CURRENT OPINION
www.current-opinion.com

Lymphocyte development
Editorial overview
Ellen Robey and Mark Schlissel

Current Opinion in Immunology 2003, **15**:155–157

This review comes from a themed issue on
Lymphocyte development
Edited by Ellen Robey and Mark Schlissel

0952-7915/03/$ – see front matter

DOI 10.1016/S0952-7915(03)00017-7

Ellen Robey

Division of Immunology, Department of Molecular and Cell Biology, 471 Life Science Addition, University of California at Berkeley, Berkeley, CA 94720-3200, USA
e-mail: erobey@uclink4.berkeley.edu

Ellen Robey's laboratory is interested in cell-fate decisions in the immune system, with particular emphasis on thymic development.

Mark Schlissel

Division of Immunology, Department of Molecular and Cell Biology, 439 Life Science Addition, University of California at Berkeley, Berkeley, CA 94720-3200, USA
e-mail: mss@uclink4.berkeley.edu

Mark Schlissel's laboratory studies the regulation of lymphocyte development and targeting of the V(D)J recombinase.

Abbreviations

AID	activation-induced cytidine deaminase
CSR	class-switch recombination
D	diversity gene segment
IL	interleukin
J	joining gene segment
NK	natural killer
SHM	somatic hypermutation
TCR	T-cell receptor
TNF	tumor necrosis factor
V	variable gene segment

During their development, lymphocytes acquire a remarkable ability to defend us from the universe of potential pathogens while maintaining tolerance to self. The study of lymphocyte development is important both for understanding how lymphocytes acquire their specificity and function, and for using as a model system of development. Indeed, the study of lymphocyte development involves the examination of diverse processes, including lineage commitment, gene regulation, receptor signaling, gene rearrangement, apoptosis and organogenesis. This section of *Current Opinion in Immunology* reviews a sample of the recent advances in each of these areas.

Two articles in this section focus on one of the earliest events in lymphocyte development: the differentiation of hematopoietic stem cells into the committed progenitors that ultimately give rise to B cells, T cells and natural killer (NK) cells. Hardy [1] attempts to reconcile various studies that defined the earliest stages of development by using cell-surface markers. He goes on to consider the roles of various cytokines and their receptors, IL-7 in particular, in early differentiation events. Finally, Hardy considers exciting new work, which resulted in the definition of a hierarchy of transcriptional regulators that interact to promote developmental progression and lineage commitment. These transcriptional regulators include Pax-5, expression of which is necessary for B-lineage commitment, and Notch, which might play a corresponding role in T cells.

The relationship between lineage choice and transcription factors is viewed in a novel and thought-provoking light by Warren and Rothenberg [2]. Avoiding the classical approach of focusing on the hypothesis that cell populations represent developmental intermediates, they concentrate instead on self-stabilizing regulatory networks of positive and negative transcription factors. In this model, the transition from an uncommitted to a committed state occurs by fluctuations in transcription factor levels, followed by a stabilization of intermediate states, and can occur by many

different pathways. The authors present a hypothetical model in which the committed states for myeloid, erythroid and lymphoid lineages are defined by activation levels of PU.1, whereas within the lymphoid lineage, E2 and the Notch/CSL family transcription factors define B, T and NK cell committed states.

A defining event of lymphocyte development is the assembly of antigen-receptor genes from their component gene segments by V(D)J recombination. Biochemical and genetic studies have identified the minimal *cis*-acting DNA sequences necessary for gene rearrangement (recombination signal sequences; RSSs) and the *trans*-acting factors, which catalyze these reactions (RAG1, RAG2 and NHEJ proteins). The mechanisms that target V(D)J recombination to specific loci in a lineage and stage-specific fashion, and the mechanism of allelic exclusion are less well understood. Bergman, Fisher and Cedar [3] discuss our growing appreciation of the various epigenetic mechanisms that might contribute to the regulation of V(D)J recombination. These include the targeted post-translational modification of histones (methylation, acetylation, phosphorylation) and the covalent modification of DNA (CpG methylation). In each case, striking new data correlates these modifications with recombinase targeting. They also summarize provocative data which suggest roles for both differences in the timing of replication and allele-specific demethylation in the regulation of certain recombination events. Finally, these authors review new experiments which suggest that the positioning of antigen-receptor loci within the nucleus may have an impact on the regulation of their rearrangement and expression.

