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Th9 Cells: Probable players in ulcerative colitis pathogenesis

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ABSTRACT

T lymphocytes represent an important part of adaptive immune system undertaking different functions to regulate immune responses. CD4+ T cells are the most important activator cells in inflammatory conditions. Depending on the type of induced cells and inflamed sites, expression and activity of different subtypes of helper T cells are changed. Recent studies have confirmed the existence of a new subset of helper T lymphocytes called Th9. Naive T cells can differentiate into Th9 subtypes if they are exposed simultaneously by interleukin (IL) 4 and transforming growth factor β and also secondary activation of a complicated network of transcription factors such as interferon regulatory factor 4 (IRF4) and Smads which are essential for adequate induction of this phenotype. Th9 cells specifically produce interleukin 9 and their probable roles in promoting intestinal inflammation are being investigated in human subjects and experimental models of ulcerative colitis (UC). Recently, infiltration of Th9 cells, overexpression of IL-9, and certain genes associated with Th9 differentiation have been demonstrated in inflammatory microenvironment of UC. Intestinal oversecretion of IL-9 protein is likely to break down epithelial barriers and compromise tolerance to certain commensal microorganisms which leads to inflammation. Th9 pathogenicity has not yet been adequately explored in UC and they are far from being considered as inflammatory cells in this milieu, therefore precise understanding the role of these newly identified cells in particular their potential role in gut pathogenesis may enable us to develop novel therapeutic approaches for inflammatory bowel disease. So, this article tries to discuss the latest knowledge on the above-mentioned field.

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KEYWORDS
Intestinal inflammation; IL-9; Th9; ulcerative colitis

Abbreviations

CMC	Chronic mucocutaneous candidiasis
DSS	Dextran sodium sulfate
EAE	Experimental autoimmune encephalomyelitis
FOXP3	Forkhead box P3
GATA	Family of transcription factors bind to "GATA" sequences
IBDs	Inflammatory bowel diseases
IELs	Intraepithelial lymphocytes
IL	Interleukin
ILCs	Innate lymphoid cells
IRF4	Interferon regulatory factor 4
JAK	Janus kinase
LPS	Lipopolysaccharide
NF-κB	Nuclear factor kappa B
NKT	Natural killer cell
NOS2	Nitric oxide synthase 2
OX40	Tumor necrosis factor receptor superfamily member 4
PU1	An ETS family transcription factor
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
STAT	Signal transducer and activator of transcription
TCR	T cell receptor
TGF-β	Transforming growth factor beta
TLR	Toll-like receptor
TNBS	Trinitrobenzenesulfonic acid
Tregs	Regulatory T cells
TSLP	Thymic stromal lymphopoietin
UC	Ulcerative colitis

1. Introduction

Effective immunologic responses are strongly dependent on the accurate induction of T cells. By expressing CD40 ligand, they provide required signals for clonal

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expansion of B cells, immunoglobulin switching, and antibody production.[1] They also regulate innate immunity through affecting macrophages and neutrophils, create memory T cell response, and manage inflammatory responses to pathogens.[2] However, uncontrolled T cell response can cause pathological alterations which may leads to allergy and autoimmunity.[3] A naive T cell in the presence of interleukin (IL)-4 and transforming growth factor (TGF)-β secretes IL-9, which drives cellular responses toward the differentiation of a novel characterized type of CD4+ cells named Th9.[4] The existence of Th9 cells and their roles as novel players in gut immunity have been confirmed in a number of studies. For example, compromised tissue integrity and sustained inflammatory responses during flare of ulcerative colitis (UC) in colon are related to IL-9 production by Th9 cells.[5,6] Tight junction proteins as principal components of intercellular adhesion mechanisms are important molecules, which maintain intestinal tissue integrity and prevent luminal antigens from being exposed to inflammatory cells present in lamina propria.[7] Recent studies have also shown some alterations in expression of these proteins by Th9-derived IL-9 that result in further gut inflammation. This article tries to discuss the harmful roles of Th9 cells in the gut.

2. Various CD4+ cells are distinctively differentiated

Multiple immune responses of the host subsequent to pathogen's crossing the innate immunity barriers are dependent on the appropriate function of T lymphocytes. According to their identifying markers and activities, T cells are divided into three major classes as follows: CD8+ T lymphocytes that are cytotoxic or killer cells and are known to be involved in response to tumor, metastatic cells, and viral infections.[8] Regulatory T cells (Tregs) that play a significant role in suppressing inflammatory responses, inducing immunological tolerance, and regulating immune responses to prevent autoimmunity through secretion of certain immunomodulatory cytokines such as IL-10, TGF-β, and IL-35 or via cell-cell contact.[9,10] CD4+ helper T cells that are major players in inflammatory milieu contributing to antibody production, regulating innate immunity, and inducing immunologic memory. Predominant types of these cell lineages including Th1, Th17, Th22, Th9, Th2, and TFH, are developed through T cell receptor (TCR) signaling and being affected by various cytokines and transcription factors (Figure 1).[11–13]

