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Th9 Cells As a New Player in Inflammatory Skin Disorders

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ABSTRACT

CD4+T cells are composed of different subpopulations that differ in developmental pathways, surface markers, and their products. Among the catalog of these cells is Th9 cell subset that has a great capacity of Interleukin (IL)-9 production. They could be involved in the pathogenic or protective immune responses. Therefore, it is important to know how Th9 cells and cytokines influence the function of the human immune system as multitasking machinery, both in isolation or after the interaction with other surrounding cells. Since an important characteristic of Th9 cells is their tropism for skin, this article reviews the physiological and pathophysiological functions of Th9 and its cytokines under normal conditions and inflammatory skin disorders.

Keywords: Autoimmunity; Inflammation; Inflammatory disorders; Interleukin-9; Skin; Th9 cells

INTRODUCTION

IL-9 producing Th9 cell is a newly recognized and distinct subset of $CD4^+$T cell. Initially, it was believed that these cells were associated with Th2 responses and to emerge following exposure of Th2 cells to TGF-β.[1] After a few years, the importance of additional stimuli in Th9 development was demonstrated by several research groups.[2-4] It can be expected that Th9 development is controlled by different signaling pathways.

In another word, Th9 cell behavior is strongly influenced by the surrounding microenvironment and by the activities and properties of neighboring cells.

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The above-mentioned characteristics provide diverse challenges in dealing with the exact functional roles of these cells. According to scientific literature, these cells play a role in normal and pathological conditions. Therefore, this paper aims to review the evidence indicating the potential role of Th9 cells and its cytokine (IL-9) in the physiology and pathophysiology of the skin.

Skin Immune System

The three basic layers of skin (epidermis, dermis, and hypodermis) are made up of several types of immune and non-immune cells. The skin immune system consists of both innate and adaptive immune system components that are designed to prevent the invasion of environmental pathogens. Moreover, they actively participate in the generation and maintenance of immune homeostasis through different tolerogenic mechanisms.[5,6]

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The continuous recirculation of immune cells between the skin, draining lymph nodes, and the peripheral circulation is essential for protective skin immunity and skin immune surveillance.

After sensing any danger(s) that are directly related to the external surfaces of the body, Langerhans cells (LCs) and dendritic cells (DCs), the resident "professional antigen presenting cells (APCs)" of the skin, are activated. They capture, process, and present antigens and then migrate to skin-draining lymph nodes, where they provide the necessary stimulus for the naïve T lymphocytes.[7] They can also influence the migratory properties of T cells and are responsible for generating lymphocytes with a skin-specific homing potential.[8]

Following an encounter with antigen, the naïve T cells become antigen- effector/memory cells that are specific to the antigen from the first exposure and their phenotypes depend on the transient up- or downregulation of a large number of genes. T cell migration to lymphoid and extra-lymphoid sites is a multi-step process that requires coordinated interactions between T cell surface molecules with their respective ligands on the vascular endothelial cells. For instance, skin-homing T cells express cutaneous lymphocyte antigen (CLA), the CC chemokine receptor 4 (CCR4) and CCR10 which bind to their ligands E-selectin, CC chemokine ligand 17 (CCL17), and CCL27 (cutaneous T-cell-attracting chemokine), respectively, on endothelial cells.[9]

T cells are the key players in skin immune responses and are composed primarily of $CD4^+$ and $CD8^+$T cells.[9] They could be divided into effector and memory populations that are at the same time heterogeneous, consist of a number of phenotypically and functionally distinct subsets.[10,11] $CD4^+$T cells can be further subdivided into different subsets on the basis of distinct molecular and functional characteristics. Th1, Th2, Th17, regulatory T (Treg), Th9, Th22, and follicular Th (Tfh) cells are the major subsets of fully differentiated $CD4^+$T cells. As a general rule, the proper regulation of differentiation and function of these cells is necessary for generating and sustaining the efficient immune responses. In contrast, their dysregulation can result in impaired pathogen clearance and development of inflammatory diseases and autoimmunity.[12] The degree of responsiveness according to each Th subtype depend on a number of factors including tissue or organ specificities. For instance, Tfh cells that are localized in the germinal center of lymphoid follicles and appear to have a critical role in the generation of effective humoral immunity may play a minor role in the skin itself. However, it was indicated that these cells are activated after immunization via the skin and skin-derived DC.[13] Moreover, some cutaneous lymphoma express an array of Tfh markers.[14]

