Single st+ epithelial progenitor cells located at the cortico-medullary junction (CMU) adopt a medullary TEC fate and actively contribute post-natal medulla growth.

The research of the laboratory of Paediatric Immunology focuses on a detailed understanding of: (i) the genetic and epigenetic control of TEC development and function. We have generated specific genetic gain and loss of function mouse models that allow a precise interrogation of particular mechanisms relevant for thymus organogenesis and function. Our research has defined the direct target genes of the TEC master regulator transcription factor Foxn1 as well as its DNA binding motif. We detailed the function of Foxn1 and demonstrated that in addition to the transcriptional control of genes involved in attraction and lineage commitment of T precursor cells, Foxn1 also regulates genes involved in antigen processing and thymocyte selection. Thus, critical events in thymic lymphostromal crosstalk and T cell selection are choreographed by Foxn1. Further studies have characterized the importance of the polycomb repressive complex 2 (PRC2) for regular TEC biology. DNA methylation and the generation of micro-RNA constitute additional epigenetic mechanisms that we have identified to play an essential role in TEC fate, maintenance and function, including the expression of PTA. The expression of some of these PTA is controlled by the nuclear protein Autoimmune Regulator (AIRE). A single cell transcriptome analysis of TEC subsets proficient or deficient in the expression of histone and DNA modifying enzymes further revealed that PTA expression by thymic epithelia is dependent on different epigenetic mechanisms. (ii) the identity of TEC stem/precursor cells and their intermediate stages in differentiation towards mature cTEC and mTEC. Using in vivo lineage tracing and fate mapping, we demonstrated that st+ cortical progenitors located at the cortico-medullary junction give rise to medullary TEC. Lineage-tracing demonstrated that the medullar TEC is populated from individual st+ cortical progenitors. These results therefore not only define a developmental window during which expansion of medulla is enabled by progenitors resident in the cortex, but also reveal the spatio-temporal dynamics that control medulla growth. (iii) the role of metabolic pathways in TEC biology. We have generated mice lacking in TEC essential components of the mTORC complex. Absence of mTORC1 signaling ensued a decrease in mTEC numbers that correlated with reductions in mitochondrial mass, respiration, endoplasmic reticulum network and reactive oxygen species. Furthermore, it lowered the affinity of positively selected TCRs and led to specific stages in T cell development. (iv) the consequences of altered thymus development on T cell function, in particular regulatory T cells (Treg). Thymic hypoplasia and ensuing peripheral lymphopenia favor the expansion of a particular potent Treg subset that can be identified by CD103 and ICOS. This phenotype represents a lymph node specific differentiation stage that requires the availability of antigen. Thus, we showed that tissue-resident cues determine the overall potency of the peripheral Treg pool by shaping its subset composition.

**Fig. 1:** Upper panel: Schematic representation of triple transgenic inducible reporter mice (3xtg). Lower panel: Immunohistological analysis of the thymus from 3xtg mice that had been treated with doxycycline at 1-week of age and followed for 2 and 14 days, respectively. Crystal sections were analysed for the expression of ZsGreen (green) and Zsgreen (grey). Note that the majority of ZsGreen positive cells are positioned at the cortico-medullary junction. c cortex, m medulla.

**Fig. 2:** Single st+ epithelial progenitor cells located at the cortico-medullary junction (CMU) adopt a medullary TEC fate and actively contribute post-natal medulla growth.

**Selected Publications**
