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Mast cells in atopic dermatitis

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Summary of Recent Advances

Mast cells play as the major effector cells in immediate hypersensitivity through activation via the high-affinity IgE receptor, FcεRI, although many other functions have recently been discovered for this cell type. Given the broad array of proinflammatory mediators secreted from FcεRI-activated mast cells, as well as sensitization to allergens, IgE elevation, and increased mast cells in a majority of atopic dermatitis patients, mast cells are believed to be involved in the pathogenesis of atopic dermatitis. Numerous animal models have been used to study this epidemic disease. Here we review the recent progress to synthesize our current understanding of this disease and potential mechanisms for a mast cell's role in the disease.

Introduction

Mast cells are hematopoietic cells that originate from progenitor cells in the bone marrow. Mast cell progenitors enter the circulation and become mature mast cells after entering destination tissues under the influence of local microenvironment [1]. Mast cells have been long understood as the key effector cell type in IgE-mediated immediate hypersensitivity and allergic disorders, as well as in protective immune responses to certain parasites and bacteria [2,3]. However, recent progress in the field has broadened their roles in many immune responses [4], ranging from innate defense against venoms of bees and snakes [5] to multiple aspects of adaptive immune responses such as antigen presentation and leukocyte recruitment to draining lymph nodes [6] as well as downmodulation of immune responses [7]. Their pathogenic roles have been extended to include not only allergic diseases and helminth and bacterial infection, but also autoimmune diseases [8,9], allograft tolerance [10], angiogenesis in tissue repair [11], and carcinogenesis [12,13].

The high-affinity receptor for IgE (FcεRI) expressed on mast cells (and basophils) consists of four subunits ($\alpha\beta\gamma_2$): an IgE-binding α chain, a signal-amplifying, receptor-stabilizing β chain, and two disulfide-bonded γ chains that are the main signal transducers [14]. Upon encounter with multivalent antigen, IgE-bound FcεRI on mast cells become aggregated or crosslinked, leading to cell activation [15]. Activated mast cells secrete three classes of substances: (1) preformed chemical and protein mediators, such as histamine, serotonin, heparin and

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chondroitin sulfates, proteases, major basic protein, acid hydrolases, cathepsin, etc., (2) lipid mediators, such as prostaglandins, leukotrienes, and platelet-activating factor (PAF), and (3) preformed and/or de novo synthesized growth factors, cytokines, and chemokines, such as tumor necrosis factor (TNF)-α, TGF-β, MIP-1α, MCP-1, VEGF, IFN-α/β/γ, GM-CSF, IL-1α/β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-18, IL-25, etc. (Fig. 1).

Anaphylactic responses to insect stings, injected medications, foods, and other agents are thought to be caused by IgE/antigen-dependent mast cell activation [16]. In addition to this classic pathway of systemic anaphylaxis [17,18], IgG antibodies can also induce anaphylaxis in a basophil-dependent manner in the mouse [19]. Histamine is primarily responsible for the development of shock in the classic pathway. In contrast, PAF is responsible in the latter alternative pathway. Despite the earlier controversy on the role of mast cells in asthma [20], recent studies clearly showed their importance [21,22]: mast cells can markedly enhance antigen-dependent airway hyperresponsiveness, airway eosinophil infiltration, and an increase in the number of proliferating cells in the airway epithelium that are induced in mouse models of asthma that either omit artificial adjuvants or use low doses of antigen challenge; mast cells' roles were also shown in a chronic asthma model [23]. In asthmatics, mast cells infiltrate airway smooth muscle and contribute to persistent inflammation in the airways [24-26]. The best evidence for the pivotal role of IgE and therefore that of FcεRI in human asthma came from clinical studies demonstrating that anti-IgE mAb Omalizumab decreases serum IgE levels and allergen-induced bronchoconstriction [27,28].

The most critical tool that has driven the high-paced findings is mast cell engraftment into mast cell-deficient animals, by which one can confirm that ‘defects’ or abnormal observations on mast cell-deficient animals can be reversed by providing exogenous mast cells [29]. Stem cell factor (SCF) is a critical growth and differentiation factor for mast cell development [30,31]. c-Kit is its receptor tyrosine kinase. Loss-of-function mutations in gene loci for this ligand (*Sl*)/receptor (*W*) pair lead to profound reductions of mast cells. Mast cell-deficient $Kit^{W/W\text{-}v}$ mice have been a choice for mast cell engraftment for more than two decades. However, these mice have various other hematopoietic and non-hematopoietic abnormalities and are cumbersome to breed. In contrast, another strain of mast cell-deficient mice, $Kit^{W\text{-}sh/W\text{-}sh}$ does not have anemia or neutropenia and are easy to breed, therefore $Kit^{W\text{-}sh/W\text{-}sh}$ mice have become a favorite animal to study the mast cell function. However, because of multiple cellular abnormalities in $Kit^{W\text{-}sh/W\text{-}sh}$ and $Kit^{W/W\text{-}v}$ mice, it is essential to demonstrate that abnormalities in these mice can be rectified by ‘knock-in’ experiments before one can conclude that such abnormalities are due to mast cell deficiency [32].

Atopic dermatitis (AD)

AD, or eczema, is a chronic or chronically relapsing, pruritic inflammatory skin disease. The incidence of this disease has been increasing for the last three decades and affects at least 15% of children [33-35]. Clinical manifestations vary with age: eczematous lesions emerge on the cheeks and the scalp in infancy. Scratching causes crusted erosions. Later in the childhood, lesions involve flexures, the nape, and the dorsal skin of the limbs. In adolescence and adulthood, lichenification (thickening of the skin with accentuated skin markings) develops in flexures, head, and neck. Throughout these ages, persistent itch that often causes sleep deprivation and disfiguration of the skin substantially impairs the quality of a patient's life.

