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The Human Lung Mast Cell

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Mast cells are present in human lung tissue, pulmonary epithelium, and free in the bronchial lumen. By virtue of their location and their possession of specific receptors for IgE and complement fragments, these cells are sentinel cells in host defense. The preformed granular mediators and newly generated lipid mediators liberated upon activation of mast cells by a variety of secretagogues supply potent vasoactive–spasmogenic mediators, chemotactic factors, active enzymes, and proteoglycans to the local environment. These factors acting together induce an immediate response manifest as edema, smooth muscle constriction, mucus production, and cough. Later these mediators and those provided from plasma and leukocytes generate a tissue infiltrate of inflammatory cells and more prolonged vasoactive–bronchospastic responses. Acute and prolonged responses may be homeostatic and provide for defense of the host, but if excessive in degree or duration may provide a chronic inflammatory substrate upon which such disorders as asthma and pulmonary fibrosis may ensue.

Introduction

The mast cell was identified in 1877 by Ehrlich as a cell capable of binding basic dyes and of staining metachromatically (*1*). Evidence accumulated in recent years suggests the mast cell has the capacity to profoundly affect the microenvironment in response to its interaction with a wide variety of potentially toxic materials. Although the precise role of this cell remains an issue of intense interest, the knowledge of the functional capabilities and constituents of the mast cell provide the rationale for assigning it a role in pulmonary defense and pathobiology.

Location, Development and Structure of Mast Cells

Mast cells are found in lung tissue in concentrations of 1–10 $\times$ 10^6 cells/g. (*2*). They are prominent in loose and dense connective tissues (*3*) such as the pleura, peribronchial regions and alveolar septa adjacent to nerves and blood vessels, particularly small arterioles and venules, and in upper and lower respiratory epithelium (*4*) and free in the bronchial lumen (*5,6*). Increased numbers of mast cells have been identified in humans in conditions of excessive pulmonary blood flow and chronic left ventricular decompensation (*7*), and in association with pulmonary fibrosis (*8*), whereas in chronic hypoxic states proliferation of mast cells has been noted in rats (*9*).

Although mast cells are prominent in bone marrow where their number correlates with that of lymphocytes (*10*) their origin is from pleuripotential stem cells. Mast cells develop in long-term tissue cultures of lymphoid cells from thymus, spleen or lymph nodes on fibroblast feeder layers (*11,12*). In addition, monolayers of rat thymus, rat embryo or mesenchymal cells from rat retina may develop mast cells in the absence of fibroblasts, suggesting that mast cells develop from a widespread primitive mesenchymal precursor. Regulation of mast cell proliferation may thus be regulated by both neuroectodermal factors (*13*) and T-lymphocytes (*12*). In rodents, mast cells divide and increase in number throughout fetal and neonatal life (*14*), but mitoses are rare later (*15*). It is uncertain how mast cells come to be situated in the lung at various sites at which they can be found; presumably, precursor mesenchymal mastoblasts differentiate locally, however, migration of mast cells through tissue may occur in some disorders (*16*). Individual mast cells are long-lived, persisting for up to one-third of the total life span in rats, and the size of the mast cell increases as the animal ages (*17*).

Mast cells are large, measuring 10 to 15 μm in diameter with the usual cellular organelles including a nucleus, one or two nucleoli, mitochondria, Golgi apparatus, ribosomes and endoplasmic reticulum. In addition, these cells possess a ruffled membrane (*18,19*) and 50 to 200 individually membrane bound secretory granules (0.5–0.7 μm diameter) to which, in the human, are apposed numerous intermediate-sized filaments (*20*). The secretory granules of the human mast cell possess a definite subgranular architecture dominated by repeating subunits of electron density 750 and 1500 mu apart

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which give the granules a scroll or whorl-like appearance (*20–22*). Microtubules have not been identified in human mast cells.

Activation of Mast Cells

A variety of agents have been demonstrated to cause mast cells to release their granules, as defined histologically or by the measurement in tissue or fluid of mast cell constituents. Mast cell degranulation in cells of tissues has been induced by IgE-dependent mechanisms and, in addition, by divalent cation ionophores (*23,24*), highly charged amines (*25*), ATP (*26*), anaphylatoxins C3a and C5a (*27*), enzymes such as chymotrypsin and phospholipases (*28*), divalent cations (*29*), cationic peptides and enzymes from inflammatory leukocytes (*30*), drugs such as morphine and curare (*31*), endotoxin (*32*), fragments of ACTH (*33*), synthetic peptide chemotactic factors, complex carbohydrates (*34*), and environmental pollutants such as NO_2 (*35*).