3. Th9 cells: Signaling pathways and cytokine profile

3.1. Characteristics and secretion sources of interleukin 9

IL-9 is a multifunctional cytokine and the most important source of IL-9 is Th9 lymphocytes. Therefore, they are most probably involved in the responses associated with increased IL-9 level during the process of inflammatory damages caused by immune system hyperactivity.[22–24] Although IL-9 is structurally different from lymphocytes growth factors, it was first identified and cloned as a growth factor of murine mast cells and T cells (T cell growth factor III) in 1980.[23,25] IL-9 is a cytokine with a common gamma-chain receptor similar to IL-4, −2, and −15, and upon binding to its receptor on target cells induces a signal through activation of janus kinase 1 (JAK1) and JAK3, creating a dimer between signal transducer and activator of transcription 3 (STAT3), STAT5, and STAT1.[26–28] The alpha subunit of IL-9 receptor contains WSXWS and BOX motifs and therefore is considered as a member of hematopoietin family.[22] The encoding gene of the protein of 144 amino acids is localized to chromosome 5 in human and chromosome 13 in mouse.[29,30] Th9 cells secrete abundant amounts of IL-9, but no specific and definite transcription factor has yet been defined for their complete differentiation.[31] First, because of increased release of IL-9 from *Leishmania*-infected murine Th2 cells, it was thought that IL-9 was generated only by Th2 cells therefore, its role has been investigated mainly in Th2-related pathologies.[32] It seems that in different immunological conditions, various factors impact induction of IL-9.[4] Via the simultaneous effects of IL-4 and TGF-β on naive T cells, their downstream signaling proteins such as GATA3, interferon regulatory factor 4 (IRF4), STAT6, and PU1 are being activated and induce IL-9 promoter transcription.[33] PU1-deficient mice exhibit potent inhibitory responses against the IL-9-dependent allergic airway inflammation. Such mice have a normal Th2 response despite having low amounts of IL-9. This indicates that PU1 play a critical role in Th9 development.[17] Evidence remains inconsistent on factors that physically interact to activate IL-9 gene. In some allergic responses such as lung inflammation and certain anaphylactic conditions, Th2 and Th9 cells are deeply proliferated.[34–36] Th17 cells that are induced in IL-6 and TGF-β containing environment, can generate IL-9 under certain conditions, however, IL-23 which promotes induction of Th17 cells was reported to decrease IL-9 generation. This indicates that IL-9 expression by Th17 completely depends on types of signals in inflammatory environment and does not occur constantly.[37,38]

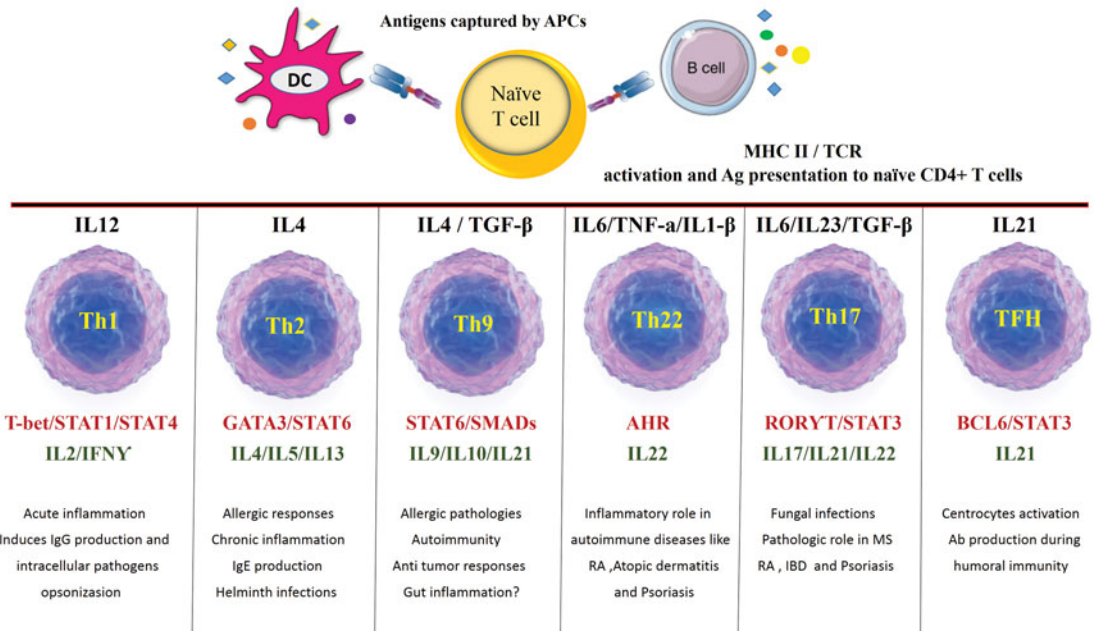

Figure 1. Differentiation pathways of CD4+ T cells. Antigen presenting cells such as dendritic cells and B lymphocytes uptake antigens from the environment and present to naïve T cells. Depending on the type of antigens, cytokines released in the environment and activation of transcription factors, various types of CD4+ cells are induced and interact with different cell types and drive inflammatory responses with respect to related proteins and chemokine receptors.[13–21]

