

Occurrence of Tertiary Lymphoid Tissue in Pancreatic Adenocarcinoma

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Context Stimulating the patient's immune system to attack malignant tumor cells is considered a promising alternative therapeutic strategy to treat pancreatic adenocarcinoma (PDAC). Recent data point to the neogenesis of organized and vascularized ectopic (or tertiary) lymphoid tissue (TLT) at the tumor site, where B and T cell responses are efficiently initiated and sustained.

Objective To investigate the occurrence of TLT in human PDAC and test whether a protocol of immunotherapy induces formation of TLT in a PDAC murine model. This might represent an alternative approach to target the tumor stroma, by creating a lymphoid like microenvironment, to increase the recruitment and activation of T cells.

Methods Occurrence of TLT was evaluated by immunohistochemistry in PDAC tissue specimens from consecutive patients who underwent surgical resection at the Humanitas Clinical and Research Centre. A dendritic-cell (DC) based vaccine was

used to immunize mice injected with Panc02 murine cells. **Results** In human PDAC tissue specimens, we identified organized lymphoid tissue, including compartmentalized T and B cell areas, DCs and high endothelial venules (HEV). In the heterogeneity of PDAC tissue, TLT occurred preferentially in the stromal compartment. The density of TLT correlated to the density of intra-tumor CD8 T cells, which displayed a phenotype indicating a defective activation status. In a murine model of PDAC, vaccination with DCs loaded with apoptotic PDAC cells occasionally induced formation of TLT. **Conclusion** Here we report the occurrence of lymphoid tissue in human PDAC, in the context of the desmoplastic stromal reaction and the correlation with CD8+ T cell infiltration. Immunotherapeutic approaches might induce formation of TLT and be exploited as alternative strategies to modify PDAC stroma and induce an anti-tumor immune response.