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Possible Roles of Basophils in Chronic Itch

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Abstract

Basophils are blood granulocytes and normally constitute less than 1% of blood peripheral leukocytes. Basophils share some morphological and functional similarities with mast cells, and basophils were once regarded as redundant and negligible circulating mast cells. However, recent studies reveal the indispensable roles of basophils in various diseases, including allergic and pruritic diseases. Basophils may be involved in itch through the mediation of a Th2 immune response, interaction with other cells in the skin, and secretion of a wide variety of itch-related mediators, *e.g.*, histamine, cytokines and chemokines (IL-4, IL-13, IL-31, and TSLP), proteases (cathepsin S), prostaglandins (PGE2 and PGD2), substance P, and platelet-activating factor. Not only pruritic skin diseases (*e.g.*, atopic dermatitis, irritant contact dermatitis, chronic urticaria, prurigo, papulo-erythroderma of Ofuji, eosinophilic pustular folliculitis, scabies, tick bites, and bullous pemphigoid) but also pruritic systemic diseases (*e.g.*, primary sclerosing cholangitis and polycythemia vera) may be affected by basophils.

Key Words

mediator, pruritogen, pruritus, pruritic skin disease, pruritic systemic disease

1. Introduction

Basophils are 5-8 μm diameter granulocytes with segmented and condensed nuclei. They normally constitute less than 1% of blood peripheral leukocytes.^[1] Basophils share some morphological and functional similarities with tissue-resident mast cells.^[2] Both basophils and mast cells contain basophilic granules in the cytoplasm, express high-affinity immunoglobulin (Ig)E receptors (Fc ϵ RI) on their cell surfaces, and release histamine and other inflammatory mediators when stimulated.^[2] These characteristics once led to the idea that basophils were redundant and negligible circulating mast cells.

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^[3] In addition, human basophils cannot be easily detected in routinely processed histological examinations. Thus, little was known about the role of basophils in human skin diseases until recently. However, new studies have shed light on the indispensable roles of basophils in allergic inflammation both in mice experiments^[4,5] and in human studies.^[6,7]

Allergic skin diseases such as atopic dermatitis (AD) and chronic spontaneous urticaria (CSU) feature chronic itch. Basophils are involved in the pathogenesis of these diseases and are likely implicated in itch. Additionally, basophils may play a role in some pruritic diseases with systemic origins. The objective of this review is to discuss the role of basophils in inducing itch (Figure 1) and the pruritic diseases in which basophils may induce or mediate itch (Table 1).

2. Basophils

Infiltrating basophils are detected in the skin lesions of pruritic diseases such as AD, prurigo, urticaria, bullous pemphigoid, and scabies.^[6]

Human basophils play a role in immune responses by secreting histamine, T helper (Th)2 cytokines, and a variety of mediators (*e.g.*, leukotriene [LT]C4) when activated through either an IgE-dependent pathway (via FcεRI-crosslinking) or an IgE-independent pathway (*e.g.*, C5a, thymic stromal lymphopoietin [TSLP], major basic protein [MBP], or nerve growth factor [NGF]).^[8-12] In rodents, the IgE-dependent pathway is associated with interleukin (IL)-3-elicited basophils; these basophils degranulate to release molecules such as histamine, LTs, and proteases when activated by antigen-IgE stimulation. On the contrary, the IgE-independent pathway is associated with TSLP-elicited basophils that are activated by cytokine stimulation (*e.g.*, IL-3, IL-18, and IL-33) and secrete cytokines (*e.g.*, IL-4 and IL-6).^[13] Whether these differences exist

in human basophils is still unclear. In addition, murine basophils are considered to function as antigen-presenting cells (APCs); however, whether human basophils also function as APCs is controversial.^[14]

3. Pruritogens Associated with Basophils

To date, researchers have identified many endogenous peripheral itch mediators that are associated with basophils (Figure 1).^[15]

3-1. Histamine

The role of histamine and its G protein-coupled receptor H1R in itch has been studied for several decades. Recent studies suggest that H4R, another G protein-coupled receptor that is expressed by sensory neurons and other cell types, is also a potential mediator of pruritus.^[16] An H4R antagonist attenuated histamine-induced itch in healthy subjects^[17] and itch in patients with AD.^[18] In addition, H4R is also involved in production of IL-31, a major pruritic cytokine, from Th2 cells and mononuclear cells in AD patients^[19] and in other immune-regulating functions during allergic inflammation.^[20]

