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Review article

Regulatory role of T helper 9/interleukin-9: Transplantation view

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ABSTRACT

T helper 9 (Th9) cells, a subset of $CD4^+$ T helper cells, have emerged as a valuable target for immune cell therapy due to their potential to induce immunomodulation and tolerance. The Th9 cells mainly produce interleukin (IL)-9 and are known for their defensive effects against helminth infections, allergic and autoimmune responses, and tumor suppression. This paper explores the mechanisms involved in the generation and differentiation of Th9 cells, including the cytokines responsible for their polarization and stabilization, the transcription factors necessary for their differentiation, as well as the role of Th9 cells in inflammatory and autoimmune diseases, allergic reactions, and cancer immunotherapies. Recent research has shown that the differentiation of Th9 cells is coregulated by the transcription factors transforming growth factor β (TGF-β), IL-4, and PU.1, which are also known to secrete IL-10 and IL-21. Multiple cell types, such as T and B cells, mast cells, and airway epithelial cells, are influenced by IL-9 due to its pleiotropic effects.

1. Introduction

Special immunologic cytokines may impact $CD4^+$ T cells and initiate their differentiation. These signals enhance the progression of $CD4^+$ T helper subsets, which is accompanied by the release of specific cytokines that play a role in regulating inflammation and immunity [1]. One of the most challenging effector T cell subsets is T helper 9 (Th9) cells [1–3]. Naive $CD4^+$ T cells in the presence of transforming growth factor (TGF)-β1 and interleukin (IL)-4 differentiate into Th9 cells via T cell receptors (TCRs). The Th9 cells produce PU.1, nuclear factor (NF)-κB, interferon regulatory factor (IRF)4, signal transducer and activator of transcription (STAT) 6, basic leucine zipper ATF-like transcription factor (BATF), and GATA-binding protein (GATA3) [4]. Although specific conditions, such as inflammation, are the reasons for Th9 cell differentiation, the exact underlying mechanisms are still unclear. In addition, a specific lineage that defines factors related to IL-9 expression has not yet been identified [5].

IL-9 is a hallmark of Th9 cells and is a pleiotropic cytokine with different effects. The Th9 cells can produce both advantageous and harmful effects due to the induction pattern. Commonly, Th9 cells are effective in protecting against parasitic infections and display powerful anticancer immunity. Nevertheless, they can be detected during multiple sclerosis, ulcerative colitis, food allergies, allergic inflammation, asthma, and transplant rejection [1,6,7]. Moreover, few studies have confirmed the importance of Th9/IL-9 in organ transplant tolerance [8]. Therefore, this study aimed to investigate the biological and immunologic characteristics of IL-9, as well as its importance in inflammation. Research has also focused on the role of IL-9, TGF-β, and Th9 cells in transplantation complications,

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including their impact on the occurrence of acute rejection and enhancement in transplant patients.

2. Th9 cells: history, definition, production, and differentiation

The adaptive immune system plays a central role in producing specific responses to pathogens. Diverse effector T cells are differentiated from $CD4^+$ T cells through costimulatory molecules and stimulation via TCRs, as well as through the cytokines secreted by the innate immune cells [9]. The $CD4^+$ T cells might further differentiate into distinct subsets because of their different molecular and functional features. The main subsets of $CD4^+$ T cells are Th2, Th17, Th1, Th9, Th22, regulatory T (Treg) cells, and follicular Th (Tfh) cells. The suitable regulation of differentiation and functionality of $CD4^+$ T cells guarantees the production of efficient immune responses. Therefore, the improper function of these cells might cause inadequate clearance of pathogens and result in autoimmunity and inflammatory diseases [10,11].

2.1. Th9 history and definition

The characteristic cytokines responsible for the polarization and stabilization of the phenotype of $CD4^+$ T helper cells, known as Th1 and Th2 cells, were initially identified in earlier research. Among these early discoveries was the identification of the T cell growth factor P40, which was produced by a T cell clone and was distinguished from the previously recognized growth factors IL-2 and IL-4. Subsequently, it was demonstrated that the growth factor P40, also known as T cell growth factor III (TCGFIII), was indeed identical to another factor [12,13]. Furthermore, the mast cell growth-promoting activity factor (MEA) was discovered and found to be identical to the previously identified P40 growth factor. These findings ultimately led to the adoption of the currently accepted name for this cytokine, IL-9 [14].

Th9 cells are a subset of $CD4^+$ T cells discovered in 2008 and defined by the release of IL-9 [15]. IL-9 can stimulate the secretion of immunoglobulin (Ig)E via B cells during allergic inflammation, which results in the accumulation and activation of mast cells, enhances eosinophil chemotaxis, and induces the production of mucin in lung epithelial cells [16]. Therefore, the induction of these cells with Th9 cell-derived IL-21 can induce interferon (IFN)-γ [17], which has important effects on autoimmune diseases, cancers, allergic airways, and inflammatory bowel disease [18] (Fig. 1).