In certain autoimmunities, such as experimental autoimmune encephalomyelitis (EAE) and type I diabetes, IL-9 is produced by Th17 phenotype.[39] During EAE, IL-9 plays two different functions. It suppresses EAE-induced inflammation by influencing Tregs function but intensifies inflammatory mediators through affecting mast cells and Th17 cells in an autocrine manner.[37,38,40–42] In type I diabetes, an autoimmune disease with Th17 dominancy, the role of IL-9 has not yet been explained.[43] Current evidence on secretion of IL-9 by Tregs are inconsistent. Although coexpression of forkhead box P3 (FOXP3) and IL-9 has been observed in murine T cells *in vivo*, it has not yet been determined whether FOXP3-expressing T cells can generate IL-9 or not.[44] IL-9 is an activator of human mast cell progenitors. As crucial regulators of innate immunity, mast cells expresses pattern recognition receptors like Toll-like receptor (TLRs) to recognize pathogen-associated molecular patterns and also are capable of producing IL-9 protein in response to stem cell factor, IL-10 and IL-3.[45,46] By expressing IL-9 receptors, they can be activated by IL-9 in an autocrine manner and also can pathologically release this protein during allergic diseases such as asthma and allergic rhinitis.[47,48] Mucosal mast cells are dominant secretors of IL-9 in experimental models of intestinal food allergy.[45] Although IL-9 is first known as a growth factor of mast cells that was named P40, they can generate IL-9 in response to lipopolysaccharide (LPS) and IL-1 through nuclear factor kappa B (NF-κB) activation.[49] In addition, there are some evidences indicating that histamine and IL-1β induce IL-9 secretion from murine bone marrow-derived mast cells.[50,51] Interestingly, remarkable infiltration of both chymase+ and trypase+ mast cells were observed by immunohistochemical staining of chronic UC lesions and it is stated that mast cells are the major source of several inflammatory mediators which can increase intestinal permeability and inflammation during gut-related pathologies.[52,53] There are reports that murine naïve natural killer T cells can also secrete IL-9 in the presence of IL-2. However, due to certain similarities in signaling pathways between IL-9 and IL-4, −5, and IL13, these proteins are secreted from these cells following IL-9 induction.[54] In natural killer cell (NKT)-CD1d deficient mouse, allergic airway inflammation leads to decreased production of IL-9 and decreased infiltration of mast cells in the lung, which confirms NKT's ability to produce IL-9 *in vivo*.[55] As a growth factor, IL-9 can cause NKTs transformation into nasal NKT cells lymphoma. In tissue sections of patients with nasal NKT cells lymphoma, the trafficking of IL-9 generating NKTs was reported.[56] Innate lymphoid cells are recently defined subtypes, which contribute to both innate and adaptive immune responses. They have diverse distribution in lymphoid and mucosal tissues and are involved in tissue remodeling and homeostasis. Type 2 innate lymphoid cells (ILCs) which are more characterized by Th2-like responses are mainly induced by effects of IL-25, IL-33, thymic stromal lymphopoietin (TSLP), IL-4, IL-7, and IL-9.[57] ILC2s

are also important regulators of epithelial responses in acute lung allergy which their effective induction in such condition is mainly dependent on IRF4 and IL-9.[58] During Th2-mediated intestinal inflammation, IL-33 is produced by damaged epithelial cells which affects ILC2s to release more IL-9 and finally more eosinophil recruitment, mucus secretion, and mastocytosis in response to IL-5 and IL-13, respectively.[59] We have given a snapshot of different sources of IL-9. Obviously, this protein plays significant roles in different diseases via its widely various functions. Now, we touch on cytokines, genes, and signaling pathways involved in Th9 development.

3.2. Differentiation pathways of Th9 cells

IL-4 and TGF-β activate two distinct pathways in T cells. The former causes transcription of GATA3 and STAT6 genes that leads to cell response toward Th2, and the latter activates FOXP3 and induces Tregs differentiation.[60,61] The simultaneous effects of these two cytokines on T cells lead to generation of IL-9 and induction of Th9 phenotype.[62] It has not yet been definitely determined which transcription factors physically interact and bind to IL-9 promoter. Different studies have reported inconsistent findings on this issue that will be distinctively quoted. Multiple proteins are considered as IL-4 and TGF-β downstream signals that contribute to amplification of IL-9 promoter as a complicate network[63–65] (Figure 2).

