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Molecular and Cellular Biology of Mast Cells and Basophils

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Abstract

In all mammalian species investigated so far, mast cells and basophils are the only cells that synthesize histamine and express plasma membrane receptors that bind IgE with high affinity (FcεRI). Human basophils and mast cells derive from distinct precursors that originate in the bone marrow and fetal liver and probably circulate in peripheral blood. There is extensive evidence that mast cells and basophils and their mediators are primary effectors of allergic inflammation. Immunologically activated human basophils release two cytokines: IL-4 and IL-13. Expression of several cytokines has been documented in a number of experimental models of human and rodent mast cells. However, to date few studies have analyzed the mechanisms of gene expression in human FcεRI+ cells. Some of these studies imply a role for NFAT and GATA family members in the IgE-mediated activation of cytokine gene transcription in basophils and mast cells. Studies of human basophils and mast cells isolated from different anatomic sites have established the different profiles of eicosanoids released by these cells. Recently, the characterization of arachidonic acid pools and the identification of novel enzymes involved in arachidonate remodeling and mobilization clarified in part how eicosanoid productions is regulated in mast cells and basophils. In addition to histamine, human mast cell secretory granules contain the neutral proteases tryptase, chymase and carboxypeptidase that possess several biochemical properties. In particular, tryptase may play a role as a fibrogenic factor and chymase might convert angiotensin I to angiotensin II. Mast cells are present in human heart and in human coronary arteries raising the possibility that local activation of cardiac mast cells might contribute to certain cardiovascular diseases. Recent evidence also suggests that mast cells and basophils can play a role during viral and bacterial infections. It is now evident that in man these two cells not only participate in inflammation associated with allergic disease, but also in chronic and fibrotic disorders affecting several organs and in host defense against bacterial and viral infections.

Key Words

Basophils
Chymase
Histamine
Leukotriene C₄
Mast Cells
Tryptase

Mast cells were first identified in human connective tissue by Paul Ehrlich (1878) thanks to the metachromatic staining properties of their prominent cytoplasmic granules [1]. Paul Ehrlich also described the circulating basophil leukocytes that contain secretory granules whose staining

properties are similar to those of mast cells [2]. In all mammalian species studied so far, mast cells and basophils are the only cells that synthesize histamine and express plasma membrane receptors that bind the Fcε portion of IgE with high affinity (FcεRI) [3]. Human basophils and mast cells

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Fig. 1. Immunogold staining for SCF of a human skin mast cell. Sections were stained for SCF (monoclonal antibody anti-human SCF). Gold particles that identify SCF are present over all secretory granules of the mast cell. Uranyl acetate and lead citrate stained. Bar scale: 1.1 μ m.

derive from distinct precursors that originate in the bone marrow and fetal liver and probably circulate in peripheral blood. Human basophils and mast cells isolated from different anatomic sites also differ with respect to the type of chemical mediators synthesized and membrane surface receptors [4].

Mast cells are usually distributed throughout normal connective tissue, where they are adjacent to blood and lymphatic vessels, near nerves, and beneath epithelial surfaces, such as those of the respiratory and gastrointestinal systems and the skin [5–7]. Under normal conditions, basophils are never found in normal human tissues. Basophils differentiate and mature in the bone marrow and circulate in the blood with a prevalence of $\cong 0.5\%$ of total leukocytes. Under certain circumstances, basophils can be recruited into the inflamed tissue during certain IgE-dependent reactions and in association with a variety of pathologic conditions [8, 9]. There is increasing evidence that basophils are involved in delayed-type hypersensitivity reactions in the human skin and lung [8–10]. Several studies have shown that *stem cell factor* (SCF), also termed 'mast cell growth factor', *c-kit* ligand (KL), or steel factor is the principal growth [11–13], differentiating, chemotactic [14] and activating factor [15, 16] of human mast cells. SCF exerts its biological activities in an interaction with *c-kit*, its cognate receptor expressed on the cytoplasmic membrane of all types of human mast cells [14, 17]. Recent evidence from our laboratory indicates that SCF is also expressed by human mast cells, suggesting that it might act as an autocrine factor [18]. The principal growth and differentiating factor of human basophils appears to be IL-3 [19, 20].

