Chapter

Therapeutic Potential of IL-9 in Allergic and Autoimmune Diseases

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Abstract

Interleukin-9 (IL-9) is a pleiotropic cytokine produced by several immune and epithelial cells. Recently, many studies have elucidated the physiological and pathological roles of IL-9 and its lineage-specific helper T cell subset (Th9). In this chapter, we will focus on the immunological role of Interleukin 9 (IL-9) in allergy and autoimmunity. We will introduce the basics of IL-9 and describe the cells involved in the secretion, signaling, and regulation of IL-9. After establishing the background, we will discuss the pathogenesis and regulation of IL-9 in allergic and autoimmune diseases. We will conclude the chapter by providing an updated therapeutics that target IL-9 and their potential uses in autoimmune and allergic diseases.

Keywords: IL-9, Th9, multiple sclerosis, Th17, IBD, uveitis, mast cells, asthma, atopic dermatitis, food allergy, diabetes, TGF-β, ILC2

1. Introduction

Interleukin-9 (IL-9) is a pleotropic cytokine that regulates diverse immunological functions (Figure 1). This cytokine was first identified in the late 1980s as a T cell growth factor [1]. Because of the molecular weight of IL-9, it was initially known as P40 [2]. Later studies revealed that the observed molecular weight was due to N-link glycosylation, and actual molecular weight for this discovered molecule is 14 kDa [3]. A similar factor was also identified from Th2 cells and mast cells where it was initially named as T-cell growth Factor III (TCGF III) and mast cell growth-enhancing activity (MEA), respectively [2, 4]. Further studies revealed that both TCGF III and MEA actually represent the P40 factor [4]. In later years, considering its pleotropic roles and the redundant nomenclature the P40 factor was renamed as IL-9 [5].

The locus encoding IL9 in mouse is about 11 kb in size, and located on chromosome 13 [6]. The Il9 locus is comprised of 5 exons and 4 introns [3]. The Il9 locus encode for a precursor peptide of 144 amino acids, first 18 amino acids of which is signal sequence peptide. The mature IL-9 peptide, a single-chain glycoprotein of 126 amino acids, and similar to other cytokines of IL-2 family folds into a four-alpha-helix bundles [7]. Human IL-9 locus is present on chromosome 5 in the region q31–35 [6]. Homology between mouse and human IL-9 is about 55%, and both of them contain a conserved 10 cysteine residue to form a disulfide bond that is critical for a mature IL-9 peptide. Interestingly, three conserved non-coding sequences,
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CNS0, CNS1, and CNS2 are present on both mouse and human il9 locus sequence similarity of which is 63% [3, 7]. CNS0 is positioned in the upstream (~6 kb) of transcription start site (TSS), CNS1 is the promoter region, and CNS2 is located at the downstream of TSS (~5.4 kb) [8]. CNS1 provide binding site to numerous transcription factors that includes PU.1, STAT5, STAT6, GATA1, GATA3, IRF1, IRF4, NF-kb, BATF, AP-1, Smads 2/3/4, Gcn5, Notch [9]. Etv5 can bind to both CNS0 and CNS2, and recruit histone acetyltransferase p300 to mediate chromatin remodeling [8–11]. Regulation of IL-9 expression by this multiple numbers of transcription factors explain the necessity of a delicate cytokine milieu that requires to stimulate IL-9 producing cells. The miscellaneous origin of IL-9 and the complexity of its regulation underscore the need for a comprehensive assessment of IL-9 function. Therefore, in this chapter, we will elucidate the basis of IL-9 function in health and diseases and its therapeutic potentials in autoimmune and allergic diseases.

2. IL-9, a lineage specific Th9 cytokine

T cells were originally thought to be the main source of IL-9 [12–14]. IL-9 was defined as a Th2 cytokine. The reason for this Th2 designation by many research findings included IL-9 genome. The il-9 gene is positioned within a Th2 cytokine clusters. Also, increased expression of IL-9 was observed in a Th2-predominate BALB/c mouse model of cutaneous leishmaniasis (BALB/c mice) but not in Th1-predominate model (using C57BL/6 mice). This finding suggested IL-9 as a Th2 signature cytokine [12]. In addition, Th2-like responses such as airway epithelial hyperplasia, proliferation of mast cells, mucin-producing cells, and eosinophils were found in the lungs of IL-9 transgenic mice [15]. More recently, the designation of IL-9 as a Th2 cytokine loses credence, due to the identification of PU.1, an ETS family transcription factor that induces IL-9 secretion. Mice with T-cell-specific deletion of PU.1 did not develop IL-9 dependent inflammation of the lungs [16]. However, the mice had similar frequencies of Th2 cells [16]. In another experiment that utilized siRNA-mediated disruption of PU.1 resulted in impaired IL-9

Figure 1. Functions of IL-9. IL-9 contributes to different immunopathology and physiology through activation of multiple cell types. Illustration by MHuzzatul.
production in human T-cells. Recently, a distinct helper T cell subset, Th9 was identified as IL-9 lineage-specific cells. Studies observed increased PU.1 expression under Th9 polarizing conditions but not Th2 conditions [16]. The finding of another helper T cell subset suggested that Th2 is not the main source for IL-9, and PU.1 as a unique transcription factor necessary for IL-9 production emphasized the identity of Th-9. Later, in vitro studies identified IL-4 and TGF-β as cytokines that facilitate the differentiation of naïve T cells to Th9 cells [17, 18]. Though IL-4 is a known Th2 cytokine, TGF-β exhibit pleotropic functions and regulates the development of other helper T cells including Th17 and Treg cells [19]. Presence of IL-4 with TGF-β facilitates the differentiation of naïve T cells into IL-9-secreting Th9 but not Tregs or Th17. Also, IL-4 can directly block the expression of FoxP3 in T cells thus reprogramming Treg cells into Th9 cells [17]. And, addition of TGF-β in culture medium reprograms Th2 cells to Th9 cells [18]. IL-4 and TGF-β-mediated induction of IL-9-producing cells are dependent on both activated STAT6 and GATA3, suggesting the initial identification of IL-9 as a Th2 cytokine. And Th2 including other helper T cells secrete small amounts of IL-9 [20].

3. Sources of IL-9

In addition to Th9 and Th2, other immune cells have been identified as potential sources of IL-9 (Figure 2). Prominent among these immune cells is Th17 cells. Th17 cells are involved in mounting immune responses against extracellular bacteria and fungi and are implicated in autoimmunity [21]. Activation of a Th17-associated transcription factor, retinoic acid receptor-related orphan receptor-γt (RORγt) with phorbol 12-myristate 13-acetate and ionomycin (PMA) leads to IL-9 secretion [22]. Tregs have also been shown to secrete IL-9 both in vivo and in vitro, however, the role is IL-9-secreting Tregs is conflicting [23, 24]. Another recently identified source of IL-9 is Vδ2 T cells in human peripheral blood. This γδ T cell subset population can be stimulated with antigens, TGF-β, and IL-15 to produce IL-9 [24]. Mast cells, natural killer T cells (NKT) have also been found to produce IL-9. Mast cells cross-linked with IgE and inflammatory mediators like histamine produce IL-9 in the presence of IL-1β and LPS [25–29]. Stimulation of NKT cells with IL-2 leads to secretion of IL-9 [30]. A large number of infiltrating IL-9 producing NKT has been found in histological section from patient with nasal NKT cell lymphomas [31]. Decreased expression of IL-9 was observed in CD1d-restricted NKT deficient mouse model of allergic inflammation suggesting NKT cell can also promote IL-9 production in vivo [32]. In addition, innate lymphoid cells such as ILC2s, eosinophils, neutrophils, and osteoblasts also have been found to produce IL-9 [33–35].