Moreover, IL-9-generating cells can increase inflammation, which is an unavoidable feature of diseases. Finally, Th9 cells can affect eosinophils and mediate cytotoxic and inflammatory reactions in allergic inflammation [1,19]. As a result, IL-9 acts in immune pathologies and protective immunity, which makes it a pleiotropic cytokine that, based on disease conditions, has multiple functional

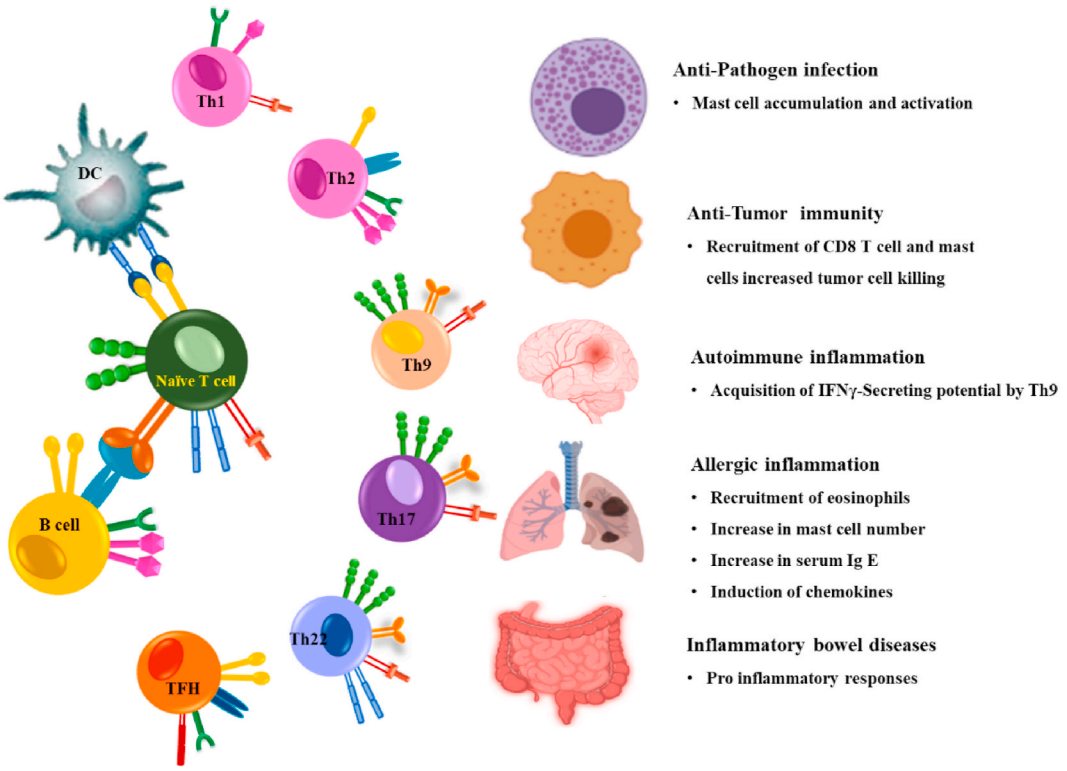

Fig. 1. Production of Th9 cells and their effect on immunopathology and immunity: naive $CD4^+$ T cells differentiate into Th9 cells and produce pleiotropic IL-9 cytokine that can activate different cell types during inflammatory reactions.

features [20]. Overall, IL-9 seems to function as a growth factor for T cells, an enhancer of IgE production from B cells, an inducer of mucus production by epithelial cells, and a promoter of the proliferation and differentiation of mast cells [21].

2.2. Th9 production

The idea that Th2 cells are the main source of IL-9 was challenged when it was discovered that naive $CD4^+$ T cells exposed to TGF-β and IL-4 highly expressed IL-9 without IL-4 expression. This finding indicates the existence of a separate group of T cells specifically focused on producing IL-9 [22–27]. Later, the development of a mouse strain with a specific reporter for IL-9 allowed for the examination of cell types that produce IL-9 *in vivo*. In this model of lung inflammation, IL-9 is generated by innate lymphoid cells (ILCs) rather than T cells [27,28]. The production of IL-9 by ILCs was temporary but played a crucial role in sustaining IL-5 and IL-13 in these cells. These ILCs, known as type 2 cytokine-producing ILC2s, were initially identified as a subset of non-B/non-T cells that produce IL-5 and IL-13 [29–33]. It was subsequently revealed to participate in helminth infections via IL-13 expression [34–37]. Furthermore, these cells play significant roles in influenza infection [38,39] and airway hyperactivity in both mice and humans [40,41].

2.3. Mechanism of Th9 cell differentiation

A regulatory network of transcription factors is essential for Th9 cell differentiation, which results in the release of different transcription regulators [9,25,26,42–46] (Fig. 2). The transcription, inflammatory, and differentiation programs of Th9 cells are not well known. In addition, a specific lineage associated with IL-9 expression has not been identified [5]. In 2008, it was discovered that the combination of TGF-β and IL-4 predominantly induced T-cell (Foxp3−, IL-9+, and IL-10+) production, and these cells were classified as a novel subset of $CD4^+$ Th cells known as Th9 cells [22,23]. Th9 cell differentiation is a complex process that involves various cytokines, signaling pathways, and transcription factors. Some of the key factors and mechanisms related to the differentiation of Th9 cells include the following:

