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Role of Interleukin 9 in Oral Lichen Planus Pathogenesis and Management

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Abstract

Background: Lichen planus (LP) is a common chronic inflammatory condition that can affect skin and mucous membranes, including the oral mucosa. Because of the anatomic, physiologic and functional peculiarities of the oral cavity, the oral variant of LP (OLP) requires specific evaluations in terms of diagnosis and management. In this comprehensive review, we discuss the current developments in the understanding of the etiopathogenesis, clinical-pathologic presentation, and treatment of OLP, and provide follow-up recommendations informed by recent data on the malignant potential of the disease as well as health economics evaluations.The term lichen planus (LP) is derived from the Greek word lichen meaning tree moss and the Latin planus meaning flat. Erasmus Wilson first described the condition in 1869, as a chronic disease affecting the skin, scalp.nails, and mucosa, with possible rare malignant transfor-mation. LP may involve the hair follicles (lichenplanopilaris, resulting in scarring alopecia), nails and moreseldom, the eyes, urinary tract, nasal mucosa and larynx. Interleukin 9 has been implicated in numerous pathogenic processes of diseases, mainly allergic diseases as asthma and atopic dermatitis. IL-9 serum levels are elevated in patients with systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis but their clinical significance is still not completely understood. It has been debated if IL-9 has a role in the pathogenesis of these diseases, or if its presence is due to an epiphenomenon caused by a broad activation of inflammatory mechanisms, and this has made it difficult to define its function in the development of the disease.

Keywords: Oral Lichen Planus (OLP), Interleukin 9.

1.Introduction:

The term lichen planus (LP) is derived from the Greek word lichen meaning tree moss and the Latin planusmeaning flat. Erasmus Wilson first described the conditionLP in 1869, as a chronic disease affecting the skin, scalp,nails, and mucosa, with possible rare malignant transfor-mation

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[1,8]. LP may involve the hair follicles (lichenplanopilaris, resulting in scarring alopecia), nails and moreseldom, the eyes, urinary tract, nasal mucosa and larynx**[1]**.

The oral variant: oral lichen planus (OLP) is a chronic inflammatory disease affecting the oral mucosa with characteristic relapses and remissions **[2,3,4].** While cutaneous lesions of LP can be self-limiting and pruritic, oral lesions are commonly chronic, non-remissive and can be a source of morbidity [8]. OLP may frequently be associated with involvement of the esophagus and therefore an endoscopy may be indicated if dysphagia was a concomitant presenting feature **[5]**.

The diagnosis of OLP is usually made by clinical and histological examinations. However, in classical lesions (bilateral, reticular pattern), it is possible to make a diagnosis based on the clinical appearance alone **[6]**. Additionally, there is a spectrum of oral lichenoid lesions (OLL) that may confuse the differential diagnosis. These include lichenoid contact lesions, lichenoid drug reactions and lichenoid lesions of graft versus host disease. For example, systemic medications, such as nonsteroidal anti-inflammatory drugs, certain antihypertensives, and oral hypoglycemics, can contribute to the development of oral lichenoid reactions (OLR) **[2,6,4].**

Dental restorative materials, including amalgam, gold and nickel may also be related to localized OLR in a number of patients **[7]**.

It is noteworthy that several dermatoses (e.g., lupus erythematosus, erythema multiforme) may exhibit some lichenoid features, clinically or histologically. Treatment of symptomatic OLP varies considerably and ranges from elimination of precipitating or provokingfactors—local or systemic, psychosocial interventions, to long-term pharmacological therapies. Thus, although Localizes to the oral cavity, there are broader implications in terms of patient management that warrant careful con-sideration. The ongoing controversy as to whether OLP is associated with an increased risk of malignant transformation adds further complexity to this disease. This review aims at presenting an overview of the accumulated knowledge and evidence on the different aspects of OLP,as well as the recent advances in each aspect.

