Mast cell: an emerging partner in immune interaction

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**INTRODUCTION: ORIGIN, DISTRIBUTION AND FUNCTIONAL HETEROGENEITY**

To develop an effective immune response, the cells of the immune system are required to communicate between each other through secretion of soluble mediators and direct cell–cell interaction. Among the cells of the immune system, mast cell (MC) appears to be one of the most powerful in terms of ability to respond to multiple stimuli and to selectively release different types and amounts of mediators (reviewed in Galli et al., 2005b).

Research on MC physiopathology has changed our perception of the role that MCs play within the immune system. Indeed, their functions extend through all the stages of the immune response, ranging from shaping the response against pathogens, regulating both innate and acquired immune cell functions, to supporting regulatory cells in the maintenance of tissue-tolerance.

MCs originate from a multipotent hematopoietic progenitors in bone marrow, and then migrate through blood to tissues where they mature (Hallgren and Gurish, 2011). In mice, an hematopoietic stem cell progresses to a multipotent progenitor, a common myeloid, and a granulocyte/monocyte progenitor (Chen et al., 2005). A monopotent MC progenitor is found in bone marrow and intestine, and a common basophil/MC progenitor is also found in mouse spleen (Chen et al., 2005). After their homing in the tissues, maturation of the MC precursors is dependent on stem cell factor (SCF) expressed on the surface of fibroblasts, stromal cells, and endothelial cells (Arinobu et al., 2005).

MCs are positioned throughout the vascularized tissues and serosal cavities where they constitute one of the first cell types of the immune system able to interact with allergens and antigens (Galli et al., 2008a). Within body tissues, micro-environmental stimuli control MC phenotypic profile leading to subtype differences from a common progenitor (Moon et al., 2010). Historically, the classification of rodent MC subtypes has been based on phenotypic differences between connective tissue MCs (CTMCs), found in the skin and peritoneal cavity, and mucosal MCs (MMCs), which are mainly present in the intestinal lamina propria. There are, however, different phenotypic characteristics between these two populations and also differences in functions, histochemical staining, content of proteases, and reactivity to selected secretagogues and anti-allergic drugs. MMCs express MC protease (MMCP)-1 and -2, while CTMCs are positive for MMCP-4, -5, -6, and carboxypeptidase A. MMCs expand remarkably during T cell-dependent immune responses to certain parasites while CTMCs exhibit little or no T cell dependence (Moon et al., 2010). Human MCs also exhibit heterogeneity and are thus classified by their content of serine proteases as tryptase-only MCs (MCTRY), which predominate in the alveolar septa and in the small intestinal mucosa, chymase-only MCs (MCCHY), present in synovial tissue, or both tryptase- and chymase-positive MCs (MCCHYTRY) which localize in skin, tonsils and small intestinal submucosa (Irani et al., 1986; Irani and Schwartz, 1994).

**MAST CELL COMMUNICATION WITHIN IMMUNE SYSTEM VIA SOLUBLE MEDIATORS**

MC heterogeneity depending on the tissue distribution, is reflected by their ability to react to multiple stimuli (Frossi et al., 2004) and by the numerous immunoglobulin E (IgE)-dependent and -independent activation pathways. A plethora of membrane...
receptors can regulate MC activation: FcεRI and Fcγ receptors, Toll like receptors (TLRs), complement receptors, cytokine and chemokine receptors, and hormone receptors (Zhao et al., 2001; Theoharides et al., 2004; Galli et al., 2005b) as summarized in Table 1. Depending on the type, property, strength, and combination of the stimuli they receive, MCs secrete a diverse and wide range of biologically active products that can trigger, direct, or suppress the immune response (Frossi et al., 2004). MC soluble products, listed in Table 2, can be divided into two categories: (a) preformed mediators, such as histamine, proteoglycans, and neutral proteases and certain cytokines, in particular tumor necrosis factor-alpha (TNF-α), that are rapidly and instantaneously released upon MC activation; (b) newly synthesized mediators, such as cytokines, chemokines, lipid mediators, growth and angiogenic factors that start to be synthesized after MC activation (Galli et al., 2005a; Metz and Maurer, 2007). Although these products are all important in both innate and acquired immunity, the rapid release of MC mediators is crucial for the initiation of the immune response at the site of infection since they are able to modulate the immune-cell trafficking and to provide co-stimulatory signals for cell activation. In particular, focusing on rapidly released mediators, histamine is the most abundant vaso-active amine that is stored in MC granules, and it targets specific receptors on several cell types. It binds to histamine receptors on airway smooth muscle cells and on gastrointestinal cells and induces contraction and vasospasm. In addition, it has been reported that histamine is able to drive dendritic cell (DC) migration and activation (Caron et al., 2001). Among early released MC products, TNF-α is a granule-stored preformed cytokine that plays a crucial role during innate immunity as, by inducing the early influx of neutrophils, it promotes the clearance of pathogens and improves survival and morbidity (Henz et al., 2001). Serine proteases, chymase and tryptase, and the metalloprotease carboxypeptidase A are the major pre-synthesized granule components. They directly protect against parasites and venoms (carboxypeptidase A; Metz and Maurer, 2007), but also favor the expulsion of nematodes by increasing intestinal permeability (mouse MC protease-1, mMCP-1; McDermott et al., 2003), by allowing tissue remodeling, fibronectin turn-over (mMCP-4; Tchougounova et al., 2003), and induction of persistent influx of neutrophils with long lasting inflammation (mMCP-6; Huang et al., 1998).