- TCR signaling pathway: the TCR signaling pathway has a crucial function in the generation of Th9 cells and the secretion of IL-9 by producing the nuclear factor of activated T cells, NF-κβ, and IRF4 [47].
- IL-4, STAT6, and GATA-3: previous studies have suggested that stimulating $CD4^+$ T cells with TGF-β and IL-4, which bind to cellular receptors, such as Toll-like receptor 2, can promote the differentiation of Th9 cells. This process involves the activation of IL-4, STAT6, and GATA-3 [48]. Similarly, TGF-β signals through Smad3, Smad2, and Smad4 induce Th9 differentiation, and a deficiency in these molecules can lead to a decrease in the induction of Th9 cells [49]. TGF-β promotes Th9 differentiation by inhibiting T-bet (a Th1-specific transcription factor) and inducing PU.1 [25,50]. Similar to that of Th2 cells, the differentiation of Th9 cells is dependent on the expression of IL-4, STAT6, and GATA-3, but Th9 cells exhibit distinct patterns of cytokine expression during development [47,48]. IL-4 plays a crucial role in Th9 cell differentiation by activating STAT6, which then binds directly to the IL-9 locus. Conversely, TGF-β induces the expression of Forkhead box (Fox) p3, which can be suppressed by IL-4-induced p-STAT6, thereby inhibiting the differentiation of Th9 cells. Therefore, IL-4 and TGF-β work together to regulate the differentiation of Th9 cells [47].
- IL-33 and IL-36γ: IL-33 promotes the development of Th9 cells independent of IL-4 signaling, and inhibiting IL-33 could hinder Th9 cell development. In addition, IL-36γ, a cytokine in the IL-1 family, facilitates the differentiation of Th9 cells [51].

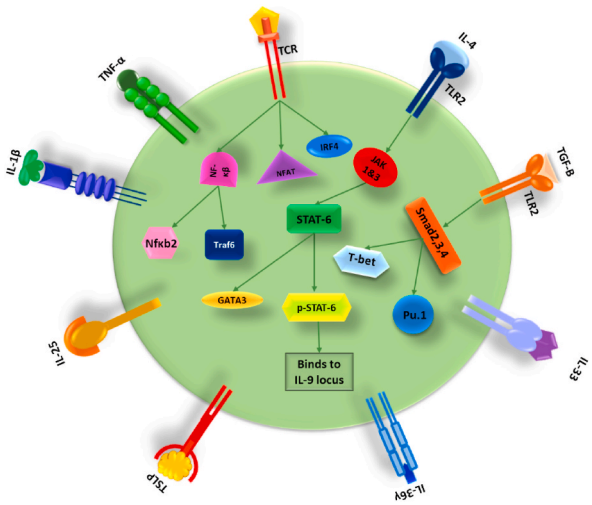

Fig. 2. Different cytokines and transcription factors are involved in the differentiation of $CD4^+$ T cells into Th9 cells.

- Tumor necrosis factor-alpha (TNF-α): TNF-α boosts Th9 cell differentiation through the NF-κB pathway, leading to the increased expression of Nfkb2 and Traf6 in T cells. Moreover, the introduction of TNF-α during Th9 cell differentiation enhances T cell survival and proliferation [52].
- Transcription factors: Numerous transcription factors, including PU.1, IRF4, and members of the STAT family, such as STAT1/5/6, play a role in regulating the differentiation of Th9 cells [52].
- Other cytokines: Studies on the underlying involved mechanisms have shown that other cytokines, such as IL-1β, TSLP, and IL-25, play critical roles in Th9 cell differentiation [24,53,54].

2.4. IL-9 cytokine: a specific cytokine for Th9 cells

Primarily, IL-9 was defined as a growth factor for T cells and mast cells and was called P40 (due to its molecular weight). Later, due to the cloning and sequencing of P40 (a 14 kDa peptide leader sequence that encodes a 144-amino acid protein), its structure was documented to be completely different from that of T cell growth factors. Finally, based on its influence on lymphoid and myeloid cells, it was renamed IL-9 [55]. IL-9 is located at the chromosomal region 5q31–35 within the Th2 cytokine cluster and belongs to the four-helix bundle cytokine family [56]. Through interactions between IL-9 and its heterodimeric receptor, which is composed of IL-9Rα and a common γ chain (γC), this cytokine exerts its biological effects. The γC chain is shared by IL-4, IL-7, IL-2, and IL-15 receptors, but the IL9Rα chain is specific for the IL-9 receptor, which is generated in both soluble and membrane-bound forms [57] (Fig. 3).

In addition to IL-9 cytokine, other cytokines, namely IL-13, IL-21, and IL-10, can be secreted from Th9 cells [9]. Moreover, IL-9 can also be produced by other Th subsets, such as Treg, Th17, and Th2 cells, in which it is expressed at lower levels than in Th9 cells [25]. However, the specific function of IL-9 generated by Tregs is not fully understood and requires further examination. In general, IL-9 produced by different T helper cell subsets, including Th9, Th17, and Th2 cells, plays distinct roles in various inflammatory diseases and immune responses, and its involvement in Tregs is still under investigation. The generation of IL-9 by Th17 cells is positively influenced by the combination of TGF-β with IL-1β, IL-6, IL-21, or IL-23, while it is negatively regulated by IL-23 alone [58]. IL-9 derived from Th17 cells can modify the gene expression profile of tumor cells and facilitate tumor growth [20]. In addition, IL-9 produced by Th2 cells has been demonstrated to contribute to the pathogenesis of allergic diseases, such as asthma and atopic dermatitis [59].

