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Editorial overview: The value of commitment in the lymphocyte world

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Dr Rudensky's research is focused on the mechanisms of differentiation and function of regulatory T cells and their roles diverse physiological and pathological settings.

The expanding complexity of the body plan during phylogeny of vertebrates was associated with the accelerated functional specialization of their cellular components and the emergence of new categories of cells, which included lymphocytes, a major cell type of the vertebrate immune system. Lymphocyte-like proliferating cells capable of inducing cytotoxicity and dividing in response to mitogens have been observed in urochordate *Ciona intestinalis*, a phylogenomically close relative of vertebrates [1]. Described as unremarkable 'colorless' mononuclear cells in the blood and lymph of vertebrates, lymphocytes were originally thought to be pretty uniform: 'there are to be recognized, in general, two varieties of lymphocytes, commonly known as large and small' [2]. Studies over the last half century revealed a remarkable diversity in the developmental origins, differentiation pathways, migration and recirculation patterns, and functionalities of distinct types of lymphocytes, which can exhibit innate or adaptive immune cell features or a mix of thereof. A dizzying array of hard-wired and environmentally induced differentiation states are associated with the ability of lymphocytes to execute and control innate and adaptive immune responses, to partake in tissue maintenance and repair, and to contribute to organ development.

Lymphocytes originate from hematopoietic stem cells in a multi-step differentiation process, which takes place in the generative or primary lymphoid organs — the bone marrow and the thymus. Differentiated lymphocytes acquire ability to respond to infection, stress or injury by recognizing the insult directly or indirectly by sensing its consequences. Upon encounter with a particular type of microbial or non-microbial challenge, naïve T and B cells — two principal classes of adaptive lymphocytes — differentiate into distinct types of effector cells capable of mounting protective response commensurate to challenge and give rise to long-lived memory cells or 'hybrid' effector-memory cells. In addition to populating secondary lymphoid organs, these multiple flavors of lymphocytes can take residence in non-lymphoid organs as tissue resident memory cells.

A recently uncovered universe of secondary lymphoid organ-lymphoid and non-lymphoid tissue-resident innate lymphoid cells (ILCs) exhibits remarkable similarity to adaptive lymphocytes manifested in expression of shared prototypical transcriptional regulators and their subordinate sets of effector molecules, foremost, cytokines. Contrary to an apparent freedom of their adaptive counterparts to assume a particular differentiation fate upon receipt of instructive cues, differentiation of the currently recognized flavors of ILCs is hard-wired. Likewise, specialized subsets of T cells expressing invariant or semi-invariant TCR and as well some T cells with a diverse TCR usage, including both αβTCR and γδTCR expressing cells, can

acquire their distinct functional predilection in the thymus as the result of TCR, growth factor or signaling pathway stimulation. Either hard-wired or imprinted by the microenvironment in the process of their generation or activation, these lymphocyte types and states exert a broad spectrum of functions they are pre-committed to.

This volume is focused on recent progress in understanding of differentiation and function of pre-committed lymphocytes. A review by Huang and Belz [3] offers an integrated view of the phenomenon of residency of innate and adaptive lymphocytes in non-lymphoid organs. The distinct milieus of blood, secondary lymphoid organs and non-lymphoid tissues and differing immunological challenges and stresses they are exposed to, exert markedly differing energetic, metabolic, and functional demands on lymphocytes and their precursors. The authors highlight emerging roles for diverse sets of transcription factors and receptors for growth factors, migratory cues (chemokines and sphingosine-1-phosphate), and cell adhesion molecules in homing, retention and survival of lymphocytes residing in different organs and in tumors. The common and distinct tissue-specific requirements are related to metabolic adaptation of resident T lymphocytes and ILCs to varying nutrient and oxygen availability in normal, perturbed or cancerous tissues.

Advances in understanding of differentiation and function of specialized 'sub-lineages' of innate-like T cells selectively seeding distinct non-lymphoid organs are discussed in the next three reviews by the leading groups in their respective fields. These innate-like T lymphocytes include embryonically and neonatally generated γδTCR T cells, intraepithelial lymphocytes expressing CD8α homodimers (CD8αα IELs), and mucosa-associated invariant T cells (MAIT) and their close relatives — natural killer T (NKT) cells.

