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Review

Mast cells, basophils and B cell connection network

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ABSTRACT

It has been proven that both resting and activated mast cells (MCs) and basophils are able to induce a significant increase in proliferation and survival of naïve and activated B cells, and their differentiation into antibody-producing cells. The immunological context in which this regulation occurs is of particular interest and the idea that these innate cells induce antibody class switching and production is increasingly gaining ground. This direct role of MCs and basophils in acquired immunity requires cell to cell contact as well as soluble factors and exosomes. Here, we review our current understanding of the interaction between B cells and MCs or basophils as well as the evidence supporting B lymphocyte-MC/basophil crosstalk in pathological settings. Furthermore, we underline the obscure aspects of this interaction that could serve as important starting points for future research in the field of MC and basophil biology in the peculiar context of the connection between innate and adaptive immunity.

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1. Introduction

Mast cells (MCs) are large granulated cells which can be found in all vascularised tissues, in close proximity to blood vessels, nerves, smooth muscle cells, mucus-producing glands and hair follicles (Galli et al., 2005). MCs originate in the bone marrow but undergo terminal differentiation in peripheral sites such as the skin and the mucosa of the gastrointestinal, respiratory and genitourinary tracts (Metcalfe et al., 1997). Because of their peculiar localization at anatomical sites directly exposed to external threats, MCs can be considered as immunological antennas at boundary microenvironments (Frossi et al., 2004). Similarly to MCs, basophils are granulated leukocytes and derive from a granulocyte–monocyte progenitor cell in the bone marrow, but, unlike MCs, they exit this site already in a mature state (Stone et al., 2010; Voehringer, 2013). During immune responses, basophils, which are normally present in very low numbers in circulation, increase in number and migrate from the blood to sites of infection and inflammation (Chirumbolo, 2012). Functionally, both MCs and basophils are critical effectors of the innate immune system, expressing on the cell surface IgE-specific Fc receptors (FcεR). Following IgE cross-linking by the antigen, these leukocytes are activated and release the content of their granules, including histamine, cytokines and lipid inflammatory mediators, responsible for anaphylactic and allergic reactions (Wedemeyer et al., 2000; Rivera and Gilfillan, 2006). In addition, it has now become clear that these two cell types play key roles also in the regulation of adaptive immunity (Galli et al., 2005; Stelekati et al., 2007). This could be mostly dependent on the ability of MCs and basophils to release a supplementary and diverse range of mediators, such as cytokines, chemokines and growth factors, which can modulate the proliferation, survival, recruitment and function of several immune cell types (Maurer et al., 2003; Henz et al., 2001). Moreover, the immune regulatory functions of MCs and basophils are further expanded by the ability of these leukocytes to be activated through several IgE-independent pathways driven, by instance, by complement fragments and bacterial or parasitic molecules (Blank et al., 2013).

Concerning the crosstalk with the adaptive immune system, the existence of an interplay between B cells and MCs or basophils has been disclosed by diverse evidences. The most immediate link between these cell types is represented by the expression of FcRs on the surface of both MCs and basophils. In particular, as already

Abbreviations: BMMC, bone marrow mast cell; CLL, chronic lymphocytic leukemia; CSR, class switch recombination; DLBCL, diffuse large B cell lymphoma; FcR, Fc receptor; FL, follicular lymphoma; HL, Hodgkin's lymphoma; LPD, lymphoproliferative diseases; MC, mast cell; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; Treg, regulatory T cell; SCF, stem cell factor; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; WM, Waldenström macroglobulinemia.

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cited, FcεRI binds IgE with high affinity and is primarily responsible for allergic sensitization and inflammatory response, while the MC FcγR engagement by IgG antibodies has been related to the pathogenesis of autoimmune diseases such as experimental autoimmune encephalomyelitis, bullous pemphigoid, rheumatoid arthritis and glomerulonephritis (Malbec and Daeron, 2007; Sayed et al., 2008). In addition to Ig receptors, MCs and basophils express a number of B cell modulating molecules, suggesting an intimate connection between these cell types. Indeed, MCs were shown to affect B cell survival and proliferation (Tkaczyk et al., 1996; Skokos et al., 2001a; Merluzzi et al., 2010) and to trigger IgE synthesis (Pawankar et al., 1997; Gauchat et al., 1993) and differentiation into IgA secreting plasma cells (Merluzzi et al., 2010). Likewise, basophils were shown to support B cell proliferation by inducing a B-helper phenotype in $CD4^+$ T cells (Denzel et al., 2008), and to directly promote plasma cell survival and Ig production (Rodriguez Gomez et al., 2010).

In spite of the relevance that these observations could have in the regulation of the immune response, the importance of the direct interaction of B cells with MCs or basophils remains underappreciated and there is still a paucity of research about how and where these cells crosstalk. This is understandable to some degree since B cells, MCs and basophils are classically known to localize in different sites and it is therefore difficult to imagine a context in which these cell types may interact. However, it is known that MCs are able to both produce mediators that attract lymphocytes into tissues (Henz et al., 2001) and to migrate from the site of antigen encounter to lymph nodes during the induction of an immune response (Wang et al., 1998). Moreover, we have shown that, in the gut mucosa of patients with inflammatory bowel disease, MCs co-localize with B cells at sites of inflammation (Merluzzi et al., 2010). Similar considerations can be made for basophils which were shown to express the lymph node-homing marker CD62L (Yoshimoto et al., 2009). Interestingly, it has been reported that basophils of $Lyn^{-/-}$ mice, which develop a systemic lupus erythematosus-like disease, upregulate CD62L expression and home to the lymph nodes and spleen (Charles et al., 2010).

