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Mast cell disorders: From infancy to maturity

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Abstract

Mast cells are typically linked to immediate hypersensitivity and anaphylaxis. This review looks beyond this narrow role, focusing on how these cells have evolved and diversified via natural selection promoting serine protease gene duplication, augmenting their innate host defense function against helminths and snake envenomation. Plasticity of mast cell genes has come at a price. Somatic activating mutations in the mast cell growth factor *KIT* gene cause cutaneous mastocytosis in young children and systemic mastocytosis with a more guarded prognosis in adults who may also harbor other gene mutations with oncogenic potential as they age. Allelic *TPSAB1* gene duplication associated with higher basal mast cell tryptase is possibly one of the commonest autosomal dominantly inherited multi-system diseases affecting the skin, gastrointestinal tract, circulation and musculoskeletal system. Mast cells are also establishing a new-found importance in severe asthma, and in remodeling of blood vessels in cancer and atherosclerotic vascular disease. Furthermore, recent evidence suggests that mast cells sense changes in oxygen tension, particularly in neonates, and that subsequent degranulation may contribute to common lung, eye, and brain diseases of prematurity classically associated with hypoxic insults. One hundred and forty years since Paul Ehrlich's initial description of "mastzellen," this review collates and highlights the complex and diverse roles that mast cells play in health and disease.

KEYWORDS

asthma, gene duplication, inflammatory bowel disease, mast cell, mastocytosis, pediatrics, tryptase

1 | FOREWORD

Scientists and clinicians alike recognize allergen-induced, IgE-dependent mast cell (MC) degranulation leading to immediate hypersensitivity reactions and anaphylaxis as the *sine qua non* of MC dysfunction. This aspect of MC dysfunction has been extensively explored in previous original research articles and reviews and will not be covered here. The aim of this review was to summarize our current knowledge of primary and secondary MC disorders focusing on those not associated with acute allergic reactions, thus providing the reader with a broader and more complete understanding of the role of this immune cell in health and disease. It also aims to highlight how an appreciation of MC dysfunction from early infancy to old age can improve our understanding of this broad and complex range of disorders. Diversification of MC function coincided with extensive duplication of tryptase and other serine protease genes.[1] Gene duplication resulting in archetypal membrane-bound proteases being secreted into the milieu led to their systemic effects and may have been promoted by a survival advantage, with secreted MC proteases rapidly degrading and neutralizing potentially deadly Hymenoptera and snake toxins.[2,3]

Abbreviations: BPD, bronchopulmonary dysplasia; CD, Crohn's disease; CM, cutaneous mastocytosis; CMP, common myeloid precursor; CSU, chronic spontaneous urticaria; HIE, hypoxic-ischemic encephalopathy; HSC, hematopoietic stem cell; IBD, inflammatory bowel disease; MCAS, mast cell activation syndrome; MC, mast cell; MCp, mast cell precursor; RDBPCT, randomized double-blind, placebo-controlled trial; ROP, retinopathy of prematurity; SIDS, sudden infant death syndrome; TRPA1, transient receptor potential ankyrin 1; UC, ulcerative colitis.

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2 | WHAT ARE MAST CELLS?

Mast cells first evolved 500 million years ago in Ascidians (sea squirts), providing host innate immunity against bacteria and parasites.[4] Over the millennia, MCs gained additional functions regulating inflammation, wound healing, coagulation, adaptive immunity, and acute allergic responses.[5,6] MCs are non-proliferating long-lived sedentary immune tissue cells. They differentiate from common myeloid precursors (CMPs) in the bone marrow. Immature MC precursors (MCp) with proliferative potential leave the bone marrow to home in on epithelial tissues in contact with the external environment such as the skin, respiratory and gastrointestinal tracts via specific integrin, and chemokine receptors (Figures 1 and 2).[7-10] They also lodge in perivascular spaces and connective tissues surrounding nerves and then terminally differentiate into non-proliferating mature MCs expressing secretory granules.[11]

When activated, MCs release inflammatory mediators from their storage granules (histamine, chymotrypsin-related serine proteases such as tryptase, chymase, carboxypeptidase), as well as via phospholipid membrane metabolism (platelet activating factor, leukotrienes, prostaglandins) and after de novo synthesis (cytokines (TNF-α, IL-4) and chemokines (IL-8, monocyte chemoattractant protein 1 [MCP-1]).[12,13] Mature human MCs are classically divided into two subpopulations. MC_{TC} expressing tryptase, chymase, carboxypeptidase, and cathepsin predominate in connective tissue and skin. In contrast, MC_T expressing tryptase but no other serine proteases predominate in healthy lung parenchyma and gut mucosa.[14,15] Inflammatory cytokines such as IL-4 can alter the balance of MC_T and MC_{TC} in the lungs, leading to a predominance of MC_{TC} in asthmatics.[16-18] These observations suggest a degree of plasticity and interconversion between these two MC subtypes depending on the microenvironment (Figure 2).

