# Mast cell functions linking innate sensing to adaptive immunity

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## Abstract

Although Mast cells are known as key drivers of type I allergic reactions, there is increasing evidence for their critical role in host defense. MCs do not only play an important role in initiating innate immune responses, but also influence the onset, kinetic and amplitude of the adaptive arm of immunity, or fine-tune the mode of the adaptive reaction. Intriguingly, MCs have been shown to affect T cell activation by direct interaction or indirectly by modifying properties of antigen-presenting cells, and can even modulate lymph node-borne adaptive responses remotely from the periphery. In this review, we provide a summary of recent findings that explain how MCs act as a link between the innate and the adaptive immunity, all the way from sensing inflammatory insult to orchestrating the final outcome of the immune response.

## Introduction

Mast cells (MCs) are well known as key effector cells of type I allergic reactions, commonly named anaphylactic responses. In this case, MCs are activated by the crosslinking of cell-surface-bound FcεRI-IgE complexes by specific antigen, which results in a three-step-response; (a) the immediate degranulation of MC secretory granules, (b) the release of lipid mediators (including thromboxanes, prostaglandins and leukotrienes), and (c) secretion of a wide spectrum of *de novo* synthesized mediators (including cytokines, chemokines and growth

factors) [1-3]. However, MCs are also equipped with a spectrum of surface receptors allowing the sensing of various pathogen associated patterns (PAMPS), danger associated molecular patterns (DAMPS), cytokines, chemokines, neuropeptides and others [1, 3-7]. Moreover, the mode of ligand-receptor based MC activation and downstream signaling determines the mode of MC action, which can consist of the full three-step-response, but can also be solely the *de novo* synthesized mediator release without degranulation [6,8]. Based on this spectrum of sensing capacities, and the ability to deploy specific responses, there is increasing evidence that MCs critically contribute to innate host defense against pathogens. Additionally, MCs influence the induction, amplitude and function of the adaptive arm of the immune defense, either by direct effects on T cells or indirectly by modifying properties of antigen-presenting cells (APCs) [6,9]. Importantly, MCs even modulate lymph node-borne adaptive responses remotely from the periphery. In this review, we provide a summary of recent findings that explain how MCs act as a link between the innate and the adaptive immune response, all the way from sensing invading pathogens, danger situations and allergens to orchestrating the final outcome of the immune reaction.

**Innate MC functions in peripheral tissues fostering adaptive responses**

MCs are tissue-resident myeloid cells, populating, in high density, tissues lining the interface to the environment, such as skin, lung and intestinal epithelium, and are also found in lower cell numbers in organ-defining barriers of the lymph nodes (LN), spleen, kidney, bone marrow (BM) and brain [3, 10]. Due to their strategic positioning, MCs critically contribute to the first line of host defense against invading pathogens [4, 11-13]. MCs are equipped with a wide array of pattern recognition receptors to identify invading pathogens, including Toll-like receptors (TLR), Fc receptors, and complement receptors [4-7,11,12]. Importantly, MCs have been also reported as sensors of cell stress and tissue damage, through alarmin and purinergic receptors [4, 13-16]. Finally, MCs can be activated or modulated by binding cytokines, growth factors like SCF, chemokines, and neuropeptides [14-16].

A unique characteristic of MCs is the high amount of intracellular secretory granules, which in turn contain each a plethora of preformed mediators, such as histamine, proteases, cytokines,

and chemokines [8]. The MC granule consists of a proteoglycan scaffold, in which the mediators are embedded based on electrostatic interactions [8,17]. Connective tissue type murine MCs utilize heparin as the dominant proteoglycan, which allows for the detection of MC granules by metachromatic staining with Giemsa or Toluidine-blue, as well as by fluorochrome-conjugated avidin. Whereas mucosal type MCs in the lung and intestinal epithelial layers contain chondroitin sulfate-based granules [8,17]. Upon IgE/FcεRI crosslinking by the specific antigen or other stimuli, MCs release these secretory granules within only seconds to minutes, in a process called degranulation [1,4].

