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Review

Mast cells: Emerging sentinel innate immune cells with diverse role in immunity

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ABSTRACT

Mast cells are phylogenetically old innate immune cells with less recognition in normal function of immune system as no such disease has been observed in humans due to their deficiency or inadequate function. Earlier mast cells were only known for their important role in the type 1 allergic reactions (i.e. anaphylaxis or some contact hypersensitivity reactions) due to release of various biochemical mediators (i.e. cytokines, chemokines, lipid mediators, proteases and biogenic amines). Several studies indicated that they do not only come in action upon binding of IgE to its corresponding receptors expressed by them but also play an important role in host immunity. Recent development in understanding the mast cell biology has established various important roles of these cells in regulating both innate as well as adaptive immune response under normal or pathophysiological conditions (i.e. acute or chronic bacterial or parasitic infections, various autoimmune disease, pregnancy, etc.). Present review is designed to accommodate up to date information regarding mast cell development (i.e. factors governing mast cell development and their homing to various compartments (i.e. skin, lungs, intestine, uterus, etc.) along with their role in innate immunity, human pregnancy and future immunomodulatory approach comprising of targeting mast cells.

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1. Introduction

Mast cells (MCs) are the innate immune cells, which were thought to contribute in the pathogenesis of type 1 or immediate allergy due to release of various biologically active cytokines (TNF- α , IL-1, IL-6, IL-10, etc.), chemokines (CCL1, CCL2, CCL3, CXCL1, CXCL2, etc.), lipid mediators [i.e. prostaglandins (PGs), leukotrienes (LTs)], proteases (i.e. tryptase, chymase, cathepsin or carboxypeptidase-A) and biogenic amines (i.e. histamine or serotonin) etc. upon cross linking of cell-bound IgE by the respective allergen (i.e. Urushiol or poison ivy induced contact dermatitis) (Table 1). Due to the involvement of mast cells in synthesis and release of large array of immune system modulators, along with remarkable staining characteristics of their proteoglycan and protease rich cytoplasmic granules, these cells have long fascinated immunologists as well as other biomedical researchers. However, there is no disease, medical or biological condition, or no animal model has yet been established conferring absolute lack of mast cells from which their biological role might be established. A step towards this is development of c-kit mutant mast cell-

deficient mice, which differ solely in lacking or having mast cell populations and can be used for evaluating various important roles of these cells in homeostasis as well as in pathogenesis of diseases (Nakano et al., 1985; Kitamura, 1987; Kawakami and Galli, 2002; Tsai et al., 2002). WBB6F1-Kit^W/Kit^{W-v} mouse is most commonly used animal model to study mast cell functions (Nakano et al., 1985; Tsai et al., 2002). However, C57BL/6-Kit^{W-sh} is another commonly used mouse model to study mast cell functions *in vivo* (Galli et al., 2005a,b). Both WBB6F1-Kit^W/Kit^{W-v} and C57BL/6-Kit^{W-sh} mice are highly deficient in mast cells and melanocytes (Stevens and Loutit, 1982; Kitamura, 1987; Yamazaki et al., 1994; Kawakami and Galli, 2002; Tsai et al., 2002; Mallen-St Clair et al., 2004; Grimbaldston et al., 2005). Besides this Kit^W/Kit^{W-sh} mice exhibit several other phenotypic abnormalities (i.e. macrocytic anemia, sterility and an almost complete lack of interstitial cells of cajal) (Nakano et al., 1985; Kitamura, 1989; Kawakami and Galli, 2002; Tsai et al., 2002), while Kit^{W-sh}/Kit^{W-sh} mice do not exhibit anemia and are not sterile (Stevens and Loutit, 1982; Duttlinger et al., 1993; Yamazaki et al., 1994; Mallen-St Clair et al., 2004; Grimbaldston et al., 2005). But due to advancement in immunology and biotechnology, mast cells have been identified as being involved in much more complex immunological as well as other biological functions [i.e. development of autoimmune diseases, like multiple sclerosis, bullous pemphigoid and rheumatoid arthritis (Gregory and Brown, 2006), peripheral tolerance (Lu et al., 2006), adaptive and/or innate immune responses (Marshall, 2004; Galli

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et al., 2005a,b; Marone et al., 2005) and congestive heart failure (Hara et al., 2002)]. Thus present review is designed to highlight newer roles of mast cells in immunity other than allergy mediators.

2. Origin, development and tissue distribution of mast cells

After their discovery by Paul Ehrlich, mast cells were continuously believed to be cells of connective tissue derived from undifferentiated mesenchymal cells (Kitamura and Ito, 2005). But efforts made by Kitamura et al. (1981) proved that mast cells arise from multipotent hematopoietic progenitors cells in bone marrow. These workers showed that BB6F1-W/W^m mice were devoid of mast cells and development of mast cells occurred in these mice when bone marrow stem cells (BMSCs) were transplanted to these mice taken from normal ones (Kitamura et al., 1978, 1981). These cells normally do not mature inside the bone marrow but circulate as immature cells through blood vascular system as immature mast cell progenitor cells and complete their maturation in their respective sites (i.e. in connective or mucosal tissues) (Okayama and Kawakami, 2006). Rodewald et al. (1996) identified progenitor mastocytes in fetal murine blood, which are characterized by surface phenotype or Thy-1^{low}Kit^{high}, containing cytoplasmic granules and expressing RNAs encoding mast cell-associated proteases without FcεR1 expression. Thy-1^{low}Kit^{high} cells reconstituted peritoneal mast cells in W/W^m mice upon transplantation. Lin[−] Kit⁺ Sca-1[−] Ly6c[−] FcεR1α[−] CD27[−] β7⁺ T1/ST2⁺, constitute mast cell progenitors (MCPs) in adult mouse bone marrow as these cells develop into mast cells in culture and reconstitute mast cell compartment upon their transplantation into mast-cell deficient mice (Chen et al., 2005). However, Lin[−] Kit⁺ FcγRII/III^{hi} β7^{hi} have been identified as bipotent progenitor cells and can give rise to both basophils as well as mast cells in mouse spleen are known as basophil mast cell progenitors (BMCPs) and can be generated mainly from granulocyte/macrophage progenitors (GMPs) in the bone marrow (Ariobu et al., 2005). These workers also identified mast cell progenitors (MCPs; CD45⁺ Lin[−] CD34⁺ β7^{high} FcεR1α^{low}) in intestine and basophil progenitors (BaPs; Lin[−] CD34⁺ FcεR1α^{high} Kit[−]) in bone marrow.

