

The role and relevance of mast cells in urticaria

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Summary

This review presents evidence that the skin mast cell, in particular the MC_{TC} subtype, is the primary effector cell in urticaria. Mast cells are located in the upper dermis, the ideal situation for wheal formation and sensory nerve stimulation. Increased numbers of mast cells are found in both lesional and non-lesional skin in CSU and inducible urticaria. Mast cell degranulation in the area of wheals has been demonstrated repeatedly by light and electron microscopy. Histamine, PGD₂ and tryptase are found in the venous blood draining wheal formation. The last 2 are specific for mast cells rather than basophils. Mast cell reactivity is increased in active urticaria by local inflammatory cytokines and neuropeptides. Mast cell cytokines and neuropeptides, particularly nerve growth factor, induce a Th2 type inflammation that is particularly obvious at the sites of whealing. In conclusion, autoimmunity, either of Type 1 viz. IgE antibodies to local autoallergens, or Type 2b, viz. IgG autoantibodies to IgE or its receptor, are considered to be the most frequent causes of CSU. In both cases, the mast cell is likely to be the axial cell in producing the wheals.

KEYWORDS

autoallergy, chronic spontaneous urticaria, mast cell, urticaria

1 | INTRODUCTION

It is now more than 100 years since Gilchrist¹ observed that there is an increase in the number of *mastzellen* in the neighborhood of the blood vessels following the induction of symptomatic dermatographism. Gilchrist also suggested that some toxin is set free into the tissues of the dermis to induce the wheals. However, further elucidation of this hypothesis had to await the discovery by Henry Dale in 1910² of the actions of histamine and the seminal studies of Thomas Lewis in 1924³ describing the liberation of a histamine-like substance from injured skin and the ability of histamine to cause wheal and flare responses similar to those seen in symptomatic dermatographism. Following their discovery in 1937⁴ and their introduction into clinical practice in 1942,⁵ H₁-antihistamines became the standard treatment for urticaria thus leading to the hypothesis that mast cell-derived histamine was axial to the development of urticarial lesions.^{6,7} However, this hypothesis has not been reviewed and critically discussed during the last 20 years. Consequently, we now provide and discuss several independent lines

of evidence that support a central role of mast cells in urticaria, primarily chronic urticaria. We also outline the current gaps of knowledge and provide unmet needs and unanswered questions.

Human mast cells are derived from bone marrow CD34⁺, CD117⁺ (Kit), CD13⁺ pluripotent progenitor cells⁸ that mature under the local environment of the tissues into which they migrate. Immunological staining of tissues have revealed 2 types of human mast cells characterized by their neutral protease content,⁹ MC_T (mast cells which are tryptase-positive but chymase-negative), and MC_{TC} (mast cells which are both tryptase and chymase-positive). Visually, the granules of mature MC_T contain complete scrolls, whereas those of MC_{TC} cells often contain grating or lattice substructures.⁹ The development, disposition, and primary functions of these mast cell subtypes are also different. MC_T are found typically at mucosal tissues such as the intestine, lung, and nose, are T-lymphocyte dependent, and are typically associated with allergic diseases when they are increased in number.¹⁰ In contrast, the development of MC_{TC} is independent of lymphocytes and they are located primarily in the skin and gastrointestinal submucosa.⁷ It is this MC_{TC} phenotype that comprises more than 99% of the mast cells in the dermis of both lesional skin and non-lesional skin of patients with

chronic spontaneous urticaria.¹¹ Early studies also showed that there were functional differences between MC_T and MC_{TC}.

Although IgE-dependent stimulation leads to degranulation of both subtypes, MC_{TC} may be activated by IgE-independent mechanisms. Human skin mast cells express the G-protein coupled receptor (GPCR) mas-related gene X2 (MrgX2) that allows them to be activated for degranulation by polybasic substances, such as compound 48/80 and poly-L-lysine.^{12–14} Mast cells also express neuropeptide receptors, such as neurokinin 1 and 2 receptors (NK1R and NK2R), calcitonin gene-related peptide receptor (CGRPR), and the neurotrophin receptors, tropomyosin-related kinase A (TrkA), TrkB, and TrkC.^{15–18} Neuropeptides such as substance P, vasoactive intestinal peptide (VIP), and somatostatin, but not eledoisin, physalaemin, neurokinin A, neurokinin B, calcitonin gene-related peptide (CGRP) stimulate both mast cell degranulation and cytokine production.^{19–21} Despite the expression of many neuropeptide receptors, the main receptor responsible for mast activation by neuropeptides appears to be MrgX2.^{22,23} Human skin mast cells also express CD88/C5aR allowing them to be activated by complement peptide C5a.^{24,25} Finally, human cutaneous mast cells are activated for histamine release and cytokine production to opiates, including codeine and morphine.^{26–33} The observation that this is only partially blocked by naloxone suggests both receptor-mediated and non-receptor mechanisms to be involved.^{34–38}

2 | PURPORTED MECHANISMS OF CHRONIC URTICARIA

Although the cause and pathogenesis of chronic spontaneous urticaria remained an enigma for many years, early histological studies indicated that it is characterized by an accumulation of mononuclear cells and mast cells with mast cell degranulation presumably associated with wheal formation.^{39–41} The observation that the infiltrate resembled that observed in cellular immune reactions tempted Kaplan and colleagues to speculate that CSU is an allergic-type reaction even though no antigen had been identified.⁴¹

