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REVIEW

The Role of Basophils in Atopic Dermatitis, from Pathogenesis to Therapeutic Perspectives

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Abstract: Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense pruritus. The principal pathological features include abnormalities in the structure and function of the epidermis, as well as skin inflammation marked by the overexpression of T helper 2 cell (Th2) cytokines. Throughout the progression of AD, various immune cells contribute to its pathogenesis. Basophils, the least abundant granulocytes in the human peripheral circulation, have historically been overlooked. However, the advent of novel research tools has facilitated a renewed focus on the role of basophils in diverse physiological and pathological conditions, including AD. Accordingly, this review will primarily summarize the association between AD and basophils, the alterations observed in basophils among AD patients, and the implications of these changes for AD patients.

Keywords: basophils, atopic dermatitis, AD, Th2 inflammation, synergistic interactions

Introduction

Atopic dermatitis (AD) is a chronic itchy inflammatory skin disease with a high prevalence, affecting approximately 20% of children and 5–10% of adults, significantly impacting patients' financial situation and quality of life.[1] The primary pathological features of AD include skin barrier dysfunction, skin dysbiosis, as well as skin inflammation characterized by the overexpression of Th2 cytokines.[2] In terms of the complex pathogenesis of AD, it involves numerous aspects such as humoral factors, cellular factors, the microbiome, and immunogens. Among these factors, immune cells play a crucial role.[3]

Basophils are the least numerous granulocytes in the peripheral circulation of the human body, accounting for less than 1% of total circulating granulocytes. Basophils mature in the bone marrow and predominantly reside in the peripheral circulation, having a short lifespan of only 1 to 2 days.[4,5] Since their first discovery in 1879, our understanding of basophils has steadily advanced.[6] Historically, basophils have been overlooked due to their phenotypic similarity to mast cells; however, researches have demonstrated that they represent distinct cell lineages. Pioneering studies conducted in the 1970s and 1980s, using mouse and guinea pig models of helminth-parasite infection, revealed that basophils may play an unrecognized role in the protective Th2 immune response against parasitic infections.[7–10] Subsequent research has shown that basophils can promote inflammatory and immune responses by releasing various cytokines such as histamine and interleukin 4 (IL-4).[11,12] Recent studies have also found that basophils can significantly increase in Th2-mediated diseases including AD.[13–15]

This review primarily summarizes the alterations observed in basophils among AD patients, the implications of these changes for AD patients, and discusses the association between AD and basophils. Finally, a brief overview to the treatment methods involving basophils will be discussed.

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Basophils in Patients with AD

As early as the 1980s, researchers observed significant basophil infiltration at the site of the purified house dust mite allergen patch test in sensitized AD patients.[16] While many studies have documented basophil infiltration in lesions, the specific role of these cells in the lesion process remains unclear.[17] Subsequent studies demonstrated that skin-infiltrating basophils in mice promote skin inflammation by producing and releasing IL-4.[18] Now researches have confirmed the presence of basophils in the skin of AD patients. A multivariable Mendelian randomization study found that higher levels of basophils in peripheral blood are associated with an increased risk of developing AD. Notably, the basophil levels in AD patients were higher than those in healthy individuals, though not necessarily exceeding the established upper limit.[19] Elevated levels of basophils in peripheral blood may correlate with the severity of AD.[20] Additionally, the number of infiltrating basophils in the skin showed a positive correlation with the number of basophils in peripheral blood.[21] However, compared to other skin diseases characterized by basophil infiltration, the basophil cell density in AD lesions is the lowest, and the ratio of basophils to eosinophils is also minimal among the various skin diseases studied.[22,23] Furthermore, researchers evaluated the activation levels of circulating basophils by measuring CD203c in the blood. Although no significant changes were observed compared to healthy control subjects, the researchers speculated that this might be due to the chronic nature of the AD patients recruited for the study, suggesting that their immune state may lean toward a Th1 immune response.[23] It was also found that the levels of CD203c, CD63, and FcεRI on the surface of basophils in AD patients are elevated compared to those in the recruited healthy subjects, indicating that basophils are more responsive to anti-FcεRI stimulation and less responsive to anti-IgE.[24–26]

The Advantages and Disadvantages Associated with the Presence and Activity of Basophils in AD

