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The Symphony of the Ninth: The development and function of Th9 cells

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Abstract

CD4+ T helper cells are obligate regulators of inflammatory disease. An expanding cadre of T helper (Th) subsets, specialized for promoting particular types of inflammation, function through the secretion of a restricted set of cytokines. The latest addition to the list of subsets is the Th9 cell that secretes IL-9 as a signature cytokine and contributes to several classes of inflammatory disease. In this review we focus on recent advances in understanding the development of Th9 cells, and how Th9 cells contribute to the orchestration of disease.

Introduction

Naïve CD4+ T helper cells, after encountering specific antigen, become activated and differentiate into effector T helper subsets, each characterized by a distinct pattern of cytokine secretion and function. Th1 cells mediate immunity to intracellular pathogens, Th2 cells provide protection against extracellular parasites, and Th17 cells are involved in resistance to extracellular bacteria and fungal infections. Another effector subset, termed Th9, secretes IL-9 and may be involved in immune-mediated diseases ranging from autoimmunity to asthma. The biology of IL-9 has been recently reviewed [1–3]; this review is focused on discussing recent advances in our understanding of the development of IL-9-secreting T cells, and the functions of Th9 cells in vivo.

The pathway towards Th9 differentiation

T helper cells secreting IL-9 are primed in response to TGF-β and IL-4 and are termed Th9 [4,5]. Both signals are required as cells that lack IL-4 or TGF-β signaling components fail to develop into IL-9-secreting cells [4–6]. Since Th9 cells require balanced signals from TGF-β and IL-4 [4–6], each cytokine likely leads to the induction of transcription factors that regulate IL-9 production, and the expression of other genes associated with the Th9 phenotype. The TGF-β signal, which induces Foxp3, also induces the expression of PU.1 [6] (Figure 1). PU.1, an ETS family transcription factor, also identified as the spleen focus forming virus proviral integration site-1 (*Sfpi1*) is a key transcription factor in the Th9 developmental program [7••]. PU.1 is expressed in Th9 cells at higher amounts than in Th2 cells. PU.1 negatively regulates Th2 cell development, and ectopic expression of PU.1

enhances production of IL-9, at least partly by binding directly to the *Il9* promoter [7••–9]. Naïve CD4+ T cells from PU.1-deficient mice, when cultured under Th9 conditions, had reduced production of IL-9 [7••].

Th9 development is clearly dependent upon the IL-4-activated transcription factor STAT6 [4–6](Figure 1). Although STAT5, downstream of IL-2, can bind the *Il9* promoter, STAT6 binds the *Il9* gene poorly compared to other genes [6,10]. Thus, the IL-4 signal likely induces *Il9* indirectly, through the regulation of additional transcription factors. IL-4 and STAT6 are required to repress expression of Foxp3, which induces a Treg phenotype and can repress IL-9 production [4–6,11,12]. IL-4 and STAT6 also repress expression of T-bet in Th9 cells, and T-bet likely cooperates with Runx3 in the repression of IL-9 in Th1 cells [6].

IL-4 and STAT6 also promote the expression of several factors common to both Th9 and Th2 cells including IRF4, c-maf and GATA3. STAT6 induces IRF4 that is required for Th9 development, in addition to its contributions to Th2 and Th17 differentiation [13–17••]. Naïve CD4+ T cells from IRF4-deficient mice, when cultured under Th9 conditions, exhibited substantial reduction in the IL-9 levels, compared with wild-type cells. IRF4 regulates Th9 development by binding to the *Il9* promoter. Ectopic expression of c-maf repressed IL-9 production, suggesting that c-maf is not directly regulating *Il9*, and might regulate other Th9 genes such as IL-21 [6,18].

