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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 (Metcalf 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 under-appreciated 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”.

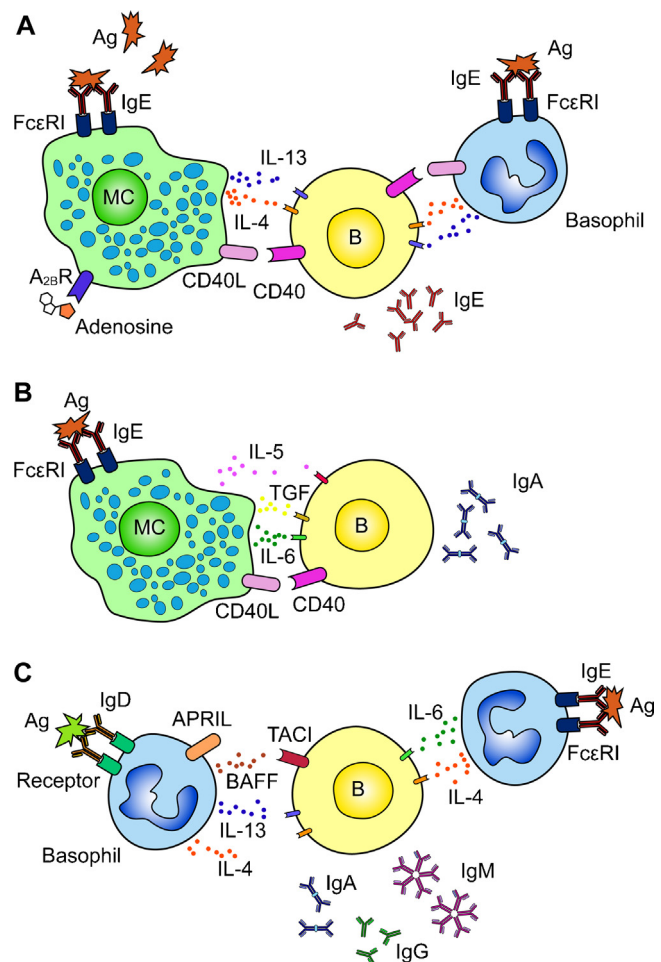


Fig. 1. MCs and basophils regulate antibody class switching and production in B cells.

(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).

The role of MCs in the regulation of antibody class switching and production in B cells is not unique to the IgE but is recognized also for IgA. Immunoglobulin A, in its secretory form, serves as first line of defence against pathogens within the mucosal tissue (Corthesy, 2007) and a variety of signals promotes the formation of IgA-producing plasma cells (Bemark et al., 2012). We have previously demonstrated that mouse bone marrow-derived mast cells (BMMCs) can directly induce the differentiation of activated B cells into IgA-secreting plasma cells since higher levels of both membrane-bound and secreted IgA were detected when activated B cells were cultured together with IgE/Ag-stimulated MCs. Interestingly, we also showed concomitant accumulation of MCs and IgA-secreting plasma cells within inflamed tissues in bioptic samples of inflammatory bowel disease patients (Merluzzi et al., 2010), reinforcing the idea that B/MC interactions may contribute to T-independent IgA response in the intestinal lamina propria. MC ability to induce IgA-producing plasma cells can also be the result of an indirect mechanism that involves regulatory T cells (Tregs). MCs were shown to be fundamental in CD4⁺CD25⁺Foxp3⁺ Treg-dependent peripheral tolerance (Lu et al., 2006) and, in turn, Tregs in the intestine express CD40L, IL-10, and transforming growth factor- β (TGF- β), and thereby promote homeostatic IgA responses by B cells (Cong et al., 2009). The intriguing idea that MCs could specifically regulate B cell function in the gut deserves further investigation given the relevance in defence against pathogens and in development of chronic inflammation.

Antibody CSR occurs in mature B cells and requires clonal expansion of B lymphocytes (Stavnezer et al., 2008). Several issues have demonstrated that MCs can promote B cell proliferation and survival. More than a decade ago, the group of Mécheri reported that both BMMCs and murine mast cell lines could activate B cells inducing blast formation, proliferation and IgM production following 48 h B/MC co-culture. Interestingly, in their experimental setting, MCs performed B cell-stimulating activity without the need of activation and physical contact with B cells (Tkaczyk et al., 1996). The authors identified in membrane vesicles named exosomes the bioactive product, through which MCs mediated the T cell-independent B cell activation (Skokos et al., 2001a). The specific role of MCs in B cell growth and differentiation was investigated more in detail by our research group which showed that mouse BMMCs can induce both survival and proliferation of primary naïve and activated B cells. Similarly to the previously mentioned study, this biological effect occurred in the absence of MC activation even if a significant increase in B cell proliferation was observed in the presence of IgE-Ag-activated MCs compared to non-sensitized MCs. Furthermore, we demonstrated that both cell–cell proximity and soluble factors contributed to B cell proliferation enhancement by activated MCs since a reduction was observed when MCs were IL-6 deficient or when a CD40L blocking antibody was added to the co-culture (Merluzzi et al., 2010).