1.1 Epidemiology

The estimated prevalence of OLP in general adult population is 0.5 to 2 % **[2,8,4]**. The reported female/males ratio is 2 to 1 and the age of onset is generally between30 and 60 years [1,1,4]. However, there have been casereports of OLP occurring in children **[9]**. Genital and cutaneous LP are associated with approximately 20 and 15 % of OLP cases, respectively, while it is estimated that OLP occurs in 70 to 77 % of patients with cutaneous LP **[1,8,10].**

1.2 Etiology

The precise etiology of OLP is unknown and only few predisposing factors are currently thought to potentially have a role in its pathogenesis. Genetic background may play a role in OLP pathogenesis as several familial cases have been reported **[11]**, however, the association has not been consistent. Genetic polymorphisms of several cytokines have been postulated to be

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associated with the clinical presentation of LP**[12].**

It has been reported that genetic polymorphisms of the first intron of the promoter gene of Interferon-gamma (IFN-c) may be an important risk factor to develop OLP, whereas an increase in the frequency of 308A tumor necrosis factor-alpha (TNF-a) allele may contribute to the development of additional skin involvement **[12].**

1.3 Psychological factors

Psychological factors are thought to play a role in the pathogenesis of OLP. OLP patients were shown to exhibit higher levels of anxiety, greater depression and increased vulnerability to psychological disorders, as opposed to healthy controls **[13].** Moreover, exacerbations of OLPhave been linked to periods of psychological stress and anxiety in some studies **[14,15]**.

In addition to the chronic discomfort that can result instress, patients with OLP were shown to be concerned about the possibility of malignancy, the contagious nature of the disease and the lack of available patient educational materials **[11].**

The levels of anxiety and salivary cortisol measured in a group of OLP patients were statistically correlated and significantly higher than a control group [50]. In spite of the presence of higher levels of psychological stress and anxiety among OLP patients, the question remains whether the psychological factors contribute to the etiology of OLP or are merely driven by the morbidity associated with the condition.

1.4 Trauma

Trauma as such has not been reported as an etiological factor in OLP, although it has been postulated as a mechanism by which other etiological factors may exert their effects **[4].**

The Koebner phenomenon, whereby OLPlesions develop in response to mechanical trauma, may partially explain why OLP lesions develop commonly insites prone to trauma, i.e., the buccal mucosa or lateral surfaces of the tongue **[2].**

1.5 Clinical-pathologic features

The classic presentation of OLP is in a bilateral, symmetrical pattern with the buccal mucosa being the most typical site of involvement, however, any other oral mucosal site can also be involved **[1,6].** Other common sites of involvement include the tongue, gingiva and labial mucosa while lesions of OLP affecting the palate, floor of the mouth, and upper lip are not common **[2,8].**

1.6 Signs, symptoms, and clinical behavior

The clinical signs and symptoms of OLP vary. In many patients, the onset of OLP is insidious and patients are unaware of their oral condition. Some patients report roughness of the lining of the mouth, sensitivity of the oral mucosa to hot or spicy foods, painful oral mucosa, red or white patches on the oral mucosa or oral ulcerations **[6].** Approximately two-thirds of the patients affected with OLP experience some degree of oral dis-comfort **[8]**.

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1.7 Histopathology

Definite diagnostic histological findings of OLP include; liquefactive degeneration of the basal cells, colloid bodies (Civatte, hyaline, cytoid), homogeneous infiltrate of lymphocytes and histiocytes in a dense, band-like pattern along the epithelium-connective tissue interface in the superficial dermis, cytologically normal maturation of the epithelium, saw-tooth rete ridges and hyperkeratosis (orthokeratosis or parakeratosis) **[2,6,8]**.