Recent studies have demonstrated functional and potentially important clinical differences between these MC subgroups. MC_T are activated by cross-linking of surface Fc(RI leading to classical IgE-mediated hypersensitivity reactions. In contrast, MC_{TC} express high levels of the Mas-related G protein-coupled receptor X2 (MRGPRX2), which activate cytoplasmic calcium release via a phospholipase C pathway.[19] MRGPRX2 can be activated by endogenous peptides such as substance P, anaphylatoxins C3a and C5a, and VIP, as well as drugs such as morphine, vancomycin, sulfamethoxazole, and cisatracurium.[20-23] Activation of MRGPRX2 on MC_{TC} induces a rapid but less extensive release of granule contents characteristic of anaphylactoid reactions.[19] MRGPRX2 activation may also be important in chronic spontaneous urticaria.[24] In addition, chymase released from MC_{TC} directly converts angiotensin I to angiotensin II, possibly contributing to vascular remodeling in asthma, atherosclerosis, and aortic aneurysms.[25-27]

3 | PRIMARY MAST CELL DISORDERS

Primary MC disorders can broadly be divided into two groups (Table I, Figure 3).[28] Mastocytosis is the clonal proliferation of MCs, usually due to a sporadic somatic activating mutation in the MC growth factor receptor c-kit/CD117.[29,30] Activating *KIT* mutations may not only promote MC proliferation and survival, but also make MCs more sensitive to degranulation.[31,32] Primary MC activation syndrome (MCAS) is characterized by exaggerated release of MC granule contents without evidence of clonal proliferation.[33] Recently, findings suggest that in many cases, MCAS may be due to excessive allelic gene duplication, particularly of the α-tryptase gene *TPSAB1*.[34,35]

3.1 | Mastocytosis—clonal MC proliferation

Mastocytosis is a rare, usually sporadic clonal disease of MCs. A family history is present in only 4% of patients. MCs may accumulate in the bone marrow, spleen, skin, and/or gastrointestinal tract. Adults typically present with raised MC tryptase, flushing, abdominal pain, diarrhea, muscle aches and pains, osteoporosis, hypotensive episodes, and neurological and psychiatric disturbances (systemic mastocytosis). Urticaria pigmentosa characterized by pigmented brown patches which urticate, particularly after rubbing the skin or changes in temperature, although more common in young children is also part of the clinical disease spectrum in adults. In 90% of cases, this is

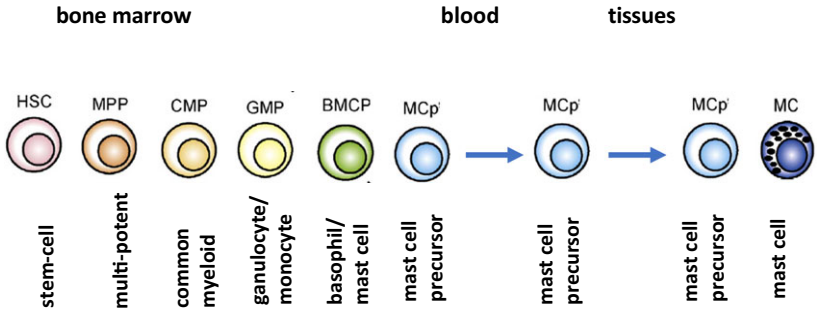

FIGURE 1 Differentiation of mast cells from bone marrow precursors. Hematopoietic stem cells (HSC) pass through a number of stages of differentiation in the bone marrow (multipotent progenitor [MMP], common myeloid progenitor [CMP], granulocyte/monocyte progenitor [GMP], basophil/mast cell progenitor [BMCP]) before reaching the mast cell progenitor (MCp). MCp are proliferating agranular MC precursors that enter the blood stream and home to tissues, where they further differentiate into mature nonproliferating granule positive mast cells (MC)

