

Review

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Review

Mast Cells as Central Orchestrators of Cutaneous Inflammation: From Acute Defense to Chronic Pathology

Running Title: Mast Cells—Relentless Sentinels or Inveterate Alarmists?

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Abstract

The innate immune system (IIS) constitutes the primary line of defense in multicellular organisms. This evolutionary conserved system provides rapid protection against a wide range of pathogens, including bacteria, viruses, and fungi. Innate responses are initiated within minutes and do not require prior antigenic exposure. Accordingly, novel pathogens are first recognized and countered by the IIS, which subsequently initiates and shapes the adaptive immune response, typically manifesting over several days to weeks. The roles of mast cells (MCs) in acute inflammation and immediate host defense are well established, growing evidence indicates that mast cells can also act as key drivers of chronic, dysregulated inflammation across a range of dermatologic diseases. This review examines the hypothesis that MCs function as highly sensitive sentinels capable of integrating danger signals, initiating cytokine–chemokine cascades, and shaping downstream immune responses. Review highlights emerging concepts regarding mast-cell-mediated transitions from acute to chronic inflammation, the molecular signals that sustain these states, and the mechanistic pathways through which mast cells shape the inflammatory microenvironment. In the context of chronic inflammatory disease, mast cells may become dysregulated, acting as persistent sources of pro-inflammatory cytokines and chemokines even after clearance of the inciting pathogen or allergen. Finally, this review discusses the implications of these insights for potential therapeutic targeting modulating mast cell activity in disorders such as rosacea, atopic dermatitis, psoriasis, and *acne vulgaris*, where mast-cell-dependent networks may contribute to disease chronicity and treatment resistance.

Keywords: inflammation; mast cells; acne vulgaris; rosacea

Introduction

The subset of IIS cells that rapidly release pro-inflammatory cytokines and chemokines includes macrophages, mast cells, natural killer (NK) cells, lymphocytes, and monocytes. Skin and mucosal surfaces serve as effective immune barriers between the internal and external environment. Mast cells are widely spread throughout tissues but are found in particularly high numbers at interfaces with the environment, such as the skin and mucosal surfaces (respiratory and intestinal) (Galli, Borregaard et al. 2011). Therefore, MCs occupy a unique position within the innate immune system, acting as highly responsive sentinels capable of initiating rapid inflammatory responses. In the skin, their localization near blood vessels, nerves, and epithelial surfaces enables them to detect a wide spectrum of external and internal stimuli, including microbes, allergens, neuropeptides, and physical injury. In addition, mast cells are naturally found in the brain, specifically in the meninges (the brain's protective layers) and on the brain side of the blood-brain barrier (BBB). They act as "guardians" at

entry points for brain fluid, like arachnoid cuff exit (ACE) points, helping to monitor for and defend against pathogens (Mamuladze, Zaninelli et al. 2025). Recently published study showed that during bacterial meningitis, pathogens exploit ACE points to access the brain. However, mast cell activation redirects CSF flow, recruits neutrophils, and limits bacterial invasion. Mice lacking dural mast cells exhibit impaired immune responses and higher brain bacterial loads (Mamuladze, Zaninelli et al. 2025).

Thus, mast cells are unique in being permanently resident near barrier sites. Figuratively, MCs function as sentinels, persistently monitoring for pathogenic “intruders” (Rodewald and Feyerabend 2012). Equipped with a wide array of surface receptors, they are capable of recognizing diverse pathogens and initiating protective immune responses. In many instances, MCs activation provides life-saving early warning signals. However, mast cell dysregulation may trigger inappropriate alarm responses, contributing to pathologies such as allergy, asthma, and inflammatory bowel disease (IBD).

Although mast cells are traditionally associated with acute, short-lived inflammatory responses, increasing evidence demonstrates that they also contribute to sustained, dysregulated inflammatory states, particularly within the skin. Their ability to produce long-lived cytokine profiles, interact with sensory neurons, and modulate adaptive immunity positions them not only as initiators but also as maintainers of chronic inflammation. For example, MCs malfunction can drive inappropriate host responses to normally benign agents (Voss, Kotrba et al. 2021). For example, aberrant activation in response to *Cutibacterium acnes* (a non-pathogenic commensal bacterium) may promote inflammation and *acne vulgaris* (Eliasse, Leveque et al. 2021). The development of rosacea is suspected to be related to Demodex, a microscopic commensal organism that resides in or near hair follicles and sebaceous glands. Direct evidence for a pathogenic role of Demodex in rosacea is currently lacking but as circumstantial evidence, non-invasive skin-detecting techniques have shown abnormally elevated numbers of Demodex in rosacea patients (Wei, Li et al. 2024). Increased cytokine levels such as IL-10, IL-8, and IL-12p70 have been observed in human sebocytes following the Demodex challenge, and acaricides have been found to be effective in rosacea therapy, all point to a close relationship between Demodex and rosacea.

