Universität Basel

Research Project

Alarmin' for T cell self-renewal

Third-party funded project

Project title Alarmin' for T cell self-renewal
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Project start 01.04.2019
Probable end 31.03.2023
Status Completed

Memory CD8 T cells with stem-like self-renewing capacity are pivotal to sustained immune defense against persisting viruses and cancer, two disease areas of major global health impact. The transcription factor T cell factor 1 (Tcf1) is necessary and at least partially sufficient to confer CD8 T cells with self-renewal capacity. Accordingly, Tcf1+ memory CD8 T cells represent the cellular substrate, which yields expanded populations of terminally differentiated effector cells upon anti-PD1/PD-L1 checkpoint inhibition. We remain, however, in need of strategies whereby to augment the pool of Tcf1+ stem-cell-like memory CD8 T cells. Working hypothesis: I) Based on our preliminary data we aim to identify key factors that serve to augment Tcf1 expression and thereby foster stem-cell-like CD8 T cell memory formation in the chronic infection context. Specifically, we will test the hypothesis that these key factors counterbalance inflammatory stimuli such as type I interferons and interleukin-12, which promote terminal differentiation of CD8 T cells through STAT4-mediated Tcf1 repression. We speculate that STAT4 is part of a negative feedback loop to sustain critical levels of Tcf1 and to enable the formation of self-renewing CD8 T cell memory. II) As the infection progresses into its chronic phase, the aforementioned key signals become scarce and self-renewing CD8 memory T cells get deprived of Tcf1-promoting signaling. Accordingly, exogenous supplementation of these key signals has the potential to augment the pool of Tcf1+ memory CD8 T cells, and to restore antiviral immune control in persistent infection.Experimental models and methods: The role of Tcf1-supporting factors be studied in the mouse model of chronic lymphocytic choriomeningitis virus (LCMV) infection. Sensing of Tcf1-promoting factors and Tcf1 levels in adoptively transferred antiviral CD8 T cells will be modulated by constitutive or conditional gene deletion as well as by transgenic and retroviral gene supplementation. We will combine genome-wide transcriptome analyses, TaqMan RT-PCR technology, cutting-edge multi-color flow cytometry and recombinant adeno-associated viral (AAV) vector-based protein delivery with state-of-the-art immunological and virological assessments.Specific aims: To define the role of Tcf1 promoting signals in the chronic viral infection context we aim to:1. Corroborate and mechanistically decipher the role of these signals for the formation of Tcf1-expressing stem-cell-like memory CD8 T cells.2. Explore the utility and potential of immunotherapies for augmenting the stem-cell-like pool of Tcf1-expressing memory CD8 T cells in chronic infection.Significance: These studies in a relevant small animal model are designed to substantially advance our understanding of stem cell-like T cell differentiation in chronic viral infection. Ultimately, they aim at delineating a strategy to augment the pool of stem-like memory CD8 T cells. This has the potential of restoring immune control in chronic microbial infection and cancer, a major goal and challenge of contemporary biomedicine.

Financed by
Swiss National Science Foundation (SNSF)

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