Activation of mast cells is thought to occur in a non-cytolytic secretory process induced by binding of activating substances to specific receptors on the mast cell membrane. This process has been most extensively studied in the rat mast cell which can be purified to homogeneity. In this cell, bridging of two cell bound IgE molecules by specific antigen or by antibody to either IgE or to the cell membrane receptor for IgE is sufficient to induce cell activation (*36*). Similiar mechanisms dependent upon IgE have been demonstrated to activate dispersed human lung cells in suspension (*37*) or enriched populations of human lung mast cells (*2*, *20*). The action of other moieties such as C3a, C5a, and chemotactic peptides are also presumed to be consequent to their ability to bind to and alter specific membrane receptors. Following binding there is an opening of membrane channels for Ca^{2+} ions, and an influx of this ion occurs, perhaps in exchange for monovalent cations. Inhibition of calcium flux or removal of this ion from the medium prevents degranulation. In association with calcium fluxes, there is intracellular granule swelling and dissolution accompanied by intermediate filament organization at the granule periphery (*20*), granule to granule membrane fusion, fusion of granular to plasma membranes (*38*), and eventually the development of membrane discontinuities exposing the partially solubilized granules to cation exchange (*39*).

Biochemical Regulation of Mast Cell Activation

The biochemsitry of mast cell activation has been derived primarily from studies with rat mast cells or from mast cell rich tissues in the human including lung fragments (*40*) or cells (*37*), partially purified human lung mast cells (*2*), nasal polyps (*41*), and skin (*42*). While mixed cell sources can provide insight into the overall effects of mast cell activation the precise role of the mast cell requires study of nearly pure cell populations. As this has only been achieved to date utilizing rat mast cells the insights gained from this model will be presented and, where relevant, the findings in human systems described.

The regulation of mast cell activation was shown to involve the nucleotide cyclic 3′5′-adenosine monophosphate (cAMP) more than 10 years ago (*40*). A series of investigations followed which demonstrated that agents which elevated levels of cAMP (PGE_2, B-adrenergic agonists, cholrea toxin, dibutyl cAMP) or prevented its degredation (methylxanthine) inhibited mediator release in lung cells of tissues; whereas agents which lowered the concentration of the nucleotide ($PGF_{2\alpha}$, alpha-adrenergic agonists) augumented mediator release (*43*). However, subsequent studies employing purified rat mast cells provided data which cast the role of cAMP into some doubt. Thus some mast cell secretagogues increased, while other decreased cAMP levels (*44*). In addition, theophylline inhibited mediator release even at concentrations insufficient to prevent cAMP degradation, while PGD_2 and 3-isobutyl-1-methylxanthine (IBMX) enhanced mast cell cAMP accumulation, and the later agent even augumented mediator release (*45*). These contradictory findings have been partially clarified by the finding that activation of rat mast cells leads to two sequential elevations in cAMP, the first occurring 15-30 sec after stimulation, and the second 90-220 sec later. The second peak can be inhibited by indomethacin and is secondary to mast cell released mediators, whereas the first is intimately associated with the secretory process (*46*). The finding that adenosine enhanced histamine release from rat mast cells led to the finding that analogs of this nucleotide were capable of altering the early peak in cAMP. Thus purine modified analogs of adenosine enhance immunologically induced early increases in cell cAMP and enhance histamine release, whereas ribose modified analogs inhibited both phenomena (*47*).

Consequent to cAMP elevation is the utilization of a cAMP dependent protein kinase (*48*), phosphorylation of intracellular proteins (*49*) and granule release. Taken together these data suggest that mast cell activation and mediator release is dependent upon activation of adenylate cyclase and increase in cell cAMP. Agents which act to augment cyclic AMP and also inhibit mediator release presumably do so by affecting concentrations of key intermediates (such as the cAMP dependent protein kinase) in a manner which prevents their effective utilization during cell activation by secretagogues.

