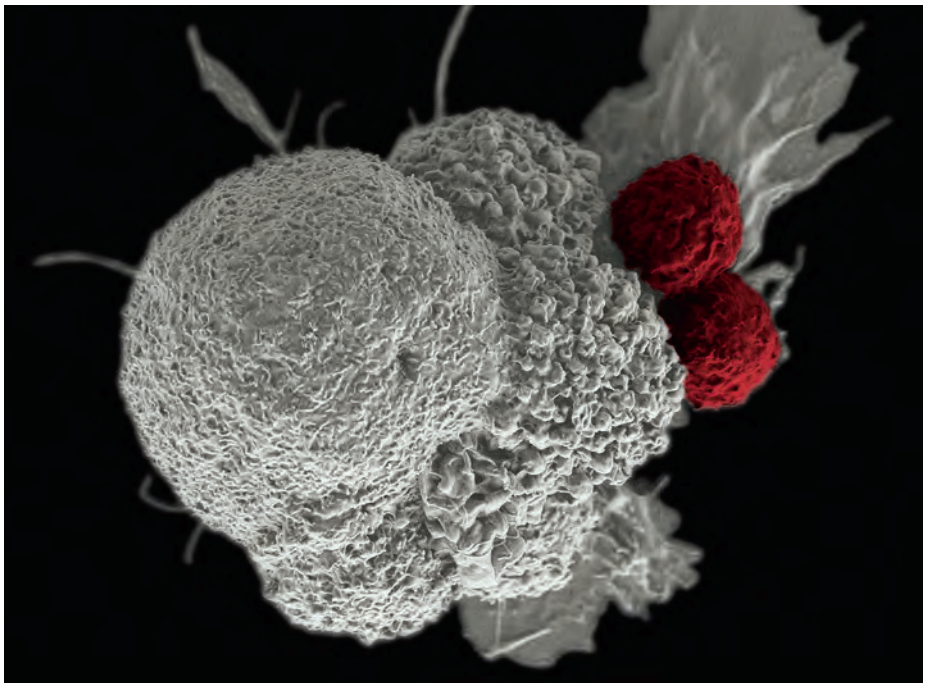
Milestone 5



T cell subsets with defined roles

By the mid-1970s, immunologists had established that the thymus-derived subset of immune cells known as T cells could perform a variety of distinct functions. For example, these cells could actively kill off tumours or other cells perceived as foreign by the body, but they could also coordinate the activation of other immune cell types.

The big question at this point was whether these 'killer' (Milestone 2) and 'helper' (Milestone 11) functions were innate to specific subsets of T cells, or whether all T cells were inherently capable of performing these various actions in response to activation. A 1975 study by Harvey Cantor and Edward Boyse helped set scientists on the path towards answering this question.

The two immunologists made use of different antisera that selectively bind to three different proteins found on the surface of mouse T cells, dubbed Ly-1, Ly-2 and Ly-3. Previous research had demonstrated that the potency of antigen-activated killer T cells is greatly reduced by treatment with Ly-2 and Ly-3 – but not Ly-1 – antisera. Cantor and Boyse expanded on that work, using these antisera to analyze and selectively deplete different subsets of non-antigen-exposed, or naive, T cells from mice. Their results showed that although the thymus produces T cells expressing all three antigens, these seem to be a transient progenitor for two distinct subsets of cells. Depletion of one subset, which only expressed Ly-1, effectively eliminated the helper T cell function, whereas depletion of the subset expressing Ly-2 and Ly-3 resulted in loss of cytotoxic T cells. These results indicated that killer and helper T cell identity is forged early on within the thymus.

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The advent of monoclonal antibody technology gave immunologists a tool for getting a closer look at these proteins and the T cells that selectively express them. In 1979, Ellis Reinherz working in the lab of Stuart Schlossman generated a series of mouse monoclonal antibodies against human T cells. One of these antibodies, OKT4, bound to only around 60% of human T cells, and the researchers subsequently used fluorescence-activated cell sorting to selectively purify these OKT4-positive T cells. They soon determined that the target of this antibody was a protein marker specifically associated with human helper T cells distinct from Ly-1 which they dubbed 'T4'. Two years later, the group achieved the same task with the human counterpart of Ly-2, termed 'T8', which enabled them to efficiently isolate cytotoxic T cells. In 1982, these two proteins were bestowed their more familiar contemporary names – CD4 and CD8 – at the inaugural Human Leukocyte Differentiation Antigen workshop in Paris.

That year also saw another important leap forwards in understanding how these proteins coordinate T cell function. Our immune cells make use of a protein assembly called the major histocompatibility complex (MHC) to present protein antigens to T cells, thereby training them to ignore healthy tissues while marshalling a response against cancerous or infected cells (Milestone 4). There are two major classes of MHC, and several studies from 1982 showed that CD8-positive cells preferentially interact with MHC class I, which is expressed by almost every cell in the body and is now known to elicit a cytotoxic T cell response. By contrast, CD4-positive cells preferentially interact with MHC class II, which is primarily expressed by specialised immune cells and fuels activation of helper T cells.

It soon become clear that CD4 and CD8 were distinct 'co-receptors' that act alongside the T cell receptor (TCR), the primary arbiter of antigen recognition (Milestone 8). The TCR and its co-receptor bind to the MHC–peptide complex in parallel, and the subsequent signalling cascade jointly coordinated by the TCR and CD4 or CD8, respectively, contributes to the initiation of the helper or cytotoxic T cell response.

Even if these behavioural differences only become obvious when a T cell meets antigen, the foundational work by scientists such as Boyse, Cantor, Reinherz and Schlossman helped to establish that these and other T cell subsets arise from distinct pools of cells in the thymus that can readily be defined by their external protein features.

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Milestone study

Cantor, H. & Boyse, E. A. Functional subclasses of T lymphocytes bearing different Ly antigens. II. Cooperation between subclasses of Ly+ cells in the generation of killer activity. *J. Exp. Med.* **141**, 1390–1399 (1975)

Further reading

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