Because they can immediately degranulate, MCs respond to invading pathogens or cell stress faster than other tissue-resident immune cells and therefore, in many cases, are the initiators of immune responses. Whenever an inflammatory insult is causing MC degranulation, the immediate release of histamine triggers vascular responses, in particular vasodilatation and vessel permeabilization, within only minutes, finally leading to tissue edema [12,18-22]. The effect of histamine on endothelial cell activation and vascular barrier disintegration is potentiated by MC release of TNF [23-25], and proteases [26-29] as well as rapid production of lipid mediators [30,31]. Complementing the vascular effects, MCs are also critical initiators of neutrophil recruitment, for example during sepsis and peritonitis [32-36], upon LPS-induced lung inflammation [37], as well as to sites of skin inflammation [18,38-40] and bone fracture [41], and to areas of arteriogenesis [42] and atherosclerotic plaque progression [43,44]. More specifically, MCs contribute to early neutrophil recruitment by release of the neutrophil chemoattractants KC and MIP-2 in addition to vascular effects [35,39,45,46]. Beside their boosting effect on neutrophil influx, MCs were also reported to enhance neutrophil effector functions [47,48].

The MC-mediated vessel permeability and subsequent edema formation further supports the recruitment of adaptive immune effector cells to the site of infection or inflammation. Indeed, by blocking the activity of MC released histamine on the vasculature, subsequent T cell–driven adaptive immune responses were severely impaired [18]. Furthermore, the edema-related relaxation of connective tissue is important for dendritic cell (DC) motility at the site of

infection/inflammation and their subsequent migration toward the draining LNs (DLN), to induce antigen-specific immune responses. Moreover, Weber et al. could show in a model of contact hypersensitivity (CHS) that the (MC initiated) neutrophil influx is required for an efficient activation and migration of DCs and hapten-specific T cell priming, and consequently for the sensitizing efficiency of the hapten [38]. Neutrophil-released mediators with alarmin activity promote DC recruitment to sites of inflammation/infection and their maturation, thereby augmenting innate and adaptive immunity (reviewed in [49]. In contrast, neutrophil extracellular traps (NETs) and cathelicidins can downregulate LPS-induced DC activation and T cell priming capacity, in part by neutralizing LPS [50-53].
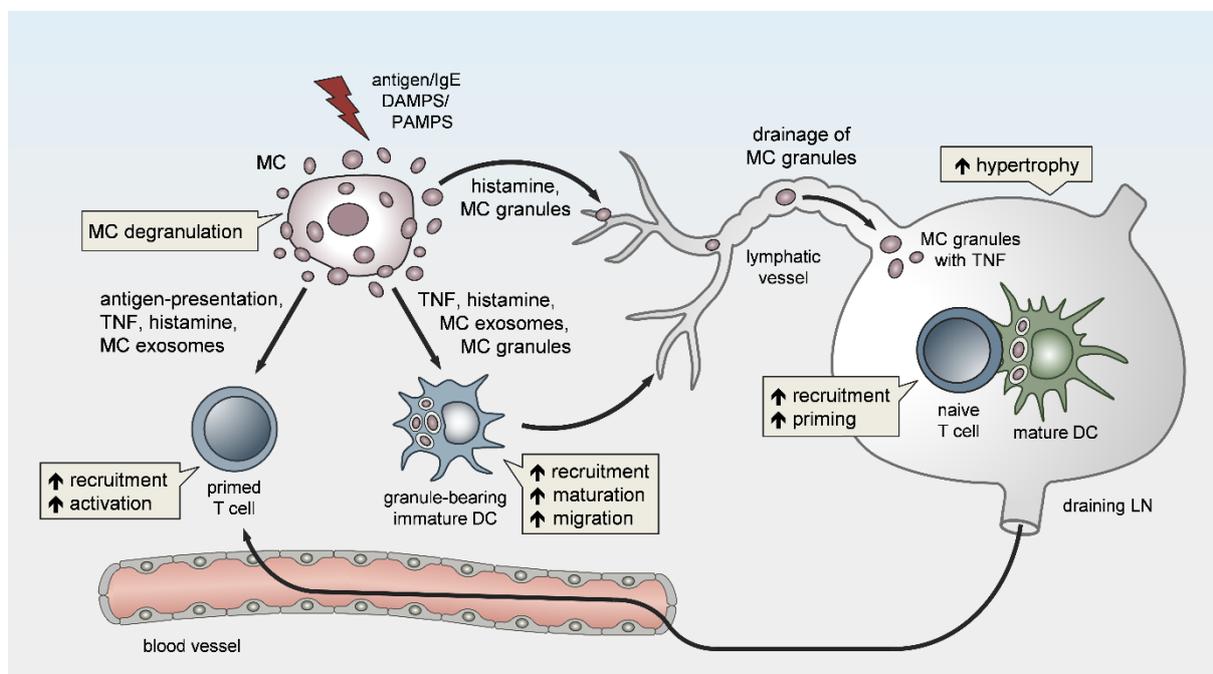