Innate lymphoid and mast cells can also produce IL-9, but there is little data on the exact mechanisms of interactions among these cells during different biological conditions and diseases [60,61]. IL-9, a mediator of inflammatory responses, is secreted by neutrophils, T cells, B cells, and mast cells [62,63]. It is similar to IL-27 in its pro- and anti-inflammatory effects. Some factors, including tissue microenvironments and cytokine milieu, can change the extent of IL-9 activity [64,65] (Fig. 4).

2.5. Il-9 gene: transcriptional regulation

The *IL-9* locus is connected to the Th2 cytokines, IL-5, IL-4, and IL-13 loci. The degree of chromatin acetylation in the *Il-9* promoter is markedly greater in Th9 cells than in other Th cells. Moreover, the level of H3K27 (a repressive chromatin modifier) trimethylated at the *Il-9* promoter is lower in Th9 cells than in the control cells. Three conserved noncoding sequences (CNS) are present near the IL-9 locus. The CNS1 region is the site at which most transcription factors bind (Fig. 5). The sequence of CNS2 has been conserved in the genomes of humans and mice [25,66].

Previously, it was shown that when naive $CD4^+$ T-cell activation is promoted by IL-2, IL-4, and TGF-β, these naive cells start producing IL-9. However, among these three cytokines, TGF-β and IL-2 are the most effective at stimulating the production of IL-9 [67]. Furthermore, TGF-β is necessary for inducing the expression of PU.1, which positively and negatively regulates the formation of Th9 and Th2 cells, respectively. In Th9 cells, PU.1 binds to the promoter of the *Il-9* gene to promote Th9 cell polarization [68]. The PU.1 and Smad proteins play critical roles in activating other Th9 genes and suppressing the production of Th2 cells [25,43,49,69]. Therefore, in differentiated Th9 cells, PU.1 activation inhibits the production of Th2 cells, leading to the significantly increased expression of IL-9 [70–73]. This overexpression boosts IL-9 generation, which is coupled with a drastic decrease in Th2 cytokine production. Molecularly, PU.1 restricts the ability of IRF-4 and GATA3 to induce Th2 cytokine efflux and decrease the generation of IL-4 in Th2 cells [50].

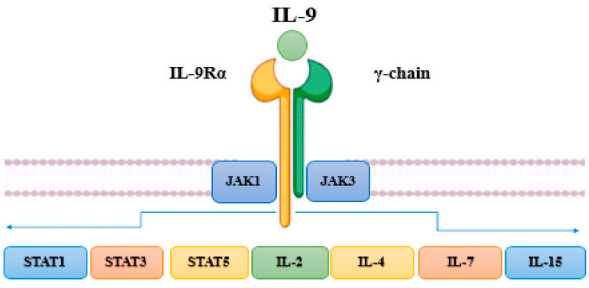

Fig. 3. In the signaling complex of the IL-9 receptor, IL-9 operates on its heterodimeric receptor, which is composed of γ-chain and IL-9 receptor α chain.

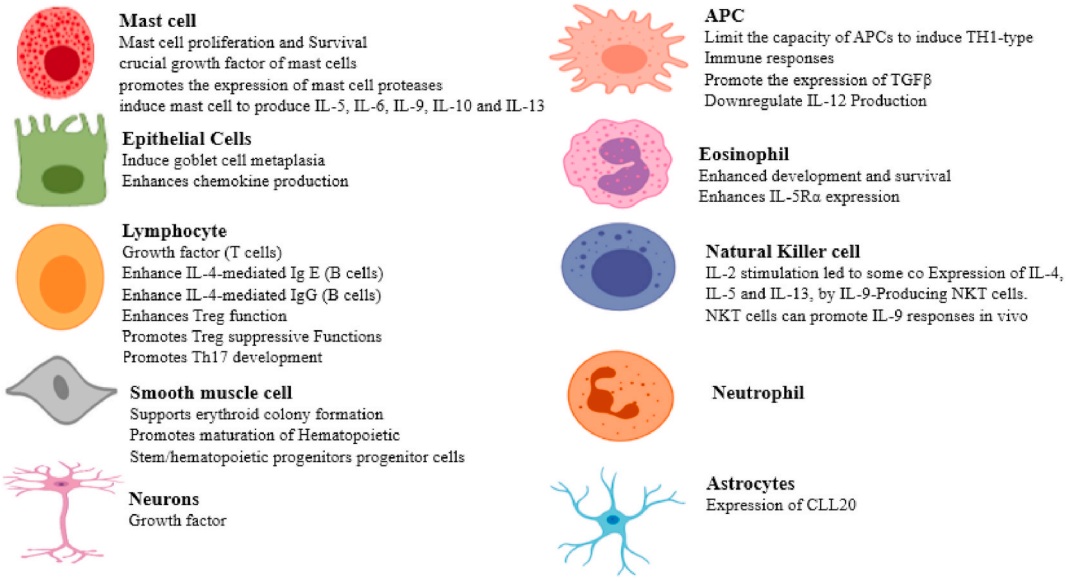

Fig. 4. Different cell types can produce IL-9; IL-9 is a pleiotropic cytokine that has multiple effects and is produced by diverse cell types and plays important roles in inflammation and immunity.