Likewise, neutral environmental allergens can provoke chronic inflammatory states, giving rise to conditions such as atopic dermatitis, chronic urticaria, and psoriasis (Numata, Harada et al. 2022). The crucial role of mast cells in initiating and maintaining chronic inflammation was underappreciated for many years, but accumulating evidence now implicates them as pivotal early mediators in multiple chronic inflammatory diseases. These include dermatologic disorders (rosacea, acne vulgaris, chronic spontaneous urticaria [CSU], chronic inducible urticaria [CIndU], and prurigo nodularis), as well as mucosal diseases such as eosinophilic esophagitis, allergic asthma, food allergy, chronic obstructive pulmonary disease (COPD), and IBD. Both CSU and CIndU are fundamentally mast cell-driven diseases, in which pruritus is a key symptom in addition to wheals and/or angioedema (Zuberbier, Aberer et al. 2018). In urticaria, the degranulation of hyperactive subcutaneous mast cells and release of their mediators (histamine, bradykinin, kallikrein, and other vasoactive substances) in the superficial dermis cause the symptoms by activating sensory nerves, capillary and venous vasodilatation, leukocyte infiltration that led to skin severe inflammation. Antihistamines are drug of choice in chronic urticaria and CIU/CSU. However, they are relatively slow acting. Approximately 60% of patients do not achieve complete control with first-line treatment antihistamines like Cetirizine (Zyrtec), Benadryl and loratadine (Claritin), fexofenadine (Allegra), desloratadine (Clarinex) and levocetirizine (Xyzal). The anti-inflammatory steroids (prednisolone) help in faster relief of CSU/CindU symptoms. When rapid control of urticaria is needed, a short tapering course of steroids may be used, but in any other situation their role is limited. Invariably, prolonged use of steroids like Prednisone leads to numerous adverse effects and severe rebound in urticaria when withdrawal is attempted.

This short mechanistic review synthesizes current understanding of MCs activation pathways, their role in the initiation of cutaneous inflammation, and the mechanisms by which MCs promote

chronic inflammatory states. By reframing MCs as regulators of inflammatory persistence, we identify new avenues for understanding and treating chronic skin inflammation. This short mechanistic review discusses old and novel therapeutic strategies that target MCs as the initiating link in the inflammatory cascade:

1. **Direct inhibition of degranulation (MC stabilizers).**
2. **Interception of mast cell mediators** (cytokines, chemokines, histamine).
3. **Blockade of activating receptor–ligand interactions** (e.g., IgE antagonists).
4. **Activation of MC inhibitory receptors** (e.g., Siglec-8, Siglec-6, CD200R, CD300a, FcγRIIb).
5. **Systemic mast cell depletion.**

Of these, approaches that directly inhibit or prevent MCs degranulation (strategies 1, 4, and 5) are considered the most feasible for halting acute and chronic inflammation. The most radical option, systemic mast cell depletion, results in prolonged MCs absence (from weeks to months), but carries the greatest safety concerns. In contrast, interception of mediators (strategy 2) and blockade of receptor–ligand interactions (strategy 3) are indirect approaches with more moderate effects.

Several indirect therapies have reached clinical approval. These include:

- **Mediator interception:** anti-IL-4Rα mAb *dupilumab*, anti-IL-13 mAb *tralokinumab*, and H1 antihistamines.
- **Receptor antagonism:** anti-IgE mAb *omalizumab*.

However, the clinical efficacy of these agents has been variable. For example, omalizumab (Xolair) was the first drug approved for CSU in patients unresponsive to H1 antihistamines, functioning by sequestering free IgE and downregulating FcεRI expression on mast cells and basophils. Despite success, next-generation anti-IgE mAb *ligelizumab* failed to demonstrate superiority over omalizumab in the Phase III PEARL 1 and PEARL 2 trials, despite meeting placebo-controlled endpoints.

Dupilumab, an IL-4Rα antagonist, blocks IL-4 and IL-13 signaling and has been approved for atopic dermatitis, prurigo nodularis, and, more recently (in 2025), CSU. Tralokinumab, an anti-IL-13 mAb, is approved for moderate-to-severe atopic dermatitis, though comparative efficacy appears lower than dupilumab. Tezepelumab, a TSLP inhibitor, failed to meet primary endpoints in a Phase II trial for CSU. Similarly, silencing strategies targeting inhibitory receptors, such as anti-Siglec-8 mAb Lirentelimab and the CD200R agonist LY3454738, failed to meet primary efficacy endpoints, leading to program discontinuation.