2.2. B/basophil interaction

Similarly to MCs, basophils were also shown to deliver helper signals to B cells and drive their differentiation toward antibody-producing cells. The ability of basophils to directly induce IgE synthesis in B cells was first demonstrated by two different groups. In the previously cited report of Gauchat et al., 1993 it was shown that, in addition to MCs, also the human basophil cell line KU812 and human blood basophils were able to provide the minimal signals required to induce IgE production by B cells. Furthermore, by Fc ϵ RI activation, human basophils derived from umbilical cord blood mononuclear cells were shown to secrete significant amounts of IL-4 and IL-13 and to express detectable CD40L that induced B cells to synthesize IgE and IgG4 (Yanagihara et al., 1998). More recently, basophils were shown to provide similar B cell

helper signals by interacting with IgD, an antibody isotype present in the immune system either in a membrane or in a secretory form. Membrane IgD is the major component of the mature lymphocyte BCR while secretory IgD is produced mainly by plasma cells of the upper respiratory tract (nasal mucosa, adenoids, salivary and lachrymal glands and tonsils) (Preud'homme et al., 2000). In this environment, IgD can contribute to mucosal immunity by binding pathogenic airborne bacteria such as *Moraxella catarrhalis*, that presents binding affinity for secretory IgD thanks to the surface protein MID (Forsgren et al., 2003), and *Haemophilus influenzae*, that can be recognized by IgD through two different outer membrane proteins, namely protein D and protein E (Ronander et al., 2008). Interestingly, Chen et al., 2009 demonstrated that circulating IgD can interact with basophils through a calcium-fluxing receptor and that IgD cross-linking induces the production of B cell activating cytokines which in turn facilitate IgM secretion as well as IgG and IgA class switching in B cells.

B cell activation by basophils can also occur through an indirect mechanism that involves T cells. Starting from the *in vivo* evidence that a much lower humoral memory response was observed in mice depleted of basophils, the group of Mack demonstrated that activated basophils could induce T cells to switch to a B helper-like phenotype. The model proposed by the authors is that when Ag-specific IgE are produced after primary immunization, they are captured by high-affinity IgE receptors on basophils and, after rechallenge with antigen, basophils efficiently bind free antigen and become activated. Activated basophils, by expressing CD40L, IL-4 and IL-6, induce the conversion of activated CD4⁺ T cells into Th2-like cells, which support B cell proliferation and IgM and IgG1 production (Denzel et al., 2008). Very interestingly, a couple of years later, the same research group reported that the effect of basophils on B cells was not only limited to the induction of antibody CSR and production. Rodriguez Gomez et al., 2010 demonstrated in fact that basophils were able to support, both *in vitro* and *in vivo*, the survival of plasma cells. In this case, basophils acted directly on B cells and activation stimuli seemed not to be such important since non-activated basophils were able to supply the mediators needed to support plasma cell survival.

3. Multiple mechanisms for B/MC and B/basophil communication

MCs and basophils are the key players in the orchestration of the immune response as they add a valuable piece to the mosaic of functions that innate immune cells endorse in adaptive immunity (Wedemeyer and Galli, 2000). Both cell types participate to a form of immunological synapse by producing several cytokines and expressing important co-stimulatory molecules (Gri et al., 2012; Maddur et al., 2010), many of which can affect B cell biology. Moreover, MCs can modulate important physiological activities at distal sites through the release of membrane vesicles, bearing critical immune mediators (Amin, 2012; Kunder et al., 2009), whose activity could be directed toward B cells. Table 1 summarizes the molecules that were shown to play a role in B/MC and/or B/basophil interaction.

3.1. Soluble factors: cytokines, chemokines and others

Cytokines constitute a class of small proteins that are released by diverse immune cell types and act as signalling molecules at very low concentrations and even at long distances (Vilcek, 2003). Cytokines affect cell behavior since they regulate processes such as growth, survival and differentiation. Moreover, a particular family of cytokines, named chemokines, can induce leukocyte migration and regulate the trafficking of immune cells in different locations

Table 1
Multiple mechanisms of communication between B cells and MCs or basophils.

