Determination of the WWOX gene function in AP-2 γ signaling pathway in metastatic bladder cancer.

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The WWOX gene is one of the unusual tumor suppressor genes, whose molecular function has not been fully understood in bladder cancer. The gene encodes a protein containing two N-terminal WW domain and the centrally located short chain dehydrogenase domain (SDR). The first WW domain interacts with AP-2γ transcription factor (encoded by TFAP2C gene) and inhibits its oncogenic activity by inducing the redistribution of AP-2γ to the cytosol, modulate proliferation and tamoxifen response in breast cancer. Moreover, the most malignant type of breast tumour, the triple negative cancer, showed high expression of AP2γ and frequent loss of WWOX.

In the present study, an in vitro model of CAL29 bladder cancer cell line (grade 4) with different level of WWOX and high TFAP2C was created. We used knock-in lentivirus and CRISPR-Cas9 system to overexpress and silence WWOX gene, respectively. The WWOX gene modifications induced higher expression of TFAP2C gene in compare to control. The aim of our study was to assess the effect of different WWOX expression level and high AP2γ on biological processes such as adhesion to extracellular matrix proteins, colony formation, apoptosis, growth in 3D, activity of metalloproteinases, mitochondrial redox potential.

In a high WWOX/high TFAP2C variant, we observed lower the ability of a single cell to grow into a colony, decreased expression of metalloproteinase MMP2 and proliferation potential, but increased adhesion to collagen I, collagen IV, laminin, lower mitochondrial redox potential and forming smaller spheres in matrigel, which can suggest a reduction of aggressive potential. However, in this model was noticed a decline number of caspase positive/death cells after induction of apoptosis by staurosporine.

Our results suggest a relevant biological role of WWOX gene in metastatic bladder cancer with high expression of AP2γ transcription factor.

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