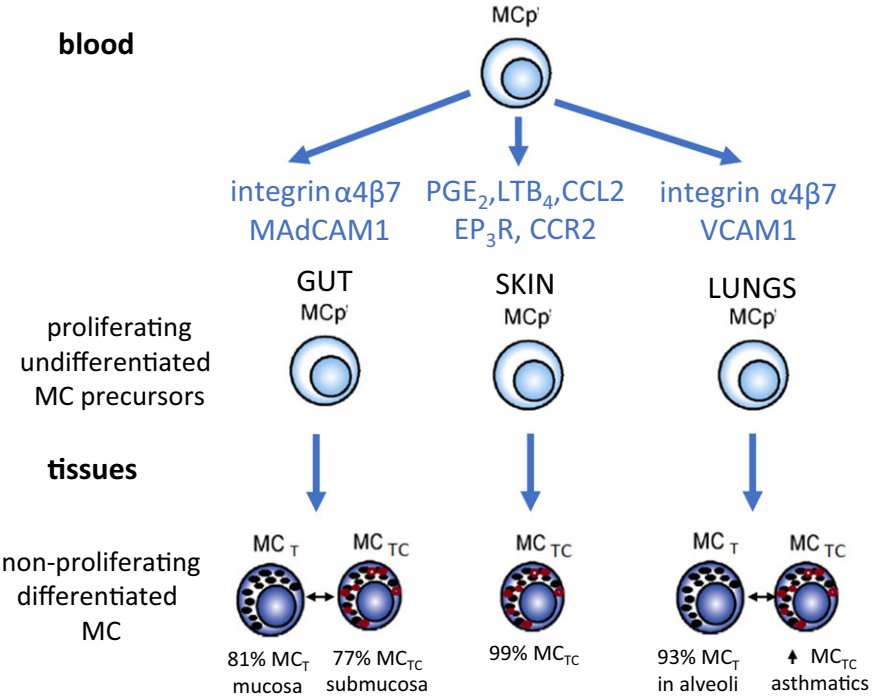

FIGURE 2 Homing of mast cell progenitors (MCp) from the bone marrow and peripheral blood into tissues. Homing of MCp depends on the expression of specific adhesion molecules and chemokines. In the gut, integrins α4 β7 on MCp bind to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1) on blood vessel endothelium, while in the lung these integrins bind vascular cell adhesion protein 1 VCAM-1. In the skin, MCp are attracted by prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB_4), and chemokine (C-C motif) ligand 2 (CCL2) also known as monocyte chemoattractant protein 1 (MCP1) to prostaglandin EP_3 receptor and CCR2. Percentages of MC_T and MC_{TC} in tissues are based on information from reference 15

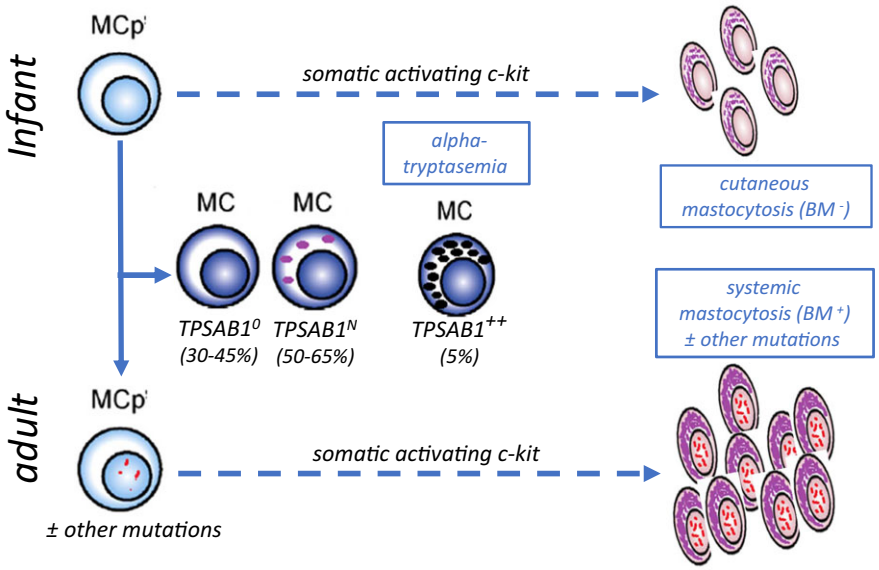

FIGURE 3 Spectrum of primary mast cell diseases. Infants (i) sporadic activating *KIT* mutations (cutaneous mastocytosis), (ii) dominantly inherited *TPSAB1* gene duplication (α-tryptasemia), Older children and adults sporadic activating *KIT* mutations ± other activating mutations (systemic mastocytosis)

associated with somatic D816V activating mutations of the MC growth factor receptor *KIT* gene in bone marrow MC progenitors.[30] The clinical course ranges from indolent to malignant (acute or chronic MC leukemia, MC sarcoma).[36] Adults with Hymenoptera venom anaphylaxis should also be investigated for systemic mastocytosis, even if baseline MC tryptase is normal and there are no skin signs.[37] The reported prevalence of underlying clonal mast cell disease in venom allergy varies greatly from 7% to 94%, but is higher in patients suffering from hypotension and syncope,[37,38] and also in adults suffering from anaphylactic reactions after discontinuation of immunotherapy. The latter observation suggests that these patients may require lifelong venom immunotherapy.[39] Although bone marrow examination is conventionally not recommended for patients where their MC tryptase mast cell tryptase is less than 20 ng/mL (or 11.5 ng/mL in those with severe anaphylaxis or other features suggestive of mastocytosis), normal MC tryptase does not exclude the diagnosis. *KIT D816V* mutations have been detected in the blood of 92% of adults with Hymenoptera venom-induced anaphylaxis, reducing the need for more invasive tests in some patients.[40]

