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Review

Th9 cells and IL-9 in autoimmune disorders: Pathogenesis and therapeutic potentials

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ABSTRACT

Naïve CD4$^+$ T cells are pleiotropically divided into various T helper (Th) cell subsets, according to their pivotal roles in the regulation of immune responses. The differentiation of Th9 cells, an interleukin (IL)-9 producing subset, can be impacted by specific environmental cues, co-stimulation with transforming growth factor β (TGF-β) and IL-4, and other regulatory factors. Although IL-9 has been recognized as a classical Th2-related cytokine, recent studies have indicated that IL-9-producing cells contribute to a group of autoimmune disorders including systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel diseases (IBD), rheumatoid arthritis (RA) and psoriasis. Studies of Th9 cells in autoimmune diseases, although in their infancy, are expected to be of growing interest in the study of potential mechanisms of cytokine regulatory pathways and autoimmune pathogenesis. Several in vitro and in vivo pre-clinical trials have been conducted to explore potential therapeutic strategies by targeting the IL-9 pathway. Specifically, anti-IL-9 monoclonal antibodies (mAbs) and IL-9 inhibitors may potentially be used for the clinical treatment of allergic diseases, autoimmune diseases or cancers. Here, we review recent research on Th9 cells and IL-9 pertaining to cell differentiation, biological characteristics and pivotal cellular inter-relationships implicated in the development of various diseases.

Contents

Abbreviations: IL, interleukin; TGF-β, transforming growth factor β; SLE, systemic lupus erythematosus; MS, multiple sclerosis; IBD, inflammatory bowel diseases; RA, rheumatoid arthritis; mAb, monoclonal antibody; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor alpha; Tregs, regulatory T cells; EAE, experimental autoimmune encephalitis; ETS, E26-transformation-specific; STAT, activators of transcription; JAK, Janus kinase; NO, nitric oxide; LPS, lipopolysaccharide; ILC2, type II innate lymphoid cells; ROI, reactive oxygen intermediates; TPO, thrombopoietin; EPO, hemopoietin; SCF, stem cell factor; ASM, airway smooth muscle; SLEDAI, SLE disease activity index; dsDNA, double-stranded DNA; CNS, central nervous system; MOG, myelin oligodendrocyte glycoprotein; CCL20, chemokine ligand 20; RR-MS, relapsing-remitting multiple sclerosis; CD, Crohn's disease; UC, ulcerative colitis; CIA, collagen-induced arthritis.

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1. Introduction

$CD4^+$ T helper (Th) cells functionally differentiate into various subsets, which are involved in the development of allergic, inflammatory and autoimmune diseases. In the past 20 years, Th1 cells and Th2 cells, characterized by different cytokine secretion patterns, have been regarded as the two main quintessential archetypes differentiated from naive $CD4^+$ T cells. Th1 cells mainly produce IL-2, interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), whereas Th2 cells predominately secrete IL-4, IL-5, IL-6 and IL-13. In recent years, several other distinct subsets of Th cells have been identified, including Th17, Th22 and regulatory T cells (Tregs). These distinct subsets can be distinguished by the specific cytokines and transcription factors, which each expresses, and their products define the functional roles of different Th cell subsets in diseases (Table 1).

In a broad sense, various $CD4^+$ T cell subsets such as Th1, Th2, Th17, Th22 and Treg cells have been implicated in the pathogenesis of systemic lupus erythematosus (SLE) [1], multiple sclerosis (MS) [2], inflammatory bowel diseases (IBD) [3], and rheumatoid arthritis (RA) [4]. More recently, a new effector T-cell subset that secretes the cytokine IL-9 has been identified as Th9 cells. The expression of IL-9 in this effector T cell subset occurs in the presence of both IL-4 and TGF-β, whereas IL-4 alone has a minimal effect on IL-9 expression during naive T-cell polarization [5]. Research over the last decade has suggested that Th9 cells possess a myriad of opposing pro-inflammatory and anti-inflammatory functions in autoimmune diseases.

Autoimmune diseases are a series of disorders characterized by immune system dysregulations, leading to inflammatory damage in genetically and environmentally susceptible individuals. Although the exact mechanism underlying autoimmune diseases remains elusive, recent studies have revealed a functional role of Th9 cells and IL-9 in their pathogenesis, especially in experimental autoimmune encephalitis (EAE), a classical experimental model for MS [2,6–8]. The lack of any significant efficacy in the conventional treatment of autoimmune diseases based on previously known cytokines produced by subsets such as Th1 and Th2 cells may suggest the existence of other factors attributable to the pathogenesis of these diseases. This unmet need to identify these factors has led to a great deal of research in defining IL-9-mediated clinical syndromes. Current studies of IL-9 and the Th9-cell subset have provided new insights in understanding the pathogenesis and therapeutic potentials of various autoimmune diseases.

2. Th9 cells

2.1. The regulation of Th9-cell differentiation

Among various T cell subsets such as Th1 and Treg cells, the polarization of each lineage-specific T-helper-cell subset primarily involves a spectrum of cytokine signal modulation. Th9 cells, one of the newly identified T cell subsets, mainly secrete IL-9 and require TGF-β and IL-4 for their induction [9–11]. IL-4 was identified as a prototype of Th2-cell cytokines, whereas TGF-β mediates the induction of Tregs by regulating the expression of Foxp3 [11]. However, without the delicately balanced stimulation of TGF-β and IL-4, naive $CD4^+$ T cells fail to differentiate into IL-9-producing cells in culture [9,11]. In the presence of both TGF-β and IL-4, naïve $CD4^+$ T cells synergistically develop into a lineage-specific subset, now known as Th9 cells, which express lower levels of Foxp3 and IL-4 than Tregs and Th2 cells, respectively.

A strong TGF-β signal plays a central role in driving the differentiation of Th9 cells in response to diversified cytokine stimuli. The ETS-family transcription factor PU.1 is critically involved in the TGF-β-mediated signaling of Th9-cell polarization. As an essential regulator, PU.1 is induced by TGF-β and appears to promote the development of Th9 cells in both mice and humans [12]. An initial report identified PU.1 as a versatile transcription factor for its ability to promote the Th2-cell phenotype and inhibit GATA3- or IRF4-targeting loci encoding cytokines [12]. Moreover, PU.1 can bind to the IL-9 promoter directly to promote Th9 subset polarization. Additionally, TGF-β is vital to the Smad2-, Smad3- and Smad4-signaling pathways, which are required for Th9 cell differentiation in vitro. Due to the activation of the transcription factors Smad2 and Smad3 by TGF-β signaling, interactions between Smad2/3 and IRF4 cooperatively transactivate the IL-9 promoter, resulting

Table 1
Signature cytokines of different T-cell subsets.

Cell subset	Th1	Th2	Th9	Th17	Th22	Tregs
Differentiation	IL-12	IL-4	TGF-β, IL-4	TGF-β, IL-6, IL-1, IL-23	IL-6, TNF	TGF-β
Transcription factor or regulator	T-bet, TAT4	GATA3,vSTAT6	PU.1, IRF4	RORγt STAT3	AHR	Foxp3, STAT5
Production	IFN-γ, TNF	IL-4, IL-5, IL-13	IL-9, IL-10	IL-17, L-22, IL-9	IL-22	IL-10, TGF-β