Nemazee and Hogquist [4] continue this examination of the control of antigen-receptor gene rearrangement by considering the phenomena of receptor revision and editing. The Igκ light-chain and T-cell receptor (TCR) α-chain loci are organized to allow an upstream V gene to rearrange with a downstream J gene, thereby replacing or 'editing' a pre-existing V–J rearrangement. Various researchers have shown that receptor editing is an important mechanism of B-cell tolerance, and that TCRα revision is involved in the generation of TCRs that can undergo positive selection. The authors compare these processes in B and T cells, identifying many similarities. They go on to consider how editing is regulated, and whether evidence for receptor editing in peripheral transgenic T cells implies that editing is also a tolerance mechanism in the T-cell compartment.

In addition to V(D)J recombination, developing B cells perform two additional novel reactions that result in adaptive alterations to Ig genes — class-switch recombination (CSR) and somatic hypermutation (SHM). Both of these reactions occur in response to antigenic stimulation and T-cell help. Kenter [5] reviews what is unarguably the most significant finding in this field in many years — the discovery of the AID (activation-induced cytidine deaminase) gene and its role in SHM and CSR. The AID gene was discovered by subtractive cDNA cloning and was shown, by genetic experimentation, to be required for SHM and CSR in both humans and mice. AID is homologous to other cytidine deaminases, which are known to perform RNA-editing reactions in which cytidine residues in specific mRNAs are deaminated to form uridine, thus altering the sequence of the encoded polypeptide. Kenter considers the consuming debate in this field — whether AID works by editing an unknown mRNA or by directly deaminating DNA, thereby either causing mutations directly or contributing to the generation of DNA breaks, which lead to CSR or SHM. In addition, she presents and discusses molecular models for how DNA deamination might lead to either mutation or recombination. Finally, this review examines potential mechanisms by which SHM and CSR are developmentally regulated and targeted.

Signals through various forms of the T-cell antigen receptor (αβTCR, γδTCR, preTCR) play a central role in T-cell development. These forms of the TCR share a common signaling pathway and one puzzling issue is how signaling through these three closely related receptors can lead to so many distinct cellular fates. These fates include: survival and proliferative expansion of $CD4^+$ $CD8^+$ thymocytes (preTCR), negative selection, positive selection, development of regulatory T cells, and anergy induction (αβTCR) or γδ T-cell development (γδTCR). As discussed by Love and Chan [6], the answer lies in part in the subtle differences between the structures and signaling mechanisms of the different receptors, as well as in the quantitative differences in the signaling pathways that they trigger. They also discuss evidence that triggering distinct branches of the TCR signaling pathway can lead to distinct outcomes, a striking example of which is the ability of calcium signals to induce anergy in mature T cells.

Proliferation is an important feature of the early stages of both T- and B-cell development, and a number of distinct signaling pathways appear to be involved in its regulation. Considerable attention has been given to the role of antigen receptor (preTCR and preBCR) and cytokine (IL-7 and stem-cell factor) signaling in driving this proliferation, whereas the role of the Wnt signaling pathway has been less well studied. Staal and Clevers [7] discuss this evolutionarily ancient signaling pathway, and review compelling evidence for the role of various components of the Wnt pathway in driving proliferation during the early stages of T-cell development. They also discuss evidence to suggest that Wnt signaling has various roles in the later stages of thymocyte development, thymic stromal cell development and B-cell proliferation.

Another common characteristic of B- and T-lymphocyte development is the extensive role played by programmed cell death or apoptosis. Sohn, Rajpal and Winoto [8] focus on mechanisms that regulate apoptosis in response either to a failure to produce a functional Ig or TCR, or to negative selection due to self-specificity. $CD4^+CD8^+$ double-positive T cells are exquisitely sensitive to apoptosis. The authors review evidence that TCR signals, transmitted through protein tyrosine kinases and MAP kinases with the involvement of specific adapter proteins such as grp2, are critical for the activation of apoptosis. They describe how signaling through a specific MAP kinase, ERK5, in concert with the transcription factor MEF2, results in the activation of Nur77, an orphan steroid receptor involved in apoptosis signaling. The significance of studies of apoptosis during thymic selection is increased by the observation that thymocyte apoptosis is only partially blocked by caspase inhibitors, suggesting the involvement of novel regulatory mechanisms. The authors also discuss data that suggest apoptosis in developing B cells might be due to the failure of co-stimulation and might also depend upon phosphatidylinositol-3 kinase and protein kinase Cβ. Apoptosis has been characterized as non-inflammatory cell death. Signals that promote the specific phagocytosis of apoptotic cells and their remnants, and the role of the phosphatidyl serine receptor c-mer are also reviewed.