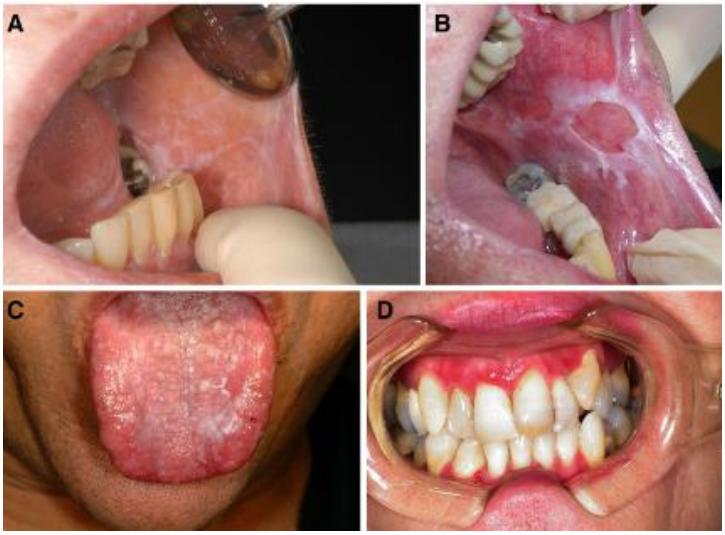

Figure (1): Clinical patterns ofOLP.Areticular,Berosive/ulcerative, C atrophic and plaque-like, and D desquamative gingivitis (atrophic and erosive forms)**(8)**

Table (1): Original WHO diagnostic criteria of OLP**(8)**

Modified WHO diagnostic criteria of OLP and OLL
Clinical criteria
Presence of bilateral, more or less symmetrical lesions
Presence of a lacelike network of slightly raised gray–white lines (reticular pattern)
Erosive, atrophic, bullous, and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa
In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term "clinically compatible with" should be used
Histopathologic criteria
Presence of a well-defined, band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Signs of liquefaction degeneration in the basal cell layer
Absence of epithelial dysplasia
When the histopathological features are less obvious, the term "histopathologically compatible with" should be used
Final diagnosis of OLP or OLL
To achieve a final diagnosis, clinical as well as histopathological criteria should be included
OLP
A diagnosis of OLP requires fulfillment of clinical and histopathologic criteria
OLL
The term OLL will be used in the following conditions:
1. Clinically typical of OLP but histopathologically only compatible with OLP
2. Histopathologically typical of OLP but clinically only compatible with OLP
3. Clinically compatible with OLP and histopathologically compatible with OLP

2.Interleukin 9

Interleukin 9 belongs to a family of cytokines that use the common IL-2Rγc for signal

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transduction, and similar to other family members (i.e., IL-2, IL-4, IL-7, IL-15 and IL-21), IL-9 was believed to be a T-cell growth factor and its chief function was to drive T-cell proliferation. However other studies showed that IL-9 has a weak effect in proliferation of primary T cells **(16).**

Despite the fact that proliferation of certain T-cell clones can be strongly stimulated by IL-9, instead, IL-9 exhibits other functions, most noticeably in proliferation of mast cells, goblet cells and airway mucin-producing cells. Thus, in many ways, it is different from other IL-2Rγc cytokines as a T-cell growth factor. Interleukin 9 signals through the JAK/STAT system **(17).**

Specifically, upon binding to its cell surface receptor, which consists of a private IL-9Rα chain and the common IL-2Rγc, IL-9 induces recruitment of JAK1 and JAK3 to the IL-9Rα chain and the common IL-2Rγc, respectively, followed by cross-phosphorylation and activation of JAK1 and JAK3. This leads to the activation of STAT1, STAT3 and STAT5. Consequently, STAT1 and STAT5 form homodimers, while STAT1 and STAT3 form heterodimers, and such dimeric complexes translocate to the nucleus to drive transcription of IL-9-inducible genes **(16).**

These gene products are involved in cell survival, proliferation and secretion of inflammatory mediators. Interleukin 9 is often seen in the context of Th 2 cells in vitro or Th 2 associated inflammatory conditions in vivo, especially in allergic inflammation **(18)**.

Thus, for a long time, IL-9 was considered just another Th2 cytokine and thought to be redundant among other Th2 cytokines (i.e., IL-4, IL-5 and IL-13). Furthermore, IL-9 is not confined to Th2 cells, and other cell types including mast cells, NKT cells, Th17 cells or even T reg cells can become IL-9 producers **(19).**

The discovery that IL-9-producing cells are a unique subset of CD4+ helper T cells that is different from other subsets, with distinct features and transcriptional controls, generates renewed interest in the field **(9).**

The Th9 cells are a recently described new helper T-cell subset; the signature cytokine for Th9 cells is IL-9 (without IL-4). Together with other Th subsets, the Th9 cells form a complex array of effector mechanisms in the immune system. The frequency of Th9 cells is very low (~5%), even under optimal polarizing conditions in vitro **(24).**

