milestones

Milestone 11

T helper cells: a house divided

In 1986, Timothy Mosmann, Robert Coffman and colleagues at DNAX Research Institute stimulated a panel of mouse $CD4^+$ T cell lines and discovered two subpopulations of murine $CD4^+$ T cells with distinct profiles of cytokine secretion that they defined as T helper 1 (T_H1) or T helper 2 (T_H2) subsets. This pivotal finding noted that T_H1 cells secrete the cytokines IL-2, IL-3 and IFNγ, while T_H2 cells produce IL-3, IL-4 and IL-5. This finding led to a paradigm shift in our understanding of $CD4^+$ T cell biology and the emergence of the complex and heterogeneous composition of the $CD4^+$ T cell lineage.

Owing to the emergence of these two distinct T_H cell lineages, one aspect of research focused on understanding and establishing the functional role of these cells. A study by Phillip Scott and colleagues showed that in mice infected with *Leishmania major*, adoptive transfer of IFNγ-producing T_H1 cells could confer significant protection against disease, while transfer of IL-4^+IL-5^+ T_H2 cells exacerbated parasitic lesions. Consistent with these findings, Hienzel et al. reported a strain-specific response to *L. major* infection, observing clearance of infection in C57BL/6 mice within in a few weeks, whereas in Balb/c mice, the authors documented substantive disease progression. It was also shown that the underlying cause of this differential response was linked to an increased expression of IFNγ mRNA in recovering mice and an increased expression of IL-4 and IL-5 mRNA in mice that displayed progressive infection.

Following these discoveries, William Paul and colleagues uncovered the critical role of the cytokine milieu during the development of $CD4^+$ T_H cell responses. They and others found that naive $CD4^+$ T cells induced the formation of T_H2 cells and were linked to the phosphorylation of STAT6 when treated with IL-4 and IL-2. By contrast, stimulation with IFNγ resulted in preferential development of T_H1 cells and inhibition of T_H2-related cytokines. Further work also showed a role for IL-12 in the production of IFNγ, which drives the skewing of naive T cells toward the T_H1 lineage. Subsequent work also showed that T_H2 cells secreted a regulatory cytokine identified as IL-10, which effectively led to the suppression of T cell proliferation and cytokine secretion.

"a paradigm shift in our understanding of $CD4^+$ T cell biology and the emergence of the complex and heterogeneous composition of the $CD4^+$ T cell lineage"

Evidence for T_H subsets in humans was obtained in 1991 when the team of Sergio Romagnani reported distinct T_H1 and T_H2 populations in humans, which was consistent with the initial reports in the murine setting. Further studies suggested that bacterial and viral antigens result in T_H1-type responses, and fungal or helminth-derived antigens resulted in the elicitation of T_H2 responses. Taken together, these and other studies built a consensus in the association of T_H1 responses with intracellular pathogens and a requirement for support for cytolytic-type responses, whereas T_H2 responses were linked to extracellular pathogens and allergens owing to their ability to support strong antibody responses.

Along with characteristic cytokines, the T_H1/T_H2 subsets are also associated with characteristic lineage-specific transcription factors. In 1997, Zheng and Flavell identified GATA3 as the master transcription factor that regulates the T_H2 subset. The same study also reported that silencing of GATA3 in cell lines resulted in the loss of T_H2 cytokines, and showed that naive T cells committed to the T_H1 pathway also downregulate GATA3 expression. Subsequent work from Laurie Glimcher and colleagues further identified T-bet as the master transcription factor for T_H1 cells.

Enabled by these seminal discoveries and others, we now have a clearer view of the composition, diversity and immunological function of the $CD4^+$ T cell compartment. T_H1 and T_H2 cells, and the subsequent other T_H cell lineages (see Milestones 15, 18 and 19), now have well-defined roles in critical aspects of immunological homeostasis, immunopathology and immune regulation, and this positions them as key therapeutic targets in the modulation of the immune response to combat disease.

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Milestone study

Mosmann, T. R. et al. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J. Immunol.* **136**, 2348–2357 (1986)

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