Another important issue that must be considered is a unique identity profile of each individual Th cell subset. These cells have their own peculiarities, including differential developmental requirements or specific cytokine patterns. The mentioned characteristics are essential for the induction and maintenance of particular immune defense mechanism. This means that distinct Th cell subsets promote the development of different types of immune response.[15] Therefore, the ability to identify the specific role of each Th subset for both normal and abnormal conditions is essential for basic immunological research and the improvement of new immunotherapies.

The role of various T cell subsets from normal and diseased human skin has been widely investigated.[16,17] Nonetheless, the current knowledge on the newly identified Th9 subset and their function in skin-related immune responses is limited because Th9 cells have not been investigated to the same extent as many of the other established Th subsets. Consequently, the next parts of this article will be dedicated to the critical topics including key regulators of Th9-cell development and the role of these cells in skin health and disease.

Th9 Cell Differentiation

IL-9 is a 14-kiloDalton glycoprotein that was originally defined by its ability to support the growth of T cells and mast cells, respectively[18,19] and its cDNA was initially cloned in murine helper T-cell clones.[20] Several years later, following IL-9 recognition, a newly specialized subset of $CD4^+$T cells, that dedicated to the production of IL-9 (Th9 cells) was identified. The polarization of naïve T cells towards Th9 fate is a complex phenomenon and several transcription factors (TFs) and cytokines have been implicated in this process.

At least 3 conserved noncoding sequences (CNS), CNS1, CNS2, and CNS0, CNS-6, have been identified close to the IL-9 gene. They serve as binding sites for the various Th9-associated TFs and are considered as

regulatory elements of the IL-9 gene.[21] This array of TFs are necessary for Th9 polarization, but not restricted to a specific Th cell subset. For instance, STAT-dependent pathways have been shown to participate in the differentiation of naïve $CD4^+$T cells to various effector subsets including Th9 and Th17.[22] Nonetheless, differential use of TFs provides specificity of individual signaling pathways. These signaling events can be triggered by specific cytokines that in turn can activate lineage-specific TFs. For instance, IL-12 and IL-4 promote Th1 and Th2 cells development, respectively.[23] However, under certain conditions (including Th9 cell development), the combination of cytokines determines T cell subset fate via a temporary shift in the gene expression of a panel of TFs.

Since IL-4 and TGF-β are essential for Th9 development from naïve T cells, elucidation of their related signaling pathways aids the recognition of the factors that affect Th9 subset development. Several lines of evidence indicate that TGF-β signaling induces the expression of PU.1 (also known as Spi-1), which is critical for Th9 cell development and negatively regulates Th2 cell development. Pu.1 binds to IL-9 promoter in Th9 cells and its absence leads to impaired Th9 polarization.[24]

Like TGF-β, IL-4 plays a pivotal role in Th9 development. IL-4 stimulation leads to tyrosine phosphorylation and activation of STAT6 which in turn facilitates the transcription of GATA3 and interferon-regulatory factor 4(IRF4).[25] IRF4 is an indispensable TF for the development and function of Th9 cells[26] and IRF4 deficiency in $CD4^+$T cells results in the development failure of IL-9 producing Th cells. Moreover, IRF4-specific siRNA blocks Th9 differentiation of wild-type $CD4^+$T cells.[26]

