Seminars in Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Mast cells, basophils and eosinophils: From allergy to cancer

A. Rigoni[a], M.P. Colombo[a,*], C. Pucillo[b]

[a] Molecular Immunology Unit, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milano, Italy
[b] Department of Medicine, University of Udine, 33100 Udine, Italy

ARTICLE INFO

Keywords:
Mast cell
Eosinophils
Basophils
Allergy
Cancer

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-5Rα-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

* Corresponding author at: Molecular Immunology Unit, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori, via Amadeo, 42 20133 Milano, Italy.
E-mail address: mario.colombo@istitutotumori.mi.it (M.P. Colombo).

https://doi.org/10.1016/j.smim.2018.02.001
Received 10 August 2017; Accepted 2 February 2018

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 bounds. 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 C300a 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