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Cellular sources and immune functions of interleukin-9

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Abstract

Interleukin-9 (IL-9) has attracted renewed interest owing to the identification of its expression by multiple T helper (T_H) cell subsets, including T_H2 cells, T_H9 cells, T_H17 cells and regulatory T (T_{Reg}) cells. Here, we provide a broad overview of the conditions that are required for cells to produce IL-9 and describe the cellular targets and nature of the immune responses that are induced by IL-9.

Interleukin-9 (IL-9) was originally identified in mice as a T cell growth factor and is a member of the common γ-chain-receptor cytokine family, with other members including IL-2, IL-4, IL-7, IL-15 and IL-21. The *IL9* gene loci of both humans and mice have a similar organization, consisting of five exons, and share a 55% amino acid homology at the protein level. The IL-9 receptor consists of the cytokine-specific IL-9 receptor α-chain (IL-9Rα) and the γ-chain[1]. IL-9-induced receptor activation promotes the cross-phosphorylation of Janus kinase 1 (JAK1) and JAK3. This cross-phosphorylation leads to the downstream activation of signal transducer and activator of transcription (STAT) complexes, specifically STAT1 homodimers, STAT5 homodimers and STAT1–STAT3 heterodimers[2–4] (FIG. 1). Although the contribution of IL-9 to the activation of these pathways in primary cells has not been fully elucidated, it may be of relevance *in vivo*.

Here, we summarize the cellular sources of IL-9, focusing principally on T cells. We also describe the main targets of IL-9 *in vivo* and discuss the downstream effects of IL-9-induced signalling on leukocyte function and overall immunity.

Cellular sources of IL-9

T_H2 cells

IL-9 was first linked to T helper 2 (T_H2) cells, which express IL-4, IL-5 and IL-13, following the report that levels of IL-9 expression were high in the T_H2-prone BALB/c mouse strain but low in the T_H1-prone C57BL/6 mouse strain during infection with *Leishmania major*. The same study showed that T cells were the main producers of IL-9 *in*

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vivo and that the levels of IL-9 expression correlated with the expansion of T_H2 cell populations. Futhermore, blockade of IL-4, which is a crucial mediator of T_H2 cell differentiation, could suppress IL-9 production[5]. Owing to the recent characterization of T_H9 cells (which express IL-9 but not the key signature cytokines of other T_H cell subsets, such as IL-4 (T_H2 cells), interferon-γ (IFNγ) (T_H1 cells) and IL-17 (T_H17 cells)) it is now unclear whether the correlation between IL-9 levels and T_H2 cell numbers is due to the direct production of this cytokine by T_H2 cells or whether T_H2-cell derived IL-4 supports the development of T_H9 cells from either naive $CD4^+$ T cells or T_H2 cells. Currently, only one group has reported low but detectable co-expression of IL-4 and IL-9 during *in vitro* differentiation of T_H2 cells[6]. Surprisingly, to date there have been no reports addressing whether these cytokines are co-expressed by effector $CD4^+$ T cell populations that differentiate *in vivo* during a T_H2-type immune response.

T_H9 cells

T_H9 cells are a recently described subset of T_H cells that express IL-9 but not other T_H cell lineage-specific cytokines or transcription factors[7,8] (FIG. 2). The most definitive work that supports the existence and functional relevance of T_H9 cells *in vivo* has come from the study of mice with a T cell-specific deletion of the transcription factor PU.1. These mice do not develop IL-9-dependent allergic inflammation in the lungs and have only low levels of IL-9 in bronchoalveolar lavage fluid, but still develop normal numbers of T_H2 cells. This finding indicates that, at least in this setting, T_H9 cells are the main T cell subset expressing IL-9 and that PU.1 is crucial for their development[6]. Another transcription factor that is associated with T_H9 cell development both *in vitro* and *in vivo* is interferon-regulatory factor 4 (IRF4)[9], which also regulates T_H2 and T_H17 cell differentiation[10–12]. Characterization of T_H9 cells *in vitro* has shown that their generation is dependent on transforming growth factor-β (TGFβ) and IL-4 (REF. 13). The addition of IL-25 along with these two cytokines can further enhance IL-9 production by T cells *in vitro*. T_H9 cells from IL-25-deficient mice have decreased IL-9 expression and reduced airway inflammation in a model of asthma[14]. There have also been conflicting reports that various cytokines, such as IL-1β, IL-6, IL-10, IL-12, IL-21, IFNα and IFNβ, may have an additive effect in promoting T_H9 cell generation in the presence of TGFβ and IL-4 *in vitro*[15,16]. In addition, culturing human memory T cells in the presence of TGFβ (alone or in combination with IL-1β, IL-4, IL-6, IL-12, IL-21 or IL-23) was shown to promote IL-9 production with or without co-expression of IFNγ and IL-17 (REFS 16,17).