A parallel event in mast cell activation is that of lipid methylation. Within seconds of activation, three methyl groups may be transferred to phosphatidylethanolamine to generate phosphatidylcholine. The initial methylation occurs at the inner aspect of the plasma membrane,

whereas the latter two are at the outer membrane surface. Agents capable of inhibiting methylation inhibit mediator release and also block Ca^{2+} uptake by the activated cells (*50*). Lipid methylation is associated with increases in membrane fluidity and perhaps in regulating activity of a putative calcium channel (*51*). The calcium ionophore A23187 does not require a calcium channel as it directly induces Ca^{2+} influx, and this secretagogue does not augment lipid methylation (*52*). It is of great interest that inhibitors of lipid methylation prevent mediator release but do not alter early cAMP increases, and conversely inhibitors of early cAMP accumulation prevent mediator release, but not lipid methylation (*53*).

Other lipid alterations also occur consequent to mast cell activation. Diacylglycerol, a potent fusogen, is generated following the action of a putative phospholipase C upon membrane phospholipids (*54*) and there are rapid increases in turnover of phosphatidic acid, arachidonic acid, phosphatidyl inositol and phosphatidyl ethanolamine. The liberation of arachidonic acid and its metabolism appears critical to degranulation. Indomethacin, which inhibits the cyclooxygenase pathway of arachidonic acid metabolism may enhance mediator release, whereas inhibitors of both lipoxygenase and cyclooxygenase dependent pathways of arachidonate metabolism inhibit mediator release. Hydroperoxides of various lipids including those of arachidonate enhance mast cell mediator release (*55*). Arachidonic acid may be liberated from mast cell lipids by phospholipase A2 active on intact phospholipids or by diacylglycerol lipase action on diacylglycerol.

Other steps in cell activation have been postulated. The role of microtubules, microfilaments, and other cytoskeletal elements have been proposed. Direct evidence for the existence of intermediate filaments have been obtained in human lung mast cells (*20*), and these structures become closely associated with the cell and granule membrane during activation. Microfilament participation has been suggested by the inhibitory effect on mediator release of cytochalasin B, but the concentrations required to demonstrate this effect are far in excess of those needed to affect microfilaments in other tissues (*56*). The participation of a serine esterase in cell activation has been postulated (*57*) and questioned (*58*).

Mast Cell Mediators

The activation of mast cells leads to the release of preformed granule-associated molecules and to the generation and release of other, unstored, materials. In toto, these complex, biologically active molecules termed mediators may best be classified as to their biological effects. Thus, mast cell related materials with vasoactive, smooth muscle reactive properties (Table 1), with chemotactic potential (Table 2) as well as active enzymes and structural proteoglycans (Table 3) have been recognized.

Mediators Acting on Smooth Muscle and Vasculature

Histamine

The first mast cell mediator identified, histamine (β-imidazolylethylamine), is formed by the action of histadine decarboxylase upon the amino acid histidine. The amine, in amounts of 10 to 30 $\mu g/10^6$ cells in the rat (*59*) and 1 to 5.5 $\mu g/10^6$ mast cells in the human (*2*), is stored preformed in the granules where it is bound to proteoglycan, or protein carboxyl residues. Histamine content of human lung approximates 10 to 20 $\mu g/g$. Catabolism of histamine proceeds via two pathways (*60*) both active in lung (*61*). The majority (46-55%) is transformed to 3-methylhistamine by the action of imidazole-*N*-methyl transferase. A remaining 25-34 percent of histamine is oxidized to imidazole acetic acid, and its riboside, by the action of diamine oxidase. The remainder, 2 to 3%, is excreted unchanged in the urine.

Histamine induces contraction of airway smooth muscle (*62*), resulting in increased resistence and diminished compliance (*63–65*). The amine also causes increased mucous secretion, pulmonary vasoconstriction and induces bronchial venular leakage resulting in pulmonary edema (*66*). Transient increases in heart rate and cardiac output, as well as slowed A-V conduction, follow its injection (*67,68*).

