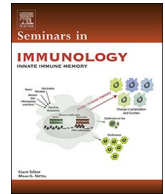




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Mast cells, basophils and eosinophils: From allergy to cancer

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ABSTRACT

Basophils, eosinophils and mast cells were first recognized by Paul Ehrlich in the late 19th century. These cells have common, but non-redundant roles, in the pathogenesis of allergic diseases and in the protection against parasites. Nevertheless, in virtue of their shared-adeptness to produce a huge variety of immunological mediators and express membrane-bound receptors, they are able to interact with immune and non-immune components of the tissue microenvironment, contributing to the regulation of tissue homeostasis and immune response while participating to further deregulation of tissues transforming into neoplasia.

1. Introduction

Basophils, eosinophils and mast cells (MC) are specialized effector cells of the immune system known to play pivotal roles in defense against parasites and in hypersensitivity type I reactions. Nevertheless, these cells exert different effector functions beside the expression of very similar receptors and cytokines. MCs are tissue resident and do not circulate in the bloodstream whereas basophils can be found in the blood of healthy individuals, and they are rapidly recruited within tissues in the presence of inflammation. Eosinophils not only circulate in the blood but also populate the hematopoietic and lymphatic organs, such as the bone marrow, spleen, lymph nodes and thymus, ready to migrate to sites of allergic reactions. However, aside from their shared similarities, all these three cell types have non-redundant role in the immune response and newly identified activities in shaping the tissue microenvironment under both physiologic and pathologic conditions.

2. Mast cell, eosinophils and basophils: a combination of shared and unique features

2.1. Origin

MCs take origin from hematopoietic stem cells (HSC) in the bone marrow (BM), circulate through the vascular system as immature progenitors and undergo terminal differentiation in tissues where they are ultimately resident [1]. On the basis of their location, histochemical staining, and content of proteases two major subtypes of MCs have been described in rodents: mucosal-type MCs, which express MC protease (MMCP)-1 and -2; and connective tissue-type MCs, which are positive

for MMCP-4, -5, -6, and carboxypeptidase A. In humans, mucosal MCs preferentially express mouse MC protease (MMCP)-1 and -2, whereas connective tissue MCs express MMCP-4, -5, -6, and carboxypeptidase A. However, single cell analysis of MC transcriptome has shown a greater heterogeneity across tissues than previously appreciated [2] making reductive the division into only two subtypes.

Several growth factors, cytokines and extracellular components are involved in MC growth and differentiation both in rodent and human systems such as stem cell factor (SCF), nerve growth factor and interleukins (IL)-3, -4 and -9. SCF, also known as Kit ligand, and Kit signaling are essential for the development of mouse and human MCs. Accordingly, mutations in *Kit* and *SCF* gene loci in mice have dramatic effect on the numbers of tissue MCs. Also, SCF is responsible for MC chemotaxis under both physiological and pathological conditions [3,4].

Differently from MCs, basophils complete the differentiation and maturation usually in the BM and then circulate in the bloodstream, constituting less than 1% of circulating leukocytes. IL-3 plays a pivotal role by directing granulocyte-monocyte progenitors to differentiate into basophil lineage, especially under pathological conditions [5]. Under certain circumstances, and in particular upon their activation, basophils may leave the bloodstream to enter extravascular (inflamed) tissues [6]. Accordingly, they are classically involved in reactions of atopic dermatitis in the skin and in airway inflammation. Also, the life span of basophils, about 2–3 days, is shorter than that of long-living MCs, which remain alive in tissues for 2–3 weeks [7,8].

Similarly to basophils, eosinophils differentiate in the bone marrow from IL-5R α -positive progenitors, and then they migrate into blood, constituting about 1–6% of circulating leukocytes. The presence of intracellular granules stained with the acidophilic dye eosin, allow their

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discrimination from other granulocytes such as neutrophils and basophils.

2.2. IgE and IgE receptor

Immunoglobulin E (IgE) is the only class of Ig found exclusively in mammals and its plasma concentration is the lowest among the five classes of Ig (199 ng/ml). It plays a crucial role in type I hypersensitivity [9] which manifests in various allergic diseases, such as allergic asthma, sinusitis, rhinitis, food allergies, and specific types of chronic urticaria and atopic dermatitis. Nevertheless, IgE production is also involved in the defense against parasites, especially protozoa and helminths.