3.2.1. Positive regulators

As shown in Figure 2, all of these proteins contribute somehow to the induction of Th9 cells. Here, they will be discussed individually. IRF4 is the first factor of interest whose key role has been demonstrated in increasing transcription of IL-9 gene in T lymphocytes. Phosphorylation of STAT6 occurs following IL-4's binding to its receptor, and then IRF4 is activated and binds to IL-9 gene.[66,67] However, appropriate induction of other cells such as Th17 and Th2 depends on the presence of this factor.[68,69] IRF4-deficient mouse cannot induce IL-9-secreting T cells, and also silencing of IRF4 mRNA by relevant SiRNA prevents development of Th9 phenotype and activation of IL-9 promoter.[70] GATA3 is the other factor that is activated by STAT6 and causes destruction of T-Bet and FOXP3. It has not yet been determined whether GATA3 binds to the IL-9 gene directly or not.[30] After TGF-β binding to its receptor, a factor called PU1 activates IL-9 promoter through binding to IRF4.[71] PU1 is an ETS family transcription factor whose increased expression has been reported in certain Th9-dependent pathologies such as allergic inflammation and inflammatory bowel disease (IBDs).[17,72] Although the signaling pathways of Th9 and Th2 cells are partly similar, increased expression of PU1 causes downregulation in Th2 response. This indicates that differentiation of these two subsets may be completely separated under different conditions.[73] Effects of PU1 on inducing Th9 cells is due to histone modifications caused by this factor, and T cells that do not have such factor are not able to generate IL-9 in IL-4 and TGF-β-containing culture media. As with IRF4, silencing of PU1-related mRNA by SiRNAs leads to decreased response of Th9 and also inability to generate IL-9.[17] Other factors which become activated following TGF-β's effect on T cells are SMADs molecules that potentially play a role in activating IRF4. A study with an experimental model of asthma demonstrated that SMAD2 and SMAD3 bound to IRF4 directly and exerted exponential effects on IL-9 production

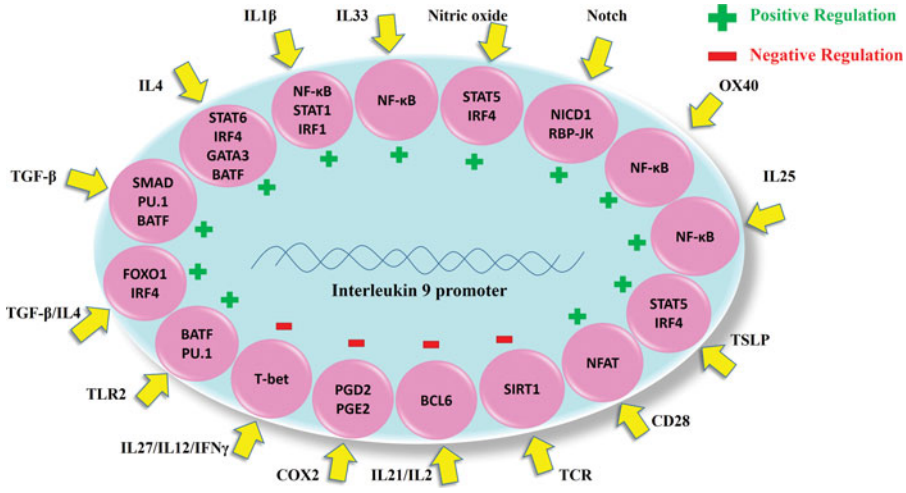

Figure 2. A complex set of cytokines and transcription factors involved in Th9 phenotype induction and IL-9 production by murine and human lymphocytes. Interactions among these factors in different diseases to bind to the gene and amplify IL-9 mRNA varies, which represents the plasticity of T helper cells and dependency of their differentiation on the types of inflammatory responses involved in the environment.

by T cells. This study, inconsistent with the previous studies, demonstrated that instead of PU1, SMAD2 and SMAD3 directly bound to IRF4 via MH1 and MH2 domains and therefore activated IL-9 gene.[74] Differentiation of Th9 cells seems to be varies under different conditions depending on the involved transcription factors and the way they get activated. Besides that, TSLP, nitric oxide, and IL-1β play important roles in activating Th9 cells, such that increased expression of IL-9 has been reported in response to such stimuli in mouse and human T lymphocytes.[75,76] In addition to the effects of IL-4 and TGF-β on T cells, TCR signaling causes increase in certain factors such as intracellular domains NFAT, AP1, Notch1, and NF-κB that are likely to contribute to binding to the IL-9 gene promoter.[77] Differentiation of Th9 cells and IL-9 secretion can even be dependent on type I interferons and IL-21.[78] It has been shown that basic leucine zipper ATF-like transcription factor (BATF), as an AP1 family transcription factor, can directly affect Th9 induction, such that the IL-9-dependent secretion of BATF is greater in atopic children's T cells compared to healthy children's T cells. In addition, BATF-deficient T cells cannot produce IL-9 through allergic responses in the mouse model.[79] In addition, engagement of TLR2 signaling in CD4+ T cells under Th9 differentiation increased the expression of BATF and PU1, which are crucial for IL-9 transcription.[80] Recently a study indicated that induction of IL-9 protein could be positively dependent on transcription factor FOXO1 in cooperation with IRF4. FOXO1 is a member of forkhead family transcription factors which has been shown to promote both Th9 and Th17 allergic responses through IL-9 induction.[81] It has also been shown that nitric oxide can positively impact on Th9 polarization and expression of IRF4/STAT5 by increasing IL-4R and TGF-βR on human and mouse CD4+ T cells. Accordingly, in an ovalbumin (OVA)-induced airway inflammation, nitric oxide synthase 2 (NOS2)-negative mice exhibited less Th9 response in comparison with wild-type model.[82]

