Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Cellular and molecular regulators of the anti-tumor γδ T cell response in the tumor microenvironment

Synopsis:

Tumors are infiltrated by many immune cells that influence several aspects of cancer progression and outcome, including tumor growth, invasion, formation of metastasis, and response to treatments. In fact, the therapeutic manipulation of these immune cells has recently led to significant advances in cancer treatment. Among tumor-infiltrating lymphocytes (TILs), the host laboratory has identified two distinct gamma delta (γδ) T cell subsets with opposite roles on tumor progression: whereas interferon-γ (IFN-γ)-producing γδ T cells are associated with tumor surveillance and regression, IL-17-secreting γδ T cells promote primary tumor growth and metastasis in mice, which has also been validated in human cancer patients[1,2]. However, the cellular and molecular factors controlling the balance between these antagonistic subsets and their actions in the tumor microenvironment (TME) remain unknown.

The host laboratory has recently demonstrated that tumor-associated neutrophils strongly suppress IL-17$^+$ γδ T cell proliferation, revealing an unanticipated crosstalk between tumor-infiltrating myeloid cells (in this case neutrophils) and γδ T cells in TME[3].

We now aim to **provide a novel and thorough perspective on how different myeloid and lymphoid tumor-infiltrating immune cells may act on the protective IFN-γ$^+$ γδ T cell subset to promote their anti-tumor response in the TME**. We have evidence that while antibody depletion of CD4 T cells leads to an increased frequency of IFN-γ$^+$ γδ T cells, by contrast depletion of NK cells reduces their frequency. These preliminary data provide a strong background to study the molecular basis of the crosstalk between the IFN-γ$^+$ γδ T cell subset and other immune subsets infiltrating the TME.

Methodology: We will use different mouse tumor models, namely upon subcutaneous injection of breast cancer and colon cancer cell lines in C57BL/6J mice (WT mice). On one hand, since CD4$^+$CD25$^+$Foxp3$^+$ regulatory T cells (Tregs) are also ablated during the depletion of CD4 T cells, we will analyze their specific contribution to this phenotype by using Foxp3^{DTR} mice (Jackson Laboratory) where dipheteria toxin (DTx) treatment results in a specific ablation of Treg cells[4]. On the other hand, we will also study the impact of NK cells on the regulation of IFN-γ$^+$ γδ T cells in the TME by using a mouse genetic model that is Nkp46^{Cre}Rosa26^{DTR} mice, where DTx treatment induces the elimination of NK cells[5]. We also aim to assess the role of myeloid cells (neutrophils and macrophages) on the IFN-γ$^+$ γδ T cells.

In the various settings, tumor volume will be measured every two days; and the immune infiltrate will be analysed 2 weeks after tumor implantation, particularly the presence and function of TCRγδ$^+$CD3$^+$IFN-γ$^+$ and TCRγδ$^+$CD3$^+$IL-17A$^+$ γδ T cells.

Conclusions: With this project we aim to identify the upstream regulators and potential crosstalk signals that support the presence of IFN-γ$^+$ γδ T cells in the TME. Overall, we expect to uncover druggable molecular pathways capable of promoting the antitumor IFN-γ$^+$ γδ T cells for cancer immunotherapy.

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