T_H17 cells

There have also been reports that T_H17 cells can produce IL-9. *In vivo* differentiated T_H17 cells, which were identified by their expression of either IL-17F or the T_H17-associated transcription factor retinoic acid receptor-related orphan receptor-γt (RORγt), could produce IL-9 after re-stimulation with phorbol 12-myristate 13-acetate and ionomycin[18]. In addition, some groups also reported co-expression of IL-17 and IL-9 during T_H17 cell generation *in vitro*[18,19]. However, IL-23, which is important for the expansion of T_H17 cells after their initial differentiation, has been shown to inhibit the expression of IL-9 by T cells in mice[19]; therefore, this finding suggests that the expression of IL-9 by T_H17 cells could be transient and may decrease over time.

Human T_H17 cells have also been shown to produce IL-9 *in vitro*. After multiple rounds of differentiation *in vitro*, some T_H17 cells acquire expression of IL-9. In memory T cells, T_H17-promoting cytokines, such as IL-1β and IL-21, can also enhance the co-production of IL-9 and IL-17. However, these cultures also contain IL-9-producing T cells that do not co-express IL-17 and are presumably bona fide T_H9 cells[16].

T_{Reg} cells

There have been contradictory reports regarding the expression of IL-9 by T_{Reg} cells. Data from mice have shown that co-expression of forkhead box P3 (FOXP3) and IL-9 can occur in T_{Reg} cells that are found in tolerant allografts *in vivo*[20], as well as in purified T_{Reg} cell populations *in vitro*[18,21]. However, other groups did not report co-expression of FOXP3 and IL-9 in T cell cultures that were generated *in vitro*[8,19]. Similarly, there have been conflicting data from studies of T_{Reg} cells from healthy human donors[15–17]. As one group showed that retinoic acid can downregulate IL-9 expression by T_{Reg} cells[22], a possible explanation for the discrepancy between the data is that there may be differences in the levels of retinoic acid present in cultures *in vitro* and in the local microenvironments *in vivo*.

For all of the above $CD4^+$ T cell subsets, TGFβ seems to be the unifying factor for promoting IL-9 production; an inability to respond to TGFβ *in vivo* prevents IL-9 expression by T cells[8]. The main exception to this observation is that TGFβ does not seem to be necessary for IL-9 production by T_H2 cells; however, one possible explanation for this finding could be the presence of endogenous TGFβ in the culture media that is used for T_H2 cell differentiation.

Mast cells as a source of IL-9

Although mainly studied as a target of IL-9, mast cells have also been reported to produce this cytokine. Production occurs in an autocrine manner in response to IL-9-induced signals and as a consequence of the crosslinking of IgE molecules on the surface of mast cells. Crosslinking of surface IgE molecules results in mast cell degranulation and leads to the immediate release of numerous pre-formed mediators. Two of these products, histamine and IL-1β, can promote further IL-9 production[23,24]. As IL-9 is a growth factor for mast cells, it is thought that these pathways promote the survival and expansion of mast cells during an active immune response.

Natural killer T cells

Studies using natural killer T (NKT) cells from naive mice have shown that following stimulation with IL-2, but not IL-15, these cells can produce IL-9. IL-2 stimulation also led to some coexpression of IL-4, IL-5 and IL-13, but not IFNγ, by IL-9-producing NKT cells[25]. In a mouse model of allergic airway inflammation, deficiency of CD1d-restricted NKT cells correlated with decreased IL-9 expression and reduced mast cell recruitment to the lungs. This finding suggested that NKT cells can promote IL-9 responses *in vivo*[26].

