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Integrating innate and adaptive immune cells: Mast cells as crossroads between regulatory and effector B and T cells

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ABSTRACT

A diversity of immune mechanisms have evolved to protect normal tissues from infection, but from immune damage too. Innate cells, as well as adaptive cells, are critical contributors to the correct development of the immune response and of tissue homeostasis. There is a dynamic "cross-talk" between the innate and adaptive immunomodulatory mechanisms for an integrated control of immune damage as well as the development of the immune response.

Mast cells have shown a great plasticity, modifying their behavior at different stages of immune response through interaction with effector and regulatory populations of adaptive immunity. Understanding the interplays among T effectors, regulatory T cells, B cells and regulatory B cells with mast cells will be critical in the future to assist in the development of therapeutic strategies to enhance and synergize physiological immune-modulator and -suppressor elements in the innate and adaptive immune system.

1. Introduction

Mast cells (MCs) originate in the bone marrow from lineage-specific multipotent hematopoietic progenitors, circulate as CD34+ precursors until they migrate to tissues and mature into effector cells in proximity of blood vessels. MCs display functional diversity depending on the tissue in which they differentiate. This distribution permits them, along with dendritic cells and tissue macrophages, to be among the first cells of the immune response to interact with environmental antigens and allergens, invading pathogens or toxic compounds (Galli et al., 2011). In the intestinal tract, MCs are distributed in the lamina propria and contribute both to tolerance for food as well as to sustain the immune response against pathogens. The best known mechanism of MC activation is dependent on antigenic stimulation through the cross-linking of immunoglobulin E (IgE)-bound high affinity receptor for IgE (FcεRI). However, to sense tissue microenvironment, MCs are equipped with other receptors such TLRs and cytokines and chemokines receptors (reviewed in Gri et al. (2012) and Sibilano et al. (2012)). Moreover, the function of these receptors is finely modulated by co-stimulatory molecules (OX40, CD40L, CD80, CD86, PD-L1, PD-L2), either enhancing or inhibiting MC responses (Gri et al., 2012; Migalovich-Sheikhet et al., 2012).

MCs are specialized to serve functions that can amplify or suppress innate or acquired immune responses (Galli et al., 2008; Hershko and Rivera, 2008). Such functions mainly reflect the ability of MCs to secrete a wide spectrum of preformed or newly synthesized biologically active products, many of which can potentially mediate pro-inflammatory (IL-1, IL-6, IL-8, IL-17) or immunosuppressive functions (IL-10, TGF-β) (Frossi et al., 2011; Galli et al., 2008). However, the MC can be considered a "social" cell since both positive and suppressive effects on immune responses are amplified or mediated through the interaction with different effector or regulatory immune cells. The cross-talk between MCs and effectors or regulatory T and B cells will be discussed in the present review. Additionally, physical pathways will be dissected as possible targets of immune intervention in diseases in which MCs play a role.

Abbreviations: EAE, experimental autoimmune encephalomyelitis; EGF, epidermal growth factor; MC, mast cell; PCMC, peritoneal cell-derived mast cells; SMZL, splenic marginal zone lymphoma; Teff, effectot T cells; Tph-1, tryptophan hydroxylase-1; Treg, regulatory T cells

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2. Interactions between MCs and adaptive effector cells

2.1. Effector T cells activate MCs

Observations such as the close physical proximity between MCs and T cells in inflamed tissues and the capability of the former to release a wide range of immunomodulatory mediators and to express surface molecules important in costimulation in both adaptive and innate immunity, have led investigators to propose a functional bi-directional relationship between these two cell populations (Mekori, 2004; Bachelet et al., 2006; Kalesnikoff and Galli, 2008; Tsai et al., 2011; Gri et al., 2012). Indeed, morphologic studies have documented an increase in the local density of MCs and their activation during T cell-mediated inflammatory processes, as observed in cutaneous delayed-type hypersensitivity, graft-versus-host reactions, sarcoidosis, Crohn's disease, rheumatoid arthritis, and psoriasis (Mekori, 2004; Bachelet et al., 2006; Kalesnikoff and Galli, 2008; Dudeck et al., 2011, Rabenhorst et al., 2012). Both in vitro and in vivo studies have demonstrated that MCs or their products are pivotal in mediating leukocyte recruitment into inflammatory sites, are capable of presenting antigens to T cells, interact directly with and affect the function of cells of the adaptive immune system, and mediate tissue remodeling (Biedermann et al., 2000; Mekori, 2004; Bachelet et al., 2006; Kalesnikoff and Galli, 2008; Dudeck et al., 2011; Tsai et al., 2011; Gri et al., 2012). However, the nature of the T cell-derived signals that lead to MC activation has not yet been fully elucidated. A wide range of soluble mediators have been regarded as triggers, but increasing evidence indicates the importance of intercellular communication involving the binding of cell surface molecules.