Figure 2.
Cellular sources of IL-9 and IL-9 receptor (IL-9R) heterocomplex. Illustration by MHuzzatul.
4. IL-9 receptor signaling

IL-9 exerts its biological effect on its target cells through IL-9R receptor. The IL-9R is a heterocomplex of the alpha chain (IL-9Rα) and the common gamma chain [36]. IL-9Rα is specific only to IL-9, whereas the gamma chain is present in the receptor complexes of several other cytokines such as IL-2, IL-4, IL-7, IL-13, IL-15, and IL-21 [37–39]. About 25% of the IL-9Rα exist in complex with the gamma chain outside IL-9 heterocomplex. IL-9Rα is of 522 amino acids in human, and 468 amino acids in mouse, and contains 11 exons [40]. This 64 kDa glycoprotein is a member of type I hematopoietin receptor super family due to the presence of the Box1 and Box2 motifs in the intracellular domain, and WSXWS motif in the extracellular domain [41]. Formation of a heterocomplex with the γ-chain is enhanced as IL-9 binds to IL-9Rα (Figure 2) [42]. The binding of IL-9 to IL-9Rα results in a conformational change in IL-9R. This conformational change recruit JAK molecules to Box1 motif which results in the phosphorylation of tyrosine residues of IL-9Rα-associated JAK1 and γ-chain associated JAK3 [41]. BOX1 motif is very critical in IL-9 mediated signaling as disruption of Box1 results in loss of

**Figure 3.**
Schematic representation of IL-9 signaling pathway. IL-9 cytokine binds to IL-9R complex. This leads to phosphorylation of JAKs. The phosphorylated JAKs activate STATs, PI3 kinase, and the MAP kinase pathway. IL-9R, interleukin-9 receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PI3K, phosphatidylinositol-3 kinase; PIP, phosphoinositide; PDK1, pyruvate dehydrogenase kinase 1; bad, GSK3, glycogen synthase kinase 3; PS6K, IRS, insulin receptor substrate; SOS, suppressors of cytokine signaling; GRB2, ERK, extracellular signal regulated kinase; Src; Ras/Raf/MEK, mitogen-activated protein kinases; illustration by MHuzzatul.
phosphorylation of JAK1 and JAK3 [43]. Activated JAK molecules then phosphorylate a tyrosine residue (Tyr407) in the IL-9Ra, which results in the phosphorylation of intermediate molecules, STAT molecules (STAT1, STAT3, and STAT5), MAPK, and IRS-PI3 pathways (Figure 3) [44–46]. Activation of these pathways contribute to the upregulation of IL-9, as well as important in the growth, differentiation, and development of the IL-9 targeted cells [47, 48].

5. IL-9 and allergic diseases

Allergic diseases including respiratory, food, and skin allergies are mainly mediated by Th2 cells through the expression of various cytokines such as IL-4, IL-5, and IL-13 (reviewed in [49]). The cytokine IL-9, which was initially studied in the context of Th2-mediated immune response and later associated with T-helper 9 (Th9) cells, has been shown to play an important role in allergic inflammation [50, 51]. IL-9 and its receptor IL-9Ra regulate antibody synthesis, specifically IgE, in both murine and human B cells [52, 53]. To contribute to allergic disease pathogenesis, IL-9 also promotes activation and recruitment of inflammatory cells [54–57].

6. Asthma including airway allergies

Various studies have shown that IL-9 and its receptor contribute to airway allergic diseases and asthma. Sputum, serum, and lungs of patients with asthma were shown to have increased concentrations of the cytokine [58–60]. IL-9 levels were also increased in the airways of murine asthma models [61]. IL-9Ra is expressed on human tonsillar germinal center and memory B cells, and smooth muscles in the airways. IL-9/IL-9Ra signaling in B cells induces STAT3 and STAT5 pathways to potentiate IgE production [52, 53, 55, 62, 63]. Overexpression of IL-9 in transgenic mice or treatment with recombinant cytokine induces expansion of B-1 cells, and accumulation of mast cells in the tissues [64]. IL-9 induces the release of proteases and pro-inflammatory cytokines by the mast cells to promote survival of eosinophils and increase airway permeability [66, 67]. IL-9/IL-9Ra signaling also stimulates human airway smooth muscle to secrete eotaxin1/CCL11 and induces production of IL-13 in airway epithelial cells. Eotaxin1/CCL11 and IL-13 significantly increase eosinophil recruitment and cause lung epithelial cell hypertrophy. These effects result in asthma-like symptoms, including lung inflammation, bronchial hyper-responsiveness, and mucus accumulation. Moreover, IL-9 worsens lung injury in a murine model of chronic obstructive pulmonary disease (COPD) [63, 68, 69]. The cytokine also appears to be a critical player in allergic rhinitis. Serum IL-9 in patients strongly correlates with irritative nasal symptoms including rhinorrhea [70]. In mice, Th9 cells are significantly upregulated during allergic rhinitis and neutralization of IL-9 alleviates symptoms. Blocking IL-9 decreases the level of inflammatory cytokines (IFN-γ, IL-4, and IL-17) and eosinophils infiltration in the nasal mucosa. This causes a decrease in the frequency of sneezing and nasal rubs in experimental models of allergic rhinitis [71].

7. Food allergies

Studies in patients with food allergy and experimental oral hypersensitivity have shown that allergic reactions in the gastrointestinal tract are mediated by various players, including Th2-secreted cytokines, such as IL-4 and IL-9 [72–74]. Various
studies have shown that IL-9 drives intestinal inflammation and plays a critical role in food allergies [75, 76]. In patients with food allergies, the severity of clinical symptoms strongly correlates with increased intestinal permeability [77]. *In vitro* experiments have shown that patients with peanut allergy have increased levels of IL-9. The memory T helper cell response specific to peanuts in allergic children is dominated by IL-9. Thus, cytokine levels can be used as a biomarker to determine individuals with peanut allergy [78, 79]. In mice, overexpression of intestinal IL-9 or induction of IL-9-producing mucosal mast cells (MMC9s) also increases susceptibility to food allergy [80]. Migration of mast cell progenitors and their development into MMC9s is regulated by basic leucine zipper transcription factor ATF-like (BATF) and Th2-secreted IL-4 [81]. The large amount of MCC9s-derived IL-9 and other mast cell mediators cause intestinal mastocytosis and increased intestinal permeability, which is central to the induction of experimental oral hypersensitivity [82]. The actions of the IL-9-stimulated mast cells cause allergic diarrhea and hypothermia [75]. IL-9 can additionally be secreted by the group 2 innate lymphoid cells (ILC2) and Th9 cells to amplify the intestinal allergic inflammatory response, which may lead to anaphylaxis [83–88].

8. Skin allergies

IL-9 has been identified as a potential mediator of cutaneous allergies, including atopic dermatitis (AD) and allergic contact dermatitis (ACD). Patients with atopic dermatitis have a significantly higher level of IL-9 in the serum and skin lesions [89]. The concentration of the cytokines also positively correlates with the severity of the disease and serum IgE levels [90]. These observations were made in both adult and pediatric patients [91, 92]. A study in a Korean population also linked IL-9 and IL-9R gene polymorphisms to AD [93]. IL-9 induces IL-5 and IL-13 by ILC2. ILC2 and the cytokines are associated with AD pathogenesis. IL-5 and IL-13 contribute to the defective skin barrier in AD patients by downregulating tight junctions genes [94, 95]. IL-9 also promotes the secretion of the vascular endothelial growth factor (VEGF) by keratinocytes and mast cells [92, 96]. An increased level of VEGF contributes to the dilatation of capillaries, erythema, and inflammatory edema characteristics of AD [97, 98]. Moreover, IL-9 has been shown to regulate Th1-mediated allergic contact dermatitis. Patients with positive patch tests to nickel have a higher level of allergen-specific IL-9 expression in skin, peripheral blood mononuclear cells (PBMCs). Also, IL-9 potentially mediates infiltration of eosinophils in the skins as its levels strongly correlate with the cell infiltration in the tissues. This demonstrates a potential pathogenic role of the cytokine IL-9 in ACD [99, 100].