	Soluble factors	Effects on B cells
MC/B cell*	IL-4	IgE isotype switch and production
	IL-4/IL-13	IgE isotype switch and production
	IL-5	Proliferation and IgM production by B-1 cells
	IL-6	Proliferation, survival, IgA isotype switch
	IL-33	Proliferation and IgM production by B-1 cells
Basophil/B cell	Chymase	IgE and IgG1 production
	Histamine	Proliferation, IgM and IgG4 production
	IL-4	IgE isotype switch and production
	IL-4/IL-6	Ig production and survival of plasma cells
	IL-4/IL-13	IgE, IgG4 and soluble CD23 production
	IL-4/IL-13/BAFF	IgM secretion, IgA and IgG isotype switch
	Histamine	Proliferation, IgM and IgG4 production
MC/B cell*	Co-stimulatory axis	Effects on B cells
	CD40/CD40L	Proliferation, survival, IgE, IgA isotype switch
	CD30/CD30L	Proliferation
	CD27/CD70	Survival and proliferation
Basophil/B cell	CD40/CD40L	Proliferation and IgE isotype switch

*Another type of intracellular communication is mediated by exosomes, VESICLES that contain soluble factors, membrane co-stimulatory molecules and RNAs.

of the body (Bonecchi et al., 2009). MCs and basophils can produce a wide array of cytokines and chemokines that are responsible for many of their immunoregulatory functions (Metz and Maurer, 2007; Falcone et al., 2000; Schneider et al., 2010). As it can be inferred by the previous section, several of these cytokines can regulate, directly or in combination with other factors, B cell development and function. Concerning MC and basophil capacity to induce IgE switching, all the previously cited studies reported the need of IL-4 and IL-13, two cytokines well known for their importance in B cell CSR (Shapira et al., 1992; Oettgen, 2000). The key role of these two cytokines is pinpointed by the study of Pawankar et al., 1997 that showed that the differential ability to induce IgE production of nasal MCs from patients with perennial allergic rhinitis and with chronic infective rhinitis was due to a different expression of IL-4 and IL-13 in response to stimulation with specific antigen. Besides, IgD-activated basophils have been shown to upregulate the production of IL-4 and IL-13 as well as of B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL; Chen et al., 2009). The last two factors are crucial for B cell survival and proliferation and together with IL-4 and IL-13 can promote IgG and IgA class switch other than IgM secretion (Mackay and Schneider, 2009).

The importance of IL-6 was underlined for both MC-induced B cell proliferation and IgA switching and for the survival and antibody production of plasma cells driven by basophils. In both cases, the blockade or the absence of IL-6 did not completely abolish, but significantly interfered with the supportive effects of MCs and basophils (Merluzzi et al., 2010; Rodriguez Gomez et al., 2010).

Recently, two other cytokines, IL-5 and IL-33, have gained attention in the context of B/MC interaction. In an elegant study, Komai-Koma et al., 2011 showed that IL-33, the latest described cytokine of the IL-1 family (Schmitz et al., 2005), can activate B-1 cells, which constitute the main B cell population in the peritoneal and pleural cavities, and are best known for the production of natural IgM and for their role in maintaining tissue homeostasis, as well as in immune defence against mucosal pathogens (Baumgarth, 2011; Martin et al., 2001). On the basis of their data, the authors propose two pathways for IL-33-induced B-1 cell activation. The first

is an indirect mechanism, by means of which several cell types, including MCs, after stimulation with IL-33, produce IL-5 that, in turn, induces B-1 cell-proliferation and IgM synthesis. The second foresees the direct binding of IL-33 to the ST2 receptor on B cells which leads to the synthesis of IL-5 that acts in an autocrine manner (Komai-Koma et al., 2011). Since MCs can not only bind, but also produce IL-33 (Hsu et al., 2010), the latest mechanism indirectly suggests a role for MC-produced IL-33 in B-1 cell activation.

Scant evidence for involvement of chemokines in the B/MC or B/basophil interaction exists (Fischer et al., 2003), but several indirect considerations, already mentioned in the introduction, prompt us to anticipate an important role of these chemoattractant proteins and their receptors in the crosstalk between MCs/basophils and B cells.

Moreover, several other factors can be involved in the crosstalk of MCs and basophils with B cells. Among the molecules synthesized and stored in MC granules, there is the serine-protease chymase, which plays important roles in inflammation and tissue remodelling (Fukami et al., 1998). Yoshikawa et al., 2001, on the basis of the observation that synthetic chymase inhibitors lowered serum IgE levels in animal models of inflammation, sought to investigate whether MC chymase could also function as an enhancer of Ig production. They reported that the addition of purified rat chymase, at physiological concentrations, in cultures of murine spleen B cells stimulated with LPS and IL-4, enhanced IgE and IgG1, but not IgG3, synthesis. As discussed by the authors, this could be the result either of an expansion of the IgE- and IgG1-producing B cell population or of an increase in IgE and IgG1 syntheses by individual B cells.