The first evidence that CSU may have an immunological basis came from reports that autologous sera, some with CSU, re-injected intradermally produced a wheal at the site of injection.^{42–44} This is the so-called autologous serum skin test (ASST).⁴⁵ Subsequent studies showed that the IgG antibodies to the patient's own IgE or its high affinity receptor (FcεRI) are instrumental in causing mast cell degranulation and subsequent wheal development^{46–48} (Figure 1A). Studies showing the presence of IgG-anti-IgE and IgG-anti-FcεRI antibodies are summarized in Table 1. The evidence in support of this mechanism of CSU has been reviewed recently.^{49,50} Removal of IgE and subsequent loss of mast cell FcεRI would explain the slow onset of action of omalizumab seen in up to 30% of patients responding to omalizumab.^{51,52} However, some 60% of responders to omalizumab become symptom free quite rapidly, usually within a week.^{52,53} In these individuals, a Type-1 allergic mechanism appears likely even though there is no obvious external allergen as in classical allergy (Figure 1A). Thus, an autoallergy is postulated in which IgE is directed to an element of self.⁵¹ This is supported by studies that

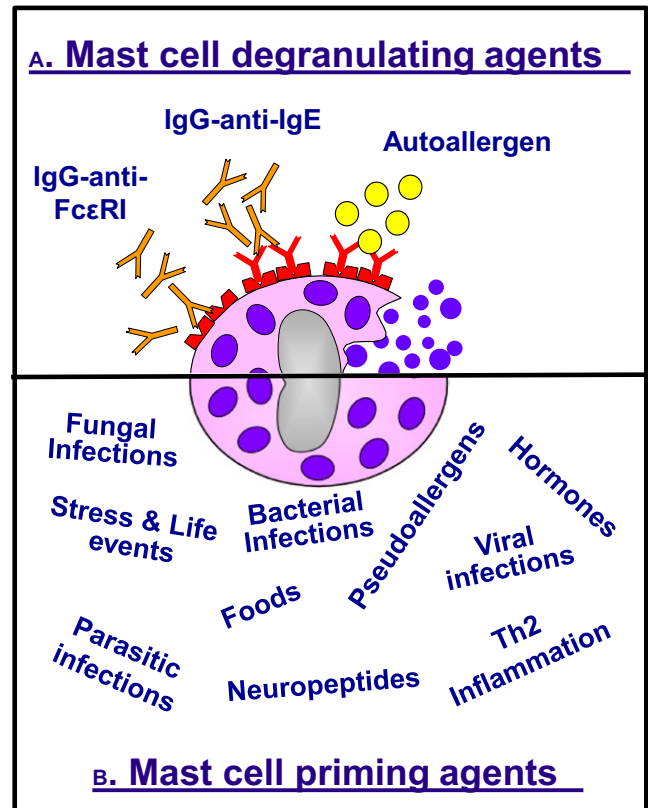


FIGURE 1 (A) The potential autoimmune mechanisms of chronic spontaneous urticaria. (B) Agents that may prime mast cells for activation

have shown that patients with CSU have high levels of IgE autoantibodies such as IgE-anti-TPO and IgE-anti-dsDNA in their blood.^{50,54,55} More recently, using array analyses, over 200 IgE-autoantigens were found in CSU patients that were not present in controls. Of these, IgE-anti-IL-24 was found in all CSU patients indicating IL-24 to be a dermal autoantigen in CSU.⁵⁶ While this study focused on CSU, the effectiveness of omalizumab in a wide range of chronic inducible urticarias^{53,57,58} suggests that similar autoantigens and IgE-dependent mechanisms may also underlie these forms of urticaria.⁵⁹

In conclusion, autoimmunity, either of Type 1 viz. IgE antibodies to local autoallergens, or Type 2b, viz. IgG autoantibodies to IgE or its receptor, is considered to be the most frequent causes of CSU.⁴⁹ In both cases, the mast cell is likely to be the axial cell in producing the wheals. Let us now consider potentially confirmatory evidence.

3 | MAST CELL LOCATION AND CHANGES IN NUMBER IN CHRONIC URTICARIA

Mast cells in urticaria patients, as in healthy individuals, are located in the upper and lower dermis with a prevalent perivascular and periadnexal pattern.^{60,61} Highest numbers are found in superficial dermal skin lesions and the lowest numbers in lower reticular dermis.^{62,63}

Although the disposition of mast cells in the skin of urticaria patients is normal, do their numbers change in chronic urticaria? Reports