This often casts considerable concerns over whether Th9 cells are truly a distinct Th cell subset. They are closely associated with Th2 cells, which co-express both IL-4 and IL-9 in the early phase of differentiation, and the Th2 cytokine IL-4 provides one of the key signals for Th9 induction. Furthermore, some of the transcription factors in Th2 development are also involved in Th9 induction. A clear example is that STAT6 knockout CD4+ T cells fail to develop to Th2 cells; they also fail to become Th9 cells **(20,21).**

In some Th2 cultures, CD4+ T cells that express IL-4 and IL-9 (Th2 cells) are completely segregated in that only those that lose the ability to express IL-4 will become IL-9 producers (Th9). Interestingly, only a small fraction of Th2 cells acquire the ability to continually express

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IL-9. Importantly, the transcriptional regulation mechanisms of Th9 and Th2 cells are strikingly different from each other, thus clearly setting Th9 and TH2 cells apart **(10,24).**

In most reports showing low levels of Th9 cells under TGF-β and IL-4 culture conditions, that they co-express IL-10, which is another Th2 cytokine. It is likely that such Th9 cells are derivatives of Th2 cells as a consequence of induction of additional transcription factors such as purine-rich box 1 (PU.1) and interferon regulatory factor 4 (IRF4) which shut off IL-4 and turn on IL-9 . However, other studies suggested another pathway of Th9 induction in which T0 cells can be directly converted to Th9 cells at high levels (up to 80% of the CD4+ T cells) by TGF-β and IL-4 when CD134 co stimulation is engaged **(23).**

2.1. Sources of IL9

Th2 Cells:
One of the first cells studied in association with IL9 are Th2. They were studied in murine models infected in vivo with Leishmania major and these cells were found to co-express other cytokines as well including IL-4, IL-5, and IL-13. Initially believed to be the main producers of IL-9, a correlation was found between Th2 cell expansion and IL-9 levels (**23).**

NKT Cells:
It has been demonstrated that under certain conditions NKT cells can produce IL-9. Studies using NKT cells from naive mice have shown that after stimulation with IL-2, these cells can produce IL-9. Stimulation with IL2 also triggers the expression of IL-4, IL-5, and IL-13 in NKT cells, but not IFN-γ, suggesting that these cells assist in the humoral immune response. Naïve NKT cells in the presence of TGF-β and IL-4 polarize and secrete IL-9 in murine and human thymic invariant natural killer cell (iNKT)cells .It has been observed that in the absence of CD1d, pulmonary NKT cells decrease IL-9 expression accompanied by decrease in mast cell recruitment to the lungs in allergic airway inflammation **(24,25).**

Mast Cells:
It has also been discovered that activated mast cells can secrete IL-9. Several cytokines were found to stimulate IL-9 production by mast cells, while IL-9 acts as a growth factor and promotes mast cell expansion. Mast cells are stimulated in an autocrine manner in response to IL-9-induced signals and the cross-linking of Ig E molecules on the surface of mast cells triggers release of numerous other cytokines. Histamine and IL-1β, two cytokines released after mast cell degranulation, have been found to further induce IL-9 production, and along with IL-9 itself, seem to behave in a positive feedback loop inducing IL-9 production **(26).**

Th 9 Cells:
A distinct CD4+ T subpopulation based on the cultivating CD4+ murine lymphocytes under different groups of inductor cytokines which polarized the differentiation toward Th1, Th2, Th17, Treg, and CD4+IL-9+ cells. There was evidence that these cells, which acquired the IL-9 phenotype lost expression of other characteristic cytokine of T effector lymphocytes including IL-4, IL-5, IL-13 (Th2), IL-17-α (Th17), or IFN-γ (Th1) **(27).**

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Th17 Cells:

Studies have demonstrated that polarized mouse Th17 cells can produce IL-9 while co-expressing IL-17 as well. However, IL-23 was observed to suppress IL-9 production and given its importance in the maintenance of Th17 cells it remains unclear whether this IL-9 production by Th17 cells is transient. In vitro studies have shown that human Th17 cells also produce IL-9. Differentiated T0 need repeated stimulation by Th17 inducing conditions to co-express IL-17 and IL-9. Memory CD4+ T cells subjected to Th17 inducing cytokines such as IL-1β and IL-21 result in the co-expression of IL-9 and IL-17 **(26).**