IL-4 and STAT6 are required for the induction of GATA3, a master regulator of the Th2 phenotype. In contrast to a detailed understanding of a role for GATA3 in Th2 cells [19], the role of GATA3 in Th9 development is complex. Although GATA3 is expressed in Th9 cells, albeit at lower levels than in Th2 cells, and it is required for the development of Th9 cells, ectopic expression of GATA3 decreased production of IL-9 [4–6]. Moreover, while GATA3 induces IL-4 and IL-13 when transduced into *Stat6*−/− Th2 cells, it did not induce IL-9 when transduced into *Stat6*−/− Th9 cultures [6] suggesting that it does not directly act on the *Il9* gene. One possibility is that GATA3 plays a role in the STAT6-dependent repression of Foxp3 [20], although the recent description of a requirement for GATA-3 in Treg development makes this less likely [21,22]. Together, these results suggest that the requirement for GATA3 in Th9 development may be temporally confined, and that the amount of GATA3 present within Th9 cells is tightly controlled.

Other cytokines also regulate IL-9 production. Schmitt *et al.* demonstrated that IL-9 production from murine CD4+ T cells is IL-2 dependent and is inhibited by IFN-γ [23]. IL-25, a member of the IL-17 cytokine family, enhances IL-9 production in the presence of TGF-β and IL-4 through IL-17RB. IL-17RB is differentially expressed in T helper subsets with the highest expression in Th9 cells and both IL-4 and TGF-β significantly enhanced the expression of IL-17RB in activated T cells [24•]. In addition to TGF-β and IL-4, IL-1 family members promote IL-9 production from CD4+ T cells independently of IL-4 [25]. Each of these cytokines activates transcription factors including NF-κB, which bind to the *Il9* promoter [26,27].

Naïve human CD4+ T cells also acquire a Th9 phenotype when differentiated in presence of TGF-β and IL-4 [7,17,28–31]. Among other inflammatory cytokines, IFN-α, IFN-β and IL-21 were potent enhancers of IL-9 production. Blocking IL-21 decreased IL-9, whereas IFNγ and IL-27 inhibited IL-9 production in a dose dependent manner [32]. TGF-β has also been shown to induce IL-9 production in human Th17 cells, and repeated stimulation under Th17 conditions, resulted in the co-expression of IL-17A and IL-9. As with their mouse counterparts, human Th9 cells require PU.1 and IRF4 for expression of IL-9 [7,17].

Functions of Th9 cells

Th9 cells are pro-inflammatory, but appear to function in a broad spectrum of autoimmune diseases and allergic inflammation. Their precise function likely depends upon the tissue microenvironment and other T helper cell cytokines that are present in the inflammatory milieu.

Th9 cells contribute to inflammation in several autoimmune disease models. Th9 cells induce inflammation in a T cell transfer colitis model [5]. Mice that received Th9 cells only, lost weight and developed a moderate colitis. Moreover, mice that received effector T cells together with Th9 cells developed a more severe colitis. A similar pro-inflammatory role of Th9 cells was demonstrated in an EAE model [33]. MOG-specific naïve CD4+ T cells were differentiated in vitro under Th1, Th2, Th17 and Th9 polarizing conditions before adoptive transfer. All mice that received Th9 cells developed severe EAE and lesions in the CNS. Cells in the CNS of Th9 recipients retained IL-9 producing capacity, but also produced IFN-γ. Although Th1, Th17 and Th9 cells induced EAE with similar severity, differences in CNS pathology suggested Th9 cells promote inflammation through distinct mechanisms [33]. In agreement with these results, treatment with anti-IL-9 antibody or IL-9 receptor deficiency ameliorates EAE, possibly by decreasing MOG-reactive Th1 and Th17 cells, and lymph node mast cell numbers [34•, 35•]. This is consistent with the ability of IL-9 to promote Th17 development and as a growth factor for mast cells [36–38].

The pathogenic ability of Th9 cells was further supported in an adoptive transfer model where Th9 cells specific for hen egg lysozyme (HEL) were transferred into recipient mice expressing HEL in the eye lens. Ocular inflammation developed in mice that received Th9 cells, although in this model the IL-9-secreting phenotype was not stable and cells recovered from the inflamed site produced primarily IFN-γ [39]. Moreover, anti-IL-9 did not protect these mice from disease, suggesting that the flexibility in cytokine production of the transferred cells, rather than IL-9 itself, was pathogenic [39].