MC leukemias (90% of which are aleukemic) and sarcomas (30% of which progress to MC leukemia) make up <1% of patients with systemic mastocytosis, stain for CD117 and tryptase, and are often associated with additional mutations in *PDGFR*, *FIPIL1*, *TET2*, *SRSF2*, *ASXL2*, or *K/N-RAS* genes.[41,42] MC cancers usually present with fever,

weight loss, cytopenias, bone pain, and hepatosplenomegaly (c-findings). The absence of symptoms and signs of organ damage (c-findings) is associated with a more stable clinical course and better prognosis.[43] Serum MC tryptase is usually >200 ng/mL. Response to radiotherapy and chemotherapy is usually transient and the prognosis is poor with median survival of less than 2 years. Chemotherapy combined with midostaurin (a multi-tyrosine kinase inhibitor) and followed by hematopoietic stem cell transplantation may be curative, but due to the rarity of these cancers, definitive data on the efficacy of this approach are limited. The pathogenesis and clinical disease spectrum of systemic mastocytosis parallel sporadic *JAK2V617F* gain of function mutations known to drive adult-onset myeloproliferative disorders.[44] Systemic mastocytosis with activating *KIT* mutations in bone marrow MCs is rare in children.

Children usually present with cutaneous rather than systemic mastocytosis (CM). Up to ninety percent have benign MC aggregates due to somatic *KIT* mutations confined to the skin.[45,46] The common D816V is only found in 34%-42% of cases. In one study, an additional 44% of patients had gene mutations outside exon 17.[47] Seventy-five percent have multiple brown skin patches. In a quarter, the rash is noticed at birth and in 90% by the age of 2 years old.[48-51] Patches urticate on rubbing or bathing (urticaria pigmentosa) (Figure 4). CM can also present as one or more circumscribed reddish skin lesions (mastocytoma, 20%) or as a diffuse rash (5%). In two-thirds of children, the disease regresses by puberty. NSAIDs, opiates, muscle relaxants, insect stings, and physical factors such as temperature changes with bathing or swimming can trigger urtication and rarely hypotension. Treatment with second- or third-generation antihistamines is usually effective. The risk of anaphylaxis after insect venom stings in children with CM is currently considered very low.[52,53] Prescription of an adrenaline auto-injector is left to individual specialist, rather than being a mandatory requirement.[54]

3.2 | MC activation syndrome (MCAS) including α-tryptasemia

Primary MCAS is characterized by excessive activation of MCs, and although its characteristics are yet to be fully defined, diagnosis is based on clinical features and increased MC tryptase, where mastocytosis and secondary allergic triggers have been excluded.[33] Histamine and prostaglandins may also be elevated,[55] but further work is required before definitive recommendations can be provided regarding use of these measurements in the diagnosis of MCAS.[56]

α-tryptase gene allele frequency varies between individuals. Twenty-nine percent of people (up to 45% in white Europeans) express no α-tryptase genes.[57] Five percent of individuals are thought to have allelic *TPSAB1* gene duplications inherited in an autosomal dominant pattern. Adults and children with *TPSAB1* gene replications have serum MC tryptase ≥8.0 ng/mL and clinical features of MCAS.[34] These include flushing and angioedema, abdominal pain, diarrhea and food intolerances, joint hypermobility, systemic reaction to Hymenoptera, hypotensive episodes, and autonomic dysfunction. Triplications and even quintuplications are less common, associated with even higher serum MC tryptase concentration and more severe disease (Table 1).[34,35] Serum MC tryptase is a simple screening test for this disorder. Treatment is symptomatic with antihistamines and MC stabilizers. Anecdotal experience suggests that imatinib is not effective.

4 | SECONDARY MAST CELL DISORDERS (EXCLUDING IMMEDIATE IgE-MEDIATED HYPERSENSITIVITY)

As mentioned in the Foreword, this review focuses on MC diseases other than acute IgE-mediated allergic reactions. This section discusses secondary disorders of MCs associated with less well-recognized, chronic features of MC dysfunction. Secondary MC dysfunction is often a poorly recognized feature of common chronic inflammatory disorders. Some of these secondary MC disorders may in the future be recognized as symptoms of primary MC disorders, for example, α-tryptasemia and *ADGRE2*-associated vibratory urticaria. There is also growing evidence that hypoxic insults in neonates and infants may trigger MC degranulation and subsequent pathology in the eyes (retinopathy of prematurity [ROP]), brain (hypoxic-ischemic encephalopathy [HIE]), lungs (bronchopulmonary dysplasia (BPD)), and circulation (sudden infant death syndrome [SIDS]) (Table 2). Furthermore, neovascularization and vascular remodeling may well contribute to atherosclerotic vascular disease, aneurysms, and cancer growth and metastases.

