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There was a time, not long ago, when it was not patently obvious that T cell development follows the now well-rehearsed steps defined by CD4 and CD8 expression. With the discovery of the thymus as the source of T lymphocytes (1), a concerted effort to understand how this organ induces and supports T cell differentiation was started and continues to this day (2, 3). Along the way, early studies established that the thymus is seeded by bone marrow-derived progenitors (4, 5). These findings were extended by analysis of fetal thymic development (6) that led to the initial characterization of what appeared to be a set of sequential differentiation steps taken by developing thymocytes, beginning with cells that lack the expression of CD8 and CD4 (also known as Lyt-2 and L3T4, respectively). These are now routinely referred to as CD4 and CD8 double-negative (DN) cells; however, it was not until the work of Fowlkes et al. (7) that we began to understand what these cells were all about.

During the heady days of the mid-80s, when an array of new mAbs became available and flow cytometry allowed for multiparameter analyses, it became possible to start defining clear and distinguishable subsets of thymocytes and to ask that most fundamental question: where do we (T cells) come from? Among the different cell types present in the adult thymus, it was not clear which subset, as defined by CD4 and CD8 expression, possessed the ability to give rise to both immature and mature thymocytes (also known as cortical and medullary thymocytes, respectively). A solution to this mystery was provided by B.J. Fowlkes and her National Institutes of Health colleagues (7) by showing in radiation chimeras that a purified subset of adult thymocytes that lack CD4 and CD8 expression, but express low levels of CD5 (Ly-1), possessed the ability to home back to the thymus and function as progenitors for all other thymocyte subsets.

The work by Fowlkes, Mathieson, and others (7) became a watershed publication for many reasons in that it not only definitively showed that DN cells contain intrathymic progenitors, it also established that the thymus does not have any resident stem cells, as these DN thymocytes possessed only limited, short-term self-renewing potential, confirming the notion that the thymus requires routine seeding of marrow-derived progenitors to replace these cells (8). Additionally, the approach took advantage of congenic markers such as allelic forms of CD5 and CD45 to distinguish thymic engrafting donor cells at different time points, which made it possible to decipher the sequential order of T cell differentiation, starting from the CD5low DN cells to CD4 and CD8 double-positive (DP) cells and ending with CD4 or CD8 single-positive (SP) cells. Of note, their work also showed that the other thymocyte subsets, DP or SP cells, do not possess thymic homing function. Accordingly, these cells, even if present within the DN preparation, could not be the ones giving rise to the DP and SP cells that were observed when CD5low DN cells were transferred to the irradiated recipients. The use of CD5 expression as an additional determining factor for defining the DN population proved to be critical for the significance of the work, because it not only allowed for the use of CD5.2 vs CD5.1 congenic strains of C57BL6 mice to aid in tracking donor and host cells, but differential CD5 expression, together with CD4 and CD8 staining, helped to distinguish progenitor DN cells from other immature and mature thymocytes that express higher levels of CD5.

This paper defined the adult thymus DN subset as the earliest recognizable T cell progenitor; however, it was already clear back then, and presciently stated by the authors, that it would be important to “determine whether this subpopulation contains cells in different states of maturation and/or cells already committed to more than one T cell lineage”. Given our present and continued efforts to fully identify and characterize the initial or earliest blood-borne, thymus-homing progenitor cell (9, 10), the work by Fowlkes et al. (7) provides to this day the framework for future approaches. Additionally, the intrathymic cells that they functionally characterized became the defining starting thymocyte population from which others “sliced and diced” further subsets (11), giving us a four-DN breakdown of CD4+CD25− (DN1), CD4+CD25+ (DN2), CD4−CD25− (DN3), and CD4−CD25+ (DN4) with further refinements (12) and, with the additional subsetting of the earliest DN1 fraction, five and possibly more subsets (13). Moreover, not only is the physical identity of the earliest thymocyte still investigated, but the second point raised by Fowlkes as to the level of lineage commitment possessed by these early thymocyte progenitors also remains in question, particularly the elucidation of the molecular programming that yields this intrathymic progenitor cell.

The mid-1980s can be thought of as an important period of discovery for the study of early thymocytes and their function. This work (7) and that of other groups (14, 15) provided us with a set of clear and defined stages of T cell development that remarkably remains as our current framework, guiding the next

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2 Abbreviations used in this paper: DN, double negative; DP, double positive; SP, single positive.

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generation of investigations. Thus, except for the name changes, the characters in play remain the same. No matter what we now call these cells, the search continues, as the precise nature of the progenitor that first enters the thymus on its way to becoming a T cell awaits further elucidation.

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