Author	No. of patients	Found?	Significantly higher levels as compared with controls?	Antibodies
Ulabmayar et al ²¹¹	125	Yes	Yes	IgG-anti-FcεRI ^a
Auyeung et al ²¹²	46	Yes	Yes	IgG-anti-FcεRI
Sun et al ²¹³	100	Yes	Yes	IgG-anti-FcεRI ^a , anti-IgE ^b
Cho et al ²¹⁴	27	No	No	IgG-anti-IgE
Eckman et al ²¹⁵	73	Yes	No	IgG-anti-FcεRI, anti-IgE
Vasagar et al ²¹⁶	9	Yes	No	IgG-anti-FcεRI
Puccetti et al ²¹⁷	133	Yes	-	IgG anti-FcεRII/CD23
Pachlopnik et al ²¹⁸	19	Yes	No	IgG-anti-FcεRI ^b , anti-IgE ^b
Atta et al ²¹⁹	46	Yes	No	IgG-anti-IgE
Hidvegi et al ¹⁰⁴	50	Yes	Yes	IgG-anti-FcεRI ^c
Sabroe et al ²²⁰	78	Yes	Yes	IgG-anti-FcεRI ^a , anti-IgE ^a
Zuberbier et al ²²¹	48	Yes	Yes	IgG-anti-FcεRI
Ferrer et al ²²²	53	Yes	Yes	IgG-anti-FcεRI
Fiebiger et al ²²³	281	Yes	Yes	IgG-anti-FcεRI
Tong et al ²²⁴	50	Yes	Yes	IgG-anti-FcεRI, anti-IgE
Fiebiger et al ²²⁵	32	Yes	Yes	IgG-anti-FcεRI
			No	Anti-IgE
Gruber et al ⁴³	6	Yes	-	IgG-anti-IgE

^aHigher in ASST+ CSU patients as compared to ASST- CSU patients.

^bLevels were not significantly different between ASST+ CSU patients and ASST- CSU patients.

^cAll FcεRI-antibody-positive CSU patients had a positive ASST response; -: not defined in the paper.

about this are conflicting. The earliest study in CSU reported an increase in the percentage of dermal mast cells from 11% to 14%.⁴¹ Increased mast cell numbers in both lesional and non-lesional skin have been reported in several other studies,^{64,65} while others report increases in areas of whealing or recent whealing⁶⁶⁻⁷⁰ or in both lesional and uninvolved skin of patients with prolonged (>10 weeks) disease.⁶³ One study which compared mast cell subtypes in lesional skin of CSU patients and healthy skin is particularly noteworthy.⁷¹ This study showed that there are no differences between the numbers of MC_{TC}, the so-called connective tissue mast cell, between the 2 groups. However, the increased number of MC_T in CSU lesional skin was highly significant ($P < .001$). As it is the MC_T subtype of mast cells that is particularly associated with allergic disease⁷², this would support an allergic mechanism for CSU. In contrast, other studies found no difference between mast cell numbers in the skin of chronic urticaria patients and healthy individuals.^{11,60,61,73-76}

4 | EVIDENCE OF MAST CELL DEGRANULATION

Evidence for mast cell degranulation using both light and electron microscopy has been shown in the dermis immediately underlying

TABLE 1 Studies exploring the presence of IgG-anti-FcεRI and IgG-anti-IgE in the blood of patients with CSU

wheals in many types of urticaria including CSU,^{67,77} symptomatic dermographism,⁷⁸ cold-induced urticaria,^{30,78-80} heat-induced urticaria,⁸¹ cholinergic urticaria,⁸² and delayed pressure urticaria^{78,83} (Table 2).

Many histological studies report a mononuclear cell and eosinophil perivascular infiltration into the area of wheal.^{67,77,78,81-83} The infiltration of eosinophils, many of which appear activated,^{67,84} suggests that the molecular immunopathology of CSU is similar to that of the allergic skin late phase response with a Th0 rather than a Th2 cytokine profile.^{65,77} Furthermore, many cytokine measurements have been made which support a chronic inflammatory response in CSU. These are summarized in Table 3.

5 | EVIDENCE OF INCREASED MAST CELL MEDIATORS

It is now more than 50 years since the first demonstration of histamine in the plasma of a patient with cold urticaria.^{85,86} This observation has been repeated for CSU^{68,87,88} and many types of inducible urticaria including cold urticaria,⁸⁹⁻⁹⁵ heat-induced urticaria,^{81,89,96,97} solar urticaria,⁹⁸ symptomatic dermographism,⁹⁹ cholinergic urticaria,⁹¹ delayed pressure urticaria,¹⁰⁰ and aspirin-induced urticaria.¹⁰¹ Increased