How Do Basophils Exacerbate AD

Activation and Migration of Basophils into Skin Tissue

Basophils are widely recognized as innate immune cells that promote Th2 immune responses. Although they primarily reside in the peripheral circulation after maturation in the bone marrow, they can be recruited into inflammatory tissues such as the intestine, lungs, and skin, during inflammatory processes. Multiple studies have shown that basophils can migrate in response to various chemokines, including C5a and prostaglandin D2.[27–30] Additionally, an investigation revealed that intradermal injection of CCL2 in humans induces basophil accumulation, while CCL3 does not.[31] In mouse models, researchers have identified that basophils can be recruited to the skin by mediators such as thymic stromal lymphopoietin (TSLP) and IL-3, with keratinocytes and CD4+T cells serving as potential sources.[32,33] As previously mentioned, while basophils generally exist in the peripheral circulation, their presence in the skin lesions of AD patients suggests an active migration from circulation to inflammatory tissues. However, our understanding of the mechanisms underlying this migration is limited. Various cytokines regulate the development and activation of basophils, including IL-3,[34] granulocyte–macrophage colony stimulating factor, Toll-like receptors, and TSLP.[35–37] The phenotype of basophils can vary depending on the cytokines involved. For instance, TSLP-induced mouse basophils exhibit a highly activated phenotype, characterized by increased expression of key activating cytokine receptors such as IL-18 and IL-33 receptors, compared to IL-3 activated basophils. Consequently, these TSLP-induced basophils are rapidly responsive to IL-18 and IL-33, leading researchers to designate them as "skin-homing basophils".[38] Siracusa et al also demonstrated that two populations of basophils induced by TSLP and IL-3 exhibit distinct phenotypic and functional heterogeneity.[39] It is noteworthy despite the limited lifespan of basophils in peripheral circulation—typically 1 to 2 days—, basophils isolated from lesions of dermatitis can remain stable in the skin for up to 12 days or longer after recruitment into inflammatory lesions.[40,41] Furthermore, these basophils exhibit different transcriptional profiles and morphological characteristics compared to their circulating counterparts.[26,42] Overall, the recruitment and infiltration of basophils is pivotal in various diseases, including AD. The structural and functional differences between peripheral and infiltrating basophils, as along with the variability of basophil populations induced by different factors in the skin, further substantiate this significance.

Synergistic Interactions Between Basophils and ILC-2 Cells

Both basophils and group 2 innate lymphoid (ILC-2) cells can accumulate and induce type 2 cytokine-related inflammation in inflamed AD-like skin lesions.[39,43] This observation suggests possible interactions or cross-regulation between these two cell types. Imai et al found that ILC-2 cells were significantly induced in diseased skin in an IL-33-induced AD mouse model.[44,45] In this model, researchers further demonstrated that basophils activate ILC-2 cells through IL-4. Depleting basophils led to a decrease in ILC-2 cell populations and alleviated inflammation in mouse models, while depletion of other cell types did not show corresponding changes. Consequently, researchers speculate that basophils and ILC-2 cells can synergistically mediate inflammation in AD mouse models, although the precise mechanism remains to be explored.[46] Kim et al further demonstrated that the response of basophils occurs earlier than that of ILC-2 cells, and that basophil-derived IL-4 is essential for the activation and proliferation of ILC-2 cells. This conclusion is supported by observations of both basophils and ILC-2 cells populations accumulating in close proximity within inflamed skin of both human and murine models.[40] In the skin lesions of AD patients, the frequency of basophils is positively correlated with the proportion of ILC-2 cells, and negatively correlated with the proportion of circulating ILC-2 cells, indicating that basophils may induce ILC-2 cell infiltration into the skin.[22]

Basophils Promote the Polarization of Th2 Cells

AD has always been considered to be associated with abnormal activation of Th2 type immune response, and many cytokines involved in it are associated to basophils, such as IL-33 and TSLP.[47] The initial discovery of the involvement of basophils in Th2 immune responses originated from studies of animal immune responses to helminthic and parasitic infections.[7,10,48] The successful identification of basophil populations and the development of mouse models for studying basophils have enhanced our understanding of the role of these cells in immunity.[49,50] In various conditions, such as acute AD, chronic IgE-mediated dermatitis, airway inflammation, and eosinophilic esophagitis-like diseases, basophils are crucial in inducing Th2-mediated cytokine inflammation.[39,51–53]