Another molecule released by activated MCs and basophils is histamine, a biogenic amine that exerts effects on cell proliferation and differentiation of many cell types (Schneider et al., 2011). Banu and Watanabe, 1999 reported that histamine enhances the rate of splenic B cell proliferation induced by cross-linking of antigen receptors with anti-IgM. This effect was shown to depend on the H1 receptor and to be specific for the antigen receptor-mediated signalling pathway. As stated by the authors, these data do not demonstrate the direct participation of MCs and basophils to the modulation of B cell functions but indicate that one of their most important mediators may play a direct role in acquired immunity. Interestingly, a series of issues published some years before had clearly revealed a role of histamine also in the regulation of antibody production. It was first reported that histamine, through the induction of autocrine IL-6 production, induced IgM secretion by the BMNH Epstein-Barr virus-infected B lymphoma cell line but not in the lymphoblastoid B cell line CESS (Falus, 1993). Furthermore, Kimata et al., 1996 showed that histamine provision to B cells from healthy donors treated with anti-CD58 mAb plus IL-4 or IL-13, upregulated IL-6 and IL-10 production which, in turn, enhanced IgE and IgG4 (but not IgG1, IgG2, IgG3, IgM, IgA1 or IgA2) secretion. All together, the latest reviewed reports reveal a certain degree of variability in the effect of histamine on antibody production, which could depend on both the type of stimuli and target B cells used for the experiments.

3.2. Co-stimulatory molecules

MCs and basophils can regulate several immunological reactions through the expression of cell surface molecules that enable them to interact with different partners of the immune system, including B and T lymphocytes (Maddur et al., 2010; Frossi et al., 2010). Indeed, MCs and basophils communicate with B cells through the co-stimulatory pathway constituted by CD40 and CD40L. Although for long time, the CD40-CD40L axis was thought to be merely required for the thymus-dependent humoral response, nowadays we know that it is associated with diverse physiological

and pathological processes due to the broad expression of both the ligand and its receptor (Schonbeck and Libby, 2001). CD40 is a type I transmembrane protein belonging to the TNF receptor superfamily and its engagement on B cell surface triggers distinct signalling mechanisms that lead to a potent polyclonal activation and to the production of antibodies. (Danese et al., 2004; Jabara et al., 1990). In this regard, we have previously demonstrated that the redox factor APE/Ref-1 acts as a key signalling intermediate in response to CD40-mediated B cell activation since it translocates from the cytoplasm to the nucleus, where it modulates the DNA binding activity of the nuclear transcription factors Pax5a and EBF (Merluzzi et al., 2004). Several studies have detected CD40L on the surface of both MCs and basophils (Merluzzi et al., 2010; Pawankar et al., 1997; Gauchat et al., 1993), even if the expression levels were shown to be different depending on the cell source and on the type of activation. Both at the mRNA and protein level, Gauchat et al., 1993 showed that while the immature basophilic cell line KU812 expressed low levels of CD40L already at steady state, the mast cell line HMC-1 required activation with phorbol myristate acetate and ionomycin. Furthermore, Merluzzi et al., 2010 reported that the constitutive expression level of this marker on BMMCs was enhanced by IgE-Ag stimulation. Recently, Hong et al., 2013 have demonstrated that the upregulation of CD40L observed on BMMCs after activation with IgE/Ag depends on the Ca^{2+} -dependent enzyme transglutaminase 2. All the previously described MC/basophil-induced effects on B cell biology required the CD40-CD40L axis; however, it must be emphasized that the CD40/CD40L dyad is necessary but insufficient for optimal sustenance and differentiation of B cells since soluble factors are also required.

Evidences for the contribution of other membrane-bound molecules to the B/MC and/or B/basophil interaction are corroborated by studies in the context of B cell malignancies, as will be thoroughly described in Section 4 of this review. Among these receptor-ligand axes, an interesting pair of molecules is represented by CD30 and CD30L, which both belong to the TNF family. CD30 was first identified as a cell surface molecule upregulated on Hodgkin and Reed Sternberg cells of Hodgkin's disease, where it has been demonstrated that CD30 triggering by MC CD30L stimulates the expansion of the malignant B cell clone (Molin et al., 2001). Indication for another potentially interesting pathway to study, CD27-CD70, comes always from a B cell malignancy, in this case represented by Waldenström macroglobulinemia (WM; Ho et al., 2008).

3.3. A third mechanism of intercellular communication: exosomes

Cell to cell contact and cytokine release are not the only ways by which intercellular communication and immune regulation can take place. The extracellular environment contains a large number of mobile membrane vesicles which have gained increasing interest due to their ability to mediate long-range transfer of information from a donor to a recipient cell (Thery et al., 2009). These vesicles contain transmembrane proteins, soluble mediators and RNAs of the cell, from which they originate, and they transfer information through two different mechanisms that are: (i) the adhesion of the vesicle to the target cell through specific receptor-ligand interaction and (ii) the direct internalization of the whole vesicle by the recipient cell (Camussi et al., 2010). Membrane vesicles include activation- or apoptosis-induced microparticles, apoptotic bodies and exosomes. The latest are small vesicles of 30–100 nm in diameter that originate from the endosomal compartment and are released either spontaneously or during activation from many cell types including dendritic cells, T cells, B cells, epithelial cells and tumor cells (Gyorgy et al., 2011).