TABLE 2 Cytokines found in the blood of patients with CSU

Author	No. of Patients	Significantly higher levels as compared to controls?	Cytokines
Zheng et al ¹⁷⁶	28	Yes	TGF- β 1
		No	IL-33, IL-1 β , IL-9, IL-4, and IL-17A
Grzanka et al ¹²²⁶	52	Yes	IL-17
Chen et al ²²⁷	60	Yes	IL-2, IL-5, IL-6, IL-12p70, IL-13, IL-21, IL-23, IFN- γ , TGF- β 1, TNF α , and TNF β
Trinh et al ²²⁸	191	Yes	TNF α , IL-6, IL-10
Hong et al ⁶⁸	72	Yes	TNF α , TGF β , IL-4, IL-5, IL-6, TG2
Wang et al ²²⁹	23	Yes	IFN- λ 1
Bae et al ²³⁰	84	Yes	IL-13
Varghese et al ²³¹	45	Yes	IL-18
Kasperska-Zajac et al ²³²	58	Yes	IL-6
Grzanka et al ²³³	17	Yes	IL-6
Alasandagutti et al ²³⁴	100	Yes	IFN- γ , IL-6
Rasool et al ²³⁵	62	No	IL-18, IL-6
Chandrashekar et al ²³⁶	45	Yes	IL-17, TGF- β
Atwa et al ²³⁷	75	Yes	IL-17, IL-23, TNF α
Arshi et al ²³⁸	41	No	IL-17, IL-10, TGF- β
Rajappa et al ²³⁹	45	Yes	IL-6
Ucmak et al ²⁴⁰	53	Yes	IL-6
Puxeddu et al ¹⁷⁴	73	Yes	IL-18, IL-18BP
		No	IL-33
Puxeddu et al ²⁴¹	87	Yes	CCL5/RANTES, sICAM-1, sVCAM-1
		No	CXCL8/IL-8
Metz et al ¹⁷⁵	>30	No	TNF, IL-6, IL-9, IL-18, IL-31, IL-33, TSLP
Ciprandi et al ²⁴²	109	Yes	IL-9
Kurt et al ²⁴³	55	Yes	IL-18
Kasperska-Zajac et al ²⁴⁴	58	Yes	IL-6
Raap et al ¹⁹⁵	46	Yes	IL-31
Serhat Inaloz et al ²⁴⁵	27	Yes	IL-2R, TNF α , IL-5
Dos Santos et al ²⁴⁶	29	Yes	TNF, IL-1 β , IL-6, IL-12p70, and IL-10
Kasperska-Zajac et al ²⁴⁷	18	Yes	IL-6
Tedeschi et al ²⁴⁸	34	No	IL-18
Caproni et al ²⁴⁹	68	Yes	IL-13
		No	IL-4, IFN γ , MIP-1 α
Mohamed et al ²⁵⁰	25	Yes	IL-4
Ferrer et al ²⁵¹	60	Yes	IL-4
		No	IFN γ , IL-5

CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; IFN, interferon; IL, interleukin; MIP, macrophage inflammatory protein; sICAM, sVCAM, soluble adhesion molecules; TG2, transglutaminase 2; TGF, transforming growth factor; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin.

levels of histamine in the tissues have also been demonstrated. The results of these studies are shown in Table 4. More recently histamine liberated into the tissues in cold-induced urticaria in response to cold provocation was demonstrated by dermal microdialysis.³³

While these studies clearly demonstrate the involvement of histamine in urticaria, they do not differentiate between mast cells

and basophils as its source. However, the increase in plasma levels of skin mast cell-derived PGD₂^{94,102,103} in cold urticaria and mast cell tryptase in CSU¹⁰⁴⁻¹⁰⁶ are strong indicators of the involvement of mast cells rather than basophils. Furthermore, in the microdialysis study, the concentration of histamine collected during the first 20 minutes following cold challenge was not significantly changed by

TABLE 3 Studies exploring the presence of mast cell degranulation in biopsies from patients with chronic urticaria

Author	Urticaria type	No. of patients	Method	Found?	Site
Koh et al ⁸⁴	Heat	1	LM; EM	Yes	Wheal
				No	Normal skin
Ying et al ⁷⁷	CSU	13	ICC	Yes	Wheal
Toyoda et al ⁶⁷	CSU	43	LM; EM	Yes	Wheal
Tillie-Leblond et al ⁸⁰	Cold	5	EM	Yes	Wheal
Grattan et al ⁴⁶	CSU	5	EM	Yes	Wheal
Lawlor et al ⁷⁹	Cold	6	EM	Yes	Wheal
				No	Normal skin
Keahey et al ³⁰	Cold	1	EM	Yes	Wheal
				No	Tolerant skin
Mekori et al ⁸³	DPU	5	EM	Yes	Wheal
Murphy et al ⁷⁸	Cold dermatographism	3	LM; EM	Yes	Wheal
		4		Yes	Wheal
Mayou et al ⁸²	Cholinergic dermatographism	1	LM; EM	Yes	Wheal
Koro et al ²⁵²	Heat	1	LM	No	Wheal
Irwin et al ⁸¹	Heat	2	EM	Yes	Wheal
Winkelmann ²⁵³	Cold	5	EM	No	Wheal
Winkelmann ²⁵⁴	Dermatographism	12	LM	No	Wheal
Czarnetzki et al ⁶⁹	DPU	7	EM	Yes	Wheal
Johansson et al ²⁵⁵	Heat	1	LM	No	Wheal
Keahey et al ²⁷	Solar	3	EM	Yes	Wheal
				No	Tolerant skin
Ting et al ²⁵⁶	Vibratory angioedema	1	LM; EM	Yes	Wheal
				No	Normal skin
Natbony et al ⁴⁰	CSU	43	LM	Yes	Wheal
Sibbald et al ²⁵⁷	Aquagenic	2	LM	Yes	Wheal
Hawk et al ⁹⁸	Solar	4	EM	Yes	Wheal
James et al ²⁵⁸	Cold	4	LM	Yes	Wheal
	Solar	5		Yes	Wheal
	Pressure	4		Yes	Wheal
	Factitious	3		Yes	Wheal
	Aquagenic	2		Yes	Wheal
	Cholinergic	2		Yes	Wheal
	Heat	1		Yes	Wheal
Daman et al ²⁵⁹	Heat	1	EM	No	Wheal
Levine ²⁶⁰	CSU	1	LM; EM	No	Wheal
Juhlin and Shelley ²⁶¹	Cold	2	-	Yes	Wheal

CSU, chronic spontaneous urticaria; DPU, delayed pressure urticaria; LM, light microscopy; EM, electron microscopy; ICC, immunocytochemistry.

pretreatment of individuals with the H₁-antihistamine, bilastine, while the sample collected between 20 and 60 was significantly reduced. This suggests that histamine in the earlier sample was primarily mast cell derived while the later sample included histamine from influxing basophils.³³

6 | IS MAST CELL REACTIVITY CHANGED?