In addition, NKT cells that have undergone transformation to nasal NKT cell lymphoma cell lines also produce IL-9; in this setting, IL-9 functions as an autocrine growth factor. Histological sections from patients with nasal NKT cell lymphomas contained large numbers of infiltrating IL-9-producing NKT cells, which suggested that IL-9 may promote disease progression[27]. It is currently unclear whether IL-9 can also have effects on other cell types in the nasal mucosa of these patients. For example, the effects of IL-9 on mast cells might contribute to cancer progression by promoting the production of angiogenic factors that increase the vasculature of the tumour.

Immune cell targets of IL-9

The downstream effects of IL-9 have been primarily associated with mast cells; however, this does not preclude IL-9 from exerting effects on other cell types. Here, we summarize the observed effects of IL-9 on mast cells and other cell types (FIG. 3). However, as there is currently no way to definitively confirm the expression of IL-9Rα on specific, rather than

heterogenous, cell populations, it can be difficult to determine the relative importance of each individual cell type.

Mast cells

One of the main targets of IL-9 is the mast cell and, as mentioned earlier, initial studies described a role for IL-9 in promoting the expansion of mast cell populations[28]. Subsequent work in mice that were deficient for both IL-9 and IL-9Rα showed that IL-9 is not required for the generation of mast cell precursors, as the basal numbers of mast cells in these mice were normal. However, mice that were deficient for IL-9 or IL-9Rα showed defective expansion and recruitment of mast cell populations in response to intestinal nematode infection or following the induction of experimental autoimmune encephalomyelitis (EAE)[18,29]. IL-9 can induce mast cell production of TGFβ, which can have pro-inflammatory downstream effects on neurons in a murine stroke model and on epithelial cells during intestinal inflammation[30,31]. Following antigen-specific crosslinking of surface IgE molecules on mast cells, IL-9 can enhance mast cell expression of several cytokines, including IL-1β, IL-5, IL-6, IL-9, IL-10 and IL-13 (REF. 24). Of these cytokines, IL-5 and IL-13 are of particular interest, as the previously described direct effects of IL-9 in promoting eosinophilia and mucus production in the lung and the gut instead seem to be indirect effects mediated through the induction of these cytokines by IL-9 (REFS 32–36).

T cell subsets

There are some indications that IL-9 can target certain T cell subsets, specifically, T_H17 cells and T_{Reg} cells. In the case of T_H17 cells, IL-9 seems to function as an autocrine growth factor that facilitates the expansion of T_H17 cell populations *in vitro*[19]. This is also supported by the decreased accumulation of T_H17 cells that is seen in IL-9Rα-deficient mice during EAE[18]; however, because this is a global defect *in vivo*, the possibility that this is an indirect effect of IL-9 deficiency cannot be entirely dismissed. By contrast, IL-9 does not seem to facilitate the survival or expansion of T_{Reg} cells. Instead, standard suppression assays show that T_{Reg} cells from IL-9Rα-deficient mice are less able to inhibit the proliferation of effector $CD4^+$ T cells *in vitro*[19]. This suggests that IL-9 can enhance the regulatory function of T_{Reg} cells through an unknown mechanism.

Antigen-presenting cells

Although a careful analysis of the specific antigen-presenting cell (APC) subsets that express the IL-9 receptor has not yet been carried out, there are indications that professional APCs are also targets of IL-9. During lipopolysaccharide-induced activation of a heterogenous population of macrophages and monocytes, IL-9 can promote the expression of TGFβ; this results in a decrease in the oxidative burst of these cells, as well as in decreased expression of tumour necrosis factor (TNF)[37,38]. In addition, the culture of peripheral blood mononuclear cells (PBMCs), which contain both T cells and monocytes, with IL-9 leads to decreased production of IL-12 and IFNγ in response to treatment with extracts from *Mycobacterium tuberculosis*. Under these conditions, it was also shown that the addition of IL-9-specific blocking antibodies to the cultures upregulates PBMC production of IL-12 (REF. 39). Overall, these data suggest that IL-9 might limit the capacity of APCs to induce T_H1-type immune responses.