4.1 | MC dysfunction in chronic atopic and inflammatory disorders

Mast Cells have a well-recognized role in the gastrointestinal defense against parasites, particularly helminths.[58,59] Upon detecting

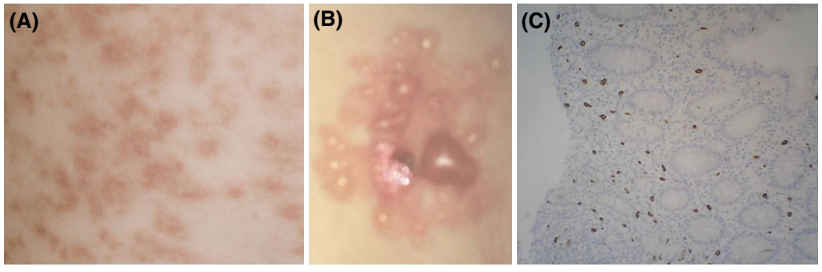

FIGURE 4 Examples of clinical features and histology in mast cell disorders. A, Cutaneous mastocytosis, B, Darier's sign—urtication of skin lesions after rubbing, C, excessive mast cell influx (stained with CD117) within the gastrointestinal tract in a patient with α-tryptasemia

TABLE 1 Primary mast cell disorders

Mastocytosis		
Overview	Clonal MC proliferation, rare, sporadic, activating gene mutations	
Subtypes	**SYSTEMIC** (bone marrow involvement) common in adults, rare in children	**CUTANEOUS** (usually without bone marrow involvement) more common in children than adults diffuse, multicentric (urticaria pigmentosa), solitary (mastocytoma)
Histology	Multifocal, dense infiltrates of MC (≥15 mast cells in aggregates) in bone marrow and/or other extracutaneous organs MC may have atypical morphology, for example, spindle-shape, CD2/CD25 expression or in more aggressive forms an undifferentiated phenotype	
Clinical course	Ranges from indolent to malignant (acute or chronic leukemia)	Indolent, starts in infancy, usually regresses before puberty
Clinical features	Flushing, abdominal pain, diarrhea, muscle aches and pains, fractures, neurological and psychiatric symptoms, hypotension/anaphylaxis with malignancy: fevers, weight loss, hepatosplenomegaly	Flushing, urticaria, angioedema, non-cutaneous symptoms less common
Genetics	Sporadic D816V activating c-kit mutation in 90%, may have additional mutations in PDGFRA/B, TET2, N-RAS	Sporadic D816V activating c-kit mutation in 20%-40%, other activating c-kit mutations in 60%
MC tryptase	>20 ng/mL	<20 ng/mL
Potential therapies	Second- or third-generation antihistamines, ranitidine, mast cell stabilizers (cromoglycate, ketotifen), corticosteroids, imatinib only if no D816V mutation, midostaurin (protein kinase inhibitor), chemotherapy for leukemia	Second- or third-generation antihistamines usually suffice
Mast cell activation syndromes		
Overview	Excessive mast cell activity without clonal proliferation or obvious secondary triggers; α-tryptasemia is a common autosomal dominant condition occurring in a subset of patients	
Subtypes	**α-TRYPTASEMIA** (up to 5% of general population)	**IDIOPATHIC** (no evidence of mastocytosis, α-tryptasemia, or secondary cause)
Histology	May have increased number of MC, particularly in GI tract, but do not form aggregates, may be associated with increased eosinophils	No MC aggregates
Clinical course	Variable, may depend on degree of gene replication, other genetic or environmental cofactors	Similar to α-tryptasemia
Clinical features	Flushing, urticaria, angioedema, abdominal pain, diarrhea, but have mucous and blood muscle aches and pains, headaches, hypermobile joints, POTS, neurological and psychiatric symptoms assess parents and siblings	Similar to α-tryptasemia
Genetics	Allelic *TPSAB1* gene replication usually autosomal dominant	No defined genetic cause
Basal MC tryptase	≥8.0 ng/mL	No consensus regarding MC tryptase, histamine, or prostaglandin concentrations
Potential therapies	Second- or third-generation antihistamines, ranitidine, mast cell stabilizers (cromoglycate/ketotifen), dietary manipulation, imatinib typically ineffective	As for α-tryptasemia

foreign antigens, MCs situated close to nerves trigger enteric nerves, leading to epithelial ion secretion and propulsive peristaltic activity, which help to expel the pathogen.[60,61] MCs also regulate intestinal epithelial and endothelial permeability, barrier function, and mucin secretion.[61] MCs release cytotoxic factors from their granules inducing recruitment of other proinflammatory cells and granuloma formation, all of which promotes parasite containment.[62] For instance, in *Trichinella spiralis* (tissue-dwelling roundworm) infections, MCs enhance intestinal epithelial permeability and Th2-cell infiltration resulting in parasite expulsion.[63] *Fasciola hepatica* (common liver fluke) invasion is accompanied by increased MC infiltration and inflammation.[64] MCs have also been associated with enhanced responses to helminth infections in other tissues, such as in cutaneous leishmaniasis.[65]