3.2.2. Negative regulators

Th9 cells have been shown to considerably promote antitumor activity in a pulmonary melanoma model through a CCR6-dependent recruitment of specific CD8+ CTLs in tumor tissue; however, Th9-related tumor suppression can be promoted by a deficiency in histone deacetylase SIRT1, which cooperates with mTOR-TAK1-HIF1α complex in glycolysis pathway.[83,84] SiRNA-related or conventional inhibition of SIRT1 in human and mouse CD4+ T cells promoted both pathologic allergic responses and antitumor activity by Th9 cells.[83] The transcriptional B cell repressor lymphoma 6 (BCL6), which is mainly required for follicular helper T cell development, can impair Th9 induction and IL-9 transactivation. Ectopic expression of IFNγ, IL-2, and IL-21 in EAE results in BCL6-dependent inhibition of IL-9 which can exacerbate the disease symptoms.[65,85] Also, it has been reported that IFNγ can increase the expression of IL-27 by mast cells through the activation of STAT1.[86] As indicated before, more pronounced Th9 response is significantly relate to allergic lung inflammation. In an experimental model of allergic lung failure, it was observed that cyclooxygenase enzyme 2 was the main inducer of prostaglandins D2 and E2 which were the pivotal downregulators of Th9-derived IL-9 through the inhibition of IL-17 receptor B. In addition, Cox2-negative CD4+ T cells can considerably express IL-9 protein in a culture media containing IL-4 and TGF-β, which confirms the negative effects of Cox2 on Th9 activation.[87]

4. Th9 cells: Infection and allergic responses

IL-9 and Th9 cells play significant roles in mucosal immunogenicity throughout asthma-induced allergic responses, airway inflammation, and allergic rhinitis.[88] Genetically, chromosome 5, IL-9 and its receptor, and the secretion rate of serum IgE are directly associated.[89,90] The pathogenicity of IL-9 has been frequently demonstrated in the mouse model of allergy such that injecting mice with this protein has led to increased serum IgE levels, eosinophils infiltration, and airway hyperresponsiveness (AHR).[91,92] In mouse aspergillosis, IL-9 causes such responses in transgenic state.[93] In addition, in experimental models of asthma, several factors such as TSLP, tumor necrosis factor receptor superfamily member 4 (OX40), TRAF6 ligase, BATF kinase, NIK, and NF-κB are the stimulators of IL-9 promoter, and therefore play critical roles in activating Th9 cell-dependent inflammatory pathways in these models.[75,94–97] Goblet cell metaplasia is also one of the IL-9 effects throughout allergic inflammation which is associated with IL-13 and the activation of hematopoietic cells.[35] Anti-IL-9 antibody therapy in a mouse model of allergy alleviated the symptoms, although allergic reactions and the infiltration of mast cells may occur even in the experimental model of asthma in transgenic mice in the absence of the gene.[98,99] In asthmatic patients, the secretion levels of IL-9 and its receptor increase significantly.[100] Besides that, IL-9 can cause increase in mucus secretion, infiltration of eosinophils, mastocytes, and neutrophils, and disruption of airway tissue collagenous structure.[101] High amounts of IL-9 have also been demonstrated in allergic rhinitis, which is directly correlated with the infiltration rate of nasal eosinophilia.[102] Recently, traces of Th9 cells and IL-9 have been reported in certain infections. Regarding parasitic infections, evidence on IL-9 effects

are inconsistent. Increase in IgG generation and bowel hypermotility as well as effect on muscles to excrete the parasite, the activation of tissue mastocytosis, and ultimately increased activity of eosinophils to fight nematodes such as *Trichinella* and *Trichuris muris* are all dependent on IL-9 and its protective effects. On the other hand, blocking IL-9 by antibody in these models led to opposite outcomes that confirm its effect on intestinal clearance.[103,104] In contrast, in mouse experimental models of *Giardia lamblia* and *Nippostrongylus brasiliensis* infections, no effect was reported on defense mechanisms against the parasites in the absence of IL-9, and they were easily cleared of infection.[105] Besides that, in mouse model of schistosomiasis, it is noteworthy that granuloma derived from Schistosomia eggs was formed even in the absence of IL-9.[106] In patients with alveolar echinococcosis, who are predisposed to acute liver damages, the secretion rate of IL-9 and the expression of IRF4 and PU1 were dramatically increased in peripheral blood mononuclear cells (PBMCs) and inflamed liver tissues, which represents enhanced activity of Th9 cells in this condition.[107] Certain effects of IL-9 have also been reported in viral infections. Respiratory syncytial virus (RSV) is one of the most common causes of viral infections in children that is closely associated with asthma incidence and also causes bronchitis or chronic inflammation of the bronchi.[108] In experimental model, increased IL-9 in RSV infection and rapid clearance of the virus in case of blocking this protein were reported.[109] Throughout infection with gram-negative bacteria such as Pseudomonas, the symptoms are relieved after injecting IL-9 to mice infected with this bacterium, which is due to decrease in TNFα and IFNγ, and increase in IL-10 secretion.[110] In patients with chronic mucocutaneous candidiasis (CMC), the levels of IL-9 were decreased compared to healthy controls, which indicates that Th1 and Th17 responses are dominant in this milieu.[111] Table 1 demonstrates the effects of IL-9 and Th9 cells during certain infections.[107,110,112–119]

