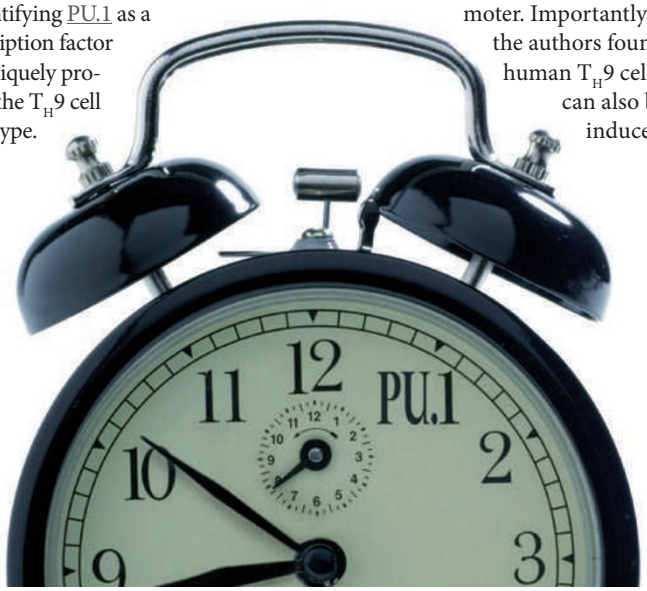
T CELL RESPONSES

PU.1 in time saves nine

The differentiation of T helper (T_H) cell subsets is controlled by unique sets of transcription factors; these regulate the expression of cytokines and other genes that are important for the effector functions of each subset. Recent reports have described an interleukin-9 (IL-9)-producing population of T cells, which is induced *in vitro* following culture with IL-4 and transforming growth factor-β (TGFβ). These cells are related to the T_H2 cell lineage but express lower levels of T_H2-type cytokines, and they have therefore been proposed to be a new subset of 'T_H9' cells. However, this classification has been controversial owing to the lack of any T_H9 cell-specific transcription factor (or factors). Now, Chang *et al.* have strengthened the case for a 'T_H9 cell lineage' by identifying PU.1 as a transcription factor that uniquely promotes the T_H9 cell phenotype.

Previous studies showed that PU.1 can suppress the production of T_H2-type cytokines, prompting the authors to examine the role of this transcription factor in the induction of T_H9 cells. Following culture under T_H9 cell-promoting conditions, PU.1-deficient T cells produced substantially lower levels of IL-9, suggesting that PU.1 was important for T_H9 cell development. In further support of this, there were higher levels of PU.1-encoding mRNA in T_H9 cells than in T_H1, T_H2 or T_H17 cells. PU.1 was required for chromatin modifications at the *Il9* locus, with chromatin immunoprecipitation and DNA-affinity precipitation assays showing direct binding of PU.1 to conserved non-coding sequences in the *Il9* promoter. Importantly, the authors found human T_H9 cells can also be induced *in vitro* in response to culture with IL-4 and TGFβ, and PU.1 was also necessary for human T_H9 cell differentiation.



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Next, the authors investigated the function of T_H9 cells *in vivo*, examining their roles in allergic responses. In a model of allergic airway inflammation, mice with a T cell-specific deficiency in PU.1 showed lower levels of lung inflammation than wild-type mice. This was characterized by fewer inflammatory infiltrates and decreased airway hyperresponsiveness and seemed to be due to the specific absence of T_H9 cells, as both T_H2 and T_H17 cells developed normally in these animals. Treating wild-type mice with IL-9-specific blocking antibodies during the induction of airway inflammation led to a similar decrease in inflammation, suggesting that IL-9 itself was important for promoting the inflammatory response in the lung.

The identification of PU.1 as a specific transcription factor for T_H9 cells suggests that these cells may be a bona fide T_H cell lineage. Furthermore, these data suggest that targeting IL-9 could be a useful therapy for treating patients with asthma and other allergies.

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ORIGINAL RESEARCH PAPER Chang, H.-C. *et al.* The transcription factor PU.1 is required for the development of IL-9-producing T cells and allergic inflammation. *Nature Immunol.* 2 May 2010 (doi:10.1038/ni.1867)