4.1.1 | Inflammatory bowel disease

By disrupting mucosal epithelial barriers, MCs may also contribute to the pathogenesis of inflammatory bowel disease (IBD).[66-68] MC infiltrate and degranulate in ulcerative colitis (UC), particularly in areas of inflammation. This is less obvious in Crohn's disease (CD).[69-71] MCp and other immune cells such as T lymphocytes home to the gut via integrin α4β7.[3] Vedolizumab, a neutralizing α4β7 monoclonal antibody, is now licensed for the adults with IBD poorly responsive

TABLE 2 Neonatal and pediatric disorders associated with secondary MC dysfunction

	Tissue MC infiltration and degranulation	Pathology	Increased serum MC tryptase	MC inhibitor blocks activity	MC inhibitor blocks pathology
Disorders associated with chronic atopic and inflammatory disorders					
Helminth infections	++	Promotes peristalsis and epithelium ion secretion→ expulsion, granuloma → containment	NT	NT	NT
Inflammatory bowel disease	++	Unknown	NT	NT	?vedolizumab
Asthma	++	Asthma flares, acute death		Cromoglycate imatinib	Imatinib
Disorders associated with hypoxic insults or vascular remodeling possible TRPA1 oxygen sensor triggered MC degranulation and inflammation					
Retinopathy of prematurity	–	Neovascularization stage 3 + ROP	++	Cromoglycate nafamostat (tryptase inhibitor)	Cromoglycate nafamostat (tryptase inhibitor)
Hypoxic-ischemic encephalopathy	++	Neuronal death	NT	Cromoglycate	Cromoglycate
Bronchopulmonary dysplasia	++	Disrupts alveoli	NT	NT	?ketotifen
Sudden infant death syndrome	–	Anaphylaxis	++	NT	NT
Atherosclerotic vascular disease	++	Ischemic heart disease, Kounis syndrome	++	Cromoglycate	Cromoglycate
Vascular aneurysms (brain, aorta)	++	Abdominal aortic aneurysms, cerebral aneurysms	++	Cromoglycate	Cromoglycate
Neovascularization of tumors	++	More aggressive growth and metastasis	–	Cromoglycate	Cromoglycate, gabexate, mesylate, nafamostat

NT, not tested.

to other therapies. It is currently not clear as to the extent to which the therapeutic effects of vedolizumab are via MCs or T lymphocytes, but it is interesting that, in keeping with the in vitro data, RDBPCT suggests a greater beneficial effect in UC than CD.[72-74]

4.1.2 | Asthma

Mast Cells have been implicated in the pathogenesis and severity of asthma in both children and adults.[75] MC stabilizers such as inhaled cromoglycate have been used to treat asthma for over 50 years, although since 1990 their use has been largely replaced by inhaled steroids and leukotriene receptor antagonists. A Cochrane review of 24 studies concluded that there was insufficient evidence of a beneficial effect of cromoglycate over placebo in children with moderately severe asthma.[76]

In 2001, anti-IgE monoclonal antibody therapy (omalizumab) was shown to be effective in reducing exacerbations and medication use in a subset of asthmatic who had evidence of clinical allergen sensitivity, suggesting a role for IgE-induced MC degranulation in acute asthma.[77,78] Omalizumab has since been licenced by the U.S. Food and Drug Administration (FDA) and other licencing bodies around the world for older children and adults, having positive skin or blood tests to aeroallergens, moderate to severe persistent allergic asthma not controlled by inhaled corticosteroids and require frequent courses of oral steroids. These clinical findings are supported by histological evidence of MC infiltration into the bronchial smooth muscle and the alveolar parenchyma of asthmatics, particularly those with frequent exacerbations.[79-81] Basal serum MC tryptase can be significantly higher in chronic asthmatics (4.2-4.7 ng/mL) than healthy controls and patients with mild disease (2.5-3.1 ng/mL).[82] MC tryptase is more likely to be high in certain subgroups of asthmatics: older, obese patients, and non-atopic females with salicylate sensitivity.[83] Serum MC tryptase was also significantly higher in post-mortem lung from individuals who died of asthma (58-120 ng/mL) compared with those dying from other causes.[84,85]

In 2017, a RDBPCT of 62 adults with severe, poorly controlled asthma despite high-dose inhaled or systemic corticosteroids showed that imatinib led to a significant reduction in not only serum MC tryptase but also methacholine airway responsiveness.[86] Although the patients in this trial were not selected for their allergic predisposition, they had an mean on three positive skin prick test results. Overall, the current evidence indicates that MCs may well be important in severe allergic asthma and that drugs inhibiting MC activity can be beneficial.