All Igs are tetramers composed of two heavy and two light chains linked by disulfide bonds. Antigen specificity is generated by variable sequences located at the N-terminus of the heavy and light chains. The IgE Cε2-4 constant domain is responsible for the isotype specificity to its high- and low-affinity receptors FcεRI and FcεRII (CD23), respectively [10].

In both human and mouse, a tetrameric form of FcεRI is expressed by MCs and basophils. Among the subunits, the α chain is responsible for the binding of IgE whereas a dimer of disulfide-bonded γ chains is deputed to the activation of the signaling transduction. The FcεRIβ chain can amplify both the expression of the receptor and its signaling pathway [11].

FcεRI also exists in a trimeric complex, composed of one alpha-chain and two disulfide-bonded gamma-chains [12,13], in other immune populations, such as subsets of human dendritic cells (DC) (but not in mice) [14], monocytes, neutrophils and eosinophils.

In MCs and basophils, the activation of FcεRI, triggered by the cross-linking with antigen-specific IgE, results in the release of their granule content composed by inflammatory mediators, which are responsible of early and late-phase anaphylactic reactions. The released mediators comprise histamine, proteases, cytokines and chemokine, which may act locally on other inflammatory cells but also on vessels and smooth muscle to activate protective responses [15,16]. IgE binding to FcεRI also stabilizes the receptor expression on the surface of MCs and basophils [17,18] thereby increasing the numbers of FcεRI on the cell membrane [19]. The consequence of the highest density of FcεRI on cell surface was associated with 73% and 156% increase in the amount of histamine and leukotriene C4 (LTC4), respectively, secreted by the cells after challenge with IgE [20].

Eosinophil expression of FcεRI is minimal, its aggregation is not associated with cell activation, and it is of unclear functional significance. However, eosinophils express a wide array of cell surface molecules, whose aggregation can provoke eosinophils activation, such as receptors for IgG (FcγRII/CD32) and IgA (FcαRI/CD89); complement receptors (CR1/CD35, CR3, and CD88); cytokine receptors (IL-3R, IL-5R, GM-CSF, which promote eosinophil development, along with receptors for IL-1α, IL-2, IL-4, IFN-α, and TNF-α); chemokine receptors (CCR1 and CCR3). Also, they express adhesion molecules (very late antigen 4 (VLA4) and α4β7), siglec-8 and toll-like receptors (particularly TLR7/8) (reviewed in [21]). Recent evidences also show that eosinophils could be regulated by IL-33 during inflammatory responses. Moreover, IL-33 can stimulate eosinophils differentiation from their progenitors in a IL-5-dependent manner [22]. Additionally, eosinophils also express several inhibitory receptors [23]. The integration of the positive and inhibitory signals received by the microenvironment are leading to different secretory pathways: exocytosis [24] compound exocytosis [25], piecemeal degranulation, which is a form of exocytosis involving the fusion of small and rapidly mobilized secretory vesicles with cell membrane [26] and cytolysis, involving the release of the whole and intact granules following the rupture of cell membrane [27]. The latter two pathways are typically activated into tissues during allergic inflammation [28].

2.3. Costimulation

The extent of degranulation and the type of mediator released depends on several factors, such as the signal, its intensity and the local cytokines milieu. Thus, signaling molecules and adaptor proteins regulate FcεRI signaling. This complex network is responsible not only for the coordination of the degranulation process but also for the regulation of cell migration, adhesion and survival. Moreover, the crosstalk between membrane receptors and costimulatory molecules might result in either additive or inhibitory effects of the triggered responses.

Activating FcRs are characterized by Immunoreceptor Tyrosine-based Activation Motifs (ITAMs) in their intracytoplasmic domains that are required to generate activation signals after FcRs aggregation on the cell membrane. Inhibitory FcRs are single chain receptors containing an Immunoreceptor Tyrosine-based Inhibition Motif (ITIM) in their intracytoplasmic domain. In MCs and basophils, the major ITAM subunits are the widely expressed FcRγ subunit and the mast cell/basophil-specific FcRβ subunit.