Histamine exerts its effects on lung by interacting with two cell membrane-associated receptors termed H1 and H2 (*69*). The interaction of histamine with those receptors has been assessed employing analogs with selective H1 (2-methylhistamine) or H2 (4-methylhistamine) action, or by the use of specific H1 or H2 inhibitors. H1 blocking agents comprise the so-called classical antihistamines whereas the H2 inhibitors include only the closely related metiamide, burimimide and cimetidine. Both H1 and H2 receptors are present in human lung (*70*), and analysis of the role of each in the effect of histamine indicates that pulmonary vasoconstriction, bronchial smooth muscle contraction, and systemic vasodepression are H1 effects (*67*), whereas H2 activation is associated with pulmonary vasodepression, augmentation in cardiac output and heart rate (*67*), and inhibition of anaphylaxis (*71*). The latter effect is thought secondary to histamine induced inhibition of mediator release secondary to cAMP elevation (*72,73*). Histamine also mediates the wheal and flare response in skin due to its ability to cause venular disconnections (*74*), and causes pain and itch (*75*). Cutaneous edema resists H1 and H2 blockage and may reflect histamine induced $PGE_2\alpha$ generation (*76*). In addition, histamine can modify the action of a variety of inflammatory cells. Thus by H2 induced accumulations

Table 1. Vasoactive mediators.

Mediator	Structural characteristics	Function	Inhibition	Inactivation
Histamine (mast cells)	β-Imidazolyl-ethylamine, MW 111	Contraction of smooth muscle Increase of vascular permeability Stimulation of suppressor T-lymphocytes (H_2) Generation of prostaglandins Enhancement of (H_1) or inhibition (H_2) of chemotaxis Elevation of cAMP (H_2) and cGMP (H_1) Increase mucus production	H_1 and H_2 antihistamines	Histamine (diamine oxidase) or Histamine *N*-methyl transferase
SRS-A (Neutrophils monocytes ?mast cells)	Leukotrienes C = 5 (S)-OH-6 (R)-*S*-glutathionyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid	Contraction of smooth muscle Increased vascular permeability Synergistic with histamine Generation of prostaglandins Vasodepressor Cutaneous Vasoconstriction (C)	FPL-55712	Arylsulfatases A and B Peroxidases Lipoxygenase Peroxides
	D = 5-(S)-OH-6(R)-S-cysteinylglycyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid E = 5(S)-OH-6(R)-S-cysteinylglycyl-7,9-*trans*, 11,14-*cis*-eicosatetraenoic acid	Vasodilatation (D,E)		
Serotonin (platelets)	5-OH-tryptamine, MW 182	Contraction of some smooth muscle Increased vascular permeability	Hydroxyzine Cyproheptadine lysergic acid	Monoamine oxidase
PAF (neutrophils monocytes ?mast cells)	1-O-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine	Release of platelet amines Platelet aggregation Sequestration of platelets Vasodepression Bronchospasm Increased vasopermeability	Unknown	Phospholipases
Prostaglandins D_2 (mast cells)	C-20 fatty acids	Contraction of smooth muscle Vasodepressor Elevation of cAMP	Synthesis blocked by nonsteroidal anti-inflammatory agents	Specific dehydrogenases
E_2 "		Lower cAMP, contract smooth muscle		
I_2 "		Elevate cAMP, inhibit platelet aggregation, contract smooth muscle		
Thromboxane A_2 Many		Contract smooth muscle, stimulate platelet aggregation		
Endoperoxides " (G_2, H_2)		Contract smooth muscle		

of cAMP or prostaglandin F 2α the amine inhibits eosinophil, neutrophil and basophil leukocyte chemotaxis (*77,78*) and activates suppressor lymphocytes (*79*), while (perhaps by its ability to augment cGMP levels) H1 actions enhance cell motility (*80*). Histamine also inhibits lymphocyte mediated cytotoxic responses (*81*) and activates suppressor cells.