AD is characterized by skin inflammation, impaired skin barrier function, and IgE-mediated sensitization to food and environmental allergens. Histologically, acute eczematous lesions exhibit spongiosis (epidermal intercellular edema), hyperkeratosis (thickening of the stratum corneum), and parakeratosis (retention of nuclei in the stratum corneum), and chronic lesions

are characterized by acanthosis (diffuse epidermal hyperplasia) and perivascular infiltration of lymphocytes and mast cells.

The etiology of this disease is incompletely understood, but it is multifactorial and the disease is manifested by complex interactions between genetic and environmental factors. Currently, there are two major schools of hypothesis to explain the pathogenesis of this probably heterogeneous disease: (I) one assumes that the primary defect is an immune dysregulation that causes Th2-predominant inflammation and IgE-mediated sensitization. In the other hypothesis (II), an intrinsic defect in skin barrier function underlies as a primary cause of the disease. In the latter scenario, even the uninvolved phase of the disease presents with cutaneous hypersensitivity of nonlesional skin, resulting from a defective (probably genetically predisposed) skin barrier that allows the penetration of allergens and microbial pathogens [36]. The acute phase characterized by eczematous skin lesions is facilitated by allergen/IgE-bound Langerhans cells and by an infiltration of skin-homing Th2 cells. Eczematous skin lesions develop as the result of complex immune and inflammatory responses driven by the release of proinflammatory cytokines and chemokines from various resident cell types. In the immune dysregulation hypothesis (I), on the contrary, defective skin barrier is interpreted as a consequence of inflammation. Regardless how to explain the disease progression, the chronic phase is characterized by lichenification of skin, an infiltration of Th1 cells, and tissue remodeling with increased collagen deposition and dermal thickening.

Genetics of AD

Genome-wide association studies have identified several chromosomal loci as the possible locations of AD-associated genes, including 1q21, 3q21, 11q13, 16q, 17q25, 20p, and 3p26 [37,38]. These studies identified the AD susceptibility genes that support both (I) immune dysregulation and (II) impaired skin barrier function hypotheses: the involvement of *IL4*, *IL13*, *IL18*, and *TIM1* genes supports the importance of $CD4^+$ T cells and dysregulation of Th1 and Th2 genes in the pathophysiology of AD [39,40]. Recent studies also showed that thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine, plays a crucial role in differentiation and maintenance of Th2 cells by activating myeloid dendritic cells (mDCs) [41]. TSLP-activated mDCs induce proliferation of $CD4^+$ T cells, which differentiate into inflammatory Th2 cells that produce IL-4, IL-5, IL-13, and TNF-α, but little IL-10 [42]. TSLP is highly expressed in keratinocytes from AD patients [41], and transgenic (Tg) mice expressing TSLP in keratinocytes develop AD-like skin lesions [43,44]. On the other hand, impaired skin barrier function has been increasingly recognized as an underlying mechanism for the pathogenesis of AD [45,46]: *SPINK5* (serine protease inhibitor, Kazal type 5) encodes a protease inhibitor LEKTI that is expressed in the uppermost epidermis and inhibits two serine proteases involved in desquamation [39,40]. Gene variants of SPINK5 [47-49] or filaggrin, a protein important for skin barrier and terminal differentiation of the epidermis, are linked to AD. Up to 15% of atopic dermatitis patients have mutations in the *filaggrin* gene [50-53]. The *filaggrin* gene is also mutated in the mouse model of AD, *flaky tail* [54].

Furthermore, involvement of the *NOD1* and *NOD2* genes, which encode cytosolic pathogen recognition receptors [39,40], and Toll-like receptors [39,40], suggest an important role for microbes in the pathogenesis of AD [55]. Indeed, AD patients often suffer from skin infections and a majority of the patients are colonized with *Staphylococcus aureus*, an infection thought to be critical for the pathogenesis and/or worsening of skin lesions [56,57]. Consistent with this, expression of antimicrobial peptides (LL-37 and HBD-2) in the epidermis is significantly decreased in AD patients, compared to psoriasis patients [17]. The combination of LL-37 and HBD-2 showed synergistic antimicrobial activity by effectively killing *S. aureus*. AD patients are also vulnerable to severe viral infections known as eczema vaccinatum and eczema herpeticum (EH) caused by vaccinia and herpes simplex viruses, respectively. A recent study

showed that AD patients with a history of EH have a more severe Th2-polarized disease with greater allergen sensitization and more commonly have a history of food allergy, asthma, or both, compared to AD patients without EH [58]. AD patients with EH are more susceptible to cutaneous infections with *S. aureus* or molluscum contagiosum.

Mouse models of AD

Numerous mouse models of human AD have been developed since the first description of AD-like skin lesions in the dermatitis-prone NC/Nga mice in 1997 [59]. These models are essential for our current understanding of human AD, as they have been providing novel insights into the disease pathogenesis. There are two types of mouse models: (I) some mice develop skin lesions spontaneously; (II) in another type of model, skin lesions are induced by epicutaneous or intradermal challenge of immunized mice with a single allergen or a mixture of allergens. Another feature in the study of AD models is the use of genetically manipulated mice, but AD models of transgenic or gene-knockout mice either spontaneously develop skin lesions or are prone or resistant to skin lesion induction. As mouse AD models were reviewed in recent publications [60,61] and are reviewed in this issue, we discuss only major points below in the text and Table 1 (see our web site for a more comprehensive list: www.liai.org/pages/faculty-kawakami).