5. Th9 and intestinal inflammation

5.1. Intestinal tolerance: A unique feature

The digestive immune system is the evolutionary oldest and the most sophisticated organ of the body, which designed pivotal tolergenic mechanisms and a specific cellular map to maintain the mucosal layers sterile and separated from the luminal antigens that is estimated to be 100 million microbial cells.[120,121] Effective mucosal homeostasis is mostly dependent on early encountering to various microorganisms of normal flora and also proper nutrition. For instance, early exposure to some clostridium subtypes is necessary for accumulation of CD4+CD25+ Tregs in the colon which have protective effects on IBDs. Accordingly, reduced clostridium serotypes in IBD patients were observed.[122–124] Intraepithelial lymphocytes (IELs) are other important cells participated in colon homeostasis which are involved in mucosal defense and wound repair and their differentiation is associated mainly with aryl hydrocarbon receptors. It has been reported that a cruciferos vegetables-depleted nutrition negatively affects Ahr and IELs polarization leads to invasion of pathogens and intensified inflammatory responses.[125] Also deficiency in vitamins A and D, tryptophan, and milk-derived taurocholic acid all are related to Tregs dysfunction and impaired antimicrobial peptides which may result in epithelial damage and intestinal inflammation.[126,127] Goblet cells are the main source of glycosylated mucins which construct two distinct mucosal layers on epithelium surface and restrict the direct adhesion of microbial pathogens to the epithelium. Severe functional defects of goblet cells specially MUC2 gene have been reported in UC patients.[128–130] Paneth cells are other protective cells that play an important role in maintaining hemostasis in small intestine through the secretion of antimicrobial peptides. Genetical defects in autophagy-related genes NOD2, ATGL16, and XBP1, which are severely associated with Crohns disease incidence, can impair the release of antimicrobial proteins from paneth cells.[120,131] As a secondary source of IL-9, NKT cells recruit to inflammation sites in response to CXCL16 chemokine and produce IL-13, which promotes UC pathogenesis. It has been reported that intestinal colonization of a neonatal mouse with microbial normal flora inhibits infiltration of iNKT cells and protects from oxazolone-induced colitis.[132,133]

5.2. Th9 and experimental ulcerative colitis

Recent studies on mouse models of IBD and patients with IBD especially UC, demonstrated that the production of IL-9 and Th9-related transcription factors are increased.[6,72,134,135] Here we discuss how these cells potentially exhibit pathological activity through the inflammatory responses in the large intestine. Crohn's disease and UC are two important types of IBD that cause inflammation of the gastrointestinal tract lining tissues due to genetical predisposition and effects of environmental factors. Although these diseases share certain characteristics, they are completely different in terms of pathophysiology, the types of cell response, and genes involved in the incidence of the disease.[136] Crohn's disease causes deep inflammation alongside sporadic (but not continuous) involving of submucosa throughout the whole gastrointestinal tract from the mouth to the anus, while UC causes superficial inflammation restricted

Table 1. Pathologic and protective activity of Th9 cells in several microbial infections.

Type of infection	Secretion sources of IL-9	Related effects	Ref.
Parasitic—*Schistosoma japonicum*	Th9 cells-CDS+ cells-NKT cells-yo T cells	Promote liver failure and hepatic damages	115
Parasitic—*Trichinella spiralis*	Th9 cells-Th2 cells	Promote bowel mastocytosis and intestinal permeability leading to parasite expulsion	112
Parasitic—*Trichuris muris*	Th9 cells-Th2 cells	Increase muscle contraction and goblet cells hyperplasia and promote worm expulsion	112
Parasitic—*H. polygyrus*	CD4+ T cells (CTLA4 dependent)	Single infection: low amount, decreased mastocytosis in mice coinfection with *T. spiralis*: high amount, increased mast cells hyperplasia and worm expulsion in mice	112,114
Parasitic—*Strongyloides stercolaris*	Th9 cells	Increase Ag-specific responses and protection in human patients	112,114
Parasitic—*Giardia lambiia, Nippostrongylus brasiliensis*	Th9 cells	Complete parasite clearance even in absence of IL-9	112,114
Parasitic—*Echinococcus mutilocularis*	Th9 cells	Increase parasite persistence in host in human patient	107,112,114
Bacterial—*Pseudomonas aeruginosa*	T cells	Protective effects through suppression of TNF-a and induction of IL-10	110
Bacterial—*Chlamydia muridarum*	CD4+ T cells	No significant effect on Ab response and protection against lung infection in mice	116
Viral—Coxsackievirus B3	CD4+ and CD8+ T cells	Protective effects—inhibited virus replication	118
Viral—RSV	CD4+ T cells	Increase mucus production and lung failure	108,117
Fungal—*Candida albicans*	Th2, Th9 cells	General defect in IL-9 induction—protective effects in CMC	119