Platelet Activating Factor (PAF)

Platelet activating factor (PAF) was first described as an activity which was generated during anaphylaxis in the rabbit (*82*), capable of aggregating rabbit platelets and releasing their stored amines. PAF has been identified structurally as 1-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine (*21*). This mediator is generated by rabbit basophils after IgE-dependent activation but, in the human, neutrophilic polymorphonuclear leukocytes appear to be the source (*83*). In addition, mononuclear leukocytes (*84*), kidney, and spleen (*85*) can generate this principle. Direct evidence for PAF generation by mast cells or during anaphylactic reactions in human tissue is lacking. In human skin, synthetic PAF has been demonstrated to cause a wheal-and-flare reaction when concentrations as low as $10^{-11}M$ are injected (*86*). In animals, PAF causes hypotension, pulmonary mechanical alterations (*87*), is a cardiac depressant, and induces the aggregation and sequestration of platelets into lung and skin, as well as causing circulating neutropenia and basopenia (*88,89*). *In vitro* destruction of PAF can be mediated by a specific acetyl hydrolase (*90*), and by phospholipases C and D (*91*).

Serotonin (5-HT)

In the human, serotonin is synthesized by sequential hydroxylation and decarboxylation of the amino acid trytophan (*92*), and is then degraded in plasma or tissue

Table 2. Chemotactic mediators.

Mediator	Structural characteristics	Function	Inhibition	Inactivation
ECF-A (mast cell)	Val/Ala-Gly-Ser-Glu MW 360-390	Chemotactic attraction and deactivation of eosinophils and neutrophils	Gly-Ser-Glu Val-Gly-Ser	Amino-peptidase Carboxy-peptidase A
ECF-oligopeptides (mast cell)	Peptides, MW 1300-2500	Chemotactic attraction and deactivation of eosinophils Chemotactic attraction of eosinophils and mono nuclear leukocyte deactivation of eosinophils	Unknown	Unknown
NCF (?mast cell)	Neutral protein, MW > 750,000	Chemotactic attraction of deactivation of neutrophils	Unknown	Unknown
Lipid chemotactic factors (unknown)	HHT (C_{17} fatty acid) HETE (C_{20} fatty acid) Leukotriene B Oxidized arachidonic acid	Chemotactic attraction of neutrophils and eosinophils Chemokinesis of neutrophils Deactivation of neutrophils	ETYA (HHT, HETE, and leukotriene B) Nonsteroidal anti-inflammatory agents (HHT)	Specific dehydrogenases
Histamine (mast cells)	β-Imidazolyl-ethylamine, MW = 111	H_1 chemotactic and chemokinetic activation of eosinophils H_2 chemotactic and chemokinetic inhibition of neutrophils and eosinophils	H_1 and H_2 antihistamines	Histaminase (diamine oxidase) or Histamine N-methyltransferase

Table 3. Mast cell enzymes and proteoglycans.

Mediator	Structural characteristics	Function	Inhibition	Inactivation
Proteoglycans				
Heparin (preformed)	Proteoglycan MW 60,000	Anticoagulation Antithrombin III interaction Inhibition of complement activation Liberation of lipoprotein lipase and phospholipase	Protamine	Heparinase
Enzymes				
Arylsulfatase (preformed)	Proteins, MW = 100,000 (A) 60,000 (B)	Hydrolysis of SRS-A and various sulfate esters	PO_4, SO_4 product, substrate	Unknown
N-Acetyl-β-D-glucosaminidase	Proteins, MW = 158,000	Cleavage of glucosamine	Product	Unknown
Tryptase (kallikrein) anaphylaxis	Protein, MW ≅ 400,000	Proteolysis with tryptic specificity Cleavage of kinin from kininogen Cleavage of Hageman factor	Tryspin inhibitors	Unknown
β-Glucuronidase	Protein, MW ≅ 300,000	Cleavage of glucuronide conjugates	Product	Unknown
Superoxide dismutase	Protein	Cleavage of O_2^-	Unknown	Unknown
Myeloperoxidase	Protein	Cleavage of H_2O_2	Unknown	Unknown

by monoamine oxidase (*93*). The human platelet, but not the mast cell, takes up and stores this amine in its dense granules from which it may be liberated by the action of PAF and other secretagogues. The blood platelet content of serotonin is 0.1 to 0.2 ng/mL (*94*). Serotonin is a vasoconstrictor but is a relatively ineffective agonist upon human pulmonary vasculature or bronchial smooth muscle.