Obata et al demonstrated that basophils significantly contribute to chronic allergic inflammation using a mouse model of eosinophil depletion. Their study suggested that basophils may act as upstream promoters during skin inflammation by secreting chemokines and cytokines.[51] Hida et al revealed that IL-4 secreted by basophils following various stimuli is vital for inducing T cell differentiation into Th2 cells both in vivo and in vitro.[54] Keunhee Oh et al proposed that basophils aid in Th2 T-cell differentiation by secreting IL-2 and facilitating cell-to-cell contact.[55] Castillo et al found that in mechanically damaged skin, basophils infiltrate the tissue and produce large amount of IL-4, which subsequently triggers skin derived dendritic cells to promote Th2 polarization following antigen exposure.[56] Hashimoto et al reported that the interplay among basophils, TSLP, and periostin enhances IL-31 expression in macrophages, which may contribute to the pruritus associated with AD.[57] Furthermore, Hou et al observed a significant decrease in the Th2 cell population in the ear and spleen of a mouse model following depletion of basophils, indicating that basophils are critical in driving the polarization of naive T cell into Th2 cells.[58]

Alternate Mechanisms Involving Basophils in AD

In addition to ILC-2 and Th2 cells, basophils can also recruit other inflammatory cells, such as eosinophils and neutrophils, into the skin during chronic skin inflammation, contributing to the onset, persistence, or exacerbation of lesions.[51] Joerg U et al found that basophils can increase the levels of chemokines such as TSLP and CCL24 in inflammatory tissues to recruit additional effector cells, focusing primarily on the biological effects of eosinophils in the downstream.[59] Additionally, researchers have observed that innate immune cells actively participate in the worsening of AD symptoms due to *Staphylococcus aureus* by activating basophils, eosinophils and dermal fibroblasts through NOD2/TLR2 signaling.[60] Tristetraprolin (TTP) is an RNA binding protein known to induce RNA degradation by binding to the 3'untranslated region, and its role in mast cells has been recognized.[61] Recently, some researchers have identified that TTP plays a crucial role in basophils and skin inflammation. Ito et al reported that following antigen stimulation, the expression of TTP in basophils is upregulated, as is the mRNA expression of inflammatory factors in TTP-deficient basophils. Specifically, TTP deficiency enhances stability of IL-4 mRNA in basophils, resulting in increased IL-4 mRNA expression. Furthermore, animal experiments have shown that basophil-specific TTP deficiency exacerbates skin allergic inflammation, underscoring the importance of TTP in regulating skin allergic inflammation within basophils.[62]

How Do Basophils Alleviate AD

Basophils in AD inflammation serve not only inducers of inflammation, but also possess beneficial effects that promote inflammation resolution. Infiltrating basophils in AD skin contain sphingosine-1-phosphate, a substance that has been shown to reduce the migration of basophils into the skin, thereby exerting an anti-inflammatory effect.[63] Egawa et al discovered that during the IgE-mediated cutaneous allergic inflammation reaction, basophil-derived IL-4 induces monocytes to differentiate into M2-like macrophages facilitating their anti-inflammatory functions and negatively regulating allergic inflammation.[64] Additionally, Pellefigues et al found that basophils can regulate the efferocytosis of macrophages residing in the dermis, promoting the clearance of apoptotic cells from tissues and thereby facilitating recovery from inflammation. Their study also demonstrated that basophils and IL-4 collaboratively promote the resolution of leukocyte landscape during inflammation.[65] Basophils can also promote the expression of key genes such as *Filaggrin* and *Desmoglein 1α*, which are essential for the recovery of the skin barrier.[65]

In summary, despite the disturbing role of basophils and their secretion of IL-4 and other inflammatory factors in the onset and progression of AD, their positive contributions should not be overlooked.