Human mast cells also originate from cells generated in bone marrow as mast cell progenitors from pluripotent hematopoietic progenitors (Kirshenbaum et al., 1991). These progenitors circulate in circulation as mononuclear leukocytes, which lack characteristic secretory granules (Castells et al., 1996) and express CD13, CD33, CD38, CD34 and Kit, but rarely express HLA-DR (Rottem et al., 1994; Kempuraj et al., 1999; Kirshenbaum et al., 1999).

Stem cell factor (SCF or *c-kit* ligand) and *c-kit* an play important role in growth and differentiation of mast cells. Relatively stable numbers of mast cells are maintained in connective as well as mucosal tissues (Hu et al., 2007). This is due to constitutive expression of SCF in membrane-bound and soluble forms by stromal cells and by the expression of *c-kit* on mast cells at all stages of differentiation (Hu et al., 2007). Both *W* and *Sl* mice having mutations in chromosomal loci coding for *c-kit* and SCF show profound deficient numbers of tissue mast cells (Chabot et al., 1988; Copeland et al., 1990). SCF also promotes growth and differentiation of human mast cells and is encoded by gene located on chromosome 12 (Flanagan and Leder, 1990). IL-3 has also been recognized as an important growth factor for the development of mast cells *in vitro* but not *in vivo* as IL-3 deficient mice do not show mast cell deficiency (Heib et al., 2008). However, IL-3 is not required for the development of human cord blood-derived mast cells in the presence of low oxygen concentration (Kinoshita et al., 1999). But IL-3 can enhance SCF-dependent mast cell development at low cell densities in methylcellulose culture at normal oxygen concentration (Saito,

2005). Besides IL-3, IL-4 also exhibits mast cell growth factor activity and promotes phenotype switching to connective tissue-type differentiation of mast cells in mice (Hamaguchi et al., 1987). IL-4 was shown to inhibit SCF-dependent human mast cell differentiation (Nilsson et al., 1994; Sillaber et al., 1994; Xia et al., 1997; Oskeritzian et al., 1999) but according to other workers IL-4 and SCF synergistically increase proliferation of human intestinal mast cells but do not show any effect on human pulmonary mast cells (Bischoff et al., 1999; Oskeritzian et al., 1999). Thus, IL-4 mediated effect on mast cell development and differentiation in the presence of SCF depends on mast cell developmental microenvironment or the subtype of mast cell under development. In BMMC, IL-4 suppresses IL-9 induced accumulation of mMCP-1 and mMCP-2 transcripts, IL-10 induced accumulation of mMCP-1 and mMCP-2 transcripts and SCF induced accumulation of mMCP-4 transcript, but not IL-3 induced accumulation of mMCP-5 transcript. IL-3 also suppresses IL-9 induced accumulation of mMCP-1 and mMCP-2 transcripts. Thus IL-4 and IL-3 both inhibit final stages of differentiation and maturation of mast cells (Eklund et al., 1993).

IL-9 alone does not have any effect on bone marrow derived mast cells (BMMCs) proliferation but IL-1 in the presence of SCF enhances long-term viability of BMMCs (Eklund et al., 1993). While mouse BMMCs undergo phenotypic changes in the presence of IL-9 in combination with SCF and induces accumulation of mMCP-1 and mMCP-2 transcripts, leading to development of mucosal mast cell phenotype (Okayama and Kawakami, 2006). IL-10 alone does not support the growth and differentiation of mast cell progenitors (MCPs) (Thompson-Snipes et al., 1991). However, when combined with IL-3 or IL-4, IL-10 enhanced their growth. In human system, IL-5 and IL-9 stimulate SCF-mediated proliferation of mast cells from cord blood cells, bone marrow and peripheral cells (Kirshenbaum et al., 1999; Ochi et al., 1999; Matsuzawa et al., 2003).

In comparison to Th2 cytokines, Th1 cytokine IFN-γ suppresses SCF-induced differentiation of mast cell progenitors from murine and human bone marrow, human peripheral blood and human cord blood cells (Takagi et al., 1990; Kirshenbaum et al., 1998; Ochi et al., 1999). In mouse mast cells IFN-γ induces Stat-1 mediated apoptosis (Mann-Chandler et al., 2005). Other Th1 cytokines like TNF-α and IL-6 do not act as mast cell growth factors but can help in their developmental process (Hu et al., 1997). A combination of SCF, IL-6 and IL-10 are capable of inducing the development of homogeneously pure metamastocytes from uncommitted mouse bone marrow cells (Yuan et al., 1998). IL-6 exhibits mast cell growth promoting and antiapoptotic action on blood derived mononuclear cell cultures and CD34⁺ cells (Yanagida et al., 1995; Kirshenbaum et al., 1999; Ochi et al., 1999; Oskeritzian et al., 1999). Mechanism of action of IL-6 on mast cell development involves direct modulation of SCF-mediated mast cell development of CD34⁺ blood cells by gp130 signaling induced signal transducers and activators of transcription-3 (Stat-3) expression (Kinoshita et al., 1999). IL-6 also inhibits mast cell growth and decreases *c-kit* expression, besides increasing cell size, histamine content and number of chymase positive mast cells (Kinoshita et al., 1999).

Nerve growth factor (NGF) promotes differentiation and proliferation of mouse BMMCs in the presence of IL-3 (Matsuda et al., 1991). However, NGF does not affect human mast cell survival (Yanagida et al., 1995). In the absence of SCF it does not show its mast cell-growth promoting action but in combination with SCF it synergistically suppresses mast cell apoptosis (Kanbe et al., 2000). TGF-β1 suppresses both IL-3-dependent growth of mouse mast cells and SCF-dependent growth of human intestinal mast cells (Broide et al., 1989; Gebhardt et al., 2005). Thrombopoietin (TPO), a hematopoietic growth factor also stimulates an early stage of mast cell development along with SCF (Sawai et al., 1999).

The fully developed mast cells are widely distributed throughout all the vascularized tissue, where they reside in close proximity

Table 1

Major secretory products of mast cells and their immunomodulatory action.