Arachidonic acid-derived prostaglandins and leukotrienes are de novo synthesized metabolites of cyclooxygenase and lipoxygenase enzymes. They improve the innate response by increasing MC numbers at inflammation sites, through the recruitment of immature MCs and/or progenitors (Weller et al., 2005). MC-secreted cathelicidins reduce bacterial numbers, thus directly driving bacterial clearance (Di Nardo et al., 2003). MC-secreted compounds also contribute to the acquired immune response, serving as mediators for B and T cell recruitment and activation. MC-derived leukotriene B4 induces chemotaxis of effector CD8+ T cells in the course of allergic inflammation (Ott et al., 2003), while MC-derived TNF-α is crucial in the recruitment of CD4+ cells.

Table 1 | MC membrane-bound receptors.

| Receptor family | Members | Reference |
|-----------------|---------|-----------|
| FcR | FcεRI | Kinet (1999) |
| FcγR | FcγRI, FcγRII, FcγRIIIb | Malbec and Daëron (2007) |
| TLR | TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10a | Marshal et al. (2009) |
| MHC | MHC class I, MHC class II | Svensson et al. (1997) |
| Complement receptor | CR1, CR2, CR3, CR4, CR5, C3aR, C5aR | Füreder et al. (1995) |
| Cytokine receptor | CD117, IL-1R, IL-3R, IL-10R, IL-12R, INFγR, TGFβR | Edling and Hallberg (2007), Moritz et al. (1998), Frossi et al. (2004) |
| Chemokine receptor | CCR1, CCR3, CCR4, CCR5, CCR7, CXCR1, CXCR2, CXCR3, CXCR4, CXCR6, CX3CR1 | Juremalm and Nilsson, (2005) |

RECEPTOR FOR ENDOGENOUS MOLECULES

| Histamine receptor | H1/H2/H3/H4 receptor | Sander et al. (2006) |
| Others | Endothelin-1, neurotensin, substance P, PGE2, adenosine | Galli et al. (2005b) |
| Adhesion molecules | ICAM-1, VCAM, VLA4, CD226 (DNAM-1), Siglec8, CD47, CD300a, CD72 | Hudson et al. (2011), Collington et al. (2011), Sick et al. (2009), Bachelet et al. (2006) |

CO-STIMULATORY MOLECULES

| TNF/TNFR family members | CD40L, OX40L, 4-1BB, GITR, CD153, Fas, TRAILR | Juremalm and Nilsson (2005), Nakae et al. (2006), Nakano et al. (2009) |
| B7 family member | CD28, ICOSL, PD-L1, PD-L2 | |
| TIM family members | TIM1, TIM3 | |
| Notch family members | Notch1, Notch2 | |

Some molecules have been detected only in studies on humana or murineb MCs where not indicated, molecules are expressed in both species.
Table 2 | Major MC-derived mediators.