Although STAT6, GATA3, and IRF4 are critical in the generation of Th9 cells, they can also function in other settings such as Th2 lineage commitment. In other word, STAT6, GATA3, and IRF4 are shared TFs between Th2 and Th9 cell subsets. Based on the laboratory investigations, GATA3 does not seem to act directly on the transcriptional regulation of the IL-9 gene, but its effects are mediated through the downregulation of forkhead family transcription factor Foxp3, a molecule that could negatively affect Th9 development.[27]

In addition to TGF-β and IL-4, production of IL-9 can be influenced by other cytokines such as IL-2. This finding has been confirmed by the results from other investigations. For instance, Schmitt et al indicated that the production of IL-9 is IL-2 dependent and is inhibited by IFN-γ.[28] IL-25 has also been considered as an important cytokine in driving the Th9 subset. This cytokine has been described to act via IL-17RB that is differentially expressed on Th subgroups with the highest amount in Th9 cells.[29] Other cytokines including IL-1 family members, IL-33 and IL-21 also play a major role in promoting Th9 responses.[30,31] Therefore, a complex network of cytokines exists that is responsible for the initiation of the Th9 cell lineage commitment and determining their exact roles in dictating Th9 subset development will certainly provide a better understanding of the molecular pathways that control Th9 decisions.

Th9 Cell Functions in Skin Immunity

Normal human adult skin harbors nearly 20 billion T cells, approximately twice the number existing in the total blood volume. They contribute to several cellular processes of both normal and diseased skin[32] and their functions are also crucial for the effective control of the strength and the type of immune response. Skin is protected by several subsets of $CD4^+$Th cells. Interestingly, these different subsets are found among the CLA^+ skin-homing T cell population and participate in cutaneous defense responses against bacterial, viral, and fungal pathogens as well as in immune responses toward allergens and autoantigens. This phenotypical and biological diversity of skin lymphocytes covers a wide range of protective skin immune responses.[7] However, it has also provided new challenges in the attribution of a particular effect to a certain subtype.

Lymphocyte homing to the skin depends on different factors including expression of skin-specific chemokine receptors and the chemokine repertoire that distinct Th cells induce in the skin. Recent studies indicate that Th9 cells are skin-tropic or skin-resident. They are found among skin-homing CLA^+ effector T cells and are part of human healthy skin. These cells play a critical role in protecting against certain extracellular pathogens that invade damaged or even healthy skin.[33] The anticancer efficacy of IL-9 against melanoma is another evidence for the role of Th9 cell subset in cutaneous immunity.[34-36]

Although the exact mechanisms underlying the protective function of Th9 cells are not fully understood, several plausible explanations have been

proposed. They can induce apoptosis in their targets through a granzyme-B-dependent manner.[35] These cells have also autocrine and paracrine pro-inflammatory capacity. They produce IL-9 that is required for maximal production of IL-9 itself as well as for the production of additional inflammatory cytokines including IFN-γ, IL-17, and IL-13 in skin tropic Th cells. Neutralization of IL-9 activity by anti-IL-9 antibody prevented the subsequent elevation of IL-9, IFN-γ, IL-13, and IL-17 in CLA^{+}Th cells.[33] Th9 cells and their products orchestrate other effector cells of the immune system, including $CD8^{+}$ T cells and NK cells. On the one hand, Th9 cell-derived IL-21 has been shown to favor the induction of IFN-γ from NK and $CD8^{+}$T cells.[37] On the other hand, IL-9 has been reported to enhance the cytotoxic ability of murine melanoma-specific $CD8^{+}$T cells.[36] Therefore, Th9 cells play essential roles in skin host defense by direct execution of their effector functions or via their indirect effect on the other immune cells.

Th9 Cells in Chronic Inflammatory Skin Disorders

While the important roles of Th9 cells in skin immune response and the maintenance of skin immune homeostasis have been stated previously, their uncontrolled or inappropriate activation may also cause tissue damage during an autoimmune or exacerbated inflammatory response. Research on Th9 cells and autoimmune diseases is still in its early stages. Nonetheless, there are ongoing studies which investigate the role of Th9 cells in these types of disorders.