4.1.3 | Chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU) is associated with frequent, often daily urticaria for 6 weeks or more. Symptoms often continue

for many months or even years. Episodes of angioedema occur in half of cases. Unlike acute urticaria, specific IgE tests are not recommended in these patients. Symptomatic treatment of CSU is with a regular second- or third-generation antihistamine. Where these fail, omalizumab may be considered. Recent evidence suggests that complete responders have significantly higher serum total IgE concentrations than non-responders, suggesting that IgE-dependent MC degranulation may play a role in CSU.[87,88]

In 20% of patients, there is a clear physical trigger, such as pressure, temperature changes, or sun exposure.[89] CSU is usually sporadic and the underlying pathogenesis unknown, but in a rare autosomal dominant form triggered by vibration and rubbing of the skin, activating mutations in the dermatan sulfate-binding *ADGRE2* cell surface receptor on MC promotes MC degranulation with physical forces.[90]

4.2 | MC dysfunction, vascular remodeling, and response to hypoxia

4.2.1 | Cancer neovascularization and growth

Paul Ehrlich was the first to notice that MCs congregate around blood vessels of cancers and other tissues. He hypothesized that these cells helped to remodel the vasculature, promoting delivery of oxygen and nutrients, leading him to coin the term mastzellen (feeding cells).[91] In vascular, hematological, and solid tumors, MC accumulation correlates with neovascularization, more rapid tumor growth, and metastases. In a pancreatic cancer model, MC recruitment was an absolute requirement for tumor expansion. Treatment of established tumors with the MC stabilizer cromoglycate triggered hypoxia and cell death.[92] Cromoglycate has been used as an adjuvant for the treatment of other cancers.[93] Inhibitors of MC tryptase such as gabexate mesilate and nafamostat mesylate have also been considered as adjuvant treatment of tumors.[94,95] The clinical relevance of MCs and impact of manipulating MC function in cancer therapy still remains unclear.

4.2.2 | Retinal neovascularization in premature infants

Matsuda et al (2017) discovered that MC tryptase was essential for neovascularization in murine models of retinopathy of prematurity (ROP).[96] MC-deficient mice did not develop retinal neovascularization (stage 3+ ROP), while retinopathy was induced after infusion of MCs or MC tryptase. Intraperitoneal cromoglycate blocked retinal neovascularization and prevented severe ROP. Plasma MC tryptase in human preterm neonates (28-32 weeks' gestation) with ROP was found to be 5-fold higher (median 62 ng/mL) than in age-matched controls (12 ng/mL). Results of this study also allow a better understanding of the mechanism linking hypoxic insults and MC degranulation. Transient receptor potential ankyrin 1 (TRPA1) acts as an O_2 tension sensor in MCs, triggering degranulation. The development of ROP could be blocked with a specific TRPA1 inhibitor.

4.2.3 | Vascular remodeling and damage to the aorta, and cerebral and coronary arteries

Mast Cells contribute to the development of atherosclerosis, as well as destabilization and rupture of atherosclerotic plaques with ensuing atherothrombotic complications.[97] In infarct-related coronary events, the number of degranulated MCs in the adventitia backing ruptured plaques is increased. Histamine released from the degranulated MCs may reach the media, where it provokes local coronary spasm.[98] There are many published case reports describing the association between myocardial ischemia and acute allergic reactions (Kounis syndrome).[99,100] In a subgroup of patients, myocardial insufficiency may not be an independent co-morbidity but rather a direct consequence of chronic allergic disease. Although in the majority of patients suffering acute myocardial infarction, MC tryptase is not elevated,[101] it may be elevated in patients dying of acute coronary disease and of acute dissecting aorta.[102,103] The effect of MCs on primary cardiac function is complex. On the one hand, there is evidence that renin released directly by myocardial MCs can activate the renin-angiotensin system and promote arrhythmias,[104,105] and that chymase may exacerbate damage after acute ischemia/reperfusion injuries.[106] On the other, in murine models of myocardial infarction and myocarditis, MCs have been shown to improve rather than worsen cardiac contractility.[107,108]

There is also evidence for the role of MCs in disrupting the integrity of blood vessels in the brain leading to saccular intracranial artery aneurysms,[109] and also the aorta resulting in abdominal aortic aneurysms. In a mouse model, MC tryptase MCP6$^{-/-}$ mice or treatment with MC inhibitors prevented the development of aneurysms.[27,110,111] MC-deficient rats showed reduction of tPA-mediated cerebral hemorrhage compared with wild-type littermates.[112] It will be interesting to study the prevalence of these vascular diseases in patients with inherently higher MC tryptase concentrations, such as those with α-tryptasemia.