in the large intestine.[137] In Crohn's disease, Th1- and Th17-related cytokines are involved, while in UC, Th2 responses are dominant.[138] Due to the similarity and dependence of Th2 and Th9 responses on each other, increased IL-9 and Th9 cells represents a component of UC pathogenesis. In other words, these cells do not receive their required signals to completely differentiate in Crohn's disease inflammatory milieu. First, we touch on evidence about the presence of Th9 cells in the experimental models of IBD. In mouse model of oxazolone-induced colitis where Th2 responses are dominant as with human colitis, the gene expression of the IL-9 in the inflamed intestinal tissue and CD4+ cells in the spleen are increased compared to wild-type model. In this model, immunohistochemical analysis confirmed the presence and increased frequency of mucosal CD4+IL-9+ cells. Although the production of small amounts of IL-9 by innate lymphoid cells, CD117+ mast cells, and CD11c+ cells has been reported, Th9 lymphocytes are the most important source of this protein in oxazolone-induced colitis.[105] After rectal injection of oxazolone and inducing intestinal inflammation in mice, Gerlach et al. induced IL-9 deficiency in mice via two methods as follow: using anti-IL-9 antibody and inducing genetic defect in producing this cytokine. In both models of IL-9 deficiency, histopathological investigations demonstrated that inflammation was much lower compared to the wild-type model according to weight loss, clinical scores calculated by high-resolution miniendoscopy, and reactive oxygen species (ROS) bioluminescence evaluation. These evidences are indicative of the effective role of IL-9 in regulating intestinal inflammatory responses in this model. Inducing deficiency in PU1, a critical factor of Th9 induction in this model, caused decrease in the expression of IL-9 and Th2 cytokines and significantly decreased the disease symptoms. Increased expression of the IL-9 receptor on the Epcam+ intestinal epithelial cells, also confirms IL-9 activity against the tolergenic property of this tissue.[6] In both patients with UC and experimental model of this disease, pathogenic changes were induced by IL-9 in the intestinal epithelial barriers and tight junction proteins. In oxazolone-induced colitis where Th2 response is dominant, expression of intestinal tissue-permeable proteins such as claudins 1 and 2 increases, but in contrast, claudin 3 and occludin that increase the inhibitory activity of lining barriers significantly, were not changed. Bacterial translocation and fluorescein isothiocyanate-dextran effect on decreased permeability of the intestinal tissue lining membrane, demonstrated that the permeability of these membranes to many antigens decreased if the IL-9 was eliminated.[6] Through using organoid cell culture, creating three-dimensional crypts of the intestine, and exerting IL-9's effect on them, a study reported that IL-9 caused disruption in tissue remodeling mechanisms and cell proliferation.[6] Gerlach et al. conducted surgery to induce injury in mouse intestinal tissue to investigate the slowdown of tissue repair process and IL-9-dependent wound healing. Two days after surgery, recombinant IL-9's effect showed that the duration of wound healing increased considerably, which confirmed the potential role of IL-9 in wound healing process.[6] In an experimental model, namely trinitrobenzenesulfonic acid (TNBS)-induced colitis, in which Th1 response is dominant as with human Crohn's disease, in contrast to the former model, IL-9 had no effect on the expression of claudin 2 but affected the expression of occludin and claudin 1. This

indicates that in addition to IL-9, other factors regulate the expression of these molecules in different inflammatory conditions. In TNBS-induced colitis in wild-type and IL-9 deficient mice, the rates of inflammation and weight loss in IL-9 knockout mice were much lower than those in wild-type mice. Besides that, goblet cell dysfunction, wound induction, and mononuclear cells accumulation were much less pronounced in IL-9 knockout model. The immunofluorescence study of lamina propria cells revealed increased frequency of PU1+CD4+ cells in the wild-type model, representing that the expression of this factor depends on the frequency of the Th9 cells and the amount of IL-9 in this model.[5] Real-time PCR, western blotting, and study of the tight junction proteins expression in TNBS-induced colitis showed that unlike claudin 1, the expression of claudins 4 and 7, Jam-A, and occludin increased in the IL9-deficient model compared to the wild-type model. Inconsistency in findings on claudins expression in the models of oxazolone and TNBS-induced colitis is due to different dominant cell responses of these two models, such that it can be argued that IL-9 and Th9 cells exhibit regulatory activity in the TNBS-induced colitis model due to similarity of this condition to Crohn's disease and Th1/Th17 dominancy.[5] Immunohistochemical analyses of another experimental model of intestinal colitis that was induced by the effect of dextran sodium sulphate (DSS), showed an increase in Th9 cells expressing PU1 and CD3 markers. In addition, anti-IL-9 antibody treatment for 2 weeks caused relief of the disease symptoms and decreased the inflammatory mediators due to decline in activated lymphocytes in the lamina propria of mouse intestine.[139] Taken together, it can be argued that although Th9 cells need different transcription factors to differentiate in various inflammatory conditions, these cells increase in CD4+ cells-related inflammation, dysfunction of the intestinal lining barriers, and tolergenic dysfunction of epithelial cells by changing the expression of tight junction proteins, through secretion of IL-9 in the experimental models of IBDs especially UC (Figure 3).

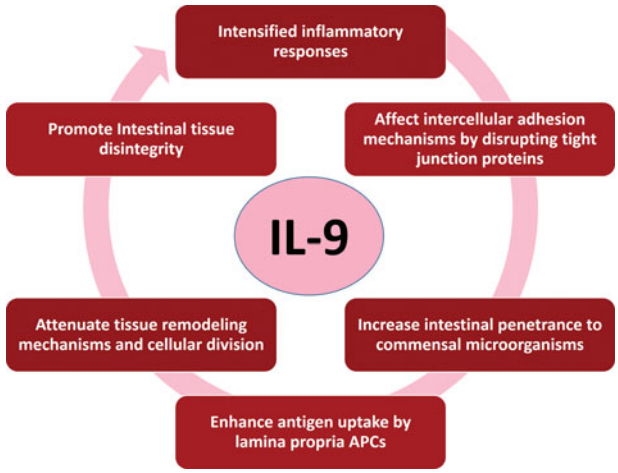

Figure 3. Pathological effects of IL-9 on expression of tight junction proteins and tissue repair mechanisms leads to dysfunction of epithelial barriers and declined tolergenic nature of intestinal tissue.

