Abstract

The members of p90 ribosomal S6 kinase (RSK) family of Ser/Thr kinases are downstream effectors of MAPK/ERK pathway that regulate diverse cellular processes including cell growth, proliferation and survival. In carcinogenesis, RSKs are thought to modulate cell motility, invasion and metastasis. Elevated level of RSK1 and RSK2 was found in about 50% of breast tumours and is associated with a poor survival outcome.

The project aims to investigate the role of RSK kinases in breast cancer progression out at three complementary levels: *in vitro* studies, *in vivo* experiments in mouse model and analyses of samples from breast cancer patients.

We demonstrated for the first time that in breast epithelial and cancer cell lines stimulation of FGFR2 (*fibroblast growth factor receptor 2*) with FGF2 induced indirect activation of RSK2-Tyr529 by p38 kinase and that this new signalling pathway promoted anchorage-independent cell proliferation, formation of focal adhesions and cell migration. In addition, we found out that RSK2 not only mediates pro-migratory effects of FGFR2 but is also involved in regulation of FGFR2 intracellular trafficking. In clinical analyses FGFR2 showed a positive correlation with RSK2 at both protein ($p = 0.003$) and mRNA ($p = 0.001$) levels. The values of correlation coefficients were the highest in triple-negative breast cancer (TNBC), which is more aggressive and has a poorer prognosis than other breast cancer subtypes. Moreover, expression of FGFR2 and/or activated RSK (RSK-P) significantly correlated with poor disease-free survival (DFS) of patients ($p = 0.01$). In animal studies we demonstrated that RSK1 supports murine TNBC tumour growth and lung metastasis as well as migration and survival in non-adherent conditions *in vitro*.

Taken together, our results suggest that FGFR2-RSK2 signalling pathway is associated with breast cancer progression and further studies of RSK1 and RSK2 may contribute to the development of new therapeutic strategies in the management of patients with breast cancer.