Cytokine Expression in Mast Cells and Basophils

Experiments with murine mast cells have clearly demonstrated that IgE cross-linking initiates the synthesis and secretion of several cytokines [21], while information on human mast cells and basophils is more limited and still incomplete. There is good evidence that immunologically activated human basophils release IL-4 and IL-13 [22–24]. Expression of IL-4 and other cytokines, mostly related to IL-4 and typically associated with a Th2 phenotype (IL-3, IL-5, IL-13 and GM-CSF), has been so far documented in a number of human or murine cells exhibiting a mast cell/basophil-like phenotype, including: (1) mouse transformed mast cell lines (ABFTL-2, ABFTL-3, P815, MMC34) [25]; (2) mouse factor-dependent bone marrow- or fetal liver-derived mast cells (PB-3c, CFTL12, CFTL15, CPII) [26]; (3) freshly isolated mouse splenic or bone marrow Fc ϵ R+ Kit⁺ cells [27]; (4) human bone marrow Fc ϵ RI+ cells [28]; (5) human lung and skin mast cells [29–31]; (6) the human mast cell/basophilic leukemia lines KU812 and HMC-1 [32, 33], and (7) human leukemic basophils from patients with chronic myelogenous leukemia [34]. There is immunohistochemical evidence that human mast cells contain IL-4, IL-5, IL-6 and TNF- α [29–32]. We have recently demonstrated the presence of SCF, the principal growth, differentiating, chemotactic and activating factor of human mast cells, in secretory granules of human mast cells by immunogold staining [18]. Figure 1 shows that after immunogold staining of human skin tissue with a monoclonal antibody antihuman SCF, gold particles appeared throughout all the secretory granules of a mast cell. Thus, mast cell-derived

SCF might represent an autocrine factor sustaining mast cell hyperplasia and increased releasability in different pathological conditions. In vitro studies using human mast cells isolated and purified from different tissues to explore the conditions of mast cell cytokine production have yielded inconclusive results.

Transcriptional Regulation in Mast Cells and Basophils

Few studies have been conducted to date to analyze the mechanisms of gene expression in FcεRI+ cells. Most of these studies have focused on IL-4 gene transcription in transformed mouse mast cell lines. These cells express high levels of IL-4 mRNA constitutively, a feature shared with other transformed cell lines. It has been shown that cell-specific differences exist in the control of IL-4 transcription in mast cells and T cells. A 670-base-pair (bp) *Bgl*II fragment located within the second intron of the mouse IL-4 gene, identified by DNase I hypersensitivity studies, exhibited enhancer activity in mouse mast cell lines but not in the mouse T cell line EL-4 [35]. Mutations of two elements within this region decreased enhancer activity by almost 50% [36]. Nuclear proteins binding to these elements, including GATA-1, GATA-2 and PU.1, are specifically expressed in different murine mast cell transformed and IL-3-dependent lines, suggesting a critical role in cell-restricted activity of this intronic enhancer. An additional mast cell-specific enhancer has been located by deletion analysis between bp -6300 and -797 of the mouse IL-4 promoter, while a possible mast cell-specific negative regulatory element was identified in the region between bp -797 and -442 [35].

Human basophils express mRNA for GATA-2 and GATA-3, suggesting a role of these proteins in gene regulation in these cells [37]. IgE cross-linking and SCF induce increased mRNA levels for the AP-1 factors c-Fos, c-Jun and JunB in mouse bone marrow-derived mast cells [38]. More recent studies have investigated the role of nuclear factor of activated T cells (NFAT)-1 and related proteins in cytokine expression in FcεRI+ cells. NFAT-1 has been involved in the transcription of most cytokine genes expressed in mast cells and basophils, including IL-3, IL-4, IL-5, GM-CSF, TNF-α, and, perhaps, IL-13 [39]. An inducible NFAT-like factor has been found to cooperate with a constitutive GATA family member in mediating IgE-mediated stimulation of the human IL-5 promoter in a mouse mast cell line [40]. A 41-kD factor has been identified in an IL-3-dependent mouse mast cell line (CFTL15) by UV crosslinking to the mouse IL-4

promoter [41]. This factor is antigenically related to NFAT-1, but, unlike NFAT family members, is present in the nuclei of unstimulated cells and binds to DNA irrespective of the cell activation state [41].