9. IL-9 and autoimmunity

The etiology or trigger of autoimmune diseases is not well understood [101, 102]. However, there is a consensus that many factors, including genetic, environmental, and cytokine dysregulation are implicated in causing aberrant immune responses that drive tissue damage [102–104]. Many studies on divergent immune responses in autoimmunity have shown dysfunction of helper T cell subsets, which include Th1, Th17, and/or Treg cells [104, 105]. Studies in the last decade have identified IL-9-secreting Th9 cells as another T helper cell subset involved in immune responses [23, 106]. The IL-9 cytokine has become the focus of many autoimmune studies [107, 108]. Initial studies showed IL-9
to be a growth factor and a Th2 cytokine [13, 108]. More recently, IL-9 has been characterized as a lineage-specific cytokine for Th9 cells [109]. Thereafter, many immune cells involved in autoimmunity, such as Th17 and Treg cells, have demonstrated secretion of IL-9 [16, 110]. In EAE, a rodent model of MS, researchers identified Th9 and its signature cytokine, IL-9, in driving the disease process [111]. Its close association with Th17 and TGF-β has renewed interest in the role of IL-9 in the pathogenesis of autoimmune diseases [23]. In this section, we will examine the role of IL-9 in some autoimmune diseases such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), and uveitis.

10. IL-9 and IL-17 dynamics in autoimmunity

The role of IL-9 in autoimmunity was illuminated when many studies reported that IL-9 and IL-17 are intricately related in driving the pathogenesis of diseases [111]. Human and animal studies revealed that Th17 cells secrete some amount of IL-9, in addition to other proinflammatory cytokines [112]. During the differentiation of naive T cells, TGF-β, a key driver of Th17 polarization, plays an important role in the differentiation of Th9 cells [23]. This was well elaborated in a study by Nowak et al in which in vitro polarization of MOG-specific Th17 cells was shown to generate IL-9-secreting Th9 [22, 113]. Secretion of IL-9 was further enhanced by the addition of IL-18 or IL-21 to the culture [113]. In addition, TGF-β and IL-6 induce Th17 cells that co-express IL-9 and IL-17 [22]. Studies have shown an increased frequency of memory CD4 cells that co-express IL-9 and IL-17 in patients with Type 1 diabetes [23].

On the other hand, IL-9 potentiates Th17 functions in an autocrine manner on Th17 cells [22, 110]. Th17 is a predominant helper T-cell subset that expresses IL-9 receptors (IL-9R) [22]. Through this receptor, IL-9 acts as an activator of Th17 cells [22]. IL-9 also synergizes with TGF-β to differentiate naive T cells into Th17 cells [110]. The presence of IL-9 in T cell cultures leads to the expansion of Th17 cells [110]. The importance of IL-9 in Th17 cell function is emphasized in IL-9R-deficient experimental autoimmune encephalomyelitis (EAE) model. Mice that lack IL-9 signaling showed decreased Th17 cells and defective migration of Th17 cells into the CNS [22, 114]. Neutralization of IL-9 led to attenuation of disease in EAE [22]. This unique relationship between IL-9 and Th17 provides the premise to examine the role of IL-9 in Th17-mediated autoimmune diseases.

11. Multiple sclerosis (MS)

Most autoimmune diseases like MS occur due to alteration of immune responses, which leads to tissue damage. The importance of IL-9 in MS has been enhanced through our understanding of the roles of IL-9-secreting T cells in EAE, an animal model of MS orchestrated by helper T cells [115]. Most studies revealed IL-9 plays a pathogenic role in EAE [22]. Th9 cells and Th17 cells were observed in the central nervous system (CNS) during EAE [115]. Blockade of IL-9 signaling in EAE resulted in contradictory conclusions. One study reported increased severity of disease in IL9Ra KO mice on a C57BL/6 background through a loss of Treg function and increased secretion of GM-CSF [116]. Other studies showed attenuation of disease and decreased Th17 cell infiltration into the CNS of SJL mice treated with IL-9 blocking antibody [22, 117]. This opposing view in disease outcome may be due to differences in the helper T cell composition and dysfunction driving the
pathogenesis in the mouse strains. Also, IL-9 has been shown to increase chemokine CCL20, which enhances migration of Th17 into the CNS [22]. Accumulation and activation of mast cells during the Th17-IL9 immune response could explain the feedback loop [113]. Adoptive transfer of IL-9+ Th9 into recipient mice resulted in EAE [118]. Th9-EAE model manifested a unique disease profile independent of Th1 and Th17 EAE models [118].

The role of IL-9 in MS patients is complex. A study by Roucco et al showed that IL-9 activates STAT1 and STAT 5, which are inhibitors of Th17 function [119]. IL-9 directly interfered with IL-17 expression in Th17 cells. Levels of IL-9 in the cerebrospinal fluid (CSF) of relapsing and remitting MS patients were inversely correlated with the disease pathogenesis and the disability indices [119]. These findings suggested the immunoregulatory role of IL-9 in MS. In another study, CSF of MS patients showed increased amounts of IL-9, and levels of IL-9 correlated well with IL-17 [120]. Therefore, more studies are needed to understand the functional role of IL-9 in MS.

12. Uveitis

Unlike other autoimmune diseases, uveitis is a heterogeneous disorder that results in inflammation of the eye [121]. In animal models of uveitis, adoptive transfer of in vitro polarized Th9 cells induced ocular inflammation [122, 123]. However, IL-9 was not detected in the eyes or lymph nodes of these mice [123]. Analysis of inflammatory cytokines in the vitreous humor of patients with uveitis detected increased levels of IL-9, among other proinflammatory cytokines [124]. However, the biological relevance of increased IL-9 in the study was not elaborated.

Another study examined the role of IL-9 in patients with Vogt-Koyanagi-Harada (VKH) disease. VKH is a systemic autoimmunity that manifests with bilateral panuveitis [125]. Patients with active disease had significantly higher levels of IL-9 in culture supernatants and higher IL-9 mRNA in PBMCs than did healthy controls and inactive patients [126]. The synergy of IL-9 and IL-17 was demonstrated in the study. The secretion of IL-17 by IL-9-treated PBMCs of active patients was significantly higher compared to the controls or inactive patients [126]. In a study that evaluated the serum of patients with Behcet’s disease, another complex autoimmune disease with uveitis, serum IL-9 was neither elevated in disease state nor correlated with disease index [127]. More studies are needed to understand whether IL-9 signaling plays any immunological role in the eye.

13. Rheumatoid arthritis (RA)

The study of IL-9 in RA highlights its functional relationship with Tregs. In an antigen–induced animal model of arthritis, mice that lacked IL-9 had a chronic disease [128]. Treatment with rIL-9 resolved the joint inflammation, swelling, and tissue damage. The absence of IL-9 led to impaired suppressive functions of Treg cells [128]. Type 2 innate lymphoid cells (IL-C2) are documented to express IL-9 and have an anti-inflammatory function [128, 129]. These studies highlight the role of IL-9 in the resolution of inflammation in arthritis [130]. In human studies, IL-9-producing IL-C2 cells were also identified in the PBMCs of RA patients [130, 131]. In a study of treatment-induced remission of RA, synovial fluid of patients showed high levels of IL-9 [128].
14. Systemic lupus erythematosus (SLE)

Proinflammatory cytokines are generally believed to be involved in the pathogenesis of SLE. High levels of IL-9 mRNA and Th17 cells were seen in SLE patients compared with healthy controls (HC) [132, 133]. Dantas et al, evaluated the level of IL-9 in SLE and observed that patients with SLE had elevated IL-9 compared with levels in healthy individuals [134]. Further, IL-9+ CD4 cells were more abundant in patients with SLE [132]. Serum IL-9 and mRNA of IL-9 were significantly elevated in SLE patients [132]. Also the elevated serum IL-9 and mRNA correlated with the SLE severity index [132, 135]. Animal studies corroborated these findings. Spleens and kidneys of lupus-prone mice showed high expression of IL-9 [136]. Neutralizing antibodies of IL-9 decreased kidney manifestation of SLE (lupus nephritis) and decreased anti-dsDNA antibody titers in these animal models [136].