Mast cell secretory product	Immunomodulatory action
1. Histamine and Serotonin or 5-Hydroxytryptamine (5-HT)	Promotes DC migration, Suppresses T cell mediated adaptive immune responses, causes vasodilation, promotes angiogenesis, pain
2. TNF- α	Promotes recruitment of innate immune cells (i.e. neutrophils), Enhances protective antigen-specific antibody dependent immune response
3. IL-4	Promotes inflammation and increases the pathological changes in multiple sclerosis or experimental autoimmune encephalitis
4. IL-1	Promotes inflammation and model of antibody-mediated arthritis
5. IL-10	Suppresses adaptive immunity, promotes peripheral tolerance to skin allograft, suppresses innate immune response to chronic UVB radiation exposure
5. Lipid mediators (i.e. LTC ₄ , LTB ₄ , PGD ₂ and PGE ₂)	Recruit effector cells, regulate immune responses and promote angiogenesis, edema and bronchoconstriction
6. Chemokines CCL2, CCL3, CCL4, CCL5, CCL11 and CCL20	Recruit effector immune cells (i.e. neutrophils, monocytes and dendritic cells)
7. Chemokines CXCL1, CXCL2, CXCL8, CXCL9, CXCL10 and CXCL11	Recruit immune cells and regulate immune response
8. VEGF and FGF ₂	Angiogenesis
9. Growth factors SCF, GM-CSF, GnRH-1, b-FGF, NGF, VEGF	Promote mast cell development, differentiation, maturation and proliferation

to blood vessels, nerves, smooth muscle cells, mucus producing glands and hair follicles (Galli and Tsai, 2008). In addition, mast cells are abundant in those anatomical sites which are in direct contact with environment (i.e. skin, airways and gastrointestinal tract) (Kitamura et al., 1989; Metcalfe et al., 1997; Galli et al., 2005a,b; Marone et al., 2005). However, this homing of mast cells to peripheral tissues was remained unknown. Now it is shown that constitutive basal homing to the small intestine in mice was directed by binding of $\alpha_4\beta_7$ integrin expressed on mast cells to the mucosal address in cell adhesion molecule-1 (MadCAM-1) and to vascular cell adhesion molecule-1 (VCAM-1) as endothelial counter ligands for this integrin for transendothelial migration of MCPs into small intestine (Gurish et al., 2001). Lack of $\alpha_4\beta_7$ disrupts protective immunity against intestinal helminthic parasites (Artis et al., 2000; Issekutz et al., 2001). Also during inflammatory process mediated by mast cell progenitors (MCPs) recruitment to the lungs requires both $\alpha_4\beta_7$ and $\alpha_4\beta_1$ binding to VCAM-1, which implicates organ specific control of MCP influx (Gurish and Boyce, 2006). T-bet, a transcription factor expressed in dendritic cells (DCs) is required for efficient homing of MCPs to mucosal surfaces (Alcaide et al., 2007). Furthermore mast cells express selected receptors to instill tissue specific responsiveness in local mast cell populations. For example thyroid mast cells express thyroid hormone receptors (Melander et al., 1971; Catini and Legnaioli, 1992) and genital tract mast cells are responsive to estrogen and luteinizing hormones (Maurer et al., 2003). Human mast cells present in lungs, uterus and skin express common β -chain of β_1 -integrins (CD29), the α -chain of VLA-4 (CD49e), the common β -chain of β_2 -integrins (CD6), and the α -chain of vitronectin receptor (CD51) (Sperr et al., 1992). Bladder mast cells (MCs) located near nerve endings and also involved in the pathogenesis of Interstitial cystitis (a syndrome characterized by urinary frequency, urgency, nocturia and suprapubic and pelvic pain) (Letourneau et al., 1996). The inhabitation and count of mast cells in habenula of brain is associated with behavioral and endocrine status of the host because it is affected by both courtship behavior as well as gonadal hormone status (Zhuang et al., 1993; Wilhelm et al., 2000). However, mast cells are absent in avascular tissues like, mineralized bone, cartilage and the cornea (Crivellato et al., 2004).

3. Types of mast cells in rodents and humans

Rodent mast cells can be classified on the basis of phenotypic differences; (a) connective tissue mast cells (CTMCs) (i.e. skin and peritoneal cavity mast cells), and (b) mucosal mast cells (MMCs) (i.e. mast cells of intestinal lamina propria (Metcalfe et al., 1997). Both these subtypes of mast cells differ in their function (i.e. response to various drugs or chemicals and scetragogues) (Metcalfe

et al., 1997). For example, MMCs expand effectively under the influence of T cell mediated immune response to various parasitic infections of intestine (Ruitenberg and Elgersma, 1976; Mayrhofer and Fisher, 1979), whereas no such activation of CTMCs has been observed in either athymic nude mice or rats with same numbers of mast cells as occurring in normal animals (Aldenberg and Enerback, 1985).

Similarly human mast cells can also be categorized into two different subtypes depending on the presence of different proteases granules (Irani et al., 1986), which comprise very important component of mast cell granules for their quantitative measurement (i.e. granule-associated neutral proteases are found only in mast cells) (Hologate et al., 1988; Metcalfe et al., 1997). Thus human mast cells differ in their protease content and may have different levels of various proteases (i.e. tryptase, chymase, a cathepsin-like G protease or Carboxypeptidase) (Schwartz et al., 1993; Pejler et al., 2009). Cells containing tryptase alone are called MC_T whereas mast cells with only chymase are called MC_C and mast cells with both tryptase as well as chymase are known as MC_{TC}. MC_T are particularly abundant in alveolar septa of lungs and in mucosa of small intestine, whereas MC_{TC} are present in large amount specifically in skin and in sub mucosa of small intestine (Schwartz, 1993; Vliagoftis and Befus, 2005a,b). However, MC_C are newly identified third type of mast cell and are located mainly in sub mucosa and mucosa of stomach, small intestinal sub mucosa and colonic mucosa (Irani and Schwartz, 1994). Intestinal mucosal or sub mucosal MC_T but not MC_C are found to reduced in their numbers in patients suffering from either congenital combined immunodeficiency or acquired immunodeficiency syndrome, indicating that these MC_T require T cells for their generation, development and maintenance (Irani et al., 1987a,b). Normal synovium in humans only have MC_{TC} but in patients of rheumatoid arthritis synovium contains the mixture of MC_T and MC_{TC} cells (Irani et al., 1987a,b).