| Class                  | Mediators                                                                 | Physiological effects                                                                 |
|------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **PREFORMED**          |                                                                           |                                                                                        |
| Biogenic amines        | Histamine, 5-hydroxytryptamine                                            | Vasodilatation                                                                         |
|                        |                                                                          | Leukocyte regulation, pain, vasoconstriction                                        |
| Proteoglycans          | Heparin, heparin sulfate, Chondroitin sulfate                             | Angiogenesis, coagulation                                                               |
|                        |                                                                          | Tissue remodeling                                                                      |
| Proteases              | Tryptase, Chymase, MC-CPA/Carboxypeptidase A, Cathepsins B, C, D, E, G, L, S | Inflammation, pain, tissue damage, PAR activation                                      |
|                        |                                                                          | Inflammation, pain, tissue damage                                                     |
|                        |                                                                          | Enzyme degradation                                                                      |
|                        |                                                                          | Pathogen killing, tissue remodeling                                                     |
|                        |                                                                          | Pathogenesis of asthma and other allergic disorders                                    |
| Lysosomal enzymes      | β-hexosaminidase, β-glucuronidase, β-galactosidase, arylsulfataseA         | ECM remodeling                                                                         |
| Others                 | Nitric oxide synthase, Endothelin, Kinins                                 | NO production                                                                          |
|                        |                                                                          | Sepsis                                                                                 |
|                        |                                                                          | Inflammation, pain, vasodilatation                                                     |
|                        |                                                                          | Anti-inflammatory effects                                                               |
| **NEWLY SYNTHESIZED**  |                                                                           |                                                                                        |
| Lipid-derived          | LTB₄, LTC₄, PGD₂, PAF                                                    | Inflammation, leukocyte recruitment, endothelial adhesion, smooth muscle cells contraction, vascular permeability |
| Cytokines              | IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-11β, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-22, IL-25, IL-30, MIF, TNFα, IFNα, IFNβ, IFNγ | Inflammation, leukocyte proliferation and activation, immunoregulation                  |
| Chemokines             | CCL1, CCL2, CCL3β, CCL4α, CCL5β, CCL7αβ, CCL8α, CCL11β, CCL13α, CCL16α, CCL17, CCL19β, CCL20α, CCL22αβ, CCL25α, CXCL1α, CXCL2, CXCL3α, CXCL4, CXCL6, CXCL8α, CXCL10α, CX3CL | Leukocyte chemotaxis                                                                  |
| Growth factors         | TGFβ, SCFα, G-CSF, GM-CSF, VEGF, NGFβ, LIFβ, bFGF                       | Growth of various cell types                                                           |
| Antimicrobial species  | Antimicrobial peptides, NO, superoxide, ROS                              | Pathogen killing                                                                        |

Some mediators have been detected only in studies on human *or* murine *MCs or not investigated* where not indicated molecules are expressed in both species.

General references: Galli et al. (2005a), Metz and Maurer (2007).

T cells to draining lymph nodes, during *Escherichia coli* infection (McLachlan et al., 2003). In addition, a TNF-α-dependent effect on Langerhans cells that migrate from skin to draining lymph nodes following response to bacterial peptidoglycan has been reported (Jawdat et al., 2004).

The anti-inflammatory properties of MCs were explored in *vivo*, providing evidence about MC ability to suppress the development and magnitude of the adaptive immune response (reviewed in Galli et al., 2008a). Indeed, MC-derived histamine seems to be responsible of the systemic immunosuppression of contact hypersensitivity (CHS) responses achieved by the ultraviolet B (UVB) irradiation of the skin (Hart et al., 1998), while MC-derived IL-10 limits the response to allergic contact dermatitis (Grimaldèston et al., 2007). MC-derived IL-10 has been implicated as a mechanism of negative immune-modulatory effects following *Anopheles* mosquito bites or in peripheral tolerance to skin allograft (Depinay et al., 2006; Lu et al., 2006), but other soluble or surface molecules might be responsible for MC negative immunomodulatory functions. The mechanisms controlling the immunosuppressive function of MCs are under investigation and might be considered for pharmacological intervention to modulate the immune system in inflammatory diseases.

**PATTERN OF MC MEMBRANE-BOUND MOLECULES REGULATING IMMUNOLOGICAL EFFECTOR FUNCTIONS**

Mast cells express a broad array of cell surface receptors and ligands involved in cell–cell and cell-extracellular-matrix adhesion, which mediate the delivery of co-stimulatory signals that empower these cells to interact with different immune- and non-immune cells. These interactions are often bi-directional, fulfilling mutually regulatory, and/or modulatory roles, including influences on several cellular processes, such as proliferation and gene transcription. Accordingly, MC effector function plasticity might depend not only on the activatory/inhibitory signals and on the specific released mediators, but also on the secondary, co-stimulatory signals that they receive from their cellular partners in the microenvironment. Thus, MCs specialize in establishing reliable, wideband communication with other cells, orchestrating the overall immune response (Bachelet and Levi-Schaffer, 2007).
Here, we aim to describe the recent advances in contact-mediated co-stimulatory pathways connecting MC with innate and acquired immune cells. The molecules that mediate the cross-talk between MCs and their cell partners are all listed in Table 3.

### MC AND INNATE IMMUNE CELLS

#### MCs and dendritic cells

The close apposition of MCs and DCs in sub-epithelial areas as sentinel of invading antigen, has led investigators to propose their potential functional partnership in modulation of the immune responses to environmental changes (Mazzoni et al., 2006; Otsuka et al., 2011). DCs do not only represent a single uniform population but display a considerable degree of heterogeneity which complicates the network of interactions with MC subtypes (Shortman and Liu, 2002). MCs express several molecules (TNF-α, histamine, PGD2, chemokines) that might affect DC function in peripheral inflamed tissues. Both human and mouse IgE-activated MCs have been widely implicated in the process of DC mobilization from tissue to secondary lymphoid organs (Jawdat et al., 2004; Suto et al., 2006; Dawicki et al., 2010), DC maturation (Skokos et al., 2003; Kitawaki et al., 2006), and DC capacity to promote T cell responses (Kitawaki et al., 2006; Leonard et al., 2006; Mazzoni et al., 2006; Dudeck et al., 2011).