To our knowledge, for basophils there are no data that show the production of exosomes. However, they do contain numerous

electron-lucent vesicles of 50–70 nm that often have contents similar to granules and that may be associated with a form of mediator exocytosis. (Dvorak, 2005). Conversely, it is ascertained that MCs of both human and murine origin produce exosomes (Shefler et al., 2011). Several groups have analyzed the content of MC exosomes and nowadays we know that it is quite heterogeneous and includes factors such as CD13, ribosomal protein S6 kinase, annexin V, Cdc25, γ -actin-like protein, γ -actin and cytoplasmic- γ -actin (Skokos et al., 2001a), a whole set of phospholipases together with interacting proteins such as aldolase A and heat shock protein 70 (Subra et al., 2010), but also functional mRNAs and small RNAs, including microRNAs (Valadi et al., 2007; Ekstrom et al., 2012). Of note for the B/MC interaction is the observation that MC-derived exosomes also contain immunologically relevant factors such as MHC class II proteins (Vincent-Schneider et al., 2002, 2001), co-stimulatory (CD86, CD40, CD40L) and adhesion-related (LFA-1, ICAM-1) molecules (Skokos et al., 2001a). The group of Mécheri was the first to show that MCs use this type of intercellular communication to crosstalk with B cells. They initially demonstrated that unstimulated BMMCs induced resting B cells to proliferate and to produce IgM, through a mechanism that did not involve neither cell contact nor IL-4 or IL-6 production (Tkaczuk et al., 1996). Some years later, the same research group reported that exosomes released by MCs were responsible of MC-driven B cell proliferation and activation, and that they had the capacity to induce B cell production of IL-2, IL-12, INF- γ , IgG1 and IgG2, but not of IL-4 (Skokos et al., 2001a, 2001b). Interestingly, Skokos et al. demonstrated the occurrence of lymphocyte-stimulating activity by MC-derived exosomes also *in vivo* and this result is very relevant in the context of B/MC interaction, especially considering that exosomes can act at long distances.

Finally, since B cells are also capable to secrete exosomes (Raposo et al., 1996), the possibility of a bi-directional role of exosomes in the B/MC interaction should also be taken into account.

4. Role of MCs and basophils in B cell malignancies growth and survival

The tissue microenvironment that surrounds tumor plays an important role in delivering signals that affect the growth of cancer cells (van Kempen et al., 2003). In particular, infiltrating inflammatory cells are recognized as an important driving force in cancer promotion and progression, even if the exact mechanisms by which such immune effectors regulate the neoplastic homeostasis have been elusive for a long time.

MCs and basophils have been described to represent an important component of the inflammatory tumor cell background. Moreover, the wide array of effector and immunomodulatory functions of MCs and basophils has been recently recognized in the context of cancer, where these leukocytes can contribute either to the acceleration or arrest of tumor growth, depending on the strength and nature of the received stimuli (Theoharides and Conti, 2004; Murdoch et al., 2008). The complexity of MC and basophil functions in cancer setting is mirrored by the recent acknowledgment that these leukocytes participate also to adaptive immune responses, displaying partly overlapping functions and influencing the homeostasis of a wide array of immune cells, including B lymphocytes. Moreover, the release of MC and basophil products triggers profound biological effects, remodelling the surrounding tissue and hence influencing several aspects of tumor biology such as intratumour microvessel density, cancer growth and tumor metastatic potential (Galinsky and Nechushtan, 2008).

On the other hand, the continuous crosstalk between MCs (and basophils) and the adjacent microenvironment selects distinct types of MCs (and basophils) that differ in granule content

and surface receptor expression (Galinsky and Nechushtan, 2008; Crivellato et al., 2011). Indeed, Satodate et al., 1977 described the association between MCs and B cell neoplasms, highlighting the existence of different MC phenotypes, with different granule morphology, that correlate with a peculiar MC tissue distribution and particular types of B cell neoplasm. This phenotypic heterogeneity of MCs (and basophils) in the cancer setting is in line with their physiological plasticity, as exemplified by the ability to adapt to the local habitat during differentiation and immune responses (Crivellato et al., 2011).

The compliance to the surrounding environment requirements, both in cancer and in normal tissue, is fostered by the fact that, as mentioned before, MCs and basophils can be activated by multiple stimuli coming from the surrounding microenvironment. In particular, MCs can be activated in an IgE-independent manner by a plethora of soluble molecules, including stem cell factor (SCF), or by contact with surrounding cells such as fibroblasts and T or B lymphocytes (Theoharides et al., 2007). Such a type of activation is mainly linked to chronic inflammation and is implicated in cancer-associated MC functions (Ribatti and Crivellato, 2009a). In this context, activated MCs (and basophils) may selectively release a subset of preformed or newly synthesized mediators by “piecemeal” degranulation giving rise to an immediate inflammatory response that may subsequently acquire a chronic character (Rudich et al., 2012).

