 Canonical Wnt signalling is required for thymus organogenesis

S. Zuklys1, T. Bartholomé2, J. Gill3, M. Keller1, S. Zhanybekova2, M. Haun3, K-J. Na4, K. Hafeni5, E. Illingworth6, A. Moor7, Y. Hamazaki8, G. Holländer9
1 University Children’s Hospital of both Cantons of Basel (Basel, CH); 2 University System Health Science Center (Huston, USA); 3 University of Utah School of Medicine (Salt Lake City, USA); 4 Kyoto University (Sakyo-ku, JP)

The thymus achieves two interrelated functions essential for the adaptive immune system: the life-long generation of new T cells and the selection of a repertoire of T cells tolerant to self-antigens but reactive to foreign peptides. Thymus organogenesis is initiated in the mouse at embryonic day 10.5 when endodermal cells of the third pharyngeal pouch come committed to a thymus fate. The formation of an epithelial primordium and the subsequent differentiation of thymic epithelial cells (TEC) into distinct subpopulations constitute the necessary prerequisite for the formation of a thymus to support T cell development. However, the precise molecular signals that dictate TEC fate commitment and differentiation remain largely unknown. Wnt signaling has, however, been implicated in thymus organogenesis. Here, we demonstrate that thymus organogenesis is differentially affected depending on the timing of the loss in canonical Wnt signalling. Deletion of canonical Wnt signaling during developmental stages prior to the formation of a thymus anlage causes thymic agenesis. In contrast, loss of canonical Wnt signaling at the CD4+ stage does not preclude the formation of a regularly structured and composed thymic microenvironment but leads to thymic hypoplasia despite normal T cell development. Taken together, these results demonstrate an essential role for canonical Wnt signaling during early stages of thymus organogenesis whereas activation through the same pathway determines thymus cellularity during later stages and organ maintenance of the thymus.

T-cell development occurs in the combined absence of the canonical Wnt signal-transducers beta- and gamma-catenin

1 LICR (Epalinges, CH); 2 Max-Delbrück Center for Molecular Medicine (Berlin, D); 3 EPFL (Epalinges, CH)

The canonical Wnt signaling pathway plays key roles in stem cell maintenance, expansion of committed progenitor cells and control of lineage decisions in a variety of tissues including the hematopoietic system. Beta-catenin is the central molecule in the canonical Wnt signaling pathway. Beta catenin transmits Wnt signals into the nucleus, where it acts as transcriptional co-activator by binding to members of the LEF/TCF (Lymphoid enhancer factor/T cell factor) family of transcription factors. The related molecule gamma catenin (plakoglobin) can fulfill similar functions to activate target genes upon Wnt signaling. Gene ablation of TCF-1 impaired T cell development, TCF-1 deficiency resulted in incomplete blocks within the CD4-8- thymocyte compartment and at the transition from immature single positive to the CD4+8+ stage. Strikingly, a genetic complementation approach showed that the N-terminal domain of TCF-1 was essential to rescue thymocyte development in TCF-1 deficient mice. This domain in TCF-1 includes a beta catenin binding site. We show that this domain also contains a gamma catenin interaction site, suggesting that catenin binding to TCF-1 is critical for T cell development. However, results obtained by individual gene ablations of the two known signal transmitters beta- and gamma catenin did not recapitulate the phenotype of TCF-1-deficient mice. Based on this discrepancy we analyzed thymopoiesis in the combined absence of beta- and gamma catenin. Unexpectedly, we find that T cell development occurs normally in the combined absence of the two known Wnt signal transmitters beta- and gamma catenin. We performed reporter assays to address whether canonical Wnt signaling was not needed for thymocyte development or whether such signals were transduced in the absence of beta- and gamma catenin. We find that beta- and gamma catenin-deficient thymocytes and peripheral T cells retain a significant capacity to transduce canonical Wnt signals. These data suggest a novel mechanism of TCF-1/Wnt signal transduction in the hematopoietic system.