γδT cells — the second major branch of thymus-generated lymphocytes — encompass both adaptive ('multipotent') and pre-programmed cells with developmentally defined localizations and functions. The latter are reviewed by Kang et al. [4] with a focus on skin-resident IL-17-producing γδT cells or so-called Tγδ17 cells, whose likely essential role is in the tissue maintenance. The developmental origin and transcriptional regulation of Tγδ17 cell differentiation are compared and contrasted to those of other innate lymphocytes - ILCs, B1-B cells, and NKT cells, as a counterpoint. Based on their own discovery of an essential and early role for an HMG family member Sox13 in differentiation of Vγ2-expressing and Vγ4-expressing Tγδ17 cells, the authors offer a more nuanced view of their lineage commitment from early embryonic precursors. The proposed fetal and neonatal progenitor heterogeneity preceding expression of TCR is contrasting to currently predominant model of a strength of TCR signaling as a singularly important determinant in differentiation of innate and adaptive T lymphocytes.

Continuing with a theme of lymphocyte pre-commitment in the thymus, Hogquist and Ruscher provide an overview of 'life cycle' of unconventional lineage of CD8αα and TCRαβ co-expressing IELs found within the epithelial layer at the other major barrier site – the intestine [5]. CD8ααTCRαβ IELs appear to be escapees of negative selection of thymocytes by 'self' peptides-MHC class I complexes and therefore exhibit activated phenotype. In this regard, CD8ααTCRαβ IELs can be considered loosely analogous to the regulatory CD4 T (Treg) cell lineage, expressing transcription factor Foxp3, whose origin has been ascribed to self-reactive MHC class II-restricted escapees of negative selection [6]. The authors' summary of the emerging molecular and cellular mechanisms of CD8ααTCRαβ IEL differentiation, migration and tissue residence and their functional features includes unanswered questions in biology of these cells and points to future research directions.

In contrast to CD8ααTCRαβ IELs, whose discovery and current knowledge of owes to mouse studies, intense investigation of evolutionary conserved MAIT cells has been in part driven by their abundance in humans as well as their specificity for intermediates of microbial vitamin B2 biosynthesis and potentially other structurally related compounds of non-microbial origin including drugs. As reviewed by Lantz and Legoux [7], MAIT cells exhibit remarkable resemblance to their 'older' (in order of discovery) sibling, NKT cells, in recognizing non-polymorphic MHC class I-like molecules — MR-1 and CD1, respectively, and dependence on a partially overlapping set of transcriptional regulators and cell surface receptors. In addition, the authors highlight parallels between MAIT cells and Treg cells, γδT cells and ILCs.

Shifting from the thymus to peripheral cell fate commitment, the review by Omilusik and Goldrath [8] features discussion of transcriptional and epigenetic mechanisms guiding generation of memory CD8 TCRαβ T cells and their precursors during acute infection or vaccination and mechanisms underlying their maintenance and phenotypic heterogeneity. Contrasting the functional longevity of self-renewing memory CD8 T cells capable of protecting against reinfections, progressive terminal differentiation of antigen-specific CD8 T cells results in a loss of proliferative and immune effector characteristics. Schietinger [9] reviews the advances in studies of processes leading to acquisition of the latter states, known as 'exhaustion' or 'terminal dysfunction', by tumor antigen-specific and pathogen-specific CD8 T cells in cancer and during chronic infections, respectively. This rapidly evolving area of basic and translational research has attracted intense interest due to its relevance to cancer immunotherapy. Recent studies by the Schietinger laboratory and other groups, which uncovered distinct transcriptional, epigenetic and phenotypic features of a step-

wise process of CD8 T cell terminal differentiation, suggest potential means of its therapeutic prevention or reversal. Finally, a review by Willis and Nutt [10] focuses on components of gene regulatory networks guiding terminal differentiation of conventional B cells (B-2 B cells) and a specialized subset of self-reactive B-1 B cells and highlights generalizable organizational principles of transcriptional control of lymphocyte differentiation and commitment.

Together this series of reviews emphasizes recurring themes in innate and adaptive lymphocyte commitment to specialized functional fates and inspires future studies aimed at deeper understanding of lymphocyte biology based on unifying and generalizable mechanistic principles.

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