The impact of Th9 cells and related cytokines on autoimmune processes is complex in nature. One important reason for this complexity is related to its complex biological activities (Figure 1). For instance, IL-9 itself has pro- and anti-inflammatory effects. These activities can be affected by several factors including cytokine milieu and tissue microenvironment that dictate the effects of the immune response.[38] Another challenging issue is the existence of different cellular sources of IL-9, each having its own characteristics and effector functions. To date, most research has focused on the importance of IL-9 in the development of human autoimmune diseases without addressing the definite cellular origin of this cytokine. The purpose of this section is to provide an overview of the current state of knowledge on the role of IL-9 and Th9 cells in the pathogenesis of several inflammatory skin diseases.

Psoriasis

Psoriasis is a T-cell– mediated autoimmune disease in which skin lesions usually appear as red, dry, thick and itchy areas.[39-41]

Psoriasis is classically considered as a Th1-based disorder, but the discovery of several new T cell lineages has provided new insights into the disease pathogenesis.[39] There have been no extensive studies regarding the involvement of Th9 cells in psoriasis. Nonetheless, new research findings point to the potential role of IL-9-producing T cells in disease. Increased numbers of IL-9 expressing $CD4^{+}$Th cells are observed in skin lesions and peripheral blood mononuclear cells(PBMCs) of psoriasis patients.[33,42] Evidence also indicates that IL-9R expression levels are high in psoriatic skin lesions.[33,43] Upregulation of Th9-associated transcription factors PU.1, is another possible reason for the role of Th9 cells in psoriasis and help us to distinguish Th9 cells from other cellular sources of this cytokine.[41,44] The positive effects of IL-9 blockade on disease consequences have similarly demonstrated a key role for IL-9 in psoriasis.[43]

The exact role of Th9 cells in the disease process is not yet completely understood, but there are several mechanisms which could explain how these cells may participate in disease pathogenesis. The pro-inflammatory properties of IL-9 that promote secretion of IL-17, IL-13, IFN-γ, and TNF-α may be a possible mechanism underlying the pathophysiology of psoriasis.[33] Activation of Th9 cells and release of cytokines, which act in an autocrine and paracrine manner could initiate inflammation and lead to enhanced activation of Th1, Th2, Th9 or Th17 cells and increased production of their cytokines. Further support for this notion is provided by a report which indicates that IL-9 production precedes the upregulation of other inflammatory cytokines including IL-17, IL-13, and IFN-γ.[33]

IL-9 responsiveness of multiple activated cell types (including T cells, APCs and keratinocytes) in psoriasis lesional skin might be an additional indirect hint for a putative involvement of Th9 cells in psoriasis.[45]

A typical feature of psoriasis is morphological and functional changes of microvessels and IL-9 has the potential to be a direct mediator of angiogenesis. Moreover, it was indicated that IL-9 increases the presence of angiogenic markers (vascular endothelial

growth factor (VEGF) and CD31) in an experimental model of psoriasis. It has also direct effects on endothelial cells and stimulates the formation of new vessels.[43] Emerging evidence also proposes a probable relationship between IL-9 and Th17 pathway in psoriasis.[33,43] IL-9 induces the differentiation of Th17 cells and enhances the secretion of their signature cytokine, IL-17. Moreover, Th17 cells are the source of IL-9 under certain conditions and acts as a growth factor for several types of immune cells.[46] Therefore, IL-9 may have a role in the progression of psoriatic skin lesions via the formation of new blood vessels or Th17-associated inflammation. However, further studies are required to illuminate the precise role of Th9 cells in the disease process.

Allergic Contact Dermatitis (ACD)

ACD results from exposure of the skin to a contact allergen and belongs to eczema/dermatitis group. The most common symptoms of this inflammatory skin disease are large, burning, and itchy rashes, which can appear anywhere on the body.[47] It has been shown that $CD4^+$T cells are involved in the disease process and among various Th cell subsets, Th1 cells are considered as the main cellular players in inflammation,[48] although other cell types, including Th2 and Th17 cells, may also be involved in disease development.[49,50] In recent years, growing attention has been paid to the role of Th9 cells in ACD and current evidence indicates the potential relevance of these cells to disease pathogenesis.