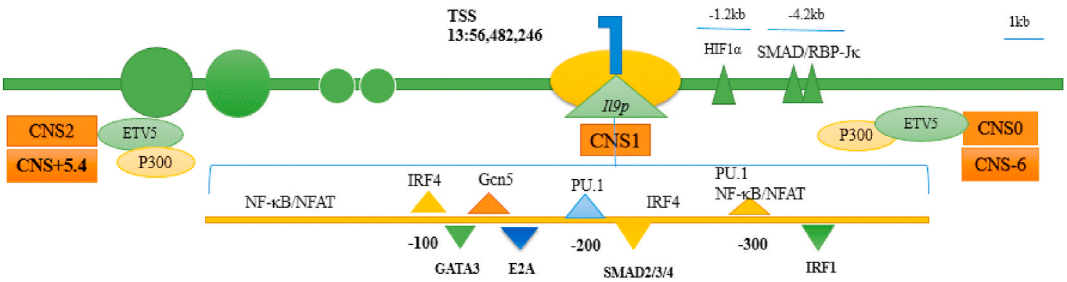

Fig. 5. Regulation of the Il-9 gene: three elements near the *Il-9* gene.

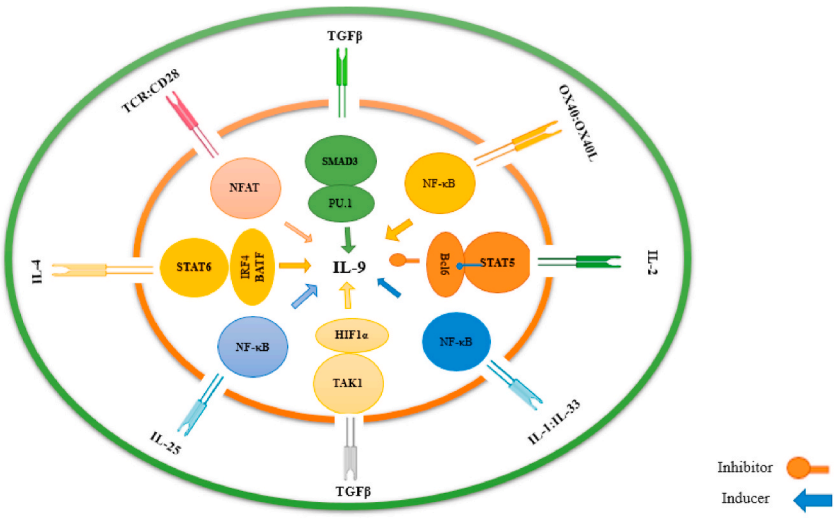

Fig. 6. The transcriptional diagram of Th9 cells indicates that the increase in T cells releasing IL-9 is influenced by the engagement of a wide range of surface receptors and cytokines. The roles of different cytokines and costimulatory molecules in the differentiation and function of Th9 cells are summarized in this figure.

STAT6 (known as an IL-9 suppressor) is exclusively important for cell polarization because it helps suppress the TGF-β-mediated expression of FOX P3 [42]. Foxo1 directly binds to the *Il-9* promoter and induces the expression of IL-9 in iTregs, Th17 cells, and Th2 cells [74,75]. Both IRF4 and BATF are the mediators of the active production of IL-9, and deficiency of each of these two molecules results in the inability of cells to efficiently produce IL-9 [26,43,76]. BATF deficiency leads to a noticeable defect in the expression of genes related to Th9 cells [43].

The pathway through which NF-κB is induced via TNF receptor superfamily units is strongly regulated by IL-9 expression through a different mechanism. OX40, which is the first TNF receptor superfamily member, and antigen-presenting cells expressing OX40L or antibodies against OX40 are powerful inducers of IL-9 in Th9 cell cultures. The activity of OX40 begins with the binding of the RelB-p52 heterodimer to the promoter of *Il-9* and initiating the TRAF6/NF-κB RelB-p52 pathway. The OX40 activation of IL-9 production is responsible for STAT6 but not PU.1 [77] (Fig. 6).

3. Th9/IL-9 function at the time of inflammation

Th9 cells enhance allergic inflammation partly through activating mast cells but directly affecting tissue-resident cells. It has remained unclear whether the function of Th9 cells contributes to inflammatory disease or pathogen immunity [78]. Additionally, the pattern in which Th9 cells interact with other Th cell lineages during recruitment to the site of inflammation has not been fully elucidated [1]. Moreover, several studies have detected the role of Th9 cells in proinflammatory responses during allergic inflammation and autoimmune diseases [1,79].

Th9 cells participate in the development of viral diseases, such as hepatitis B virus (HBV) infection and hepatic fibrosis. In addition, antiviral therapy and Th9 cell levels are limited during viral disease treatment, especially during hepatitis C virus (HCV) therapy. Nevertheless, it seems that Th9 cells in HCV-infected patients are directly related to disease prognosis and development [80]. The number of circulating Th9 cells was greater in the control patients than in the chronic HBV patients. Furthermore, Th9 cell percentages negatively correlated with HBV-DNA loads [81]. Th9 cells are also detected during inflammation induction and subsequently exacerbate inflammatory diseases, such as allergic asthma, multiple sclerosis, rheumatoid arthritis, ulcerative colitis, systemic lupus erythematosus, infections caused by various pathogens [18,82–84], and autoimmune [85] and inflammatory diseases [86–88].

