Lymphoid development; a dynamic interplay of timing and dosing
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SUMMARY
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Mature lymphocytes originate from a common multipotent progenitor which undergoes successive steps of increasingly divergent differentiation. The outcome of lineage decisions is regulated by endogenous factors, such as transcription factors, but also environmental factors, like cytokines, antigens and cell-cell interactions. The studies described in this thesis focus on specific factors involved in lymphoid lineage decisions and the subsequent maintenance of the generated populations, with a particular interest for T lymphocytes. In chapter 1 a general introduction is given on which factors are known to be important in T cell, B cell, NK cell and pDC differentiation.

Chapter 2 discusses methods to replenish the peripheral T cell compartment in aged or immunocompromised individuals and describes interventions aiming at increasing both T cell development and homeostasis. Options encompass rejuvenation of the thymus tissue, pre-conditioning of hematopoietic stem cells (HSC) by Notch signaling before transfer, or infusion of mature T cells. Administration of IL-7 may enhance both T cell development and survival. To enrich the T cell repertoire of patients with impaired pathogen or tumor specific immunity, infusion of pathogen-specific CTL or T cells that are modified to express specific TCRs can restore specific immunity.

Chapter 3 introduces a model of in vivo human lymphoid development well-suited to assess the factors that contribute to lymphoid development. This model is based on newborn BALB/c Rag2−/−γc−/− mice transplanted with human hematopoietic progenitor cells to produce “human immune system” (HIS) mice. These mice demonstrate proper human engraftment and in situ multilineage human hematopoietic development. In order to manipulate the expression of genes of interest, the human hematopoietic progenitor cells can be genetically engineered ex vivo by lentiviral transduction before performing xenograft transplantation.

In chapter 4 we made use of the in vivo HIS mouse model of human lymphoid development to dissect the role of IL-7 signaling at different stages of T cell development and in the maintenance of mature T cells. We show that premature IL-7 signaling at the HSC stage, prior to entrance in the thymus, impeded T cell development, whereas increased intra-thymic IL-7 signaling significantly enhanced the maintenance of immature thymocytes. Increased thymopoiesis was also observed when we transplanted human HSC transduced with the anti-apoptotic genes BCL-2- or BCL-XL. Homeostasis of peripheral mature T cells was not improved by either increasing IL-7 signaling or enforced expression of anti-apoptotic
genes, highlighting the notion that IL-7 availability is but one of many signals that condition peripheral T cell homeostasis.

In chapter 5 the focus is on the effect of TSLP on early B cell development. TSLP is a cytokine closely related to IL-7 and both cytokines signal via a complex containing the IL-7Rα chain. Although the roles of IL-7 in murine and human B cell development are practically clarified, the role of TSLP in human B-cell development has not been elucidated yet. We find that TSLP can induce activation and proliferation of ex vivo isolated human early precursor B-cell subpopulations. TSLP, unlike IL-7, is able to sustain and enhance the development of human B-cells from fetal HSCs in vitro.

In chapter 6 the response of early T cell progenitors to TSLP was investigated. We specifically addressed the question whether TSLP was able to substitute for IL-7 in human T cell development. We found that early T cell progenitors are the most responsive to TSLP and that TSLP can fully rescue T cell development in the absence of IL-7, but only when the levels of TSLPR expression and signaling are optimal. In addition, we made use of the HIS mice and found that enforced expression of human TSLP by human cells leads to enhanced accumulation of T cells, including thymic CD4+CD25hi cells.

In chapter 7 we report on TCRαβ gene transfer into human hemopoietic progenitors from postnatal thymus or umbilical cord blood, with subsequent culture of these precursors on OP9 stromal cells expressing the Notch human ligand Delta-like1. We find that enforced expression of the TCR leads to enhanced T cell lineage commitment and TCR surface expression, and that fully mature, functional T cells with controlled Ag specificity develop from such cultures. The obtained Ag-specific T cells exert cytolytic activity against their cognate Ag and expand in vitro upon specific TCR stimulation. This technique provides a way to produce large numbers of autologous mature Ag-specific T cells in vitro from undifferentiated hemopoietic progenitors.

Chapter 8 aims to further elucidate the role of E-proteins in TCRαβ+ T cell development. We show that thymic progenitors transduced with Id2 are blocked in their T cell development and that this can be rescued by simultaneous overexpression of both a TCRα- and TCRβ-chain, but not with a TCRβ-chain alone. However, the T cells which develop from TCR x Id2 transduced progenitors do not pass through the CD4+CD8+ DP stage and acquire a CD4−CD8− DN CD3+TCRαβ+ mature T cell phenotype, suggesting commitment to the
TCRγδ lineage. These data reveal essential requirements for E-proteins in in TCRαβ T cell development apart from the processes related to the assembly of functional pre-TCR / TCR genes. Additionally, we observed that the TCR x Id2 transduced progenitors require sustained Notch induced signals to seal the commitment to the T cell lineage; otherwise cells phenotypically resembling NK cells or NKT cells are generated.

In Chapter 9 the particular prolonged plasticity of developing T cells is reviewed, leaving us to speculate on an superimposed default pathway determining cell fate when a TCR and Id2 are simultaneously expressed. Furthermore, the tools we used in our experiments to generate T cells and evaluate lymphoid development are discussed and we comment on their value, for both fundamental and preclinical purposes, in current and future research on the human immune system.