***Figure 1. Peripheral mast cells (MCs) orchestrate the induction and amplitude of local innate responses and distant lymph node-borne adaptive immunity.*** Sensing of pathogens or danger associated patterns by MCs or MC activation by IgE crosslinking in the periphery, may result in MC degranulation and/or *de novo* synthesis of pro-inflammatory mediators. Peripheral MCs exert remote effects on LN hypertrophy via histamine, TNF and drainage of intact secretory MC granules. The migration, maturation and antigen-presenting capacity of DCs is promoted by MC soluble mediators, secretory granules and exosomes, thereby subsequently facilitating the T cell expansion in DLNs. Finally, MCs enhance the homing of effector T cells to peripheral sites of inflammation/infection and may contribute to effector T cell activation.

## MC functions in LN conditioning and hypertrophy

Besides local vasoactivation and edema formation, peripheral MCs support APC and lymphocyte influx in DLNs by exerting remote effects. Increased TNF levels have been

detected in prenodal lymph [54] and in DLNs [55], as early as one hour after peripheral MC activation. Indeed, McLachlan et al. showed that upon intradermal bacterial challenge, peripheral MC-derived TNF is the main driver of DLN hypertrophy and recruitment of circulating T cells. In addition, MCs play a pivotal role in the TNF-independent but complement-regulated LN hypertrophy and Langerhans cell mobilization following intradermal peptidoglycan injection [56]. Moreover, *Anopheles mosquito* bite-induced dermal MC degranulation was not only shown to lead to local inflammation and neutrophil influx, but also required for T-cell and DC recruitment to the DLN, a prerequisite for T- and B-cell priming [57]. The mechanisms that underlie peripheral MC long-distance effects on the DLNs, and facilitate LN hypertrophy and circulating lymphocyte influx are barely examined but might be related to MC mediator drainage. Gashev and colleagues showed that, in rats, MCs reside close to mesenteric lymphatic vessels (MLVs) and direct the recruitment of MHC class II positive cells [58,59]. The histamine release of perilymphatic MCs impacts on the lymphatic microenvironment in an NFκB-dependent manner [60,61]. Importantly, the perilymphatic mesenteric MCs directly regulate themselves via histamine receptors in an autocrine loop, that is essential for acute inflammation-induced trafficking of MHC class II-expressing leukocytes [62]. Given the significant distance between the inflamed peripheral site and the DLN, it is still unclear how peripheral MC-derived cytokines, such as TNF, can reach the LN without being degraded or diluted to ineffective concentrations, in particular considering the short half-life period of TNF *in vivo* [63]. The remote effect of MC-derived TNF may be explained by its storage in the proteoglycan-backbone of the secretory granules. Importantly, we and others could visualize *in vivo* that the secretory granules are released by peripheral MCs in an intact and stable form [**Error! Bookmark not defined.**,64,65]. Mediators like histamine that are not highly charged, rapidly diffuse from the proteoglycan matrix upon MC granule secretion to the extracellular fluid. In contrast, other mediators such as MC proteases and TNF are released slowly and sequentially from the secreted granules, which may enhance their activity and prolong their presence in the extracellular tissue [65-67]. Kunder et al. reported that upon topical application of PMA, resulting in peripheral MC degranulation, some of the MC granules can enter the

lymphatics and drain to local LNs, while no degranulation of LN-resident MCs was detected [65]. Furthermore, the authors demonstrated that the drained granules, carrying TNF, could efficiently elicit profound LN hypertrophy. Due to this adjuvant effect of MC granules, the same group modelled synthetic carbohydrate-backbone particles with encapsulated inflammatory mediators and showed their efficiency to enhance adaptive immune responses upon influenza virus haemagglutinin vaccination [68].