Among the different costimulatory molecules, the CD300 family plays a pivotal role in regulating the signaling in MCs, basophils and eosinophils.

The CD300 family includes both activating (CD300b and e) and inhibitory (CD330a and f) immunoglobulins receptors expressed by many immune cells. These receptors are transmembrane proteins with a IgV-like extracellular domain, a transmembrane region and a cytoplasmic domain containing inhibitory ITIM motifs or an adaptor protein with activating ITAM.

The inhibitory receptors CD300a and f are expressed on MCs in both human and mice. CD300a is expressed on eosinophil and it has been recently identified on basophils. CD300a is able to reduce survival of MCs and eosinophil decreasing the effect of c-kit and IL-5/GM-CSF, respectively [29].

The best-known ligands for CD300a receptors are phosphatidylserine (PS) and phosphatidyl-ethanolamine (PE) expressed on the activated and viral infected cells but also apoptotic and tumors cells, suggesting their involvement in regulating processes linked to these conditions. Nevertheless, the presence of CD300a on MCs, basophils and eosinophils and its capacity to downregulate their activity indicates a possible role in the different phases of the allergic response.

For this reason, bispecific antibodies targeting CD300a and other receptors, have been designed with a therapeutic purpose and tested in mouse models [30]. Interestingly, a bispecific antibody fragment linking CD300a to FcεRI-bound IgE, acting specifically onto FcεRI-expressing cells in halting allergic and inflammatory responses in models of asthma and IgE-dependent passive cutaneous anaphylaxis [31]. Also, a bispecific antibody for MCs and eosinophils, obtained targeting CD300a and CCR3 inhibited mediator release, lung inflammation and remodeling and consequently reduced inflammation in a model of chronic asthma [32].

2.4. MC interaction with immunoregulatory cells in the tumor microenvironment

In the tumor microenvironment, MCs have intimate interactions with different regulatory cells, contributing to their development, expansion, polarization or to their conversion from anti- to pro-inflammatory cells [33]. Central to this function is MCs partnership with immunosuppressive cells like myeloid-derived suppressor cells (MDSC). The microenvironment of different tumors can contain MDSCs and MCs in strict cell-to-cell contact [34]. Colon cancer induces the accumulation of CD11b⁺Gr1⁺ immature MDSCs and the recruitment of pro-tumoral MCs at the tumor site [35]. *Ex vivo* analyses revealed that MCs have the ability to increase the suppressive properties of spleen-derived monocytic-MDSCs, through a mechanism involving IFN-γ and nitric oxide production. In addition, it has been demonstrated that the CD40:CD40L crosstalk between the two populations is responsible for

the instauration of a pro-inflammatory microenvironment and for the increase in the production of mediators that can further support MDSC mobilization and tumor growth [36].

The activation process, the production and the release of mediators by basophils and MCs are the result of coordinated signaling machinery. The best-studied pathway follows FcεRI triggering, as described above.

FcεRI lacks intrinsic tyrosine kinase activity; its activation requires the downstream phosphorylation of several Src kinases. To date, four Src kinases (Lyn, Syk, Fyn, and Hck) have mainly been studied in mast cells [37]. The activity of the Src kinases is interconnected and FcεRI ligation causes the simultaneous activation of all the Src kinases and gives rise to a complex signalosome that regulates mast cell exocytosis, vesicular trafficking, and gene transcription [37]. However, following a massive Ag aggregation of IgE-occupied FcεRI, some of the first events to occur are the phosphorylation of receptor by Lyn, which is constitutively associated, and subsequent Syk recruitment to the receptor and activation [38]. Moreover, the aggregation of FcεRI also induces the rapid phosphorylation of Grb2-associated, binder-like protein 2 (Gab2), an event that requires Fyn kinase (p59Fyn). Lyn kinase negatively regulates the Gab2 pathway and MC degranulation but positively regulates the activation of Syk. Syk successively phosphorylates many signaling proteins required for the assembly of membrane-localized signaling networks. Among these proteins, the linkers for activation of T cells 1 (LAT1) and LAT2 play essential roles as scaffolds in organizing, coordinating, and propagating the generated signals [37] and phosphorylation of linker for activation of T cells (LAT), a complex that is required for normal MC calcium responses.

