

REVIEW

Mast cell heterogeneity

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Introduction

Mast cells have long been recognized as major effector cells of the allergic or type I hypersensitivity reaction by virtue of their high-affinity surface receptors for IgE. The wide distribution of mast cells throughout the human body in general, and at mucosal surfaces in particular, in atopic and non-atopic individuals alike, as well as the recognition of mast cell activation by non-immunological means, suggest that these cells also may be involved in non-atopic conditions. Thus, mast cell mediated events have been postulated to play a role in host defence against parasitic diseases of the intestine, in wound healing and scar formation in the skin, and in promoting tumour angiogenesis.

The concept of mast cell heterogeneity has emerged as a fundamental principle for the understanding of the possible roles of mast cells in health and disease. Two types of mast cells are typically recognized, both of which stain metachromatically with cationic dyes such as alcian blue and toluidine blue. The nomenclature used for distinguishing these two types of mast cells varies depending on the species, the tissue source or the biochemical characteristic under study (Table 1). Thus, in the rodent, mucosal and connective tissue types of mast cells are recognized that are also referred to as atypical and typical or formalin sensitive and formalin resistant, respectively. A similar nomenclature has been used in the human. In addition, rodent mast cells have been defined according to their proteoglycan content (H or heparin-containing cells and E or chondroitin sulphate-containing cells) and human mast cells have been defined according to their tissue of origin (lung, skin, gastrointestinal mucosa) and their neutral protease content (T or tryptase-positive, chymase-negative cells, and TC or tryptase-positive, chymase-positive cells).

This review will focus upon the evidence for the presence of mast cell heterogeneity, first in the rodent system and then in humans.

Rodent mast cell heterogeneity

Two types of mast cells, which will be referred to as connective tissue and mucosal, have been defined in rodents, based on different phenotypical, biochemical, functional and ontogenic properties.

Phenotypic differences (Table 2)

Histochemical evidence for the presence of two distinct types of mast cells in the rat was first provided by Enerback in 1966 when the small intestinal mucosal mast cells (MMC) were found to require fixation in Carnoy's solution, a mixture of isotonic formaldehyde and acetic acid, or Mota's basic lead acetate in order to be stained by cationic dyes such as alcian blue, while fixation with typical aldehyde fixatives such as neutral buffered formalin blocked the binding of MMC to these dyes [1]. In contrast, staining of connective tissue mast cells (CTMC) was possible regardless of the type of fixative used. Furthermore, in Carnoy's fixed specimens, staining with alcian blue yields a blue colour in both MMC and CTMC while counterstaining with safranin O results in a red colour in CTMC only [2]. Similarly, berberine sulphate, a basic fluorescent dye, results in a strong bright yellow fluorescence of CTMC but not MMC, regardless of the type of fixation used. Since binding to cationic dyes is primarily a function of the negative charge density and isoelectric point of granule proteoglycans, these differences in the staining characteristics of MMC and CTMC probably reflect differences in their proteoglycan content as will be discussed later. More recently, Wingren and Enerback have shown that treatment of formalin-fixed sections with trypsin or their prolonged staining with toluidine blue will unmask the cationic dye binding

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Table 1. Mast cell nomenclature

Differentiation criteria	Nomenclature	
Tissue localization	mucosal	connective tissue
Fixation	formalin sensitive	formalin resistant
Normality	atypical	typical
Proteoglycan content	E	H
Neutral protease content	T	TC

groups in MCC and thus allow their visualization with metachromatic dyes [3]. Ultrastructural analysis reveals that the cytoplasmic granules of CTMC appear homogeneous with an average diameter of 0.2–0.4 μm while the granules of MMC also appear amorphous but smaller [4].

MMC defined by formalin sensitivity were found by Enerback to be located in the rat small intestinal mucosa while CTMC were located in the rat small intestinal submucosa, skin and peritoneum. More recently, the distribution of MMC and CTMC was studied throughout the rat gastrointestinal system and CTMC were found to be the exclusive type seen in the cheek, tongue, oesophagus and non-glandular stomach. MMC were found in large numbers in the glandular stomach, small and large intestine and caecum where they outnumbered CTMC by up to 20:1 [5].

Biochemical differences (Table 3)

Mast cell mediators are divided into two major classes: preformed mediators which are stored in the secretory granules and released upon activation of the mast cell, and newly generated mediators which are synthesized *de novo* and secreted upon activation of the mast cell.

Preformed mediators. Preformed mediators of interest to the present discussion include a biogenic amine (histamine), neutral proteases (rat mast cell proteases I and II, carboxypeptidase A and tryptase) and proteoglycans (heparin and/or chondroitin sulphates).

Histamine is present in all mast cells. In the rat, MMC dispersed from the small intestinal lamina propria contain less histamine per cell than dispersed peritoneal CTMC (1.3 pg/cell *vs* 15 pg/cell, respectively) [6]. This quantitative, but not qualitative, difference could be related to differences in the state of maturity and activation or local environment of the cell rather than to mast cell type.

Two serine proteases with chymotrypsin-like activity are found in rat mast cells. Rat mast cell protease I (RMCP I or chymase) has been localized by immunofluorescence to CTMC in the submucosa of the rat small

intestine [7], and by immunohistochemistry to CTMC in skin, tongue, intestinal serosa and lung parenchyma [8]. RMCP II is an antigenically distinct serine protease [9] which is found in MMC of the rat intestine and bronchial epithelium [8,10]. The availability of specific polyclonal antibodies to RMCP I and RMCP II, respectively, allows for the phenotypic differentiation of CTMC and MMC by the presence of the respective serine protease [8]. In addition, a carboxypeptidase A-like enzyme appears to be selectively concentrated in the rat peritoneal CTMC [11,12]. Low levels of tryptase are found in rat peritoneal CTMC [13]; its presence in mucosal mast cells has not been evaluated.

Proteoglycans consist of a peptide core covalently linked to glycosaminoglycan side-chains composed of repeating disaccharide units. The nature of the alternating sugar groups and their sulphation determines the class of proteoglycan. Heparin accounts for the majority of the proteoglycans synthesized by rat serosal CTMC [14], while little, if any, is produced by rat intestinal MMC [15] and mouse bone marrow-derived mast cells (BMMC) [16]. These latter two types of mast cells contain the over-sulphated chondroitin sulphate proteoglycans di-B [17] and E [18], respectively. The higher degree of sulphation of heparin (2.5 sulphate and 1 carboxyl per disaccharide) compared to chondroitin sulphates (1.5 sulphate and 1 carboxyl per disaccharide) imparts a higher negative charge density to this compound, which results in the differential metachromatic staining properties of CTMC *vs* MMC. However, it is interesting to note that rat serosal mast cells normally contain small amounts of over-sulphated chondroitin sulphate proteoglycans [19] and when incubated with β -D-xyloside (which competes with core protein as a glycosaminoglycan acceptor) this mast cell type has the capacity to polymerize chondroitin sulphate E glycosaminoglycan onto the exogenous acceptor while synthesis of heparin proteoglycan continues onto the endogenous proteoglycan peptide core [20]. Although this originally had suggested the existence of distinct core peptides that direct the type of glycosaminoglycan produced, it was later found that a single gene encodes the core peptide of both types of proteoglycan [21]. In addition, mouse BMMC activated with calcium ionophore secrete protein–proteoglycan complexes which contain heparin glycosaminoglycans as well as complexes containing chondroitin sulphate E glycosaminoglycans [22]; and finally, rat basophilic leukaemia cells (which resemble BMMC in their content of RMCP II) contain both classes of glycosaminoglycans [23]. Therefore, the enzymatic pathways for both classes of glycosaminoglycans are present in the two types of rodent mast cells, suggesting that proteoglycan synthesis may be regulated by signals independent of cell type.