In summary, selective inhibition of MC-derived cytokines has demonstrated partial efficacy, with some agents achieving approval. In contrast, receptor-silencing approaches have largely failed, and indirect therapies such as anti-IgE and anti-TSLP antibodies have shown only modest or inconsistent benefits.

This review will present a comparative analysis of two **direct approaches**: suppression of mast cell degranulation via MC stabilizers versus systemic mast cell depletion. We will further evaluate safety considerations, particularly the potential off-target immunosuppressive consequences of long-term systemic MC depletion in the treatment of inflammatory skin diseases.

Role of Mast Cells in Early Pathogen Response and Mast Cell–Driven Disorders

1. Mast cells as sentinels of cutaneous danger

MCs are long-lived innate immune cells strategically located at tissue interfaces with the external environment, including the skin, gastrointestinal tract, and airways. Thus, MCs are uniquely positioned as early detectors of tissue perturbation (Marshall, King et al. 2003). Constantly surveying their surroundings, MCs act as sentinels capable of rapid activation and degranulation upon pathogen encounter (Lin, Maher et al. 2003, Marshall, King et al. 2003). Through this function, they provide essential protection against microbial invasion and, in many cases, preserve host health without notice. Their activation is triggered not only by IgE–FcεRI engagement but also by a diverse array of non-IgE pathways, including Toll-like receptors (TLRs), complement fragments (C3a, C5a),

neuropeptides, alarmins (such as IL-33), and physical stimuli such as mechanical stress or temperature changes (Cao and Gao 2024). Through these multimodal sensors, MCs integrate signals from pathogens, allergens, damaged keratinocytes, and neural inputs. This capacity allows MCs to respond rapidly and variably depending on the nature of the trigger, tailoring the inflammatory response with precision. Unlike other innate immune cells, MCs release mediators both immediately (via degranulation) and in a delayed, transcriptionally regulated manner, enabling both acute and sustained inflammatory programs. Upon activation, MCs release a remarkably broad set of mediators. The early-phase response includes histamine, tryptase, chymase, heparin, and pre-formed TNF- α , which increase vascular permeability and facilitate leukocyte extravasation (Mukai, Tsai et al. 2018). In parallel, MCs generate lipid mediators such as prostaglandin D2 and leukotriene C4, which enhance vasodilation, itch, and recruitment of Th2-associated cells (Marshall, King et al. 2003).

Beyond this immediate burst, MCs initiate a second wave of cytokine and chemokine production through *de novo* transcription (Katsanos, Anogeianaki et al. 2008). These include IL-4, IL-5, IL-6, IL-13, IL-31, GM-CSF, and CCL2, CCL5, CCL20, each contributing to sustained immune activation. This delayed phase is of particular importance for chronic inflammation: even in the absence of continuous antigen exposure, MCs can remain partially activated and continue producing inflammatory mediators for extended periods.

The breadth of MC-derived cytokines allows them to influence nearly every component of the cutaneous immune response, from T-cell differentiation to fibroblast activity. Through these mediators, MCs effectively set the tone and magnitude of inflammation, promoting either rapid resolution or prolonged, pathogenic signaling.

Keratinocytes, long appreciated for their barrier function, are now recognized as active participants in innate immunity. MCs communicate bidirectionally with keratinocytes via cytokines, proteases, and exosomes (Redhu, Franke et al. 2022). Keratinocytes produce IL-33, TSLP, and ATP in response to injury or microbial invasion, which directly activate MCs. In turn, MC-derived IL-4, IL-13, and TNF- α modulate keratinocyte differentiation, tight-junction integrity, and antimicrobial peptide production (Redhu, Franke et al. 2022). This reciprocal signaling can create feed-forward loops that intensify and prolong inflammation, particularly in barrier-compromised skin. Additionally, MC proteases such as tryptase can activate protease-activated receptor 2 (PAR-2) on keratinocytes, enhancing release of pro-inflammatory cytokines and pruritogens (Molino, Barnathan et al. 1997). These interactions are central to conditions characterized by chronic itch, such as atopic dermatitis and chronic urticaria.

The skin's dense innervation allows MCs to respond rapidly to neuropeptides such as substance P, CGRP, and neurotensin. These signals trigger MC degranulation and cytokine release, amplifying neurogenic inflammation (Babina, Franke et al. 2022). Reciprocally, MC mediators sensitize peripheral nerves, enhancing itch and pain signaling. This bidirectional communication results in neuroimmune amplification—a cycle in which nerves activate MCs and MCs activate nerves. Such amplification may underpin chronic pruritus, neurodermatitis, and inflammatory flares triggered by stress.

This neuroimmune interface is a defining feature of chronic cutaneous inflammation and represents a distinct mechanism through which MCs promote inflammatory persistence.