Fyn kinase positively regulates Gab2 and its association with phosphatidylinositol 3-kinase (PI-3K) and is essential for initiation of cell degranulation. It is known that LAT signals contribute to the activation of Tec family kinase activation (Btk/Itk). Signals generated by the two distinct adaptor complexes (LAT and Gab2) may be integrated via adhesion and degranulation-promoting adapter protein, a protein that binds Fyn and Src homology 2-containing leukocyte specific protein of 76 kDa (SLP-76) and regulates cytokine production, MC degranulation, and integrin clustering [37].

3. Health and disease

3.1. Mast cell, basophil and eosinophil activation in allergy and cancer

MCs, basophils and eosinophils are activated under several pathologic conditions such as allergic reactions, infections, autoimmune disorders and cancer. Allergic diseases, including asthma, allergic rhinitis, atopic dermatitis and food allergy, may develop in different organs but with similar pathogenic mechanisms.

Some individuals can bear a predisposition to produce specific IgE antibodies against allergens that are normally harmless, a condition called atopy. When these individuals encounter an allergen, they produce high levels of IgE through the activation of T helper 2 cells that sensitize tissue resident MCs binding the FcεRI. The interaction of the allergen with FcεRI causes MC activation and preformed mediator release in connective or mucosal tissues in which they reside. The prompt release of preformed mediators cause skin reactions such as erythema and edema, sneezing, bronchospasm and mucus secretion in the respiratory tract and hypotension [39]. A few hours later, additional immune cells, namely granulocytes, lymphocytes and macrophages also infiltrate these tissues starting the late phase reactions.

Eosinophils represent the most important cell population interacting with MCs in late reactions and when the response becomes chronic [40]. Accordingly, eosinophilic inflammation and IgE-mediated hyper-reactivity, often accompanying allergic inflammation, are induced by allergen-specific T helper 2 cells and Th2 cytokines [39].

In addition, eosinophils and basophils are involved in non-atopic asthma, a reaction involving innate immune cells but not characterized by allergen-specific IgE [41].

Obviously, the outcome of allergic reactions depends on the complex interactions occurring in the inflamed microenvironment between immune cells and structural cells. A similar situation is occurring in the tumor microenvironment, where inflammatory immune cells play a pivotal role [42]. Both MCs and basophils are known to infiltrate several types of tumors but, due to the wide range of mediators they release, it is difficult to define their specific pro- or anti-tumoral activity. Accordingly, MCs and basophils could modify different aspects of tumor development, acting under tissue remodeling, angiogenesis, and invasive capacity, but also interacting with other innate and adaptive cells [4].

Moreover, their plasticity allows phenotypic changes depending on the composition of the tumor microenvironment. In particular, MCs could be activated in many ways, beside classical Ig-E antigen crosslink, by soluble mediators such as SCF or through the interplay with other immune and structural cells.

Even though MCs and basophils accumulation in the tumor microenvironment has been demonstrated in mouse models of cancer and in primary human tumors, their role in either promoting or inhibiting tumor growth remains mostly unclear. For example, MCs contribute to tumor growth promoting angiogenesis and invasion through the release of proteases as occurring in prostate adenocarcinomas [43]. Nevertheless, it has also been shown, through prostate biopsies, that the presence of MCs in the tumor could negatively regulate angiogenesis and tumor growth whereas their localization in peritumoral areas could favor tumor progression [44].

Also, eosinophils have been shown to participate not only in host protection from external attacks but also in allograft rejection and in anti-tumor immunity [45,46].

Accordingly, eosinophil degranulation and tumor-associated tissue eosinophilia have been observed in many solid and hematological cancers with a good and poor prognostic significance, respectively [47]. Existing reports sustain a pro-tumorigenic role for eosinophils through the enhancement of tumor angiogenesis and connective tissue formation. In contrast, it is known that eosinophil may mediate anti-tumor effects by direct cytotoxicity or exerting an IL-4 mediated immunomodulatory function [46], which regulates the skewing of the immune response from a Th1 to a Th2 [48]. Nevertheless, eosinophils activated in tumor microenvironment dominated by Th1 factors have been described to favor CD8 cytotoxicity and recruitment also through normalization of tumor vasculature [49].

