

The phenotype of human eosinophils, basophils, and mast cells

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Basophils, eosinophils, and mast cells (MCs) are specialized effector cells of the immune system. They are involved in inflammatory and allergic reactions and store and release multifunctional mediator molecules including vasoactive substances, lipid mediators, or cytokines.¹⁻³ Several different agonists, such as immunoglobulin, complement components, peptides, or cytokines and their specific receptors are involved in the activation of basophils, eosinophils, and MCs for mediator secretion.¹⁻⁴

MCs, basophils, and eosinophils originate from uncommitted multipotent progenitor cells.⁵ Precursor cells giving rise to eosinophils and basophils (CFU eo/ba) are responsive to T cell-derived factors,^{6, 7} whereas MC precursor cells (CFU-MAST) are responsive to stroma-cell-derived cytokines.⁸ Basophils, eosinophils, and MCs form separate cell lineages and the committed precursor cells (giving rise to either MCs, basophils, or eosinophils) clearly are different cells.^{4, 9} Basophils and eosinophils usually complete their differentiation in the bone marrow. After maturation both cells leave the marrow and are circulating cells. Under certain circumstances, and in particular on cell activation, basophils and eosinophils may leave the bloodstream to enter extravascular (inflamed) tissues.³ In contrast, MCs derive from circulating multipotent progenitor cells (CFU-MIX), and after extravasation/homing of progenitors, undergo and complete their differentiation in extramedullary organs.¹⁰ However, MCs may also migrate in the tissues and appear at sites of inflammation.

Abbreviations used

GM-CSF:	Granulocyte-macrophage colony-stimulating factor
ICAM:	Intercellular adhesion molecule
IFN:	Interferon
IL:	Interleukin
LFA:	Leukocyte function antigen
mAb:	Monoclonal antibodies
MC:	Mast cell
MGF:	Mast cell growth factor
SCF:	Stem cell factor
TGF:	Transforming growth factor
TNF:	Tumor necrosis factor
VCAM:	Vascular cell adhesion molecule
VLA:	Very late activation antigen

Molecules involved in the regulation of migration and localization of MCs, basophils, or eosinophils and of their progenitor cells include cytokines, chemokines, endothelial cell receptors, matrix receptors, and other adhesion molecules.

Differentiation and function of eosinophils, basophils, and MCs are regulated by a complex network of growth factors and cytokines. Differentiation of human eosinophils and basophils is inducible by interleukin 3 (IL-3), IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF).^{11, 12} For basophils, IL-3 is the most potent agonist. The functional properties of mature eosinophils and basophils can also be triggered by IL-3, IL-5, and GM-CSF.¹³⁻¹⁶ MC differentiation is inducible by stem cell factor (SCF), also termed *c-kit* ligand, steel factor, or mast cell growth factor (MGF).^{17, 18} Moreover, SCF is a unique activation factor for human MCs.¹⁹⁻²¹

METHODS

Basophils were obtained from normal donors ($n = 15$) and from donors with chronic myeloid leukemia ($n = 10$). Basophils were enriched by Ficoll preparation (MNC). Normal basophils were purified to homogeneity ($> 99\%$) by elutriation followed by magnetic cell depletion of CD14+ cells and sorting for CD17+ +

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TABLE I. Cytokine receptors expressed on human eosinophils, basophils, and MCs

Cytokine receptor	CD	Eosinophils	Basophils	MC
IL-1RI	121a	—	—	—
IL-1RII	121b	NT	+	—
IL-2R α	25	$\pm$	+*	—
IL-2R β	122	—	—	—
IL-3R	NC	+*	+*	—*
IL-4R	124	+*	+*	$\pm$
IL-5R	125	+*	+*	NT
IL-6R	126	—	—	—
IL-7R	127	—	—	—
IL-8R	128	+*	+*	NT
IL-10R	NC	NT	—	—

NC, Not yet clustered; NT, not tested.