**MCs affect adaptive immunity via the modulation of dendritic cells**

Beside the effect on LN conditioning and hypertrophy, MCs are implicated in LN-borne adaptive immune responses indirectly via the modulation of DC functions. In peripheral tissues, and particularly those lining the interface to the environment such as the skin, MCs reside in a dense network of tissue resident innate immune cells and are involved in a variety of intercellular interactions [69,70]. We have previously shown that MCs and macrophages (Mph) cooperate in initiating the recruitment of neutrophils in a model of LPS-induced peritonitis [35]. However, despite their close proximity, the interaction between MCs and Mph and its impact on the recruitment and activity of effector T cells remains elusive. To this time, several studies reported the intense communication between MCs and DCs and the MC-driven modulation of DC migration, maturation and function, thereby linking MCs to adaptive responses [70,71]. On one hand, peripheral MC activation is critical for the recruitment of additional DCs to sites of bacterial infection and protective immunity [72]. On the other hand, MCs promote DC migration from the skin to the DLN after IgE-mediated activation [73,74], and in response to bacteria [72] or bacterial products [75,76].
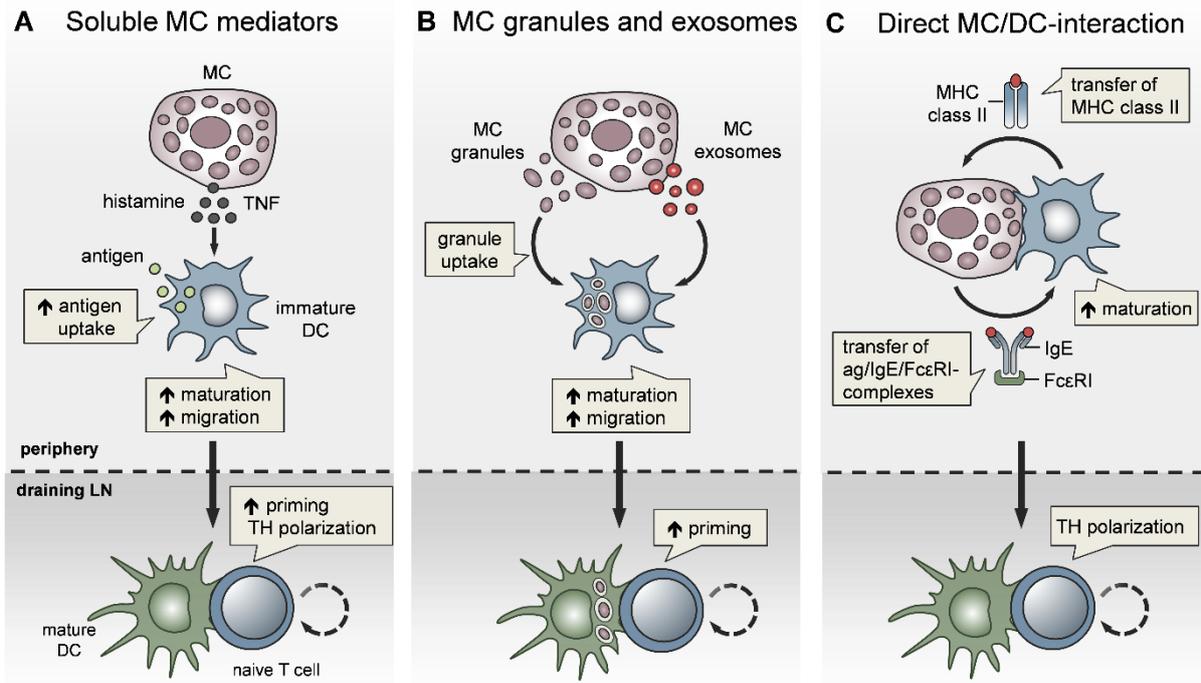
***Figure 2. MCs impact on T cell activation by modulating DC functionality.*** MCs communicate with DCs in three different modes. (A) Soluble MC mediators, in particular histamine and TNF, promote the migration, maturation and antigen-presenting capacity of DCs, thereby enhancing T cell priming and fine-tuning $T_H$ cell polarization. (B) MC exosomes and intact MC secretory granules, engulfed by DCs upon MC degranulation, facilitate DC migration and maturation, and consequently, boost T cell priming. (C) MCs and DCs undergo dynamic physical interaction and synapse formation allowing a bidirectional exchange. MCs transfer endocytosed antigen-IgE-FcεRI complexes, to DCs, which facilitates activation of allergen-specific T cells. In turn, MCs are "cross-dressed" by DCs with MHCII complexes thereby enabling activation of effector T cells by MCs with antigen processed by DCs.