Basophils store histamine in granules and release histamine following various stimuli. The most studied pathway by which basophils release histamine is the IgE-dependent pathway. Ishizuka *et al.* first described histamine release from human peripheral basophils through IgE-anti-IgE or allergen-IgE antibody reactions. In addition, anti-IgG treatment also provokes histamine release from basophils.^[21] This histamine-release is provoked through the cross-linking of the IgE receptors on basophils by anti-IgG treatment.^[22] Interestingly, human basophils with IgE are also able to release histamine in the absence of an antigen when they interact with IgE-binding lectin that is expressed by a certain type of epithelial cells.^[23] NGF, a neurotrophin that

may also be involved in itch through multifocal pathways, ^[24] enhances histamine release from human basophils via its receptor tropomyosin receptor kinase A (TrkA). ^[25]

Stimuli other than IgE or IgG can also promote histamine release from basophils. Complement, especially C5a, promotes histamine release from basophils, ^[26-28] and is partially responsible for the pathogenesis of chronic urticaria. ^[29] TSLP, substance P (SP), MBP, and lysophosphatidic acid (LPA) also promote histamine release from human basophils. ^[9,10,30-32]

3-2. IL-4 and IL-13

IL-4 and IL-13 are key cytokines involved in Th2 immunity, which is predominant in many allergic skin diseases such as AD. ^[33] Although Th2 cells represent major cellular source of IL-4 and IL-13, other immune cells including basophils are capable of producing these cytokines. ^[34-36]

Human basophils release IL-4 and IL-13 through both IgE-dependent and non-IgE mediated mechanisms (*e.g.*, C5a, TSLP, and IL-31). ^[9,37-41] In mice, TSLP-elicited basophils preferentially produce IL-4. ^[13] Whether this distinction in TSLP-elicited and IL-3-elicited basophils exists in humans is uncertain. ^[9,42]

Until recently, IL-4 and IL-13 were considered to be involved in itch only through indirect pathways. ^[15,43] In 2017, Oetjen *et al.* reported that IL-4 and IL-13 directly activate sensory neurons to exacerbate chronic itch. ^[44] This signaling pathway is dependent on IL-4 receptor subunit alpha (IL-4R α), which is a shared receptor subunit for IL-4 and IL-13, and Janus kinase (JAK) type 1. In addition, JAK inhibitor treatment improved recalcitrant itch in patients who had not responded to other

immunosuppressive therapies. ^[44] Dupilumab, a monoclonal antibody against IL-4R α for the treatment of AD, demonstrates an antipruritic effect in the first 4 weeks of treatment prior to its anti-inflammatory effect suggesting a direct effect of this drug on the neural system. ^[45-47]

3-3. IL-31

IL-31 is a pruritogenic Th2-type cytokine that induces itch in addition to skin inflammation. ^[48] CD4(+) Th2 cells express H4R and release IL-31 partially through H4R reaction. ^[19] IL-31 is implicated in itch in various diseases including AD, CSU, prurigo nodularis, uremic pruritus, mastocytosis, localized cutaneous amyloidosis, and cutaneous T-cell lymphoma. ^[49-53] Its receptor is a heterodimeric complex comprising IL-31 receptor A and oncostatin M receptor β that is expressed by epidermal keratinocytes, eosinophils, activated monocytes/macrophages, dorsal root ganglia neurons, and peripheral nerve fibers. ^[49,54] Recently, basophils have been confirmed to express IL-31, which may contribute to pruritus in CSU. ^[38]

3-4. TSLP

TSLP is an IL-7-like cytokine and is expressed by keratinocytes, dendritic cells, mast cells, and fibroblasts. ^[55] Basophils are also reported to secrete TSLP in mice. ^[56,57] Intradermal injection of TSLP directly activates sensory neurons via TSLP receptors and evokes an itch response in mice. ^[58] Similarly, TSLP receptors are also expressed in human dorsal root ganglia, and TSLP is considered to evoke itch in humans as well. ^[58]

3-5. Proteases

Both endogenous and exogenous proteases can induce non-histaminergic itch via protease-activated receptors (PARs), mainly PAR-2 and probably PAR-4.^[59]

Cathepsin S is an endogenous protease that can activate PAR-2 and PAR-4 and induce itch.^[60] Human basophils can produce cathepsin S.^[61] However, the significance of basophil cathepsin S for itch is still uncertain.

