University of Basel

DBM Basel
Department of Biomedicine

MASTER THESIS PROJECT

Investigating the impact of intra-cellular cytokine signals on the epigenetically programmed CD8 T cell exhaustion state using gain-of-function mutants of STAT(s) transcription factors.

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Immunobiology and Cancer Immunotherapy
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Field – Immunology – Cancer Immunotherapy – Molecular engineering
Key words – CD8 T cell exhaustion – Cytokine signals – epigenetic reprogramming

Scientific Background

Cancer immunotherapies have revolutionized the field of clinical oncology. Over the last decade, strategies such has targeting the immune checkpoints (e.g. PD-1) have proven more efficient than standard cares and these approaches are now first or second line treatment, alone or in combination in more than 50 different cancer types. However, despite many clinical successes, current cancer immunotherapies still fail at achieving long-term benefits in a majority of patients. Exhaustion of CD8 T cells is a major limitation. This process gradually deprives anti-cancer CD8 T cells from their main effector functions and is reinforced by a stable epigenetic program. Developing complementary strategies to epigenetically reprogram exhausted CD8 T cells towards more durably protective cell-states is the next challenge. However, our lack of understanding of the exhaustion process has hindered the design of relevant therapeutic interventions. Recent work demonstrated that specific cytokine signals such as those provided by the gamma-chain (gc) cytokine IL-2 and its downstream adaptor molecule STAT5 could partially reprogram the epigenetic landscape of exhausted CD8 T cells (Beltra et al., Immunity 2023). These studies provided first proof of concept for the possibility of therapeutically rewiring exhausted CD8 T cells towards more protective cellstates. Yet, whether alternate members of the gc family of cytokines (e.g. IL-4, -7, -9 and -21) can also impact the exhaustion program and complement the therapeutic action IL-2 remains to be determine.

Hypothesis

Here, because each gc cytokine activates unique combinations of STAT transcription factors (Stat 1-to-6), we hypothesized that these cytokines may exert non-redundant and possibly synergistic therapeutic functions on exhausted CD8 T cells. Resolving this biology will pave the way towards nextgeneration
cytokine-based therapy.

Your role

Using state-of-the-arts molecular biology approaches, you will be in charge of developing and validating gain-of-function mutants for members of the STAT family of transcription factors based on correspondent mutations evidenced in patients with STAT-related immune disorders. After careful validation steps, the constructs will be encoded into retroviruses for further transfection of murine CD8 T cells and subsequent in vivo testing. Notably, CD8 T cells transduced with STAT mutants of interest will be adoptively transferred into mice recipients infected with the LCMV virus, a gold-standard model for the study of CD8 T cell exhaustion. These experiments will allow to investigate how augmented STAT-signaling impacts establishment of the exhaustion program in CD8 T cells. Read-out from these experiments will include advanced flow-cytometry, ex vivo functional assay and, if relevant, epigenomic approaches
(scRNAseq, ATASeq).

Your profile

- B.Sc. in Biology or equivalent
- Familiar with basic molecular biology techniques (plasmid design/cloning)
- Strong interest in Immunology and Cancer Immunotherapy
- Fluent in French or English (required)

We offer

The successful candidate will join a vibrant cross-disciplinary and collaborative environment with opportunities to master state-of-the-art immunological concepts and approaches as well as next generation sequencing techniques. The candidate will benefit from all the technological platforms available at the Department of Biomedicine, careful supervision by a Ph.D. student and an experienced research assistant and mentoring by the lab's head (Dr. Beltra). Within this dynamic environment, the candidate will have all the support needed for the success of his/her/their Master thesis and achievement of future career goals.

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