In CHS, the mouse model of the T cell-driven disease allergic contact dermatitis, we found that upon hapten sensitization MCs promote DC migration to skin-DLNs and DC maturation, and thereby critically enhance T cell expansion [18]. Consequently, the expansion of both CD4^{+} and CD8^{+} T cells in skin-DLNs, and the T cell-triggered adaptive skin inflammation upon hapten challenge, was markedly reduced in absence of MCs [18]. In particular, peripheral TNF release by MCs is required for efficient initiation of skin and airway DC migration to DLNs [76-78]. Using an MC-specific TNF knockout, we could show *in vivo*, that MC-derived TNF predominantly targets cDC1 migration and priming capacity upon hapten sensitization, thereby promoting CD8^{+} effector T cell responses [78].

In addition to their effect on DC migration, MCs have been reported to enhance DC maturation, antigen processing, and T-cell priming capacities. In more detail, histamine promotes DC maturation [79], antigen uptake and cross-presentation [80] and regulates the DC cytokine

response thereby polarizing T cells toward a Th2 phenotype [81]. In line with this, IgE stimulated MCs control the Th1/Th2 balance by promoting Th2 generating DCs [82,83]. Importantly, MCs exert effects on DC functionality not only by soluble mediators but also via the secretory MC granules, MC-derived exosomes, and by physical contacts. By means of MC granule staining *in vivo,* directly inside the MCs, and intravital 2-photon-microscopy, we could monitor MC degranulation and track the fate of MC granules after their exocytosis. We found that upon skin inflammation, dermal DCs accumulate at the site of MC degranulation, engulf the intact MC granules and shuttle them actively to skin-DLNs [64]. The MC granule uptake facilitates DC migration and maturation, and boosts the T cell priming capacity. The cDC1 subpopulation was most efficient in MC granule uptake in a partially TNF-dependent mechanism. Importantly, the intradermal (i.d.) injection of MC granules into MC-deficient mice was sufficient to induce a profound expansion of T cells indicating their adjuvant effect. Extending the finding of Kunder et al. [65], we provided evidence that MC degranulation in the periphery may exert long-distance effects on LN-borne adaptive T cell responses in two ways: (a) trafficking of MC granules via lymphatic vessels towards the DLNs, and (b) active shuttling of MC granules by DCs along with DC modulating effects [64].

Beside MC granules, MC-derived exosomes offer an additional mechanism for intercellular communication, by having greater stability in the interstitial space compared to soluble mediators [69,84] and being able to promote DC maturation and antigen-presenting capacity [85,86].

Confirming our findings in CHS, Otsuka et al. showed impaired skin DC maturation and migration in the absence of MCs and the relevance of a direct interaction between DCs and MCs, leading to an upregulation of membrane-bound TNF by MCs [87]. Given the close proximity of MCs and DCs in peripheral tissues, especially in the skin, a physical cell-to-cell-interaction was considered likely and studied in several *in vitro* studies. Non-activated peritoneal MCs, reflecting the connective tissue type of skin MCs, underwent a direct crosstalk with immature DCs, inducing DC maturation and CD4$^+$ T-cell polarization toward Th1 and Th17 responses [88]. Upon Fc$\varepsilon$RI crosslinking, MCs have been shown to form immunological