3.2. Interaction with other immune cells and type 2 responses

MCs, eosinophils and basophils are multifunctional cells able to contribute to both innate and adaptive immune responses thanks to the expression of a wide range of receptors and to the ability to release panoply of immune mediators. In this way they create a dense network of interactions with other innate and adaptive immune cells.

The principal effector function exerted by MCs and basophils relies on the activation of FcεRI as occurring in allergic diseases. Nevertheless, the role of these cells in the regulation of adaptive immunity through the release of their granule content is now well accepted [50]. In addition to the well-known expression of Ig receptors, MCs and basophils express molecules, such as ad CD40L, involved in the regulation of other immune cell types such as B cells [51].

Accordingly, MCs were shown not only to affect B cell proliferation and survival but also to induce the differentiation of IgA secreting plasma cells. Similarly, basophils could induce CD4⁺ T cells to support B cell proliferation and interact with plasma cells favoring their survival and Ig production [52] (Fig. 1).

In addition, MCs basophils and eosinophils are involved in the orchestration of type 2 immune responses, activated in response to allergens and parasitic infections. Immune responses of type 2 are regulated by several cytokines, namely IL-4, IL-5, IL-9 and IL-13 secreted by innate immune cells, including eosinophils. In particular, IL-4 could

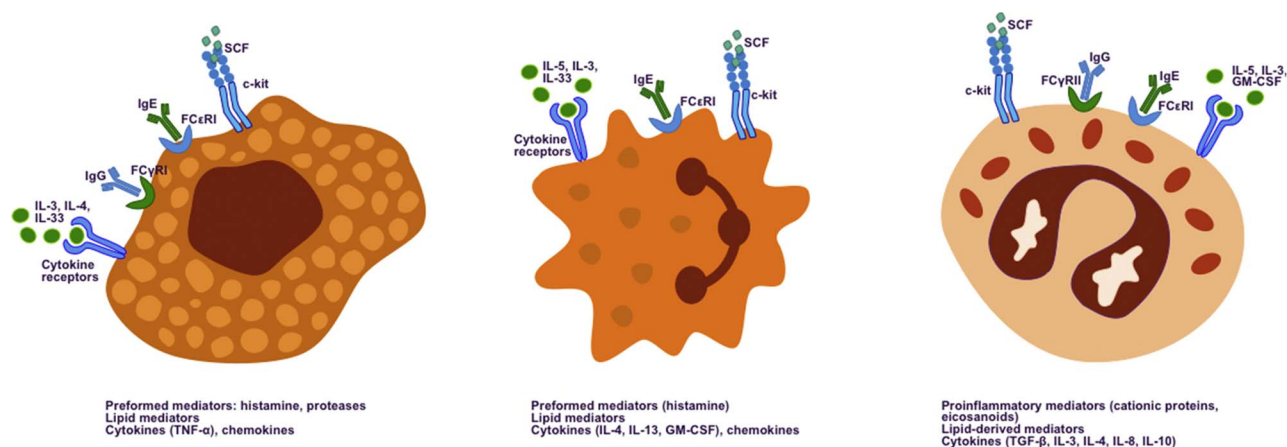


Fig. 1. Schematic representation of receptors and mediators characterizing MCs, basophils and eosinophils. MCs basophils and eosinophils share the expression of several receptors. Also, they are similarly capable of releasing a wide range of preformed or newly synthesized media. Their plasticity, however, allow their participation in several physiological and pathological processes with different effector functions.

promote IgE production by B cells in the presence of a specific antigen thus activating allergen specific responses through the link with FcεRI on MCs and basophils. Thus, these cell type not only participate in the acute phase as effector molecules but are able to initiate Th2 polarization of responses in the late phases interacting with adaptive immune cells [53]. Moreover, eosinophil could spread Th2 inflammation through additional mechanisms such as the release of CCL17 and CCL22 and the interaction with DCs [54]. IL-4 produced by basophils acts on a wide range of immune cells, T and B cells, monocytes, fibroblasts and macrophages. In particular, type 2 macrophages, activated via IL-4, may play a regulatory role in the immune system from defense from parasites and helminthic infections to tissue repair and tumorigenesis [55].