NC/Nga mouse model

NC/Nga mice spontaneously develop AD-like skin lesions under conventional (non-SPF [specific pathogen-free]) conditions [59]. Skin lesions in NC/Nga mice are characterized by infiltration of IL-4- and IL-5-producing $CD4^+$ T cells, mast cells, and eosinophils, as well as high expression levels of Th2 chemokines (thymus and activation-regulation chemokine/CCL17 and monocyte-derived chemotactic cytokine/CCL22) and their receptor, CCR4 [62]. The elevation of serum IgE correlated with the onset of skin lesion development [59,62]. Constitutive activation of Jak3 may be involved in the hypersensitivity of B cells to IL-4 that leads to IgE elevation in these mice [63]. However, deficiency in Stat6, a critical signal transducer for IL-4 receptor, in NC/Nga mice did not inhibit skin lesion development [64]. Stat6-deficient NC/Nga mice had the skin microenvironment of IFN-γ production and an accumulation of IFN-γ-producing T cells in draining lymph nodes, suggesting that skin lesions in these mice are IgE- and Th2-independent. Under conventional conditions NC/Nga mice are infested with rodent mites [65,66], and the eradication of the mites with ivermectin (a broad-spectrum antiparasitic) leads to healing of skin lesions and reduced IgE levels [65]. However, the incidence of skin lesions in these mice under SPF conditions drastically varies from facility to facility (<5% in our facility). To overcome this problem, several groups including our own used mite extracts to induce dermatitis in NC/Nga mice [67-71]. By applying *Dermatophagoides farinae* (Der f; a common mite on humans) extracts and Staphylococcal enterotoxin B (SEB; a superantigen secreted by *S. aureus*) on the skin of NC/Nga and C57BL/6 (B6) mice, we established a highly efficient model to induce AD-like skin lesions with histologic and immunologic characteristics similar to those of spontaneously occurring skin lesions [72]. Using this dermatitis-inducible mice, we developed a mouse model of eczema vaccinatum [73]. Infection of eczematous skin with vaccinia virus induced severe erosive skin lesions, but not in the skin of healthy mice. Eczematous mice exhibited lower NK cell activity. The role of NK cells in controlling vaccinia virus-induced skin lesions was demonstrated by experiments depleting or transferring NK cells. IL-17 reduces NK cell activity in mice with preexisting dermatitis. Given low NK cell activities and increased IL-17 expression in AD patients, these results can explain the susceptibility of AD patients to eczema vaccinatum.

Tape-stripping/epicutaneous (EC) OVA sensitization model

EC exposure of protein antigens with or without disruption of the stratum corneum generally induces Th2 cytokines [74,75]. Raif Geha and colleagues developed an induction model in several strains including BALB/c and C57BL/6 mice by repeated EC sensitization of tape-stripped skin with ovalbumin (OVA) [76,77]. Dermatitis in this model mimics skin lesions of human AD in terms of infiltration of $CD4^+$ T cells and eosinophils, and local expression of Th2 cytokines and chemokines. This model has been extensively used to study the cellular and molecular players in the development of skin lesions [61]. Interestingly, αβTCR (T cell receptor) T cells, but not γδTCR T, NKT, B, or mast cells, are required for the development in this model. Differential roles of IL-4, IL-5, and IFN-γ in skin lesion development and leukocyte infiltration were demonstrated using gene-manipulated mice, whereas IgE was not required for skin lesion development in this model [77]. In addition to these molecules, regulators that have been found to be positively involved in the development of skin lesions and inflammation in this model include TSLP, IL-10 (Th2 cytokine), CCR3 (chemokine receptor expressed in eosinophils), CCR4 (chemokine receptor expressed in skin-homing T cells), and the complement component C3. Negative regulators of skin inflammation in this model include C3a receptor and cyclooxygenase 2. In parallel to an increased realization of the importance of the impaired skin barrier in AD pathogenesis, e.g., filaggrin mutations, this group also emphasizes their findings that mechanical injury, i.e., tape stripping in their model, is critical for the development of skin lesions. Interestingly, they found that skin injury induces changes in the local environment that nurture Th2 and Th17 differentiation by increased expression of cytokines (IL-6, IL-23, IL-1, and IL-10), chemokines, and other genes [78].

Pathogenic roles of mast cells

As most studies showed increased numbers of mast cells in skin lesions in the AD models, it is generally assumed that mast cells contribute to skin inflammation. Unfortunately, however, few studies have directly addressed whether, to what extent, or by what mechanism mast cells play a role in spontaneous or induced development of AD-like skin lesions. An EC OVA sensitization study showed that skin inflammation is comparable in wild-type and $Kit^{W/W\text{-}v}$ mice [79]. However, IFN-γ mRNA expression was increased in sensitized skin of $Kit^{W/W\text{-}v}$ mice. In contrast, Der f/SEB induction experiments on $Kit^{W\text{-}sh/W\text{-}sh}$ mice suggested a nonessential, but contributory role for mast cells to skin lesion development (T.A., M.K., and T.K., unpublished). Similarly, skin inflammation induced by EC sensitization with cedar pollen antigens was abolished in $Kit^{W/W\text{-}v}$ and $Kit^{Sl/Sl\text{-}d}$ mice [80]. This cedar pollen dermatitis model was found to be independent of Stat6 and IgE, but dependent on CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells), a prostaglandin D2 (PGD_2) receptor. However, careful mast cell-reconstitution experiments have not been performed in either study. Interestingly, a recent study showed that FcεRI and FcRγ are involved in an EC OVA sensitization model [81]. However, what cell type is involved was not investigated in this study. Skin lesions were completely absent in FcRγ-deficient mice but partially inhibited in either FcεRIα- or FcγRIII/CD16-deficient mice. FcεRI controled both Th1 and Th2 skin responses, mast cell recruitment into draining lymph nodes, and IgE production. On the other hand, FcγRIII regulated only Th2 skin response, as well as T cell proliferation and IgG1 production. Considering the restricted expression of FcεRI in mast cells and basophils in mice and negative results on a mast cell's role in EC OVA sensitization experiments [79], these results collectively suggest that basophils might be involved in skin inflammation through the activation of FcεRI. However, a rigorous study needs to directly address this point using this induction protocol and to investigate apparent differences in the mast cell requirement between EC OVA sensitization- and Der f/SEB-induced dermatitis (or EC cedar pollen-induced dermatitis).

