INTRODUCTION

Human Basophils are circulating granulocytes, representing only 0.5% of blood leukocytes. They arise and mature in the bone marrow then circulate in blood as mature cells that are recruited into tissues particularly at sites of immunologic and inflammatory responses ***(Galli and Tsai, 2008).***

Mast cells are rounded or elongated cells that arise in bone marrow but complete their maturation in tissues. They are rarely found in circulation and are mainly present near blood vessels and nerves and in connective tissues beneath surfaces that are exposed to the external environment. Tissue mast cell numbers increase at sites of parasitic infestations and in certain allergic disorders in addition to autoimmune disorders as their role in autoimmune disorders has been recently discovered **(*Sayed et al., 2008).***

The functions of basophils and mast cells are similar but not identical. Both of them play a key role in allergic inflammations, both cells express the high affinity receptor of immunoglobulin E (IgE) on their surface and can be activated to secrete diverse preformed lipid and cytokine mediators. Histamine and leukotriene C4 are common mediators while other mediators are specific for each cell such as interleukin 4, which is specific for basophils and heparin, prostaglandin D2, platelet activating factor, interleukin 6, and vascular endothelial growth factor which are specific to mast cells as they play an

important role in wound healing and tissue remodeling ***(Galli and Tsai, 2008; Rao and Brown, 2008)*.**

A variety of systemic disorders have been associated with changes in numbers of blood basophils and numbers of tissue mast cells. Diseases associated with basophilia include allergy, inflammations, infections, endocrinopathies as well as various neoplasias. These neoplasias include basophilic leukemia, myeloproliferative diseases such as, chronic myeloid leukemia, polycythaemia vera and primary thrombocythaemia. Disorders associated with increase in mast cell population, include IgE hypersensitivity reactions, connective tissue disease, infections as well as multiple neoplastic disorders. These disorders include lymphoproliferative disease and haematopoietic stem cell disease, mastocytosis and mast cell leukemia ***(Pullarkat et al., 2007).***

Basophilopenia has been recorded in association with elevated levels of glucocorticoids, hyperthyroidism and some hypersensitivity reactions. Mast cell number deficiency was observed in primary or acquired immune deficiency disorders and long term treatment with glucocorticoids ***(Rao and Brown, 2008).***

Discriminating benign and malignant disorders of basophils and mast cells is mandatory by using various diagnostic tools such as bone marrow and extra-cutaneous organ biopsy sections, serum tryptase assessment, tryptase

immunohistochemistry which is confirmatory for malignancy, c-Kit mutation detection in bone marrow, immunophenotyping as well as assessment of basophil and mast cell functions ***(Bunimovich et al., 2009).***

AIM OF THE WORK

Our study aims to highlight the development and biologic functions of basophils and mast cells as well as their disorders. The study aims also to identify diagnostic approaches and their recent advances of such disorders.

BASOPHILS

In the bone marrow are cells called pleuripotential hemopoietic stem cells (PHSCs), from which all the cells in the circulating blood are derived (Figure 1) ***(Koury et al., 2009).***