We have recently detected an NFAT-1-immunoreactive protein by immunofluorescence staining of human basophils (manuscript in preparation). Like NFAT-1, this protein is constitutively expressed in the cytoplasm, while IgE- or Ca²⁺-mediated stimulation induces its translocation to the nucleus (fig. 2). This phenomenon occurs rapidly (within 5 min) and is typically blocked by cyclosporin A or FK506. However, translocation appeared to be transient, in that the protein spontaneously returned to the cytoplasm within 30 min. This is at significant variance with previous studies showing prolonged staining (>5 h) of nuclear NFAT-1 in T cells stimulated with ionomycin or anti-CD3 [42]. Taken together, these findings, summarized in figure 2, open the possibility that unique transcription factors contribute to basophil- or mast cell-restricted cytokine gene expression.

Arachidonic Acid Metabolism in Human Basophils and Mast Cells

Large quantities of arachidonic acid are stored in membrane glycerolipids of human mast cells and basophils. Upon cell activation, arachidonic acid is mobilized from the storage pools by different phospholipases and is converted to prostanoids by cyclooxygenases (COX) and to leukotrienes by 5-lipoxygenase (5-LO) [43]. The profile of eicosanoids generated by activated human mast cells and basophils has been extensively studied [44, 45]. Mast cells isolated from human lung, heart and gut tissues synthesize predominantly prostaglandin D₂ (PGD₂) and leukotriene C₄ (LTC₄) when challenged in vitro with IgE-mediated stimuli [46–48]. Skin mast cells produce PGD₂ but little or no LTC₄ [49]. In contrast, human basophils generate only LTC₄ when stimulated with IgE-dependent stimuli [50, 51]. Active secretion of LTA₄ has been shown in vitro in mast cells after stimulation [52]. The secretion of LTA₄ could provide a means for marked amplification of leukotriene formation at inflammatory sites. Endothelial cells and platelets containing LTC₄ synthase [53] can generate LTC₄ from mast cell- and neutrophil-derived LTA₄ [54].

The biochemical basis for the different profile of eicosanoids released by basophils and mast cells isolated from different anatomical sites is not known. However, our knowledge on the mechanisms of eicosanoid synthesis in mast cells and basophils has greatly extended in the last few years with the identification of novel enzymes and regulatory