Although mast cells are increased in skin lesions of most AD cases and animal models, mastocytosis (an abnormal proliferation and accumulation of mast cells) is not associated with

higher incidence of allergic diseases including AD [82]. Related to this issue, two kinds of keratinocyte-targeted K14-SCF Tg mice were generated: one produced both soluble and membrane-bound SCF, and the other produced only membrane-bound SCF [83]. The former (soluble/membrane) Tg mice caused cutaneous mastocytosis, but did not develop dermatitis.

Extrinsic vs. intrinsic AD – IgE in AD

A majority of AD patients have elevated serum IgE levels. In contrast with this so-called extrinsic AD, 20-30% of patients have low or normal levels of IgE. The latter, intrinsic AD, patients sometimes experience increases in serum IgE later in their life. Although AD might well be a syndrome caused by multiple etiologies (i.e., involving different combinations of multiple sets of cell types or multiple signaling pathways), it is also possible that the presence of intrinsic AD followed by a late-onset IgE elevation might suggests that IgE is not essential for the development of human AD, at least for the initiation of the disease. Several mouse studies support this notion: for example, Caspase 1 Tg mice, in which dermatitis development depends on IL-18, develop dermatitis even in the Stat6-deficient background. The aforementioned cedar pollen dermatitis does not require Stat6 or IgE [80], and skin lesions induced by Der f/SEB are normal in B cell-deficient mice (T.A., M.K., and T.K., unpublished). Furthermore, IL-18 has been increasingly recognized as an important player in AD pathogenesis. Clinically, IL-18 levels closely parallel disease severity [40,84]. Protein A (SpA), a virulence factor expressed on the surface of *S. aureus*, infection with which exacerbates AD, stimulates mouse keratinocytes to secrete IL-18 [85]. Disruption of the skin barrier with a subclinical dose of sodium dodecyl sufate, a detergent, plus daily EC application of SpA causes AD-like skin lesions in an IL-18-dependent manner [86]. This model does not induce elevation of serum IgE levels, thus similar to intrinsic AD. While treatment with detergent induces moderate Th1 cell response, additional SpA treatment is a prerequisite for differentiation of naive T cells toward unique Th1 cells, termed ‘super Th1 cells’, capable of producing both Th1 (IFN-γ) and Th2 (IL-13) cytokines and IL-3, as well as expressing CXCR3 (receptor for CXCL10 and CXCL11) and CCR5 (receptor for CCL3, CCL4, and CCL5). Induction of ‘super Th1 cells’ requires IL-18 stimulation. IL-18 was shown to be important for the development of infection-associated AD by induction of IL-3 from ‘super Th1 cells’. Cutaneous mastocytosis in this model is dependent on IL-18-dependent IL-3 production. Considering the increased Th1 cells in skin lesions of the chronic phase of AD and the prevalent infection with *S. aureus*, this model represent features of the chronic inflammation of human AD. Another potential player that counterbalance the Th2 predominance is IDECs (inflammatory dendritic epidermal cells), as these cells can produce IL-12 and IL-18 [87]. K14-IL-4-Tg/SKH1 mice, generated by crossing K14-IL-4-Tg/CByB6 mice with SKH1 (hairless, but apparently immunocompetent) mice, are another model of intrinsic AD [88]. The resulting hairless IL-4-Tg mice develop an inflammatory skin disease like that of the normally haired IL-4-Tg mice, accompanied by prominent skin infiltrations of T cells, mast cells, and eosinophils, as well as Th2 and Th1 cytokine up-regulation in chronic skin lesions. The inability of $CD4^+$ T cells of the K14-IL-4-Tg/SKH1mice to up-regulate CD40L expression upon stimulation might account for their inability to up-regulate the IgE level. Another model of intrinsic AD is Tg mice overexpressing IL-31, a cytokine produced by activated T cells (Th2 cells express more IL-31 than Th1 cells) [89]. These models suggest that there can be multiple mechanisms for the development of intrinsic AD.

PGD_2 and AD

Mast cells not only produce PGD_2 abundantly upon FcεRI stimulation but also express a functional receptor CRTH2 for PGD_2 [90]. PGD_2 binds to two membrane receptors, D prostanoid receptor (DP)1 and DP2 (aka CRTH2). A DP2 agonist (13,14-dihydro-15-keto-PGD_2) increases eosinophil recruitment at inflammatory sites and skin inflammation in an EC

OVA sensitization model, whereas a DP1 agonist failed to induce eosinophil chemotaxis [91]. Administration of a CRTH2 antagonist, compound A, ameliorated skin inflammation caused by either EC OVA or FITC sensitization [92,93]. Compound A reduced total IgE, as well as antigen-specific IgE, IgG1, and IgG2a antibody levels. In compound A-treated mice, there were reduced activities of DCs to migrate to the draining lymph nodes and to stimulate naïve $CD4^+$ T cells in response to FITC application to the skin. Ear-swelling responses induced by hapten-specific IgE and chronic contact hypersensitivity induced by repeated hapten application were less pronounced in CRTH2-deficient mice, compared to wild-type mice, whereas in vivo migration of Langerhans cells and DCs to regional lymph nodes was not impaired in CRTH2-deficient mice [94].