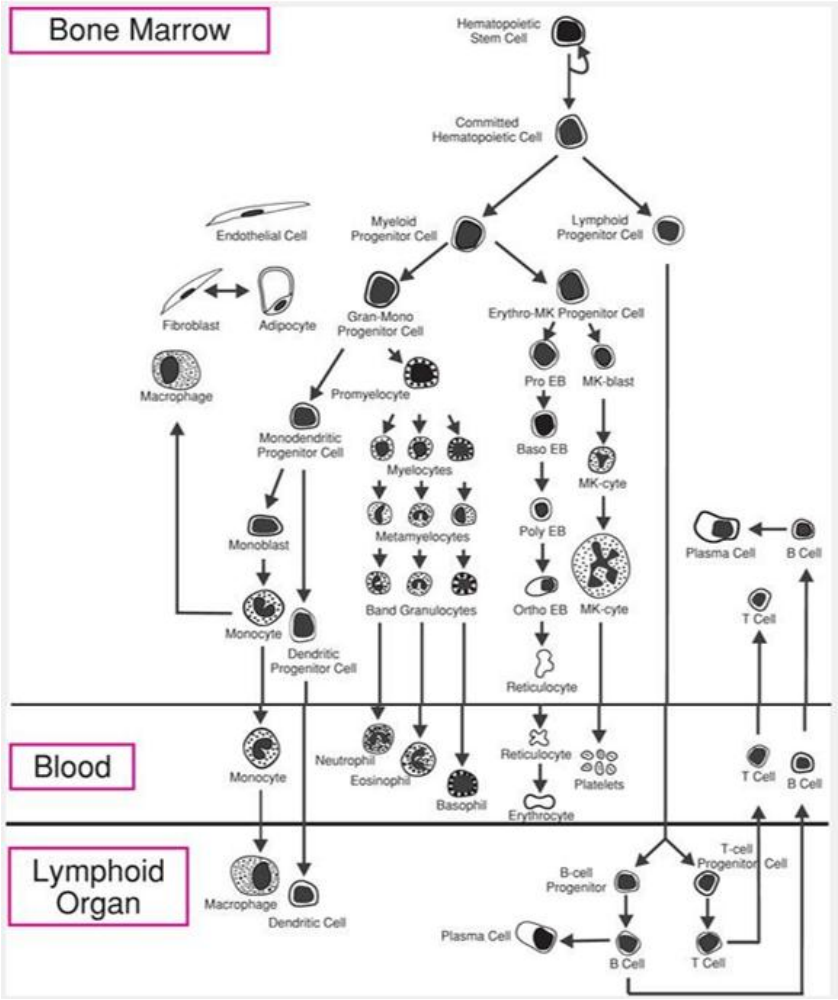


Figure (1): Successive divisions of the pleuripotential cells to form the different peripheral blood cells ***(Koury et al., 2009).***

Basophils are the least common leucocyte and constitute less than 1%, precisely 0.4% of leucocytes in circulating blood and approximately 0.3% of nucleated marrow cells. Basophil is characterized by large intensely basophilic cytoplasmic granules, hence the name granulocyte. The basophils share many structural and functional similarities with tissue mast cells. Basophils are formed in the bone marrow sharing a common precursor with the other granulocytes up to the myeloblast stage; from here, development proceeds through analogous stages as for neutrophils and eosinophils (Figure 2) ***(Williams et al., 1990)***.

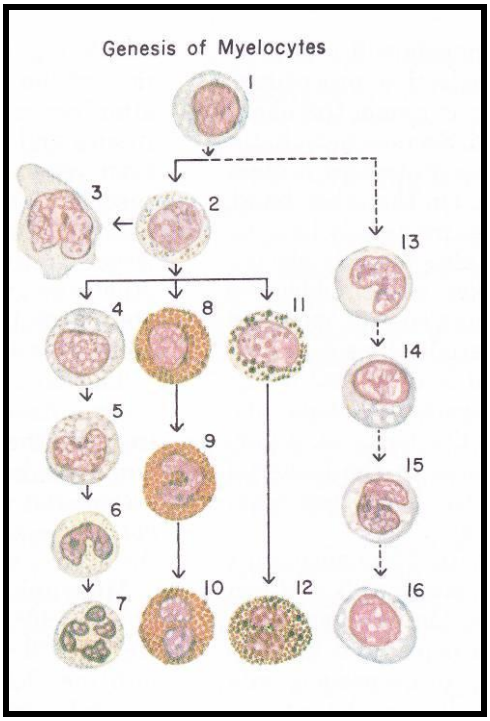
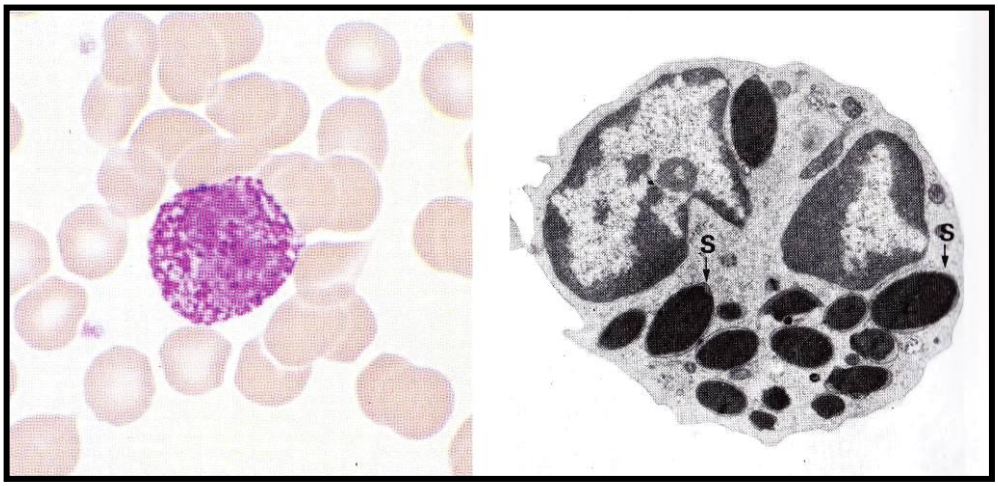