Table 2. Rodent mucosal and connective tissue mast cells

Properties	Mucosal	Connective tissue
Tissue localization	Small intestinal mucosa	Small intestinal submucosa, skin, skeletal muscle, serosal surfaces
Dye binding after fixation		
Carnoy's, Mota's lead acetate, isotonic formaldehyde acetic acid	+	+
Neutral buffered formalin	-	+
Staining		
Alcian blue/safranin O	Blue	Red
Berberine sulphate	-	+
Morphology		
Size of cytoplasmic granules	<0.2 μm	0.2-0.4 μm
Surface markers		
Forssman glycolipid	-	+
T lymphocyte dependent proliferation	+	-

Table 3. Mediators of the rodent mucosal and connective tissue mast cells*

Mediator	Mucosal	Connective tissue
Histamine (pg/cell)	0.1-2	1-30
Proteases (pg/cell)		
RMCP I	—	20-30
RMCP II	10-40	—
Carboxypeptidase A	n.d.†	10-25
Tryptase	n.d.†	0.5
Proteoglycans		
Chondroitin sulphates	95%	Minor
Heparin	5%	Major
Newly generated lipids‡ (ng/10 ⁶ cells)		
LTC ₄ rats	29	<0.7
mice	17-28	n.d.†
LTB ₄ rats	12	<0.5
mice	3-4.9	n.d.†
PGD ₂ rats	4.7	7.5-13
mice	0.8	n.d.†

* From references 5,6,9-13,14-18,25-29,45.

† n.d. = not determined.

‡ Following immunological stimulation.

Newly generated mediators. The newly generated mediators secreted by activated mast cells reflect the presence of specific enzymes for the generation of each mediator: 5-lipoxygenase leads to the generation of leukotrienes from arachidonic acid, whereas cyclo-oxygenase leads to the production of prostaglandins and thromboxanes. Immunologically activated rat connective tissue mast cells from the serosal surface metabolize arachidonic acid largely to prostaglandin (PG) D₂ with little production of leukotrienes [24-26], while immunologically activated rat intestinal MMC generate the leukotrienes LTC₄ and LTB₄ as well as PGD₂ [26]. Mouse BMMC which are thought to resemble mouse MMC are characterized by the generation of LTC₄ and LTB₄ with little production of PGD₂ [27-29]. This serves to illustrate that variations in mast cell phenotypes may result from inter-species as well as intra-species differences.

Surface markers. Mouse bone marrow-derived MMC and serosal CTMC have been shown to display characteristic surface phenotypes as defined by a panel of rat monoclonal antibodies [30,31]. Thus MMC are B 1.1⁻ and B 23.1⁺, while CTMC are B 1.1⁺ and B 23.1⁻. The B 1.1 antibody has specificity for globopentaosylceramide (Forssman glycolipid). Both MMC and CTMC express a similar surface epitope recognized by the B 54.2 rat monoclonal antibody. The epitopes recognized by all three monoclonal antibodies are not specific for mast cells and are also expressed on the surface membrane of activated mononuclear phagocytes.

Table 4. Functional properties of the rodent mucosal and connective tissue mast cells

Property	Mucosal	Connective tissue
Response to secretagogue		
IgE dependent	+	+
A 23187	+	+
Substance P	+	+
Compound 48/80	-	+
Bee venom peptide	-	+
Dextran/phosphatidylserine	-	+
Other neuropeptides (VIP, somatostatin, neurotensin)	-	+
Inhibition of activation/secretion		
Disodium cromoglycate	-	+
Theophylline	-	+
Quercetin	+	+
Doxantrazole	+	+

Functional differences (Table 4)

Functional differences between mast cell types are illustrated by their responses to different secretagogues, and their susceptibilities to pharmacological inhibition of activation.

Response to secretagogues. Both MMC and CTMC are activated via IgE-dependent mechanisms to secrete preformed and newly generated mediators. However, various non-immunological secretagogues demonstrate selective activity towards a specific type of mast cell. The most widely studied of these, compound 48/80, is a potent activator of rat serosal and cutaneous CTMC [32,33] but fails to activate MMC from the rat intestine *in vivo* [5,34] or *in vitro* after enzymatic dispersion [6]. Similarly, bee venom-derived peptide 401 and the combination of Dextran and phosphatidyl serine induce histamine release from rat serosal CTMC mast cells but not from rat intestinal MMC [35]. On the other hand, all mast cells studied respond to challenge with the calcium ionophore A 23187 although the degree of responsiveness varies with the tissue of origin and the animal species [36]. Substance P causes histamine release from both rodent MMC and CTMC while other neuropeptides such as VIP, somatostatin and neurotensin selectively activate CTMC [37].

Effect of pharmacological agents. A variety of compounds modulate mast cell activation and/or secretion. Perhaps the best known of these are the anti-allergic compounds disodium cromoglycate and theophylline which inhibit antigen-induced histamine release from rat serosal

CTMC but not from rat MMC isolated from intestine [38]. In contrast, the flavonoid quercetin, which is structurally related to cromoglycate and the orally active tetrazole, doxantrazole, equally inhibited antigen-induced histamine release from both cell populations [38,39]. The same profile of inhibition was seen when these compounds were tested for their effect on substance P-induced histamine release from mast cells [40]. A selective enhancing effect of phosphatidyl serine on antigen-induced histamine release was demonstrated for the rat CTMC but not MMC [5,41].

Growth and differentiation

An important development in the field of mast cell differentiation was the ability to generate relatively pure populations of mast cells from mouse and rat bone marrow cultured in the presence of T lymphocyte factors [42-44], particularly interleukins IL-3 and IL-4 [45,46]. BMMC were found to have characteristics similar to MMC inasmuch as they are not stained by safranin O; they contain RMCP II and not I [44]; the over-sulphated chondroitin sulphate E is present in great excess over heparin [18]; and they are activated by IgE-mediated pathways but not by compound 48/80 [47]. Furthermore, proliferation of rodent MMC in response to parasitic infestation was found to be dependent on the presence of functional T lymphocytes [48-50]. MMC can be grown in large numbers from bone marrow and thereby provide a useful model for analysing the biological characteristics of this cell type. More recently, mouse mast cell lines with characteristics of CTMC have been established by transforming mouse peritoneal mast cells with a mouse sarcoma virus [51].

There is good evidence to suggest that rodent connective tissue and mucosal mast cells are derived from a common precursor located in the bone marrow. Intravenous injection of bone marrow cells from normal mice into mast cell-deficient mice results in the development of mast cells of donor origin in the recipients [52]. When BMMC [53] or an isolated mast cell from the peritoneal cavity (presumably the connective tissue type) [54] are injected into the mast cell-deficient mouse, mucosal mast cells appear in the gastric mucosa and connective tissue mast cells appear in the skin of the recipient. Furthermore, BMMC, when co-cultured with fibroblasts, acquire staining characteristics of connective tissue mast cells [55], suggesting that interconversions between mast cell types occurs and that the phenotype might be regulated in part by the tissue micro-environment. The possibility of trans-differentiation whereby one type of mature mast cell de-differentiates into the precursor cell and re-differentiates into the other type of mast cell has been suggested by the

finding that injection of either type of mast cell into the stomach wall of a mast cell-deficient mouse results first in disappearance of metachromatic cells and then in the reappearance of mucosal-like mast cells in the mucosa and connective tissue-like mast cells in the muscularis propria [56,57].

Human mast cell heterogeneity

Two types of human mast cells termed T (tryptase-positive, chymase-negative) and TC (tryptase-positive, chymase-positive) mast cells have recently been described based on differences in neutral protease content. They appear analogous to the rodent MMC and CTMC, respectively. Associated evidence for functional and morphological heterogeneity of human mast cells has also been established.