The involvement of Th9 cells is highlighted by several observations: (1) significant upregulation of IL-9 gene expression in positive skin patch reactions of ACD patients;[51,52] (2) elevated levels of IL-9 in the supernatant of allergen-stimulated PBMCs from ACD patients in a dose-dependent manner;[51] (3) increased level of IL-9 in blister fluid of ACD patients in comparison to normal human serum controls and other blistering disorders;[52] (4) the higher expression of Th9-associated TFs[(PU.1, E26 transformation-specific sequence-1 (ETS-1), interferon regulatory factor 4 (IRF4), and general control non-derepressible 5 (GcN5)] in patch test–positive biopsies of ACD patients in comparison to paired control skin and finally the detection of Th9 lymphocytes in the inflammatory infiltrate of ACD.[51]

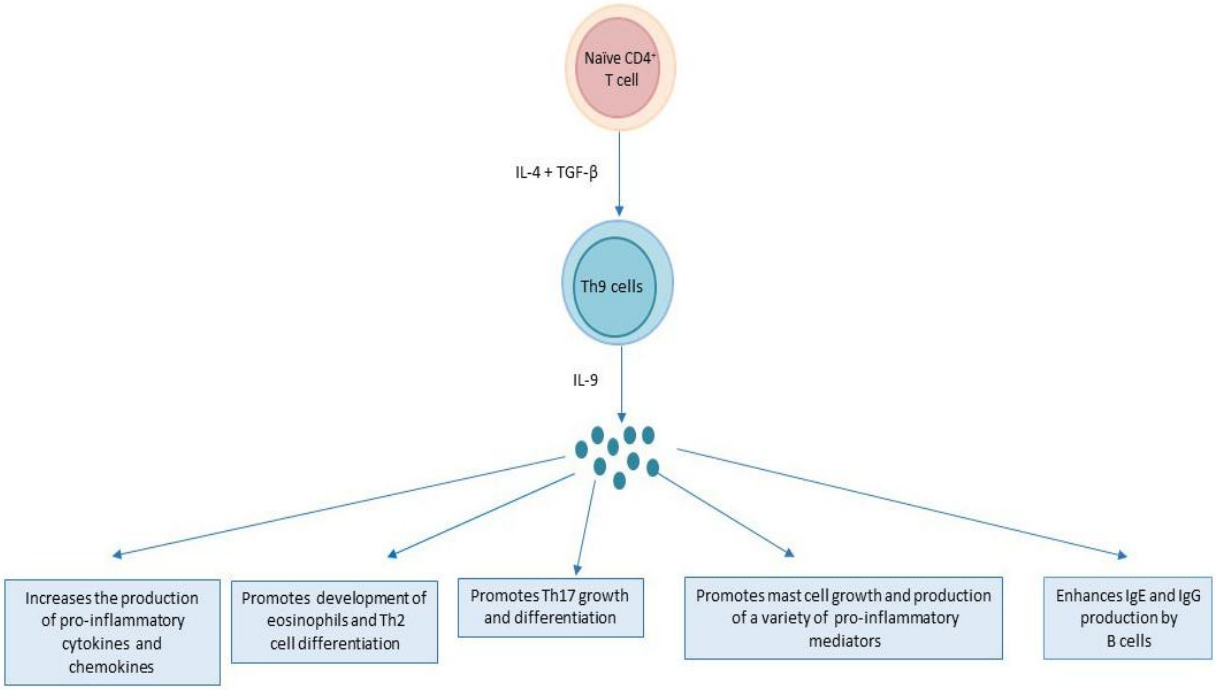

Figure 1. This schematic diagram illustrates that IL-9 activates inflammatory responses through multiple pathways. In the presence of IL-4 and TGF-β, naïve $CD4^+$ T cells become committed to the Th9 phenotype. IL-9 can activate various cell types that participate in inflammatory reactions.