In this regard, a direct physical contact between MCs and activated T lymphocytes was found to induce MC activation and mediator release. Both murine and human MCs could be activated to release granule-associated mediators, such as histamine and matrix metalloproteinase-9 (MMP-9); to produce several cytokines (i.e. TNF-α, IL-4, IL-6 and IL-8); and to induce MC adhesion to extracellular matrix components on physical contact with activated, but not resting, T cells (Inamura et al., 1998; Baram et al., 2001; Brill et al. 2004; Salamon et al., 2005, 2008). Furthermore, the expression and release of these mediators, were also induced when MCs were incubated with cell membranes isolated from activated T cells (Baram et al., 2001; Salamon et al., 2005, 2008; Shefler et al., 2008). Gene expression profiling validated by qRT-PCR has demonstrated the expression and production of cytokines (oncostatin M) and enzymes (MMP-9) that were specifically induced by this novel here-to-fore unknown pathway of activation (Salamon et al., 2008). Studies with murine MCs and myristate 13-acetate (PMA) – or anti-CD3-activated T cells, attributed the T cell-induced MC activation to interactions of surface molecules, such as intercellular adhesion molecule-1 (ICAM-1)and lymphotoxin-β receptor (LTβR), with their respective ligands (Inamura et al., 1998; Stopfer et al., 2004). Thus, direct contact between surface molecules on activated T cells and on MCs, was found to provide the stimulatory signal in MCs necessary for degranulation and cytokine release, independent of T-cell intracellular function, and in the absence of demonstrable soluble mediators. Indeed, separation of the two cell populations by a semipermeable porous membrane prevented this pathway of MC activation (Bhattacharyya et al., 1998; Baram et al., 2001).

The biological relevance of this pathway of MC activation can be envisaged from the findings with oncostatin M, a known fibrogenic cytokine. Both oncostatin M mRNA and protein were induced in human MCs specifically by means of heterotypic adhesion to activated T cells. MC-derived oncostatin was found to induce the proliferation of lung fibroblasts and its presence was demonstrated in MCs in the lungs of patients with sarcoidosis, a disease known to be mediated by T cells that culminates in fibrosis (Salamon et al., 2008). These results suggest that human MCs may contribute to T cell-mediated fibrotic inflammatory processes by means of local release of fibrogenic cytokines (i.e., oncostatin) following direct activation by T cells.

Other possible candidates of surface molecule-induced MC activation, are membrane vesicles that are secreted by T cells (Al-Nedawwi et al., 2009; Thery et al., 2009; Shefler et al., 2011). These vesicles contain cytosol and expose the extracellular side of the membrane they form from at their outer surface. Thus, membrane transfer is a mode of intercellular communication that may also involve T cell-induced MC activation within inflammatory sites in which both cell populations have been shown to be involved (Shefler et al., 2011). Indeed, T cell-derived microvesicles induced degranulation and cytokine (IL-8 and oncostatin M) release from human MCs with kinetics that resembled MC activation by activated fixed T cells or by whole membranes of the latter (Shefler et al., 2010). Thus, by releasing microvesicles, T cells might convey surface molecules similar to those involved in the activation of MCs by cellular contact.

Recently, it was shown that T cell-derived microvesicles were internalized by MCs in a time-dependent manner by an active (energy dependent) process, resulting in upregulation of several proinflammatory genes that have been here-to-fore unknown to be expressed in human MCs on “classical” activation through FcεRI cross-linking. Among these, IL-24 appeared to be a hallmark of microvesicle-induced activation. MC-derived IL-24, in turn, activated keratinocytes in vitro, as manifested by STAT 3 phosphorylation, and was found to be produced by MCs in psoriatic skin lesions (Shefler et al., 2014), a T cell-mediated disease wherein keratinocyte activation and MC involvement are noticed (Rabenhorst et al., 2012).

It therefore may be concluded that, through the generation of microvesicles, activated T cells may facilitate distant contact-mediated activation of MCs which are not in direct contact with T cells at the inflammatory sites (Shefler et al., 2011; Mekori and Hershko, 2012).

2.1.1. Stimulation of effector T cells by MCs

Stimulation of effector T cells by MCs was shown in the late 1980s in experimental autoimmune encephalomyelitis (EAE; Orr, 1988), a mouse model mimicking multiple sclerosis. In this T cell-mediated inflammatory disease MCs clearly enhanced tissue damage (Secor et al., 2000) by the induction of CD4+ and CD8+ T-cell expansion in the central nervous system (Gregory et al., 2005).

The ability of MCs to be antigen presenting cells appears to underlie their capacity to enhance T-effector activity (Frandji et al., 1996). This was demonstrated in a study where exposure to LPS and IFN-γ induced expression of MHC class II by MCs (Kambayashi et al., 2009). Consequently, MHC class II-expressing MCs effectively supported activated T effectors and caused the expansion of regulatory T cells (Tregs). LPS injection increased the number of MCs in the lymph nodes of mice, and induced both the expression of MHC Class II and the positive costimulatory B7 family members CD80 and CD86 (Kambayashi et al., 2009). This observation was supported by another study (Gaudenzio et al., 2009) in which treatment of peritoneal cell-derived MCs (PCMCs) with IFN-γ and IL-4 induced expression of MHC class II molecules. This caused the activation and proliferation of effector T cells and the formation of an immunological synapse between the PCMC and the T cell (Gaudenzio et al., 2009). Notch signaling was reported to induce MHC class II and OX40L expression on MCs leading to proliferation of T cells with a Th2 phenotype (Nakano et al., 2009). Taken together, these studies indicate that upregulation of MHC class II on MCs is a pivotal factor for stimulating T effector cells. Furthermore, MHC class I-dependent cross presentation of MCs to CD8+ T cells was shown to increase CD8+ T cell proliferation and effector functions (Stelekati et al., 2009). This observation was corroborated in vivo, by EAE studies showing that MCs could regulate CD8+ T