To date, while exchange of soluble mediators between MCs and DCs has been well characterized, data regarding MCs-DCs direct cross-talk are very scarce. Nonetheless, some clues are been unveiled.

In an *in vitro* cultured human system, a combinatorial effect of various factors which are able to activate human cord blood-derived MCs, including those acting in a cell contact-dependent fashion, are required for the optimal induction of Th2-promoting human monocyte-derived DCs (Kitawaki et al., 2006). Moreover, it has been shown that murine peritoneal MCs (PCMCs) can undergo a dynamic interaction with immature DCs, inducing DC maturation and the release of the T cell modulating cytokines IFN-γ, IL-2, IL-6, and TGF-β. Such PCMCs-primed DCs subsequently induced T cell proliferation and Th1 and Th17 responses (Dudeck et al., 2011). Studies in mice report that bone marrow-derived MCs

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### Table 3 | MC physical interactions with other immune cells.

| Cell types | MC molecule | Partner molecule | Effect on MC | Effect on partner cell | Reference |
|------------|-------------|------------------|--------------|------------------------|-----------|
| MC-DC     | ICAM-1      | LFA-1            | ↑ Ca++ influx | ↑ Maturation and chemotaxis, Maturation and chemotaxis | Otsuka et al. (2011) |
| MC-MDSC   | ICAM-1      | LFA-1            | ↑ Recruitment and survival | ↑ Migration and suppression activity, Migration and suppression activity | Yang et al. (2010) |
|            | n.i.        | n.i.             | ↑ Recruitment and survival | ↑ Recruitment and chemotaxis, Migration and suppression activity | Burke et al. (2008) |
|            | n.i.        | n.i.             | ↑ Recruitment and chemotaxis | ↑ Migration and suppression activity | Vosskuhl et al. (2010) |
| MC-NK     | CXCL8       | CXCR1            | n.i.         | ↑ Recruitment, Migration and suppression activity | Bachelet et al. (2006) |
|           | OX40L       | OX40             | n.i.         | ↑ Recruitment, Migration and suppression activity | Elishmereni et al. (2010) |
| MC-Eos    | CD226       | CD112            | ↑ Degranulation | ↑ Migration and suppression activity | Minai-Fleminger et al. (2010) |
|           | CD48        | 2B.4             | n.i.         | ↑ Migration and suppression activity | |
|           | n.i.        | n.i.             | ↑ Migration and suppression activity | ↑ Migration and suppression activity | |
| MC-CD4+T | ICAM-1      | LFA-1            | ↑ Degranulation and cytokine release | ↑ Activation and proliferation | Inamura et al. (1998), Mekori and Metcalfe (1999) |
|            | ICA-M       | LFA-1            | Adhesion to endothelial cell | ↑ Activation and proliferation | Brill et al. (2004) |
|            | LTβR        | LTβR ligand OX40L | ↑ Cytokine release | ↑ Activation and proliferation | Stopfer et al. (2004) |
|            | MHC-II      | TCR              | n.i.         | ↑ Activation and proliferation | Frandji et al. (1993), Fox et al. (1994) |
|            | ICOSL       | ICOS             | n.i.         | ↑ Activation and proliferation | Kashivakura et al. (2004) |
| MC-CD4+B  | MHC-I       | TCR              | ↑ Expression of co-stimulatory molecules and degranulation | ↑ Cell activation, Cell activation | Malaviya et al. (1996), Stelekati et al. (2009) |
|            | MHC-I       | TCR              | n.i.         | ↑ Cell activation, Cell activation | |
| MC + Treg | OX40L       | OX40             | ↓ Degranulation | ↓ Cell activation, Cell activation | Gri et al. (2008), Piconese et al. (2009) |
|            | TGFβR       | TGFβ membrane-bound | ↑ Degranulation, ↑ IL-6 production | ↓ Cell activation, Cell activation | Ganeshan and Bryce (2012) |
| MC + B    | CD40L       | CD40             | n.i.         | ↑ Proliferation and Ig switch, Proliferation and Ig switch | Gauchat et al. (1993), Merluzzi et al. (2010) |
| n.i., not investigated. |            |                  |              |                        |           |
(BMMCs) promote the maturation and chemotactic activity of bone marrow DCs through direct cell–cell interaction during the sensitization phase of CHS response. BMMCs and bone marrow derived immature DCs interact throughout intracellular adhesion molecule (ICAM)-1 and lymphocyte function-associated antigen (LFA-1) enhancing DC expression of the CD40, CD80, CD86, and CCR7 co-stimulatory molecules, thus promoting maturation and chemotaxis of DCs (Otsuka et al., 2011). It is possible to argue that DCs make use of MC-induced active LFA-1 to control the contact duration with naive T cells and to promote T cell priming (Balkow et al., 2010). On the other hand, co-cultures of stimulated bone marrow derived DCs with BMMCs increases calcium influx and up-regulate membrane-bound TNF-α (Otsuka et al., 2011).