synapses with DCs, enabling the transfer of endocytosed antigen from MCs to DCs to activate T cells [89]. However, there was still low *in vivo* evidence for a functional relevance of the MC/DC cell-to-cell interaction. In a recent study, we have shown for the first time *in vivo*, using intravital 2-photon-microscopy of MC/DC double reporter mice, that upon skin inflammation MCs and DCs rapidly undergo a highly dynamic interaction evolving to long-term synapses [90]. The MC/DC communication culminates in a protein exchange from DCs to MCs, including MHC class II complexes. Intriguingly, the DC "cross-dressing" of MCs with functionally active MHC class II complexes equipped the MCs with antigen-presenting capacity, which subsequently enhanced T cell–driven skin inflammation. This MC bestowal with antigen-presenting capacities, particularly of antigens that have been engulfed and processed by DCs before leaving the peripheral tissue towards the DLN, suggests a role for MCs in activating effector T cells that enter the peripheral tissue [90].
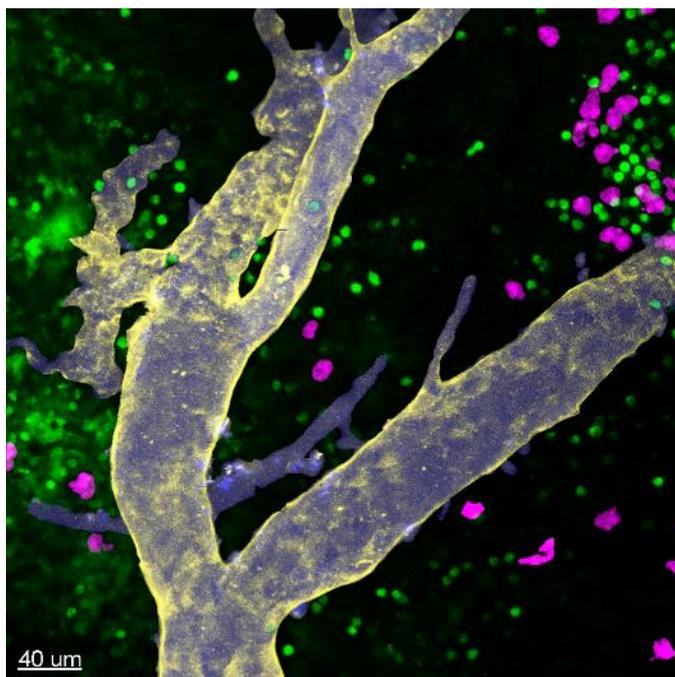


**Figure 3. MC accumulation in LN T cell zones upon immunization**. Two-photon-microscopy of MC/T cell double reporter mice revealed the accumulation of MCs in the T cell zone and colocalization with T cells in inguinal LNs six days after intradermal immunization with collagen/CFA. Green: T cells; purple: MCs; blue: vessel tracer Angiospark 750; yellow: anti-CD31Ab. (Quantification and more detailed information in [99]).

### Direct role for MCs in T cell activation

Beside the modulation of APC function yet in the periphery, MCs have been reported to directly impact on T cell activation. Here, MCs may exert promoting effects by two modes of action, by

direct antigen-presenting capacities or by modulating T cell expansion, differentiation and polarization via soluble mediators.

***Antigen-presenting capacity of MCs.*** The capacity of MCs to directly present antigen to T cells has been speculated by several reports based on the finding that MCs may express MHC class II complexes under certain conditions. An early study showed a selective ability of BM-derived mouse MCs (BMMCs) to present exogenous antigens, that is supported by GM-CSF [91]. Kambayashi et al. demonstrated the MHC class II expression and antigen-presenting capacity by BMMCs and splenic mouse MCs, in response to LPS and IFN-γ *in vitro* and upon inflammatory insult *in vivo* [92]. This finding was supported by Gaudenzio et al. showing the expression of MHC class II and costimulatory molecules (CD80 and CD86) on mature peritoneal mouse MCs stimulated with IFN-γ and IL-4 [93]. Interestingly, the antigen-presenting capacity relied on direct MC/T cell crosstalk where CD4^{+} T cells formed immunological synapses and polarized their secretory machinery toward the antigen-loaded MCs [93]. In BMMCs, the MHC class II expression is induced by Notch ligand Delta-like 1 (Dll1)/Notch signalling through activation of class II transactivator (CIITA) [94,95]. Furthermore, IgE/antigen-stimulated BMMCs enhance T cell activation by expression of various costimulatory molecules, including ICOSL, PD-L1, PD-L2, Ox40L, Fas, and 4-1BB, and a TNF-mediated increase of the surface expression of the respective counterreceptors on T cells [96].