*Expression determined/confirmed by radioreceptor assay.

cells (selected experiments).⁹ Chronic myeloid leukemia basophils were purified (>95%) by negative selection techniques using monoclonal antibodies (mAb) and complement.^{4, 16} Eosinophils were prepared and enriched from the blood of three patients with hyper eosinophilic syndrome (sedimentation, purity 85% to 91%). MCs were enriched from human lung ($n = 4$) and uterus ($n = 15$) using collagenase. Tissue MCs were purified to homogeneity by mAb and complement.⁴ Expression of cell surface membrane antigens on MCs, basophils, and eosinophils was analyzed by indirect immunofluorescence staining techniques using mAb to previously established or novel CD antigens. Pure cells were analyzed by flow cytometry. In primary cell suspensions, MCs and basophils were analyzed by a combined toluidine blue/immunofluorescence staining technique.^{4, 12, 16} Expression of cytokine binding sites was analyzed by mAb to CD antigens and by radioreceptor analyses.¹⁶ Results have been compared and are discussed in the light of previously published data.

RESULTS

Cytokine receptors

As assessed by radioreceptor analyses, eosinophils and basophils express high affinity receptors for IL-3 (CD123), IL-5 (CD125), and GM-CSF (CD116) (Tables I and II). These receptors are composed of a specific α chain and a common β chain, and cross competition in binding between recombinant IL-3, IL-5, and GM-CSF on basophil and eosinophil granulocytes has been observed.^{22, 23} Correspondingly, basophils are recognized by mAbs to IL-3R α and IL-3R β . Human basophils also express antigens recognized by mAb to IL-1 receptor type II (CD121b)²⁴ and IL-2 α chain (CD25).²⁵ Expression of IL-2R receptors α on basophils (low affinity binding) was confirmed by radioreceptor analyses. Moreover, basophils

expose high affinity receptors for IL-4,²⁶ IL-8,²⁷ interferon α (IFN- α) and IFN- γ (Valent and Virgolini, unpublished observations). Basophils lack G-CSF receptor and M-CSF receptor. Human MCs express SCF binding sites and transcripts for *c-kit*.²⁸⁻³¹ In contrast, MCs lack substantial amounts of IL-3 or GM-CSF binding sites, IL-1R, IL-2R, M-CSFR, IL-6R, or G-CSFR.^{28, 32} Tables I and II provide a summary of cytokine receptors expressed on human eosinophils, basophils and MCs.

Little is known about expression of cytokine receptors on precursor cell subsets and cells that give rise to mature eosinophils, basophils, or MCs. Basophil and eosinophil progenitor cells supposedly express receptors for IL-3, IL-5, and GM-CSF. These cells may also express receptors for negative regulators of hemopoietic cell growth such as transforming growth factor- β (TGF- β), tumor necrosis factor- α (TNF- α) or the interferons. MC precursors are responsive to myeloid growth regulators as well. Interestingly, in contrast to primary MCs, the human MC precursor cell line HMC-1 is recognized by mAbs against IL-1 receptor type II (CD121b),³⁴ APO-I/Fas antigen (CD95), TNF receptor (CD120a and CD120b), IFN- α/β receptor (CD118), IFN- γ receptor (CD119) and gp130 (CD130).²⁸ In contrast to blood basophils, the human basophil precursor cell line KU-812 produces detectable amounts of *c-kit* (CD117), although surface expression is mostly restricted to a small non-granulated fraction of cells. KU-812 cells also display TGF receptors (CD105), whereas mature basophils do not. It is hypothesized that the precursor cells giving rise to eosinophils, basophils, or MCs express a common or similar pattern of receptors for positive and negative regulators of myeloid cell

TABLE II. Cytokine receptors expressed on human eosinophils, basophils, and mast cells II

Cytokine receptor	CD	Eosinophils	Basophil	MC
M-CSFR	115	—	—	—
GM-CSFR	116	+ *	±	—
G-CSFR	NC	—	—	—
IFN- α / β R	118	NT	+ *	NT
IFN- γ R	119	—	+ *	NT
TGF- β R/E	105	—	—	—
TNFR I	120a	—	—	—
TNFR II	120b	—	—	—
gp130	130	NT	—	—
APO-1/FAS	95	—	—	—
NGFR related	40	—	+	—
SCFR/c-kit	117	—	± †	+

NC, Not yet clustered; NT, not tested; NGF, nerve growth factor.