Paradoxically, IL-9 might also promote Treg function. Elyaman *et al.* found that blocking IL-9 signaling with anti-IL-9 reverses nTreg-mediated suppression in vitro whereas addition of rIL-9 enhances Treg suppressive capacity [36]. Consistent with this, they observed that *Il9r*−/− mice developed more severe EAE than wild-type mice when immunized with MOG-peptide, and a higher frequency of Th1 and Th17 cells in the *Il9r*−/− mice both in the periphery and CNS as compared to WT mice. It is still not clear how the differences between Nowak *et al.* and Elyaman *et al.* can be reconciled [34,36]. There are modest protocol differences in the induction of EAE and source of reagents that might impact the types of Th or Treg cells induced and ultimately effect disease. The different outcome in these studies might indicate something important about the induction of IL-9-producing cells.

Th9 cells also contribute to allergic inflammation and disease. IL-9 is highly expressed in the lungs of asthmatic patients [40,41]. More recently our group and others have found that IL-9 production was significantly higher in T cells from atopic infants in comparison with a non-atopic group [7,29,42]. In mice, transgenic expression of IL-9 in the lungs induces an asthma-like response, and blocking IL-9 in an asthma model results in reduced airway inflammation [7,43,44]. Similarly blocking IL-9 in a chronic model of lung inflammation inhibits mastocytosis and airway remodeling [45]. Inflammation similar to allergic disease is also observed during helminthic parasite infection, and experiments with transgenic mice expressing a dominant negative TGF-βR demonstrated a requirement for Th9 cells in immunity to Trichuris muris [4].

There are several reports documenting a role of Th9 cells in the development of allergic airway disease (AAD). In an adoptive transfer model, Rag−/− recipients of either Th2 or Th9 cells developed severe asthma symptoms characterized by increased airway reactivity to methacholine, increased goblet cell metaplasia, and greater eosinophil infiltration after airway challenge. Administration of anti-IL-9 antibody resulted in a remarkable amelioration of AAD in Th9 cell recipients, whereas Th2-recipient *Rag2*−/− mice showed only slight improvement in AAD symptoms with antibody treatment [17]. The role of Th9 cells in an OVA/alum-induced allergic inflammation model was demonstrated in mice with a conditional deletion of PU.1 in T cells. These mice have normal Th2 and dendritic cell development, but have greatly diminished Th9 development. These mice not only exhibited less inflammation in lung but also demonstrated significantly less airway hyper-responsiveness in response to methacholine challenge compared to wild-type mice [7]. However, the role for Th9 cells may not be universal in all models. A recent report, using IL-9 reporter mice, confirmed that the primary IL-9-producing population in the OVA/alum model was CD4+ T cells. However, in a papain-induced airway inflammation model, innate lymphoid cells (ILCs) were the main source of IL-9 [46•]. Some T cell production of IL-9 was observed in this model, although IL-9 production was transient in both populations of cells.

Concluding remarks

The Th9 subset develops in response to combined signals from TGF-β and IL-4 among a cacophony of other cytokines in the extracellular milieu. The transcriptional network that regulates Th9 development includes TGF-β-induced *Sfpi1,* and IL-4-induced STAT6 that induces IRF4 as it represses Foxp3 and T-bet (Figure 1). Additional transcription factors, possibly downstream of these and additional cytokines, undoubtedly harmonize in efficient transcription of the *Il9* gene.

IL-9 promotes inflammation by stimulating growth of hematopoietic cells, particularly mast cells, and the secretion of factors including chemokines that recruit additional cells to inflamed sites. Th9 cells are capable of promoting autoimmune inflammation, although whether Th9 cells are required as a source of IL-9 for autoimmune inflammation is still not clearly established. Among the obstacles to defining these functions is that lack of a more detailed understanding of sensitization conditions that prime IL-9-producing T cells. More evidence supports an important role for Th9 cells in allergic inflammation, but how Th9 cells contribute to allergic disease, and how they cooperate with Th2 cells in promoting inflammation is the focus of ongoing investigation. Moreover, whether the mechanisms of Th9 cells contributing to autoimmune and allergic inflammation are distinct has not been examined. The next steps in this area will be to define the orchestration of Th9 cells, and the direction by Th9 cells, in the symphony of inflammation.

