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IMMUNOSUPPRESSIVE AND METASTASIS-PROMOTING MATRISOME PROTEINS IN PANCREATIC CANCER

The role of galectin 4 and SERPINB5

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Akademisk avhandling

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Abstract
In Sweden 1200-1300 people are diagnosed with pancreatic ductal adenocarcinoma (PDAC) every year. Late diagnosis, together with poor treatment response and resistance to checkpoint inhibitor immunotherapy, contributes to the poor prognosis of the disease. PDAC is characterized by abundant deposits of extracellular matrix constituting the matrisome of the tumor. Several highly expressed matrisome proteins are involved in oncogenesis, including immunosuppression and metastasis formation, therefore contributing to the poor prognosis. In this thesis the pathophysiological role of several matrisome proteins in PDAC tumor progression was studied. Serine protease inhibitor clade B member 5 (SERPINB5), agrin, and cystatin B (CSTB), were selected for study based on their known roles in metastasis. SERPINB5, agrin and CSTB were found to increase metastasis in models of PDAC by affecting epithelial to mesenchymal transition, ECM degradation and extravasation. In PDAC tumors, high levels of extracellular SERPINB5 correlated to reduced survival. Galectin 4 (Gal 4) was selected for study based on its known immunosuppressive effects. Gal 4 is highly expressed in PDAC and was found to inhibit T cell infiltration and induce apoptosis in CD8+ T cells by binding to CD3 on the surface of T cells. Low Gal 4 was associated with better survival in PDAC patients. Datasets analysis revealed that gal 4 expression correlates with other cancer cell-derived immunosuppressive proteins of the galectin family, galectin 3 and galectin 9, while negatively correlating with the stroma-derived factors galectin-1 and TGFBI. Findings in this thesis show that targeting of matrisome proteins in PDAC can be a promising therapy strategy. Blocking extracellular SERPINB5 could result in reduced metastasis and increased survival. Blocking intracellular gal 4 could increase anti-tumor immunity and synergize with checkpoint inhibition therapy. The identified co-expression and coregulation of different immunosuppressive proteins indicate that different tumors can be classified based on their predominant immunosuppressive mechanisms. Combination therapies against these different immunosuppressive mechanisms could represent a promising treatment strategy for PDAC patients.

Keywords
Galectin 4, SERPINB5, pancreatic cancer, immunosuppression, extracellular matrix

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