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ABSTRACT

Analysis of tumour microenvironment – cancer cell interplay can deliver crucial information on disease progression. Changes in growth factor receptors expression and their signalling pathways modulate cell response to stimuli from cancer stroma. *FGFR2* (Fibroblast growth factor receptor 2) was described as a breast cancer susceptibility gene and its activity promotes tumour progression. It was previously discovered that expression of FGFR2 in breast cancer cells inversely correlated with tetraspanin CD151 (a negative prognostic factor in breast cancer) level. Recently, it has been suggested that growth factors receptors may regulate estrogen receptor (ER) function resulting in impaired response to the endocrine treatment (anti-ER drugs, e.g. tamoxifen).

The aim of this project was to study FGFR2 role in breast cancer by analysing a role of CD151 in function and expression of FGFR2 as well as by evaluating the effect of FGFR2-triggered signalling on ER activity and response to tamoxifen treatment.

Herein it was found that depletion of CD151 increased both FGFR2 protein and mRNA level in breast cancer cell lines thereby suggesting that CD151 regulates transcription of the receptor. Upregulation of the FGFR2 expression in CD151-depleted cells correlated with better cell response to FGFs treatment. Experiments with tetraspanin CD151 reconstitution demonstrated that the activity towards FGFR2 requires an association of CD151 with laminin-binding integrins and involves activation of p38 kinase. Accordingly, fibroblast growth factor (FGF)-dependent proliferation of breast cancer cells in three-dimensional laminin-rich Matrigel was inhibited in the presence of SB202190, a specific p38-inhibitor. These results illustrate functional interdependency between CD151-laminin-binding integrin complexes and FGFR2, therefore suggesting an entirely new role of CD151 in breast tumorigenesis.

This study presents also that FGFs stimulation promotes breast cancer cell growth in the presence of tamoxifen. The strongest observed effect was exerted by FGF7 acting through FGFR2. The FGF7/FGFR2-triggered signalling was found to determine fibroblasts-dependent resistance to tamoxifen. FGF7/FGFR2-induced pathway induced ER phosphorylation, receptor`s ubiquitination and subsequent proteasomal degradation, which counteracted tamoxifen-promoted ER stabilization. PI3K/AKT signalling targeting ER-Ser167 and regulation of Bcl-2 expression were described as mediators of FGFR2-

dependent resistance to tamoxifen. Above results indicate on a complex regulation of ER function by FGFR2-mediated signalling which may reflect contribution of tumour microenvironment to endocrine therapy resistance and transition towards hormone-insensitive breast cancer.

The regulation of FGFR2 expression and function by CD151 as well as FGFR2-mediated disruption of response to tamoxifen treatment are novel mechanisms which point on a great importance of FGFR2 role in progression of breast cancer.