4. Mast cells in innate immunity

Innate immune system serves as a first line of defense against various acute (i.e. sepsis) (Kumar and Sharma, 2008) as well as chronic infections (i.e. tuberculosis, HIV etc.) (Young, 2003; Vergne et al., 2004; Nguyen and Pieters, 2005; Hladik and McElarth, 2008). Mast cells also comprise an important effector arm of innate immune cells along with other cells (i.e. macrophages, neutrophils, dendritic cells, natural killer cell, etc.) comprising innate immunity. Toll like receptors (TLRs) play an important role in innate immunity. They act as biological sensors of various infectious agents (i.e. virus, bacteria or fungi) or their products like lipopolysaccharide (LPS), lipoteichoic acid (LTA), Peptidoglycan (PGN), etc. and are expressed by various innate immune cells (i.e. macrophages, neu-

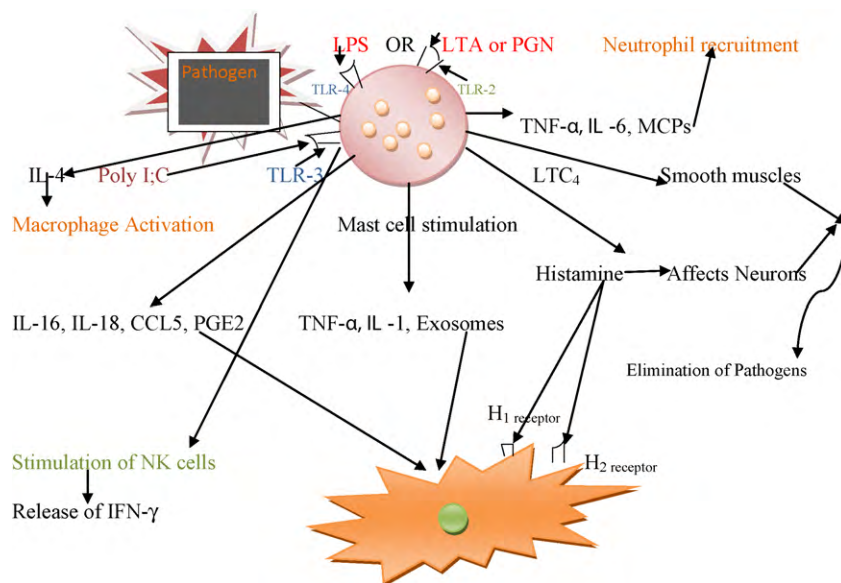


Fig. 1. Activation of mast cells by various agents and release of mast cells mediators influencing innate immune cells (i.e. DCs, Neutrophils, Natural Killer (NK) cells and Macrophages). LPS, Lipopolysaccharide; LTA, Lipoteichoic acid; PGN, Peptidoglycan; TLR-4 and -2, Toll like receptor-4 and -2; LTC₄, Leukotriene C₄.

trophs or dendritic cells) (Iwasaki and Medzhitov, 2004; Cook et al., 2004). Besides, recognizing external dangers, TLRs also regulate immune response by recognizing endogenously produced danger signals (i.e. necrotic cells, heat shock proteins or ECM breakdown products) (Beg, 2002).

Mast cells have also been found to express different types of TLRs but their expression can be influenced by the type of MCs and the site where they are located (Vliagoftis and Befus, 2005a,b). Murine mast cells express TLR-1, 2, 4 and 6 (McCurdy et al., 2001; Applequist et al., 2002; Supajatura et al., 2002). Thus, mouse mast cells can easily be activated by different types of TLR ligands (i.e. bacterial multiple triacyl lipopeptides, multiple glycolipids, bacterial PGN or LPA, fungal zymosan, LPS, or multiple diacyl lipopeptides of mycoplasma). Stimulation of TLR-2 by bacterial Peptidoglycan or lipoteichoic acid causes release of IL-4 and IL-5 from mast cells without induction of IL-1 β , but TLR-4 stimulation causes release of IL-1 β and TNF- α only instead of IL-4 and IL-5 in mice (Supajatura et al., 2002). Whereas mast cells present in the skin of mouse express higher levels of TLR-3, -7 and -9 and upon stimulation with corresponding ligand (i.e. viral double stranded RNA and Poly I:C, single stranded RNA (ssRNA), and bacterial unmethylated CpG DNA) produce TNF- α , IL-6, regulated upon activation normal T cell expressed and secreted (RANTES), macrophage inflammatory protein-1 α (MIP-1 α) and MIP-2 (Matsushima et al., 2004). Human cord blood cell derived mast cells have also been found to express TLRs i.e. TLR-1, -2, -4 and -6 whereas mast cells derived from human peripheral blood cells express TLR-1, -2, -3, -4, -5, -6, -7 and -9, which release IFN- α and - β upon stimulation of TLR-3 (McCurdy et al., 2003; Varadaradjalou et al., 2003; Kulka et al., 2004).

Besides expressing various TLRs, MCs also regulate the migration, maturation and functions of other innate immune cells (i.e. neutrophils and dendritic cells) (Fig. 1). The cytokines TNF- α and IL-1 secreted from activated mast cells facilitate migration and maturation of dendritic cells (Steinman and Inaba, 1999; Cumberbatch et al., 2000) (Fig. 1). Reports by Mazzoni et al. (2006) have shown that along with TNF- α and IL-1 MC derived exosomes also induce maturation of dendritic cells. Similarly TNF- α and superoxide anions released by activated mast cells also stimulate neutrophil recruitment at the site of infection and inflammation and also exhibit bactericidal properties (Zhang et al., 1992; Barrett, 1994). However, other potential mediators (IL-16, IL-18, CCL5 and PGE₂)

released by mast cells also promote DC migration (Kaser et al., 1999; Cumberbatch et al., 2001; Sozzani et al., 1995; Yamazaki et al., 1998; Carramolino et al., 1999; Robbani et al., 2000; Kabashima et al., 2003) (Fig. 1). Mast cell derived TNF- α and exosomes induce functional maturation of DCs by up-regulating expression of $\alpha_6\beta_4$ and $\alpha_6\beta_1$ integrins along with MHC class II molecules, CD80, CD86 and CD40 (Ioffreda et al., 1993; Skokos et al., 2003) (Fig. 1). Histamine can also stimulate expression of MHC class II molecules along with other co-stimulatory molecules on DCs by binding to histamine H₁ and H₂ receptors (Caron et al., 2001) (Fig. 1). Jawdat et al. (2004) have also shown that histamine released from skin mast cells upon stimulation with IgE or antigens enhance migration of Langerhans cells to draining lymph nodes by binding to histamine H₂ receptors.