MC-derived cytokines and chemokines exert powerful effects on leukocyte trafficking (Cote, Tremblay et al. 2008). TNF- α , GM-CSF, and CCL2 promote recruitment of monocytes, basophils and dendritic cells; IL-5 and IL-13 enhance eosinophil accumulation; IL-6 and IL-1 β influence Th17 polarization; and histamine modulates T-cell and neutrophil migration through H1 and H4 receptors (Nedoszytko, Sokolowska-Wojdylo et al. 2014, Otsuka and Kabashima 2015, Cardamone, Parente et al. 2016). MCs also shape adaptive immunity by influencing antigen-presenting cell maturation and promoting T-cell differentiation toward Th2 or Th17 lineages depending on the inflammatory context. In chronic dermatitis, this orchestration contributes to sustained leukocytic infiltration and prolonged inflammatory signaling long after the initial insult.

A key emerging concept is that MCs serve as critical regulators of the transition from acute to chronic inflammation. Multiple mechanisms contribute:

a. Persistent Low-Level Activation

MCs can remain in a “primed” state after initial stimulation, producing cytokines for days or weeks without full degranulation (Hein 2002).

b. Epigenetic Reprogramming

Recent studies show that MCs undergo transcriptional and chromatin-level changes that favor prolonged cytokine production (Schcolnik-Cabrera, Ramirez-Yautentzi et al. 2025).

c. Autocrine Feedback Loops

MCs respond to their own cytokines (e.g., IL-33, IL-6), reinforcing activation (Cop, Ebo et al. 2018, Seirin-Lee, Yanase et al. 2020).

d. Crosstalk with non-immune cells

Keratinocytes, fibroblasts, and neurons each provide signals that prolong MC activation.

e. Delayed mediator synthesis

De novo production of IL-4, IL-13, and TNF- α allows continued signaling well beyond the immediate phase response. The convergence of these pathways provides a mechanistic explanation for why MC-driven inflammation can persist even when antigen exposure ceases—a hallmark of chronic skin diseases (Krishnaswamy, Kelley et al. 2001).

2. Mast cell–driven disorders

However, inappropriate or exaggerated mast cell activation can result in false alarm signaling, driving a wide spectrum of MC-mediated disorders and allergic conditions (Galli and Tsai 2012). In addition to initiating acute inflammatory responses, mast cells contribute to chronic cycles of inflammation, tissue remodeling, and fibrosis. They are central to the pathophysiology of allergic diseases, including asthma, food allergy, allergic rhinitis, and anaphylaxis (Galli and Tsai 2012). Regardless of whether activation is triggered by genuine or aberrant stimuli, mast cell degranulation results in the release of diverse mediators such as histamine, platelet-activating factor, proteases, lipid metabolites, and multiple cytokines and chemokines (e.g., TNF- α , IL-1, IL-4, IL-6, and IL-13). In the setting of mast cell dysfunction, therapeutic strategies capable of disrupting this amplification loop offer significant potential for alleviating MC-driven and MC-associated diseases (Tanghetti 2013).

Evidence from clinical and preclinical studies highlights the therapeutic benefit of mast cell inhibition across several disease contexts. In rosacea, for example, mast cells play an integral role by releasing inflammatory mediators (Wang, Wang et al. 2019). This has led to the proposal of mast cells as potential therapeutic targets (Marchitto and Chien 2021, Fisher, Travers et al. 2023). Interestingly, patients with refractory erythema and rosacea flushing have demonstrated clinical improvement following intradermal injection of botulinum toxin (BoNT), although the mechanism was initially unclear (Dayan, Pritzker et al. 2012, Park, Hyun et al. 2015, Dayan, Ashourian et al. 2017). BoNT, a neuromuscular blocking agent approved by the U.S. Food and Drug Administration (FDA) in 1989 for blepharospasm, hemifacial spasm, and strabismus, has since been hypothesized to exert direct effects on mast cells. Experimental studies suggest that BoNT inhibits mast cell degranulation by cleaving SNARE proteins, indicating both neurogenic and direct mast cell–targeted mechanisms of action (Choi, Werbel et al. 2019).

Classical mast cell stabilizers, such as disodium cromoglycate (cromolyn sodium) and nedocromil sodium (the latter now discontinued), were approved for indications including systemic mastocytosis (oral solution) and asthma (inhalation). There were attempts to test mast cell stabilizer cromolyn sodium for treatment of erythematotelangiectatic rosacea. 10 randomized adults with erythematotelangiectatic rosacea were chosen to apply a solution containing either the MC stabilizer (4% cromolyn sodium) or placebo, topically to their face, twice daily. Investigators detected that facial erythema levels decreased in the cromolyn treatment group. In addition, MMP activity was significantly decreased in the cromolyn treatment group while KLK activity and Cath LL-37 protein levels only showed a mild decrease (Muto, Wang et al. 2014). Authors concluded that the stabilization of MCs could be a target therapy for erythematotelangiectatic rosacea.