Treg Cells:

Few studies have suggested the production of IL-9 by Treg cells. Although a couple of studies have confirmed that IL-9 is produced by Treg cells, there are conflicting reports under the circumstances which this occurs. One study reported co-expression of Foxp3 and IL-9 in Treg cells in tolerant murine allografts. This has not been reported in other studies, which studied the function of Treg cells in vitro. Additionally, in human donors the co-expression of Foxp3 and IL-9 has not been reported either **(28).**

Innate lymphoid cells:

It was discovered as a subset of innate lymphoid cells (ILC) that release type 2 cytokines named group 2 ILC cells. Studies with IL-9 reporter mice in vivo have demonstrated that in certain inflammatory milieu, ILC2 cells have been found to express IL-9 cells to variety of stimuli. In a papain-induced lung inflammation model in mice. Interleukin 9 was discovered to be largely produced by ILC2 cells. This production was demonstrated to be dependent on IL-2, but rapidly diminished as other the production of other cytokines, such as IL-13 and IL-5 increased. When IL-9 production was neutralized in ILC2 cells, a lower expression in IL-13 and IL-5 was observed, suggesting that the production of IL-9 by ILC2 cells may play a role in regulation of Th2 cells **(28).**

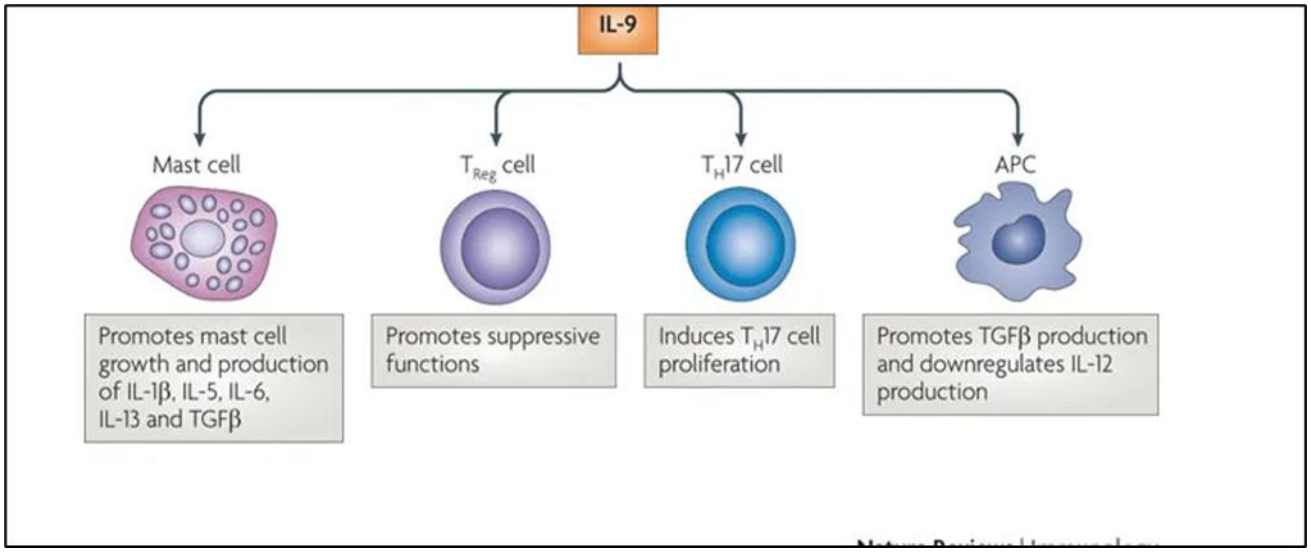

Figure 2: Targets of IL-9 function **(29,30)**

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2.2. Immune cell target of IL 9

The 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. The observed effects of IL-9 on mast cells and other cell types were summarized in figure (1). However, as there is currently no way to confirm the expression of IL-9Rα on specific, rather than heterogenous, cell populations, it may be difficult to determine the relative importance of each individual cell type **(29,30).**