**MCs and natural killer cells**

Concerning the cellular interactions that play a role in innate immune defense, emerging evidences show MC-dependent natural killer (NK) cell recruitment and activation. NK cells are granular cytotoxic and circulating lymphocytes involved in the clearance of transformed and pathogen-infected cells. As a part of the innate immune system, their recruitment to the site of infection is mediated by a large spectrum of chemokines which bind to the chemokine receptors, CCR2, CCR5 and CXCR3 on NK cells. Activated MCs can induce NK cell accumulation in different disease models. For instance, immune surveillance by MCs is important for NK cell recruitment and viral clearance during Dengue infection (St John et al., 2011). Human cord blood-derived MCs stimulated with virus-associated TLR3 agonist can recruit human NK via the CXCL8 and CXCR1 axis, underlining MC role as sentinel cell during early viral infections (Burke et al., 2008). Lipopolysaccharide (LPS)-activated BMMCs induce cell contact-dependent IFN-γ secretion by NK cells, without affecting cell-mediated cytotoxicity. Cellular interaction is partly mediated by OX40L expression on MCs (Vosskuhl et al., 2010). In the cited work, authors underline that different MC signals of activation confer different results in terms of NK activation. In fact, in addition to LPS, stimulation of MCs via TLR3 and TLR9, but not with IgE/antigen, amplifies IFN-γ secretion by NK cells (Vosskuhl et al., 2010). Similarly, in a model of hepatocarcinoma, MC protumoral role is associated with reduction of NK cell number and activation. This effect was due to the fact that, in the tumor micro environment, SCF-activated MCs release adenosine that inhibit production of IFN-γ by NK cells (Huang et al., 2008). Enhanced CCL3-mediated recruitment of NK cells is instead observed in a orthotopic melanoma model in which TLR2-activated MCs exert antitumor properties by secreting large amounts of this chemokine (Oldford et al., 2010).

**MCs and eosinophils**

Mast cells and eosinophils (Eos) co-exist in tissues during the late and chronic phases of allergic reaction where the intracellular events following IgE/Ag-induced MC activation lead to the release of pro-inflammatory mediators, which cause the immediate, early-phase of the allergic process within minutes of allergen exposure (Williams and Galli, 2000), and induce the recruitment of inflammatory cells, i.e., macrophages, T cells, Eos, basophils, and perhaps invariant NK T cells (Galli et al., 2008b). These cells, and mainly the Eos, cause the onset of the late phase of allergic response that usually occurs a few hours later (Metz et al., 2007). Nevertheless, a clear cut interplay between MCs and Eos has been proven not only in allergic inflammatory tissues (Minai-Fleminger and Levi-Schaffer, 2009; Wong et al., 2009), but also in gastric carcinoma (Caruso et al., 2007), chronic gastritis (Piazuelo et al., 2008), Crohn's disease, and Ascaris infection (Bell et al., 2002), leading to new perspectives of the current research in this area.

Eos and MCs may mutually influence each other functions by a variety of paracrine and receptor/ligand-dependent signals. In this context, some surface molecules are potential candidates to mediate MC-Eos physical contact. A considerable advance in understanding MC-Eos interaction in a human system was made by Levi-Schaffer and coworkers. CD48 and 2B4 expressed by human cord blood-derived MCs and peripheral Eos, respectively mediate the MC-Eos physical interface as a co-stimulatory signaling switch, inducing effect on Eos viability and activating Eos to release eosinophil peroxidase, IFN-γ and IL-4 (Elishmereni et al., 2010). Similarly, evidence for a role of CD226/CD112 interaction in Eos-dependent enhancement of IgE-induced MCs activation has been described (Bachelet et al., 2006). Other ligand-receptor interactions between MCs and Eos seem to be mediated through LFA-1 and ICAM-1. This pathway can be activated upon MC degranulation and results in the recruitment of eosinophils at the site of inflammation (Elishmereni et al., 2010). Moreover, by transmission electron microscopy it has been possible to demonstrate that human peripheral blood Eos and cord-blood-derived MC functionally adhere to each other as Eos peroxidase (EPO) is transferred from Eos to MCs and tryptase from MCs to Eos, thus indicating that MCs and Eos show signs of reciprocal activation (Minai-Fleminger et al., 2010).