Cromolyn sodium was first synthesized during experiments for the drug khellin used for cardiovascular disease treatment. It is the most commonly used MC stabilizer that binds specifically to the Ca^{2+} -binding protein on MC membranes, forming a ternary complex with Ca^{2+} (Geller-Bernstein, Mazurek et al. 1987). The ternary complex creates a blockage that stabilizes MC membranes and prevents degranulation (Geller-Bernstein, Mazurek et al. 1987). Recently, it was also shown that cromolyn sodium is modestly potent agonist of GPR3 (Jenkins, Brea et al. 2010) which is predominantly expressed in the gastrointestinal tract and is closely related to inflammatory bowel diseases (Duan, Liu et al. 2022). Therefore, further investigation concerning this potential mechanism is necessary. Cromolyn has a potent MC stabilizing effect, especially on lung MCs. Thus, it is widely used for the treatment of allergic diseases such as rhinitis and asthma. Due to its large molecular weight, highly hydrophilic and ionizable character, cromolyn is poorly absorbed by the gastrointestinal tract. Thus, inhalation is the preferred delivery method. Cromolyn must be taken 4–8 times daily due to its short half-life (Sinniah, Yazid et al. 2017) which results in a poor compliance. While generally well tolerated and biologically active, their clinical utility has been limited by the need for high doses and frequent administration, combined with poor bioavailability. (Haider 1977). The apparent cromolyn half-life 1.75 h for single dose and 1.91 h for double dose (Brazier, Perry et al. 2017). For example, the oral bioavailability of cromolyn sodium (Nalcrom® oral solution) is approximately 1%, while inhaled formulations (Intal™ nebulizer solution) achieve ~10% (Abd-Elaziz, Oude Elberink et al. 2020). Efforts have been made to improve delivery through topical formulations, such as a 4% cutaneous emulsion (Altoderm®) designed to enhance dermal penetration. Clinical studies reported limited systemic absorption (mean $1.46 \pm 0.91\%$, range 0.03–2.68%), suggesting potential for localized activity with minimal systemic exposure (Edwards, Matthews et al. 2010). Other study with 4% sodium cromoglycate in oil in water cream showed skin bioavailability $0.44 \pm 0.02\%$ ranged from 0.01% to 2.75% of the applied dose (Ariyanayagam, Barlow et al. 1985). Cromolyn sodium has molecular weight of 468.37 Da and this polar molecule has two negative charges at pH 7. Skin permeation of such polar and charged molecules does act by diffusion through the intercorneocyte lipid matrix, they can penetrate only through the appendageal paths of human skin i.e. via sweat pores and partly via hair follicles. Since hair follicles are usually clogged by sebum produced by adjacent sebaceous glands, only the sweat glands could provide shunt routes for hydrophilic and charged molecules like cromolyn sodium through the stratum corneum. But since the orifices of sweat pore appendages were estimated to represent not more than 0.1% of the total skin surface, the bioavailability of polar molecules has become very low (Otberg, Richter et al. 2004, Wosicka and Cal 2010). These facts can explain very low bioavailability of topical cromolyn sodium formulation. And it is expected that enhanced skin absorption may improve clinical efficacy of this effective and safe mast cell stabilizer.

Although traditionally considered a Th17-mediated disease, psoriasis also involves mast-cell activation, particularly in early lesion development (Zhou, Chen et al. 2022). Mast-cell-derived $\text{TNF-}\alpha$, IL-6, and tryptase can promote keratinocyte hyperproliferation and enhance neutrophil recruitment. Their proximity to nerve fibers and vasculature suggests roles in neurogenic inflammation and microvascular remodeling. Increasing evidence links mast-cell activation to disease severity and flare initiation.

Mast cells are prominently increased in lesional AD skin and contribute to hallmark features such as pruritus, barrier disruption, and chronic inflammation (Jia, Che et al. 2024). Through release of IL-4, IL-13, and histamine, mast cells promote Th2 polarization, impair keratinocyte differentiation, and enhance itch via direct communication with sensory neurons. Mast cells also respond to neuropeptides such as substance P and NGF, creating a neuro-immune loop that sustains disease activity.

Mast cells are enriched around hair follicles and sebaceous glands, placing them at key anatomic sites of acne pathogenesis (Eliasse, Leveque et al. 2021). They respond to Cutibacterium acnes-derived signals, lipid mediators, and neuropeptides. Tryptase, $\text{TNF-}\alpha$, and IL-1 β released by mast cells may amplify local inflammation and contribute to tissue remodeling and scarring. Recent work

suggests mast-cell-driven IL-17 production and communication with perifollicular fibroblasts may be particularly relevant in chronic or treatment-resistant acne.

