Mechanisms regulating NFAT5 dependent inhibition of anti-tumor response in exhausted CD8 T cells

Despite promising recent reports of successful immunotherapy against metastatic cancers, we are still far from being able to manipulate selectively the immune system to restore immune responses potent enough to eradicate established tumors in high percentages of patients. A key challenge is that cancer induces T cells that phenotypically and functionally strongly differ from "classically activated T cells" i.e., the ones known to protect from disease. In cancer patients, T cells are strongly suppressed by the tumor micro-environment and are poorly functional, so-called "exhausted", similarly to what has been described in chronic infection. Molecular pathways regulating this state are still only partially understood. We have found that the transcription factor NFAT5 is specifically regulating this state of exhaustion in CD8 T cells in tumors but not in chronic infection. These discoveries are at the base of the current project which aims at understanding i) why NFAT5 has a differential role in chronic infection and cancer by comparing the level of regulation of NFAT5 in these two settings; ii) what are the signals that drive NFAT5 expression/activity in tumor infiltrating lymphocytes (TILs); iii) what is the effect of NFAT5 on T cell metabolism and epigenetic landscape in tumor exhausted CD8 T cells.

We generated new mouse strains to study to compare the regulation of NFAT5 at the transcriptional level, at post-translational levels and at the level of mRNA stability in tumors and in chronic infection. This project aims at deciphering *in vitro* and *in vivo* the pathways that differentially regulate these features in the TILs to uncover new ways to inhibit NFAT5 in CD8 T cells, either genetically or by using inhibitors. The candidate will study in detail how NFAT5 regulates T cell exhaustion at the epigenetic level by combining omics and reporter-based studies. We will also study the consequences of NFAT5 inactivation on the metabolism of the T cells, which is critical for their functions. For that we will use a new technique based on flow cytometry that allows to study T cell metabolism directly recovered from the tumor microenvironment.

This project will provide both novel basic scientific knowledge and potentially clinically relevant insights. Identifying molecular mechanisms of T cell exhaustion, and learning how to alter them therapeutically, provides the basis for improving immunotherapy. The identification of novel therapy targets within T cells is particularly meaningful for adoptive T cell transfer (ACT) therapy, a setting that allows to manipulate the cells before they are administrated to the patient. In conclusion, our findings will likely have implications for future developments of immunotherapy, not only for melanoma but also for other frequent cancer types (such as lung, breast, prostate, or pancreas cancer), as illustrated by the continuous progress in immunotherapy of cancer patients.