Phenotypic differences

The first evidence for the presence of human mast cell heterogeneity was provided by Strobel *et al.* [58] who found that the numbers of mast cells visualized in the human gastrointestinal mucosa depend on the fixative employed, similar to the situation in rodents. These findings were confirmed by numerous other studies [59–62]. Thus, human MMC were formalin sensitive or 'atypical' because they failed to display metachromatic staining when fixed in neutral buffered formalin, while human CTMC were formalin resistant or 'typical'. The inherent limitations of these studies are exemplified by the inability to recognize different types of mast cells in a single tissue section. Instead, adjacent sections of frozen tissue or comparable tissue samples must be subjected to different fixatives and compared for the number of stained mast cells.

The ultrastructure of human mast cells has been extensively studied. Of particular interest to the present discussion are the various substructural features of mast cell secretory granules described in the lung [63], the gastrointestinal tract [64] and the nasal mucosa [65]. Mast cells with granules having predominantly scrolls and others with lattices and gratings have been observed, but were thought to represent different states of activation and/or differentiation of the same cell type. A recent study indicates that these ultrastructural characteristics can be used to differentiate the two types of human mast cells. Thus, discrete scrolls were found exclusively in granules of T mast cells while TC mast cells were the only type with grating or lattice substructures in their granules; in addition, TC mast cell granules were more uniformly electron dense and larger than T mast cell granules [66].

Using histochemical techniques, MMC were found to

Table 5. Tissue distribution (%) of human T and TC mast cells

Tissue localization	T	TC
Skin	12	88
Lung		
Bronchial epithelium	99	1
Bronchial subepithelium	77	23
Alveoli	93	7
Dispersed lung cells	90	10
Small intestine		
Mucosa	98	2
Submucosa	13	87
Nasal mucosa		
Epithelium	100	0
Subepithelium	60	40
Conjunctiva		
Epithelium	100	0
Subepithelium	20	0

predominate in the intestinal mucosa and lamina propria [59,60], in nasal scrapings and nasal epithelium of subjects with allergic rhinitis [67,68], in the epithelium and lamina propria of bronchi and in the pulmonary parenchyma [69] and in bronchoalveolar lavage fluid [70]. The CTMC was the predominant type seen in the intestinal submucosa [60], the bronchial submucosa [69] and the dermis of subjects with urticaria pigmentosa [71]. An important correlate of these morphological studies was the finding that MMC and CTMC were intermixed in most tissues examined although their relative distribution varied markedly with the anatomical site. Therefore, as pointed out by several authors [61,72], the terms mucosal and connective tissue mast cells are both incorrect and misleading and should be replaced by a nomenclature that accurately reflects phenotypical, biochemical and/or functional differences between the two types of human mast cells.

In histologically normal tissues, immunohistochemical studies show the T mast cell to be the predominant type found in the lung and the small intestinal mucosa while the TC mast cell is the predominant type found in the skin and the gastrointestinal submucosa [73]. Therefore, in terms of tissue localization, the human T mast cell corresponds most closely to rodent MMC, while the human TC mast cell corresponds most closely to rodent CTMC. Table 5 shows the distribution of T and TC mast cells in tissue sections obtained from various anatomical sites not involved by a disease process (i.e. histologically normal) [73–75]. Once again, it is worthwhile to point out

Table 6. Biochemical composition of human T and TC mast cells and basophils*

Property	T†	TC‡	Basophils
Histamine (pg/cell)	1.5	1.9	1.2
Tryptase (pg/cell)	10	35	0.04
Chymase (pg/cell)	5	<0.05	<0.05
Carboxypeptidase (pg/cell)	—	10–20	n.d.
LTC ₄ (ng/10 ⁶ cells)	10–80	3.5	25–20
PGD ₂ (ng/10 ⁶ cells)	39	43	±§

* From references, 78, 80, 88, 89.

† Dispersed human lung mast cells presumed to be mostly T mast cells.

‡ Dispersed human skin mast cells presumed to be mostly TC mast cells.

§ Negative for basophils from normal subjects [109], positive for basophils from subjects with chronic myelogenous leukaemia [110].

the simultaneous presence of both T and TC mast cells in most tissues examined, making it impossible to differentiate between these two types of mast cells based on location alone.

Biochemical differences (Table 6)

Preformed mediators. Human lung mast cells fractionated according to size were shown to contain increasing amounts of histamine (from 2.5 to 10 pg/mast cell) with increasing size [76]. The histamine content of dispersed human intestinal mucosal mast cells was calculated to be 2.8 pg/mast cell, within the range found for dispersed human lung mast cells [77]. Analysis of dispersed preparations of human T and TC mast cells obtained from lung and foreskin, respectively, demonstrated similar levels of histamine in adult foreskin TC (1.9 pg/mast cell), newborn foreskin TC (1.6 pg/mast cell) and adult lung T (1.5 pg/mast cell) mast cells [78]. It appears therefore that histamine content is not helpful in differentiating between different types of mast cells.

A major development in the study of human mast cell heterogeneity was the recognition of compositional differences that distinguished between two types of mast cells based on their content of the neutral proteases, tryptase and chymase [73,78]. A double-labelling, indirect immunohistochemical procedure was developed that detected both types of mast cells in the same tissue section, thus overcoming the limitations of the previous histochemical studies. This procedure involves sequential staining of Carnoy's fixed tissue sections first with a

polyclonal rabbit anti-chymase antibody by an immunoperoxidase technique, and then with a monoclonal mouse anti-tryptase antibody by an immunoalkaline phosphatase technique. T mast cells appear blue and TC mast cells appear brown (Fig. 1). The clear distinction between T and TC mast cells allows for an accurate quantification of their respective numbers. A further advantage of this technique is its specificity for mast cells since basophils are not stained under the conditions described [79]. Videoplan measurements of mast cells stained by this technique show that the mean area of TC mast cells (76 μm^2) is significantly larger than that of T mast cells (66 μm^2); however, the overlap is extensive such that individual mast cells belonging to different types cannot be distinguished on the basis of size alone. The simultaneous presence of tryptase and chymase in the same mast cell was demonstrated by a modification of the previous experiment whereby the anti-tryptase and anti-chymase antibodies were added simultaneously. The chymase-positive cells were then stained blue by the immunoalkaline phosphatase technique and photomicroscopy was performed. Subsequently, the tryptase-positive cells were stained brown by the immunoperoxidase technique. Under these conditions, all previously blue-stained cells became brown as shown by repeat photomicroscopy of the same cells (Fig. 2). This was further elucidated by ultrastructural studies which localized both neutral proteases to the same secretory granules of the TC mast cell [66].

A carboxypeptidase enzyme has been detected in mast cells dispersed from human skin (99% TC mast cells) and in smaller amounts in mast cells dispersed from human lung (90% T and 10% TC mast cells) [80]. Carboxypeptidase may be another selective marker for the TC mast cell.

