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Toward a Layered Immune System

Minireview

Leonore A. Herzenberg and Leonard A. Herzenberg
Department of Genetics
Stanford University School of Medicine
Stanford, California 94305

The broad outlines of developmental relationships among cells in the immune system appeared to be established some years ago with the introduction of the idea that pluripotent hematopoietic stem cells emerge early in fetal life and persist as a self-replenishing population that continues to divide and differentiate throughout life without changing its original potential. Recent studies of lymphocyte development challenge this paradigm (Herzenberg and Stall, 1989; Linton et al., 1989), suggesting that there are instead several types of hematopoietic stem cells that have evolved sequentially and function at specified times during development; these create layers of progressively more advanced populations of lymphocytes and myeloid cells that collectively provide the diverse capabilities of the mammalian immune system.

According to previous dogma, the self-replenishing hematopoietic stem cells that reside initially in fetal liver and then in adult spleen and bone marrow provide a continuing source of myeloid and lymphoid stem cells. These myeloid and lymphoid stem cell populations are themselves self-replenishing and collectively give rise to all erythrocytes, myelocytes (granulocytes, macrophages, etc.), and lymphocytes found in the fetus, neonate, and adult. Thus, cells in the hematopoietic system are viewed as a single lineage that is derived from a single progenitor population, and lymphocytes are one of two major subdivisions of that lineage.

The origin of various types of B and T lymphocytes can be incorporated into an extension of this model that introduces further branchpoints in the overall lineage—one that separates developmental pathways for B cells and T cells, and others that distinguish pathways for various subsets of T and B cells. Some workers refer to each of these pathways as a separate lineage; others reserve the term lineage for those pathways that appear to originate from a distinct progenitor with (at least a limited) capacity for self-regeneration and the ability to give rise to the later cells in the pathway. However, all agree that lymphocyte differentiation proceeds along pathways that at some level merit the designation lineages, because lymphocytes originate with distinct progenitors that divide and differentiate to populate sequential stages of the pathway.

The B cell lineages proposed by Klinman and colleagues (Linton et al., 1989) fall within this general framework. The existence of these lineages is predicated on evidence indicating that, contrary to conventional textbook wisdom, virgin B cells participating in primary antibody responses are developmentally distinct from memory B cells that participate in secondary antibody responses to the same antigens. Some questions can be raised concerning the generality of these findings and their interpretation. However, the weight of the evidence presented clearly suggests that B cells are derived from two distinct developmental pathways: one that supplies B cells for primary responses and another that supplies B cells active in memory responses.

The question of whether these pathways are aptly called lineages is difficult to resolve without guidelines for distinguishing pathways and lineages. This distinction is commonly made on the basis of the differentiation state (commitment level) of the progenitors under consideration. Thus, cells derived from two types of pluripotent stem cells would belong to separate lineages, even if one of the stem cells had differentiated from the other. In contrast, plasma cells derived from two different memory B cells would more likely be considered to belong to separate developmental pathways within the same lineage (unless these pathways ultimately traced to distinct multipotent progenitors).

We wrestled with similar definitional problems when we were faced with placing CD5 (Ly-1) B cells within the lymphocyte developmental hierarchy. Initial studies revealed the existence of a second B cell subpopulation (Ly-1 B), which displayed unique properties that clearly set it apart from conventional B cells (Herzenberg et al., 1986). Furthermore, lymphoid progenitors in bone marrow that readily repopulated conventional B cells in irradiated recipients largely failed to repopulate Ly-1 B cells. These and related findings (e.g., Forster and Rajewsky, 1987) led to the proposal that conventional and Ly-1 B cells belong to separate lineages deriving from distinct progenitors emerging at different times during development; these lineages differentiate along pathways that differ substantially.

The existence of these lineages is consistent with the evolution of the immune system in stages marked by the successive differentiation of pluripotent stem cells, each of which added a new and more highly evolved lymphoid or myeloid lineage to the overall system (Davidson et al., 1988). Current evidence, including that provided by Linton et al. (1989), suggests that as many as four such lineages may exist.

If ontogeny is taken as a guide, and the most primitive lineage appears earliest in development, then the most primitive lineage generates Ly-1 B cells, which differentiate from immunoglobulin-negative progenitors during prenatal and early neonatal life and persist as a self-replenishing population thereafter. Stem cells for this lineage may also give rise to fetal erythrocytes and certain $\gamma\delta$ T cells. In this model, the next lineage gives rise to the Ly-1 B sister population, which shares many of the properties of Ly-1 B cells but arises later in ontogeny and appears to be at a somewhat more advanced functional level (Herzenberg and Stall, 1989). $\gamma\delta$ and some $\alpha\beta$ T cells could belong to this lineage.

The third and fourth lineages collectively generate the conventional B and T cell populations that constitute the majority of lymphocytes present in adult spleen and lymph nodes and produce most of the primary and secondary

antibody responses to commonly studied proteins and haptens. Unlike their more primitive counterparts, these conventional lymphocytes are generated throughout life from self-replenishing progenitors in the bone marrow and tend to be short-lived, unless they encounter antigen and differentiate to become memory cells.

The distinction between the third and fourth lineages rests on data presented by Linton et al. (1989). They show that different heavy chain V region genes are expressed in the primary and secondary responses to a hapten, (4-hydroxy-3-nitrophenyl) acetyl (NP), and the B cells that generate each response express different levels of a surface marker. Because conventional B cells produce virtually all the antibody response to NP (Forster and Rajewsky, 1987), the lineages defined by Linton et al. must reflect a subdivision within conventional B cells. This subdivision may be a consequence of differences in functional activity between the B cells derived from the two most recently evolved stem cells. Thus, the earlier lineage would give rise to virgin B cells that participate in primary antibody responses, while the later lineage generates memory B cells that produce high affinity IgG secondary antibody responses characteristic of mammals.

Viewed as a whole, the idea of an evolutionarily layered hematopoietic system offers an attactive framework for explaining the breadth and complexity of mammalian immune responses. For example, B cells associated with the earliest evolutionary layers would be expected to respond very rapidly to invading pathogens but have a relatively restricted repertoire that is rarely extended by somatic mutation. Conversely, B cells associated with later evolutionary layers would have a virtually unlimited, highly mutated repertoire that comes into play mainly when the immune system is severely challenged and secondary immune responses are required. Thus, the known differences between Ly-1 and conventional B cells become more readily understandable if the selective advantages of a layered immune system are taken into account.

Extension of these ideas to T cells and other elements of the hematopoietic system offers similar insights into the functional and developmental differences that occur among these cells (e.g., between $\gamma\delta$ and $\alpha\beta$ T cells). Forays in this area suggest that many perplexing aspects of lymphoid and myeloid development can be clarified by treating the different incarnations of particular cell types (T cells, B cells, etc.) as individual components of an effective response mechanism that has evolved in layers to protect the organism against a variety of increasingly more significant pathologic insults.

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