Th9 cells can induce immune responses to either develop autoimmunity/inflammation or tolerance, depending on the microenvironment (Fig. 7). Research has shown that Th9 cells were present in inflammatory bowel disease (IBD) [83], melanoma skin lesions [89–91], the lamina propria in ulcerative colitis patients, and the synovium of RA patients [92]. Similarly, an elevated level of Th9-secreted cytokine IL-9 was reported in the plasma and carotid plaques of patients with carotid and coronary atherosclerosis [93].

In certain circumstances, targeting Th9 cells or their products may offer therapeutic advantages. Nevertheless, the role of Th9 cells under specific conditions may prove to be therapeutically beneficial [94]. Inhibitors of Th9/IL-9 have the potential to alleviate inflammation in some contexts. For example, in allergic diseases, such as asthma and atopic dermatitis, where IL-9 is produced by Th2 cells, it has been demonstrated to contribute to pathogenesis [95]. Regarding autoimmune diseases, Th9 cells have been implicated in certain conditions, such as experimental autoimmune encephalomyelitis, and targeting them may offer a new approach to treating these diseases [94]. In addition, the role of Th9 cells remains to be determined in chronic inflammation, but targeting them may be therapeutically beneficial in some cases, such as cancer therapies [94].

4. Th9 cell function during transplantation

Graft loss is a common occurrence, and prolonged immune system suppression aimed at inducing tolerance may ultimately result in

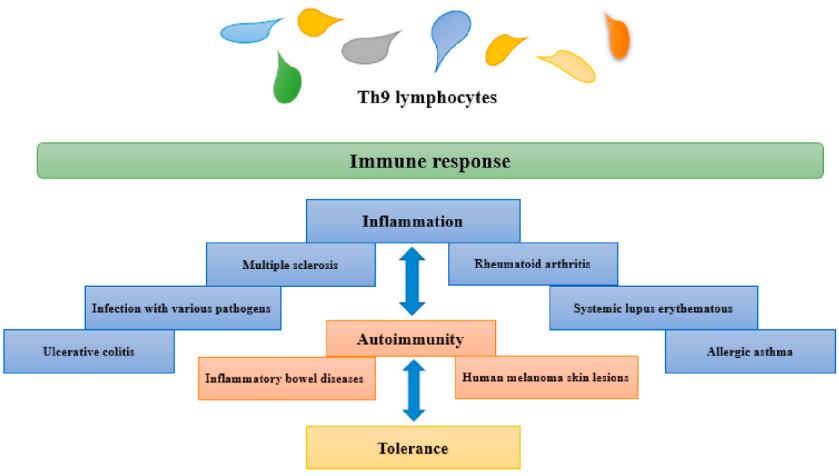

Fig. 7. Role of Th9 lymphocytes in immune responses: based on the native microenvironment, Th9 lymphocytes induce autoimmunity/inflammation or tolerance.

significant negative consequences, such as metabolic disorders, increased vulnerability to infectious diseases, and several malignancies [96]. Immune cell therapy, in which Tregs (a subset of immune cells) are specifically targeted, has emerged as a potentially effective approach for inducing tolerance and has shown promising results in research. However, its routine implementation as a treatment has not been widely accepted due to technical challenges, the risk of nonspecific immune suppression, and the inherent plasticity of T cells, which can transit between Treg and Th17 subsets [97].

Nonetheless, there is a keen interest in investigating and utilizing alternative immune cells that possess similar immunomodulatory properties but pose a lower risk of inducing immunodeficiency. Th9 cells, which demonstrate potential tolerogenic qualities, could be regarded as a viable option for T-cell therapy aimed at inducing tolerance. However, it is crucial to gain a comprehensive understanding of the specific roles of these genes in different transplant scenarios, particularly through further research [98]. Given the proinflammatory characteristics associated with mast cells and Th9 cells, it is necessary to delve deeper into the specific issue that allograft tolerance is achieved by IL-9, which requires additional explanation [20].

4.1. Th9 role in solid organ transplants

Limited evidence suggests that IL-9 can promote immune tolerance. For instance, in skin allograft transplantation, IL-9 appears to contribute to the development of a tolerant environment [99]. In other scenarios, the promotion of Th9 cells could have therapeutic benefits, and IL-9 has been associated with biological functions in T-regulatory cells *in vivo*. A study investigating tolerance during allogeneic skin transplantation reported that IL-9 was secreted by Treg cells [100]. In a mouse model of skin transplantation, a research group confirmed that tolerant grafts exhibited upregulated mast cell IL-9 production, which resulted in enhanced Foxp3+ Treg suppressive activities and allograft tolerance. Consequently, mast cell-deficient models demonstrate resistance to induced tolerance, and blocking IL-9 results in faster graft rejection. Although the functionality of Th9 cells has not been directly examined in existing studies, it appears that IL-9 has a crucial role in the establishment of donor-specific transplant tolerance via Tregs [82,100].

