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O10

Role of claudins 3, 4 and 7 in triple negative breast cancer progression

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Background: Breast cancer is the most commonly occurring malignancy and the leading cause of cancer-related death in women. Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype and is associated with high recurrence rates, high incidence of distant metastases and poor overall survival. The aim of this study was to investigate the role of cludin 3, claudin 4 and claudin 7 in TNBC promotion and progression. Claudins are tight junction (TJ) integral membrane proteins that are key regulators of the paracellular pathway. **Materials and methods:** This is a retrospective analysis of 125 patients with triple-negative breast cancer operated at the Institute of Oncology and Radiology of Serbia in the period from 2009 to 2014. The expression of claudin 3, 4 and 7 was observed using the immunohistochemical staining method. The Allred scoring system was used with cut-off values: ≤4 and >4 (low/ high expression). **Results:** Our results showed that the expression of claudins 3 and 4 correlate with higher nuclear gradus and low desease free interval (DFI). More over, the expression of claudin 3 and claudin 4 correlates (Spearman test $p<0.0001$). In addition, high expression of claudin 7 is significantly related to low DFI of patients ($p<0.005$) and distant metastases. **Conclusions:** We concluded that claudin 3, claudin 4 and claudin 7 have significant impact on TNBC progression. Namely, elevated expression of these proteins significantly correlates with low DFI and distant metastases. In other words, elevated expression of claudins is a bad news for TNBC patients. Therefore, the expression of claudins could be a good prognostic marker for TNBC patients and potential target for future therapy protocols.
Keywords: Triple-negative breast cancer (TNBC),claudin 3, claudin 4, claudin 7

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O11

Impairment of cystatin F activation can increase the cytotoxicity of NK cells

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Background: Natural Killer (NK) cells utilize granule mediated cytotoxicity as the predominant pathway in cancer cells killing. The main effector molecules required for this process, granzymes and perforin are synthetized and stored in their inactive forms and require proteolytic processing by cathepsins C, H, and L for their activation. We have identified a protease inhibitor cystatin F as a potent regulator of these cathepsins and consequently cytotoxic efficacy in NK cells. Cystatin F activity is regulated by various factors, including expression levels, N-glycosylation, and proteolytic activation. In lysosomes, cathepsin V cleaves 15 N-terminal amino acids from cystatin F, thereby activating it from an inactive dimeric form to an active monomer. Cystatin F was found expressed in glioblastoma tumor tissue. The aim of this study was to assess NK cell function in glioblastoma patients and to enhance NK cell cytotoxicity by inhibiting cystatin F activation. **Material and Methods:** To counter the cystatin F effects of on NK cell cytotoxicity, a new small molecular inhibitor of cathepsin V was developed. After molecular docking of small molecular compounds from commercial libraries with cathepsin V, selected compounds were evaluated by enzyme kinetics for enzyme inhibition, selectivity, and reversibility of binding. The effect of the most potent, selective, and reversible-acting cathepsin V inhibitor on cystatin F activation was tested by western blot. NK cells were isolated from peripheral blood mononuclear cells of healthy donors and glioblastoma patients and analysed by flow cytometry. **Results and Conclusions:** We found that patient NK cells had significantly reduced cytotoxic efficacy and increased content of cystatin F compared to healthy donor NK cells. However, even healthy NK cells were susceptible to the effects of cystatin F. Recombinant cystatin F reduced cytotoxicity, increased IFN-γ secretion, and decreased cathepsin C and granzyme B activity. Treatment of NK