Alicja Grudowska
Supervisor: prof. dr hab. Andrzej C. Składanowski
Co-supervisor: Prof. dr hab. Kazimierz Krajka

‘The role of tetraspanin CD151 in prostatę cancer progression’’

Abstract

The heterogeneity of prostate cancer (PCa) together with metastasis occurrence are acclaimed as major problems in both diagnostics and therapy of this disease. The ability of cells to invade and migrate is crucial for the formation of secondary lesions, and requires activation of multiple signaling cascades modulated by series of regulatory molecules. One of them is CD151, a member of evolutionary conserved tetraspanins. This protein family is characterized by the presence of four transmembrane domains. Tetraspanins are considered as important factors in cell proliferation, adhesion, motility and cancer progression, primarily due to formation of complexes with other key proteins. CD151 is known to create stable and direct complexes with growth factor receptors (including TGF-β1R, HGFR) as well as with laminin-binding integrins (α6β1, α6β4, α3β1), which are regulators of cellular adhesive interactions, thus influence aggressive behavior of neoplastic cells. Recent studies point to CD151 involvement in progression of prostate cancer.

The aim of the project was to investigate CD151 role in prostate cancer progression, with the emphasis on mediating signal between epithelial cells and tumor stroma, as well as in reciprocal interactions between bone microenvironment and PCa.

The study showed that stimulation of BPH-1 cells with conditioned medium from cancer-associated fibroblasts significantly enhanced cells growth in three-dimensional matrigel, however independent from CD151 status. What is more, the association between CD151, FGFR1 and Src kinase in same cells under FGF2 stimulation was found. This tetraspanin promoted expression of FGFR1, followed by activation of Src, an acknowledged pro-migratory kinase. Boyden chamber assay revealed highest migration of CD151-positive BPH-1 cells to FGF2, which may be attributed to enhanced activity of Src. Moreover, inverse correlation of CD151 expression with FGFR2 was demonstrated. On the other hand, exact opposite features of this tetraspanin were demonstrated in prostate cancer cells (PC3). In this case knockdown of CD151 resulted in acquisition of invasive phenotype. This effect was enhanced under stimulation with osteoblasts conditioned medium and was in line with increased level of matrix metalloproteinases-13 in these cells. Regardless, it is not fully understood which of molecules secreted by osteoblasts elicit pro-invasive and pro-migratory properties in shCD151 cells, as no comprehensive studies on osteoblasts-PC3 interactions has been reported so far. Nonetheless, it can be assumed that despite

few reports stated pro-tumorigenic properties of CD151 in PC3 cells, obtained results provided new insights into CD151 mechanism of action, which could be contradictory depending on the cell type and disease stage in case of prostate. Nevertheless, the reciprocal interactions between tetraspanin CD151, FGFR1 and Src can be considered as significant for prostate cancer development and/or progression.