Recent study by Dawicki et al. (2010) have shown that Peptidoglycan stimulation of mast cells leads to release of various inflammatory molecules and play an important role in homing of DCs in inflamed lymph node (Fig. 1). For example their study showed that IL-6 released from mast cells was required the influx of CD11b⁺ DCs, T cells and B cells but not for pDCs, which is regulated by histamine H₂ receptor dependent pathway. Thus, recruitment of individual DC subpopulations to inflamed lymph node can be uncoupled from each other in addition to total lymph node cellularity. NK cells are important cells of innate immune system and play an important role against viral infections and tumors. Thus, their functional interaction with mast cells can play an important role in understanding the regulation of function of these cells. Recent study by Vosskuhl et al. (2010) has shown that mast cells cause increased release of IFN- χ from NK cells upon their stimulation with TLR-3, -4, and -9 agonists like poly I:C, LPS and CpG DNA, which is TNF- α independent (Fig. 1). Also this mast cells mediated release of IFN- χ from NK cells is dependent on the direct cell-cell interaction between mast cells and NK cells, which is mediated by OX40L (Vosskuhl et al., 2010). NK cells are the major cells producing IFN- χ in endotoxin-induced sepsis (Heinzel, 1990; Emoto et al., 2002; Etogo et al., 2008), thus stimulation of mast cells by LPS during endotoxemia leads to release of IFN- χ by NK cells, which causes macrophage stimulation and increased antimicrobial action (Schroder et al., 2006).

Mast cells (MCs) derived interleukin-10 (IL-10) also plays an important role in regulation of immune response and exhibits immunomodulatory action by significantly reducing the magni-

tude and duration of inflammatory immune response (Frossi et al., 2010). MC-derived IL-10 promotes the lowering as well as resolution of innate immune response to chronic low dose ultraviolet (UV) B irradiation induced inflammatory immune response and contact hypersensitivity reaction induced by exposure to a hapten 2,4-dinitro-1-fluorobenzene (DNFB) (Grimbaldeston et al., 2007). This lowering of inflammatory response by MC-derived IL-10 is mediated by lowering of number of granulocytes, macrophages and T cells at the site of inflammation along with decrease of local tissue edema, epidermal hyperplasia and necrosis and ulceration (Grimbaldeston et al., 2007). Besides this, in the inflammatory environment of inflammatory bowel disease (IBD) MCs also act as source of IL-10 and thus help in the resolution or lowering of inflammatory tissue damage (Frossi et al., 2010).

5. Mast cells (MCs) in infectious diseases

Along with other innate immune cells (i.e. Macrophages, neutrophils, DCs or NK cells), mast cells have also been reported to play an important role in the pathogenesis of infectious diseases and also possess antimicrobial activity (Feger et al., 2002) and phagocytose pathogens to clear infection (Maurer and Metz, 2005). This is because at the very beginning of the infection mast cells play an important role in conveying a message regarding the presence of pathogen to other innate as well as adaptive immune system cells present near to the site of the infection or distally in draining lymph node (Abraham and John, 2010). For the facilitation of this interaction, mast cells are located at the host-environment interface, proximal to both blood as well as lymphatic vessels along with that they are also located along with nerve fibers, in addition to that they are also present closer to tissue resident immune cells (i.e. DCs) (Abraham and John, 2010). Mast cells play an important role in elicitation and development of effective innate immune response (i.e. enhancement of neutrophil recruitment at the site of infection) in mice suffering from sepsis and other bacterial diseases (Echtenacher et al., 1996; Malaviya et al., 1996). Mast cells can increase survival of septic mice even in the absence of TNF- α (Maurer et al., 1998), just by increasing their numbers and releasing other protective mediators playing important role in immunity (Metz et al., 2008). These mediators may involve chymase or cathelecidins, which have both direct antibacterial actions as well as innate immune system modulatory properties (Di Nardo et al., 2003; Orinska et al., 2007). Also, mast cells limit toxicity of peptide called endothelin 1 (ET-1), whose levels are increased in cases of sepsis or acute bacterial peritonitis by releasing the proteases stored in their granules, which degrades ET-1 (Maurer et al., 2004; Schneider et al., 2007). Neurotensin is a peptide, which causes hypotension and elevated plasma level of this peptide has been observed in both mouse model of sepsis as well as in human cases of sepsis or cardiogenic shock (Piliponsky et al., 2008). In septic mice neurotensin level is highly correlated with increased mortality of animals but mast cells increase their survival by simply degrading this peptide by releasing a peptide called neurolysin (Piliponsky et al., 2008). Besides establishing their protective role in sepsis, various workers have shown that mast cells provide resistance as well protections to host against infections caused by different kinds of bacteria (i.e. *Escherichia coli*, *Staphylococcus aureus*, *Mycoplasma pulmonis*, *Haemophilus influenza*, *Klebsiella pneumoniae*, *Citrobacter rodentium*, *Helicobacter felis* and *Pseudomonas aeruginosa*) (Malaviya et al., 1996; Supajatura et al., 2002; Ebmeyer et al., 2005; Wei et al., 2005; Velin et al., 2005; Xu et al., 2006; Siebenhaar et al., 2007).

Mast cells express various receptors for complement system activation products [i.e. receptors for CD11b (CR3), CD11c (CR4), C3aR and C5aR (CD88)] (Nilsson et al., 1996). However, in humans

C5aR (CD88) is expressed only by skin and cardiac mast cells and are absent in mast cell isolated from uterus, lungs or tonsils (Fureder et al., 1995). Mice lacking both CR3 and CR4 are more susceptible to infection and show decreased mast cell activation (Prodeus et al., 1997). Complement system products C3a and C5a also act as chemotactic molecules for mast cell recruitment at the site of infection or sepsis associated peritonitis (Prodeus et al., 1997). In cecal ligation and puncture (CLP) induced mouse sepsis model, Rosenkranz et al. (1998) have shown that C3b receptor (CR3^{-/-}) deficient animals exhibited impaired mast cell activation and neutrophil recruitment, associated with reduced bacterial clearance and increased mortality. *Salmonella typhimurium* upon opsonization with iC3b, a cleavage product of activated complement system is recognized by CR3 receptor expressed on mast cells (Sher et al., 1979), which leads to activation of these cell causing phagocytosis of these bacteria as well as release of inflammatory mediators required for potential host immune response against bacteria to protect host (el-Lati et al., 1994). Besides this, various bacterial strains of *Escherichia coli*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* bind avidly to mouse bone marrow derived mast cells (BMMCs) in a manner similar to *S. typhimurium* (Malaviya et al., 1994). Mast cells also express CD48, which binds to FimH protein found on fimbriated *Escherichia coli* and causes their activation to cause their degranulation and release of TNF- α in addition to causing their phagocytosis and intracellular killing through the generation of superoxide anions (Malaviya et al., 1994, 1999). However, bacteria lacking FimH proteins are less susceptible to mast cell mediated phagocytosis and intracellular killing (Malaviya et al., 1994).