Oxidative Products of Arachidonic Acid

Arachidonic acid, a C_{20} fatty acid with four double bonds, is a prevalent fatty acid in mammalian membrane phospholipids. It is liberated from intact phospholipids by the action of phospholipase A_2 or from diacylglycerol by the action of diacylglycerol lipase. The phospholipase A_2 mediated liberation of arachidonic acid from phospholipids is inhibited by glucocorticoids (*95*), possibly due to steroid induced synthesis of macrocortin (*96*), a phospholipase A_2 inhibitor. Once liberated, the metabolic fate of arachidonic acid is extremely variable, with many potential end products known. However, each cell generates only a few selected metabolites. Two major enzymes, lipoxygenase and cyclooxygenase, regulate the fate of arachidonic acid.

Cyclooxygenase. The action of cyclooxygenase, an enzyme inhibitable by aspirin and other nonsteroidal anti-inflammatory drugs, generates the cyclic endoperoxides, PPG_2 and PGH_2 (*97*). These, in turn, are substrates for other enzymes which generate prostacycline (PGI_2), PGE_2, $PGF_{2\alpha}$, PGD_2, HHT, and thromboxane A2 (*98*). Many of the cyclooxygenase products have potent effects on smooth muscle and vasculature. The cyclic endoperoxides, PGG_2 and PGH_2,

and thromboxane A2 are vasoconstrictors (*99*), whereas PGI_2 is a potent vasodilator (*100*). PGI_2 is the major prostaglandin product in blood vessel walls, and may be relavent to the development of edema and erythema directly and also by its ability to potentiate the edema and erythema induced by other inflammatory mediators, such as bradykinin (*101*). PGE_2 and PGD_2 are potent molecules capable of inducing edema, erythema, vasodepression, vasodilatation, and smooth muscle contraction (*102*), however PGE_2 is a bronchodilator (*102*). $PGF_2\alpha$, a potent bronchoconstrictor, is thought also to augment vasopermeability. The isolated cell of the human and rat generates only PGD_2 upon immunologic stimulation (*103*), and patients with mastocytosis have been reported to excrete large quantities of a PGD_2 metabolite in their urine (*104*).

Lipoxygenase. The initial product of lipoxygenase action on arachidonic acid is hydroperoxy eicosatetraenoic acid. This is then further metabolized to a series of monohydroxy eisosatetraenoic acids (HETEs) or to the leukotrienes (*105*). Leukotriene C is a glutathionyl (Gys-Gly-Glu) derivative of leukotriene A, whereas D lacks the terminal glutamine residue and E the terminal glycylglutamyl residues (*106,107*). All are bronchoconstrictors in nanogram amounts, and C and D are systemic vasodepressors (*106*). Leukotriene C is a vasoconstrictor, whereas D is a vasodilator. The sequential conversion of the leukotrienes from C to D to E is likely, with leukotriene D the most potent of the three is most assay systems. These molecules comprise what has heretofore been termed slow-reacting substances of anaphylaxis (SRS-A).

Rat mast cells have been demonstrated to generate leukotrienes upon calcium ionophore-induced activation, and release of these molecules induced by immunologic secretagogues has been demonstrated in the guinea pig and human lung mast cells. As IgE activation in lung tissue (*40*) and cells (*37*) is associated with SRS-A production, but SRS-A generation may decrease as mast cells are purified (*2*), it is possible that other cell types also generate these products for export. Inhibitors of lipoxygenase activity (such as ETYA) inhibit histamine release, and it is conceivable that the major site of action of mast cell lipoxygenase products is within the cell.

Bradykinin

A nonpeptide cleaved from kininogen by kallikrein, bradykinin has potent activity on smooth muscle and alters vascular permeability. Direct evidence for its generation in human disease, particularly mast cell-dependent processes, however, is lacking. Bradykinin is a vasoconstrictor but in humans can cause hypotension due to peripheral arterial dilatation. In addition, it increases vascular permeability. Bradykinin is rapidly inactivated and its half-life in serum is less than 60 sec. Although the presence of bradykinin in tissue extracts in disease has been reported, the rapid turnover of this molecule and the ease of its generation following tissue extraction make interpretation of these reports difficult.