**MCs and neutrophils**

Polymorphonuclear neutrophils (PMNs) constitute the most abundant leukocyte population in the peripheral blood of humans, make a highly significant contribution to the host defense, and are particularly well studied in the context of bacterial infection. However, PMN are more versatile as there is increasing evidence for their participation in acute and chronic inflammatory processes, in the regulation of the immune response, in angiogenesis, and in the interaction with tumors (Fridlender et al., 2009; Mantovani et al., 2011). PMNs have emerged as an important component of effector and regulatory circuits in the innate and adaptive immune systems. In contrast to the traditional view of these cells as short-lived effectors, evidence now indicates that they have diverse functions. By responding to tissue- and immune cell-derived signals and by undergoing polarization, PMNs are reminiscent of macrophages (Fridlender et al., 2009; Biswas and Mantovani, 2010). PMNs engage in bi-directional interactions with diverse components of both the innate and adaptive immune systems and can differentially influence the response depending on the pathological context. With the advent of MC-deficient mice and the ability to selectively reconstitute their deficiency it has been possible to show that MCs are critical for the PMN activation. Thus, in a model of immune complex-mediated peritonitis, the rapid recruitment of PMNs turns out to be initiated by LT produced by MCs, which are strategically located at the host-environment.
A complex network of cellular interactions characterizes tumor populations have not yet been described.

The unique ability of MCs to store and immediately release TNF-α on demand, and subsequently as newly synthesized inflammatory molecule, is essential for the rapid onset and for the sustaining of inflammatory reactions (Vershil et al., 1991). A cornerstone in this context was the observation that MCs and MC-derived TNF-α initiate the life-saving inflammatory response rapidly upon encountering microbes and microbial constituents through the influx of neutrophils in mouse models for acute bacterial infections (Echtenacher et al., 1996). In murine infectious peritonitis it has been published that, besides TNF-α, several other MC-derived molecules have a role in the recruitment of PMNs. In fact, MC-derived LT (Ramos et al., 1991), mouse MC protease 6 (mMCP-6; Caughey, 2007), and the chemokine MIP-2 (CXCL2; Wang and Thorlacius, 2005) are critical for a rapid and protective influx of PMNs. The available data suggest that mMCP-6 triggers the release of MIP-2 from endothelial cells ("activation" of endothelial cells), which in turn enhances the release of MC-derived TNF-α, followed by sustained secretion of LT.

However, in this context in which a clear functional interaction between MC and PMNs has been established, receptors-ligand pair that might physically mediate the cross-talk between these two cell populations have not yet been described.

**MCs and myeloid derived suppressor cells**

A complex network of cellular interactions characterizes tumor microenvironment with the presence of immune-suppressive and pro-inflammatory cells. MCs are known actors in cancer setting thanks to their ability to directly influence tumor growth, angiogenesis, and tissue remodeling and to exert an indirect function by immune-modulating cancer microenvironment. A closed loop amongst MCs and myeloid derived suppressor cells (MDSCs), also involving regulatory T (Treg) cells, has been recently described in murine hepatocarcinoma tumor microenvironment. MCs promote the migration and suppressor function of tumor MDSCs by CCL-2 and 5-lipoxygenase release, further exacerbating tumor inflammatory microenvironment. Indeed, MCs stimulate MDSCs to secrete the pro-inflammatory cytokine IL-17 which stimulate Treg cells to release IL-9 which in turn, strengthen the survival and protumoral effect of MCs (Yang et al., 2010; Cheon et al., 2011).

These are preliminary studies that disclose a novel relationship between MDSCs, MCs, and Treg cells. Further analysis will determine whether these cells physically interact through co-stimulatory molecules.

**MC AND ADAPTIVE IMMUNE CELL**

**MCs and effector T cells**

The close physical apposition between MC and T cell has been observed during T cell-mediated inflammatory processes (Mekori and Metcalfe, 1999), such as cutaneous delayed-type hypersensitivity (Dvorak et al., 1976; Waldorf et al., 1991), sarcoidosis (Bjermer et al., 1987), and in chronic inflammatory processes associated with the pathology of inflammatory bowel disease and rheumatoid arthritis (Marsh and Hinde, 1985; Malone et al., 1986). Moreover, morphological studies have revealed that MCs reside in close physical proximity to T cells in inflamed allergic tissues and at sites of parasitic infections (Friedman and Kaliner, 1985; Smith and Weis, 1996).

Some of such influences have been attributed to the biological effects of a wide range of soluble mediators; however increasing amounts of literature documents recognize the importance of intercellular communication involving the binding of cell surface molecules.