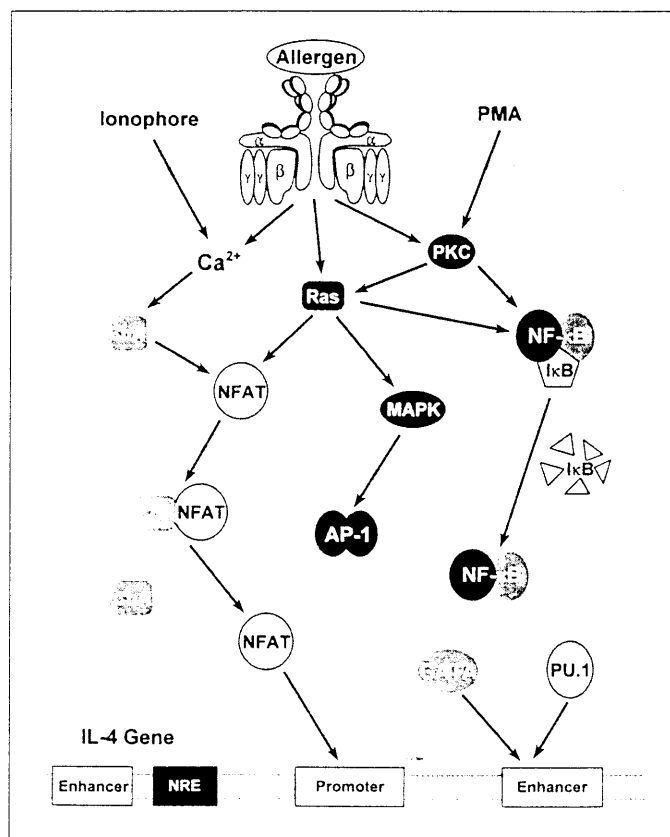


Fig. 2. Schematic representation of the signal transduction pathways leading to the induction of cytokine gene expression in basophils and mast cells. Stimulation of these cells via FcεRI cross-linking by multivalent allergen induces a cascade of intracellular signaling events leading to the activation of several DNA-binding factors. IgE-mediated signaling induces an increase in intracellular Ca^{2+} , resulting in activation of the phosphatase calcineurin (CnA). Dephosphorylation of NFAT family members by calcineurin induces their nuclear translocation. IgE-mediated signals also increase p21^{ras} (Ras) activity, which results in activation of the Erk, Frk, and Jnk kinases (MAPK) as well as nuclear translocation of NF- κ B. MAPK act to regulate the expression and function of Fos and Jun factors that activate transcription from AP-1, OAP, and some NFAT sites in several cytokine gene promoters. The activation of Ca^{2+} - and p21^{ras} -dependent pathways can be mimicked in part by simultaneous stimulation with PKC-active phorbol esters (PMA) and Ca^{2+} ionophores. However, Ca^{2+} - and calcineurin-mediated activation of NFAT appears to be sufficient for maximal IL-4 transcription in human basophils. Also shown is the contribution of PU.1 and GATA factors, shown to bind to a mast cell-specific enhancer located within the second intron of the murine IL-4 gene (see text).

molecules involved in arachidonic acid metabolism. The major discoveries in this area are schematically illustrated in figure 3. At least two major phospholipases A₂ (PLA₂) are involved in arachidonate mobilization in mast cells: a high-molecular-weight cytosolic PLA₂ (cPLA₂) and a low-

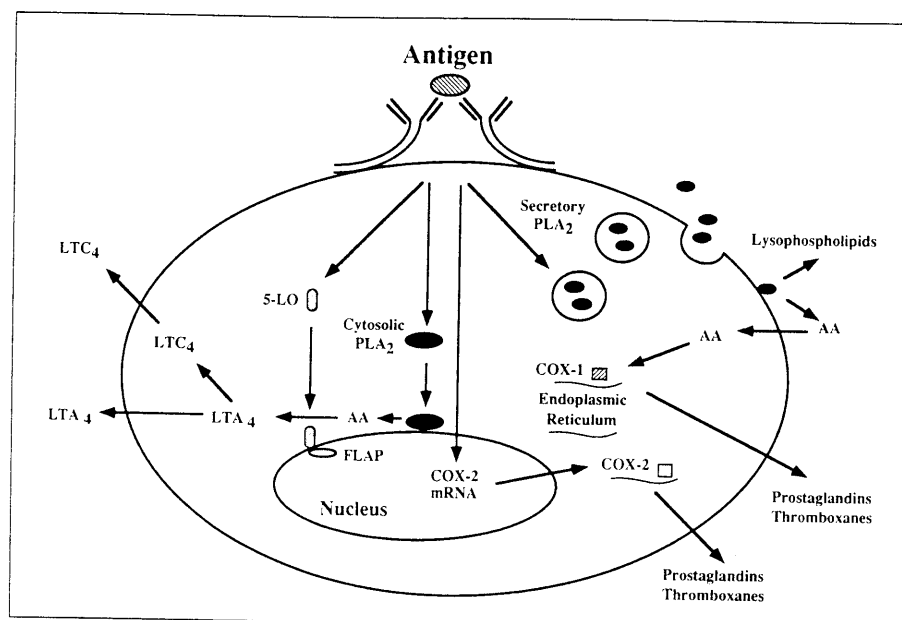
molecular-weight secretory PLA₂ (sPLA₂) [55, 56]. cPLA₂ is an arachidonate-selective PLA₂ activated by micromolar Ca^{2+} concentrations [57]. Upon translocation to the nuclear membrane, cPLA₂ generates free arachidonate that is mostly converted to leukotrienes. Two mechanisms of upregulation of cPLA₂ exist in mast cells activated by IgE-dependent stimuli: a rapid mechanism occurring within minutes after cell activation, based on phosphorylation mediated by MAP kinase, and a delayed mechanism based on transcription and expression of new enzyme molecules [58]. The latter mechanism requires several hours to be effective and is strongly modulated by cytokines [59].

