Universität Basel

Research Project

Transcriptional control and Epigenetic Mechanisms of Thymic Epithelial Cell Development and Function

Third-party funded project

Project title Transcriptional control and Epigenetic Mechanisms of Thymic Epithelial Cell Development and Function
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Organisation / Research unit
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Department
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1.1. Background

The thymic microenvironment is unique in its ability to promote the development and selection of naïve T cells with a repertoire purged of vital “Self” specificities but prepared to react to injurious “Non-Self”. Essential for this competence are thymic epithelial cells (TEC). These constitute the major component of the thymic stroma and are categorized into separate cortical (c) and medullary (m) lineages based on their specific molecular, structural and functional characteristics. cTEC attract blood-borne precursor cells, commit them to a T cell fate, foster their differentiation and positively select cells that express a T cell antigen receptor (TCR) of sufficient affinity for self-antigens. Subsequently, both cTEC and mTEC deplete thymocytes that display a TCR with significant reactivity to self-antigens, a process known as negative selection, authorizing the generation of a diversified T cell repertoire with versatile antigen-recognition capacity. TEC differentiation and growth are dependent on the expression of the transcription factor FOXN1, a master regulator required for normal TEC biology. The precise molecular and cellular mechanisms that control TEC formation, their differentiation into separate lineages, their life-long homeostatic maintenance and the preservation of their complex function are, however, only incompletely understood. Detailed knowledge of the genetic and epigenetic mechanisms that control regular TEC biology will therefore provide important insight into an essential component of the adaptive immune system.
This research proposal (i) seeks to identify distinct cellular stage in cTEC and mTEC maturation, respectively, and probe the genetic control that commends their differentiation (Specific Aim 1); (ii) explores the role of the proteasome component β5t, a target of FOXN1 (Specific Aim 2); and (iii) elucidates the plasticity in mTEC development as a function of epigenetic regulation (Specific Aim 3).

1.2. Working Hypothesis

The proposed research is based on the testable hypotheses that the differentiation of thymic epithelia into the functionally separate cortical and medullary lineages is instructed by specific genetic circuits that require FOXN1-mediated target gene expression in conjunction with the correct placement of epigenetic marks.

1.3. Specific Aims:

#1: To identify the genetic control of TEC differentiation into distinct cortical and medullary linages
#2: To investigate the role of Psmb11, a developmentally regulated Foxn1 target gene, in cTEC function

#3: To examine the Polycomb Repressive Complex 2 (PRC2)-independent pathway of mTEC differentiation

1.4. Expected Value of the Proposed Project
The proposed research will establish in unprecedented molecular details the mechanisms important in TEC lineage differentiation and function. Specifically, information gained from the outlined studies will allow a refined understanding of the genetic and epigenetic mechanisms operative in regular TEC biology. This insight is not only essential to appreciate the immune systems' competence to establish tolerance to "Self" whilst maintaining an ability to generate a protective response to "Non-Self" but is also fundamental for the design of efforts aimed in the immediate future to regenerate thymus function in the context of congenital and acquired deficiencies.

The research consortium
The research proposed here builds on original observations made, in part, jointly and over the course of the last 10 years by the laboratories of the two principal applicants, G. Holländer and Y. Takahama. Using innovative in vivo lineage fate mapping models, their research has recently established at single cell resolution the spatio-temporal dynamics that control the growth and maintenance of the separate TEC compartments. These results form the basis for the submitted research programme.

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