However, subsequent studies did not confirm the direct effect of IL-9 on promoting the survival or proliferation of Foxp3+ Treg cells. Instead, it seems that IL-9 simplifies the suppressive effects of Tregs and efficiently prevents immune responses against allografts [82,100]. Gorczynski et al. revealed the suppressive effects of the interaction between CD200 (a transmembrane type Ia glycoprotein) and its receptor on alloreactivity in skin grafts. This interaction causes the infiltration of mast cells and the induction of Tregs. However, when mouse skin allografts were treated with anti-IL-9, the mast cell frequency decreased, and CD200/CD200R1 tolerance reduced. These findings provide additional evidence for the crucial role of IL-9 secreted by Tregs in mast cell recruitment and the induction of tolerance [101].

In the context of skin transplantation, Treg cells have been found to play a more significant role than Th9 cells in producing IL-9. However, it remains unclear whether Tregs that produce IL-9 play a role in promoting tolerance at other transplant locations [102]. It appears that IL-9 and TGF-β mediate immune tolerance by enhancing the function of Treg cells after transplantation [79]. Research has demonstrated that the expression of IL-9 by Treg cells can promote graft tolerance by recruiting immunosuppressive mast cells. IL-9 has been identified as a critical factor in regulating mast cell recruitment and effector cell functions [99]. The interaction between Treg cells and mast cells via IL-9 and TGF-β production forms a positive feedback system that facilitates cross-talk between these cells [94]. This interaction is involved in inducing immunosuppression in long-lived allografts. Inhibition of IL-9 signaling can decrease the expression of Treg-related genes, mast cell-related genes, and monocyte-related genes in tumor-draining lymph nodes and delay tumor growth in mice [58].

IL-9 is a potent growth factor in T-cell lines and mast cells, and its role in allergic and asthmatic diseases has been extensively studied in recent years. Signal transduction in Th9 cells is regulated by various factors, including the transcription factors STAT6, IRF4, and PU.1. However, IRF4 plays a crucial role in the pathogenesis of IBD. The roles of IL-9 and Th9 transcription factors IRF4 and PU.1 in ulcerative colitis were investigated, and the results suggested that IL-9 is involved primarily in the pathogenesis of ulcerative colitis [103]. Currently, no specific evidence exists on the involvement of Th9 cells in intestinal transplantation, but a deficiency in IL-9 diminishes acute and chronic colitis. Studies have shown that T cells from mice lacking PU.1 are protected against intestinal inflammation, and the use of anti-IL-9 antibodies can alleviate experimental colitis. Furthermore, patients with ulcerative colitis exhibit an increased number of T lymphocytes expressing PU.1 and IL-9 [104].

Studies have demonstrated the involvement of some cytokines, such as IL-9, IL-4, and IL-5, in the immune response of mice deficient in $CD8^+$ T cells. In a heart allograft model, major histocompatibility complex class II from IL-9 transgenic donors (CD8-deficient mice) was shown to cause acute rejection [105]. Furthermore, in an IL-9-deficient model, allograft rejection increased, while enhanced allograft rejection was observed in an IL-9-overexpressing model [106].

Chang Li et al. conducted a study on human renal transplant biopsies to investigate the gene expression of IL-9 in individuals suspicious of rejection. Unlike other cytokines that share common γ chain receptors, including IL-2, IL-4, IL-7, and IL-15, the gene expression of IL-9 was not detected in the allograft tissue. Therefore, it was concluded that IL-9 is not a major T cell growth factor involved in allograft rejection development despite its receptor complex containing the common γc chain. These findings challenge the notion that IL-9 directly participates in renal allograft rejection as it was notably absent despite the robust expression of *Il-2*, *Il-4*, *Il-7*, and *Il-15* genes during acute allograft rejection [107]. Similarly, another study used a rat renal transplant model to assess the gene expression of γ chain signaling cytokines and their receptors on post-transplant days 3, 5, and 7. Remarkably, IL-9 was detected in normal kidneys, but its expression was almost negligible during rejection [108].

Deveris et al. proposed that different conditions of organ donors can lead to varying responses to reperfusion. In particular, the reperfusion of kidneys from brain-dead donors was found to trigger the immediate production of inflammatory cytokines, including granulocyte-colony stimulating factor, IL-6, IL-9, IL-16, and monocyte chemoattractant protein-1 [109]. In another research, the serum

level of IL-9 was calculated in stable liver transplant recipients, and its impact on the dosage of immunosuppressive agents was investigated. The concentration of IL-9 was significantly higher in liver transplant recipients than in healthy individuals, and elevated levels of IL-9 in the serum were associated with a decreased immunosuppressive drug burden [110]. The involvement of Th9 cells in allograft rejection has not been fully elucidated. While there is an association between IL-9 and transplant rejection, it is noteworthy that various other cell types can also produce this cytokine [7].

4.2. Role of Th9 cells in stem cell transplantation

The exact role of Th9 cells in the development of graft-versus-host disease (GVHD) has yet to be elucidated [100]. In a study comparing stable hematopoietic stem cell transplantation (HSCT) recipients with acute GVHD during the first few months after transplantation, elevated levels of Th9 cells and IL-9 were observed in stable recipients compared to those with acute GVHD. The study also revealed a slight recovery of Th9 cells and IL-9 production following HSCT, with levels beginning to normalize on day 60 and reaching a normal value on day 90 in contrast to Th1 and Th2 cells and their associated cytokines [79]. Another investigation revealed significant alterations in the gene expression of epidermal growth factor receptor, IL-6, IL-9, and nicotinamide phosphoribosyl transferase in GVHD patients, indicating that these genes could be diagnostic biomarkers for assessing ocular surface status in patients with GVHD [111].