*Expression determined/confirmed by radioreceptor assay.

†Expression of small amounts of c-kit on basophil was observed by Columbo but could not be confirmed in this study.²⁰

growth. Apparently the decrease of such receptors during myeloid differentiation results in the different phenotypes expressed by mature cells.

Immunoglobulin receptors

MCs and basophils express substantial amounts of high affinity IgE binding sites (Fc ϵ RI), whereas eosinophil granulocytes do not. In contrast, low affinity IgE binding sites are expressed in eosinophils but not on basophils or MCs. Eosinophils and basophils (but not MCs) express the low affinity receptor for IgG (CDw32).³³ Fc γ receptor III (CD16), Fc γ receptor I (CD64), and Fc α receptor (CD89) are neither expressed on eosinophils, basophils, or on lung or uterus MCs³³ (Table III).

Receptors for complement and complement-deactivating antigens

Complement receptors on eosinophils and basophils are CR1 (CD35), CR3 (CD11b), CR4 (CD11c), and C5aR (CD88). In contrast, MCs (lung or uterus) lack CR1, CR3, CR4, and C5aR.³³ Basophils, eosinophils, and MCs lack CR2 (CD21 = Epstein-Barr virus receptor). Recently several surface antigens involved in complement deactivation have been identified and clustered as hemopoietic differentiation antigens (CD). Complement-deactivating surface antigens on human basophils and eosinophils are membrane cofactor protein (CD46), decay accelerating factor (CD55), and membrane attack complex inhibitory factor (CD59). MCs also express CD46, CD55, and CD59. Table IV provides a summary of com-

TABLE III. Ig receptor expression

Ig receptor	CD	Eosinophils	Basophils	MC
Fc α R	89	NT	—	—
Fc ϵ RI	NC	—	+	+
Fc ϵ R II	23	±	—	—
Fc γ RI	64	—	—	—
Fc γ R II	32w	+	+	—
Fc γ R III	16	—	—	—

NC, Not yet clustered; NT, not tested.

plement-associated antigens expressed on human eosinophils, basophils, or MCs.

Adhesion receptors

Several adhesion receptors are involved in the localization, migration, and accumulation of eosinophils, basophils, and MCs. Circulating basophils and eosinophils express Sialyl Lewis X, a counterreceptor for selectins that mediates rolling of leukocytes on vascular cell surfaces before adhesion and transmigration. Endothelial cell receptors expressed on human basophils and eosinophils include the β 1 integrin very late activation antigen-4 (VLA-4) and the β 2 integrin leukocyte function antigen-1 (LFA-1).^{4, 34, 35} These integrins are composed of an α and β chain. Human basophils express the common β chain of β 1 integrins (CD29) and β 2 integrins (CD18), as well as VLA-4 α (CD49d), and LFA-1 α chain (CD11a). Eosinophils also express CD11a, CD18, CD29, CD49d, and CD49f (VLA-6 α).³⁶ VLA-4 is a receptor for vascular cell adhesion molecule-1

TABLE IV. Complement-associated surface antigens

Complement antigens	CD	Eosinophils	Basophils	MC*
CR1	35	+	+	—
CR2/C3dR	21	—	—	—
CR3/C3biR	11b/18	+	+	—
CR4	11c/18	+	+	—
C5aR	88	+	+	—
MCP	46	+	+	+
DAF	55	+	+	+
MACIF	59	+	+	+

DAF, Decay accelerating factor; MACIF, membrane attack complex inhibitory factor; MCP, membrane cofactor protein.