IL-9 and immunity

IL-9 can function as both a positive and negative regulator of immune responses (TABLE 1). In general, it seems that IL-9 has detrimental roles during allergy and autoimmunity. However, during parasitic infections, IL-9 can help to clear the pathogen, and during skin transplantation, IL-9 can promote the maintenance of a tolerant environment.

Allergy

During some allergic responses in the lung, which are traditionally thought of as being T_H2 cell-mediated, IL-9 contributes to disease by promoting mast cell expansion and production of IL-13, which in turn promotes the release of mucus that contributes to airway hyperresponsiveness[33,35,40]. The initial influx of mast cells in this model is likely to be driven by IL-9 that is derived from NKT cells[26]. In addition, T_H9 cells also seem to contribute to disease in this model, as mice with PU.1-deficient T cells and a global IL-25 deficiency are protected from allergic airway inflammation[6,14]. Similarly, during food allergy, IL-9 production (presumably by T_H2 cells and/or T_H9 cells) also contributes to mastocytosis and, indirectly, to increased intestinal permeability[41].

Autoimmunity

In addition to having a pathogenic role in allergic responses in the lung and gut, IL-9 may contribute to the development of autoimmune disease. During EAE, both T_H17 cells and T_H9 cells have the capacity to produce IL-9. In addition, antibody-mediated blockade of IL-9, or IL-9Rα deficiency, attenuates disease progression[18,42]. This seems to be partly due to the direct effects of IL-9 on mast cells, as there is a decreased accumulation of these cells in the periphery[18]. However, in contrast to these findings, another study has reported that IL-9Rα-deficient mice develop more severe EAE[19]. Although these discrepancies cannot be readily explained, there is mounting evidence to suggest that IL-9 that is produced during EAE and other autoimmune diseases has pro-inflammatory effects; for example, the adoptive transfer of antigen-specific T_H9 cells promotes EAE disease[43], and the decrease in EAE severity that is seen following the induction of oral tolerance is associated with reduced levels of IL-9 (REF. 44). In addition, patients with diabetes were shown to have increased levels of IL-9^+ T_H17 cells in the blood (REF. 16).

Parasitic infections

In the context of certain nematode infections, such as *Trichuris muris* infection, IL-9 can promote the isolation and/or expulsion of parasites from the gastrointestinal tract. In these circumstances, it is thought that T_H2 cells and/or T_H9 cells are the main source of IL-9 and that the main targets of IL-9 are mucosal mast cells. IL-9 can stimulate the release of mast cell products that contribute to eosinophilia, mucus production, increased intestinal permeability and muscle contraction[45–47]. The net effect of these immune effector mechanisms is the physical expulsion of the parasite. By contrast, during lung parasitic infections, such as those caused by *Schistosoma mansoni*, IL-9-deficient mice do not show any functional defects in the formation of granulomas to isolate parasitic eggs, although decreased mucus production and mast cell accumulation are observed[29].

Transplant tolerance

During the transplantation of skin allografts, T_{Reg} cells, rather than T_H9 cells, seem to be one of the major sources of IL-9, which is possibly involved in the recruitment of mast cells that mediate tolerance without degranulation[20,48]. IL-9 may also promote the ability of T_{Reg} cells that are present at the graft site to suppress ongoing immune effector responses against the skin allograft. Currently, it is unknown whether T_{Reg} cell-derived IL-9 has a central role in promoting tolerance at other transplantation sites.

Concluding remarks

Interest in IL-9 has been renewed recently, partly fuelled by reports that IL-9 can be expressed by several distinct T cell subsets, particularly following exposure to TGFβ. However, as much of this work has been based on *in vitro* studies, a re-examination of the

main cell sources of IL-9 during different types of immune response *in vivo* is needed. This is particularly true of T_H2-type immune responses, as data from models of allergic lung inflammation suggest that T_H9 cells, rather than T_H2 cells, are the main source of IL-9 in this setting[6,14]. In addition, as T_H17 and T_{Reg} cells have been shown to be capable of producing IL-9 during autoimmunity and transplantation, the contribution of this cytokine to these processes also warrants further investigation[18–20].