The difference in neutral protease compositions between T and TC mast cells is reminiscent of the situation in rodents where antigenically distinct neutral proteases, RMCP I and II, are found in CTMC and MMC, respectively [8–10,13]. These last two types also differ with respect to their proteoglycan content as previously mentioned [15–18]. By analogy to the rodent system, the proteoglycan compositions of T and TC mast cells also might differ. The evidence so far indicates the presence of heparin in dispersed human lung mast cells [81] and mastocytosis skin [82]. In addition, chondroitin sulphate E was found in supernatants of human colonic explants, possibly derived from mast cells [83]. However, chondroitin sulphate E is not unique to the mast cell but is also present in cultured human peritoneal macrophages [84] and in human leukaemic basophils [85]. More recently, highly purified preparations of human lung mast cells (up to 99%) were shown to contain both heparin and chondroitin sulphate E [86,87]. However, whether the

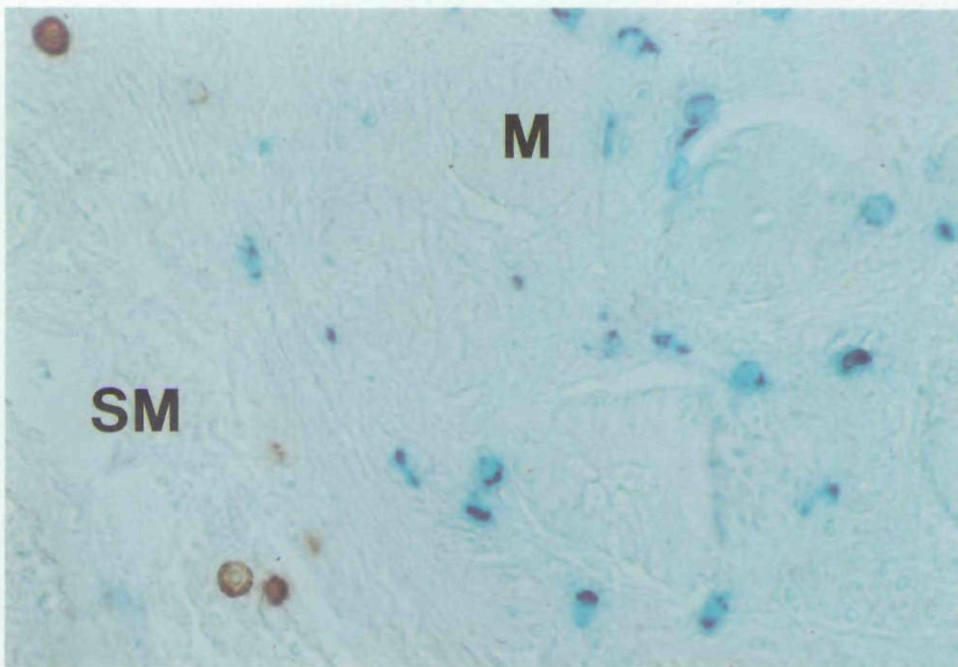


Fig. 1. Carnoy's fixed human ileum. Tissue section was incubated sequentially with anti-chymase and anti-tryptase antibodies. T mast cells appear blue. TC mast cells appear brown. M, mucosa; SM, submucosa ($\times 2260$).

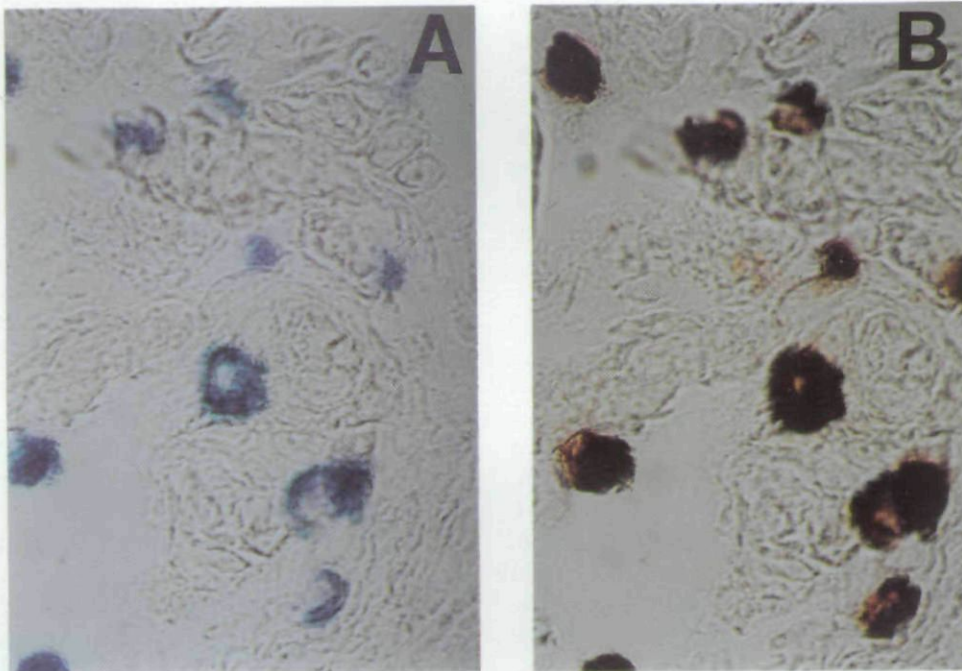


Fig. 2. Carnoy's fixed human skin. Tissue section was incubated simultaneously with anti-chymase and anti-tryptase antibodies. Chymase positive cells (A) are also tryptase positive (B) ($\times 2260$).

Table 7. Heterogeneity of the human mast cell secretory response

Property	Lung	Skin	GI mucosa
Activation agents			
α -IgE	+	+	+
A 23187	+	+	nd
Compound 48/80	—	+	—
Morphine sulphate	—	+	—
Polylysine	—	+	n.d.
Substance P	n.d.	+	n.d.
f-met peptide	—	+	—
C5a	—	+	n.d.
Inhibitory agents			
Sodium cromoglycate	±	—	n.d.
Salbutamol	+	n.d.	n.d.
Lodaxamide	+	n.d.	n.d.
Traxanox	+	n.d.	n.d.
RU 31156	+	n.d.	n.d.

purification process affects the final ratio of the mast cell subsets and whether different proteoglycans are co-expressed by the same mast cell needs to be clarified.

Newly generated mediators. Dispersed human lung and intestinal mast cells were found to generate significant quantities of both PGD₂ and sulphidopeptide leukotrienes [77,88]. Again, the distribution of T and TC mast cells was unknown. The wide variability in the levels of arachidonic acid metabolites produced by the dispersed intestinal mast cells (0.2–14.2 ng of LTE₄ per 10⁶ mast cells) may be related to differences in the ratios of mast cell subsets between different preparations. In contrast, mast cells dispersed from human skin (mostly TC mast cells) and stimulated were found to generate PGD₂ but little or no LTC₄ [89].

Functional differences (Table 7)

Degranulation of human mast cells in response to various agents and inhibition of degranulation by anti-allergic drugs have been studied in dispersed preparations of mast cells obtained from various anatomical sites [77,89–93]. In this respect, it is important to keep in mind that such preparations often contain a mixture of T and TC mast cells depending on the site examined, the pathological condition of the donor organ and the method of dispersion and purification. Perhaps the most interpretable studies are the ones utilizing adult human foreskin since this tissue has been shown to contain TC mast cells almost exclusively.

Response to secretagogues. Mast cells isolated from foreskin predominantly consist of TC mast cells (99%) and release histamine in response to immunological (antigen and anti-IgE) as well as a wide variety of non-immunological agents such as the calcium ionophore A 23187, compound 48/80, basic polypeptides (polylysine, polyarginine), morphine sulphate, f-met peptides, substance P and the anaphylatoxin C5a [89–91]. In contrast, mast cells isolated from lung are activated by anti-IgE and calcium ionophore A 23187 but not by any of the other agents listed above [91,92]. For these experiments, mast cells were obtained by enzymatic digestion of macroscopically normal human lung tissue. Such preparations consist of about 90% T mast cells and 10% TC mast cells [73]. Attempts at increasing the mast cell purity by density gradient centrifugation may result in an altered distribution of the two mast cell types. Similarly, mast cells isolated from human colonic mucosa are activated by anti-IgE and the calcium ionophore A 23187 but not by compound 48/80, morphine sulphate or f-met peptide [77,91]. The type of mast cell obtained in these preparations has not been determined; however, the tissue was obtained from subjects with adenocarcinoma or ulcerative colitis. Immunohistochemical studies have shown a predominance of T mast cells in normal colonic mucosa (75%) while the colonic mucosa from subjects with ulcerative colitis contained up to 41% TC mast cells [94]. Compound 48/80 and the anaphylatoxins C3a and C5a also are ineffective in activating dispersed human adenoidal mast cells [93], which by immunohistochemistry consist mostly of T mast cells (unpublished observations). Clearly, analysis of the distribution of T and TC mast cells in the different preparations of dispersed human mast cells is essential for the proper interpretation of the results of functional studies.