Pruritogenic role of mast cells in AD

Pruritus is one of the most prominent clinical features of AD and it disturbs the everyday life of AD patients. Itch-scratch vicious cycle also exacerbates the dermatitis by damaging the skin barrier and enhancing the itch [95]. This effect was also demonstrated in mouse models. Established dermatitis of NC/Nga mice was dramatically alleviated by clipping their toe-nails [96], while those with intact nails had sustained dermatitis. Interestingly, skin scratching was suggested to switch immune responses from Th2 to Th1 type in epicutaneously immunized mice [97]: mice sensitized epicutaneously with KLH showed Th2-biased immune response including expression of IgE and IL-13 in the local skin, whereas scratching on local abdominal skin using wire brush induced Th1 responses such as DTH reactions, increased IgG2a and IgG2b, and IFN-γ in the skin. This study suggests that scratching and its ensuing infection are important factor for the transition of the Th2-predominant acute phase to the chronic phase characterized by the presence of Th1 cells. Although mast cells respond to various AD-related stimuli, including IgE plus antigen, neuropeptides, bacterial components, and physical stimuli, the contribution of mast cells to the AD-related pruritus is not fully understood. Clinically, the major pruritogenic mediator from mast cells, i.e., histamine, turned out to be disappointing as a target of anti-itch therapeutics, because nonsedative antihistamines exhibited little effect on the eczema-related itch [98,99], while sedative antihistamines worked well both in human AD [98] and mouse AD models [99]. These results suggest the involvement of neurogenic components in the itch of AD. Since mast cells are closely located with the afferent neuron terminals in normal and inflamed tissues [100-103], functional interactions between mast cells and nerve fibers are implicated: tryptase is the primary protease produced by mast cells. Mast cell tryptase can cleave and activate its receptor, protease-activated receptor-2 (PAR-2), which is expressed on primary sensory nerves and keratinocytes [104-107]. The concentration and codein-induced release of tryptase are markedly increased in AD skin lesions, and induced itch in the atopic lesions was not suppressed by antihistamines [106]. Intracutaneously injected tryptase caused itch on the skin of healthy volunteers, which was alleviated by anti-PAR-2 neutralizing antibody and PAR-2 antagonist [107]. Moreover, while intradermal injection of a peptide that activates PAR-2 elicited pain followed by transient itch in healthy subjects, it provoked enhanced itch in AD lesions [106]. These results imply the involvement and enhancement of the tryptase/PAR2 pathway in AD skin. Mast cell-associated nerves in the skin are predominantly substance P positive [103]. Substance P can in turn activate mast cells through NK1 receptor, and released TNF-α can stimulate the neuron terminals through TNF receptors [95]. However, the roles of these interactive pathways in AD remain largely unknown. As mentioned above, IL-31 Tg mice developed AD-like skin lesions with severe pruritis. However, IL-31-induced pruritis could be observed in $Kit^{W/W\text{-}v}$ mice [89].

A dry skin mouse model, induced by acetone and diethylether treatment followed by water application, showed increased scratching with increased transepidermal water loss (TEWL, an indicator of skin barrier function) and decreased capacitance (an indicator of stratum corneum hydration). In this model, both total and degranulating mast cell numbers were unchanged after

5 days of dry skin induction. Mast cell-deficient *Kit*$^{W/W\text{-}v}$ mice showed no differences in scratching behavior than wild type littermates. Scratching was suppressed by opioid receptor antagonists [108]. On the other hand, in a repeated hapten treatment model of AD, mast cell-deficient *Kit*$^{Sl/Sl\text{-}d}$ mice showed no increase in scratching behavior than vehicle treated mice, although the histopathological findings revealed the epidermal thickening, severe inflammatory infiltrate, and IgE elevation in both wild type and *Kit*$^{Sl/Sl\text{-}d}$ mice [109]. These observations collectively suggest both mast cell-mediated and mast cell-independent mechanisms underlie the AD-related itch. Extensive explorations are needed to elucidate the role of mast cells and their interaction with the nervous system in AD.

Conclusions and future perspectives

An emerging scenario supported by clinical observations and EC OVA sensitization models (Fig. 2) is that impairment in skin barrier function will allow access of allergens and microbes to antigen-presenting cells such as Langerhans cells and dermal DCs and endow the microenvironment with a Th2 (and Th17) cell-nurturing capacity. These APCs will mature (lose the ability to uptake antigen and acquire antigen-presenting ability) during the migration to draining lymph nodes. Naïve T cells stimulated by the APCs will differentiate to Th2 cells. Th2 effector cells migrate back to inflammatory skin sites to cause damage and to recruit other immune cells such as eosinophils and mast cells. Inflammation will further damage skin barrier function. Infection with bacteria and virus will also worsen AD by various mechanisms. In contrast, other models using crude allergen extracts suggest that activation of multiple (both immune and non-immune) cell types is involved from the initial stage of disease. For instance, house dust mite extracts affect T, B, and mast cells as well as epithelial cells [110]. Human and mouse studies also showed the importance of keratinocytes as the major player not only of the skin barrier but also as a part of the immune system (keratinocytes are the major source of TSLP and IL-18).