The possibility that mast cells may become more reactive in urticaria has been mooted for many years. Initial studies indicated increased activity of compound 48/80 in non-lesional skin of CSU patients,

TABLE 4 Increase in levels of MC mediators in blood or skin following the provocation in inducible urticaria

Author	No. of urticaria patients	Type of urticaria	MC mediators	Blood/skin	Increase in levels of mediators after the provocation?
Nuutinen et al ²⁶²	6	Cold	Histamine, LTC ₄	Blood (microdialysis)	Yes (histamine), No (LTC ₄)
Baba et al ²⁶³	1	Heat	Histamine	Blood	Yes
Mijailović et al ²⁶⁴	80	Cholinergic	Histamine	Blood	Yes, in 12 patients
Tillie-Leblond et al ⁸⁰	5	Cold	Histamine, TNF	Blood	Yes (histamine in 3 patients and TNF in 2 patients)
Lawlor et al ²⁶⁵	6	DPU	LTC ₄ , LTD ₄ , LTE ₄ , PGD ₂ , LTB ₄	Skin exudate	No
Maltby et al ²⁶⁶	5	Cold	Histamine, LTE ₄	Blood	Yes (in 3 patients)
Ormerod et al ⁹⁴	6	Cold	PGD ₂ , histamine	Blood	Yes
Neittaanmäki and Fräki ⁷⁵	2	Heat+cold	Histamine	Suction blister fluid	Yes
Keahey et al ³⁰	1	Cold	Histamine	Blood	Yes
Heavey et al ¹⁰²	4	Cold	PGD ₂ , histamine	Blood	Yes
Irwin et al ⁸¹	2	Heat	Histamine	Blood	Yes
Grandel et al ⁹⁵	6	Cold	Histamine, PAF, neutrophil chemotactic activity	Blood	Yes (in some patients)
Wasserman and Ginsberg ²⁶⁷	5	Cold	Histamine	Blood	Yes
Kaplan ²⁶⁸	2	Systemic cold urticaria and cold-dependent dermographism	Histamine	Blood	Yes
Neittaanmäki et al ²⁶⁹	18	Cold	Histamine	Suction blister	Yes
Keahey et al ²⁷	3	Solar	Histamine	Blood	Yes
Wasserman et al ⁹³	8	Cold	Histamine, chemotactic factors	Blood	Yes
Atkins and Zweiman ⁹⁷	1	Heat	Histamine, neutrophil chemotactic activity	Blood	Yes
Grant et al ⁹⁶	1	Heat	Histamine	Blood	Yes
Garafalo and Kaplan ⁹⁹	6	Dermographism	Histamine	Blood	Yes (in 1 patient)
Kaplan et al ²⁷⁰	5	Cold	Histamine	Blisters over urticarial lesions	Yes
	-	Dermographism			
	2	Immediate-pressure			
	1	DPU			
	1	Heat			
	1	Solar			
	-	CSU			
Soter et al ⁹²	3	Cold	Histamine and eosinophil chemotactic factor	Blood	Yes
Bentley-Phillips et al ⁹⁰	5	Cold	Histamine	Blood	Yes
Kaplan et al ⁹¹	6	Cold	Histamine	Blood	Yes
	2	Cholinergic			
Beall ⁸⁹	1	Cold+heat	Histamine	Blood	Yes
Duner et al ²⁷¹	4	Cold	Histamine	Blood	Yes (in 3 patients)
Henderson et al ⁸⁵	1	Cold+heat	Histamine	Blood	Yes

CSU, chronic spontaneous urticaria; DPU, delayed pressure urticaria; LT, leukotriene; TNF, tumour necrosis factor; PG, prostaglandin; PAF, platelet-activating factor.

which became normal in remission.^{107,108} The skin of CSU patients has also been reported to show increased responsiveness to the neuropeptides substance P and VIP.^{109,110} One mechanism of this enhanced reactivity has been shown recently to be a significantly higher expression of MrgX2, the receptor for compound 48/80 and neuropeptides, on skin mast cells from CSU patients compared with those from healthy individuals.²³ To be clinically relevant, substance P in particular should be increased in urticaria. Several studies have shown circulating levels of substance P to be higher in CSU patients compared with healthy individuals^{111–113} although this was not confirmed by another.¹¹⁴ Furthermore, measurements of substance P and VIP in the skin showed their concentrations to be higher in urticaria patients than in controls.¹¹⁵ Finally, concentrations of substance P that are likely to occur in the skin of patients can increase the responsiveness of mast cells to other activating signals.^{116,117}