3-6. Prostaglandins

Prostaglandins (PGs) are one class of eicosanoids and are synthesized from arachidonic acid (AA). AA is released from phospholipids in the cell membrane by phospholipase A2 and then converted into PGs by cyclooxygenase and the respective PG synthases.^[62] Among the subtypes of PGs, PGE2 and PGD2 are thought to be involved in itch.

PGE2 is thought to potentiate histamine-induced itch. Conversely, PGD2 inhibits itch in animal models of pruritus^[63-65]; however, it is uncertain whether this inhibitory effect of PGD2 exists in humans.

Human basophils produce PGE2 and PGD2 when stimulated through FcεRI signaling.^[66] The significance of basophil-derived PGs in itch has not yet been elucidated.

3-7. Substance P

SP is a tachykinin neuropeptide that binds to three receptors neurokinin 1-3 receptors (NK1R-NK3R). Among these subtypes, NK1R — which is expressed by mast cells, keratinocytes, cutaneous nerve ending, and the central nervous system — mainly mediates SP-induced itch. The NK1R antagonist serlopitant significantly reduced chronic pruritus of different types.^[67]

A larger number of basophils from patients with CSU express SP and NK1R compared with those from healthy control.^[30] The significance of SP expressing basophils is still uncertain.

3-8. Platelet-activating factor

Intradermal injection of platelet-activating factor (PAF) provokes itch responses in humans.^[68] PAF promoted histamine release from human mast cells *in vivo*,^[69] and antihistamines inhibited PAF-induced itch.^[70] These findings suggest that PAF-induced itch is histamine-dependent. However, a recent study revealed that intradermal injection of PAF did not raise dermal histamine levels, suggesting that PAF-induced itch could also be histamine-independent.^[71]

Human basophils are capable of synthesizing PAF by cytosolic phospholipase A2.^[72,73] However, whether basophil-derived PAF can induce itch has not been confirmed.

4. Basophils and Pruritic Skin Diseases

4-1. Atopic dermatitis

Many factors are involved in AD itch, with a variety of receptors (*e.g.*, transient receptor potential channels, PAR-2, and H4 receptors), secreted molecules (*e.g.*, NGF, substance P, and proteases), and cytokines/chemokines (*e.g.*, IL-4, IL-13, IL-31, and TSLP).^[15]

In humans, there is a large basophilic infiltrate in the lesional skin of AD patients compared to healthy control.^[6,74,75] In animal models of AD, basophils are indispensable for IgE-mediated chronic allergic inflammation^[5] and vitamin D3-induced AD-like dermatitis.^[74] Infiltration of eosinophils into the lesional skin of IgE-dependent dermatitis was dependent on basophils.^[76] Thus, basophils are thought to play important

roles in the pathogenesis of AD. Basophils might be partially involved in itch through mediation of the Th2 immune response, interaction with other cells also involved in itch, and secretion of pruritogens, including histamine and cytokines/chemokines.

4-2. Irritant contact dermatitis

Irritant contact dermatitis (ICD) is a non-allergic type of skin inflammation that is often accompanied by itch. In the skin lesions of ICD, a large number of eosinophils are detected in the vicinity of basophils. Eosinophils play a role in the development of ICD, and basophils are thought to promote eosinophilic infiltration into the inflammation site.^[77]

4-3. Chronic spontaneous urticaria (CSU)

CSU, also known as chronic idiopathic urticaria, is a common skin disease that is characterized by recurrent spontaneous pruritic wheals lasting 6 weeks or longer.^[78,79] Histamine released from mast cells and basophils, and autoimmune etiologies are believed to play roles in CSU itch. Histamine levels are increased in lesional and non-lesional skin in patients with CSU^[80]; histamine-releasing autoantibodies against FcεRI are detected in sera of up to 40% patients with CSU.^[81] However, antihistamines do not necessarily improve the symptoms of CSU, and other factors besides histamine may also participate in the pathogenesis of CSU.