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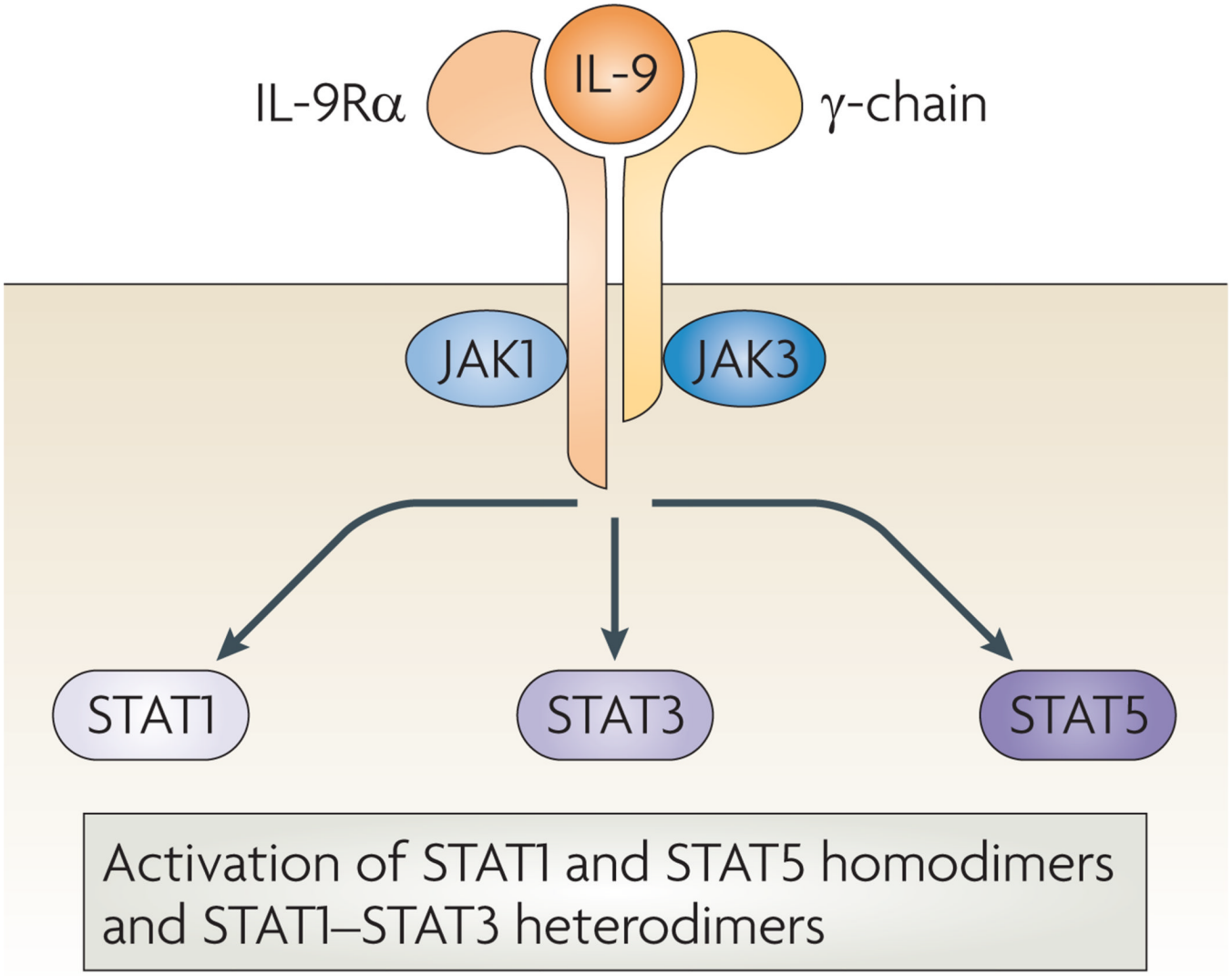

Figure 1. The IL-9 receptor signalling complex

Interleukin-9 (IL-9) activates a heterodimeric receptor that consists of the IL-9 receptor α-chain (IL-9Rα) and the γ-chain and promotes the crossphosphorylation of Janus kinase 1 (JAK1) and JAK3. This leads to the activation of signal transducer and activator of transcription 1 (STAT1), STAT3 and STAT5 and the upregulation of IL-9-inducible gene transcription.