Early studies demonstrated that intercellular contacts between MC and T cell lines are able to activate MC transcription machinery (Oh and Metcalfe, 1996). Adhesion of HMC-1 human MC line, or murine BMMCs, to activated T lymphocytes induces MC degranulation and TNF-α production (Bhattacharyya et al., 1998). Moreover, the MC-T cell cross-talk results in the release of matrix metalloproteinase (MMP)-9 and the tissue inhibitor of metalloproteinase 1 from HMC-1 human MCs or from mature peripheral blood-derived human MCs. This effect, as well as the secretion of β-hexosaminidase and several inflammatory cytokines (TNF-α, IL-4, and IL-6), is mediated by a direct contact of activated, but not resting, T cell membranes with MCs (Baram et al., 2001). In accordance with these findings, a recent study revealed that activated T cell microparticles, small membrane-bound structures released from cells during activation or apoptosis, are able to induce the production of soluble mediators from LAD2 human cell line and human cord blood-derived MC cultures. By releasing microparticles, T cells may convey surface molecules and activate distant MCs within the same inflammatory site (Shefer et al., 2010). Other heterotypic adhesion-induced effects on MC activation have been described. The proximity of activated T lymphocytes to HMC-1 promotes MC adhesion to the receptor of endothelial cells as well as to the extracellular matrix ligands (Brill et al., 2004).

The adhesion pathway mediated by LFA-1/ICAM-1 induced FcεRI-dependent murine BMMC degranulation after heterotypic aggregation with activated T cells was the first membrane-bound pathway involved in MC/T cell cross-talk to be described (Inamura et al., 1998). In addition, lymphotoxin-β receptor (LTBR) expressed on murine BMMCs can be triggered by LTBR ligands expressed by T cell lines and transduces a co-stimulatory signal leading to the release of cytokines (IL-4, IL-6, TNF-α) and chemokines (CXCL2 and CCL5) from ionomycin-activated BMMCs (Stopfer et al., 2004). Moreover, the engagement of OX40 on activated CD4+ T cells by OX40L-expressing MCs, together with the secretion of soluble MC-derived TNF-α, costimulates proliferation and cytokine production from activated CD4+ T cells (Nakae et al., 2006). Similar results were also established in a culture system of human tonsillar MCs and human T cells which confirmed the enhancement of T cell proliferation upon direct OX40/OX40L engagement demonstrating the presence of a bi-directional cellular cross-talk among these cell types (Kashiyakura et al., 2004). The existence of functional MC-T cell interaction also arises from the observation that murine BMMCs could present antigenic peptides to T cell lines and CD4+ T cell hybridoma (Frangili et al., 1995, 1996). MHC-II-dependent antigen presentation to CD4+ T cells by MCs was also demonstrated in rat and human cell systems (Fox et al., 1994; Poncet et al., 1999) reinforcing the concept that MCs can serve as unconventional antigen presenting cells for T lymphocytes (Valitutti and Espinosa, 1996).
Ag from phagocytosed bacteria for presentation via MHC class I. IL-6 promotes Th17 skewing of T reg cells with loss of both Foxp3
tact, dependent on OX40/OX40L interaction, and T cell-derived MC activation breaks peripheral tolerance. Direct cell–cell con-
2010), suggesting that a complex interaction between MCs and
of colorectal cancer, highly suppressive T reg cells lose the abil-
lymph nodes hosting T cell priming in experimental autoim-
encephalomyelitis further supporting the occurrence of an MC-mediated inhibition of Treg suppression in the establish-
ung that the IgE production was inhibited by anti-CD40L mAb
CD40L, IL-4, and IL-13 compared to NMCs from patients with
mucosal tissues (Vliagoftis and Befus, 2005; Gri et al., 2008) and to
influence each other’s function. Indeed, activated Treg cells caused a reduction in the expression of FcεRI on murine BMMCs by
contact-dependent mechanism and production of soluble fac-
tors such as TGF-β and IL-10 (Kashyap et al., 2008). Treg cells
can hinder BMMC degranulation and immediate hypersensitivity
response through the engagement of OX40L on MCs (Gri et al.,
2008). Treg cell-mediated inhibition of MC function is regulated at a single-cell level and is not restricted to BMMCs, but is a com-
mon feature of murine PCMCs and human LAD2 MC line (Frossi
et al., 2011).

A recent study confirmed that co-culture of Treg cells with
murine BMMC suppresses degranulation but primes MCs for
production of IL-6 via a contact-dependent surface-bound TGF-β
mechanism (Ganesan and Bryce, 2012). Interestingly, in a model
of colorectal cancer, highly suppressive Treg cells lose the abil-
ity to suppress human LAD2 MC degranulation (Blatner et al.,
2010), suggesting that a complex interaction between MCs and
Tregs within tumor microenvironment exists, although the mech-
anism behind these events has not been yet discovered. Conversely,
MC activation breaks peripheral tolerance. Direct cell–cell con-
tact, dependent on OX40/OX40L interaction, and T cell-derived
IL-6 promotes Th17 skewing of Treg cells with loss of both Foxp3
expression and T cell suppressive properties in vitro. Activated
MCs, Tregs, and Th17 cells display tight spatial interactions in
lymph nodes hosting T cell priming in experimental autoim-
mune encephalomyelitis further supporting the occurrence of an MC-mediated inhibition of Treg suppression in the establish-
ment of Th17-mediated inflammatory responses (Piconese et al.,
2009).