4.1. MCs and basophils in cancer microenvironment

Studies dating back to the end of the nineteenth century had already described that MCs infiltrate predominantly the periphery of developing tumours, at the interface with the surrounding healthy tissues, where they often associate with vasculature. Since then, several animal and human studies confirmed the association of MCs to a number of solid tumours, often demonstrating a correlation between MC load and prognosis (Galinsky and Nechushtan, 2008). Increased MC numbers have been observed also in hematological neoplastic lesions, including B cell malignancies such as multiple myeloma (MM; Ribatti et al., 1999), diffuse large B cell lymphoma (DLBCL; Hedstrom et al., 2007), WM (Ho et al., 2008), chronic lymphocytic leukemia (CLL; Molica et al., 2003), Hodgkin's lymphoma (HL; Molin et al., 2002) and follicular lymphoma (FL; Dave et al., 2004). The relation between the extent of MC density and tumor prognosis was observed also in the case of B cell malignancies, with MCs favouring neoplastic B cell growth in HL, MM, WM and FL, whereas inhibiting tumor expansion in some types of DLBCL. The prognostic significance of MC content holds true even following chemotherapeutic treatment, further corroborating the interplay between MCs and B cells (Taskinen et al., 2008). Additional evidence supporting a key role of MCs in B cell tumor development and growth comes from rare but recurrent cases of systemic mastocytosis associated with lymphoproliferative diseases (LPD) of B cell origin, including CLL, B-lymphoblastic leukemia, hairy cell leukemia, monoclonal gammopathy of undetermined significance (MGUS) and plasma cell myeloma (Du et al., 2010). Other *in vivo* data confirming the link between MCs and B cells come from the peculiar morphological pattern of bone marrow involvement in indolent systemic mastocytosis, consisting of MC collections spatially associated with T and B benign lymphoid infiltrates that are specifically polarized close to MC infiltrates. In such cases of systemic mastocytosis, immunohistochemical staining for SCF highlights the presence of this cytokine at sites of MC lesions, suggesting a critical role of SCF for the recruitment, growth and survival of MCs and lymphoid progenitors, which both express SCF receptors (Akin et al., 2002). On the other hand, in solid tumours, SCF-activated MCs may indirectly facilitate cancer growth, exacerbating inflammation and mediating immunosuppression (Huang

et al., 2008). Moreover, recent studies showing that SCF is frequently expressed by a wide array of indolent and aggressive B cell malignancies, including pre-B acute lymphoblastic leukemias and FL (Fox et al., 2013), put forward the hypothesis that B cells may recruit MCs at sites of neoplasia, where B/MC bidirectional triggers may then take place. In this context, direct demonstration of MC chemotaxis in response to the chemokine CCL5/RANTES released by neoplastic cells has been demonstrated in HL (Fischer et al., 2003).

Although several reports provide evidence of increased amounts of basophils in solid tumours and hematologic myeloid neoplasms, scanty data document the association between basophils and B cell LPD. Specifically, in a case of HD, the lymph node neoplastic stroma was infiltrated by basophils whose cytoplasmatic granules appeared empty even though without evidence of exocytosis (Parmley et al., 1975). Moreover, in the peripheral blood of a patient affected by CD5⁺ DLBCL, an increased number of basophils were reported. Strikingly, basophilia paralleled with the tumor burden (Tokuhira et al., 2007).

4.2. MC and basophil mechanisms of tumor growth modulation

In recent years, disparate *in vitro* and *in vivo* studies have suggested that tumor infiltrating MCs and basophils may promote cancer growth through multiple mechanisms, inducing tumor angiogenesis, tissue remodelling and immune regulation. In particular, MCs and basophils may modulate cancer development by directly interacting with the neoplastic cells or by indirectly modelling the tumor milieu. Indeed, MCs and basophils not only produce a number of cytokines, chemokines and enzymes which mediate the inflammatory process underlying the neoplastic growth, but also play a critical role in the suppression of the adaptive immune reactions by producing inhibitory cytokines and by interacting with Tregs (Heneberg, 2011; Maltby et al., 2009).

4.2.1. Direct mechanisms of B cell tumor growth modulation

The direct effect on tumor cells is mainly related to MC and basophil ability to communicate with neoplastic cells *via* cognate receptors and soluble ligands or through the release of tumor growth regulating cytokines.

