Milestone 18

T_H17 cells: a new lineage emerges

A key process in adaptive immunity is the activation of naive $CD4^+$ T cells by antigen presenting cells and their differentiation into effector $CD4^+$ T cells (Milestone 5). Prior to 2005, $CD4^+$ effector T cells were assigned to two helper T cell lineages (T_H1 cells and T_H2 cells) defined by the cytokines and key transcription factors they expressed (Milestone 11). In 2005, two papers, from Harrington et al. and Park et al., identified and characterized a distinct lineage of $CD4^+$ T cells that produced interleukin 17 (IL-17).

Interferon-γ (IFNγ)-producing T_H1 cells are crucial for the clearance of intracellular pathogens, whereas T_H2 cells produce IL-4, IL-5 and IL-13 and are involved in the clearance of extracellular pathogens. The search for a third helper T cell lineage was sparked by the work of Langrish et al. They demonstrated that IL-23 could drive the expansion of pathogenic $CD4^+$ T cells that induced autoimmune inflammation in mice. This T cell population produced a unique pattern of pro-inflammatory cytokines, including IL-17, IL-17F, IL-6 and tumour necrosis factor. Following these findings, researchers began to investigate the differentiation requirements for a subset of pathogenic IL-17-producing $CD4^+$ T cells.

"a distinct lineage of $CD4^+$ T cells that produced interleukin 17"

Using $CD4^+$ T cells isolated from various strains of mice and differentiated in vitro, Harrington et al. generated IL-17-producing $CD4^+$ T cells, which they called 'T_H17 cells'. These T_H17 cells could be generated from $CD4^+$ T cells that were activated with antigen in the presence of IL-23 and the absence of IFNγ and IL-4 signalling. The cytokines IFNγ and IL-4 are key differentiation factors for T_H1 cells and T_H2 cells, respectively. Thus, the fact that both these factors potently inhibited the development of T_H17 cells was further critical evidence of a distinct helper T cell lineage.

Mature T_H1 and T_H2 cells show phenotypic stability; that is, they do not change their phenotype when restimulated with cytokines from a different helper T cell type. Thus, when Harrington et al. showed that mature T_H17 cells were not inhibited by IFNγ or IL-4, they provided further evidence of a distinct lineage. Importantly, the generation of T_H17 cells from precursor cells did not require the presence of the T_H1 cell transcription factors STAT1 and T-bet, or the T_H2 cell transcription factors, STAT4 and STAT6. At this point, however, the identity of a T_H17 transcription factor was unknown.

Using cells isolated from different mouse models, Park et al. were also able to generate T_H17 cells from $CD4^+$ T cells. Of note, T cell activation requires signalling through costimulatory molecules (Milestone 10), as well as through the T cell receptor (Milestone 8). The generation of T_H17 cells required the co-stimulatory molecules CD28 and ICOS. Thus, Park et al. showed that the generation of IL-17-producing T_H17 cells required IFNγ- and IL-4-blocking antibodies and the presence of IL-23. Furthermore, the transcription factors STAT4, STAT6 and T-bet were not required for this process. Critically, this study also evaluated the in vivo effects of IL-17 in mice, establishing its role in tissue inflammation.

2006 was another important year for T_H17 cell research. Veldhoen et al. further characterized the requirements for T_H17 cell differentiation, finding that transforming growth factor-β (TGFβ) and IL-6 have a key role. TGFβ is a crucial factor for the differentiation of regulatory T cells (T_{reg} cells), whereas IL-6 is an acute-phase protein produced during inflammation. Bettelli et al. showed that in the presence of IL-6, the TGFβ-induced differentiation of naive T cells toward the T_{reg} lineage is inhibited and the differentiation is instead skewed toward the T_H17 lineage. Interestingly, both studies found that IL-23 was not actually required for T_H17 cell differentiation but was instead involved in the survival and expansion of T_H17 cells. Subsequently, Ivanov et al. identified the prototypic transcription factor for T_H17 cells as the orphan nuclear receptor RORγt.

These studies and others resulted in the identification, characterization and implication of the T_H17 cell lineage in a range of immunological contexts and roles in disease.

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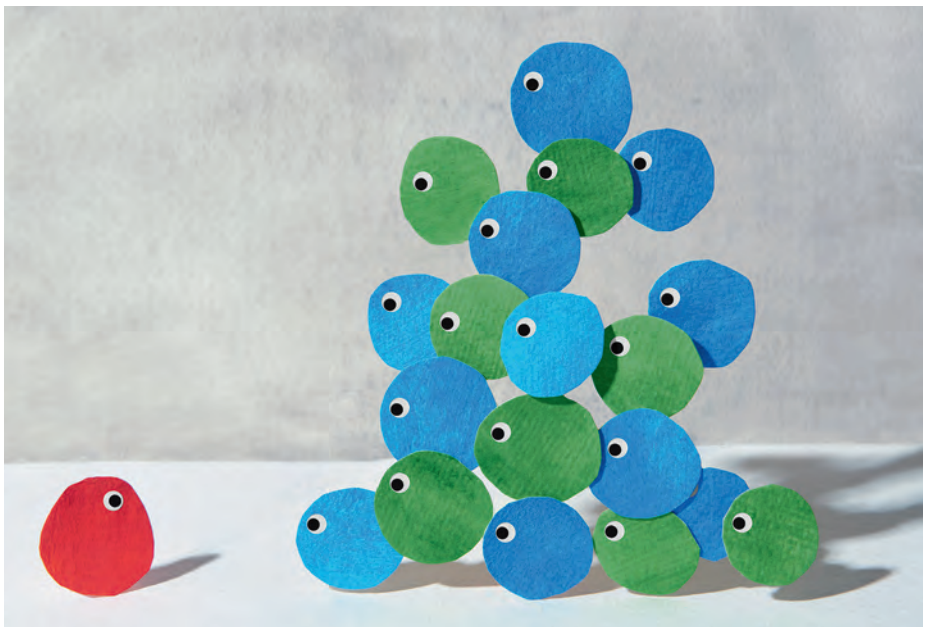

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Milestone studies

Harrington, L. E. et al. Interleukin 17-producing $CD4^+$ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat. Immunol.* **6**, 1123–1132 (2005) | Park, H. et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat. Immunol.* **6**, 1133–1141 (2005)

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