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• of special interest

•• of outstanding interest

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Highlights

- Th9 cells are a T helper cell subset that secretes IL-9 as a signature cytokine
- Th9 cell development requires transcription factors including PU.1, IRF4 and STAT6
- Th9 cells promote inflammation in autoimmunity and allergic disease

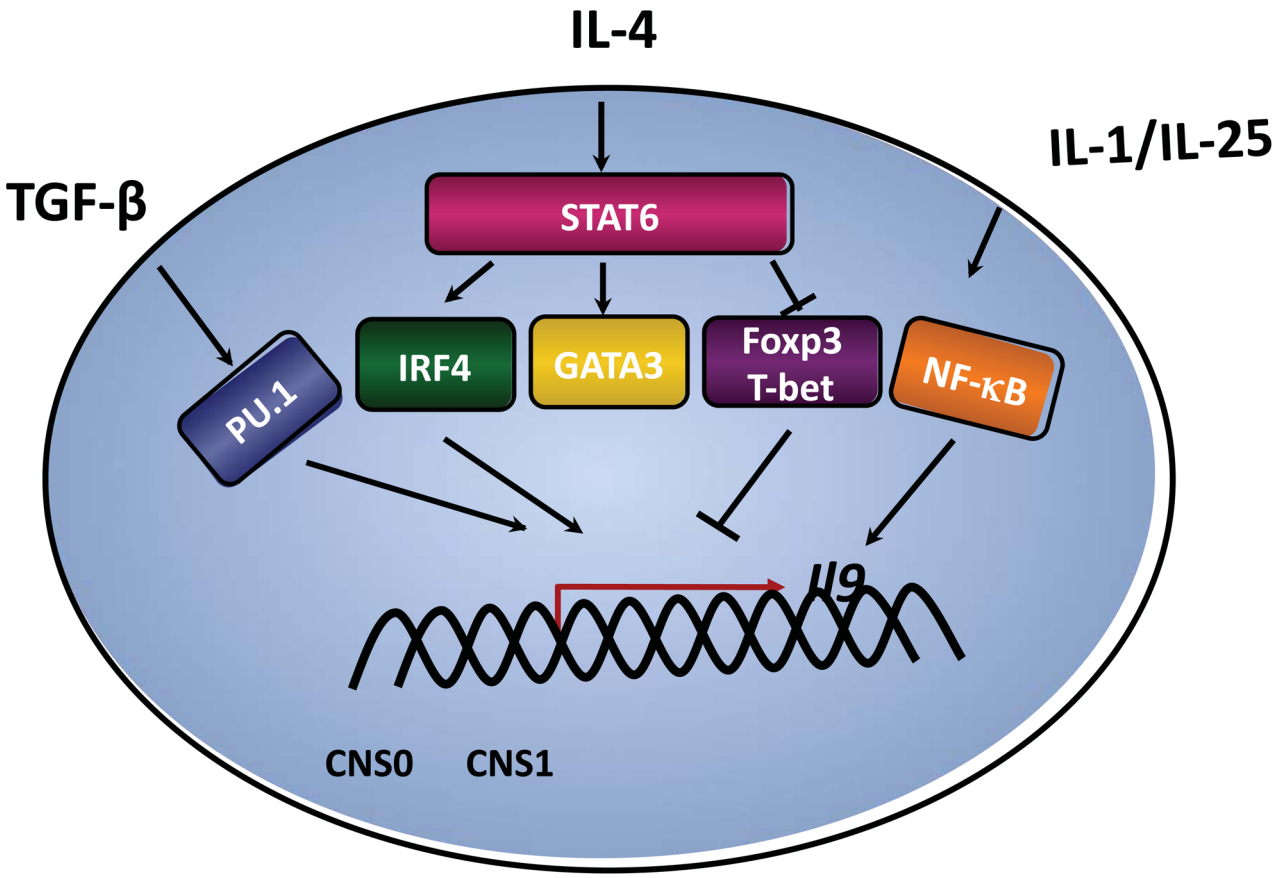

Figure.
Transcriptional network in Th9 cells. Transcription factors including PU.1, downstream of TGF-β signals, and IL-4-activated STAT6 that promotes expression of GATA3 and IRF4, contribute to the expression of the *Il9* gene in Th9 cells.