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The bigger picture

Understanding how transcription factors direct lymphocyte lineage determination requires appreciation of the myriad ways in which they interact with and influence other cellular processes.

Multipotent hematopoietic progenitors are transcriptionally 'promiscuous' in that they express gene products characteristic of multiple hematopoietic lineages. Mature lymphocytes, in contrast, show more restricted gene expression patterns. In any given lymphocyte, although genes encoding proteins required to 'shape' and maintain lymphocyte lineage identity are expressed, many genes encoding proteins that function in other lineages are repressed. For example, the genes encoding Ig-α and Ig-β B cell receptor signaling subunits are expressed in B lymphocytes but not in T lymphocytes, and vice versa with regard to genes encoding the CD3 T cell receptor signaling chains. Thus, like the transcription factor MyoD, which activates a battery of muscle-specific genes and provokes muscle differentiation when ectopically expressed in multiple cell types, transcription factors capable of molding multipotent hematopoietic progenitor cell gene expression patterns into gene expression profiles of mature lymphocytes might be capable of directing lymphocyte lineage development and function.

In this issue of *Nature Immunology*, we present a special Focus on several prominent lymphocyte lineage specification factors (http://www.nature.com/ni/focus/lymphocytespecification/html). In three Review articles, Ye Zheng and Alexander Rudensky discuss Foxp3 and its influence on regulatory T cell fate and function, Kenji Tanigaki and Tasuku Honjo draw parallels between the functions of Notch protein in mammalian lymphocyte development and *Drosophila* nervous system differentiation, and Meinrad Busslinger and coauthors discuss the seemingly ever-expanding role of Pax5 in B lymphocyte differentiation. In two Essays, Laurie Glimcher and Mark Davis tell us, from a personal perspective, about the thought processes and experimental trials and tribulations that culminated in the identification of T-bet and Blimp-1, respectively. In the Focus Overview, Ellen Rothenberg compares and contrasts the diverse molecular mechanisms employed by each of these lineage specification factors.

Also included in the Focus are summaries of recent research in the area, an annotated bibliography of 'landmark' articles that made substantial contributions to our understanding of lymphocyte lineage specification factor function, and a collection of notable articles recently published in Nature Publishing Group journals. Online access to the Focus will be free throughout the month of May.

At least initially, these transcription factors received so much attention because, like MyoD, they seemed to be both necessary and sufficient to direct commitment to a specific lymphocyte lineage. In mice, hematopoietic progenitors lacking Notch1 are unable to generate T lymphocytes, while expression of a constitutively active version of Notch results in the appearance of T-lineage cells in unusual anatomic locations. Mice lacking Foxp3 are devoid of regulatory T cells, whereas ectopic expression of Foxp3 results in direction of naive mouse $CD4^+$ T cells into the regulatory T cell lineage. Ectopic expression of the transcription factor T-bet converts T helper type 2 (T_H2) cells into T_H1 cells, and T_H1 cell differentiation is impaired in T-bet–deficient mice. B lymphocyte differentiation is arrested at the pro-B cell stage in Pax5-deficient mice, whereas constitutive expression of Pax5 promotes entry into the B lymphocyte lineage at the expense of T lymphocyte development. Finally, plasma cell differentiation is blocked in Blimp-1–deficient mice, and expression of Blimp-1 is sufficient to endow upon B cell lines characteristics of plasmablasts. Notch1, Foxp3, Pax5, T-bet and Blimp-1 were thus considered with good reason by some researchers to be, like MyoD, 'master regulators' of lineage differentiation.

The possibility of one factor being able to 'do it all'—that is, being both necessary and sufficient to direct lineage differentiation—is certainly appealing, from experimental and theoretical viewpoints. However, it is becoming increasingly clear that the functions of these transcription factors are context dependent and depend heavily on their ability to interact with and influence the expression and/or activity of other cellular proteins and processes. Hence, the descriptor 'necessary and sufficient' is in one sense somewhat misleading.

In the grand scheme of regulatory T cell differentiation, Foxp3 is indeed 'necessary', but recent experiments indicate that one of its major roles seems to be to amplify and stabilize gene expression patterns orchestrated by some other yet unidentified signal or factor(s). The number of genes whose expression is altered in the absence of Foxp3 or Pax5 is impressive, but only a minority of these genes contain consensus Foxp3- or Pax5-binding sites within their regulatory regions, which emphasizes the fact that these two factors alone are far from 'sufficient' for a particular lineage, and must utilize and depend on other proteins to put into motion the often large-scale changes in gene expression required for cell differentiation. Foxp3 efficiently 'programs' naive but not memory human $CD4^+$ T cells into regulatory T cells, and T-bet can direct primary T_H2 cells but not T_H2 clones towards a T_H1 fate. Thus, like many other transcription factors, the full potential of Foxp3 and T-bet may be realized only in specific cellular environments, and likewise may be limited in the contexts of unfamiliar gene expression profiles and/or chromatin modifications.

In no way do we intend to dilute or de-emphasize the importance of these transcription factors. Rather, with this Focus issue, we aim to highlight the enormous scope of the insights yet to be made. It is exciting to think that years after the initial recognition of the crucial roles played by these transcription factors during lymphocyte development, so many details of their functions remain to be understood. Only after the identification of the proteins and processes that are influenced directly or indirectly by these transcription factors can we accurately place them within the big picture of lymphocyte lineage specification.