In CSU, a basophilic infiltrate is frequently present in lesional skin.^[6,82] Patients with CSU show peripheral basopenia, which may reflect basophil migration into the skin from circulation. Peripheral basopenia is recovered following the administration of an anti-IgE antibody omalizumab (OMZ).^[83] OMZ improved symptoms of CSU, including itch, and reduced FcεRI expression of basophils within two weeks.^[84,85] Altered

basophil function was also noted.^[86] These findings indicate that basophils may play a significant role in the pathogenesis of CSU.^[80]

Interestingly, infiltrating basophils in the skin express IL-31,^[38] and serum levels of IL-31 are increased in patients with CSU.^[87] Therefore, basophil production of IL-31 may exert pruritogenic function in this disease.

4-4. Prurigo

Prurigo (including subacute prurigo, chronic prurigo, and prurigo nodularis) is a form of severe itching. Its main skin symptoms are multiple papules, which develop into firm nodules.^[88] A higher number of basophils were detected in the lesional skin of patients with prurigo (both subacute and chronic types) compared to healthy controls.^[6] In a mouse model of prurigo, basophils and antigen-specific IgE are indispensable. Prurigo-like skin-lesions in this model are accompanied by spontaneous scratching behavior. Furthermore, depletion of basophils attenuates scratching behavior.^[88] This suggests that basophils have an important role in prurigo itch. Following basophil depletion, there is reduced production of the pruritogenic cytokine IL-31, and decreased eosinophilic infiltration into lesions. Eosinophils are thought to be involved in itch in prurigo through interaction with sensory nerves.^[89,90] As such, basophils may be involved in prurigo itch.

4-5. Papulo-erythroderma of Ofuji

Papulo-erythroderma of Ofuji (PEO) features pruritic plaques consisting of flat-topped papules on erythroderma.^[91] These plaques spare large skin folds and form a characteristic appearance known as the “deck-chair sign.” Th2 immune responses may be involved in the pathogenesis of PEO.^[92,93] In patients with PEO, expression levels of basophil-activation markers (CD63, CD69, and CD203c) on peripheral basophils are

up-regulated.^[94] Thus, basophils might be implicated in the pathogenesis of PEO and itch.

4-6. Eosinophilic pustular folliculitis (Ofuji)

Eosinophilic pustular folliculitis (EPF) is an inflammatory skin disease with pruritic follicular papulo-pustules of unknown etiology.^[95] The most characteristic histological feature of EPF is that a number of eosinophils infiltrate around and in hair follicles in the dermis. In addition, a number of basophils are found around hair follicles and perivascular areas.^[6,96] The pathological significance of basophils in EPF remains unknown, but inducing Th2 immunity through secretion of Th2 cytokines and chemokines may contribute to the pathogenesis of EPF and to pruritus.^[96]

4-7. Scabies

Scabies is a parasitic skin disease caused by *Sarcoptes scabiei* and is characterized by severe itch.^[97] The mechanisms of itch in scabies are unclear, but likely involve the immune response.^[98,99] A large number of basophils infiltrate the lesional skin of scabies.^[6] Basophils may also regulate immune responses and be involved in itch directly and/or indirectly.

4-8. Tick bites

Ticks are ectoparasitic arthropods and their bites are known to sometimes provoke pruritus.^[100] Histologically, significant infiltration of basophils and eosinophils is seen in the lesional skin of tick bites, especially in those with more than 2 tick bites compared with those with only one tick bite. In contrast, the number of mast cells does not increase.^[101,102] Basophils are reported to play a role in antibody-mediated acquired

immunity against ticks,^[103] and they may be involved in itch through immune-regulation or an undetermined mechanism.

4-9. Bullous pemphigoid

Bullous pemphigoid (BP) is most commonly noted in the elderly and is accompanied by intense itch. The pathogenesis of BP likely involves autoreactive antibodies against BP180 antigen and Th2 immunity. IL-31 is an additional itch-related factor, which is also present in BP. The serum and blister fluid of BP patients contains high levels of IL-31, possibly emanating from eosinophils.^[104]

Basophils have received attention as itch initiators in BP. A single report demonstrated that levels of basophil CD203 expression — a reliable indicator of basophil activation — accompanied disease activity in a BP patient.^[105] In addition, circulating peripheral basophils from BP patients de-granulate and release histamine when incubated with BP180 protein.^[106,107] Serum IgE from BP patients in conjunction with BP180 antigen binds rat basophils expressing human FcεRI and promotes basophil degranulation.^[108] OMZ attenuates IgE-mediated activation and degranulation of basophils. In one report, administration of OMZ decreased itching and other symptoms in a BP patient.^[109] Collectively, basophils might play a role in BP itch through the release of histamine and/or other mediators and through other yet-undetermined pathways.