Mast cell tryptase MCP-6 also plays an important role in host immunity to infection. Mice deficient in MCP-6 are more susceptible to get infected with *Klebsiella pneumoniae* and are less efficient in clearing bacteria injected into their peritoneal cavity (Thakurdas et al., 2007). Leukotriene B₄ (LTB₄) and leukotriene C₄ (LTC₄) released by mast cells also play an important role in bacterial infections, which help in neutrophil influx and bacterial clearance as decreased clearance of *E. coli* was observed in animals treated with leukotriene synthesis inhibitors (Malaviya and Abraham, 2000). Mast cell deficient W/W^v mice challenged with *Klebsiella pneumoniae* after treatment with tryptase- β 1 showed very few viable bacteria in their lungs as compared to zymogen-pretreated W/W^v mice (Huang et al., 2001). However, besides providing protection to host against various bacterial diseases the aberrant activation of mast cells by shiga toxin produced by *Shigella dysenteriae* leads to release of excessive amount of LTC₄, which may be responsible for diarrhea (Cruz et al., 1995; Pulimood et al., 1998). Similarly in gastritis induced by *Helicobacter pylori* infection mast cell degranulation by these bacteria proves detrimental to host and severe mastocytosis has been observed in gastric mucosa of these patients (Plebani et al., 1994; Nakajima et al., 1997; Yamamoto et al., 1999). Mast cells by releasing histamine in humans and serotonin in mice can influence the behavior of neurons and also affect smooth muscle by releasing eicosanoids (i.e. LTC₄ and LTD₄) (Johnson and Krenger, 1992; Margulis et al., 2009) (Fig. 1). All these interactions help in the expulsion of pathogens from the body for example elimination of bacteria and fluids from the gut occurring during cholera and clostridium toxin infection (Klimpel et al., 1995; Pothoulakis et al., 1998). Mast cell activation can also lead to stimulation of secretion of increases mucus from epithelial cells, which helps in immobilization of microbes and helps in the removal of pathogens from nasal mucosal surfaces, gut and urinary tract (i.e. Bladder) (Bischoff, 2009).

Besides playing an important role in bacterial diseases, mast cells also play an important role in various parasitic infections. Mast cells provide immunity and resistance against various helminth infections in rodents (Askenase, 1977; Befus and Bienenstock,

1982; Jarret and Miller, 1982; Wedemeyer et al., 2000). Local stimulation of mast cells at the site of parasitic infection along with systemic increase in their products plays an important role in expulsion of these parasites (Gustowska et al., 1983; Barrett et al., 1988; Nutman, 1993). For example mice deficient in mast cell protease-1 (MCP-1) showed delayed expulsion of helminthes (i.e. *Trichinella spiralis*) and increased deposition of their larvae in muscles (Knight et al., 2000), whereas mast cell protease-6 (MCP-6) helps in clearance of chronic *T. spiralis* infection (Shin et al., 2008). The mice deficient in MCP-6 exhibit decreased eosinophil recruitment and removal of *T. spiralis* larvae from chronically infected muscles (Shin et al., 2008). Recent study in *Trichinella spiralis* infection has shown that the number of c-kit⁺/β7⁺ cells from the bone marrow correlates temporally with their appearances in the blood but precedes detection of mature mast cells in intestine (Pennock and Grecis, 2004; Dawicki and Marsahll, 2007). Thus, early innate immune system mediated signals can stimulate the initiation of mast cell development in bone marrow. Moreover, mast cells also control *Plasmodium berghii* infection in mouse model of malaria (Furuta et al., 2006) and provide an optimal host immunity against cutaneous *Leishmania major* infections (Maurer et al., 2006). However, besides playing an important role in both bacterial as well as in parasitic infections these cells also exhibit very interesting role in the pathogenesis of various viral diseases [i.e. Dengu virus infection, HIV-1 infection or AIDS, Respiratory Syncytial Virus (RSV) infection, Vaccinia virus infection and in influenza and sendai virus infection] (Marshall et al., 2003). For example, human mast cells can be activated by different HIV-1 proteins (gp120 and Tat) and act as an important source of TH2 cytokines during HIV-1 infection (Marone et al., 2000). Mast cells have the potential to recruit CD8⁺T cells upon virus challenge and can also promote the production of type 1 interferons (Kulka et al., 2004; Orinska et al., 2005). Thus, this indicates that stimulation of mast cells by virus leads to activation of T cells mediated immune response, which is associated with the clearance of intracellular viruses. In both mice and humans infected with respiratory viruses, the numbers of mast cells in lungs are found to be higher as compared to non-infected ones (Castleman et al., 1990; Sorden and Castleman, 1995). However, their exact role in these viral infections still remains to be elucidated. For example, in case of HIV-1 infection mast cell may act as reservoir cells for the latent virus within the host (Sundstrom et al., 2007). Besides these viruses, mast cells are also the target of dengue virus and respiratory syncytial viruses but these studies were carried out in neoplastic cell lines and the consequences of these interactions are remain to be elucidated (Legrand et al., 1986; Shirato and Taguchi, 2009). Thus, mast cell function modulation in these infectious diseases can also be used as future immunomodulatory approach to lower the mortality and morbidity associated with these infections.

6. Mast cells as a bridging link between innate and acquired immunity

Mast cells can act as antigen presenting cells as they express major histocompatibility complex (MHC) molecules (i.e. MHC class I molecules are expressed on mouse BMCMCs and human mast cells occurring in lungs, uterus, liver and skin) and can stimulate T cells to induce an antigen specific clonal expansion of T cells along with their polarization towards Th1 or Th2 immune response (Mekori and Metcalfe, 1999; Henz et al., 2001). Also, MCs can affect B cells by supporting their survival, proliferation and Immunoglobulin (Ig) A synthesis (Merluzzi et al., 2010) (Fig. 2). (Mekori and Metcalfe, 1999; Henz et al., 2001). However, MHC class II molecules are not expressed by most mouse or human resting cells but its expression is induced upon stimulation with TNF-α, IFN-γ, LPS or under infectious conditions (Henz et al., 2001). GM-CSF stimu-

lates expression of CD80 and CD86 expression on mouse BMCMCs (Frangji et al., 1996), while human umbilical cord blood-derived mast cells also express OX40 ligand (OX40L) and 4-1BB ligand (4-1BBL) (Sayama et al., 2002). The notch signaling can lead to OX40L and MHC class II expression on mast cells (Hershko and Rivera, 2010). Mast cells residing in human tonsils express OX40L and 4-1BBL and promote T cell activation mediated through OX40-OX40L interaction (Kashiwkura et al., 2004) but this OX40-OX40L interaction of mast cells with Treg cells causes inhibition of mast cell degranulation *in vitro* and mast cell immune response important for type 1 allergy *in vivo* (Gri et al., 2008). Thus, mast cells induce T cell stimulation by acting as APCs.