15. Inflammatory bowel disease (IBD)

Aberrant adaptive immune response to the gut epithelial cells involving both CD4 and CD8 is implicated in the IBD [137]. These T cells are shown to express α4/β7 integrin, which binds to MAdcam1 on the gut epithelium [138, 139]. Gut T cells including cells that secrete IL-9 have been shown to express high levels of this integrin, and they propagate inflammation in the gut [140]. Gene expression studies have highlighted IRF4 and GATA3 expression on immune cells that reside in the epithelial lining of the gut [141]. IRF4 is a transcription factor that drives the induction of Th9 immune responses in the gut [141]. Animal models of colitis confirmed this finding of an abundance of the IL-9-producing T cells in the gut. These T-cells-producing IL-9 are involved in breaking the intestinal barrier [142]. In a DSS colitis model, anti-IL-9 blocking antibodies suppressed mucosal inflammation, and attenuation of disease was observed [142]. Adoptive transfer of IL-9-producing T cells into Rag2 knockout (Rag2−/− KO) mice also induced colitis [143]. Furthermore, IL-9 was found to directly modulate the expression of tight junction proteins, claudin and occludin in the animal model of colitis [144]. This indicates that IL-9 directly inhibited membrane integrity.

Immunological assessment of patients with inflammatory bowel disease (IBD) revealed high expression of IL-9 in the lamina propria [145]. In addition to other gut-residing T cells in IBD, CD4 cells had increased production of proinflammatory cytokines, including IL-9, which drive gut inflammation [145, 146]. Elevated levels of IL-1β and IL-9 were observed in the serum of IBD patients, and these correlated with disease prognosis [147]. Epithelial cells of UC also showed high expression of IL-9 receptor (IL-9R) [147, 148]. This receptor expression is most pronounced in patients with active disease [147]. Ex vivo IL-9 treatment of intestinal epithelial cells from UC patients showed increased proliferation of epithelial cells and pSTAT5 expression [110].

Together, these findings highlight the role of IL-9 in IBD and colitis models. IL-9 could serve as a therapeutic target for IBD. Mice treated with GATA 3 DNAzyme showed it directly reduced IL-9 production and some Th2 cytokines to attenuate disease [149].

16. Type I diabetes

Studies by Vasanthakumar et al examined the role of IL-9 in patients with diabetes mellitus (DM) [150]. They observed that memory T cells from patients
stimulated with Th17 polarizing conditions led to IL-9 production [150]. This shows that Th17 cells from DM patients have an increased ability to secrete IL-9 [23]. The study also identified TGF-β as the critical activator of IL-9 secretion [23]. TGF-β activity links Th17 and IL-9 secretion.

IL-9 appears to play both anti- and pro-inflammatory functions in autoimmunity. The functional heterogeneity of IL-9 may result from the unique cells or the microenvironment producing it. In RA, IL-9 exhibits anti-inflammatory function [128]. Studies have elaborated the anti-inflammatory function of IL-9 as it potentiates Treg-dependent immune tolerance to allografts [151]. In the gut, it is regarded as proinflammatory [142]. Some studies have shown that the expression of the activation marker CD96 on Th9 cells may explain the immunological status of the secreted IL-9 [152]. Researchers have reported that Th9 with high expression of CD96 showed a reduced ability to cause colitis compared with Th9 with low expression of CD96, which is associated with severe intestinal inflammation [152]. More studies must be done to identify the immunological heterogeneity of IL-9.

17. IL-9 as a therapeutic target

One principle of treatment of autoimmune diseases involves inhibition of mediators of inflammation. Drugs that target proinflammatory cytokines are extensively used in the treatment of autoimmune diseases [153]. Here we explore the use of IL-9 blockade as a therapeutic target in different disease conditions.

Medimmune LLC developed a humanized anti-IL-9 monoclonal antibody, MEDI-528 [154]. This humanized anti-IL-9 monoclonal antibody was indicated for use in allergen-induced asthma in adults [154]. Results from the clinical trial of Medimmune MEDI-528 showed no increased efficacy in improving respiratory functions and control of asthma compared to placebo [155]. Preclinical studies in mice showed the efficacy of blocking IL-9 in maintaining the airway [156]. Questions remain regarding why therapy directed at IL-9 failed to produce the desired response in humans. Heterogeneity of IL-9 sources and functions could explain the differences in airway response observed in this clinic trial.

18. Other potential IL-9 treatments

IL-9R inhibitor (rhIL-9-ETA) is a chimeric toxin targeting IL9 receptor [157]. These IL-9R inhibitors have efficacy in targeting malignant cells in non-hodgkin’s lymphoma (NHL) and acute myeloid leukemia (AML) expressing IL9 and IL-9R [157]. However, the efficacy of this drug has not been tested in autoimmunity. Pfizer Inc. developed a JAK/STAT pathway inhibitor, CP-690550 [158]. It specifically targets and inhibits the activation of JAK 3 [158]. This treatment effectively prevents transplant rejection [158]. This drug could be beneficial in inhibiting IL-9 signaling, which depends on the JAK/STAT pathway. JAK inhibitors have been used in the treatment of RA and psoriasis [159]. UC patients that were treated with JAK inhibitors showed decreased Th9 cells [160].

BNZ 132-1-40 peptide, an antagonist of IL-2, IL-9, and IL-15 from Bioniz Therapeutics is undergoing safety and tolerability testing in patients with moderate to severe alopecia areata, an autoimmune disease of the skin that leads to hair loss [161]. However, no results from the clinical trial were available at the time of this review. Recently, FDA approved the use of BNZ-1 for the treatment of cutaneous T cell lymphoma (CTCL) [162]. These studies suggest BNZ-1 could be used to target IL-9 in diseases [163].
Other potential drug options include RDP58, which targets IRF4, a transcription factor involved in Th9 induction [164]. Interferon gamma (IFN-γ) has the ability to inhibit Th9 polarization through IL-27-dependent mechanisms [165]. Actimmune, an IFN-γ-based therapy by Horizon Therapeutics, is FDA-approved for the treatment of chronic granulomatous disease (CGD) [166]. The efficacy of inhibiting IL-9 by this drug could be tested in IL-9-related disorders.

The immune modulatory roles of IL-9 in health and diseases are important and provides a basis for exploring IL-9 as a therapeutic target. However, the divergent roles of IL-9 in promoting and inhibiting inflammation complicate definitive drug development. Some studies have highlighted the function of IL-9 in promoting immune tolerance. Future studies to understand cell-specific IL-9 regulation and function may resolve the conundrum of therapy development targeting IL-9. More studies in disease will broaden our knowledge about IL-9 function.

19. Conclusion

Significant progress has been made in our understanding of the functions of IL9 in health and diseases. For a long time, IL-9 was considered as a T cell growth factor, however, the identification of Th9 helper T cells has expanded our understanding on the roles IL-9 play in diseases. The pathogenic functions of IL-9 in autoimmunity and allergy suggest that IL-9 signaling can be targeted for therapy development. In this chapter, we focused on the function of IL-9 in different autoimmune diseases that include MS, SLE, RA, uveitis, and allergic conditions. We also highlighted IL-9-Th17 paradigm and its complexity in autoimmune diseases. Animal models of autoimmune diseases revealed contrasting roles of IL-9 and human studies are limited. Therefore, extensive animal and human research are necessary to elucidate the divergent immunological roles of IL-9. Such studies will be required for effective drug development that targets IL-9 signaling.

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Conflict of interest

The authors declare no conflict of interests.
References

[1] Goswami, R. and M.H. Kaplan, A brief history of IL-9. J Immunol, 2011. 186(6): p. 3283-3288.