The current situation surrounding the role of mast cells in the AD pathogenesis has resemblances to that of mast cells in asthma/airway inflammation in 1990s. Some early experiments showed that mast cells play an essential role in allergen-induced airway inflammation, whereas others showed that mast cells play no significant role. Several experiments later resolved this controversy by demonstrating that mast cells play a critical role when mice were immunized with low doses of allergen, without adjuvant, or with low frequency, while they are dispensable when immunized with high doses of allergen or together with adjuvant [21,22,111]. Thus, mast cells seem to amplify the inflammatory processes in asthma/airway inflammation. However, the role of IgE in AD is less clear, as several models have convincingly demonstrated the lack of an increase in IgE levels and/or any significant role of IgE in causation of skin lesions. This issue is also similar to that of mast cells. To resolve these related issues, experiments mimicking human AD should be performed, e.g., using real-world allergenic environments, in addition to clean experiments based on a single allegen that have an advantage of many useful (immunological and genetic) reagents and tend to provide clean-cut results. For example, use of multiple vs. single allergens and adjuvants of purified microbial agents vs. crude extracts of allergenic organisms might reveal subtle effects of IgE and mast cells on skin lesion development. Such a study might also shed novel insights into the hygiene hypothesis.

The current research focuses mainly on impaired skin barrier function and Th2/Th1 (and Th17) imbalance as the underlying mechanisms for AD. Numerous studies have revealed roles of mast cells as effector cells of allergic reactions, which might also be true in the development of skin lesions in AD. However, little is known in their potential role in modulating the course of AD disease progression. Another important point is that a large number of genes are being shown to be associated with AD through genome-wide association studies. However,

validation of such candidate genes as those truly involved in mouse models has just begun. This will probably be the most rewarding area of research, which will disclose novel cellular and molecular mechanisms of AD pathogenesis and eventually lead to novel efficacious therapeutic modalities in the next decade or so.

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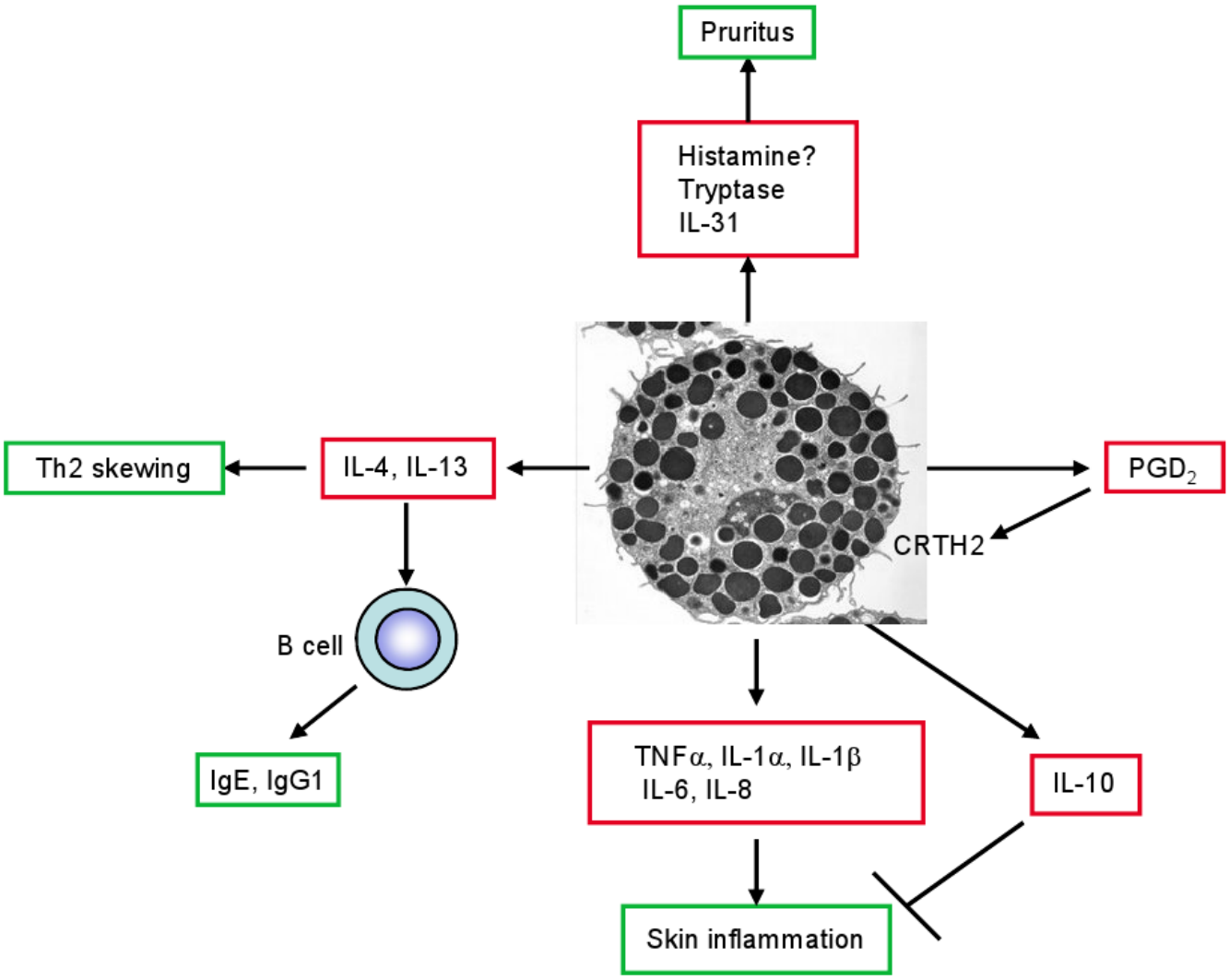

Figure 1.
Mast cells secrete a wide array of preformed and de novo synthesized proinflammatory and immunomodulatory mediators upon stimulation by IgE and antigen or other stimuli. The mediators may contribute to various aspects of systemic and local immune responses in AD.