Figure (2): Genesis of basophils among other myelocytes ***(Williams et al ., 1990)***.1.Myeloblast; 2.Promyelocyte; 3.Megakaryocyte; 4.Neutrophil myelocyte; 5.Young neutrophil metamyelocyte; 6.Band neutrophil metamyelocyte; 7.Polymorphonuclear neutrophil; 8.Eosinophil myelocyte; 9. Eosinophil metamyelocyte; 10. Polymorphonuclear eosinophil; 11. Basophil myelocyte; 12. Polymorphonuclear basophil; 13-16. Stages of monocyte formation.

I) BASOPHIL MORPHOLOGY, HISTOLOGY AND STAINING PROPERTIES:



A **B**

Figure (3): Basophil histology. **A:** Basophil by Giemsa , **B:** Basophil by E/M ***(Burkitt et al., 1996)***.

The basophil (14-16μm in diameter) is intermediate in size between the neutrophil and eosinophil. Like the latter, it has a bilobed nucleus but this is usually obscured by numerous large, densely basophilic (deep blue) granules which are larger, but less in number, than those of eosinophils. The granules are highly soluble in water and tend to be dissolved away during common blood smear preparation, thus adding to the difficulty of identifying basophils in blood smears (Figure 3) ***(Burkitt et al., 1996).***

Special techniques of fixation, embedding and staining may thus need to be used. When stained with the basic dye,

toluidine blue, the granules bind the dye which changes colour to red, a phenomenon described as metachromasia. Basophils could be stained with Geimsa or Toluidine blue stains ***(Burkitt et al., 1996).***

With electron microscopy, the characteristic bilobed nucleus of the basophil is easily seen in. The large specific granules "S" are membrane-bound, round or oval in shape and filled with closely packed, electron-dense material. The granules of basophils are larger and fewer in number than those of mast cells ***(Siraganian, 1999).***

A small population of smaller granules is also found near the nucleus. The cytoplasm also contains free ribosomes, mitochondria and glycogen whilst the plasma membrane exhibits blunt, irregularly spaced surface projections ***(Burkitt et al., 1996).***

II) BASOPHIL DEVELOPMENT:

Basophils arise from $CD34^+$ pluripotent stem cells in the bone marrow. Basophil arises from a commen basophil-eosinophil progenitor cell, mature in the marrow over a period of 2-7 days and after release in the circulation, they last up to 2 weeks ***(Boyce et al., 1995).***

Interleukin 3 (IL-3) is the main cytokine that influence basophil differentiation from $CD34^+$ progenitor cells. Whereas GM-CSF and IL-5 also influence such process**.** Therefore there

are receptors expressed on basophil cell surface for these three cytokines. They are IL-3R, IL-5R and GM-CSFR ***(Valent et al., 1989).***

III) BASOPHIL PHENOTYPE:

Mature basophils can be distinguished phenotypically from mast cells. Basophils express the alpha chain of the IL-3 receptor, which is not expressed by mast cells. Mast cells express the kit receptor, stem cell factor (SCF) receptor, which is not expressed or only weakly, on mature basophils ***(Nouri-Aria et al., 2001).***

IV) MAJOR FUNCTIONS OF RECEPTORS EXPRESSED ON BASOPHIL SURFACE:

A) Adhesion and migration.

B) Cytokine receptors expression.

C) Activation linked receptors.

D) Innate immunity associated receptors.