PLA₂ is stored within cytoplasmic granules of quiescent mast cells [60] and is rapidly released when the cells are activated by immunological stimuli or by such cytokines as SCF. sPLA₂ is a non-arachidonate-selective enzyme and requires millimolar concentrations of Ca^{2+} , such as those found in the extracellular milieu, for its activation. sPLA₂ can be considered for many aspects a mediator of inflammation because (1) it is released in discrete amounts in the extracellular environment after immunological activation of mast cells [60]; (2) it can be measured in vivo in such inflammatory fluids as bronchoalveolar lavage fluid of asthmatic patients [61] and the synovial fluid of patients with rheumatoid arthritis [62] and (3) its administration reproduces signs and symptoms of inflammation [63]. Once released, sPLA₂ can hydrolyze phospholipids on the outer layer of cytoplasmic membrane of mast cells generating arachidonate that is mostly converted to prostanoids such as PGD₂. In addition, recent evidence suggests the presence of a specific membrane receptor for sPLA₂ on murine mast cells [64]. Activation of this receptor, which is blocked by heparin, induces the release of both preformed (histamine and proteases) and de novo synthesized mediators (eicosanoids). The existence of a sPLA₂ receptor on human mast cells has not yet been demonstrated.

Two other biochemical events related to arachidonic acid metabolism occur in activated mast cells: the translocation of 5-LO and the expression of the inducible COX (COX-2). 5-LO is a microsomal enzyme in resting mast cells. Cell activation results in the translocation of this enzyme to the nuclear membrane where it interacts with an 18-kD protein referred to as 5-LO-activating protein (FLAP) [65]. FLAP stabilizes the binding of 5-LO to arachidonate released from cPLA₂, the other enzyme translocating to the nucleus, generating LTA₄ and, subsequently, the other peptide leukotrienes.

COX-1 is the stable, constitutive isoform of cyclooxygenase in most human cells and is responsible for maintaining the physiological levels of prostanoids in the kidney, liver,

Fig. 3. Biochemical events related to arachidonic acid metabolism in activated mast cells. Interaction of antigen with membrane-bound surface IgE molecules induces: (1) secretion of sPLA₂, (2) phosphorylation and nuclear translocation of cPLA₂, (3) nuclear translocation of 5-LO, (4) interaction of 5-LO with FLAP on the nuclear membrane and (5) transient expression of COX-2. sPLA₂ acts on the external surface of mast cell producing arachidonate that is mostly converted to prostanooids. cPLA₂ produces arachidonate in close proximity to 5-LO, thus generating predominantly leukotrienes.



lung and gastric mucosa [66]. In contrast, COX-2 is not detectable in resting cells but its RNA transcription and protein expression is rapidly induced in activated inflammatory cells including mast cells [67]. Data obtained mostly in murine mast cells indicate that both COX-1 and COX-2 are responsible for prostanoid production in stimulated mast cells. Current evidence suggests that COX-1 is mainly responsible for prostanoid synthesis induced by IgE-dependent mechanisms, whereas COX-2 is the major source of prostanoids generated in response to cytokines [68, 69].

Mast Cell Proteases

In addition to histamine, all mast cells contain in their secretory granules several neutral proteases. The major mast cell protease, present in all human mast cells, regardless of subtype, is tryptase. Tryptase is a tetrameric trypsin-like serine protease of approximately 130 kD that is stabilized by heparin [70]. There are two genes coding for tryptase α and β . Tryptase is virtually absent from human basophils and thus appears to be an excellent marker of mast cell activation in vivo as well as in vitro [71, 72]. The average concentration of tryptase in human mast cells varies in the skin ($\approx 35 \mu\text{g}/10^6$ mast cells), heart ($\approx 20 \mu\text{g}/10^6$ mast cells), lung ($\approx 10 \mu\text{g}/10^6$ mast cells), and synovia ($\approx 5 \mu\text{g}/10^6$ mast cells) [73, 74]. Tryptase is a mitogen and comitogen for fibroblasts [75, 76] and tracheal smooth muscle cells [77]; it ac-

tivates collagenase [78], urokinase [79] and stromelysin [80]. Whether mast cell tryptase plays a role as a fibrogen or anti-fibrogenic agent remains to be defined.