The aim of this review is to examine the current state of knowledge about the crosstalk between B cells and MCs or basophils. Particular attention is given to the mechanisms through which MCs and basophils are known to affect B cell function, since we are convinced that a better understanding of how these cell types interact is particularly relevant in order to contextualize the importance of these interactions in physiological and pathological settings. Finally, since MCs and basophils have been reported to infiltrate the tumor microenvironment of B cell neoplasms (de Jong and Enblad, 2008; Parmley et al., 1975), we revise some important issues regarding the direct role of MCs and basophils in B cell malignancies growth and survival.

2. B/MC and B/basophil interactions: state of the art

B cells form a diverse and plastic repertoire of immune cells that can be divided into different subsets characterized by the differential expression of intracellular and cell surface markers and by distinct combination of biologic properties (LeBien and Tedder, 2008). The best known role of B cells is to confer immune protection through antibody production, a process that requires cognate interaction with T helper cells (Janeway, 2005). However, as elegantly reviewed by Cerutti et al., 2012, B cells have several other "helping friends" which can provide T cell-independent signals to switch antibody responses at the mucosal interface and in the marginal zone of the spleen. Fig. 1 exemplifies the findings resulting from different groups that show how MCs and basophils are two of these "new B cell helping friends".

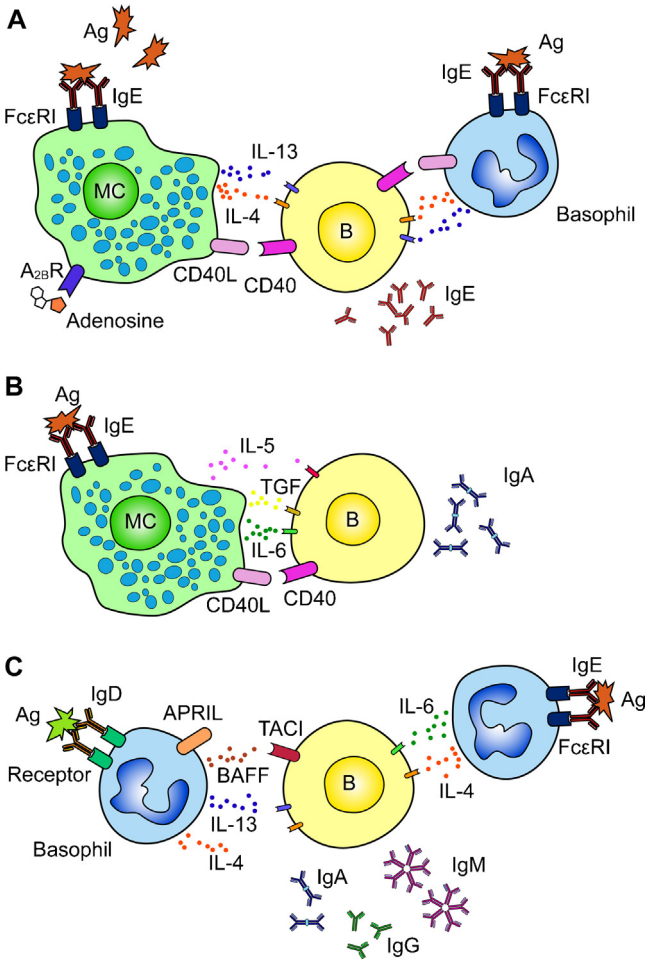

Fig. 1. MCs and basophils regulate antibody class switching and production in B cells.
(A) Ag binding to FcεR-bound IgE triggers IL-4 and IL-13 production in both MCs and basophils. These two cytokines act together with CD40 signalling to promote IgE production by B cells. The same output was shown for adenosine-activated MCs. **(B)** IgE-Ag activated MCs drive B cell differentiation toward IgA-producing plasma cells through the production of IL-6, IL-5 and TGF-β and through CD40-CD40L interactions. **(C)** Both IgE-dependent and -independent activation can induce basophils to produce membrane-bound and soluble factors, specific for the induction of IgA, IgG and IgM production by B cells.

2.1. B/MC interaction

The first evidence that antibody class switch recombination (CSR) could occur in peripheral organs such as lung or skin and that MCs could be responsible of this process, dates back to 1993 when Gauchat et al., 1993 demonstrated that both the human mast cell line Human mast cell-1 and freshly purified human lung MCs could interact with B cells to induce the production of IgE, in the presence of IL-4. Since then, the ability of MCs to support IgE synthesis by B cells was demonstrated in several other settings. Nasal MCs from patients with perennial allergic rhinitis were shown to induce IgE synthesis by purified tonsillar B cells in the presence of a mite antigen and without exogenous IL-4 (Pawankar et al., 1997). Moreover, human B cells co-cultured with adenosine-stimulated MCs, but not with unstimulated HMC-1, produced IgE (Ryzhov et al., 2004). All these studies highlighted the need of CD40L, IL-4 and IL-13 expression by MCs and support the idea that MCs might have a central role in the initiation and/or amplification of allergic reactions since they provide fundamental signals for IgE synthesis by B cells (Amin, 2012).

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