Effect of pharmacological agents. Disodium cromoglycate is widely used for the treatment of asthma, rhinitis and conjunctivitis. Its local effects are believed to be due to inhibition of mast cell degranulation and mediator release [95]. Histamine release from mast cells recovered by bronchoalveolar lavage was inhibited by disodium cromoglycate at a concentration of 100 μ M [70]. Such mast cells have been shown to consist predominantly of T mast cells except in subjects with cystic fibrosis [74] (which were not included in the above study). Pre-treatment of human adenoidal mast cells (mostly T type) with 10^{−5} M disodium cromoglycate inhibits concanavalin A-induced histamine release [93]. In dispersed human lung mast cell preparations (90% T mast cells), high concentrations of disodium cromoglycate (1000 μ M) were required to produce 25 and 33% inhibition of IgE-dependent hista-

mine release, respectively. Lower concentrations of the related anti-allergic drugs traxanox and RU 31156 (100 μM) were needed to achieve similar levels of inhibition [96]. Finally, disodium cromoglycate elicited 20% inhibition of IgE-dependent histamine release from dispersed intestinal MMC [97]. In contrast histamine release from human skin after *in-vitro* antigen challenge was not inhibited by disodium cromoglycate [98,99], nor did the addition of 2% cromolyn to ragweed antigen inhibit the skin reaction to local injection in ragweed-sensitive individuals as judged by histamine release, ultrastructural alterations of mast cells and ingress of eosinophils [100]. Since the human skin mast cell is predominantly of the TC type, there appears to be a differential although weak inhibitory effect of disodium cromoglycate on T but not TC mast cells, in contrast to the situation in rodents where CTMC but not MMC are affected.

The β -adrenoceptor agonists fenoterol and salbutamol were shown to produce 40–50% inhibition of IgE-dependent histamine release from dispersed human lung mast cells at the relatively low concentrations of 0.1 and 10 μM , respectively [96,101]. These agents have not yet been tested on human skin mast cells. *In vivo*, local instillation of nasal steroids diminished mediator release during the immediate response to a nasal allergen challenge [102]. This effect may be due to the capacity for local steroids to diminish mast cell concentrations as demonstrated in the synovium [103] and in the skin [104], or to prevent the superficial migration of mast cells that apparently occurs in atopic subjects during the allergy season [105].

Growth and differentiation

The difficulties in maintaining human mast cells in long-term cultures have hampered the studies of growth and differentiation of these cells. Mast cells are detected in tissues but not in the peripheral circulation, perhaps due to our current inability to recognize immature forms of mast cells. Cultures of bone marrow and cord blood in the presence of T lymphocyte factors have produced meta-chromatic basophil-like cells [106], while cultures of dispersed fetal liver cells in the presence of murine cell factors have resulted in growth of mast cell-like cells [107].

Immunohistochemical analysis of gastrointestinal tissue from subjects with congenital or acquired immunodeficiency disorders affecting T lymphocyte function (AIDS and combined immune deficiency) have shown a selective deficiency of the T mast cell type in the mucosa and submucosa with normal or slightly increased numbers of TC mast cells seen in the submucosa [94], suggesting a relationship between T mast cells and T lymphocyte function. By analogy with rodent mucosal

mast cells, the development and/or proliferation of human T mast cells may also be dependent on functional T lymphocytes, particularly on the T helper lymphocyte which is selectively destroyed in subjects with AIDS. The deficiency of T mast cells in intestinal mucosa of subjects with acquired as well as congenital defects in T lymphocyte function indicates that the effect of T lymphocytes on the development of the T mast cell is expressed continuously throughout the life cycle of an individual.

The distribution of T and TC mast cells can be markedly affected by pathological conditions. For example, bronchoalveolar lavage fluid of subjects with cystic fibrosis show a marked increase in the percentage of TC mast cells (without an appreciable increase in total mast cell concentration) as compared to specimens obtained from normal non-atopic controls as well as from subjects with chronic inflammatory or non-inflammatory conditions such as bronchiectasis or alveolar proteinosis [74]. This finding suggests the influence of factor(s) produced by subjects with cystic fibrosis on the development of TC mast cells. Another example is the synovium where TC mast cells are normally the exclusive type present; in rheumatoid arthritis synovium, however, T mast cells predominate in inflamed areas and TC mast cells predominate in fibrous areas [108]. The abnormal distribution of T and TC mast cells in these pathologically inflamed tissues may reflect the effect of various inflammatory factors (lymphokines, monokines, etc.) on the development and/or proliferation of a specific mast cell type.

Concluding comments

There is now strong evidence for the presence of mast cell heterogeneity in humans as well as in the rodent system. The ability to distinguish clearly two types of human mast cells, termed T and TC, in the same tissue section is an important step towards better understanding the role of these cells in health and disease. These two mast cell types cannot be distinguished on the basis of size or location alone, and their distributions in various organs may be affected by pathological conditions. Interpretation of functional and biochemical studies conducted on mast cells dispersed from various tissues therefore necessitate that the types of mast cells be determined in each case. The nomenclature used by the authors refers to the biochemical distinction of the two mast cell types based on their content of the neutral proteases, trypsin and chymase. As other functional or lineage-related characteristics of each type of human and animal mast cell are defined, a more universally acceptable nomenclature will evolve.