(Schroeder, 2009)

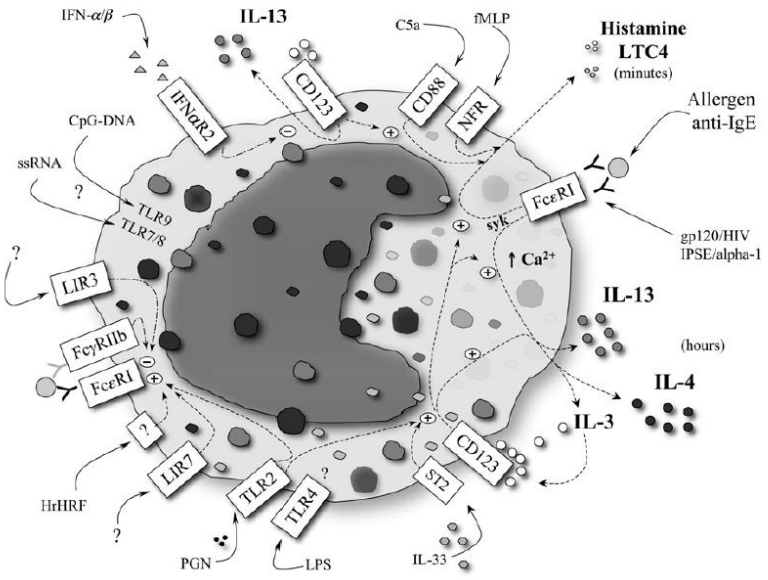


Figure (4): Basophil cell surface receptors ***(Schroeder, 2009)***.

A) Adhesion and Migration:

Basophils circulate in the blood under homeostatic conditions but will migrate into tissue during late phase reaction (LPR), which often follows acute allergic reactions. The exact mechanism of how they achieve this is not fully understood, but the adhesion molecules most likely involved in basophil migration process appears to be important for eosinophil migration as well. Because these two cells rush together, to allergic lesion sites ***(Bochner and Schleimer, 2001).***

L-selectin (CD62L) which attaches to the ligands CD34 and MAdCAM-1, is thought to initiate the attachment to the endothelium. However, firm adhesion is mediated by specific β1- and β2-integrins, along with intercellular adhesion

molecules (ICAMs) (or Ig-like molecules), and is ultimately necessary for transmigration through this barrier. Very late antigen (VLA)-4 is the β1-integrin expressed on basophils that is thought to mediate this process. Its ligand is the vascular cell adhesion molecule 1 (VCAM-1), which is the same molecule most important for the transendothelial migration of eosinophils and Th2 cells. It has long been known that IL-4 and IL-13 selectively induce VCAM-1 expression on endothelium (Figure 4) ***(Schroeder, 2009)***. Basophils by producing these cytokines, facilitates their own migration into tissue as well as that of eosinophils and lymphocytes ***(Bochner et al., 1995).***

Basophils express a variety of receptors that bind chemotactic factors and play an important role in attracting basophils into allergic lesion sites, as well as eosinophils, which explains the comigration of these two cells into allergic lesion sites. These receptors include members of the monocyte chemotactic protein (MCP) family and others, they are:

- CCL2 (MCP-1).
- CCL7 (MCP-3).
- CCL13 (MCP-4).
- CCL5 (RANTES).
- CCL3 (MIP-1α).
- CCL11 (eotaxin-1).
- CCL24 (eotaxin-2) ***(Schroeder, 2009)***.

CXCL12 (SDF-1): stromal cell–derived factor 1 is a potent chemotactic factor and a member of the CXC family that binds CXCR-4, but is only inducible on basophils cultured under a variety of conditions ***(Bochner and Schleimer, 2001).***

CXCL8 (IL-8) is the CXCR2 binding chemokine and is also reported to cause basophil migration ***(Nouri-Aria et al., 2001).***

CRTH2 (DP2) is the most recent receptor identified on basophils (as well as eosinophils and Th2 cells) and is important for selective migration of these cells ***(Esche et al., 2005).*** CRTH2, in addition to its role in basophil migration, it plays a critical role in chronic allergic inflammation by polarizing T lymphocytes to Th2 lineage responses ***(Pettipher, 2008).***

Although the chemotactic factors listed above function primarily for basophil migration, they have also been reported to cause mediator release and cytokine secretion. In fact MCP-1,-3, and-4 ***(Uguccioni et al., 1997),*** along with SDF-1 ***(Jinquan et al., 2000),*** and IL-8 ***(Krieger et al., 1992)*** are all reported to cause histamine release.