Current Promising Methods for Treating AD with Basophil Targeting

Wang et al discovered that the acute itching induced by allergens in AD mouse models is independent of mast cells, and the activation of basophils alone capable of eliciting itching behavior. They further established that basophils and lipopolysaccharide-activated T cells (LCT4) mediate acute itch flares in AD-like disease, while mast cells and histamine are crucial for acute itch under steady-state conditions. Notably, LCT4 activates a cell population that specifically expresses IL-31 receptor (IL31RA).[26] Given that basophils are a potential source of IL-31,[66] whether the IL-31 derived from basophils synergizes with LCT4 to induce acute itch needs to be explored. Treatment strategies targeting IL-31 may involve modulating basophil function. Nemolizumab, a humanized monoclonal antibody targeting IL-31 receptor A, has undergone multiple clinical trials with proven effectiveness.[67–69]

Phosphodiesterase (PDE) 4 inhibitors increase the levels of cAMP in various immune cells, including T cells and macrophages, by inhibiting PDE4, thus achieving anti-inflammatory effects.[70] PDE4 inhibitors have been approved by the FDA for treating AD patients. Recently, researchers have found that PDE4 inhibitors can also exert anti-inflammatory effects by targeting basophils. Takahashi et al speculated that difamilast alleviates skin inflammation in oxazolone-induced AD model by inhibiting the ERK phosphorylation in basophils, which subsequently downregulates IL-4 expression. Although the exact mechanism remains undetermined, their findings indicate that the PDE4 inhibitors can directly suppress basophil activation and IL-4 production, demonstrating potential therapeutic applications in basophil-related diseases.[71]

IL-37, also known as IL-1F7 and a member of the IL-1 family, is an immunosuppressive agent that inhibits the production of pro-inflammatory mediators in the immune system.[72] Hou et al found that IL-37 can downregulate the TSLP receptor on the surface of basophils, thereby reducing the activation of basophils IL-4 production, achieving the effect of reducing inflammation. However, since basophils can also be activated by other factors such as IL-3, while IL-37 can ameliorate skin dryness in mice, it does not reduce scratching behavior. This observation aligns with the finding that basophil levels in ear tissue remain unchanged.[58]

In addition to these common therapeutic targets, novel treatments involving basophils have emerged. Plant extracts, as therapeutic drugs containing multiple chemical components, may provide enhanced efficacy compared to single compounds.[73] Kwon et al discovered Forsythia velutina Nakai extract (FVE), a plant extract, can inhibit degranulation and cytokine release in basophils by suppressing high-affinity IgE receptor. Furthermore, FVE can also disrupt inflammatory cell–cell interactions, preventing the propagation and chronicization of inflammation. For instance, FVE can downregulate basophil-derived TNF-α, to interfere with the crosstalk between basophils and macrophages.[74] Given the complexity of FVE components and the diversity of its mechanisms, it could serve as a viable alternative for patients unresponsive to conventional medications, provided its safety is ensured. Similarly, Joerg U et al proposed a promising approach for combined therapeutic interventions that inhibit basophil activation while reducing eosinophil levels in the skin.[59]

Conclusion

Basophils contribute to the pathogenesis of AD through various pathways, exhibiting specific transcriptional profiles and phenotypic changes of basophils in AD. They can be recruited into the skin by chemokines and cytokines, collaborating with ILC-2 cells to secrete cytokines, thereby promoting Th2 cell polarization and acting as initiators in inflammation. Alternatively, basophils can also ameliorate AD through multiple mechanisms fostering inflammation resolution and restoring the skin barrier (Figure 1). While numerous emerging treatment methods for AD are being explored, a deeper

