SIGNIFICANCE OF FGFR2 IN REGULATION OF AUTOPHAGY IN BREAST CARCINOMA - IMPLICATIONS FOR DISEASE PROGNOSTICATION

Breast cancer (BCa) is the most common cancer among women worldwide. About 50-60% of all BCa cases belong to luminal A subtype, characterized by the presence of estrogen and progesterone receptors (ER+/PR+). Routinely these women are treated with anti-estrogen dugs, e.g. tamoxifen. Despite the success of such therapeutic approach, approximately 45% of BCa patients do not respond to treatment whereas acquired resistance to the drug ultimately develops in all long-treated patients.
Interestingly, tamoxifen was shown to induce **autophagy**, a process of removing proteins and cellular elements. In addition, it is suggested that autophagy is involved in the development of resistance to anti-estrogen agents (including tamoxifen). On the other hand it is well-known that interactions between cancer cell and tumour microenvironment (particularly CAFs – cancer associated fibroblasts) is one of key processes responsible for failure of targeted therapies.
FGFR2 (Fibroblast Growth Factor Receptor 2) plays an important role in both physiology and oncogenesis of mammary gland. Activation of FGFR2 (in response to FGF binding) initiates a number of signaling cascades which involve proteins engaged in regulation (both promotion and inhibition) of autophagy (e.g. PI3K/AKT or Bcl-2). We have recently demonstrated that FGFR2 activation by FGF7 promoted progression of luminal A breast cancer towards more aggressive phenotype. We also showed that FGFR2 transmits CAFs-derived signal which results in abrogation of tamoxifen effect for ER-positive BCa cells. Taking into account these interrelations, this grant proposal aims to study a potential **impact of FGFR2 signaling on the induction and/or inhibition of autophagy, likely to play a key role in development of resistance to anti-ER treatment of luminal BCa cells.**
The project involves three complementary levels of investigation: *in vitro*, *in vivo* and clinical analyses. *In vitro* experiments will focus on studies of FGFR2 action towards regulation of autophagy in relation to BCa cell response to tamoxifen. Clinical analysis of BCa samples will evaluate prognostic significance of FGFR2/autophagy interdependence. Animal experiments will verify the role of FGFR2-regulated autophagy in tumorigenesis and cell response to tamoxifen. Proposed research program should provide data essential for determination of FGFR2 function in regulation of autophagy with plausible consequences for luminal A BCa growth and efficacy of anti-ER therapy. Combined strategies based on FGFR and autophagy inhibitors might be beneficial for patients with developed resistance to anti-ER agents.