[2] Uyttenhove, C., R.J. Simpson, and J. Van Snick, Functional and structural characterization of P40, a mouse glycoprotein with T-cell growth factor activity. Proc Natl Acad Sci U S A, 1988. 85(18): p. 6934-6938.

[3] Van Snick, J., et al., Cloning and characterization of a cDNA for a new mouse T cell growth factor (P40). J Exp Med, 1989. 169(1): p. 363-368.

[4] Hültner, L., et al., Mast cell growth-enhancing activity (MEA) is structurally related and functionally identical to the novel mouse T cell growth factor P40/TCGFIII (interleukin 9). Eur J Immunol, 1990. 20(6): p. 1413-6.

[5] Renauld, J.C., et al., Human P40/IL-9. Expression in activated CD4+ T cells, genomic organization, and comparison with the mouse gene. J Immunol, 1990. 144(11): p. 4235-4241.

[6] Mock, B.A., et al., IL9 maps to mouse chromosome 13 and human chromosome 5. Immunogenetics, 1990. 31(4): p. 265-70.

[7] Simpson, R.J., et al., Complete amino acid sequence of a new murine T-cell growth factor P40. Eur J Biochem, 1989. 183(3): p. 715-722.

[8] Koh, B., et al., A conserved enhancer regulates Il9 expression in multiple lineages. Nat Commun, 2018. 9(1): p. 4803.

[9] Kaplan, M.H., The transcription factor network in Th9 cells. Semin Immunopathol, 2017. 39(1): p. 11-20.

[10] Staudt, V., et al., Interferon-regulatory factor 4 is essential for the developmental program of T helper 9 cells. Immunity, 2010. 33(2): p. 192-202.

[11] Jash, A., et al., Nuclear factor of activated T cells 1 (NFAT1)-induced permissive chromatin modification facilitates nuclear factor-κB (NF-κB)-mediated interleukin-9 (IL-9) transactivation. J Biol Chem, 2012. 287(19): p. 15445-15457.

[12] Gessner, A., H. Blum, and M. Röllinghoff, Differential regulation of IL-9-expression after infection with Leishmania major in susceptible and resistant mice. Immunobiology, 1993. 189(5): p. 419-435.

[13] Else, K.J., L. Hültner, and R.K. Grencis, Cellular immune responses to the murine nematode parasite Trichuris muris. II. Differential induction of TH-cell subsets in resistant versus susceptible mice. Immunology, 1992. 75(2): p. 232-237.

[14] Schmitt, E., et al., TCGF III/P40 is produced by naive murine CD4+ T cells but is not a general T cell growth factor. Eur J Immunol, 1989. 19(11): p. 2167-2170.

[15] Temann, U.A., et al., Expression of interleukin 9 in the lungs of transgenic mice causes airway inflammation, mast cell hyperplasia, and bronchial hyperresponsiveness. J Exp Med, 1998. 188(7): p. 1307-1320.

[16] Chang, H.C., et al., The transcription factor PU.1 is required for the development of IL-9-producing T cells and allergic inflammation. Nat Immunol, 2010. 11(6): p. 527-534.

[17] Dardalhon, V., et al., IL-4 inhibits TGF-beta-induced Foxp3+ T cells and, together with TGF-beta, generates IL-9+ IL-10+ Foxp3(−) effector T cells. Nat Immunol, 2008. 9(12): p. 1347-1355.

[18] Veldhoen, M., et al., Transforming growth factor-beta 'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9-producing
Interleukins - The Immune and Non-Immune Systems’ Related Cytokines

subset. Nat Immunol, 2008. 9(12): p. 1341-1346.

[19] Li, M.O., Y.Y. Wan, and R.A. Flavell, T cell-produced transforming growth factor-beta1 controls T cell tolerance and regulates Th1- and Th17-cell differentiation. Immunity, 2007. 26(5): p. 579-591.

[20] Schmitt, E., et al., IL-9 production of naive CD4+ T cells depends on IL-2, is synergistically enhanced by a combination of TGF-beta and IL-4, and is inhibited by IFN-gamma. J Immunol, 1994. 153(9): p. 3989-3996.

[21] Tesmer, L.A., et al., Th17 cells in human disease. Immunol Rev, 2008. 223: p. 87-113.

[22] Nowak, E.C., et al., IL-9 as a mediator of Th17-driven inflammatory disease. J Exp Med, 2009. 206(8): p. 1653-1660.

[23] Beriou, G., et al., TGF-beta induces IL-9 production from human Th17 cells. J Immunol, 2010. 185(1): p. 46-54.

[24] Putheti, P., et al., Human CD4 memory T cells can become CD4+IL-9+ T cells. PLoS One, 2010. 5(1): p. e8706.

[25] Hültner, L., et al., In activated mast cells, IL-1 up-regulates the production of several Th2-related cytokines including IL-9. J Immunol, 2000. 164(11): p. 5556-63.

[26] Stassen, M., et al., IL-9 and IL-13 production by activated mast cells is strongly enhanced in the presence of lipopolysaccharide: NF-kappa B is decisively involved in the expression of IL-9. J Immunol, 2001. 166(7): p. 4391-8.

[27] Stassen, M., et al., p38 MAP kinase drives the expression of mast cell-derived IL-9 via activation of the transcription factor GATA-1. Mol Immunol, 2007. 44(5): p. 926-33.

[28] Stassen, M., et al., Murine bone marrow-derived mast cells as potent producers of IL-9: costimulatory function of IL-10 and kit ligand in the presence of IL-1. J Immunol, 2000. 164(11): p. 5549-55.

[29] Wiener, Z., A. Falus, and S. Toth, IL-9 increases the expression of several cytokines in activated mast cells, while the IL-9-induced IL-9 production is inhibited in mast cells of histamine-free transgenic mice. Cytokine, 2004. 26(3): p. 122-130.

[30] Lauwerys, B.R., et al., Cytokine production and killer activity of NK/T-NK cells derived with IL-2, IL-15, or the combination of IL-12 and IL-18. J Immunol, 2000. 165(4): p. 1847-53.

[31] Nagato, T., et al., Expression of interleukin-9 in nasal natural killer/T-cell lymphoma cell lines and patients. Clin Cancer Res, 2005. 11(23): p. 8250-8257.

[32] Jones, T.G., et al., Antigen-induced increases in pulmonary mast cell progenitor numbers depend on IL-9 and CD1d-restricted NKT cells. J Immunol, 2009. 183(8): p. 5251-5260.

[33] Gounni, A.S., et al., IL-9 expression by human eosinophils: regulation by IL-1beta and TNF-alpha. J Allergy Clin Immunol, 2000. 106(3): p. 460-466.

[34] Sun, B., et al., Characterization and allergic role of IL-33-induced neutrophil polarization. Cell Mol Immunol, 2018. 15(8): p. 782-793.

[35] Xiao, M., et al., Osteoblasts support megakaryopoiesis through production of interleukin-9. Blood, 2017. 129(24): p. 3196-3209.

[36] Russell, S.M., et al., Interaction of IL-2R beta and gamma c chains with Jak1 and Jak3: implications for XSCID and XCID. Science, 1994. 266(5187): p. 1042-1045.
[37] Demoulin, J.B. and J.C. Renauld, Signalling by cytokines interacting with the interleukin-2 receptor gamma chain. Cytokines Cell Mol Ther, 1998. 4(4): p. 243-256.

[38] Renauld, J.C., et al., Expression cloning of the murine and human interleukin 9 receptor cDNAs. Proc Natl Acad Sci U S A, 1992. 89(12): p. 5690-5694.

[39] Kimura, Y., et al., Sharing of the IL-2 receptor gamma chain with the functional IL-9 receptor complex. Int Immunol, 1995. 7(1): p. 115-120.

[40] Bauer, J.H., et al., Heteromerization of the gammac chain with the interleukin-9 receptor alpha subunit leads to STAT activation and prevention of apoptosis. J Biol Chem, 1998. 273(15): p. 9255-9260.

