Tumor-derived inflammation drives T cell fate

Question: Tumor infiltrating T cells are exhausted and dysfunctional. GM-CSF is released by aggressive tumors such as lung adenocarcinoma. GM-CSF, a major inflammatory cytokine, drives the differentiation of suppressive mononuclear phagocytes whose immune function remains to be further defined. Here we sought to address the diversity of GM-CSF-dependent myeloid cells and their impact on T cells.

Methods: We have followed the immune cell infiltration in lung adenorcinoma using tumor secreting or not GM-CSF (Crisp-Cas9-targeting of endogenous GM-CSF). To decipher the implication of the different phagocyte subsets in the T cell differentiation, we used transgenic mice depleted for several specific subsets.

Results: Lung adenocarcinoma-infiltrated T cells have an exhausted phenotype, PD1+ Lag3+. Surprisingly, they produce large amount of IFNg and are proliferating. Lung adenocarcinoma microenvironment induces the recruitment of DC1 and the differentiation of inflammatory phagocytes expressing CD209a and PDL2. In one hand, the DC1 drive the exhausted phenotype of T cell. In other hand, the inflammatory phagocytes dampen the PD1 Lag3 expression. We show the tumor-derived GM-CSF as a key factor orchestrating this T cell fate.

Conclusion: The GM-CSF licenses the monocyte-derived cells but also the DC1 to control the T cell fate inside the tumor.

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