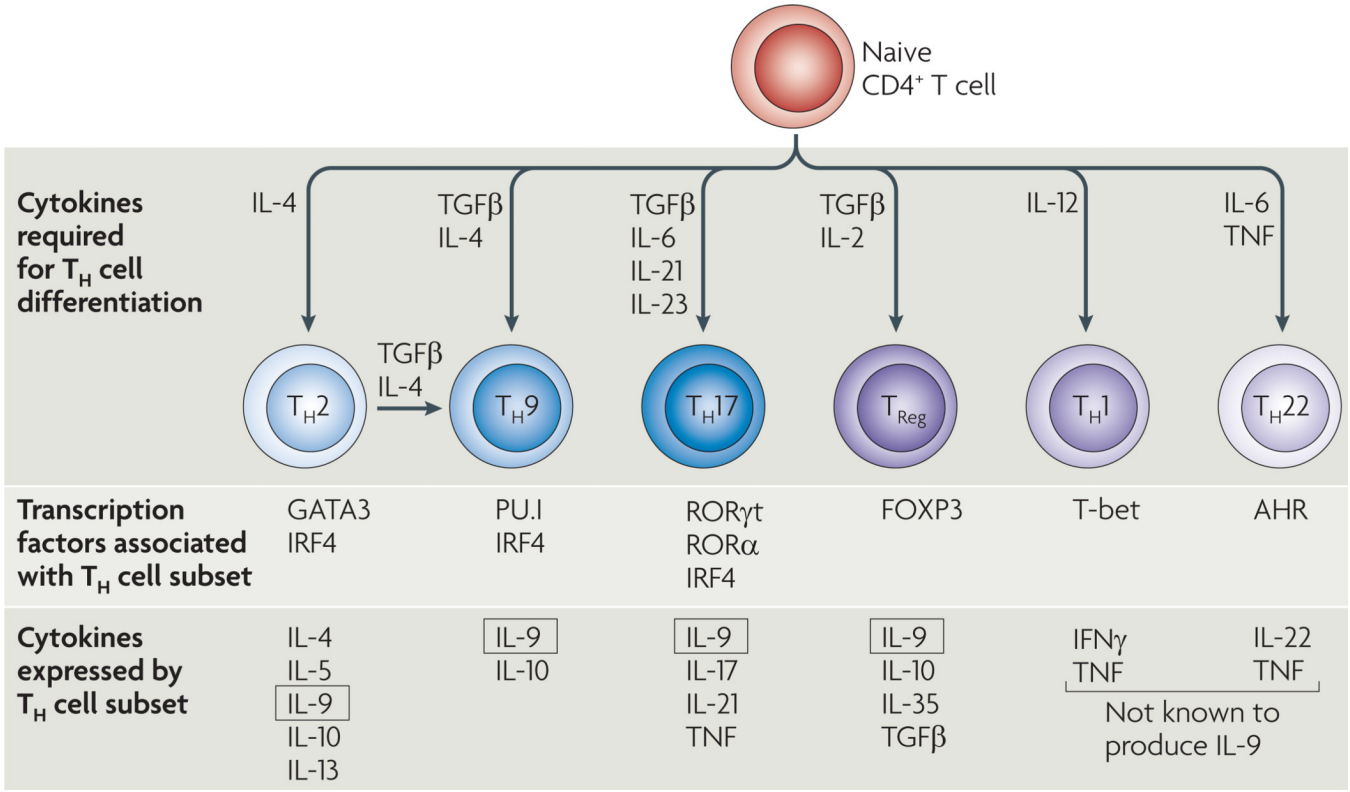

Figure 2. Expression of IL-9 by distinct T cell subsets

Different differentiation pathways of effector $CD4^+$ T cell subsets are shown, as well as the transcription factors that are necessary for their differentiation and some of the cytokines that they produce. Interleukin-9 (IL-9) has been reported to be expressed by T helper 2 (T_H2), T_H9, T_H17 and regulatory T (T_{Reg}) cell subsets, and all of these subsets, except T_H2 cells, require transforming growth factor-β (TGFβ) for IL-9 production. AHR, aryl hydrocarbon receptor; FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; IFNγ, interferon-γ; IRF4, interferon-regulatory factor 4; ROR, retinoic acid receptor-related orphan receptor; TNF, tumour necrosis factor.