Chymase is a monomeric chymotrypsin-like protease of 30 kD stored in the same secretory granules as tryptase and histamine. Some human mast cells contain both tryptase and chymase (MC_{TC}), whereas other mast cells contain only tryptase (MC_{T}) [81]. Recent studies indicate that most anatomical sites contain a mixture of MC_{T} and MC_{TC} . Thus, while MC_{T} predominates in the lung and small intestinal mucosa, MC_{TC} predominates in the skin, heart, synovia, and small intestinal submucosa [48, 74]. As a result, human mast cells cannot be classified as MC_{T} and MC_{TC} based on tissue location alone.

The enzyme activities of chymase, a chymotrypsin-like mast cell serine protease, include the activation of procollagenase [82], of gelatinase [83] and of IL-1 β to IL-1 [84], and the conversion of angiotensin I to angiotensin II [85]. Carboxypeptidase is a 35-kD metalloprotease present in mast cell granules that removes the carboxyterminal residues from a variety of peptides.

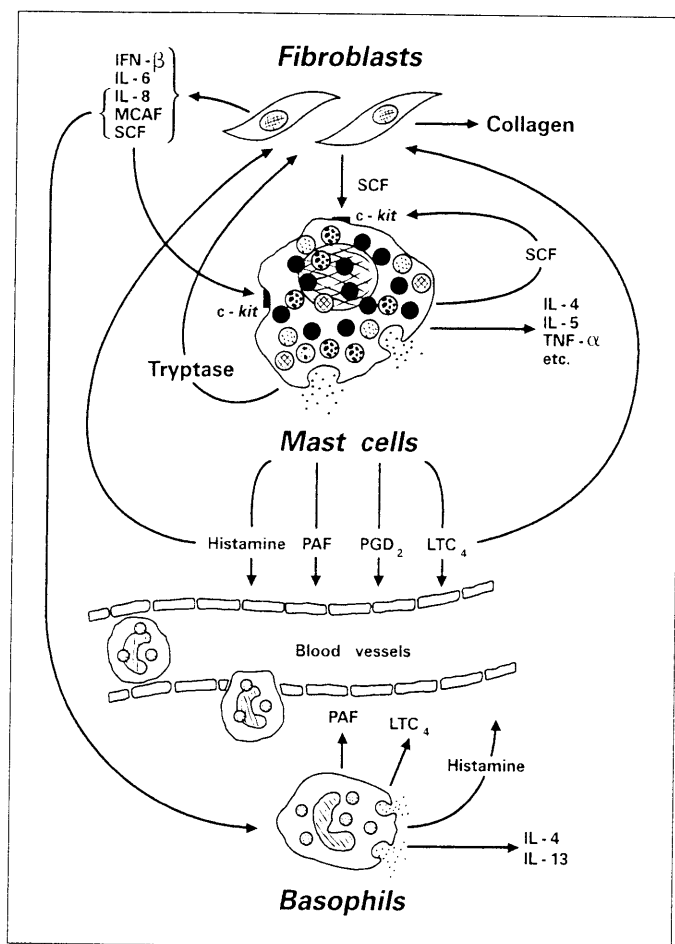


Fig. 4. Schematic representation of human mast cell-fibroblast interactions. Human mast cell activation by immunologic (antigen, anti-IgE, anti-FcεRI, C5a) or fibroblast-derived SCF results in the release of granule-stored mediators (histamine, tryptase, chymase, proteoglycans) and newly synthesized mediators (lipid mediators, cytokines). Chemical mediators released by mast cells affect blood vessels and can influence fibroblast properties (fibroblast proliferation, collagen production). In particular, tryptase, histamine, and peptide leukotrienes can activate fibroblasts to stimulate collagen synthesis, thus indicating a direct mast cell involvement in the fibrotic processes. Fibroblast-derived cytokines (IL-8, MCAF, SCF) can activate human basophils infiltrating inflamed tissues to release proinflammatory mediators and cytokines (IL-4 and IL-13). Stem cell factor contained in secretory granules of human mast cells can exert an autocrine effect on these cells.

