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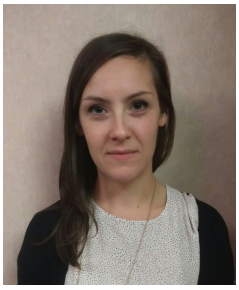

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Impact of tumor microenvironment on DC and T cell functions in a model of lung cancer

Cancer progression depends on cell intrinsic oncogenic pathways in transformed cells and their interactions with the surrounding environment, particularly immune cells. Main characters of tumor microenvironment are T cells, which could be the physiologic defense against tumor cells, but that unfortunately are often silenced leading to tumor escape. The relevance of T cell response has been recently strengthened by the demonstration in different tumor types of a direct correlation between the presence of intra-tumor $CD8^+$ T cells and the clinical outcome[1]. The extensive study of T cells in the last years resulted in the generation of cancer immune-therapies, which emerged as revolutionary therapy for many cancer patients.

Current immunotherapies are mainly based on functionally rescue T cell functions, in fact during cancer progression T cells can undergo different type of suppression, such as the expression of inhibitory receptors on T cells and their ligands on cancer cells and on immune cells (CTLA4/PD-1/PD-L1) or the accumulation of regulatory T cells that block the function of CTLs. Unluckily, despite of the revolutionary success, not all patients positively respond to immune check-point blockade, highlighting the need to identify novel targetable suppressive mechanisms to increase the proportion of responding patients and to overcome resistance to current therapies.

Recent studies showed that the success of immune checkpoint blockade depends on specialized antigen presenting cells, dendritic cells (DCs) that induce and maintain anti-tumor T cell responses. Of special interest, Baft3-dependent DC1, are uniquely capable to cross-present tumor antigens to $CD8^+$ T cells and are indispensable for the efficacy of check-point inhibitors. In parallel, several reports documented a compromised function of the DCs compartment during tumor growth, via mechanisms that remain mostly elusive. Initial hints suggest that DCs exposed to tumor-derived factors accumulate oxidized lipids that block cross-presentation, possibly via XBP-1 mediated sensing of ER stress in the tumor microenvironement (TME)[2]. Suppression of IL-12 by DCs was shown to be driven by IL-10 and PGE2 in the TME of breast cancer and melanoma respectively[3,4]

At present, how tissue resident Baft3-DC1 are affected in cancer tissues is still unknown. Here we propose to investigate DC suppression mechanisms in an

othotopic murine model of lung cancer. We will use a cell line derived from $Kras^{G12D/+}$ $p53^{-/-}$ lung tumors, that generates, once injected iv, malignant lesions hystopathologically similar to human adenocarcinoma[5].

Lung cancer is the leading cause of cancer-related morbidity and mortality worldwide (~10% survival at 5 yrs) and non-small cell lung cancer (NSCLC) is the most common form of lung cancer. Nowadays, immunotherapy is emerging as a novel promising therapeutic option also for NSCLC but unfortunately, only a small fraction of patients benefits of these therapies, eliciting the need of new therapeutic targets as a priority[6]. Recently, a study designed a multiscale immune profiling strategy to map the immune landscape of early lung adenocarcinoma lesions to search for tumor-driven immune changes. They identified alterations in tumor infiltrating myeloid cells and NK cells, pointing out a possible role of these populations in tumor-escape[7]. Nevertheless, further studies are needed to better characterize the possible target populations and their mechanisms of action.

For this purpose we will analyze tumor immune infiltrate at different time points of tumor progression correlating the changes in immune cell populations with the functionality of T cells and DCs. We will use ImmunoTools antibodies generating a multi-parameter gating strategy, for immune cell identification and single cell sorting of tumor-infiltrating DCs and T cells. The obtained purified populations will be assessed for their functionality, for example the ability of $CD4^+$ T cells to produce IL17A (ELISA ImmunoTools) or the directional migration of DCs in response to chemokines.

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includes 25 reagents

FITC - conjugated anti-mouse CD4, CD8, CD11b, CD44, CD134, Annexin V

PE - conjugated anti-mouse CD3, CD8, CD90, NK cells, gdTCR

APC - conjugated anti-mouse CD3, CD4, CD19, CD25, CD62L, GR1

mouse ELISA-set (for one 96 plate): mouse IL-17A

recombinant mouse cytokines: rm Flr3L/CD135, rm GM-CSF, rm MIP3b/CCL19, rm SDF-1a/CXCL12

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