The skin mast cell MrgX2 has also been shown to be a receptor for the eosinophil proteins major basic protein (MBP) and eosinophil peroxidase (EPO) both of which induce degranulation of human skin mast cells.²³ Significantly more eosinophils are found in the skin, and particularly in lesional skin, CSU compared with controls.^{65,67,77,118} In another study, biopsies of delayed pressure urticaria showed eosinophil infiltration with extensive MBP deposition beginning at 20 minutes. This infiltration was less marked in urticarial dermatographism.¹¹⁹ The involvement of eosinophil proteins, possibly through increased mast cell degranulation, is likely to enhance tissue reactivity in urticaria.^{23,67,120} This hypothesis is supported by the recent observation of the effectiveness of anti-IL-5 in relieving the symptoms of CSU and cold urticaria.¹²¹

Emotional stress can affect, reveal, or exacerbate a number of skin disorders including urticaria both by releasing neuropeptides and through modulating hypothalamic-pituitary-adrenal axis.^{122–126} It has been proposed that allergic inflammation and urticaria are characterized by mast cell degranulation and increased neuropeptide levels^{127–134} and that stress is able to enhance mast cell degranulation in a neuropeptide-dependent manner.^{130,135–137} This has been clearly demonstrated in a series of papers by Kimata on individuals with atopic dermatitis. These papers showed that the stress of playing video games, listening to mobile phones, and exposure to road traffic increased allergen-induced wheal responses in parallel to increased plasma levels of substance P, VIP, and nerve growth factor (NGF).^{138–140} In contrast, suckling by lactating mothers, kissing loved ones, laughter, and listening to Mozart but not Beethoven all improved mood, reduced neurotrophins and reduced the size of allergen-induced wheal responses.^{141–144} That the responsiveness to intradermal histamine was unchanged strongly suggest it was increased histamine release from the mast cell that was responsible for these effects. The possible mechanism for this involves the interaction of neuropeptides with the mast cell MrgX2 receptor as described above.

With regard to modulation of the hypothalamic-pituitary-adrenal axis, it is now well established that corticotrophin-releasing hormone (CRH) is secreted under stress not only from the hypothalamus¹⁴⁵ but also from mast cells¹⁴⁶ and eosinophils¹⁴⁷ in the skin. Mast cell membranes contain a receptor for CRH, CRH-R1, stimulation of which

through CRH increases their sensitivity to degranulation with neuropeptides and immunoglobulins.^{148,149} Quantitative real-time PCR revealed that tissue levels of CRH-R1 are elevated in chronic urticaria compared with healthy skin.¹⁵⁰

Human skin mast cells have been demonstrated to express the GPCR proteinase-activated receptor-2 (PAR2) that is activated by serine proteases including trypsin and mast cell tryptase but not thrombin.^{151–153} The ability of this receptor to be activated by mast cell tryptase suggests the presence of an autocrine loop enhancing mast cell mediator release. However, this needs to be substantiated. Human skin mast cells have also been shown to express PAR1, PAR3, and PAR4 stimulation of which by thrombin induces a direct and dose-dependent mast cell degranulation.^{152,154} The increase in thrombin generation in CSU would implicate an increase in mast cell releasability in chronic urticaria.^{155–159}

The histamine H₄-receptor (H4R) is constitutively expressed on human mast cells.^{160,161} Stimulation of H4R on mast cells by histamine may have 3 positive effects. First, it increases mast cell chemotaxis thus encouraging their accumulation at the site of an allergic response.¹⁶² Second, it upregulates the expression of mast cell FcεRI thereby priming them for allergen-induced activation¹⁶³ as well as activation by IgG anti-FcεRI (Type IIb autoimmunity). Third, it mobilizes intracellular calcium to either prime mast cells for activation or, indeed, induce degranulation.¹⁶¹ However, the role and possible upregulation of H4R in urticaria have not yet been explored.

In addition to the above, many physicians observe that other concomitant clinical conditions, including viral, bacterial, and fungal infections, hormones, hormonal changes, and ingestion of certain foods may all exacerbate urticaria. These conditions, which are summarized in Figure 1B, are suggested to upregulate mast cell reactivity.

7 | EFFECTS OF THE MAST CELL ON THE LOCAL ENVIRONMENT

7.1 | Nerve growth factor

The role of neuropeptides in stress-induced exacerbation of inflammation and their ability to prime mast cells for activation or even induce degranulation has been described earlier. Here we highlight 1 particular neuropeptide, NGF, a member of the neurotrophin family important for the development and survival of nociceptive neurons¹⁶⁴ (Figure 2). Although circulating levels of NGF are raised in allergic diseases and urticaria,¹²⁸ it is generated in large quantities from mast cells in areas of inflammation.^{165–168} The primary effect of NGF is on the local development of sensory nerves which become NGF-dependent near the target tissue.¹⁶⁹ Thus, at sites of local inflammation, the axons grow toward a higher concentration of NGF, where they arborize and terminate.¹⁷⁰ This would increase the sensitivity of the skin in the local environment to neurogenic flare, itch, and pain. NGF also promotes local inflammatory responses as it promotes the proliferation, survival, and activation many immune cells, including mast cells, Th2-lymphocytes, neutrophils, and eosinophils.¹⁶⁹ Of particular relevance to urticaria is the ability of NGF to increase the