Another interesting point is the expression of both FcεRI and CD23 on APCs to facilitate the uptake of IgE-bound allergen. FcεRI in its trimeric form is present on monocytes and DCs in many human tissues and can mediate the process of antigen presentation. Accordingly, during atopic reactions of the skin FcεRI is upregulated on dermal DCs and Langerhans cells and the activation of its signaling pathway has been shown to activate the NFκB pathway in DCs and monocytes cultured in vitro. FcεRI cross-linking may also stimulate the production of anti-inflammatory cytokines and suppress T cell proliferation in vitro [10].

4. The concept of AllergoOncology

The investigation of the existing relationship between allergy and cancer is a matter of debate [56]. Many studies were conducted to evaluate whether allergic disorders could share some mechanism of immune regulation with cancer, either with a promoting or inhibiting activity. Nevertheless, an answer to this question is not easy to find. In this scenario, in 2006, the term AllergoOncology was officially ideated [57] to describe the field aiming at studying the significance of IgE-mediated immune responses against tumors with the final goal of the identification of IgE-based treatment options against tumors.

A pioneering study was conducted in 1950 to create an *in vivo* model suitable to investigate the presence of an allergic response toward tumor growth using tumor transplant in ovalbumin-sensitized mice. This study did not show any change in tumor growth in challenged mice probably for some existing biases in the study design, namely the lack of an antigen-cross reactivity among ovalbumin and the cell lines used [58]. The connection between allergy and cancer continued later on when eosinophils, known to be central in allergic diseases, were also identified in malignant tumor tissues. In particular, hypereosinophilia in the blood was associated with metastatic spread [59].

Only the discovery of IgE made it possible to conduct better studies about allergy and cancer; IgE was detected as the most expressed immunoglobulins clustered with dendritic-like cells within the epithelial tumor tissues [60].

The hypothesis of IgE having a role in the tumor microenvironment, finds support from the evidence that patients treated with omalizumab, the therapeutic anti-IgE antibody used to control severe allergic asthma, have had a higher incidence of cancer suggesting of avoiding this type of treatment in patients with a personal or family history of cancer [61]. On the other side, the presence of high IgE levels in allergic patients raised the question of an enhanced in these subjects. In this scenario, allergic reaction and cancer may be considered as opposed processes, being the first dependent on excessive IgE response and, the second on the lack of IgE-dependent MC activation and anti-tumor surveillance [62].

Most of the evidences collected on the link between allergy and cancer have been generated with epidemiological studies and meta-analyses. Even though associated with possible biases due to the retrospective feature of these studies, an inverse association has been reported for several cancers such as glioma, pancreatic cancer and pediatric leukemia, whereas lung cancer resulted positively associated with asthma [63]. Recent evidences collected from prospective studies, based on patient reported family history of allergy, indicate an inverse correlation between the presence of allergic diseases and colorectal cancer [64]. No correlation has been shown with the risk of myeloid or lymphoid malignancies [65] whereas men who were ever diagnosed with asthma seem to be less likely to develop lethal and fatal prostate cancer [66]. Other studies, inversely correlated blood eosinophilia with colorectal cancer risk [67] and serum concentrations of soluble CD23 with an increased risk of non-Hodgkin's lymphoma [68].

5. Concluding remarks

MCs, basophils and eosinophils along with IgE activation have essential role in allergic inflammation. Nevertheless, these cell types are pivotal in other innate and adaptive immune responses, thanks to their interaction with other cells of the immune system. MCs, eosinophils and basophils are a heterogeneous group of cells characterized by different phenotypes and by the ability to respond to specific stimuli, combining the engagement of activating and inhibiting receptors expressed on their surface. The existing differences in trafficking, activation and mediator production contributes to give to each cell a peculiar role after its activation.

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