5.3. Th9 clinical manifestations in UC

Imbalance between the effector cells and the immunomodulatory cells is one of the most important reasons for the incidence and intensification of inflammatory responses particularly in gastrointestinal diseases such as gastritis or peptic ulcers.[140–143] Meanwhile, increased in T cells, such as Th17, and associated upregulation of the expression of inflammatory mediators such as IL-6, IL-23, and IL-33 is one of the important causes of different clinical presentations of *Helicobacter pylori*-related infections in the stomach such as duodenal ulcers and gastritis.[144–148] The role of helper T cells in producing inflammatory mediators has also been demonstrated during IBD. For example, Th1 and Th17 cells in Crohn's disease, and Th2 cells-related cytokines such as IL-4 and IL-13 in UC are increased in expression and function.[149,150] Following the elimination of proteins that maintain tight intercellular junctions, integrity of epithelial cells will be compromised resulting in easy pass of luminal antigens and subsequently intensification of IBD-induced inflammatory responses. Different proteins have been identified in regards to this issue such as IL-17 and IL-22.[151–153] Here we discuss mainly on the role of IL-9 and possibly Th9 cells in expediting inflammation and the pathogenicity of IBDs. The role of these cells have been studied in different diseases such as allergies, certain autoimmune conditions such as lupus, and different infections as we already discussed.[100,154] Studies on patients with UC demonstrated an important role for Th9 cells in UC pathogenesis. The study of gene-expression levels of IL-9 alongside other inflammatory cytokines such as IL-6 and IL-17A which are associated with Th17 subtype, confirmed increased expression of these genes in inflamed biopsies taken from the intestines of UC patients. Interestingly, the expression level of IL-9 mRNA was directly correlated with inflammation score.[72] Additionally, two-color immunofluorescence staining on tissue samples demonstrated an increase in the frequency of mucosal CD3+IL9+ cells in such patients. IRF4 and PU1 have positive effects on IL-9 expression in T cells in the presence of TGF-β and IL-4 and have been known as two main factors for the differentiation of Th9 cells.[66] The gene-expression levels of these molecules increase in patients with intestinal colitis and are directly correlated with intensification of inflammation and disease symptoms.[72] After culturing peripheral blood lymphocytes

under necessary conditions to induce Th9 cells, 6% of these cells secrete IL-9, and the coexpression of CD3, IRF4, and IL-9 was reported in 25% of these cells. In addition, the expression of the $\alpha 4/\beta 7$ integrin on the IL-9-generating lymphocytes increased in peripheral blood of patients with UC, which indicates their homing ability in the epithelial tissue of the large intestine. Furthermore, flow cytometric analysis has shown increased expression of IL-9 receptor on the polymorphonuclear leukocytes of the peripheral blood in patients with UC compared to controls. Finally, this study has demonstrated that the resistance of polymorphonuclear cells (PMNs) to apoptosis with IL-9 is increased in a dose-dependent manner. As a result, this protein can serve as a significant inducer of antiapoptotic signals of peripheral blood mononuclear cells in such patients.[72] Immunohistochemical staining of $\alpha E\beta 7$ and $\alpha 4\beta 7$ integrins on T lymphocytes revealed a remarkable mucosal accumulation of such cells in IBD patients. Therapeutically, targeting T cells homing in the gut is a growing field of IBD treatment now. As reported, intestinal recruitment of Th9 cells in IBD patients can be inhibited using antibody blockade of $\alpha E\beta 7$ integrin. Etrolizumab monoclonal antibody to $\alpha E\beta 7$ integrin effectively blocked Th9 adhesion on mucosal E-cadherin and MadCam1.[155]

6. Conclusion

Th9 cells are a novel described subtype of helper T cells. It seems that Th9 cells promote allergic damages in patients and experimental models. In addition, the traces of Th9 cells have been found in certain microbial infections, which require further investigation. We have already provided several evidences on the role of Th9 cells in IBD-induced pathologies. As we discussed increased frequency of CD4+IL-9+ cells, so called Th9 cells are reported in animal models and patients with UC. The changes in gene expression of IL-9 in biopsy specimens of patients with IBD, the effects of such cytokines on the expression of proteins that maintain tight intercellular junctions and their potential role on immune tolerance in the gut merits further investigations. Although the cited studies offered some answers to many questions on the role of Th9 cells and IL-9 in the pathogenesis of UC, many questions remained unanswered. Identification of specific transcription factors involved in the differentiation of these cells in inflammatory conditions such as UC and in depth understanding of how expression of this cytokine at gene and protein levels can be manipulated are essential for potential therapeutic strategies.

Competing interests

None declared.

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