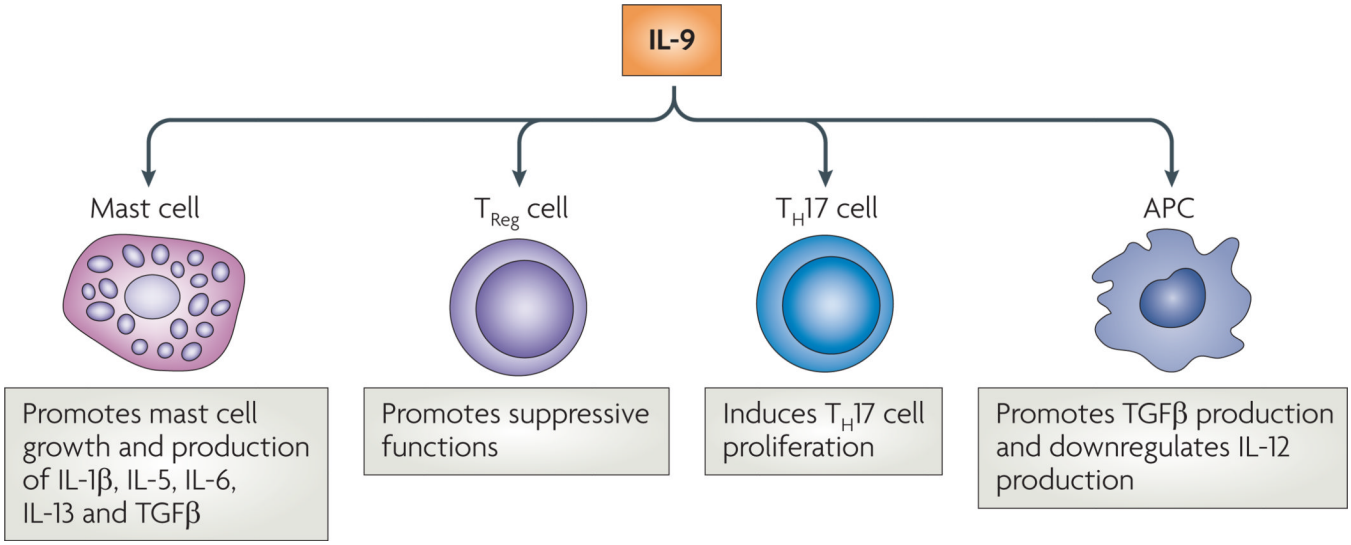

Figure 3. Targets of IL-9 function

Interleukin-9 (IL-9) has been shown to have various effects on different cell types. These effects include activating mast cells to secrete several products, including IL-13, which exerts its effects on the epithelial cells of the lung and gut. In addition, IL-9 seems to have a direct effect on regulatory T (T_{Reg}) cells, T helper 17 (T_H17) cells and antigen-presenting cells (APCs). TGFβ, transforming growth factor-β.

Table 1

Sources and targets of IL-9 during immune responses

Immune model	Sources of IL-9	Targets of IL-9	Effects of IL-9	Refs
Allergy				
Allergic airway inflammation	NKT cells and T_H9 cells	Mast cells	Promotes allergic inflammation	6,9,26,33,36,40
Oral antigen-induced anaphylaxis	T_H2 cells and T_H9 cells	Mast cells	Promotes allergic inflammation	41
Autoimmunity				
EAE	T_H17 cells and T_H9 cells	Mast cells and T_H17 cells	Promotes EAE	18, 42–44
	T_H17 cells and T_H9 cells	T_{Reg} cells	Inhibits EAE	19
Type 1 diabetes	T_H17 cells	Unknown	Unknown	16
Parasitic infection				
Lung infection with *Schistosoma mansoni*	T_H2 cells and T_H9 cells	Mast cells	No effect on granuloma formation	29
Intestinal infection with *Trichuris muris*	T_H2 cells and T_H9 cells	Mast cells	Promotes parasite expulsion	45–47
Transplantation				
Skin allograft transplantation	T_{Reg} cells	Mast cells and T_{Reg} cells	Promotes allograft tolerance	20,48

EAE, experimental autoimmune encephalomyelitis; NKT, natural killer T; T_H, T helper; T_{Reg}, regulatory T.