References

- 1 Enerback L. Mast cells in rat gastrointestinal mucosa. I. Effects of fixation. *Acta Pathol Microbiol Scand* 1966; 66: 289-302.
- 2 Enerback L. Mast cells in rat gastrointestinal mucosa. II. Dye-binding and metachromatic properties. *Acta Pathol Microbiol Scand* 1966; 66:303-12.
- 3 Wingren U, Enerback L. Mucoal mast cells of the rat intestine: A re-evaluation of fixation and staining properties, with special reference to protein blocking and solubility of the granular glycosaminoglycan. *Histochem J* 1983; 15:571-82.
- 4 Enerback L. The gut mucosal mast cell. *Monogr Allergy* 1981; 17:222-32.
- 5 Saavedra-Delgado AMP, Turpin S, Metcalfe DD. Typical and atypical mast cells of the rat gastrointestinal system: distribution and correlation with tissue histamine. *Agents Actions* 1984; 14:1-7.
- 6 Befus AD, Pearce FL, Gaudie J, Horsewood P, Bienenstock J. Mucosal mast cells. I. Isolation and functional characteristics of rat intestinal mast cells. *J Immunol* 1982; 128:2475-80.
- 7 Woodbury RG, Gruzinski G, Lagunoff D. Immunofluorescent localization of a serine protease in rat small intestine. *Proc Natl Acad Sci USA* 1978; 75:2785-9.
- 8 Gibson S, Miller HRP. Mast cell subsets in the rat distinguished immunohistochemically by their content of serine proteinases. *Immunology* 1986; 58:101-4.
- 9 Woodbury RG, Neurath H. Purification of an atypical mast cell protease and its levels in developing rats. *Biochemistry* 1978; 17:4298-304.
- 10 Woodbury RG, Miller HRP. Quantitative analysis of mucosal mast cell protease in the intestines of *Nippostrongylus*-infected rats. *Immunology* 1982; 46:487-95.
- 11 Everitt MT, Neurath H. Rat peritoneal mast cell carboxypeptidase: Localization, purification and enzymatic properties. *FEBS Lett* 1980; 110:292-6.
- 12 Schwartz LB, Riedel C, Schratz JJ, Austen KF. Localization of carboxypeptidase A to the macromolecular heparin proteoglycan-protein complex in secretory granules of rat serosal mast cells. *J Immunol* 1982; 128:1128-33.
- 13 Kido H, Fukusen N, Katunuma N. Chymotrypsin- and trypsin-type serine proteases in rat mast cells: Properties and functions. *Arch Biochem Biophys* 1985; 239:436-43.
- 14 Lagunoff D, Pritzl P. Characterization of rat mast cell granule proteins. *Arch Biochem Biophys* 1976; 173:554-63.
- 15 Tas J, Berndsen RG. Does heparin occur in mucosal mast cells of the rat small intestine? *J Histochem Cytochem* 1977; 25:1058-62.
- 16 Bland CE, Sredni B, Metcalfe DD. Direct cloning and extended cultures of basophils from mouse bone marrow: biochemical characterization of basophil proteoglycan. *J Allergy Clin Immunol* 1981; 67:105A.
- 17 Stevens RL, Lee TDG, Seldin DC, Austen KF, Befus AD, Bienenstock J. Intestinal mucosal mast cells from rats infected with *Nippostrongylus brasiliensis* contain protease-resistant chondroitin sulfate di-B proteoglycans. *J Immunol* 1986; 137:291-5.
- 18 Razin E, Stevens RL, Akiyama F, Schmid K, Austen KF. Culture from mouse bone marrow of a subclass of mast cells possessing a distinct chondroitin sulfate proteoglycan with glycosaminoglycans rich in *N*-acetylgalactosamine-4,6-disulfate. *J Biol Chem* 1982; 257:7229-36.
- 19 Katz H, Austen KF, Caterson G, Stevens RL. Secretory granules of heparin-containing rat serosal mast cells also possess highly sulfated chondroitin sulfate proteoglycans. *J Biol Chem* 1986; 261:13393-6.
- 20 Stevens RL, Razin E, Austen KF, Caulfield JP, Seno N, Schmid K, Akiyama F. Synthesis of chondroitin sulfate E glycosaminoglycan onto *p*-nitrophenyl- β -D-xyloside and its localization to the secretory granules of rat serosal mast cells and mouse bone marrow-derived mast cells. *J Biol Chem* 1983; 258:5977-84.
- 21 Tantravahi RV, Stevens RL, Austen KF, Weis JH. A single gene in mast cells encodes the core peptides of heparin and chondroitin sulfate proteoglycans. *Proc Natl Acad Sci USA* 1986; 83:9207-10.
- 22 Serafin WE, Katz HR, Austen KF, Stevens RL. Complexes of heparin proteoglycans, chondroitin sulfate E proteoglycans, and [^{3} H]diisopropyl fluorophosphate-binding proteins are exocytosed from activated mouse bone marrow-derived mast cells. *J Biol Chem* 1986; 261:15017-21.
- 23 Seldin DC, Austen KF, Stevens RL. Purification and characterization of protease-resistant secretory granule proteoglycans containing chondroitin sulfate di-B and heparin-like glycosaminoglycans from rat basophilic leukemia cells. *J Biol Chem* 1985; 260:11131-9.
- 24 Roberts LJ, Lewis RA, Oates JA, Austen KF. Prostaglandin, thromboxane, and 12-hydroxy-5,8,10,14-eicosatetraenoic acid production by ionophore-stimulated rat serosal mast cells. *Biochem Biophys Acta* 1979; 575:185-92.
- 25 Lewis RA, Soter NA, Diamond PT, Austen KF, Oates JA, Roberts LJ. Prostaglandin D₂ generation after activation of rat and human mast cells with anti-IgE. *J Immunol* 1982; 129:1627-31.
- 26 Heavy DJ, Ernst PB, Stevens RL, Befus AD, Bienenstock J, Austen KF. Generation of leukotriene C₄, leukotriene B₄ and prostaglandin D₂ by immunologically activated rat intestinal mucosal mast cells. *J Immunol* 1988; 140:1953-7.
- 27 Razin E, Mencia-Herta JM, Lewis RA, Corey EJ, Austen KF. Generation of leukotriene C₄ from a subclass of mast cells differentiated *in vitro* from mouse bone marrow. *Proc Natl Acad Sci USA* 1982; 79:4665-7.
- 28 Mencia-Herta JM, Razin E, Ringel EW, Corey EJ, Hoover D, Austen KF, Lewis RA. Immunologic and ionophore induced generation of leukotriene B₄ from mouse bone marrow-derived mast cells. *J Immunol* 1983; 130:1885-90.
- 29 Robin J-L, Seldin DC, Austen KF, Lewis RA. Regulation of mediator release from mouse bone marrow-derived mast cells by glucocorticoids. *J Immunol* 1985; 135:2719-26.
- 30 Katz HR, LeBlanc RP, Russell SW. Two classes of mouse mast cells delineated by monoclonal antibodies. *Proc Natl Acad Sci USA* 1983; 80:5916-18.