*Lung and uterus MCs were analyzed.

TABLE V. Cell surface integrins on eosinophils, basophils, and MCs

Integrin	CD	Eosinophils	Basophils	MC
β 1, common	29	+	+	+
β 1, VLA-2 α	49b	—	—	—
β 1, VLA-4 α	49d	+	+	+
β 1, VLA-5 α	49e	NT	+	+
β 1-VLA-6 α	49f	+	—	—
β 2, common	18	+	+	—
β 2, LFA-1 α	11a	+	+	—
β 2, C3biR	11b	+	+	—
β 3, common	61	—	—	+
β 3, IIbIIIa α	41	—	—	NT
β 3, VNR α	51	—	—	+
β 4 integrin	104	—	—	—

NT, Not tested.

TABLE VI. Recognition receptors on human eosinophils, basophils, and MCs

Recognition receptor	CD	Eosinophils	Basophils	MC
ICAM-1	54	NT	+	+
ICAM-2	102	NT	+	+
ICAM-3	50	NT	+	±
HML-1	103	—	—	—
VCAM-1	106	—	—	—
PECAM	31	+	+	—
PADGEM	62	—	—	—
LFA-1	11a/18	+	+	—
LFA-2	02	—	—	—
LFA-3	58	+	+	+
Leukosialin	43	+	+	+
3-FAL	15	+	—	—
Pgp-1	44	+	+	+
PLgpUb	42a	NT	—	—
PLgpIX	42b	NT	—	—
PLgpIV	36	—	—	—
T4, classII R	04	—	—	—
T8, class I R	08	—	—	—

NT, Not tested.

TABLE VII. Virus binding sites

Virus receptor	CD	Eosinophils	Basophils	MC
HIV-R	04	—	—	—
EBV-R	21	—	—	—
MV-R	46	+	+	+
RHV-R	54	—	+	+

EBV, Epstein-Barr virus; *HIV*, human immunodeficiency virus; *MV*, measles virus; *RHV*, rhinovirus.

TABLE VIII. Cell surface enzymes on eosinophils, basophils, and MCs

Enzyme	CD	Eosinophils	Basophils	MC
Endopeptidase	10	—	—	—
Aminopeptidase-N	13	+	+	—
Dipeptidylpeptidase IV	26	—	+	—
CLA phosphatase	45	+	+	+
RTK-kinase <i>c-kit</i>	117	—	±*	+

CLA, Common leukocyte antigen; *RTK*, receptor tyrosine kinase.

*A small subset of KU 812 cells express *c-kit*.

(VCAM-1) (CD106) expressed on activated endothelial cells, and LFA-1 is a receptor for intercellular adhesion molecule-1 (ICAM-1) (CD54). Binding of eosinophils and basophils to activated endothelium is primarily mediated via VLA-4/VCAM-1 and LFA-1/ICAM-1 interactions.³⁷ Basophils also express the laminin receptor VLA-5 (CD29/CD49e), but lack CD49f, CD51/CD61 (VNR), and the β 4 integrin CD104 (Table V). MCs express VLA-4, VLA-5, and the vitronectin receptor α (CD51) and β (CD61) chain,^{38, 39} but lack LFA-1 (CD11a/18) and CD104 (Table V).

Other adhesion receptors on basophils, eosinophil, and MCs are the ICAM-1 receptor CD43 (leukosialin), the Pgp-1 homing receptor (CD44), and the putative aggregation receptor CD9 (p24). The ICAM-1 antigen (CD54) is expressed on basophils and MCs^{33, 34} but not on resting eosinophils.⁴⁰ Basophils and MCs also expose ICAM-2 (CD102), ICAM-3 (CD50), and the LFA-3 antigen (CD58) on their surface, but not LFA-2 (CD2).²¹ In addition, basophils display PECAM-1 (CD31) and LAM-1 (Mell4/Leu-8). The x-hapten (CD15) is located in the basophil surface but is masked by gangliosides. Thus basophils express CD15 when exposed to neuraminidase or to sialidase-producing viruses. Tables V and VI provide a summary of adhesion receptors expressed on basophils, eosinophils, or MCs.