Chemotactic Mediators

Eosinophil Chemotactic Factor of Anaphylaxis (ECF-A)

ECF-A is released immunologically from mast cell-rich tissues and rat and human mast cells where it is stored preformed in the granules (*108*). Two tetrapeptides of the sequence Val or Ala-Gly-Ser-Glu have been extracted from whole human lung and demonstrated to possess many of the properties of ECF-A (*109*). ECF-A, as a less well characterized eosinophilotactic activity from other sources, is defined as a chemotactic activity of 300 to 700 daltons, susceptible to proteases, and which is highly acidic (*110*). ECF-A attracts eosinophils into skin *in vivo* (*111*) as well as through micropore chambers *in vitro* and is a potent chemotactic deactivator (*108*). ECF-A increases the number of eosinophil membrane receptors for C3b and C4 (*112*).

ECF-Oligopeptides

Molecules of 1000-3000 daltons with chemotactic activity for eosinophils have been identified preformed in rat mast cells and are released from them following immunologic activation (*113*). These presumptive peptides are heterogeneous. Molecules of similiar molecular weight and activity have been extracted from whole human lung (*114*).

High Molecular Weight Neutrophil Chemotactic Factor (HMW-NCF)

A factor of high molecular weight chemotactic for neutrophils is extracted from human lung tissue (*114*) and rat mast cells (*115*) and is present in serum of patients after experimental induction of IgE-dependent bronchospasm (*116*) or cold urticaria (*117*). The molecule from the latter source has a mass in excess of 600,000 daltons, a neutral isoelectric point, and in addition to chemotactic activation, it is able to deactivate neutrophils.

Histamine

Histamine is capable of modulating random and directed migration of both neutrophils and eosinophils. At low doses, histamine augments these responses by an H1 action, whereas at higher concentrations an inhibitory H2 effect predominates (*77, 80*). Histamine is capable of augmenting eosinophil C3b receptors (*112*).

Arachidonic Acid Metabolites

Although none of the products generated from arachidonic acid by mast cells has been shown to be chemotactic, a wide variety of arachidonate metabolites

are potent chemotactic factors. A cyclooxygenase product HHT (*118*) as well as some lipoxygenase products, including the family of monohydroxyeicostaetranoic acids (HETEs) (*119*), and leukotriene B_4 (*120*) are chemotactic for neutrophils, and 5-,8- and 11-HETE possess activity for eosinophils.

Other Chemotactic Factors

Uncharacterized lipids (*121*) and PAF have also been shown chemotactic for neutrophils.

Active Enzymes

Proteases

The granules of the rat mast cell contain a single-chain active chymotryptic protease of molecular weight 25,29,000 (*122*). In human mast cells, no chymotryptic enzyme is present, and instead a tryptic protease termed kallikrein has been identified. This enzyme, or family of enzymes, has been found in populations of human lung mast cells (*123*), and in anaphylactic diffusates of human lung (*124*). Little is known of the specificity, inhibitor profile, or total cellular content of mast cell tryptic proteases. The activation of Hageman factor and cleavage of bradykinin from kinonogen may be expected consequence of release of this enzyme.

Other Lysosomal Proteases

Human lung mast cells have been demonstrated to contain and release arylsulfatase, β-glucuronidase, and hexosaminidase after immunologic activation (*123*), while rat mast cells possess these enzymes, an amino peptidase and other acid hydrolases (such as β-D-galactosidase) with specificity for carbohydrate moieties (*125,126*), peroxidase (*127*), superoxide dimutase and superoxide generating enzymes (*128*).

Structural Proteoglycans

Rat and human mast cell granules contain proteoglycan heparin of high molecular weight (*129,130*) rich in N and O sulfated sugars. Heparin release from rat mast cells have been demonstrated but lags behind that of histamine due to its relative insolubility (*126*). Heparin can inhibit classical and alternative pathways to complement activation (*131,132*), and activates many enzymes due to its ability to interact with antithrombin III (*133*). In addition, heparin can liberate lipoprotein lipase and phospholipase (*134*), and induce lymphocytosis (*135*).