Mast Cells and Basophils as Effector Cells of Allergic Inflammation

There is extensive evidence that mast cells, basophils and their mediators are primary effectors of allergic inflammation [86]. Several excellent reviews have extensively examined the role of mast cells, basophils and their mediators

in allergic disorders [87, 88]. Anatomical and functional evidence has supported the notion that basophils and mast cells play a major role in the pathogenesis of allergic diseases. Basophil infiltration has been found in the lung of patients who died from asthma [89], and increased basophil and mast cell releasability has been documented in patients with bronchial asthma and allergic rhinitis [90]. The mast cell is well established as a major initiating cell of the early phase of allergic responses [88]. IgE cross-linking by specific allergens or the activation of the different membrane surface receptors on human mast cells activates a complex series of biochemical events leading to the release of pre-formed (histamine, neutral proteases, secretory phospholipases), de novo-synthesized mediators (prostaglandin D₂, peptide leukotrienes, PAF) or cytokines that are responsible for most of the early events that characterize allergic reactions of the respiratory tract, intestine and skin. Infiltrating basophils contribute with eosinophils and other cells to the chronic inflammatory events of allergic disease [8–10]. The growing evidence that IgE cross-linking initiates synthesis and secretion of several cytokines by human basophils [22–24] and mast cells [29–31] supports the hypothesis that these cells play not only a proinflammatory but also an immunomodulatory role in allergic disorders.

Relevance of Heart Mast Cells in Allergic and Cardiovascular Diseases

Mast cells are present in human heart tissue and in the adventitia and intima of coronary arteries [18, 48, 91]. The concentration of histamine and the density of mast cells are significantly increased in the arteries of patients with cardiovascular diseases, and coronary arteries from these patients are hyperresponsive to histamine in vitro [92]. Serum IgE are increased in patients with coronary artery disease [93, 94]. These findings raise the possibility that local activation of cardiac mast cells might contribute, through the release of vasoactive mediators, to certain cardiovascular diseases [18, 95].

We have recently established a complex technique for efficient dispersion of mast cells from human heart tissue (HHMC) [48], and we have identified the immunologic and non-immunologic stimuli that induce heart mast cells to release vasoactive and proinflammatory mediators [48, 96]. Interestingly, HHMC appear to be the only type of human mast cells that can be activated by certain eosinophil cationic proteins (ECP and to a lesser extent MBP) [96]. This observation raises the possibility that in patients with chronic and acute hypereosinophilia, infiltrating eosinophils can

produce cardiac derangements through the release of vasoactive and proinflammatory mediators from HHMC caused by ECP and MBP.

Role of Mast Cells in Inflammatory and Fibrotic Disorders

Paul Ehrlich, the discoverer of mast cells, noticed the presence of mast cells in chronic inflammation – a process often including fibrosis [1]. The cells and the mediators responsible for fibroblast proliferation and collagen accumulation are, at least in part, unknown. Mast cells, normally found distributed throughout connective tissues, are involved in many types of chronic inflammation and are found in increased numbers in fibrotic tissues [1, 18, 97]. Mast cells also affect fibroblast activity through the release of tryptase [75, 76], histamine [98] and LTC₄ [99]. Thus, mast cell-fibroblast interactions may have a role in health and disease (fig. 4).

Increased numbers of mast cells are found in the synovial tissue and fluid of patients with chronic inflammatory arthritides [97], and these cells can be activated by many of the substances and neuropeptides found in inflammatory synovial fluid [74, 100]. Increased histamine and tryptase content and mast cell density are also found in the failing heart of patients with idiopathic dilated and ischemic cardiomyopathies, two conditions characterised by an increase in fibrous components [101]. Finally, increased mast cell density has been documented in the lesional skin of scleroderma patients [102] and in the lung of patients with bronchial asthma [103] or fibrotic lung disorders [104]. Scleroderma patients also showed enhanced basophil releasability compared to that of controls when challenged in vitro with IL-3 and anti-IgE [105].

Whether mast cells play a fibrogenic or antifibrogenic role in chronic inflammatory disorders remains to be determined.

