Universität Basel

Research Project

The role of ZNF74 in the generation and maintenance of immunological memory

Third-party funded project

Project title The role of ZNF74 in the generation and maintenance of immunological memory
Principal Investigator(s) Recher, Mike ;
Organisation / Research unit
Departement Biomedizin / Immunodeficiency (Recher)
Department
Project start 01.04.2020
Probable end 31.03.2024
Status Completed

Adaptive immune cell (T and B cell) memory is ensuring human health despite constant encounter with pathogens. T cell memory differentiation is also essentially linked to potent immune surveillance of tumors and required for immune control of persistence prone pathogens. Proteins driving adaptive immune cell memory differentiation and/or maintenance with non-redundant roles in humans ('in natura') have only been identified in part. Primary immunodeficiencies (PID) are genetically determined human diseases presenting with susceptibility to infection, autoimmunity and impaired adaptive immune cell memory. Within a prospective cohort of patients with PID initiated by the applicant, we have identified patients with a unique PID characterized by specifically reduced adaptive memory T and B cells due to a homozygous truncating mutation in primate-specific KRAB zinc finger protein (KZFP) ZNF74. While the KZFP family has been shown to execute non-redundant roles in adaptive immune cells by influencing the T and B cell intrinsic epigenetic landscape, no specific KZFP family member has been linked to adaptive immune cell memory formation in humans.Overall Objectives:The overall objective of the proposal is to define the molecular role of ZNF74 in driving human T cell memory formation and/or maintenance, to characterize modulation of ZNF74 expression during T cell activation and function, and to identify druggable targets to deliberately dysregulate ZNF74 dependent adaptive immune cell memory.Specific Aims:The overall objectives will be experimentally assessed using the following specific aims:Specific aim (i): Identification of genes regulated by ZNF74 in human T cellsSpecific aim (ii): Characterization of the modulation of ZNF74 expression during T cell activationSpecific aim (iii): Analysis of the role of ZNF74 in memory human T cell differentiation and/or maintenanceSpecific aim (iv): Development of targeted strategies to alter ZNF4-associated T cell differentiation and/or maintenance in vitro and in vivoExpected Results:We expect, based on our preliminary experiments and concentrating on T cells, to characterize ZNF74 incompetence as a novel cause of human PID due to its essential non-redundant function to orchestrate adaptive immune cell memory formation in vitro and in vivo. ZNF74 dependent phenotypic, functional and epigenetic adaptations during human T cell activation and memory differentiation will be experimentally assessed. In addition, we might identify druggable targets dysregulated in human T cells associated with ZNF74 incompetence to subsequently concertedly facilitate ZNF74-driven adaptive immune memory formation in therapeutic or prophylactic immune therapy.Impact:From a basic immunology standpoint, characterization of non-redundant functions of ZNF74 might offer novel evidence how KZFP epigenetically regulate adaptive immunity. Translationally, the gain of knowledge from the proposed experiments may potentially accelerate the development of novel, ZNF74-targeted drugs to improve immune-mediated elimination of malignancy, to accelerate elimination of chronic virus infections and augment immune function in patients with immunodeficiency.

Financed by
Swiss National Science Foundation (SNSF)

Add publication

Add documents

Specify cooperation partners