Many roads, one destination for T cell progenitors

Howard T. Petrie and Paul W. Kincade

The thymus manufactures new T cells throughout life but contains no self-renewing potential. Instead, replenishment depends on recruitment of bone marrow–derived progenitors that circulate in the blood. Attempts to identify thymic–homing progenitors, and to assess the degree to which they are precommitted to the T cell lineage, have led to complex and sometimes conflicting results. As described here, this probably reflects the existence of multiple distinct types of T cell lineage progenitors as well as differences in individual experimental approaches.

Thymic replenishment depends on bone marrow input

Blood cells are subject to constant depletion through cellular senescence, bleeding, and other causes, and must be replenished throughout life. Most blood cells are produced in the bone marrow, which is also the site where self-renewing stem cells reside. In contrast, T lymphocytes are produced not in the bone marrow, but in the thymus, although T lymphopoiesis still relies on the bone marrow because the thymus contains no self-renewing cells (1, 2). Postnatally, the blood represents the immediate source of thymic progenitors, ostensibly from a pool of circulating stem or progenitor cells released by the bone marrow. Recruitment of these circulating progenitors into the thymus is not a constant process (3), and it has even been proposed that release of thymus progenitors into the blood is coordinated with the requirements of the thymus (4). Thus, there appears to be an unexplained communication between bone marrow and thymus, allowing the bone marrow to respond in a purposeful fashion to maintain the integrity of T cell reconstitution.

The role of the thymus in imposing T cell lineage fate

Since the time it became evident that the thymus had no self-renewing capacity, the nature of cells that seed the thymus has been questioned. Two equally plausible scenarios have been envisioned. In one, the thymus is seeded by cells with unrestricted lineage capacity, or at least the capacity to generate multiple lineages, which are then relegated to the T cell lineage by virtue of their exposure to the thymic stromal microenvironment. In the other scenario, commitment to the T cell lineage occurs before thymic entry, and the thymus specifically solicits those cells with T cell potential from a larger pool of progenitors in the blood (Fig. 1). In either case, there is little debate that the thymic microenvironment is necessary for other processes, including proliferation, differentiation into various T cell sublineages, survival, and antigen receptor selection. However, these two scenarios imply substantially different roles for the thymus in the process of T lineage commitment; if T lineage commitment occurs before entry, there is little point in studying lineage commitment signals in the thymus (or in thymocytes). In this respect, it is worth noting that although signaling through Notch, an archetypal mediator of asymmetric lineage decisions, is clearly required for T cell production by the thymus (5, 6), this requirement does not necessarily invoke a lineage commitment signal. For instance, cells at later stages of intrathymic differentiation continue to require Notch signals, even though they are already restricted to the T cell lineage (7–9). Thus, it is possible that less mature thymocytes also utilize Notch to support functions other than lineage commitment.

Diversity among lymphoid progenitors

One of the best ways to resolve the nature versus nurture question is to determine the lineage potential of thymus-seeding cells before thymic entry, i.e., while still in the bone marrow and/or blood. Some time ago, Kondo and colleagues described a bone marrow progenitor that could give rise to T or B cells, but not myeloid cells (10), thus identifying a common lymphoid progenitor (CLP) that was consistent with the long speculated bifurcation between lymphoid and myeloid lineages. However, this important discovery underscores a common dilemma in such endeavors, namely, distinguishing between what cells can do when placed under ideal (artificial) conditions from what the same cells normally do under biological conditions. Although CLP gives rise to both T and B lymphocytes when properly enticed (10–12), there is little evidence to suggest that such cells home to the thymus or efficiently make T cells under normal circumstances. A recent article also failed to identify CLP-like cells circulating in the blood (13), although both our laboratories not only find CLP-like cells in blood, but also find that they are highly efficient at generating T cells under appropriate conditions (unpublished data). Nonetheless, evidence that these blood-borne CLPs enter the thymus is lacking, and their contribution to the mature T cell pool remains undefined.

The question of whether the thymus is seeded by a progenitor possessing both B and T lymphoid potential has also been called into question by other
Multiple T cell progenitors (those that satisfy a variety of well-established criteria; see Diversity among lymphoid... section) make up the consensus pathway. Nonetheless, it remains unclear whether the blood-borne cells that initiate this sequence are already restricted to the T cell lineage or remain multipotent (especially with respect to B and T cells), and it remains possible that thymic-homing cells include a mixture of both. In addition, other progenitors that do not behave conventionally also enter the thymus. The role of these cells is not well understood, but the cells may give rise to specialized subtypes of T cells or serve to condition the thymic microenvironment. Thus, although many progenitor cell types home to the thymus and may contribute to the intrathymic T cell pool, each may differ qualitatively and quantitatively in their contribution to peripheral T cells.

Figure 1. Multiple paths for intrathymic generation of peripheral T cells. Canonical T cell progenitors (those that satisfy a variety of well-established criteria; see Diversity among lymphoid... section) make up the consensus pathway. Nonetheless, it remains unclear whether the blood-borne cells that initiate this sequence are already restricted to the T cell lineage or remain multipotent (especially with respect to B and T cells), and it remains possible that thymic-homing cells include a mixture of both. In addition, other progenitors that do not behave conventionally also enter the thymus. The role of these cells is not well understood, but the cells may give rise to specialized subtypes of T cells or serve to condition the thymic microenvironment. Thus, although many progenitor cell types home to the thymus and may contribute to the intrathymic T cell pool, each may differ qualitatively and quantitatively in their contribution to peripheral T cells.
Defining T cell progenitors

A further difficulty in identification of true T cell progenitors, whether from the bone marrow, blood, or thymus, is that definitions generated by various research groups are not uniform. This is natural, since each group approaches the problem differently and in some cases seminal observations arise by chance and therefore cannot be devised to fit existing criteria. Nonoverlapping definitions are particularly an issue for the genetic reporter strains that have been useful in dissecting the lymphoid progenitor question, including mice expressing the Thy-1.1 allele (23), human CD25 under the control of the pre-T cell promoter (24), or EGF controlled by the RAG1 or CCR9 promoters (reference 12 and see Benz and Bleul on page 21 of this issue [25]). Integration of these new progenitor definitions into existing ones from other laboratories is difficult, involving the acquisition and expansion of reporter strains and the duplication of tedious and reagent-dense experiments. However, it does seem prudent for authors of all future studies to compare their definitions to a set of consensus markers including CD44, CD117, CD135, and Sca-1, and desirable, where possible, to evaluate other promising markers, such as CD24 (11), CD27 (12), CD45R (24), and CD62L (26).

Many roads, one destination

One of the most important concepts emerging from this field is that there is more than one distinct progenitor subtype that can give rise to T cells, although the relative efficiency at which T cells are made from each can fluctuate in response to a variety of factors. Different progenitor cells certainly have inherent qualitative differences and may also behave differently depending on the experimental circumstances used. However, as described earlier, it is important to remember that lineage commitment is a gradual process, not an instantaneous one. Coupled with the fact that hematopoietic cells are migratory, it is likely that even within a single progenitor cell type, individual cells may differ as a consequence of which environments they have been exposed to and for how long. Thus, everyone is probably at least partially correct in their conclusions; the bad news is that no one is likely to be completely correct.

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