- 31 Katz HR, Schwarting GA, LeBlanc PA, Austen KF, Stevens RL. Identification of the neutral glycosphingolipids of murine mast cells: Expression of Forssman glycolipid by the serosal but not the bone marrow-derived subclass. *J Immunol* 1985; 134:2617-23.
- 32 Barrett KE, Pearce FL. A comparative study of histamine release from rat peritoneal and pleural mast cells. *Agents Actions* 1982; 129:2116-21.
- 33 Barrett KE, Ali H, Pearce FL. Studies on histamine secretion from enzymically dispersed cutaneous mast cells of the rat. *J Invest Dermatol* 1985; 84:22-6.
- 34 Enerback L. Mast cells in rat gastrointestinal mucosa. III. Reactivity towards compound 48/80. *Acta Pathol Microbiol Scand* 1966; 66:313-22.
- 35 Pearce FL. Functional heterogeneity of mast cells from different species and tissues. *Klin Wschr* 1982; 60:954-7.
- 36 Pearce FL. Calcium and histamine secretion from mast cells. *Prog Med Chem* 1982; 19:59-109.
- 37 Shanahan F, Denburg J, Fox J, Bienenstock J, Befus AD. Mast cell heterogeneity: effects of neuroenteric peptides on histamine release. *J Immunol* 1985; 135:1331-7.
- 38 Pearce FL, Befus AD, Gauldie J, Bienenstock J: Mucosal mast cells. II. Effects of anti-allergic compounds on histamine secretion by isolated intestinal mast cells. *J Immunol* 1982; 128:2481-6.
- 39 Pearce FL, Befus AD, Bienenstock J: Mucosal mast cells. III. Effect of quercetin and other flavonoids on antigen-induced histamine secretion from rat intestinal mast cells. *J Allergy Clin Immunol* 1984; 73:813-23.
- 40 Shanahan F, Lee TDG, Bienenstock J, Befus A. Mast cell heterogeneity: effect of anti-allergic compounds on neuro-peptide-induced histamine release. *Int Arch Allergy Appl Immunol* 1986; 80:424-6.
- 41 Mongar JL, Svec P. The effect of phospholipids on anaphylactic histamine release. *Br J Pharmacol* 1972; 46:741-52.
- 42 Nagao K, Yokoro K, Aaronson SA. Continuous lines of basophil/mast cells derived from normal mouse bone marrow. *Science* 1981; 212:333-5.
- 43 Nabel G, Galli SJ, Dvorak AM, Dvorak HF, Centor H. Inducer T lymphocytes synthesize a factor that stimulates proliferation of cloned mast cells. *Nature* 1981; 291:332-4.
- 44 Haig DM, McKee TA, Jarrett EEE, Woodbury R, Miller HRP. Generation of mucosal mast cells is stimulated *in vitro* by factors from T cells of Helminth-infected rats. *Nature* 1982; 300:188-90.
- 45 Razin E, Ihle JN, Seldin D, Mencia-Huerta JM, Katz HR, LeBlanc PA, Hein A, Caulfield JP, Austen KF, Stevens RL. Interleukin 3: A differentiation and growth factor for the mouse mast cell that contains chondroitin sulfate E proteoglycan. *J Immunol* 1984; 132:1479-86.
- 46 Hamaguchi Y, Kanakura Y, Fujita J, Takeda S, Nakano T, Tarui S, Honjo T, Kitamura Y. Interleukin 4 as an essential factor for *in vitro* clonal growth of murine connective tissue-type mast cells. *J Exp Med* 1987; 165:268-73.
- 47 Sredni B, Friedman MM, Bland CE, Metcalfe DD. Ultrastructural, biochemical and functional characteristics of histamine-containing cells cloned from mouse bone marrow: Tentative identification as mucosal mast cells. *J Immunol* 1983; 131:915-22.
- 48 Ruitenburg EJ, Elgersma A. Absence of intestinal mast cell response in congenitally athymic mice during *Trichinella spiralis* infection. *Nature* 1976; 264:258-61.
- 49 Nawa Y, Miller HRP. Adoptive transfer of the intestinal mast cell response in rats infected with *Nippostrongylus brasiliensis*. *Cell Immunol* 1979; 42:225-39.
- 50 Mayrhofer G. The nature of the thymus dependency of mucosal mast cells II. The effect of thymectomy and of depleting recirculating lymphocytes on the response to *Nippostrongylus brasiliensis*. *Cell Immunol* 1979; 47:312-22.
- 51 Reynolds DS, Serafin WE, Faller DV, Dvorak AM, Austen KF, Stevens RL. Immortalization of mouse connective tissue-type mast cells. *Fed Proc* 1988; 2:1234(abstr).
- 52 Kitamura Y, Matsuda H, Hatanaka K. Clonal nature of mast cells clusters formed in W/W^v mice after bone marrow transplantation. *Nature* 1979; 281:154-5.
- 53 Nakano T, Sonoda T, Hayashi C, Yamatodani A, Kanayama Y, Yamamura T, Asai H, Yonezawa T, Kitamura Y, Galli SJ. Fate of bone marrow-derived cultured mast cells after intracutaneous, intraperitoneal and intravenous transfer into genetically mast deficient W/W^v mice: evidence that cultured mast cells can give rise to both 'Connective Tissue-Type' and 'Mucosal' mast cells. *J Exp Med* 1985; 162:1025-43.
- 54 Sonoda S, Sonoda T, Nakano T, Kanayama Y, Kanakura Y, Asai H, Yonezawa T, Kitamura Y. Development of mucosal mast cells after injection of a single connective tissue-type mast cell in the stomach mucosa of genetically mast cell-deficient W/W^v mice. *J Immunol* 1986; 137:1319-22.
- 55 Levi-Schaffer F, Austen KF, Gravalles PM, Stevens RL. Coculture of interleukin 3-dependent mouse mast cells with fibroblasts results in a phenotypic change of the mast cells. *Proc Natl Acad Sci USA* 1986; 83:6485-8.
- 56 Kitamura Y, Sonoda T, Nakano T, Kanayama Y. Probable dedifferentiation of mast cells in mouse connective tissues. *Curr Top Dev Biol* 1986; 20:325-32.
- 57 Kitamura Y, Nakano T, Kanakura Y: Transdifferentiation between mast cell subpopulations. *Dev Growth Differentiat* 1986; 28:321-5.
- 58 Strobel S, Miller HRP, Ferguson A. Human intestinal mucosal mast cells: Evaluation of fixation and staining techniques. *J Clin Path* 1981; 34:851-8.
- 59 Ruitenberg EJ, Gustowska L, Elgersma A, Ruitenberg HM. Effect of fixation on the light microscopical visualization of mast cells in the mucosa and connective tissue of the human duodenum. *Int Arch Allergy Appl Immunol* 1982; 67:233-8.
- 60 Befus D, Goodacre R, Dyck N, Bienenstock J. Mast cell heterogeneity in man. I. Histologic studies of the intestine. *Int Arch Allergy Appl Immunol* 1985; 76:232-6.
- 61 Bienenstock J, Befus D, Denburg J, Goto T, Lee T, Otsuka H, Shanahan F. Comparative aspects of mast cell heterogeneity

- neity in different species and sites. *Int Arch Allergy Appl Immunol* 1985; 77:126-9.
- 62 Katz HR, Stevens RL, Austen KF. Leukotriene and prostaglandin pathway metabolism. Heterogeneity of mammalian mast cells differentiated *in vivo* and *in vitro*. *J Allergy Clin Immunol* 1985; 76:250-9.
 - 63 Caulfield JP, Lewis RA, Hein A, Austen KF. Secretion in dissociated human pulmonary mast cells. Evidence for solubilization of granule contents before discharge. *J Cell Biol* 1980; 85:299-312.
 - 64 Dobbins WO, Tomasini JT, Rollins EL. Electron and light microscopic identification of the mast cell of the gastrointestinal tract. *Gastroenterology* 1969; 56:268-79.
 - 65 Friedman MM, Kaliner M. *In situ* degranulation of human nasal mucosal mast cells: Ultrastructural features and cell-cell associations. *J Allergy Clin Immunol* 1985; 76:70-82.
 - 66 Craig SS, Schechter NM, Schwartz LB. Ultrastructural analysis of human T and TC mast cells identified by immunoelectron microscopy. *Lab Invest*, 1988; 59:682-91.
 - 67 Otsuka H, Denburg J, Dolovich H, Hitch D, Lapp P, Rajan RS, Bienenstock J, Befus D. Heterogeneity of metachromatic cells in human nose: significance of mucosal mast cells. *J Allergy Clin Immunol* 1985; 76:695-702.
 - 68 Okuda M, Sakaguchi Y, Suzuhi F, Ohtsuka H, Kawabori S. Ultrastructural heterogeneity of the basophilic cells in the allergic nasal mucosa. *Ann Allergy* 1985; 54:152-7.
 - 69 Shanahan F, MacNiven I, Dyck N, Denburg J, Bienenstock J, Befus AD. Human lung mast cells: distribution and abundance of histochemically distinct subpopulations. *Int Arch Allergy Appl Immunol* 1987; 83:329-31.
 - 70 Flint KC, Leung KBP, Pearce FL, Hudspeth BN, Brostoff J, Johnson NMcl. Human mast cells recovered by bronchoalveolar lavage: their morphology, histamine release and the effects of sodium cromoglycate. *Clin Sci* 1985; 68:427-32.
 - 71 Olafsson JH, Roupe G, Enerback L. Dermal mast cells in mastocytosis: fixation, distribution and quantitation. *Acta Derm Venereol (Stockh)* 1936; 66:16-22.
 - 72 Pearce FL. On the heterogeneity of mast cells. *Pharmacology* 1986; 32:61-71.
 - 73 Irani AA, Schechter NM, Craig SS, DeBlois G, Schwartz LB. Two types of human mast cells that have distinct neutral protease compositions. *Proc Natl Acad Sci USA* 1986; 83:4464-8.
 - 74 Irani AA, Spock A, Schwartz LB. Reverse distribution of human mast cell subsets in cystic fibrosis. *Ped Res* 1988; 23:565(abstr).
 - 75 Butrus SI, Irani AA, Tabbarah KF, Schwartz LB. Mast cell subtypes in vernal and giant papillary conjunctivitis. *Invest Ophthalmol Vis Sci* 1988; 29(suppl):269.
 - 76 Schulman ES, Kagey-Sobotka A, MacGlashan Jr DW, Adkinson Jr NF, Peters SP, Schleimer RP, Lichtenstein LM. Heterogeneity of human mast cells. *J Immunol* 1983; 131:1936-41.
 - 77 Fox CC, Dvorak AM, Peters SP, Kagey-Sobotka A, Lichtenstein LM. Isolation and characterization of human intestinal mucosal mast cells. *J Immunol* 1985; 135:483-91.
 - 78 Schwartz LB, Irani AA, Roller K, Castells MC, Schechter NM. Quantitation of histamine, tryptase and chymase in dispersed human T and TC mast cells. *J Immunol* 1987; 138:2611-15.
 - 79 Castells MC, Irani A, Schwartz LB. Evaluation of human peripheral blood leukocytes for mast cell tryptase and chymase in dispersed human T and TC mast cells. *J Immunol* 1987; 138:2184-9.
 - 80 Goldstein SM, Kaempfer CE, Proud D, Schwartz LB, Irani AA, Wintroub BU. Detection and partial characterization of a human mast cell carboxypeptidase. *J Immunol* 1987; 139:2724-9.
 - 81 Metcalfe DD, Lewis RA, Silbert JE, Rosenberg RD, Wasserman SI, Austen KF. Isolation and characterization of heparin from human lung. *J Clin Invest* 1979; 64:1537-43.
 - 82 Metcalfe DD, Soter NA, Wasserman SI, Austen KF. Identification of sulfated mucopolysaccharides including heparin in the lesional skin of a patient with mastocytosis. *J Invest Dermatol* 1980; 74:210-15.
 - 83 Eliakim R, Gilead L, Ligumsky M, Okron E, Rachmilewitz D, Razin E. Histamine and chondroitin sulfate E proteoglycan released by cultured human colonic mucosa: indication for possible presence of E mast cells. *Proc Natl Acad Sci USA* 1986; 83:461-4.
 - 84 Koisset, SO. Oversulfated chondroitin sulfate proteoglycan in cultured human peritoneal macrophages. *Biochem Biophys Res Commun* 1986; 139:377-82.
 - 85 Rothenberg ME, Caulfield JP, Austen KF, Hein A, Edmiston K, Newburger PE, Stevens RL. Biochemical and morphological characterization of basophilic leukocytes from two patients with myelogenous leukemia. *J Immunol* 1987; 138:2616-25.
 - 86 Thompson HL, Schulman ES, Metcalfe DD. Identification of chondroitin sulfate E in human lung mast cells. *J Immunol* 1988; 140:2708-13.
 - 87 Stevens RL, Fox CC, Lichtenstein LM, Austen KF. Identification of chondroitin sulfate E proteoglycans and heparin proteoglycans in the secretory granules of human lung mast cells. *Proc Natl Acad Sci USA* 1988; 85:2284-7.
 - 88 Peters SP, MacGlashan DW, Schulman ES, Schleimer RP, Hayes EC, Rokach J, Adkinson Jr NF, Lichtenstein LM. Arachidonic acid metabolism in purified human lung mast cells. *J Immunol* 1984; 131:1972-9.
 - 89 Lawrence ID, Warner JA, Cohan VL, Hubbard WC, Kagey-Sobotka A, Lichtenstein LM. Purification and characterization of human skin mast cells. Evidence for human mast cell heterogeneity. *J Immunol* 1987; 139:3062-9.
 - 90 Benyon RC, Lowman MA, Church MK. Human skin mast cells: their dispersion, purification, and secretory characterization. *J Immunol* 1987; 138:861-7.
 - 91 Tharp MD, Kagey-Sobotka A, Fox CC, Marone G, Lichtenstein LM, Sullivan TJ. Functional heterogeneity of human mast cells from different anatomic sites: *In vitro* responses to morphine sulfate. *J Allergy Clin Immunol* 1987; 79:646-53.