Focusing on soluble mediators, IL-4, IL-5, IL-6 and IL-13 were shown to be involved in the regulation of proliferation, differentiation and function of normal B cells (Gri et al., 2012). Likewise, basophils are able to release IL-4, IL-6 and IL-13 (Rodriguez Gomez et al., 2010; Schneider et al., 2010). These bioactive factors were shown to have complex effects on tumor cells and an example is given by the opposite growth response to IL-4 of B lymphocytes derived from the two main subtypes of DLBCL. Indeed, IL-4 was shown to augment the proliferation of DLBCL cells of the germinal centre-like subtype but to decrease the proliferation of DLBCL cells of the activated cell subtype (Lu et al., 2005). By releasing pro-inflammatory cytokines such as TNF- α , IL-6 and IL-1 β , that augment the inflammatory anti-tumor reaction, MCs and basophils may then perform direct anti-neoplastic functions inducing apoptosis of tumor cells (Gordon and Galli, 1990; Gooch et al., 1998). However, recent evidences show that these inflammatory cytokines mainly foster tumor growth (Lin and Karin, 2007; Dunn et al., 2004; Ullrich et al., 2007).

Molecules expressed on MC/basophil surface may interact with cognate receptors on tumor cells, directly modulating cancer proliferative behaviour. As previously mentioned, such a mechanism has been documented in the framework of HL, where CD30 positive tumor cells were stimulated to proliferate after interaction with CD30L present on MC surface (Molin et al., 2001, 2002). The nature of the CD30-CD30L interaction may be bidirectional since not only CD30-positive cells can be activated by CD30L, but also CD30L-positive cells can be activated by CD30 (Wiley et al., 1996).

and this “reverse signalling” makes more relevant the possible role of CD30L expressing MCs in HL. Indeed, it has been shown that MCs, upon stimulation with CD30, release IL-8 and MIP-1 α /MIP-1 β (Glimelius et al., 2005; Fischer et al., 2006). These factors are involved in the recruitment of granulocytes, lymphocytes and monocytes, which are infiltrating cells usually found in HL. Therefore, through CD30-CD30L bidirectional signalling, MCs play the dual role of stimulating tumor cell growth and of contributing to the accumulation of inflammatory cells in the cancer microenvironment. Moreover, the regulatory function of the CD30-CD30L axis may hold true in other CD30-positive hematological malignancies, including anaplastic large cell lymphoma and Burkitt lymphoma (Ofazoglu et al., 2009).

Similarly, in WM it was shown that CD40L expressed on MCs and basophils is able to promote cancer cell expansion via CD40 signalling (Tournilhac et al., 2006). Furthermore, Ho et al. (2008) demonstrated that neoplastic B cells of WM patients produce soluble CD27 which, engaging CD70 on MC surface, stimulates the expression of CD40L and APRIL, two important B cell growth and survival factors. This result is particularly relevant in the context of B/MC interaction since CD27 is normally expressed on the cell surface of memory B cells, from which WM is thought to derive (Stone and Pascual, 2010).

4.2.2. Indirect mechanisms of B cell tumor growth modulation

Indirect mechanisms of cancer growth regulation are mainly linked to MC and basophil capacity to shape the neoplastic stroma by promoting tumor angiogenesis, tissue remodelling and immune regulation.

4.2.2.1. Tumor angiogenesis. Angiogenesis fosters tumor progression by promoting tumor growth, invasion and metastasis. The role of MCs in inducing new vessel formation is well recognized and is supported by the observation that tumours induced in MC-deficient mice exhibit reduced angiogenesis and ability to metastasize (Starkey et al., 1988; Dethlefsen et al., 1994–1995). The pro-angiogenic role of MCs and basophils is evident in tumor stroma where these leukocytes often accumulate close to vasculature. Indeed, MCs produce several factors that can affect angiogenesis, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor, angiopoietin-1, TGF- β , TNF- α , IL-8, matrix metalloproteinase-9 (MMP-9), histamine, heparin and angiogenic proteases, such as tryptase and chymase (Ribatti et al., 2001). Basophils, instead, release a smaller number of such mediators, including histamine and VEGF (Crivellato et al., 2010).

Increasing evidences show that angiogenesis and inflammation are reciprocally dependent. Indeed, in the course of inflammatory reactions, such as local inflammation at tumor foci, immune cells produce and release bioactive mediators that boost the formation of new vessels. In particular, at onset of the angiogenic cascade, VEGF, histamine and lipid-derived mediators induce microvascular hyperpermeability which results in leakage of plasma proteins such as fibrinogen and other clotting proteins favouring the development of a strongly pro-angiogenic stroma and new vessel growth (Dvorak, 2002). At the same time, the new vessels permit the recruitment of inflammatory cells to the site of inflammation, perpetuating the process (Ribatti and Crivellato, 2009b). During this reaction, stromal and tumor cells cooperate with immune cells in stimulating endothelial cell proliferation and in releasing chemotactic factors for the recruitment of inflammatory cells.