Mast cells promote migration of T cells by directly releasing chemotactic factors (i.e. IL-16, lymphotactin or XCL1, CCL2 or MCP-1, CCL3 or MIP-1α, CCL4 or MIP-1β, CCL5 or RANTES, CCL20 or MIP-3α, CXCL10 or IP-10 and LTB₄) (Nakajima et al., 2002; Lin et al., 2003; Ott et al., 2003) (Fig. 2) or indirectly by up regulating expression of adhesion molecules (i.e. E-selectin, ICAM-1 or VCAM-1) on endothelial cells (Metcalf et al., 1997; Mekori and Metcalfe, 1999; Marshall, 2004). Histamine by acting on H₁ receptors promotes Th1 cell activation and suppresses both Th1 and Th2 immune response through H₂ receptors (Jutel et al., 2001). Mast cells also express CD154 (CD40L), which upon interaction with B cells induces class switching and forms germinal centers, leading to formation of IgE in the presence of IL-4 or adenosine (Gauchat et al., 1993; Ryzhov et al., 2004; Kumar and Sharma, 2009). However, mast cells also release several cytokines (i.e. IL-4, -5, -6, and IL-13) which act as B cell growth and differentiation factors (Paul et al., 1993; Stassen et al., 2001) (Fig. 2).

Direct contact between mast cells and T cells causes increased degranulation of mast cells following FcεR1 stimulation leading to increased T cell proliferation (Inamura et al., 1998; Kashiwkura et al., 2004). A bidirectional crosstalk between mast cells and regulatory T cells (Treg cells) also exists (Gri et al., 2008; Piconese et al., 2009) and this interaction between Treg cells and mast cells is essential for maintaining Treg cell-dependent peripheral tolerance during skin allograft (Frossi et al., 2010). CD4⁺CD25⁺Treg cells expressing forkhead/winged helix transcription factor (FoxP3) favor mast cell recruitment and activation by secreting IL-9 (Frossi et al., 2010). Recently Lu et al. (2006) have shown that neutralization of IL-9 accelerated graft rejection in tolerant mice, thus mast cell and Treg cell interaction plays an important role in maintenance of peripheral tolerance and this suppressive effect of mast cells is mediated by TGF-β and IL-10 cytokines (Hawrylowicz and O'Garra, 2005). Along with this, it has been observed that mast cell derived TNF-α is required for the development of IL-17 secreting Th17 cell development in lungs upon ovalbumin (OVA) treatment of OTII transgenic mice (Nakae et al., 2007). Recent data has also shown that mast cells can break Treg anergy and their suppression both *in vitro* as well as *in vivo* causing Th17 differentiation through mechanisms requiring IL-6 and OX40 interaction (Piconese et al., 2009) (Fig. 1). Also, the mast cell derived histamine can suppress Treg cell activity by binding to H1 receptors expressed on these cells (Forward et al., 2009). By decreasing the CD25 and FoxP3 expression but their increased expression can be restored by treatment of these cells with H1 receptor antagonist s (i.e. Loratidine) (Hershko and Rivera, 2010). However, further *in vivo* studies are required to confirm the role of mast cells in adaptive immunity.

7. Mast cells in human pregnancy

Many innate immune cells (i.e. macrophages, dendritic cells (DCs) and natural killer (NK) cells play an important role in human pregnancy (Sacks et al., 1999; Juretic et al., 2004; Laskarin et al., 2007; Laskarin et al., 2008; Kumar and Medhi, 2008). Besides these

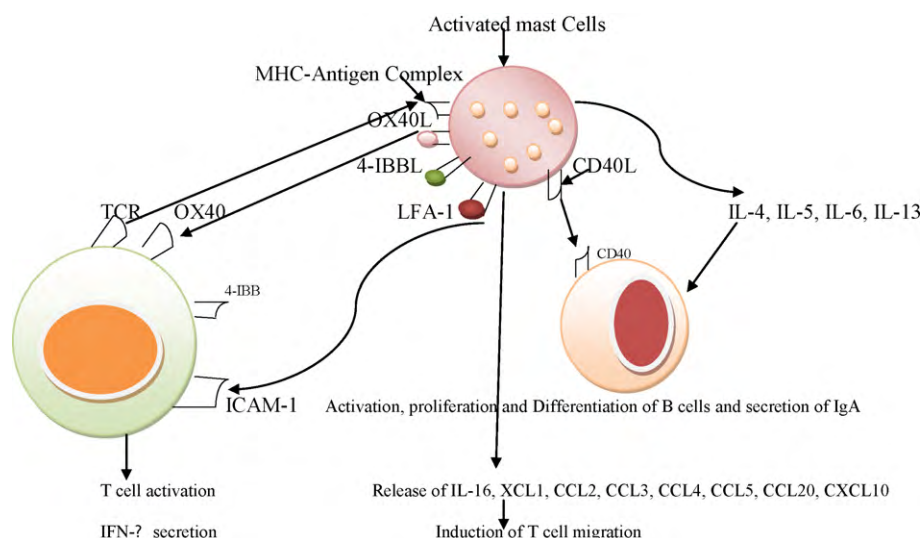


Fig. 2. Mast cell acting as bridge between innate and adaptive immunity by directly interacting with T/B cells or by releasing mediators which affect the function of T and B cells.

innate immune cells, mast cells also play an important role in human pregnancy and parturition (Rudolph et al., 2004). Mast cells located in female reproductive tract (i.e. in Endometrium, myometrium, cervix) are commonly known as uterine mast cells (Jeziorska et al., 1995; Mori et al., 1997; Cabanillas-Saez et al., 2002). These uterine mast cells are morphologically similar to skin and lung mast cells (Massey et al., 1991). A recent study by Varayoud et al. (2004) has shown that mast cell degranulation also acts as an important process required for normal angiogenesis in the cervix during pregnancy. Activity of these uterine mast cells is regulated by female reproductive hormones and content of histamine in mast cells and their number increases during second half of murine pregnancy (Padilla et al., 1990; Rudolph et al., 1997a,b), reaching to maximum by the end of gestational period (Tabb, 1994). However, this histamine content comes to normal after delivery, indicating the direct profound activation of uterine mast cells during pregnancy (Padilla et al., 1990). Uterine mast cells release histamine, serotonin (5HT), prostaglandins (i.e. PGD₂), leukotrienes, which stimulate uterine contraction by the end of pregnancy (Massey et al., 1991; Rudolph et al., 1997a,b; Bytautiene et al., 2003).

