signalling plays an essential role in various physiological processes like cell growth, migration, differentiation, survival, apoptosis. Accordingly, deregulation of FGFRs signalling has been associated with various abnormalities, including cancers. Multiple studies confirmed the relevance of FGFR signalling in development and progression of BCa. Moreover, FGF/FGFR signalling has been proved as one of the key mediators of resistance to anti-ER therapies. On the other hand, growing evidence indicates an involvement of the transcription factor **Nrf-2**, a master anti-oxidant regulator, in the promotion of cancer progression and resistance to the applied treatment including tamoxifen (the most commonly used anti-ER drug). So far, several studies implicated FGFR-dependent signalling in regulation of Nrf-2 activity and expression of its downstream genes. The function of Nrf-2 was shown to be regulated by various members of the FGFR signalling pathways, such as PI3K/AKT, PKC, JNK, ERK, and Fyn. Our previous work showed that **FGFR2** was involved in transmission of tumour microenvironment-originating signals, which counteracted the negative effect of tamoxifen on BCa cells growth. On the other hand, increased expression of Nrf-2 and its downstream genes have been revealed in the tamoxifen-resistant breast cancer cells. Given the above, it is possible that FGFR2 may be engaged in the regulation of Nrf-2 activity in luminal A breast cancer. Taking into account the abovementioned dependencies this project aims to verify the involvement of: **1) FGFR2-triggered signalling in regulation of Nrf-2 activity, and 2) FGFR2/Nrf-2 axis in growth and response to anti-ER therapies in luminal A breast cancer.** The proposed study consists of two complementary approaches: *in vitro* experiments and clinical analyses. *In vitro* studies will provide detailed information about regulation of Nrf-2 activity by FGFR2-triggered signalling in a relation to luminal A BCa response to anti-ER drugs. The clinical analyses of luminal A BCa samples will verify the prognostic significance of FGFR2/Nrf-2 interdependence. FGF/FGFR signalling has been revealed as a relevant treatment target for multiple cancers. A particular interest in FGFR inhibitors is reflected by the growing number of clinical studies. Combination of anti-ER drugs with FGFR inhibitors might be a successful strategy to overcome resistance to endocrine therapies. Results of this grant proposal may reveal an unknown role of the FGFR2/Nrf-2 axis in growth and response to anti-ER treatment of luminal A BCa. Moreover, this study may help to identify novel prognostic and predictive biomarkers in this BCa subtype.