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Although the exact mechanisms of Th9 cells participation in the pathogenic process of ACD remain unresolved, recent studies have begun to unravel the role of these cells in ACD. The results of these researches indicate that IL-9 may serve multiple roles in ACD: It may function as an inflammatory mediator,[51] may play a regulatory role via modulation of allergen-specific IFN-γ production by Th1 cells[51] or by orchestrating a complex array of cytokines, chemokines, and recruitment of different immune cells.[53] However, there are some doubts about the details of the above-mentioned mechanisms. For instance, IL-9 gene knockout mice had diminished ear swelling. Moreover, it has been indicated that IL-9 can attenuate the in vitro production of IFN-γ.[51] Other important aspects that must be taken into consideration are the existence of different cellular sources of IL-9, their distinct and redundant contribution in the inflammatory process, the possible relationship between Th9 cells and other immune cell types and Th9 cell plasticity.[54-56] Therefore, more studies are needed to shed further light on the mechanisms through which a switch toward Th9 responses could be induced in ACD.

Atopic Dermatitis (AD)

AD is a chronic inflammatory skin disorder that affects both pediatric and adult population. The etiological origin of disease remains obscure, but a combination of genetic and environmental factors appear to induce an abnormal immune response in patients with AD.[57] Recent studies indicate that various T-cell subsets are involved in the pathogenesis of AD.[58] Among these heterogeneous Th subpopulations, the exact role of Th9 cells and IL-9 are insufficiently investigated. Previous studies have indicated that serum IL-9 levels were elevated in children with AD and significantly related to the severity of symptoms.[59] Moreover, an association has been reported between IL-9 genetic variant with increased susceptibility to AD.[60] Evidence also exists for enhanced expression of IL-9 in skin lesions of intrinsic AD patients.[61] Consistent with these findings, Hamza et al. recently found differential expression of PU.1 and IL-9 between PBMCs from AD patients and HCs. Interestingly, there was a significant positive correlation between the expression levels of both IL-9 and PU.1, on the one hand, and the severity scoring of atopic dermatitis(SCORAD) index and serum IgE levels, on the other hand, .[44] These findings support those of other studies reporting a similar association between disease severity and expression levels of PU.1 and IL-9 in AD patients[42] and suggest a possible pathogenic role of Th9 cells in AD.

The underlying mechanism accounting for the pathogenic functions of Th9 cells in AD is not clearly understood, but there are several hypotheses that have been proposed to explain how these cells may be involved in the disease process. For instance, cetirizine hydrochloride-based therapeutic strategy for AD provide evidence of a potential association between Th9 cells and AD. It must be mentioned that

Cetirizine, as a potent and selective anti-histamine is used to stop the itch-scratch cycle of AD patients. It inhibits eosinophils migration towards the skin and in vivo expression of intracellular adhesion molecule-1 (ICAM-1) in nasal and conjunctival epithelium.[62,63]

This anti-histamine medication may have also some influence on Th9 cell function because of the known relationships between Th9 cells or IL-9 and key cellular contributors to disease pathogenesis including mast cells, eosinophils, and innate lymphoid cells.[64-66] However, more studies must be conducted to clarify the potential connections between Th9 cells and disease process.

Moreover, there is evidence supporting a possible link between the epithelial cells (ECs) that serve essential roles in AD pathogenesis and Th9 cells. For instance, Yao et al. indicated that thymic stromal lymphopoietin (TSLP) as an EC-derived cytokine enhances Th2 and Th9 cells differentiation of both human or mouse naïve $CD4^{+}$T cells. Moreover, they indicated a significantly higher serum IL-9 and TSLP in atopic patients than non-atopic patients, with a positive correlation between them.[67] Other indirect support for this concept can be found in experimental researches for other inflammatory disorders that influence epithelial integrity. For instance, IL-9 induces pro-inflammatory chemokines and mucus production in lung ECs of asthmatic patients or experimental models of disease.[68] IL-9 may have both direct and indirect effects (due to influences of other cytokines including IL-33) in the airway epithelium.[69]