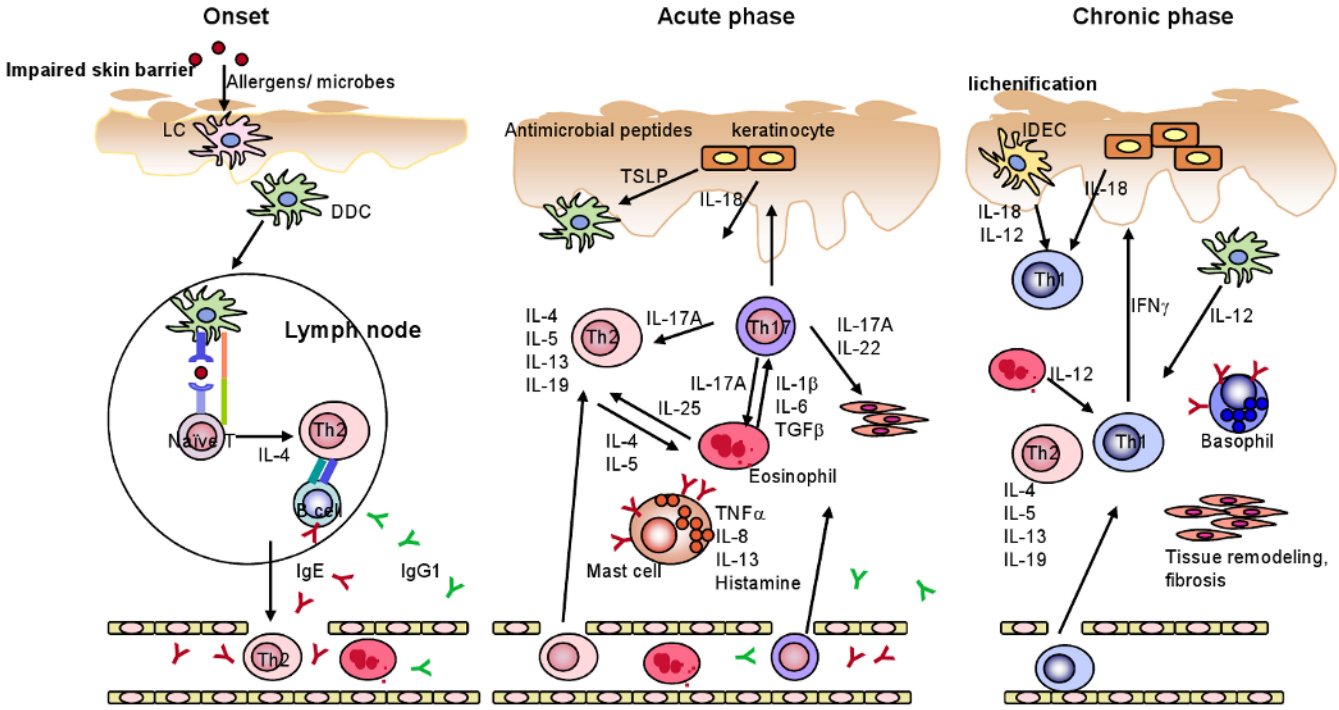

Figure 2.
Schematic showing some major cellular and molecular components that are involved in AD pathogenesis. Adapted by permission from Macmillan Publishers Ltd: Journal of Investigative Dermatology, Di Cesare et al. [112], copyright (2008).↑