Like other effector $CD4^+$ T cell subsets, Th9 cells play crucial roles in host defense and immunopathology. However, unlike those of other $CD4^+$ T cell subsets, our knowledge of the specific cytokines, lineage-specific transcription factors, and cell surface markers associated with Th9 cells, as well as the molecular and cellular mechanisms underlying the development and differentiation of human Th9 cells, is limited [112]. In summary, the influence of Th9 cells and IL-9 on allograft outcome varies according to the transplanted tissue type, while beneficial, neutral, or detrimental effects are observed. Overall, the results suggest that the immunoregulatory effects of Th9 cells and IL-9 outweigh their pro-inflammatory effects, suggesting that these cells could be possible targets for inducing tolerance after transplantation. However, supplementary studies are necessary to obtain sufficient data supporting the potential benefits of these materials or to identify any limitations for their clinical application [98].

4.3. Interconnection between TGF-β and Th9 cells during transplantation

TGF-β can impact both the immunogenic and immunoregulatory functions of $CD4^+$ T cells. In terms of immunoregulation, TGF-β can promptly suppress the activation of Th9 cells, hinder cytokine production, and enhance the expansion of inducible Tregs. On the effector side, TGF-β promotes the differentiation of Th9 and Th17 cells. To optimize transplantation outcomes, it is crucial to develop approaches that enhance the immunoregulatory effects of TGF-β and simultaneously attenuate the immunogenic effects [113]. Studies have shown elevated levels of TGF-β and its receptor in the bloodstream of transplanted patients who have achieved normal graft function after discontinuing immunosuppressive drug treatment [114]. This finding suggested that TGF-β is critical for successful or unsuccessful transplantation [115,116]. The involvement of TGF-β and its signaling pathway in immune system regulation implies that modifying its activity in transplanted patients may lead to different outcomes based on individual circumstances (Fig. 8). These findings underscore the significance of TGF-β in either promoting or hindering graft tolerance. However, the systemic inhibition of the TGF-β axis is not the ultimate solution for addressing post-transplantation issues [113].

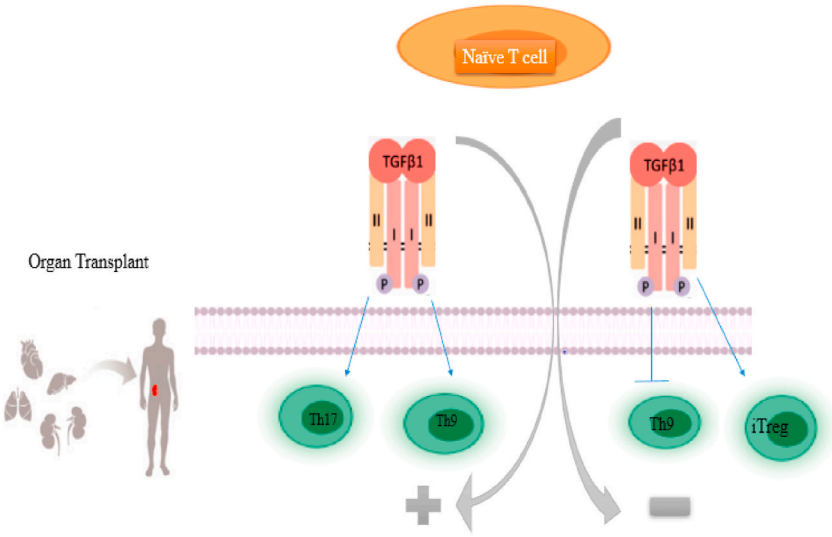

Fig. 8. Interconnection between TGF-β and Th9 cells during transplantation: TGF-β and its signaling pathway are effective in regulating the immune system and are involved in the failure or success of transplantation.

5. Conclusion

The potential regulatory role of the IL-9 pathway in inflammation, transplant complications, and tolerance situations might be accepted as a possible strategy for treating various types of inflammatory diseases. The cytokine IL-9, which is secreted from Th9 cells, is a multifunctional cytokine that can regulate both positive and negative outcomes post-transplantation. Therefore, Th9/IL-9-targeted therapies can be considered immunomodulatory immunotherapy methods for treating transplant complications and increasing transplant success. It is suggested that TGF-β could behave as a potential target for modulating immunity in transplant recipients under various conditions and can cause the differentiation of T cells, such as Th9 and Th17 cells, which have restricted capacity to coexpress other proinflammatory cytokines. TGF-β in combination with IL-23 acts as a proinflammatory moderator by regulating the pathway of Th17 development. Therefore, eliminating IL-23 from the signaling pathway can result in the decreased expression of IL-9 and other proinflammatory cytokines secreted by Th9 cells.

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Data availability statement

No data were used for the research described in this article.

CRediT authorship contribution statement

Azadeh Roostaee: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Ramin Yaghobi:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Afsoon Afshari:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Mojtaba Jafarinia:** Writing – review & editing, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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