5. Basophils and Pruritic Systemic Diseases

5-1. Primary sclerosing cholangitis

Patients with cholestatic liver disease often complain of severe itch. Bile acids, an imbalance of endogenous opioid molecules, and LPA have been suspected as pruritogens in cholestasis.^[110] Recently, basophils have been reported to play a role in pruritus in primary sclerosing cholangitis (PSC), a cholestatic liver disease. In PSC, serum levels of LPA were elevated compared with healthy controls.^[111,112] LPA stimulates basophils to release histamine, resulting in wheals and itch.^[32] However, antihistamines do not improve cholestatic itch, and other non-histaminergic itch mediators secreted by basophils should be considered.

5-2. Polycythemia vera

Polycythemia vera (PV) is a myeloproliferative neoplasm featuring erythrocytosis, and often accompanied by leukocytosis and/or thrombocytosis. Patients with PV often display a characteristic itch that occurs on exposure to water (aquagenic pruritus).^[113] Recently, the *JAK2V617F* mutated allele was reported to be involved in the pathogenesis of PV. Almost all patients with PV carry this mutation, and mutation burden is correlated with the occurrence of pruritus.^[114] Those who carry this mutation show elevated peripheral basophil counts and a greater number of CD63(+) activated basophils. Interestingly, patients with aquagenic pruritus have a significantly larger number of CD63(+) basophils.^[115] In addition, JAK2 inhibitor treatment attenuates basophil activation in PV,^[115] and the JAK 1/2 inhibitor ruxolitinib improves pruritus in PV.^[116] Although collectively, these data suggest that basophils are involved in the pathogenesis of PV itch, there are reports that peripheral basophil counts and blood histamine concentrations do not correlate with pruritus in PV, and that mast cell-derived prostaglandins are responsible for pruritus.^[117]

6. Conclusions

Basophils may be involved in itch in various pruritic diseases through the mediation of a Th2 immune response, interaction with other cells which are also involved in itch, and production and release of a wide variety of pruritogens. Further research is needed to clarify the pathogenetic roles of basophils in itch.

Abbreviations

AA, Arachidonic acid

AD, Atopic dermatitis

APC, Antigen-presenting cell

BP, Bullous pemphigoid

CSU, Chronic spontaneous urticaria

EPF, Eosinophilic pustular folliculitis

ICD, Irritant contact dermatitis

Ig, Immunoglobulin

IL, Interleukin

JAK, Janus kinase

LPA, Lysophosphatidic acid

LT, Leukotriene

MBP, Major basic protein

NGF, Nerve growth factor

NK, Neurokinin

OMZ, Omalizumab

PAF, Platelet-activating factor

PAR, Protease-activated receptors

PEO, Papulo-erythroderma of Ofuji

PG, Prostaglandin

PSC, Primary sclerosing cholangitis

PV, Polycythemia vera

Th, T helper

TrkA, Tropomyosin receptor kinase A

TSLP, Thymic stromal lymphopoietin

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Conflict of Interest

Dr. Yosipovitch has been a consultant, advisory board member and supported as a researcher for the following drug companies: Menlo, Trevi, Sienna, Opko, Sanofi, Galderma, Novartis, Pfizer, Eli Lilly, and Sun Pharma. The other authors have declared no conflicting interests associated with this manuscript.

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Author Contribution

GY designed the paper. TH reviewed the literature and wrote the manuscript. JR, KS, and GY revised it critically. All authors have read and approved the final manuscript.

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Table 1. Pruritic diseases that are or may be associated with basophils.

Skin diseases	Atopic dermatitis
	Irritant contact dermatitis
	Chronic spontaneous urticaria
	Prurigo
	Papuloerythroderma of Ofuji
	Eosinophilc pustular folliculitis
	Scabies
	Insect bites
	Bullous pemphigoid
Systemic diseases	Primary sclerosing cholangitis
	Polycythemia vera

Figure Legends

Figure 1. Involvement of basophils in itch.

Basophils are involved in itch through the mediation of the Th2 immune responses, interaction with T-cells and eosinophils, and secretion of a wide variety of itch-related mediators.

IL, interleukin; PG, prostaglandin; Th, T helper; TSLP, thymic stromal lymphopoietin.