In line with this, the expression of HLA-DR and activation of antigen-specific T cells was confirmed for human MCs that were stimulated with IFN-γ or by FcεRI crosslinking [97,98]. Here, the direct crosstalk between tonsillar human MCs and CD4^{+} T cells seemed to involve costimulation via Ox40L/Ox40 [98].

Despite robust *in vitro* evidence for an antigen-presenting potential of MCs, MC interactions with naïve T cells in LNs or with effector T cells infiltrating peripheral sites of inflammation/infection are barely explored *in vivo*. In collagen-induced arthritis (CIA), MC-depleted mice showed reduced joint inflammation due to impaired T cell expansion and T cell cytokine response upon i.d. collagen/CFA immunization [99,100]. Questioning the underlying

mechanism, we found only a few MCs in the subcapsular regions of inguinal LNs under physiologic conditions. MCs were accumulated in the LN T cell zones but only late (at day 6 after immunization), thereby succeeding effector T cell expansion and egress from the LNs [99]. This finding let us speculate that again MC effects on T cell priming may be linked to DC modulation during the immunization. Consequently, the MC antigen-presenting function may be important for effector T cell activation in the periphery rather than naïve T cell priming in lymphoid organs. Indeed, the *in vitro* studies by Gaudenzio et al. and Kambayashi et al. showed that MC antigen-presentation preferentially induced expansion of antigen-specific effector T cells and regulatory T cells over naïve T cells [92,93]. Our hypothesis of MC antigen-presentation in peripheral tissues is supported by a recent study by Kritikou et al. showing an increased MHC class II expression and *in vivo* capacity to present antigens under hyperlipidemic conditions [101]. Importantly, the authors identified HLA-DR expressing MCs in human atherosclerotic plaques in line with reduced aortic CD4$^+$ T cell numbers and proliferation in MC-deficient mice [101]. In an non-conventional way of antigen-presentation, MCs induce $\gamma\delta$ T cell activation and proliferation in dengue virus-infected peripheral tissue, due to immune synapse formation mediated by the T cell receptor and the endothelial cell protein C receptor (EPCR) [102].