For patients with mast cell-driven skin disorders, both efficacy and safety are of paramount importance. The development of topical mast cell stabilizers with enhanced skin permeability and improved bioavailability remains a highly desirable therapeutic avenue, particularly for chronic urticaria, rosacea, *acne vulgaris*, psoriasis, and other cutaneous MC-mediated diseases.

Novel Therapeutic Implications – Benefits Versus Risks

Understanding MC-driven mechanisms in cutaneous inflammation provides a framework for targeted interventions. Novel therapeutic approaches that directly target MCs fall into two main categories:

1. Systemic mast cell depletion

The most radical approach to preventing mast cells degranulation is systemic depletion, targeting both mucosal and subcutaneous populations. The pharmaceutical industry is actively developing strategies to achieve near-complete mast cell ablation as a means of reducing chronic inflammation in MC-driven skin and mucosal disorders. This approach has already advanced into human clinical trials for conditions such as chronic urticaria. Jasper Therapeutics and Celldex Therapeutics developed briquilimab and barzolvolimab, humanized monoclonal antibodies that binds the receptor tyrosine kinase KIT with high specificity, potently inhibiting its activity (Wedi 2023). Binding of these antibodies to KIT on mast cells results in dose-dependent suppression of plasma tryptase, a protease considered a biomarker of mast cell burden, consistent with systemic ablation of MCs. Both Jasper and Celldex argued that MCs are among the longest-lived immune cells and require substantial metabolic resources for repopulation. According to Jasper and Celldex publications anti-KIT antibodies induce MCs depletion, with repopulation estimated to take months or longer (Pang, Czechowicz et al. 2019, Alvarado, Maurer et al. 2022, Lee, Bouzid et al. 2025). Thus, their data suggests that the treatment with anti-KIT antibodies effectively inhibits KIT function and results in the virtual eradication of systemic, tissue and subcutaneous MCs. The eradication of MCs is detected via serum tryptase levels that decreased to the point where they were low to undetectable. However, experiments in animal models showed that mast cell-restricted tryptases (and particularly mMCP-6) has a critical immunoprotective role in bacterial infections (McNeil, Adachi et al. 2007, Thakurdas, Melicoff et al. 2007).

According to observations in patients with clonal MCs disorders who have undergone hematopoietic stem cell transplantation, the in vivo development of human MCs from donor stem cells takes at least 6 months (Fodinger, Fritsch et al. 1994). It was shown that full differentiation of human MCs from their stem and progenitor cells and full maturation in vitro takes at least 6 to 12 weeks (Valent, Spanblochl et al. 1992, Saito, Ebisawa et al. 1996). Phase 2 clinical trial data from Celldex demonstrated that barzolvolimab produced profound and durable improvements in angioedema through 52 weeks in patients with chronic spontaneous urticaria (Terhorst-Molawi, Hawro et al. 2023). However, treatment-related adverse events (generally mild in severity) were observed in >10% of patients, including hair color changes, neutropenia, urticaria, hypopigmentation, and nasopharyngitis. Of these, neutropenia is of particular concern given the critical role of neutrophils in innate immunity against bacterial and fungal infections. Severe neutropenia significantly increases the risk of life-threatening infections.

While mature neutrophils do not typically express KIT, this receptor is essential during hematopoietic development, particularly for stem cells and neutrophil progenitors. c-KIT (CD117) is expressed on Lin⁻c-KIT⁺ progenitors and early neutrophil precursors (hNePs) in the bone marrow, where it regulates proliferation and differentiation (Kim, Granick et al. 2011). Thus, KIT blockade may interfere with neutrophil lineage commitment and expansion, potentially explaining the observed neutropenia. In contrast, mature neutrophils primarily rely on alternative signaling

pathways, including pattern recognition receptors (e.g., Toll-like receptors) and Fc receptors, to mediate pathogen recognition and inflammatory responses.

Together, these findings illustrate both the promise and risks of systemic mast cell depletion. While highly effective at controlling MC-driven inflammation, KIT inhibition carries mechanistic liabilities that extend beyond mast cells, with potential for clinically meaningful immune suppression.

