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Role of Host Tissue Transglutaminase in Ovarian Cancer Anti-tumor Immune Response †

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Abstract: Tissue transglutaminase (TG2) is an enzyme that was found overexpressed in various solid tumors, including ovarian cancer. TG2 upregulation was correlated with poor clinical outcome, and it was linked to cancer metastasis and chemo- and radiotherapy resistance. TG2 function in cancer cells has been connected to enhanced tumor progression. However, its functions in the host tissues were less investigated. We assessed the role of TG2 in the host by using a TG2KO syngeneic ovarian cancer mouse model. Immune cell subsets in the peritoneal microenvironment were phenotyped using FACS. Ascites cancer cells were analyzed using RNAseq and *in vitro* cancer cell assays. We evaluated TG2 and CD8 expression in human TMAs by quantitative image cytometry. Decreased tumor burden and increased survival were observed in TG2KO mice upon, i.p., injection of ID8 cells. Lack of TG2 allowed increased infiltration of $CD8^+$ T cells, while myeloid cells were found in decreased numbers in the peritoneal ascites. $CD8^+$ T cells from tumor-bearing TG2KO mice had an enhanced effector phenotype. TG2 loss increased T cell activation by attenuating STAT3 phosphorylation. Cancer cells from ascites showed an IFN-γ responsive gene signature and were more prone to apoptosis. An inverse correlation was seen between human stromal TG2 expression and TILs. In summary, our results demonstrate decreased tumor progression and increased T cell activation in the absence of TG2 in the host.

Keywords: ovarian cancer; tissue transglutaminase; immune response.

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Conflicts of Interest

The authors declare no conflict of interest.