Table 1
Immunological features of mouse models of AD

		Genetics / Inducer	Clinical symptoms			Humoral response	Histopathology						Immune deviation			Mast cell related component / findings	Reference
Category	Model	Responsible Component	Pruritus	Chronic/relapsing	Macroscopic Eczema	IgE / IgG	Epidermal changes	Lymphocytes	Eosinophils	Mast cells	Neutrophils	Bacterial infection	Th2 cytokines	Th1 cytokines	Others		
Barrier function	NC/Nga	n.d. (link to derm1 : Thy1, Cd3d, Cd3e, Cd3g, Il10ra, Il18, Csk)[113]	+	+	+	tIgE, IgG↑	+	+	+	+	n.d.	n.d.	↑	↑	-	Anti-histone H3 IgE [114], Chymase [115,116], PAR2 [117], PGD2 [118,119]	[59]
	flaky tail	Filaggrin 5303delA [54]	n.d.	-	*	IgE→	+	+/-	+	n.d.	n.d.	n.d.	→	n.d.	-	*tail only, cures by 4 weeks	[120,121]
	hAPOC1 tg	human apolipoprotein C1	+	+	+	tIgE↑	+	+	+	+	+	n.d.	n.d.	n.d.	-	-	[122,123]
	Spink5-/- engraftment	serin protease inhibitor Kazal-type 5	n.d.	n.d.	+	n.d.	+	n.d.	+	+	n.d.	n.d.	n.d.	n.d.	-	-	[124]
	RBP-jCKO	RBP-j (the DNA-binding partner of Notch, involved in epidermal differentiation)	n.d.	+	n.d.	tIgE↑	+	n.d.	n.d.	+	n.d.	n.d.	↑	n.d.	TSLP↑	-	[125]
	Dry skin	acetone, diethylether, water	+	n.d.	n.d.	n.d.	+	-	n.d.	→	n.d.	n.d.	n.d.	n.d.	-	Mast cells were not required for pruritus [108].	[108,126]
Immunoregulation	ep IL-4 tg	interleukin-4	+	+	+	tIgE↑, IgG1↑, IgG2a→	+	+	+	+	+	SA, PA(Cv)	↑	↑	-	No IgE increase in SKH1 background mice [88].	[127]
	ep CASP1 tg	caspase-1	+	+	+	tIgE↑, IgG1→	+	n.d.	+/-	+	n.d.	n.d.	↑	↓	IL-18↑	Stat6 contributes to the mast cell recruitment and dermatitis [128]. IL-18 is required for mast cell recruitment [128]. serum histamine↑ [129]	[130]
	ep IL-18 tg	interleukin-18	+	+	+	tIgE↑, IgG1↑	+	+	+/-	+	+	n.d.	↑	↓	IL-18↑	-	[128]
	ep IL-13 tg	interleukin-13	+	+	+	tIgE↑, IgG1↑, IgG2a→	+	+	+	+	+/-	n.d.	↑	n.d.	TSLP↑	Skin histamine and β-hexosaminidase content↑	[131]
	IL-31 tg / inj	interleukin-31	+	+	+	tIgE→, IgG1→	+	+	+	+	+	n.d.	n.d.	n.d.	-	Mast cells not required for pruritus and alopecia.	[89]
	PLA2G3 tg	Group III secretory phospholipase A2	+	+	+	tIgE→, IgG1↑, IgG2a→	+	n.d.	n.d.	→	+	n.d.	↑	↑	-	-	[132]
	ep TSLP tg	thymic stromal lymphopoietin (K5-rtTA/tetO-TSLP, K14-TSLP)	+	+	+	tIgE↑, IgG1↑, IgG2a↓	+	+	+	+	n.d.	n.d.	↑	→/↑	TSLP↑	T-cells not required for dermatitis including mast cell infiltration [43]; Mast cell increases after onset of dermatitis [44].	[43,44]
	RXRab ep-/-	retinoid X receptor alpha/beta	+	+	+	tIgE↑, IgG1↑	+	+	+	+	+/-	-	↑	↑	TSLP↑ IL-17↑	AF-2 deficient skin couldn't recruit mast cells.	[44]
	NR agonist treatment	Nuclear receptor (partners of retinoid X receptors)	+	n.d.	+	tIgE↑, IgG↑	+	+	+	+	+	n.d.	↑	↑	TSLP↑	RAG1-/- developed dermatitis with eosinophil and mast cell infiltration.	[133]
	CatE-/-	Cathepsin E	+	+	+	tIgE↑, tIgG1→, tIgG2→	+	+	+	+	n.d.	SA(Cv)	↑	→	-	-	[134]
	RelB-/-	RelB (partner of NF-kB)	+	+	+	tIgE↑	+	+	+	+	+	-	↑	↑	-	-	[135]
	SOCS7-/-	suppressor of cytokine signaling 7	+	+	+	tIgE→, IgG1↑, IgG2a→	+	+	n.d.	+	n.d.	n.d.	n.d.	n.d.	-	BMMC produced increased IL-6, 13, TSLP, but not β-Hexosaminidase.	[136]
	Auf1-/-	ARE/poly-(U) binding degradation factor 1	+	+	+	tIgE↑	+	+	+	+	+	SA	↑	↑	-	-	[137]
Neuro-regulation	DS-Nh	TRPV3(Gly573Ser) [138] (mutated thermal sensor of keratinocytes)	+	+	+	tIgE↑, IgG1↑, IgG2a↑	+	+	+	+	+	SA(Cv), -(SPF)	↑	↑	-	-	[139]
	TRPV3 tg		+	+	+	tIgE↑	+	+	n.d.	+	n.d.	n.d.	↑	→	IL-17↑	-	[140]
n.d.	HR-AD	Nutrition (HR-AD diet or Low Mg&Zn diet)	+	+	+	tIgE↑	+	+	+	+	n.d.	n.d.	n.d.	n.d.	-	-	[141,142]
	NOA	n.d. (linkage analysis only)	+	+	+	tIgE↑	+	n.d.	n.d.	+	?	?	n.d.	n.d.	-	-	[143]
Sensitization	OVA sens	ovalbumin / tape stripping	+	n.d.	n.d.	t/sIgE↑, sIgG1↑, sIgG2↑	+	+	+	+	+	n.d.	↑	↑	TSLP↑ IL-17↑	Mast cells deficient mice developed dermatitis. IFNg and IgE were increased [79].	[76]
	Mite allergen and/or SEB sens	mite allergen / Staphylococcal enterotoxin B	+	n.d.	+	t/sIgE↑	+	+	+	+	+	n.d.	↑	↓/→	IL-17↑	Polyclonal IgE can stimulate BMMCs [144].	[70,72,145]
	SpA sens	Staphylococcal Protein A / Sodium dodecyl sulfate	+	n.d.	+	tIgE→	+	+	+	+	n.d.	n.d.	↑	↑	IL-18↑	-	[86]
	cedar pollen sens	cedar pollen	n.d.	n.d.	n.d.	IgG2a→, t/sIgE↑	+	+	+	+	+	n.d.	↑	→	-	Mast cells were essential for dermatitis, but not for IgE.	[80]
	Intragastr. Prot. Sens.	Cow's milk, peanut + cholera toxin	+	+	+	t/sIgE↑	+	+	+	+	n.d.	-	↑	n.d.	-	-	[146]
	hu SCID	mite allergen, SEB	n.d.	n.d.	+	t/sIgE↑	+	+	n.d.	n.d.	n.d.	n.d.	↑	↑	-	-	[147]
	Repeated Hapten	Hapten	+	n.d.	+	t/sIgE↑	+	+	+	+	+	n.d.	↑	n.d.	IL-17↑	Mast cells were required for pruritus but not for inflammation [109].	[148-150]

Abbreviations: tg, transgenic; inj, injection; tIgE, total IgE; sIgE, Ag-specific IgE; sens, sensitization; n.d., not determined or documented; Prot., protein; SA, Staphylococcus aureus; PA, Pseudomonas aeruginosa; Cv, conventional facility; SPF, specific pathogen free facility; ↑, increased; ↓, decreased; →, no change; BMMC, bone marrow derived mast cells