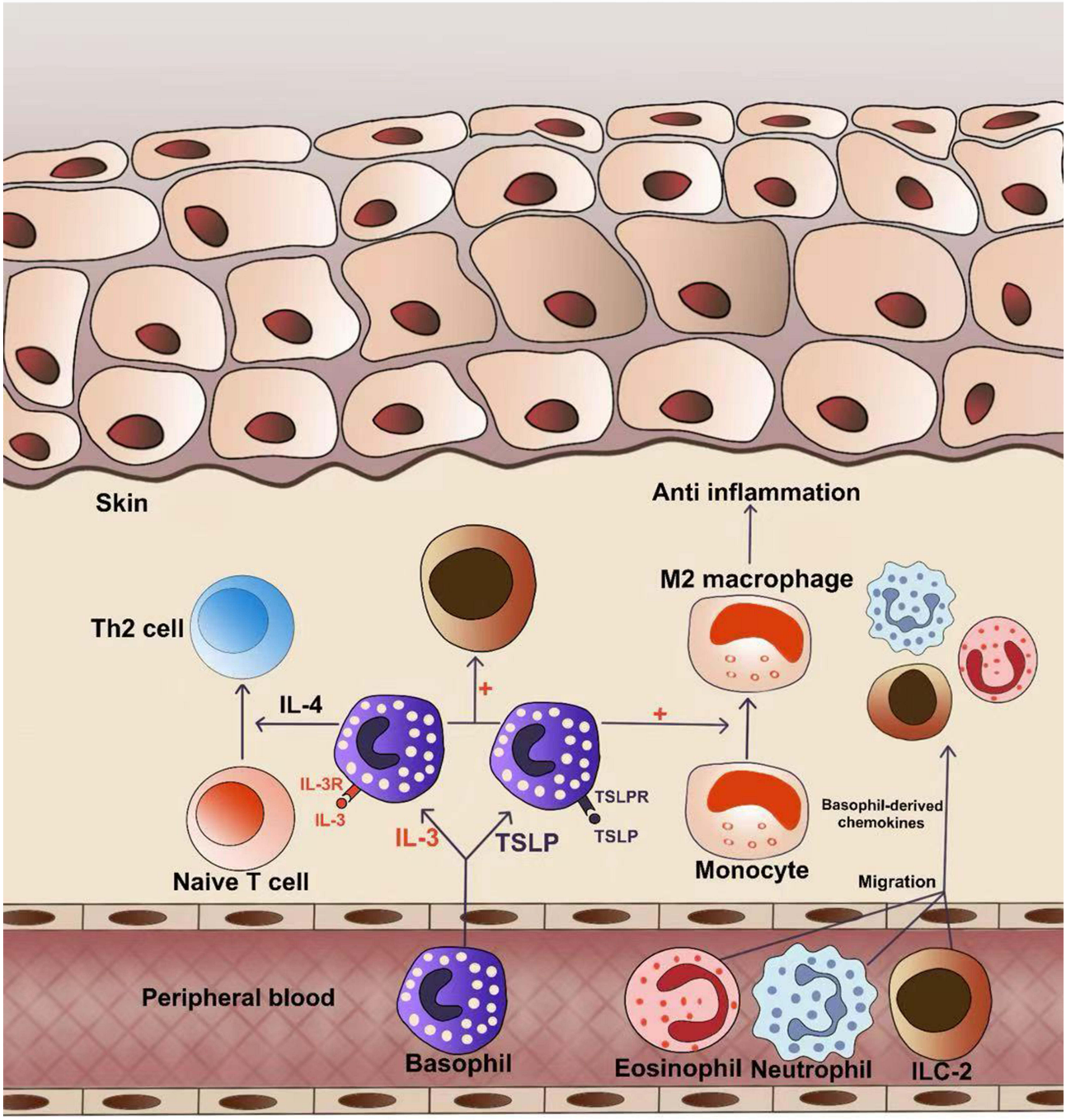

Figure 1 The involvement of basophils in the pathogenesis of AD. Basophils are recruited to cutaneous tissues by cytokines (eg, IL-3, TSLP) and exhibit diverse phenotypes. These skin-infiltrating basophils can synergize with ILC-2 cells and promote TH2 cell polarization, thereby exacerbating inflammation, while also recruiting other inflammatory cells such as neutrophils and eosinophils. Furthermore, basophils possess anti-inflammatory capabilities, exemplified by their ability to induce the differentiation of monocytes into M2-type macrophages.

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understanding of the role of basophils in AD enhance the development of novel therapeutic strategies and inform the reassessment of existing treatment approaches.

Abbreviations

AD, atopic dermatitis; IL, interleukin; CD, cluster of differentiation; TSLP, thymic stromal lymphopoietin; IgE, immunoglobulin E; ILC-2 cells, group 2 innate lymphoid cells; TLR, toll-like receptor; CCL, chemoattractant cytokine ligand; NOD2, nucleotide-binding oligomerization domain 2; TTP, tristetraprolin; LCT, lipopolysaccharide-activated T cells; PDE, phosphodiesterase; cAMP, cyclic adenosine monophosphate; FDA, food and drug administration; ERK, extracellular regulated protein kinases; TNF-α, tumor necrosis factor-α; FVE, Forsythia velutina Nakai extract.

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Disclosure

The authors report no conflicts of interest in this work.

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