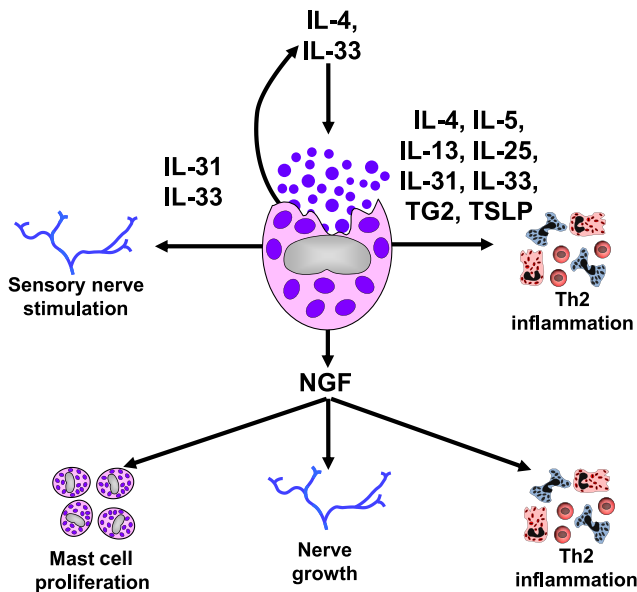


FIGURE 2 The autocrine and paracrine effects of nerve growth factor and cytokines potentially released in wheals in chronic urticaria

local accumulation of mast cells.^{171,172} However, in contrast to the neuropeptides substance P and VIP, NGF does not stimulate mast cell degranulation.²⁰ These data suggest that the local generation of NGF in inflammation and its ability to stimulate sensory nerve growth and promote the inflammatory response indicate its potential to act as an important local mediator in allergy and urticaria.

7.2 | Cytokines

As stated earlier in Table 2, a plethora of cytokines have been found in the circulation of patients with urticaria. These can induce a perivascular infiltration into the area of urticarial wheals of mononuclear cells, neutrophils, and eosinophils^{67,77,78,81-83} suggesting the response to be similar to late phase allergic responses.^{65,77}

The cytokine IL-33, a member of the IL-1 superfamily of cytokines, induces a strong Th2 cytokine response and also acts as an “alarmin” by alerting the immune system to tissue damage or stress.¹⁷³ Although not upregulated in the plasma in CSU,¹⁷⁴⁻¹⁷⁶ IL-33 is, at least in mice, expressed locally in inflamed skin by both keratinocytes¹⁷⁷ and mast cells but not basophils.¹⁷⁸ In CSU, marked elevations of IL-33⁺ cells, particularly endothelial cells, fibroblasts, macrophages, and mast cells, have been shown in the dermis of lesional skin.¹⁷⁹ IL-33 has 2 actions that may be of significance in urticaria. First, it activates primary sensory neurons that mediate the sensation of itch.¹⁷⁷ Second, it can modulate many aspects of mast cell function, including adhesion, maturation, degranulation, and production of a variety of Th2-like cytokines.¹⁸⁰⁻¹⁸⁵ In this latter role, IL-33 will contribute to the induction of the Th2-like inflammation seen in chronic urticaria^{65,179,184,186} and has the potential to act in a positive autocrine loop for further mast cell degranulation (Figure 2).

An elevated expression of IL-25, a member of the IL-17 cytokine family that is a powerful promoter of Th2 cell-dependent

inflammation,¹⁸⁷ has also been shown in epithelial cells, mast cells, and eosinophils in lesional skin in CSU.¹⁷⁹ The observation that mast cells can produce IL-25 following IgE-dependent activation¹⁸⁷⁻¹⁸⁹ suggests a possible innate immune pathway that promotes Th2 cytokine responses in CSU (Figure 2).

A second member of the IL-17 cytokine family, thymic stromal lymphopoietin (TSLP), has also been shown to be elevated in lesional skin in CSU.¹⁷⁹ While the cellular provenance of TSLP was not reported in this study, increased numbers of TSLP-positive mast cells have been reported in the bronchial tissue in asthma.^{190,191} Furthermore, cultured human mast cells have been shown to produce TSLP following aggregation of FcεRI in the presence of IL-4.¹⁹¹ The primary role of TSLP in the skin is suggested to be augmenting, through dendritic cell recruitment and activation, the development of Th2-type T cells in allergic inflammation.¹⁹² TSLP does not induce mast cell degranulation per se but stimulation by TSLP in the presence of IL-1 and TNF induces them to produce and release high levels of the proinflammatory cytokines/chemokines IL-5, IL-13, IL-6, GM-CSF, CXCL8, and CCL1 over the following 24 hours.¹⁹³