- 92 Church MK, Pao GJK, Holgate ST: Characterization of histamine secretion from mechanically dispersed human lung mast cells: effects of anti-IgE, calcium ionophore A 23187, compound 48/80, and basic polypeptides. *J Immunol* 1982; 129:2116-21.
- 93 Schmutzler W, Delmich K, Eichelberg D, Gluck S, Greven T, Jurgensen H, Riesener KP, Risse G, Pult P. The human adenoïdal mast cell. Susceptibility to different secretagogues and secretion inhibitors. *Int Arch Allergy Appl Immunol* 1985; 77:177-8.
- 94 Irani AA, Craig SS, DeBlois G, Elson CO, Schechter NM, Schwartz LB. Deficiency of the tryptase-positive, chymase-negative mast cell type in gastrointestinal mucosa of patients with defective T lymphocyte function. *J Immunol* 1987; 138:4381-6.
- 95 Cox JSG. Disodium cromoglycate (FPL 670, Intal): A specific inhibitor of reaginic antibody-antigen mechanisms. *Nature* 1967; 216:1328-9.
- 96 Church MK, Hiroi J. Inhibition of IgE-dependent histamine release from human dispersed lung mast cells by anti-allergic drugs and salbutamol. *Br J Pharmacol* 1987; 90:421-9.
- 97 Befus AD, Dyck N, Goodacre R, Bienenstock J. Mast cells from the human intestinal lamina propria: isolation, histochemical subtypes, and functional characterization. *Immunology* 1987; 138:2604-10.
- 98 Pearce CA, Greaves MW, Plummer VM, Yamamoto ES. Effect of disodium cromoglycate on antigen-evoked histamine release from human skin. *Clin Exp Immunol* 1974; 17:437-40.
- 99 Clegg LS, Church MK, Holgate ST. Histamine secretion from human skin slices induced by anti-IgE and artificial secretagogues and the effects of sodium cromoglycate and salbutamol. *Clin Allergy* 1985; 15:321-8.
- 100 Ting S, Zweiman B, Lavker RM. Cromolyn does not modulate human allergic skin reactions *in vivo*. *J Allergy Clin Immunol* 1983; 71:12-17.
- 101 Peters SP, Schulman ES, Schleimer RP, MacGlashan Jr DW, Newball HH, Lichtenstein LM. Dispersed human lung mast cells. Pharmacologic aspects and comparison with human lung tissue fragments. *Am Rev Respir Dis* 1982; 126:1034-9.
- 102 Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman P, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *New Engl J Med* 1987; 316:1506-10.
- 103 Malone DG, Wilder RL, Saavedra-Delgado AM, Metcalfe DD. Mast cell numbers in rheumatoid synovial tissues. Correlations with quantitative measures of lymphocytic infiltration and modulation by anti-inflammatory therapy. *Arthritis Rheum* 1987; 30:130-7.
- 104 Lavker RM, Schechter NM. Cutaneous mast cell depletion results from topical corticosteroid usage. *J Immunol* 1985; 135:2368-73.
- 105 Enerback L, Pipkorn U, Granerus G. Intraepithelial migration of nasal mucosal mast cells in hay fever. *Int Arch Allergy Appl Immunol* 1986; 80:44-51.
- 106 Ishizaka T, Dvorak AM, Conrad DH, Neibyl JR, Marquete JP, Ishizaka K. Morphologic and immunologic characterizations of human basophils developed in cultures of cord blood mononuclear cells. *J Immunol* 1985; 134:532-40.
- 107 Seldin DC, Caulfield JPL, Hein A, Osathanondh R, Nabel G, Schlossman SF, Stevens RL, Austen KF. Biochemical and phenotypic characterization of human basophilic cells derived from dispersed fetal liver with murine T cell factors. *J Immunol* 1986; 136:2222-30.
- 108 Irani AA, Golzar N, DeBlois G, Gruber B, Schwartz LB. Distribution of mast cell subsets in rheumatoid arthritis and osteoarthritis synovia. *Arthritis Rheum* 1987; 30:66.
- 109 MacGlashan DW Jr, Schleimer RP, Peters SP, Schulman ES, Adams GK, Sobotka AK, Newball HH, Lichtenstein LM. Comparative studies of human basophils and mast cells. *Fed Proc* 1983; 42:2504.
- 110 Rothenberg ME, Caulfield JP, Austen KF, Hein A, Edmiston K, Newburger PE, Stevens RL. Biochemical and morphological characterization of basophilic leukocytes from two patients with myelogenous leukemia. *J Immunol* 1987; 138:2616-25.

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