2. Mast Cell Stabilizers

For skin inflammatory disorders such as atopic dermatitis, chronic urticaria, rosacea, psoriasis, and acne vulgaris, topical mast cell inhibition represents a safer and more targeted approach compared with systemic MC ablation. Numerous preclinical and clinical studies show that MCs inhibition alleviates inflammation and disease symptoms. For example, cathelicidin (LL-37)-induced skin inflammation depends on mast cell activation; MC-deficient mice fail to develop rosacea-like pathology following LL-37 injection, and stabilization with cromolyn sodium reduces inflammation in both mice and humans. Similarly, intradermal botulinum toxin A (BoNT-A) has demonstrated clinical benefit in papulopustular rosacea (Dayan, Pritzker et al. 2012, Park, Hyun et al. 2015), with mechanistic studies indicating BoNT may suppress MC degranulation by cleaving SNARE proteins, in addition to its neuromodulatory effects (Choi, Werbel et al. 2019).

Newer strategies are also emerging. Kaplan and colleagues recently showed that glutamate and its analogs, such as SYM2081, suppress MCs degranulation via GluK2 receptor signaling (Zhang, Keshari et al. 2024). In murine rosacea and eczema models, topical SYM2081 markedly reduced inflammation, supporting the feasibility of skin-permeable GluK2 agonists as novel MC-targeted therapies. Thus, skin-permeable GluK2 agonists could be a novel class of MC-targeted therapies for skin inflammatory diseases.

Evidence for MC involvement in acne vulgaris is also accumulating. In a recent case series, tranilast (an oral MC stabilizer) combined with minocycline improved severe acne and prevented post-acne scarring more effectively than antibiotics alone, suggesting that MCs modulation may be important for preventing fibrosis and remodeling in acne (Horiuchi 2022, Horiuchi 2023). Topical and skin-permeable mast cell stabilizers for skin inflammatory diseases could be safer alternative in comparison with oral ones (Cao and Gao 2024).

Major Open Questions

There is currently no recognized medical term for the complete absence of mast cells in organism, such as “amastocytosis” or “mastoabsentia”. To date, no reports exist of humans or other mammals naturally lacking mast cells. A plausible explanation is that complete absence of MCs may be incompatible with life, with lethality occurring during development. Recently, pharmacological MC ablation with anti-KIT has shown clinical benefit in disorders such as chronic urticaria and chronic inducible urticaria (Terhorst-Molawi, Hawro et al. 2023). However, this approach can simultaneously compromise host defense. In particular, combined absence of systemic and cutaneous MCs with neutropenia presents a dangerous immunological gap. Without mast cells to initiate alarm signaling and with inadequate neutrophil numbers to mount immediate antimicrobial response, even commensal bacteria of the skin, oral cavity, and gut can precipitate severe illness. Opportunistic pathogens such as *Vibrio vulnificus*, *Staphylococcus aureus*, *Streptococcus pyogenes* (necrotizing fasciitis), *Klebsiella pneumoniae* and *Clostridioides difficile* pose especially high risks under such conditions.

The pharmaceutical industry is advancing systemic MCs depletion strategies to manage MC-driven inflammatory disorders. Yet, the evidence summarized above underscores that complete ablation—or even profound suppression—of mast cells may have unintended health consequences, particularly when combined with secondary effects such as KIT-related neutropenia.

Animal studies provide direct insight into the consequences of MC deficiency. WBB6F1-Kit^{W/Kit^{W-v}} (W/W^v) mice, which carry a c-Kit mutation leading to profound mast cell deficiency, rapidly succumb to septic peritonitis after cecal ligation and puncture (CLP). Reconstitution of these

mice with cultured wild-type MCs rescues survival, demonstrating the indispensable role of MCs in bacterial defense (Echtenacher, Mannel et al. 1996, Mannel, Hultner et al. 1996). In 1996, Echtenacher et al. noted that *W/W^v* mice quickly die from septic peritonitis after their caecum is ligated and punctured (Echtenacher, Mannel et al. 1996). Mast-cell-deficient WBB6F1-*W/W^v* mice (*W/W^v*) were up to 20-fold less efficient in clearing enterobacteria *Klebsiella pneumoniae* infection of their peritoneal cavities or lungs than control WBB6F1 *+/+* (*+/+*) mice or mast-cell-reconstituted *W/W^v* (*W/W^v* + MC) mice (Malaviya, Ikeda et al. 1996). The same phenomenon was observed in *tg/tg* mice confirming the importance of MCs in innate immunity (Jippo, Morii et al. 2003). When acute bacterial peritonitis was induced in WBB6F1-*+/+*, WBB6F1-*W/W^v*, and WBB6F1-*tg/tg* mice, the proportion of surviving WBB6F1-*+/+* mice was significantly higher than that of surviving WBB6F1-*W/W^v* or WBB6F1-*tg/tg* mice. The poor survival of WBB6F1-*W/W^v* and WBB6F1-*tg/tg* mice lacking the transcription factor MITF was attributed to the deficient influx of neutrophils into the peritoneal cavity (Jippo, Morii et al. 2003). All this data further confirms the role of MCs in innate immunity.