Transglutaminase 2 (TG2) activity has recently been shown to be significantly higher in serum samples from patients with CSU than samples from healthy controls. Furthermore, colocalization of TG2 with the mast cell surface marker c-kit was significantly increased in lesional skin of patients with CSU compared with that in healthy controls suggesting the mast cell to be its primary source.⁶⁸ In an in vitro study, human mast cells were demonstrated to release TG2 following IgE-dependent activation.⁶⁸ In allergic asthma, TG2 has been shown to serve as a key initiator of airway inflammation by activating the TH2 immune response via the induction of interleukin IL-33 expression in airway epithelial cells.¹⁹⁴ This led Hong and colleagues to conclude that TG2-expressing mast cells may induce the production of cytokines in an autocrine and paracrine manner, resulting in the activation of other inflammatory cells, such as T cells and eosinophils, which contributes to the pathogenesis of CSU.⁶⁸

Serum levels of IL-31, a member of the IL-6 cytokine family, have been shown to be higher in patients with CSU than in healthy controls, but lower than patients with atopic dermatitis.¹⁹⁵ IL-31 promotes Th2 inflammation¹⁹⁶ but has also been reported to induce itch by its interaction with specific IL-31 receptors on sensory nerves.^{197,198} Although primarily secreted by Th2 lymphocytes,¹⁹⁶ IL-31 has also been reported to be released from human mast cells.¹⁹⁹ For this reason we have recently investigated the potential role of this cytokine in causing itch in CSU.²⁰⁰ While IL-31 levels were reduced in patients following successful treatment with omalizumab, we did not consider it to be a primary mediator of itch in this condition for 3 reasons. First, there was no correlation between IL-31 levels and the severity of CSU or itch scores assessed by UAS7. Second, 7 of the 22 patients examined had no detectable serum IL-31 even though they had severe disease. Third, the highest level of IL-31 detected was 30 ng/mL, considerably lower than the 1 mg/mL concentration required to induce only inconsistent mild and delayed itch sensations when pricked into human skin.²⁰¹

The cytokine interleukin-5 (IL-5) is an important chemoattractant for eosinophils. In lesional skin of chronic spontaneous urticaria patients, an increase in interleukin-5 (IL-5)-positive cells has been described,¹⁷⁹ and eosinophils are significantly increased in skin lesions in chronic spontaneous urticaria in humans⁶⁵ and horses.²⁰² Eosinophil-derived MBP induces the degranulation of skin mast cells.^{203–205} Also, eosinophils can induce activation of blood coagulation generating thrombin which in turn can increase vascular permeability both directly, acting on endothelial cells, and indirectly, inducing degranulation of mast cells with release of histamine.^{159,206} The potential role of IL-5 in urticaria has been highlighted recently by benefit of the anti-IL-5 monoclonal antibody, reslizumab, in reducing the symptoms of a patient with CSU and cold urticaria.¹²¹

IL-4 and IL-13, both of which are well established as causative cytokines of Th2 inflammation,^{179,207} are secreted by mast cells in addition to Th2 lymphocytes.^{21,72,179,208} In addition, mast cells express the IL-4 receptor, IL-4R α , which is also stimulated by IL-13. Stimulation of mast cell IL-4R α has been shown to also promote degranulation, adhesion, and chemotaxis, and to enhance Fc ϵ R1 expression.^{209,210}

8 | CONCLUSIONS AND AREAS OF NEED FOR FURTHER RESEARCH

It is clear from this review that the mast cell is the primary effector cell in urticaria. The evidence in support of this includes:

- Mast cells, in particular the MC_{TC} subtype, are located in the upper dermis, the ideal situation for wheal formation and sensory nerve stimulation.
- Increased numbers of mast cells are found in both lesional and non-lesional skin in CSU and inducible urticaria.
- Mast cell degranulation in the area of wheals has been demonstrated repeatedly by light and electron microscopy.
- Histamine, PGD₂, and tryptase are found in the venous blood draining wheal formation. The last 2 are specific for mast cells rather than basophils.
- Mast cell reactivity is increased in active urticaria by local inflammatory cytokines and neuropeptides.
- Mast cell cytokines and neuropeptides, particularly NGF, induce a Th2 type inflammation that is particularly obvious at the sites of whealing.

While we have made much progress recently into the mechanisms of chronic urticaria, particularly the role of autoallergens and IgG autoantibodies, there is still a long way to go before we have really good understanding of the condition. Some of the questions that need to be addressed by future studies are: Are IgE autoantibodies directed to autoallergens and IgG autoantibodies against IgE and its receptor the most common inducers of mast cell degranulation in CSU? Do CSU patients express these autoantibodies before

the onset of disease, and do they stop making them when their CSU goes into spontaneous remission? On a molecular level, what are the key modulators and facilitators of mast cell degranulation in CSU? On the cellular level, how do eosinophils, neutrophils and basophils, in CSU, contribute to the degranulation of mast cells and their modulation? What are the drivers of mast cell degranulation in chronic inducible urticaria? Answers to these questions can help to better understand the pathogenesis of chronic urticaria and to develop better treatment options.

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CONFLICTS OF INTEREST

Martin Church has been a speaker or consultant for Almirall, FAES Pharma, Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach. Pavel Kolkhir has been a speaker for Novartis. Martin Metz has been a speaker and/or consultant for Bayer, Celgene, GSK, Moxie, Novartis, Roche, Sanofi, Shire. Marcus Maurer has been a speaker and/or consultant for Aralez, FAES Pharma, Genentech, Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach.

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