[41] Zhu, Y.X., et al., Critical cytoplasmic domains of human interleukin-9 receptor alpha chain in interleukin-9-mediated cell proliferation and signal transduction. J Biol Chem, 1997. 272(34): p. 21334-21340.

[42] Malka, Y., et al., Ligand-independent homomeric and heteromeric complexes between interleukin-2 or -9 receptor subunits and the gamma chain. J Biol Chem, 2008. 283(48): p. 33569-33577.

[43] Fujiwara, H., et al., Homodimerization of the human interleukin 4 receptor alpha chain induces Cεpsilon germline transcripts in B cells in the absence of the interleukin 2 receptor gamma chain. Proc Natl Acad Sci U S A, 1997. 94(11): p. 5866-5871.

[44] Ihle, J.N. and I.M. Kerr, Jaks and Stats in signaling by the cytokine receptor superfamily. Trends Genet, 1995. 11(2): p. 69-74.

[45] Demoulin, J.B., et al., A single tyrosine of the interleukin-9 (IL-9) receptor is required for STAT activation, ant apoptotic activity, and growth regulation by IL-9. Mol Cell Biol, 1996. 16(9): p. 4710-6.

[46] Levy, D.E. and J.E. Darnell, Jr., Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol, 2002. 3(9): p. 651-662.

[47] Malik, S. and A. Awasthi, Transcriptional Control of Th9 Cells: Role of Foxo1 in Interleukin-9 Induction. Frontiers in Immunology, 2018. 9: p. 995.

[48] Humblin, E., et al., IRF8-dependent molecular complexes control the Th9 transcriptional program. Nature Communications, 2017. 8(1): p. 2085.

[49] Ngoc, L.P., et al., Cytokines, allergy, and asthma. Current opinion in allergy and clinical immunology, 2005. 5(2): p. 161-166.

[50] Veldhoen, M., et al., Transforming growth factor-β reprograms the differentiation of T helper 2 cells and promotes an interleukin 9–producing subset. Nature immunology, 2008. 9(12): p. 1341-1346.

[51] Gessner, A., H. Blum, and M. Röllinghoff, Differential regulation of IL-9-expression after infection with Leishmania major in susceptible and resistant mice. Immunobiology, 1993. 189(5): p. 419-435.

[52] Dugas, B., et al., Interleukin-9 potentiates the interleukin-4-induced immunoglobulin (IgG, IgM and IgE) production by normal human B lymphocytes. European journal of immunology, 1993. 23(7): p. 1687-1692.

[53] Takatsuka, S., et al., IL-9 receptor signaling in memory B cells regulates humoral recall responses. Nature immunology, 2018. 19(9): p. 1025-1034.

[54] MURPHY, K. and C. WEAVER, JANEWAY’S 9TH EDITION.
[55] Petit-Frere, C., et al., *Interleukin-9 potentiates the interleukin-4-induced IgE and IgG1 release from murine B lymphocytes*. Immunology, 1993. 79(1): p. 146.

[56] Dong, Q., et al., *IL-9 induces chemokine expression in lung epithelial cells and baseline airway eosinophilia in transgenic mice*. European journal of immunology, 1999. 29(7): p. 2130-2139.

[57] Longphre, M., et al., *Allergen-induced IL-9 directly stimulates mucin transcription in respiratory epithelial cells*. The Journal of clinical investigation, 1999. 104(10): p. 1375-1382.

[58] Sherkat, R., et al., *Innate lymphoid cells and cytokines of the novel subtypes of helper T cells in asthma*. Asia Pacific Allergy, 2014. 4(4): p. 212-221.

[59] Hoppenot, D., et al., *Peripheral blood Th9 cells and eosinophil apoptosis in asthma patients*. Medicina, 2015. 51(1): p. 10-17.

[60] Erpenbeck, V.J., et al., *Increased expression of interleukin-9 messenger RNA after segmental allergen challenge in allergic asthmatics*. Chest, 2003. 123(3): p. 370S.

[61] Kim, M.S., et al., *Effects of interleukin-9 blockade on chronic airway inflammation in murine asthma models*. Allergy, asthma & immunology research, 2013. 5(4): p. 197-206.

[62] Fawaz, L.M., et al., *Expression of IL-9 receptor α chain on human germinal center B cells modulates IgE secretion*. Journal of allergy and clinical immunology, 2007. 120(5): p. 1208-1215.

[63] Gounni, A.S., et al., *IL-9-mediated induction of eotaxin1/CCL11 in human airway smooth muscle cells*. The Journal of Immunology, 2004. 173(4): p. 2771-2779.

[64] Levitt, R.C., et al., *IL-9 pathway in asthma: new therapeutic targets for allergic inflammatory disorders*. Journal of Allergy and Clinical Immunology, 1999. 103(5): p. S485-S491.

[65] Temann, U.-A., et al., *Expression of interleukin 9 in the lungs of transgenic mice causes airway inflammation, mast cell hyperplasia, and bronchial hyperrresponsiveness*. The Journal of experimental medicine, 1998. 188(7): p. 1307-1320.

[66] Wiener, Z., A. Falus, and S. Toth, *IL-9 increases the expression of several cytokines in activated mast cells, while the IL-9-induced IL-9 production is inhibited in mast cells of histamine-free transgenic mice*. Cytokine, 2004. 26(3): p. 122-130.

[67] Matsuzawa, S., et al., *IL-9 enhances the growth of human mast cell progenitors under stimulation with stem cell factor*. The Journal of Immunology, 2003. 170(7): p. 3461-3467.

[68] Temann, U.-A., et al., *IL9 leads to airway inflammation by inducing IL13 expression in airway epithelial cells*. International immunology, 2007. 19(1): p. 1-10.

[69] McLane, M.P., et al., *Interleukin-9 promotes allergen-induced eosinophilic inflammation and airway hyperresponsiveness in transgenic mice*. American journal of respiratory cell and molecular biology, 1998. 19(5): p. 713-720.

[70] Ciprandi, G., *Serum interleukin 9 in allergic rhinitis*. Annals of Allergy, Asthma & Immunology, 2010. 104(2): p. 180-181.

[71] Gu, Z.W., Y.X. Wang, and Z.W. Cao, *Neutralization of interleukin-9 ameliorates symptoms of allergic rhinitis by reducing Th2, Th9, and Th17 responses and increasing the Treg response in a murine model*. Oncotarget, 2017. 8(9): p. 14314.
[72] Osterfeld, H., et al., Differential roles for the IL-9/IL-9 receptor alpha-chain pathway in systemic and oral antigen-induced anaphylaxis. J Allergy Clin Immunol, 2010. 125(2): p. 469-476.e2.

[73] Nakajima-Adachi, H., et al., Critical role of intestinal interleukin-4 modulating regulatory T cells for desensitization, tolerance, and inflammation of food allergy. PLoS One, 2017. 12(2): p. e0172795.

[74] Burton, O.T., et al., Direct effects of IL-4 on mast cells drive their intestinal expansion and increase susceptibility to anaphylaxis in a murine model of food allergy. Mucosal Immunol, 2013. 6(4): p. 740-750.

[75] Shik, D., et al., IL-9-producing cells in the development of IgE-mediated food allergy. Semin Immunopathol, 2017. 39(1): p. 69-77.

[76] El Ansari, Y.S., C. Kanagaratham, and H.C. Oettgen, Mast Cells as Regulators of Adaptive Immune Responses in Food Allergy. Yale J Biol Med, 2020. 93(5): p. 711-718.

[77] Ventura, M., et al., Intestinal permeability in patients with adverse reactions to food. Digestive and liver disease, 2006. 38(10): p. 732-736.

[78] Xie, J., et al., Elevated antigen-driven IL-9 responses are prominent in peanut allergic humans. PloS one, 2012. 7(10): p. e45377.

[79] Brough, H.A., et al., IL-9 is a key component of memory TH cell peanut-specific responses from children with peanut allergy. Journal of allergy and clinical immunology, 2014. 134(6): p. 1329-1338. e10.

