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Tissue transglutaminase as a new immunomodulatory target in ovarian cancer tumor microenvironment

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Abstract

Tissue transglutaminase (TG2) is a multifunctional protein with roles in multiple diseases including cancer. It was found overexpressed in many solid tumors in the past two decades. In ovarian cancer, it emerged as a potential therapeutic target due to its involvement in processes like metastasis and chemo- and radiotherapy resistance. Generally, TG2 expression in cancer cells has been extensively studied and linked to increased tumor progression. However, its role in the host was less studied. Our research explored the anti-tumor immune response using a TG2KO syngeneic ovarian cancer mouse model, as compared to wild-type animals. We observed decreased tumor burden and increased survival upon i.p. injection of ID8 mouse ovarian cancer cells in TG2KO mice, as compared to wild-type. In the absence of TG2 in the host, an increased infiltration of $CD8^+$ T cells in ascites was evidenced by FACS, while myeloid cells were less present. The TG2KO $CD8^+$ T cells showed increased activation and increased effector function. Moreover, these cells showed an increased cancer cell killing capacity. At the molecular level, this phenotype was supported by attenuated STAT3 phosphorylation. Cancer cells in ascites collected from TG2KO mice showed a gene signature corresponding to IFN-γ response. Overall, these data show decreased tumor progression and increased effector phenotype in $CD8^+$ T cells when TG2 is absent in the host (Sima LE et al. (2021) Journal for ImmunoTherapy of Cancer 9, e002682). When looking to confirm these results in human OC tumor microarrays (TMAs), we found an inverse correlation between human stromal (but not tumor) TG2 expression and $CD8^+$ T cells infiltration by IHC staining followed by StrataQuest image cytometry. Using Opal-based multiplex IHC staining, we identified TG2 in a subset of cancer associated fibroblasts (CAFs). TG2 was previously reported as a non-toxic druggable target involved in “outside-in” signaling downstream of integrins. Further, we used inhibitors developed towards TG2-fibronectin interaction (Sima LE et al. (2019) Mol Cancer Ther 18, 1057-1068) to evaluate how they affect the cancer cells-fibroblasts cross-talk. This treatment prevented the self-assembly of heterospheroids. This is relevant for the situation in the tumor microenvironment, where we found TG2-FN interaction present in both stroma and tumor areas. These results support the potential use of TG2 directed agents in ovarian cancer therapy, as we propose TG2 as a new immunomodulatory target. Our current efforts also include using FLASH radiation to sensitize cancer cells to immunotherapy.