Role of Mast Cells and Basophils in Bacterial and Viral Infections

A protective function for mast cells and their mediators has long been proposed on the basis of some worm infection models. Although human basophils possess surface receptor for formyl-containing bacterial peptides [106], no evidence existed as to the in vivo significance of mast cells in bacterial infections. Two recent reports have demonstrated that mast cells, which are selectively located at the portals of

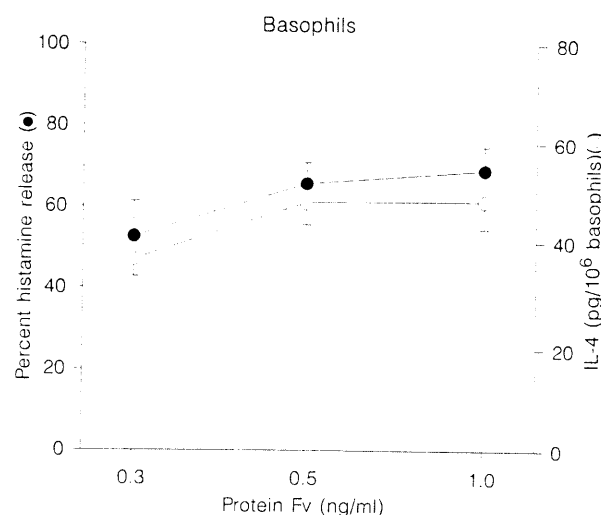


Fig. 5. Effect of increasing concentrations of protein Fv on histamine and IL-4 secretion from human basophils obtained from 5 normal donors. Values are expressed as the mean $\pm$ SEM.

bacterial entry, are important to host defense [107, 108]. Mast cell-deficient mice (W/W^V) are significantly less efficient than normal +/+ littermates in clearing enterobacteria and this phenomenon is, at least in part, due to decreased TNF- α production [107, 108]. Moreover, leukotriene-deficient mice manifest enhanced lethality from *Klebsiella pneumoniae* [109]. These results revealed a previously unrecognised role of mast cells in bacterial infections.

It is important to note that such bacterial factors as pepstatin A [106, 110], type I fimbriae of *Escherichia coli* [111], protein A of *Staphylococcus aureus* [112, 113], protein L of *Peptostreptococcus magnus* [114] can activate human basophils and/or mast cells through different immunologic mechanisms. Interestingly, such viral products as gp 120 of HIV and protein Fv, in vivo induced during viral hepatitis, can also activate human basophils and mast cells to release proinflammatory mediators and immunoregulatory cytokines [72]. Recently, in collaboration with Jean-Pierre Bouvet we have found that protein Fv, which is an endogenous superantigen released in vivo in patients suffering from viral hepatitis [115], stimulated not only the release of histamine from purified peripheral blood basophils, but also the de novo synthesis of IL-4 (fig. 5).

Taken together, these observations suggest that mast cells that are located near surfaces exposed to the external environment, can play a not yet explored role(s) during viral and bacterial infections.

Immunopharmacology of Human Basophils and Mast Cells

Numerous studies have focused on the *in vitro* and *in vivo* effects of drugs that modulate the release of preformed and *de novo* synthesized mediators from human basophils and mast cells isolated from different tissues [73, 100, 116–118]. Significant differences have been documented: (a) between mast cells and basophils as regards the pharmacological agents and the mediators they produce; (b) between mast cells isolated from different anatomical sites, and (c) between compounds of the same pharmacologic class. In addition, this approach has significantly contributed to clarifying the biochemical mechanisms by which these cells release mediators in response to immunologic and nonimmunologic stimuli [95, 111–114].

Concluding Remarks

In this brief review we have touched on some recently elucidated aspects of human mast cell and basophil molecular and cellular biology and immunology. The availability of sufficient numbers of human basophils and mast cells isolated from different tissues is paving the way to the characterization of the molecular and biochemical aspects of these cells that have intrigued immunologists since their original discovery. It is now evident that in man these two

types differ biochemically, immunologically and pharmacologically and play different roles in allergic and inflammatory reactions.

It is now becoming increasingly evident that basophils, mast cells and their mediators participate not only in inflammation associated with allergic disease, but in chronic and fibrotic disorders affecting several organs. Mast cells and basophils presumably play a role in host defense against bacterial and viral infections. Mast cells could also be involved in the formation and progression of atherosclerotic lesions and different cardiomyopathies. These cells, directly or through mediator generation, affect the function of different cells in inflammatory arthritides.

Yet the fundamental question remains: do mast cells and basophils play a prominent proinflammatory and immunoregulatory role or do they help to orchestrate protective host inflammatory responses in different pathological conditions?

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