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# TGFß1-mediated crosstalk in the tumor microenvironment upregulates expression of PAI-1, which predicts poor prognosis in melanoma patients

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Malignant melanoma can be well controlled in early stages, but despite new therapeutic options, the five-year survival rate decreases down to 9 % in metastatic disease. For this reason, markers are required to identify patients with worse prognosis. The metastatic propensity of melanoma is a result of the interaction between cancer cells and their microenvironment. Especially cancer-associated fibroblasts and tumor-associated macrophages play an important role. Factors produced by cancer-associated stromal cells are a promising source of potential biomarkers, but they currently remain underinvestigated in melanoma. Tumor-derived TGFβ1 activates cancer-associated fibroblasts; and high systemic levels of TGFβ1 correlate with poor prognosis in many tumors including melanoma. SAA is an inflammatory molecule released by the liver upon host injury, but it can also be produced by malignant cells and tumor-associated stromal cells. In this context, SAA is involved in the formation of a metastatic niche and has been associated with poor prognosis in melanoma.
Therefore, the expression of SAA and TGFβ1 in primary melanoma was investigated by immunohistochemistry and qPCR, showing that both molecules were present in tumor and stromal cells. Next, the response of human dermal fibroblasts and THP-1 cells to SAA and TGFβ1 was assessed. SAA upregulated the expression of factors implicated in melanoma invasion, matrix remodeling, angiogenesis, immune evasion and therapy resistance in THP-1 cells through TLR4, including its own expression. TGFβ1 stimulated its own expression, as well as that of SAA and the CAF marker α-SMA in fibroblasts. Furthermore, TGFβ1 induced PAI-1 in both fibroblasts and THP-1 cells. In melanoma patients, the systemic levels of TGFβ1 and PAI1 positively correlated with each other. Importantly, increased PAI-1 protein expression was associated with poor prognosis in melanoma patients of the TCGA cohort.
PAI-1 is a TGFβ1-inducible molecule and represses plasminogen activators, regulating clot formation in thrombosis. It inhibits the plasmin-mediated degradation of the extracellular matrix, which would impede tumor progression. But PAI-1 has additional roles, including antiapoptotic effects, angiogenesis and macrophage recruitment to melanoma, and therefore fosters tumor progression. Nevertheless, the origin of locally elevated PAI-1 in melanoma remains unclear. These results indicate that TGFβ1-activated stromal cells, especially fibroblasts, are an important source of PAI-1 besides melanoma cells themselves. Systemic PAI-1 levels are elevated in many tumors and have been linked to poor outcome. In breast cancer, high PAI-1 levels are used to monitor the risk for therapy resistance and worse survival. In melanoma, systemic PAI-1 has not yet been investigated as a diagnostic marker.
In conclusion, this thesis shows that melanoma cells condition fibroblasts and monocytic macrophages via TGFβ1 and SAA to create a tumor promoting milieu. Furthermore, TGFβ1-stimulated HDF are an important source of locally overexpressed PAI-1, which predicts poor prognosis in melanoma patients. Therefore, PAI-1 might be a new diagnostic tool in melanoma.