Cell surface enzymes

Basophils express the N-formyl-methionyl-leucyl-phenylalanine degrading enzymes, ami-

nopeptidase N (CD13) and dipeptidylpeptidase IV (CD26).³³ Eosinophils display CD13 but insignificant amounts of CD26. MCs lack both surface enzymes (Table VII). The neutral endopeptidase (CD10) is neither expressed on eosinophils nor on basophils or MCs. The pan leukocyte antigen (CD45), a transmembrane phosphatase, is produced by MCs, basophils, and eosinophils.

Virus binding sites

Recently several CD antigens have been identified as binding sites for viral epitopes. The rhinovirus binding site CD54 is expressed on basophils and MCs. Basophils, MCs, and eosinophils contain the measles virus binding site CD46 (Table VIII). Usually these cells do not express the HIV receptor CD4 or the Epstein-Barr virus receptor CD21.

Gangliosides and glycolipids

Several glycolipids and gangliosides are located on the cell surface of basophils, eosinophils, or MCs. Basophils typically express large amounts of lactosylceramide (CDw17) and can be purified to homogeneity using CDw17 mAb.⁹ Basophils also express CD43 (leukosialin), the N-linked glycan CD47, and VIM-2 reactive epitopes of the ceramide-dodesacharide sequence CD65.³³ Basophils lack CDw60 (Neu-Ac-Neu-Ac-Gal linked) and CD77 (globo-sialyl-ceramid). Human eosinophils possess CD43 and CD65 but lack CD17. MCs express CD43 and CD47 but do not display CDw17, CD60, CD65, VIM-2, or CD77.

Activation antigens

Basophil activation antigens include CD18, CD63, and Leu-8. Activation of basophils may be associated with increased expression of CD18 and CD63 and decreased expression of Leu-8.^{41, 42} Human MC activation antigens have not been identified thus far.

Conclusion

Knowledge of cell surface membrane antigens expressed on human eosinophils, basophils, and MCs has led to a better definition and classification of normal and malignant cells, novel isolation techniques providing pure populations of cells, and a better understanding of how eosinophils, basophils, and MCs interact with surrounding epitopes and thus contribute to allergic and inflammatory processes.

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Cytokine generation by eosinophils

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Eosinophils are prominent cells in allergic inflammation, asthma, and immune reactions against parasitic helminths.^{1, 2} The association between eosinophils and asthma has been extensively documented. Large numbers of eosinophils and their granule products have been observed in the airways of patients with asthma,² and an inverse correlation between the degree of bronchial hyperreactivity and peripheral blood eosinophilia was shown in subjects in whom a late-phase response developed after antigen challenge.³ With use of fiberoptic bronchoscopy it was possible to correlate the number of activated eosinophils with the degree of bronchial hyperresponsiveness.⁴ However,

Abbreviations used

GM-CSF:	Granulocyte-macrophage colony-stimulating factor
IFN:	Interferon
IL:	Interleukin
MIP:	Macrophage inflammatory protein
TGF:	Transforming growth factor
TNF:	Tumor necrosis factor

despite this close association, the evidence of a cause and effect relationship between eosinophil products and tissue damage remains unproven.

The accumulation of eosinophils into the site of the inflammatory focus in allergic-type responses is believed to be regulated by a complex series of events that involves T cells and cytokines.^{1, 5, 6} Cytokines, particularly interleukin-3 (IL-3), IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF), influence eosinophil growth, maturation, and differentiation. IL-5 is of particular interest because it is unique in that it promotes terminal

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