B) Cytokine Receptors Expression:

Human basophils express several cytokine receptors, raising the possibility that they communicate with a variety of other leukocytes ***(Toba et al., 1999).*** Among those identified

receptors are the receptors for these interleukins IL-2, IL-3, IL-4, IL-5, and most recently IL-33 ***(Smithgall et al., 2008).***

Basophils and immature plasmacytoid dendritic cells (pDCs) are the only two cells that express IL-3 receptors (CD123) at exceedingly high levels. This fact made (CD123) expression a useful marker for basophils and pDCs by flow cytometric analysis ***(Dzionek et al., 2000)***.

Actually IL-3 play an important role in the maturation of basophils from their precursors and is recently an important growth factor for pDCs as well, thus the two cells retain high levels of CD123 expression throughout their development, and are responsive to IL-3 protein having reached maturity. IL-3 is the most important cytokine that is known to have a great impact on basophil survival or on the ability to augment secretion ***(Schimtz et al., 2005).***

Recently, IL-33 is not far behind IL-3 in affecting basophil function. This cytokine binds to the innate immune associated receptors ST2. IL-33 is a member of the IL-1 family. IL-33 binding to ST2 expressed on basophils has been shown to synergise with IL-3 to induce IL-4 and IL-13 secretion, even in the absence of IgE receptor dependent activation ***(Schmitz et al., 2005).*** Basophils upregulate ST2 expression following IL-3 exposure, which may partially explain the need for this cytokine in order for IL-33 activity to take place ***(Smithgall et al., 2008).***

Nerve growth factor (NGF) and human recombinant histamine releasing factor (HrHRF) are two other cytokines that enhance functional responses in basophils ***(Burgi et al., 1996).***

For NGF, this activity is mediated by its binding to TrKA receptor found on basophils. NGF like IL-3, also has the capacity to directly induce IL-13 production from basophils, and to augment mediator release and cytokine secretion, stimulated through the IgE receptor ***(Sin et al., 2001).***

Human recombinant histamine releasing factor (HrHRF) has long been known to induce histamine release and IL-4 secretion from basophils ***(Escura et al., 1998).***

C) Activation Linked Receptors:

The high affinity IgE receptors (FcεRI) is the most significant activation-linked molecule known on basophils (and mast cells), which by its association with immediate hypersensitivity reactions, has essentially defined these cell types for the past 40 years ***(Gould and Sutton, 2008).***

The IgE receptors found on basophils and mast cells is comprised of 4 subunits (alpha, beta, and 2 gamma chains) to form a tetramer structure (αβγ2). The two extracellular domains on the α-subunit allow IgE binding, whereas signaling events are initiated through immunoreceptor tyrosine-based activation motifs (ITAMs) located within the intracellular portions of the β and γ-subunits ***(MacGlashan, 2005).***

The number of FcεRI molecules expressed on human basophils ranges between 5000 and 1 million and is driven by serum IgE concentrations ***(MacGlashan, 2005).***

There is a phenotype of basophils called the "nonreleaser" phenotype. It fails to release histamine upon antigenic stimulation, regardless of FcεRI expression levels. This unresponsiveness was correlated with the inability to detect levels of spleen tyrosine kinase (syk)-an early signaling component in FcεRI-dependent responses ***(Kepley et al., 1999).***

An analysis of six signaling components by MacGlashan revealed that syk levels accounted for much of the variance in basophil responses therefore it was pointed to the levels of syk as being a key predictor of basophil function among the general population ***(MacGlashan, 2007).***

Mast cells (MCs) are reported to express receptors for IgG, including FcγRI (CD64) and FcγRIIα that are demonstrated to provide activating responses in these cells. In contrast basophils express the low affinity IgG receptor FcγRIIβ (CD32). This receptor has been associated with negative regulation in several other cell types. Recent studies proved that coaggregating FcγRIIβ and FcεRI inhibits basophil mediator release and cytokine secretion that normally results from FcεRI aggregation alone ***(Kepley et al., 2000).***

Basophils among a few other cells are reported to express CD40 ligand CD40L. Others include mast cells, activated T