[80] Chen, C.-Y., et al., Induction of Interleukin-9-Producing Mucosal Mast Cells Promotes Susceptibility to IgE-Mediated Experimental Food Allergy. Immunity, 2015. 43(4): p. 788-802.

[81] Tomar, S., et al., IL-4–BATF signaling directly modulates IL-9 producing mucosal mast cell (MMC9) function in experimental food allergy. Journal of Allergy and Clinical Immunology, 2021. 147(1): p. 280-295.

[82] Forbes, E.E., et al., IL-9- and mast cell-mediated intestinal permeability predisposes to oral antigen hypersensitivity. J Exp Med, 2008. 205(4): p. 897-913.

[83] Osterfeld, H., et al., Differential roles for the IL-9/IL-9 receptor α-chain pathway in systemic and oral antigen–induced anaphylaxis. Journal of allergy and clinical immunology, 2010. 125(2): p. 469-476.e2.

[84] Ahrens, R., et al., Intestinal mast cell levels control severity of oral antigen-induced anaphylaxis in mice. The American journal of pathology, 2012. 180(4): p. 1535-1546.

[85] Chen, C.-Y., et al., Induction of interleukin-9-producing mucosal mast cells promotes susceptibility to IgE-mediated experimental food allergy. Immunity, 2015. 43(4): p. 788-802.

[86] Tomar, S., et al., IL-4–BATF signaling directly modulates IL-9 producing mucosal mast cell (MMC9) function in experimental food allergy. Journal of Allergy and Clinical Immunology, 2020.

[87] Steenwinckel, V., et al., IL-9 promotes IL-13-dependent paneth cell hyperplasia and up-regulation of innate immunity mediators in intestinal mucosa. The journal of immunology, 2009. 182(8): p. 4737-4743.

[88] Forbes, E.E., et al., IL-9–and mast cell–mediated intestinal permeability predisposes to oral antigen hypersensitivity. The Journal of experimental medicine, 2008. 205(4): p. 897-913.

[89] Ma, L., et al., Possible pathogenic role of T helper type 9 cells and interleukin
(IL)-9 in atopic dermatitis. Clin Exp Immunol, 2014. 175(1): p. 25-31.

[90] Klonowska, J., et al., New Cytokines in the Pathogenesis of Atopic Dermatitis- New Therapeutic Targets. Int J Mol Sci, 2018. 19(10).

[91] Ciprandi, G., et al., Serum interleukin-9 levels are associated with clinical severity in children with atopic dermatitis. Pediatric dermatology, 2013. 30(2): p. 222-225.

[92] Ma, L., et al., Possible pathogenic role of T helper type 9 cells and interleukin (IL)-9 in atopic dermatitis. Clinical & Experimental Immunology, 2014. 175(1): p. 25-31.

[93] Namkung, J.-H., et al., An association between IL-9 and IL-9 receptor gene polymorphisms and atopic dermatitis in a Korean population. Journal of dermatological science, 2011. 62(1): p. 16-21.

[94] Stockinger, B.B., et al., Interleukin 9 fate reporter reveals induction of innate IL-9 response in lung inflammation. 2011.

[95] Brunner, P.M., E. Guttman-Yassky, and D.Y. Leung, The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. Journal of Allergy and Clinical Immunology, 2017. 139(4): p. S65-S76.

[96] Sismanopoulos, N., et al., IL-9 induces VEGF secretion from human mast cells and IL-9/IL-9 receptor genes are overexpressed in atopic dermatitis. PLoS One, 2012. 7(3): p. e33271.

[97] Zhang, Y., H. Matsuo, and E. Morita, Increased production of vascular endothelial growth factor in the lesions of atopic dermatitis. Archives of dermatological research, 2006. 297(9): p. 425.

[98] Chen, L., et al., The progression of inflammation parallels the dermal angiogenesis in a keratin 14 IL-4-transgenic model of atopic dermatitis. Microcirculation, 2008. 15(1): p. 49-64.

[99] Liu, J., et al., IL-9 regulates allergen-specific Th1 responses in allergic contact dermatitis. Journal of Investigative Dermatology, 2014. 134(7): p. 1903-1911.

[100] Louahed, J., et al., Interleukin 9 promotes influx and local maturation of eosinophils. Blood, The Journal of the American Society of Hematology, 2001. 97(4): p. 1035-1042.

[101] Sarvetnick, N., Etiology of autoimmunity. Immunol Res, 2000. 21(2-3): p. 357-362.

[102] Jörg, S., et al., Environmental factors in autoimmune diseases and their role in multiple sclerosis. Cell Mol Life Sci, 2016. 73(24): p. 4611-4622.

[103] Smith, D.A. and D.R. Germolec, Introduction to immunology and autoimmunity. Environ Health Perspect, 1999. 107 Suppl 5(Suppl 5): p. 661-5.

[104] Rosenblum, M.D., K.A. Remedios, and A.K. Abbas, Mechanisms of human autoimmunity. J Clin Invest, 2015. 125(6): p. 2228-2233.

[105] Kaur, G., K. Mohindra, and S. Singla, Autoimmunity-Basics and link with periodontal disease. Autoimmun Rev, 2017. 16(1): p. 64-71.

[106] Li, J., et al., IL-9 and Th9 cells in health and diseases-From tolerance to immunopathology. Cytokine Growth Factor Rev, 2017. 37: p. 47-55.

[107] Pan, L.L., et al., IL-9-producing Th9 cells may participate in pathogenesis of Takayasu’s arteritis. Clin Rheumatol, 2016. 35(12): p. 3031-3036.

[108] Deng, Y., et al., Th9 cells and IL-9 in autoimmune disorders: Pathogenesis and
Therapeutic Potential of IL-9 in Allergic and Autoimmune Diseases
DOI: http://dx.doi.org/10.5772/intechopen.96266

therapeutic potentials. Hum Immunol, 2017. 78(2): p. 120-128.

[109] Weigmann, B. and M.F. Neurath, Th9 cells in inflammatory bowel diseases. Semin Immunopathol, 2017. 39(1): p. 89-95.

[110] Elyaman, W., et al., IL-9 induces differentiation of TH17 cells and enhances function of FoxP3+ natural regulatory T cells. Proc Natl Acad Sci U S A, 2009. 106(31): p. 12885-12890.

[111] Malik, S., V. Dardalhon, and A. Awasthi, Characterization of Th9 Cells in the Development of EAE and IBD. Methods Mol Biol, 2017. 1585: p. 201-216.

[112] Noelle, R.J. and E.C. Nowak, Cellular sources and immune functions of interleukin-9. Nat Rev Immunol, 2010. 10(10): p. 683-687.

[113] Nowak, E.C. and R.J. Noelle, Interleukin-9 as a T`helper type 17 cytokine. Immunology, 2010. 131(2): p. 169-173.

[114] Zhou, Y., et al., IL-9 promotes Th17 cell migration into the central nervous system via CC chemokine ligand-20 produced by astrocytes. J Immunol, 2011. 186(7): p. 4415-4421.

[115] Elyaman, W. and S.J. Khoury, Th9 cells in the pathogenesis of EAE and multiple sclerosis. Semin Immunopathol, 2017. 39(1): p. 79-87.

[116] Yoshimura, S., et al., IL-9 Controls Central Nervous System Autoimmunity by Suppressing GM-CSF Production. J Immunol, 2020. 204(3): p. 531-539.

[117] Li, H., et al., IL-9 is important for T-cell activation and differentiation in autoimmune inflammation of the central nervous system. Eur J Immunol, 2011. 41(8): p. 2197-2206.

[118] Jäger, A., et al., Th1, Th17, and Th9 effector cells induce experimental autoimmune encephalomyelitis with different pathological phenotypes. J Immunol, 2009. 183(11): p. 7169-7177.

[119] Ruocco, G., et al., T`helper 9 cells induced by plasmacytoid dendritic cells regulate interleukin-17 in multiple sclerosis. Clin Sci (Lond), 2015. 129(4): p. 291-303.