Increased expression of E-selectin in vascular endothelium of myometrium of women in labor causes increased leukocytosis and is linked to increased released of TNF- α by uterine mast cells (Thompson et al., 1999). Thus, uterine mast cells play an important role in parturition by acting as potent inflammatory cells both at myometrium and cervix (Bokstrom et al., 1997; Thompson et al., 1999). Martinez et al. (1999) have also shown that uterine contractions induced by estrogen are predominately mediated by uterine mast cells. With the involvement of uterine mast cells in pregnancy now it can be inferred that immunological mechanism behind transition from pregnant stage to parturition or delivery of the young one involve a common pathway homologous to allergic inflammatory reaction in which mast cells play a major role. Also drugs (β -adrenergic agonist or corticosteroids) which stabilize mast cells or prevent mast cell degranulation prevent preterm labor (Krishnaswamy et al., 1997; Martinez et al., 1999).

8. Future perspectives

Recent studies in the field of mast cell biology have explored new and diverse roles of these innate immune cells in homeostasis of various immunological functions and established that these cells are not only foe to host (i.e. major cells of type 1 allergic

reactions for example anaphylaxis or contact hypersensitivity reactions) but are also friend for host. Mast cells can be categorized as an innate immunomodulatory cells which can act as both negative as well as positive regulator of immunity depending on the immunological status of the host (Galli et al., 2008). For example, McLachlan et al. (2008) have shown that subcutaneous or intranasal administration of small molecule mast cell activators (i.e. c48/80) with vaccine antigens stimulated profound increase in antigen-specific serum immunoglobulin G (IgG) responses in mice. They showed that this increase in immunity against vaccine antigen was mast cell dependent and correlated well with increased dendritic cell and lymphocyte infiltration into the draining lymph nodes. Also, nasal administration of c48/80 stimulated nasal associated lymphoid tissue (NALT) and evoked antigen-specific secretory immunoglobulin A (IgA) as well serum IgG antibodies and serum obtained from mice challenged with c48/80 plus protective antigen obtained from *Bacillus anthracis* protected macrophage cell line from anthrax lethal toxin challenge *in vitro*. This protection was not limited to only *in vitro* conditions but also protected animals against vaccine virus after treatment with c48/80 plus B5R poxvirus protein (McLachlan et al., 2008). Thus, mast cell activators can be used for effective tuning of innate immune system to activate adaptive immune system (T and B cell Immune response) and will prove as future adjuvant to increase potency and antigenicity of potential antigen candidates to develop vaccines for both infectious as well as noninfectious diseases (i.e. cancer) by carrying out more preclinical studies before applying to humans. Recent study by Ramos et al. (2010) has shown that stabilization of mast cells during sepsis may prove an experimental therapeutic approach to treat sepsis by lowering the pro-inflammatory cytokines as well as by inhibiting the pro-inflammatory activity of HMGB1, a late mediator of sepsis.

Mast cells have also been shown to play a very important role in the pathogenesis of various autoimmune (i.e. Multiple sclerosis, bullous pemphigoid as well as in rheumatoid arthritis) and other chronic inflammatory disease (i.e. pulmonary fibrosis) (Metz et al., 2007). Further investigation may lead to development of promising candidate molecules, which by modulating function of mast cells in these chronic inflammatory disorders may lower associated inflammatory damage.

Besides releasing inflammatory mediators through the activation of Fc ϵ RI-dependent degranulation of mast cells various other mechanism involved in release of mast cell inflammatory mediators without their degranulation have currently been rec-

ognized, which comes in action during various conditions (i.e. viral or bacterial antigens, inflammatory cytokines, growth factors and hormones). This phenomenon involves *de novo* synthesis of inflammatory mediators [i.e. IL-6, vascular endothelial growth factor (VEGF)] (Theoharides et al., 2007). Thus, better understanding of this inflammatory pathway will prove helpful for scientists and researchers involved in development of better therapeutic molecules by targeting mast cells to lower severity of inflammatory damage associated with profound activation of these cells. Recent studies have also shown that mast cells synthesize corticotrophin-releasing factor (CRF) and its structurally related peptide urocortin (Ucn) upon stimulation and express the corresponding receptors for CRF and Ucn (Theoharides et al., 2004). Binding of CRF and Ucn to their corresponding receptors expressed on mast cells stimulate them to release inflammatory mediators thus CRF and Ucn receptor antagonists may be used together with retinol or flavonoids to inhibit mast cell activation in various chronic inflammatory conditions exacerbated by stress (Grammatopoulos and Chrousos, 2002; Kaneko et al., 2003; Theoharides et al., 2004). Mast cell carboxypeptidase (CPA) play an important protective role in snake bite poisoning (Metz et al., 2006; Rivera, 2006). This is because mice lacking mast cells were highly susceptible to the poisoning caused by Burrowing Asp (*Atractaspis engaddensis*) venom (A.e.v) or sarafotoxin 6b purified from A.e.v (Pejler et al., 2009). Animals reconstituted with MCs having decreased levels of MC-CPA, developed by RNA interference (RNAi) showed less protection to snake venom as compared to wild type animals (Pejler et al., 2009). Interestingly CPU (also called CPR), a protease related to MC-CPA, showed similar protection against cobra venom factor (Asai et al., 2004). Besides this important role in host defense mast cells also play an important role in human pregnancy and parturition.

9. Conclusion

In conclusion, mast cells are emerging as new innate immune cells, which besides playing an important role in type 1 allergy also play an important role in providing a resistant to various infectious (i.e. bacterial, viral, fungal or parasitic infections) diseases by affecting both innate as well as adaptive immune system. Thus, advanced studies establishing role of mast cells in innate immunity as well as in other physiological or pathological conditions will enlighten our understanding about the exact role of mast cells in immune system. Future research will enable us to unravel the hidden role of mast cells as a linker between innate and adaptive immunity and in various infectious, autoimmune or chronic inflammatory conditions and in pregnancy.

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