Lymphocyte development and function are critically dependent on the presence of specialized tissues, such as the thymus in the case of T-cell development and secondary lymphoid organs in the case of lymphocyte activation. Müller and Lipp [9] review recent data to highlight the involvement of chemokines and their G-protein-coupled receptors in secondary lymphoid organ development. The authors discuss how analyses of various targeted mutant mice resulted in an appreciation of how both specific chemokines and the lymphotoxins α and β cooperate in the formation of Peyer's patches, at least in part, by regulating activity of NF-κB–p52/relB transcription factor complexes, and how ectopic expression of chemokines can stimulate lymph node formation in the pancreas. They also describe the surprising results that different chemokines and TNF-family members are involved in the formation of different groups of lymph nodes.

Manley and Blackburn [10] discuss the current state of our understanding of thymic organogenesis, with particular emphasis on the origins of thymic epithelial cells. These cells are crucial for the 'education' of developing T cells and they reside in both the cortex, where they are in contact with immature $CD4^+CD8^+$ thymocytes, and in the medulla, where they are in contact with mature thymocytes awaiting export to the periphery. The authors discuss two alternative models for the origin of thymic epithelial cells, a dual-origin model, which maintains that cortical and medullary epithelial cells derive from distinct embryonic regions, and a single-origin model in which both epithelial cell types derive from a single endodermal region. They argue that the bulk of current data supports a single-origin model, including the striking reports of a discrete population of embryonic thymic epithelial cells that can give rise to all known thymic epithelial cells. They also identify a number of unanswered questions in the field of thymic organogenesis.

The importance of the third class of lymphocytes, NK cells, is becoming increasingly apparent. NK cells recognize and kill target cells that have been modified by infection or transformation and thus complement the activity of T and B lymphocytes. NK-cell reactivity is controlled by a series of activating and inhibitory receptors, including a set of receptors specific for class I MHC. Recognition of self-MHC class I by NK receptors generally inhibits their function, and loss of class I MHC proteins due to transformation or immune evasion strategies can trigger destruction of the MHC-efficient cell by NK cells. Held, Coudert and Zimmer [11] discuss MHC class I NK receptors, reviewing recent progress in understanding how the NK-cell repertoire and NK-cell reactivity is shaped by the expression of self-class I MHC molecules.

References

1. Hardy RR: **B-cell commitment: deciding on the players.** *Curr Opin Immunol* 2003, **15**: in press.
2. Warren LA, Rothenberg EV: **Regulatory coding of lymphoid lineage choice by hematopoietic transcription factors.** *Curr Opin Immunol* 2003, **15**: in press.
3. Bergman Y, Fisher A, Cedar H: **Epigenetic mechanisms that regulate antigen receptor gene expression.** *Curr Opin Immunol* 2003, **15**: in press.
4. Nemazee D, Hogquist KA: **Antigen receptor selection by editing or downregulation of V(D)J recombination.** *Curr Opin Immunol* 2003, **15**: in press.
5. Kenter AL: **Class-switch recombination: after the dawn of AID.** *Curr Opin Immunol* 2003, **15**: in press.
6. Love PE, Chan AC: **Regulation of thymocyte development: only the meek survive.** *Curr Opin Immunol* 2003, **15**: in press.
7. Staal FJT, Clevers HC: **Wnt signaling in the thymus.** *Curr Opin Immunol* 2003, **15**: in press.
8. Sohn SJ, Rajpal A, Winoto A: **Apoptosis during lymphoid development.** *Curr Opin Immunol* 2003, **15**: in press.
9. Müller G, Lipp M: **Concerted action of the chemokine and lymphotoxin system in secondary lymphoid organ development.** *Curr Opin Immunol* 2003, **15**: in press.
10. Manley NR, Blackburn CC: **A developmental look at thymus organogenesis: where do the non-hematopoietic cells in the thymus come from?** *Curr Opin Immunol* 2003, **15**: in press.
11. Held W, Coudert JD, Zimmer J: **The NK cell receptor repertoire: formation, adaptation and exploitation.** *Curr Opin Immunol* 2003, **15**: in press.