4.2.4 | Hypoxic-ischemic encephalopathy

Animal studies have shown infiltration of MCs and histamine release in the brain after hypoxic-ischemic insults in neonatal rats.[113,114] MC stabilization with cromoglycate during the first 24 hours after hypoxic injury was neuroprotective, limiting neuronal loss, brain atrophy, and microglial activation. The results suggest that MC degranulation may exacerbate ischemia-induced neuronal death in the preterm brain.

4.2.5 | Bronchopulmonary dysplasia

Mast cells may also contribute to the development of BPD in premature neonates. Bhattacharya et al (2012) used genome-wide expression profiling in lung tissue obtained at biopsy from 11 neonates with BPD and 17 age-matched controls.[115] Expression of 159 genes was significantly different, with three of the five most significantly dysregulated genes encoded MC biomarkers. Immunohistochemistry

demonstrated a 50-fold increase in chymase-expressing MCs in BPD tissue biopsies when compared with controls.

A recent animal study of hyperoxia-induced lung injury provided further evidence on the potential mechanistic role of MCs.[116] Increased MC numbers and expression of MC *TPSAB1*, *TPSAB2*, and *CPA3* genes were found in mouse lung after exposure to hyperoxia conditions compared with controls. Alveoli were disrupted in the test mice, but not in MC-deficient mice or controls, suggesting that MC may also disrupt lung structure and function.

4.2.6 | Sudden infant death syndrome

Serum MC tryptase has been found to be elevated in SIDS in some studies and it has been suggested that anaphylaxis may have a role in the pathogenesis of this syndrome in some patients.[117-119] In one study of 50 infants with SIDS, mean serum MC tryptase was 6.2 ng/mL compared with 1.1 ng/mL in controls.[120] Forty percent of SIDS cases had MCT >10 ng/mL compared with none of the controls. In contrast, Nishio et al (2004) found that MC tryptase was normal in 21 infants with SIDS and 14 controls.[121] Genetic testing for *KIT* and *TPSAB1* mutations in these patients might provide further insights into the pathogenesis of this disease.

5 | CONCLUSIONS

Despite 140 years having elapsed since Paul Ehrlich first described the MC,[91] there are still exciting new discoveries in MC biology. In early childhood, somatic activating mutations in the *KIT* gene of MC precursors can lead to cutaneous mastocytosis, with MC aggregates localizing to the skin and usually following a benign remitting course. In contrast later in life, somatic activating *KIT* gene mutations manifest in bone marrow MC precursors rather than in the skin and are associated with systemic disease and a more aggressive course, particularly if additional somatic oncogene mutations have accumulated as an inherent part of aging.

Extensive MC protease gene replication over the millennia is now recognized to have driven diversification of MC function. Indeed, gene replication is a common mechanism by which all plant and animal species diversify and avoid extinction.[122,123] Recent studies have highlighted how common gene variability is in chymotrypsin-related serine proteases, particularly in *TPSAB1*. The gene is completely absent in a third to a half of the population, while duplication occurs in approximately 5%. *TPSAB1* gene plasticity may have provided communities living in the tropics with a survival advantage after snake envenomation and may explain the absence of *TPSAB1* from a higher proportion of Europeans where the risk of being bitten poisonous snake is less. Excessive *TPSAB1* gene duplication causes raised basal MC tryptase activity and a propensity to multi-system disease. Until now, the underlying diagnosis of many of these patients with non-specific symptoms may have gone unrecognized. Measurement of basal serum MC tryptase offers a simple screening test, and if ≥8.0 ng/mL a possible explanation for their disease.

There is no doubt that MC infiltrate and degranulate in the tissues of patients with IBD and asthma, but the relevance of this to clinical disease remains unclear. There are, however, clues that as with eosinophilia, which is now deemed clinically relevant and effective suppressed with mepolizumab in a subset of severe asthmatics,[124] dampening down MC activity using imatinib in patients with refractory asthma is showing some promise.

Finally, studies of animal models of common neonatal diseases of the lungs, eye, and brain suggest that MC may well have an important role in their pathogenesis. Although it is important to remain cautious when translating finding from animals into human, these results should provide the impetus to look for new solutions to these diseases with high healthcare burdens.[125] Furthermore, results from these studies suggest an important role of changes in O_2 tension in triggering MC degranulation.

140 years on, MCs remain central to allergic and inflammatory diseases, well beyond IgE-dependent degranulation and immediate hypersensitivity. The challenge for scientists and clinicians alike is to look beyond the current dogma if old problems are to be solved with new therapies.

COMPETING INTERESTS

None declared.

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