Under certain conditions such as in inflammation and immune
reactions, increasing expression of ICOSL might contribute to
the regulatory role of MCs. Indeed, in vitro experiments and the
in vivo model of neutrophilic airway inflammation, allowed the
identification of an intimate link between LPS-stimulated murine
BMMCs, which upregulate ICOSL surface expression, and the
generation of IL-10 producing inducible regulatory CD4+ T cell
with inhibitory ability on effector T cells function. Indeed, ICOSL-
deficient BMMCs are not able to sustain IL-10 producing T cell
activation (Nie et al., 2011).

MCs and B cells
Mast cells produce several cytokines, such as IL-4, IL-5, IL-6, and
IL-13, that are known to regulate, directly or in combination with other factors, B cell development and function. Moreover,
the CD40L co-stimulatory molecule is expressed on the surface of activated-BMMCs, skin MCs, and MCs under allergic inflam-
matory conditions (Gauchat et al., 1993; Pawankar et al., 1997).
These data further support the existence of a functional cross-
talk between these two cell types. The first evidence of an effective
MC-B cell cross-talk, mediated by the physical interaction through
the CD40L:CD40 axis, was reported by Gauchat and coworkers.
They showed that CD40L was expressed on both freshly puri-
fied human lung MCs and on the human cell line HMC-1 and
further demonstrated that these MCs can interact with B cells
to induce the production of IgE, in the presence of IL-4 and in
absence of T cells (Gauchat et al., 1993). Furthermore, the role
of the CD40-CD40L axis in the induction of IgE production by
B cells was also observed in perennial allergic rhinitis (PAR), an
IgE-mediated atopic disease. Nasal MCs (NMCs) from patients
with PAR displayed significantly higher expression levels of FcεRI,
CD40L, IL-4, and IL-13 compared to NMCs from patients with
chronic infective rhinitis (CIR). The essential role of CD40L in
this allergic disease context was further substantiated by the find-
ing that the IgE production was inhibited by anti-CD40L mAb
(Pawankar et al., 1997). The group of Méchéri was the first to
show that unstimulated BMMCs were able to induce resting B cells
to proliferate and to become IgM-producing cells. In this case, B
cell activation was mediated by MC-derived factors and contact
between these two cell types seemed not to be required (Tkaczyk
et al., 1996). Some years later, the same research group reported
that membrane vesicles, released by the MC cytoplasmic granules
and termed exosomes, were responsible of MC-driven B cell prolif-
eration and activation. Interestingly, they showed that important
co-stimulatory molecules, such as MHC-II, CD86, CD40, CD40L,
LFA-1, and ICAM-1, were associated with exosomes (Skokos et al.,
2002).

Only recently the study of the specific role of MCs in B cell
growth and differentiation has been investigated more in detail.
Merluzzi and coworkers proved that both resting and activated
MCs were able to induce a significant inhibition of cell death and an increase in proliferation of naïve B cells. Such proliferation was further enhanced in activated B cells. This effect required cell–cell contact and MC-derived IL-6. Activated MCs were shown to regulate CD40 surface expression on unstimulated B cells and the interaction between CD40 and CD40L on MCs, together with MC-derived cytokines, were involved in the differentiation of B cells into CD138⁺ plasma cells and in selective IgA secretion. These data were corroborated by in vivo evidence of infiltrating MCs in close contact with IgA-expressing plasma cells within inflamed tissues (Merluzzi et al., 2010).

CONCLUDING REMARKS

In the last few years, our perception of MCs function has dramatically changed. In fact, there has been mounting evidence that the function of these cells is not limited to acting as first line of defense against invading pathogens or as effector cells in allergy, but is extended to perform additional and unexpected activities in strict collaboration with adaptive immune and other non-immune cells. Thus, MCs together with other innate and adaptive immune cells orchestrate complex functional programs to promote host defense, to control the development of self-tolerance, and to avoid autoimmunity. In this context, the gene expression pattern, the phenotype, as well as MC function must rapidly change in a coordinate, time-dependent manner in response to micro-environmental soluble and cellular signals. In view of their extensive assortment of membrane receptors able to mediate delivery of co-stimulatory signals, of molecules involved in cell–extracellular-matrix adhesion and in cell–cell contacts and of soluble pro- and anti-inflammatory mediators, MCs may profoundly influence the development, intensity, and duration of adaptive immune responses that ultimately serve for host defense, allergy, and autoimmunity. Considering the continuously emerging findings in the field, it is predictable that in the next years we will assist to the discovery of additional, unsuspected biological features that MCs possess.

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