Efforts to dissect the mediators underlying this protection identified the mast cell-restricted serine protease mMCP-6 as a critical factor (Thakurdas, Melicoff et al. 2007). Although mMCP-6^{-/-} mice display normal MC morphology, granule composition, and FcεRI-dependent responses, they exhibit profound susceptibility to *K. pneumoniae*. Only ~10% of mMCP-6^{-/-} mice survive 72 hours after a low inoculum of 1000 CFU, compared with ~80% of wild-type controls. This phenotype was linked to impaired early neutrophil recruitment into the peritoneum, despite normal circulating neutrophil counts, leading to uncontrolled bacterial proliferation and systemic dissemination. These results highlight how mast cell-derived tryptase functions as an immunoprotective signal bridging MCs activation with neutrophil recruitment (Thakurdas, Melicoff et al. 2007).

Collectively, such studies demonstrate that mast cell deficiency—whether global or mediator-specific—compromises innate immunity by delaying neutrophil mobilization and amplifying bacterial lethality. Complete mast cells absence in organism, especially for a long time could be very dangerous situation if pathogen attack happens.

These findings support the hypothesis that mast cells are an initiating “first link” in inflammatory cascades across multiple skin disorders. MCs could be drivers of transition of acute inflammation to chronic one via autocrine feedback loop when MCs respond to their own cytokines (e.g., IL-33, IL-6), reinforcing and supporting persistent activation and recruitment of other effector cells to sites when antigen/pathogen exposure already ceases—a hallmark of chronic skin diseases.

Conclusions and Perspectives

Mast cells (MCs) have long been associated with immediate hypersensitivity reactions, yet a growing body of evidence now establishes them as central regulators of cutaneous inflammation across multiple time scales. Positioned strategically within the skin and equipped with an expansive sensory repertoire, MCs translate environmental cues into potent immunologic responses. Their ability to release pre-formed mediators in seconds, followed by sustained cytokine and chemokine production over hours to days, uniquely positions them to initiate, amplify, and perpetuate inflammation. Increasing mechanistic insight shows that MCs not only orchestrate early stages of immune activation but also play a decisive role in the transition from acute to chronic inflammation. Through persistent low-level activation, autocrine signaling and intensive crosstalk with keratinocytes, fibroblasts, neurons, and infiltrating leukocytes, MCs establish inflammatory circuits that are self-sustaining and difficult to terminate. This expanded paradigm explains their involvement across a wide spectrum of chronic dermatologic diseases—including atopic dermatitis, urticaria, rosacea, chronic pruritus, and *acne vulgaris*—where MC-driven pathways reinforce disease chronicity and symptomatic persistence. Therapeutically, MCs present a diverse array of actionable targets. MC stabilizers, H2 and H1 receptor antagonists, MCs proteases inhibitors, JAK-STAT and SYK pathway blockers, KIT inhibitors, and neuroimmune modulators represent emerging strategies capable of disrupting MC-mediated inflammatory networks. As precision dermatology expands,

interventions aimed at MCs signaling may help interrupt inflammatory loops at their point of origin, offering relief for patients with persistent or treatment-resistant diseases.

In summary, modern research positions MCs not as passive effectors of allergic reactions but as dynamic, multifunctional regulators that critically influence the trajectory of cutaneous inflammation. Recognizing MCs as both sentinels and potential “alarmists” underscores the need for continued investigation into their molecular programs, interactions within the skin microenvironment, and therapeutic vulnerabilities. A deeper understanding of MC-driven pathways will be essential for advancing targeted therapies and improving clinical outcomes in chronic inflammatory skin disorders.

Unlike systemic ablation, short-term inhibition of MC activation through topical delivery provides localized benefit without impairing systemic host defense. Topical application restricts exposure to inflamed lesions, sparing mast cells elsewhere in the skin and preserving submucosal MC populations in the gut and airways. Importantly, mast cell function resumes rapidly upon cessation of treatment, reducing long-term risks.

Taken together, it is increasingly clear that mast cells are not vestigial remnants of immunity but essential sentinels for tissue defense and homeostasis. Their role may be analogous to the appendix, once considered vestigial but now recognized as an immunological niche supporting gut microbiota and adaptive immunity (Girard-Madoux, Gomez de Agüero et al. 2018). Appendectomy is linked with increasing risk of development of ulcerative colitis and inflammatory bowel diseases (Koutroubakis and Vlachonikolis 2000, Frisch, Johansen et al. 2001). The loss of MCs—like the loss of the appendix—may have subtle but far-reaching consequences, predisposing to recurrent or severe infections and inflammatory diseases. Modern therapeutic strategies should therefore aim not at eradicating mast cells, but at modulating their activity with precision, preserving their sentinel role while preventing maladaptive, chronic activation.

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