Role of Mast Cells and Mast Cell Mediators in Disease

The most compelling evidence for the role of mast cells and mediators derives from experiments in skin in which mast cell activation was induced by specific antigen. The participation of other immunologic classes, and thus other potential inflammatory pathways, was excluded in these experiments by use of purified antigen-specific IgE and passively sensitized non-allergic hosts (*136*). Injection of specific antigen to such passively sensizited hosts induced mast cell activation and a clinical response described as a dual phase reaction (*136,137*). The initial phase is characterized clinically by a wheal-and-flare beginning in minutes, persisting several hours, which is histologically represented by mast cell degranulation, dermal edema, and endothelial cell activation. After 4 to 12 hr a large inflammatory, indurated lesion develops which persists for 18 to 24 hr and which is represented histologically by edema, infiltration of the dermis by neutrophils, eosinophils, basophils, lymphocytes, and mononuclear leukocytes, and in some instances hemorrhage, blood vessel wall damage, and fibrin deposition of sufficient severity to warrant the diagnosis of vasculitis (*136*). The mediators responsible for these pathophysiologic manifestations have not yet been identified; however, they can be surmised by their known effects as isolated mediators. Thus, the initial phase is most likely due to the concerted action of the vasoactive mediators. The effect of these mediators to induce edema and alter blood flow may also permit the localization in tissue of immunoglobulin, complement, and the proteins of the clotting, fibrinolytic, and kinin generating pathways. These proteins acting together with the chemotactic factors may well be responsible for the later inflammatory phase seen in the skin. Vasculitis may well reflect the hydrolytic action of infiltrating leukocyte lysosomal enzymes, but may also be due to direct action of the mast cell acid hydrolases.

No studies of such elegance, employing lung tissues, have been reported. However, early and late bronchospastic responses to antigen have been recorded in humans. As both pulmonary responses may be inhibited by the mast cell active agent disodium cromoglycate (*138*) while only the latter is inhibited by corticosteroids it is reasonable to suggest similiar mast cell dependent inflammatory pathophysiologic alterations can occur in lung.

Mast Cells and Mediators in Pulmonary Responses to Toxic Agents

There is little direct evidence implicating or ruling out the participation of mast cells and/or mediators in the response of the lung to toxic materials, save for the extensive body of knowledge concerning IgE-dependent responses to airborne allergens. More narrowly defined toxic exposure may however involve the mast cell and its vasoactive, smooth muscle reactive, chemotactic and enzymatic mediators. The presence of mast cells free in the bronchial lumen and in the pulmonary epithelium (see above) serve to place the mast cell at the host-

environment interface. Whether the role of the mast cell is harmful or beneficial may reflect the intensity, duration or character of the stimulus, the presence and nature of underlying systemic or pulmonary disease (i.e., immotile cilia syndromes, cystic fibrosis, α_1-antitrypsin deficiency, etc.), individual responsiveness to individual mediators as well as differences in degradation of mediators and/or recruitment of alternate pro- or anti-inflammatory systems.

It is known that NO_2 exposure (1 ppm for 2 hr or 0.5 ppm for 4 hr) induces mast cell destruction in rats (*35*). Oxygen toxicity is exacerbated by histamine and decreased by antihistamine (*139*), a fact which may reflect direct mast cell participation in O_2 toxicity. In addition, lipid peroxides, known to be generated during exposure to high partial pressures of O_2, may enhance mast cell mediator release. Studies of the histopathologic alterations in lung consequent to O_2 toxicity fail to discuss mast cells. This may reflect the relative paucity of epithelial mast cells but may also indicate that mast cells are degranulated, and this no longer visible, following induction of O_2 toxicity. Rat mast cells and human lung tissue also can generate oxygen radicals during IgE-dependent mast cell activation, while the mast cell also possesses superoxide dismutase and peroxidase, enzymes thought capable of blunting oxygen induced toxicity.

It is also possible that the mast cell, present at the host-environment interface may provide a "detoxification" role. Such a role is suggested by the long life of this cell, its highly charged granule core, its content of active enzymes, its known capacity to ingest particulate materials by phagocytosis or pinocytosis and the prolonged presence of indigestible materials in mast cell granules (i.e., ThO_2) (*17,140*). Moreover, the ability of the mast cell mediators to alter local blood flow, to alter pulmonary airflow by affecting airway diameter and mechanics, to induce mucous production, and to stimulate irritant receptors could provide a mechanism for preventing and/or removing inhaled toxic materials before they can impact upon the lung itself. The recruitment of plasma systems and leukocytes also potentially benefit clearance and/or localization of toxic inputs. When toxic exposures are excessive then mast cell mediated protection may be overcome, or excessive mast cell activation may provide edematous, exudative and inflammatory alterations harmful to the host.

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