A study performed by Nakayama et al., 2004 demonstrated that MC-derived angiopoietin-1 and VEGF, together with plasmacytoma-derived VEGF, promote new vascularization in a murine model of MM. Studies in humans confirm that angiogenesis is involved in the pathogenesis of MM and of a number of other B cell LPD, including B cell non-HLs, acute lymphocytic leukemia and

CLL, where MC density, bone marrow microvessel count and clinical prognosis were shown to be correlated (Bertolini et al., 2000). Moreover, angiogenesis is associated with tumor growth also in MGUS and it has been demonstrated that microvessel area and MC numbers increase simultaneously in active MM (Ribatti et al., 1999). In B cell non-HLs and MM, the ultrastructural picture of MCs in close proximity to blood capillaries is suggestive of ongoing piecemeal partial degranulation of the secretory granules that typically occurs during chronic inflammation (Ribatti et al., 1988).

4.2.2.2. Tissue remodelling. MCs and basophils, recruited at tumor sites through the new vessels, can remodel the cancer tissue by producing a variety of proteases and other bioactive substances and by stimulating fibroblasts and different stroma cells (Shin et al., 2009; Pejler et al., 2010). Proteases, such as tryptase and chymase, may directly shape the extracellular matrix or may regulate the functions of matrix-processing enzymes, inducing, for example, the conversion of pro-MMP-9 in its active form (Tchougounova et al., 2005). It has been proposed that, in the cancer setting, MCs may be able to disrupt the extracellular matrix around the tumor, fostering its dissemination and releasing bound pro-angiogenic factors such as SCF and basic fibroblast growth factor from the extracellular matrix. In turn, the angiogenic compounds further stimulate MCs and promote endothelial cell migration and proliferation favouring tumor spread and growth (Maltby et al., 2009). This peculiar neoplastic stroma homeostasis highlights the close connection between tissue remodelling and angiogenesis during cancer development. Indeed, strikingly, a recent study puts forward direct evidence that MCs promote the growth of HL by remodelling the cancer microenvironment through marked neovascularization and fibrosis (Mizuno et al., 2012).

4.2.2.3. Immune regulation. A particular aspect of tissue remodelling through which MCs and basophils may modulate tumor growth is represented by the ability of these leukocytes to fine-tune the immune response, recruiting eosinophils and neutrophils and activating adaptive T and B responses. However, most of the evidences supporting MC role in immune modulation derive from murine studies and/or disease models different from cancer. In an asthma model, it has been reported that MCs can attract eosinophils (Blanchet et al., 2007), which have been recently suggested to play active roles in tumor rejection (Maltby et al., 2009). Moreover, under certain conditions, MCs and basophils can activate T lymphocytes by functioning as antigen presenting cells, and thereby potentially modulating tumor rejection. MCs are also implicated in the regulation of migration, maturation and function of dendritic cells and hence in the modulation of the initiation of acquired immunity (Crivellato et al., 2011). On the other hand, MCs may promote tumor growth, exerting immunosuppression through the production of TNF- α and IL-10 (Grimbaldeston et al., 2007). Under the same view of a potential setting of permissive environment for the neoplastic clone growth, MCs were shown to interact with Tregs. MCs inhibit Treg suppression and promote a Th17-skewed immune response through IL-6 release and OX40 engagement (Piconese et al., 2009), creating an environment of “smoldering” inflammation conducive to cancer growth. In literature, there are evidences of increased Treg numbers in B cell LPD. An example is given by CLL, where the Treg load correlates with the progression of the disease (D’Arenza et al., 2011). However, it is unknown whether MCs contribute to the mechanism of Treg expansion in this setting.

5. Concluding remarks

This review has surveyed the literature related to B/MC and B/basophil crosstalk, both in a physiological and pathological context, and has attempted to identify aspects of these interactions that

warrant further attention. MCs and basophils play important roles in the induction and progression of several inflammatory diseases as well as in the regulation of tumor progression. Indeed MCs were found to co-localize with IgA-secreting B cells in biopsies of patients with inflammatory bowel disease and increased MC numbers are detected in B cell LPD.

So far, studies have focused mainly on the outcome of the B/MC or B/basophil interaction on B cells. However, it would also be interesting to study the effect of B cells on MCs and basophils, especially now that a regulatory, suppressive function of B lymphocytes has come to light. Whatever the direction, the relevance of the interaction of B cells with MCs or basophils is provided by co-stimulatory molecules as well as soluble mediators. Exosomes have prompted great interest and their investigation is considered the emerging field in cell communication.

Altogether we believe that there is still much to be studied to fully understand the crosstalk between B cells and MCs or basophils, and that a better analysis of these interactions could be particularly relevant in the context of the development and amplification of inflammatory responses.

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