[120] Khaibullin, T., et al., Elevated Levels of Proinflammatory Cytokines in Cerebrospinal Fluid of Multiple Sclerosis Patients. Front Immunol, 2017. 8: p. 531.
Interleukins - The Immune and Non-Immune Systems’ Related Cytokines

[129] Karagiannis, F. and C. Wilhelm, *More Is Less: IL-9 in the Resolution of Inflammation*. Immunity, 2017. **47**(3): p. 403-405.

[130] Wu, X., *Innate Lymphocytes in Inflammatory Arthritis*. Front Immunol, 2020. **11**: p. 565275.

[131] Hughes-Austin, J.M., et al., *Multiple cytokines and chemokines are associated with rheumatoid arthritis-related autoimmunity in first-degree relatives without rheumatoid arthritis: Studies of the Aetiology of Rheumatoid Arthritis (SERA)*. Ann Rheum Dis, 2013. **72**(6): p. 901-907.

[132] Ouyang, H., et al., *Increased interleukin-9 and CD4+IL-9+ T cells in patients with systemic lupus erythematosus*. Mol Med Rep, 2013. **7**(3): p. 1031-1037.

[133] Leng, R.X., et al., *Potential roles of IL-9 in the pathogenesis of systemic lupus erythematosus*. Am J Clin Exp Immunol, 2012. **1**(1): p. 28-32.

[134] Dantas, A.T., et al., *Increased Serum Interleukin-9 Levels in Rheumatoid Arthritis and Systemic Lupus Erythematosus: Pathogenic Role or Just an Epiphenomenon?* Dis Markers, 2015. **2015**: p. 519638.

[135] Ouyang, H., et al., *[Abnormality and significance of interleukin-9 and CD4(+)interleukin-9(+) T-cells in peripheral blood of patients with systemic lupus erythematosus]*. Zhonghua Yi Xue Za Zhi, 2013. **93**(2): p. 99-103.

[136] Yang, J., et al., *Interleukin-9 Is Associated with Elevated Anti-Double-Stranded DNA Antibodies in Lupus-Prone Mice*. Mol Med, 2015. **21**(1): p. 364-370.

[137] Funderburg, N.T., et al., *Circulating CD4(+) and CD8(+) T cells are activated in inflammatory bowel disease and are associated with plasma markers of inflammation*. Immunology, 2013. **140**(1): p. 87-97.

[138] Wittner, M., et al., *Comparison of the integrin α4β7 expression pattern of memory T cell subsets in HIV infection and ulcerative colitis*. PLoS One, 2019. **14**(7): p. e0220008.

[139] Kurmaeva, E., et al., *T cell-associated α4β7 but not α4β1 integrin is required for the induction and perpetuation of chronic colitis*. Mucosal Immunol, 2014. **7**(6): p. 1354-1365.

[140] Jovani, M. and S. Danese, *Vedolizumab for the treatment of IBD: a selective therapeutic approach targeting pathogenic a4b7 cells*. Curr Drug Targets, 2013. **14**(12): p. 1433-1443.

[141] Malik, S. and A. Awasthi, *Transcriptional Control of Th9 Cells: Role of Foxo1 in Interleukin-9 Induction*. Front Immunol, 2018. **9**: p. 995.

[142] Yuan, A., et al., *IL-9 antibody injection suppresses the inflammation in colitis mice*. Biochem Biophys Res Commun, 2015. **468**(4): p. 921-926.

[143] de Heusch, M., et al., *IL-9 exerts biological function on antigen-experienced murine T cells and exacerbates colitis induced by adoptive transfer*. Eur J Immunol, 2020. **50**(7): p. 1034-1043.

[144] Gerlach, K., et al., *IL-9 regulates intestinal barrier function in experimental T cell-mediated colitis*. Tissue Barriers, 2015. **3**(1-2): p. e983777.

[145] Hufford, M.M. and M.H. Kaplan, *A gut reaction to IL-9*. Nat Immunol, 2014. **15**(7): p. 599-600.

[146] Matusiewicz, M., et al., *Systemic interleukin-9 in inflammatory bowel disease: Association with mucosal healing in ulcerative colitis*. World
[147] Gerlach, K., et al., *TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells*. Nat Immunol, 2014. 15(7): p. 676-686.

[148] Vyas, S.P. and R. Goswami, *A Decade of Th9 Cells: Role of Th9 Cells in Inflammatory Bowel Disease*. Front Immunol, 2018. 9: p. 1139.

[149] Popp, V., et al., *Rectal Delivery of a DNAzyme That Specifically Blocks the Transcription Factor GATA3 and Reduces Colitis in Mice*. Gastroenterology, 2017. 152(1): p. 176-192.e5.

[150] Vasanthakumar, R., et al., *Serum IL-9, IL-17, and TGF-β levels in subjects with diabetic kidney disease (CURES-134)*. Cytokine, 2015. 72(1): p. 109-112.

[151] Burrell, B.E., et al., *Regulatory T cell induction, migration, and function in transplantation*. J Immunol, 2012. 189(10): p. 4705-4711.

[152] Stanko, K., et al., *CD96 expression determines the inflammatory potential of IL-9-producing Th9 cells*. Proc Natl Acad Sci U S A, 2018. 115(13): p. E2940-e2949.

[153] Willrich, M.A., D.L. Murray, and M.R. Snyder, *Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases*. Transl Res, 2015. 165(2): p. 270-282.

[154] Antoniu, S.A., *MEDI-528, an anti-IL-9 humanized antibody for the treatment of asthma*. Curr Opin Mol Ther, 2010. 12(2): p. 233-239.

[155] White, B., et al., *Two first-in-human, open-label, phase I dose-escalation safety trials of MEDI-528, a monoclonal antibody against interleukin-9, in healthy adult volunteers*. Clin Ther, 2009. 31(4): p. 728-740.

[156] Kim, M.S., et al., *Effects of interleukin-9 blockade on chronic airway inflammation in murine asthma models*. Allergy Asthma Immunol Res, 2013. 5(4): p. 197-206.

[157] Klimka, A., et al., *A deletion mutant of Pseudomonas exotoxin-A fused to recombinant human interleukin-9 (rhIL-9-ETA) shows specific cytotoxicity against IL-9-receptor-expressing cell lines*. Cytokines Mol Ther, 1996. 2(3): p. 139-146.

[158] Flanagan, M.E., et al., *Discovery of CP-690,550: a potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection*. J Med Chem, 2010. 53(24): p. 8468-8484.

[159] Kvist-Hansen, A., P.R. Hansen, and L. Skov, *Systemic Treatment of Psoriasis with JAK Inhibitors: A Review*. Dermatol Ther (Heidelb), 2020. 10(1): p. 29-42.

[160] Imam, T., et al., *Effector T Helper Cell Subsets in Inflammatory Bowel Diseases*. Front Immunol, 2018. 9: p. 1212.

[161] NCT03532958, P.T.o.B.-i.P.W.M.t.S.A.A., 2019.

[162] Wang, T.T., et al., *IL-2 and IL-15 blockade by BNZ-1, an inhibitor of selective γ-chain cytokines, decreases leukemic T-cell viability*. Leukemia, 2019. 33(5): p. 1243-1255.

[163] Li, J., et al., *Toll-like receptors as therapeutic targets for autoimmune connective tissue diseases*. Pharmacology & Therapeutics, 2013. 138(3): p. 441-451.
[165] Murugaiyan, G., et al., IFN-$\gamma$ limits Th9-mediated autoimmune inflammation through dendritic cell modulation of IL-27. J Immunol, 2012. 189(11): p. 5277-5283.

[166] Green, D.S., et al., Production of a cellular product consisting of monocytes stimulated with Sylatron® (Peginterferon alfa-2b) and Actimmune® (Interferon gamma-1b) for human use. Journal of Translational Medicine, 2019. 17(1): p. 82.