Mast cells

One of the main targets of IL-9 is the mast cell and initial studies described a role for IL-9 in promoting the expansion of mast cell populations. 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. Interleukin 9 was reported to induce mast cell production of TGFβ, which can have pro-inflammatory downstream effects on neurons and epithelial cells during intestinal inflammation **(29).**

T cell subsets

There are some indications that IL-9 can target certain T cell subsets, specifically, Th17 cells and Treg cells. In the case of Th17 cells, IL-9 seems to function as an autocrine growth factor that facilitates the expansion of Th17 cell populations in vitro. This is also supported by the decreased accumulation of Th17 cells seen in IL-9Rα-deficient mice during autoimmune encephalomyelitis **(29,30).**

Antigen-presenting cells

A careful analysis of the specific antigen-presenting cell (APC) subsets that express the IL-9 receptor has not yet been carried out. However, 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 TNF **(30).**

2.3. Functions of IL9

Interleukin 9 exerts its effect on multiple types of cells and different tissues and initially was considered as a growth factor of activated T cells. Later, its potent proliferative effects were demonstrated in other cell types mainly mast cells hematopoietic erythroid precursors and on myeloid leukemia cell lines **(31).**

Allergic Inflammatory Processes

Interleukin 9 plays an important role in the regulation of airway inflammation and airway hyperresponsiveness. It has been demonstrated that IL-9 exerts proliferative effects on goblet cells and cells that produce mucin in the airways, which is reflected with an increased production of mucus, favoring allergic inflammation in the respiratory tracts. Increased Th9 cell numbers in peripheral blood of allergic patients correlated with IgE titers. In B lymphocytes, IL-9 in the presence of IL-4 increases secretion of IgG1 and IgE and it also promotes an isotype switch contributing to the pathogenesis of allergic diseases of the respiratory tract, specifically in asthma and bronchial hyperreactivity **(32).**

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Effect on Neoplasia

Interleukin 9 has been demonstrated to play an important role immune regulation in neoplasia. One important aspect is related to hematologic neoplasms. Animal studies have demonstrated that ectopic expression of IL-9 induces the proliferation of mouse thymic lymphomas. In humans, in vitro studies have observed increase of IL-9 production in cells of Hodgkin's lymphoma by promoting the growth of these cultured cells. The effect of IL-9 in neoplasia may depend on whether the tumor is solid or not. In solid tumors, specifically in melanoma, it has been demonstrated that Th9 and IL-9 have an important antitumor effect favoring the recruitment of both innate adaptive immune cells, reducing tumor burden **(33).**

Immunity against parasites

It has also been shown that IL-9 participates in immunity against parasites, IL-9 transgenic mice overexpressing IL-9 eradicate Trichinella spiralis infections faster than wild-type mice. This nematode requires a great amount of intestinal mast cells for its elimination. Nevertheless, IL-9 −/− mice did not show alterations in the development of T cells, in the antibody-mediated response or the clearance of the infection caused by Nippostrongylus brasiliensis, which suggests a high redundancy for IL-9 function and the intervention of other cell phenotypes, such as Th2 cells **(31).**

Anti-inflammatory Effects

Apart from inflammatory effects of IL-9, anti-inflammatory effects of the cytokine were demonstrated to depend on the cell types expressing it as well as on the microenvironment in which it is produced. Secretion of IL9 by Treg cells participates in the induction of tolerance. It has been demonstrated that IL-9 stimulates the differentiation of non-allergic mast cells with the capability of inducing local tolerance during allogeneic skin transplants on mice. In contrast, neutralization of IL-9 via monoclonal antibodies promotes an accelerated rejection to skin allotransplants on previously tolerant mice. This anti-inflammatory regulation demonstrates the important role IL-9 plays in immune tolerance (**34).**

Autoimmune Disease

Interleukin 9 has been implicated in numerous pathogenic processes of diseases, mainly allergic diseases as asthma and atopic dermatitis. IL-9 serum levels are elevated in patients with systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis but their clinical significance is still not completely understood. It has been debated if IL-9 has a role in the pathogenesis of these diseases, or if its presence is due to an epiphenomenon caused by a broad activation of inflammatory mechanisms, and this has made it difficult to define its function in the development of the disease**(33)**.

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