In spite of the above-mentioned findings, conflicting reports are available on the role of IL-9 in AD patients. For instance, Yanaba et al did not observe any significant differences in the serum IL-9 levels between patients and HCs.[70]

These differences may in part rely on different factors including the age, disease activity or duration, the type and stage of disease, and treatment. These factors may affect some aspects of the immune system and may lead to an altered balance of Th cell subpopulations and the cytokines they release.

Therefore, the selection of patients is an essential issue and further molecular studies based on patient characteristics will increase our understanding of AD etiology and pathogenesis.

Spontaneous Urticaria (SU)

Urticaria is a heterogeneous disease characterized by wheals and flares and sometimes occurs concomitantly with angioedema. It may be caused by both internal and environmental factors and according to duration, can be divided into acute spontaneous urticaria (ASU) and chronic spontaneous urticaria (CSU).[71] Some evidence proves that aberrant immune responses play a significant role in determining the progression and severity of the disease. Clinical studies also increasingly show that aberrant T-lymphocyte development and function plays an important role in the disease process.[72,73]

Therefore, phenotypic and functional characterization of T cells from urticaria patients will certainly help us to better understand the immune mechanisms that lead to this common skin disorder.

Several earlier studies reported that Th1 and Th2 cells play a decisive pathogenic role in the development of SU.[74] However, recent studies have identified a potential role for other T cell subpopulations including Th9 cells.[75]

There were several reasons for suspecting that Th9 cells might be involved in disease pathogenesis. First, Th9 cells are important for the initiation of mast cell accumulation and activation[76] that is considered as a potential contributor to the pathogenic mechanism of disease.[77] Second, IL-9 producing cells can intensify the inflammatory process[78] which is an inevitable characteristic of the disease. Third, strong evidence exists regarding the effects of Th9 cells on eosinophils, which are thought to mediate inflammatory and cytotoxic events during allergic inflammation.[79]

In spite of the above-mentioned findings, the possible contribution of Th9 cells in disease pathogenesis is largely unknown. The most recent results presented by Zheng et al. indicated that the percentage of Th9 cells in peripheral blood and serum IL-9 level was significantly elevated in ASU patients compared to CSU patients and healthy controls (HCs). Moreover, increased expression of PU.1 in PBMCs was found in ASU patients as when compared with those of CSU patients or HCs. They also observed a positive correlation between the percentage of Th9 cells with the PU.1 mRNA expression and the concentration of IL-9 in serum.[75] These results are consistent with earlier findings, with emphasis on the pivotal role of Th9 cells in disease pathogenesis.[80] Nonetheless, there are also inconsistencies within studies. For instance, Metz et al. did not find significant differences in serum IL-9 levels between patients and HCs.[81] These opposing results may be the outcome of several factors, including sample size, intro and inter-population variations in survey sampling, etiological heterogeneity or the presence of different pathogenic mechanisms that exist for the different type of disease.[82-84] Therefore, further studies are needed to illuminate the possible relationships between Th9 cells and disease precipitating factors.

CONCLUSION

Recent studies on Th9 cells underscore the potential relevance of this $CD4^+$T-cell subset in the pathogenesis of skin inflammatory disorders. To date, there are several unresolved questions concerning the molecular mechanisms underlying the pathogenic effects of these cells. Therefore, understanding of the mechanisms behind the induction and regulation of Th9 cells is an essential and clinically relevant issue. It must be noted that the outcome of the above-mentioned disorders depends on the collaboration between different immune cell subsets and factors. Hence, defining the role of these cells and mediators can help identify disease-causing agents and their causal relationship to the disease process. The paradox of plasticity in T-cell phenotype and function is another layer of complexity. Addressing these questions will certainly provide new insight into disease pathogenesis and treatment strategies.

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