Pediatric Immunology

Georg Holländer
Department of Biomedicine
Immunology
University Children's Hospital Basel and Children's Hospital University of Oxford, UK

Group Members

Domenika Anselm*
(Undergraduate Student)
Dr. Thomas Barthlott
(Postdoc)
Damian Beck*
(Undergraduate Student)
Dr. Chiara Beilin*
(Postdoc)
Caroline Berkemeier*
(PhD Student)
Simon Bornschein*
(Undergraduate Student)
Dr. Marco Catucci*
(Postdoc)
Elli Christen
(Technician)
Simone Dertschnig*
(Postdoc)
Martha Gaio
(Administrative Assistant)
Sanjay Gawade
(Postdoc)
Katrin Hafen
(Technician)
Veysel Kaya
(Undergraduate Student)
Carlos Eduardo Mayer
(Postdoc)
Elisa Rösti*
(Undergraduate Student)
Dr. Noriko Shikama*
(Postdoc)
Dr. med. Gabor Szinnai
(Postdoc)
Hong Ying Teh
(PhD Student)
Dr. Saule Zhanybekova*
(Postdoc)
Dr. Saulius Zuklys
(Postdoc)

*left during report period

The Immunobiology Of The Thymus

T cell responses play a crucial role in providing protective immunity. At the same time the effector molecules and cells of this defense system can also be responsible for a broad range of autoimmune pathologies when directed against an individual's own tissues. Lineage commitment and maturation of T cells is instructed during the cell's intrathymic development and result from a physical and functional interaction with the stromal microenvironment. Thymic epithelial cells (TEC) constitute an essential component of this stroma whereby cortical (c) and medullary (m) TEC have distinct structural, antigenic and functional features. cTEC provide signals that commit hematopoietic precursor cells to a T cell fate and select those immature T cells for further differentiation that express a functionally competent and for the individual largely useful T cell receptor (TCR). In contrast, mTEC contribute to the establishment of self tolerance via the expression of peripheral tissue-specific antigens (PTA).

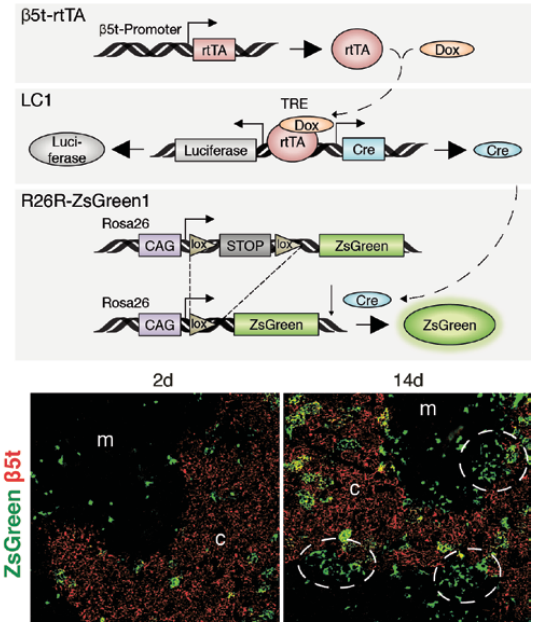

Fig. 1: Upper panel: Schematic representation of triple transgenic inducible reporter mice (3xtg^{β5t}). Lower panel: Immunohistological analysis of the thymus from 3xtg^{β5t} mice that had been treated with doxycycline at 1-week of age and followed for 2 and 14 days, respectively. Cryostat sections were analysed for the expression of β5t (red) and ZsGreen (green). Note that the majority of ZsGreen positive cells are positioned at the cortical-medullary junction. c: cortex, m: medulla

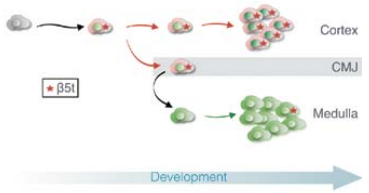

Fig. 2: Single β5t$^+$ epithelial progenitor cells located at the cortico-medullary junction (CMJ) adopt a medullary TEC fate and actively contribute post-natal medulla growth.

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 it's 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 cell precursors, 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 fate mapping, we demonstrated that β5t+ cTEC-like progenitors give rise to the medullary TEC compartment. Lineage-tracing demonstrated that the postnatal medulla is expanded from individual β5t+ cortical progenitors located at the cortico-medullary junction. These results therefore not only define a developmental window during which the 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 mTOR complex. Absence of mTORC1 signalling 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 reduced negative selection. Hence, our findings link bioenergetic changes in TEC 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.

Selected Publications

Zuklys S, Handel A, Zhanybekova S, Govani F, Keller M, Maio S, Mayer CE, Teh HY, Hafen K, Gallone G, *et al.* (2016) Foxn1 regulates in postnatal thymic epithelial cells key target genes essential for T cell development. Nat. Immunol. In press

Mayer CE, Zuklys S, Zhanybekova S, Ohigashi I, Teh HY, Sansom SN, Shikama-Dorn N, Hafen K, Macaulay IC, Deadman ME, *et al.* (2016) Dynamic spatio-temporal contribution of single 5t+ cortical epithelial precursors to the thymus medulla. Eur. J. Immunol. 46, 846–56

Barthlott T, Bosch AJ, Berkemeier C, Nogales-Cadenas R, Jeker LT, Keller MP, Pascual-Montano A, Holländer GA. (2015) A subpopulation of CD103(pos) ICOS(pos) Treg cells occurs at high frequency in lymphopenic mice and represents a lymph node specific differentiation stage. Eur. J. Immunol. 45, 1760–71

Sansom SN, Shikama-Dorn N, Zhanybekova S, Nusspaumer G, Macaulay IC, Deadman ME, Heger A, Ponting CP, Holländer GA. (2014) Population and single-cell genomics reveal the Aire dependency, relief from Polycomb silencing, and distribution of self-antigen expression in thymic epithelia. Genome Res. 24, 1918–31

Hauri-Hohl M, Zuklys S, Holländer GA*, Ziegler, SF.* (2014) A regulatory role for TGF-β signaling in the establishment and function of the thymic medulla. Nat. Immunol. 6, 554–61.* Shared senior authorship