In addition to MHC class II dependent activation of CD4$^+$ T cells, MCs have been shown to induce CD8$^+$ T cell activation and proliferation, and to promote CD8$^+$ T cell cytokine release and cytoxicity in a direct cell contact and MHC class I dependent manner [103]. This finding was confirmed *in vivo*, since adoptive transfer of antigen-pulsed MCs induced CD8$^+$ T cell priming in experimental autoimmune encephalomyelitis (EAE).
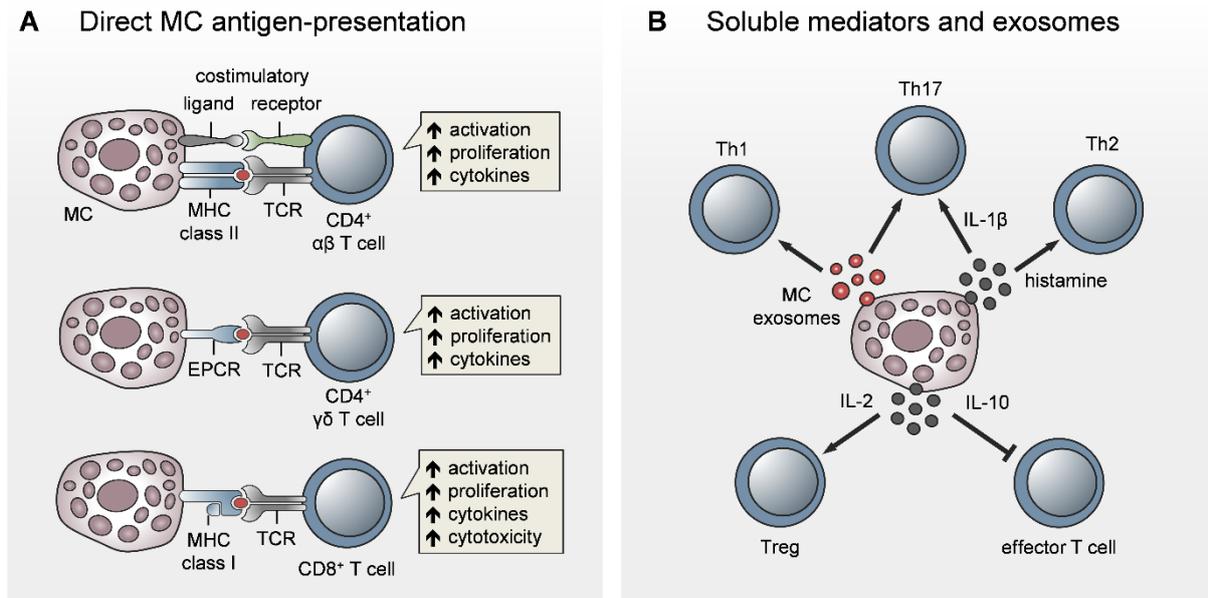
**Figure 4. Direct role for MCs in activation and modulation of T cell responses.** There is increasing evidence that MCs contribute to T cell activation by direct antigen-presenting potential as well as by modifying the outcome of the T cell response. (A) A direct MC/T cell interaction and synapse formation, and the antigen-presenting capacity of MCs has been shown for CD4$^+$ $\alpha\beta$ T cells, for $\gamma\delta$ T cells, and for CD8$^+$ T cells. (B) Beyond direct activation, MCs can modulate the T cell activation by exosomes and soluble mediators. Here, MCs skew T cell polarization towards Th1, Th17 or Th2 dependent on the mode of MC stimulation. In addition, MCs provide anti-inflammatory effects by promoting T$_{reg}$ activation via IL-2 or by inhibiting conventional T cell activation via IL-10 in a T$_{reg}$ independent way.

**MC modulation of T cell priming, differentiation and polarization.** In addition to potential MC functions as APCs, several studies reported MC-driven modulatory effects on T cell priming, differentiation and polarization. Still, most of the work has been done *in vitro* using immature BMMCs, which complicates interpretation of the functional relevance under disease conditions. For example, co-activation of T cells in presence of IgE/antigen-activated BMMCs skewed the T cell response towards IL-4 producing Th2 cells [104]. In particular, MC-derived histamine may regulate the Th1/Th2 balance by differential expression of H1 and H2 histamine receptors [105]. In contrast, Liu et al. recently reported a role for the MC-derived Mcpt6 (mouse mast cell-protease 6) in counterregulating Th2 polarization and cytokine release by increasing Bcl-6 in Th2 cells that subsequently inhibited GATA-3 [106]. Human MCs have been demonstrated to enhance the Th17 fraction within the memory CD4$^+$ T cell population by an inflammasome-independent IL-1$\beta$ release[107].

In addition to soluble MC mediators, B and T cell activation is regulated by secretion of MC exosomes harboring immunologically relevant molecules such as MHC class II, CD86, LFA-1

and ICAM-1 [69,86,108]. Purified MC exosomes have been demonstrated to induce blast formation, T cell proliferation, IL-2 and IFN-$\gamma$ production while being inefficient in induction of IL-4 [108]. IL-2 production by BMMCs, in response to concomitant IL-33 signaling and Fc$\varepsilon$RI activation, resulted in expansion of regulatory T cells *in vitro*. Salamon et al. demonstrated elevated IL-33 levels and increased numbers of IL-2-expressing MCs in human skin with chronic inflammation and in mouse ear skin upon allergic dermatitis and conclude a role for MC-derived IL-2 in Treg stimulation and suppression of allergic dermatitis [109]. Independent of regulatory T cells, MCs have been reported to suppress graft-versus-host disease by decreasing conventional T cell proliferation via release of the anti-inflammatory cytokine IL-10 [110]. MC delivered exosomes are further involved in a recently described non-conventional mechanism, supporting the Th17 response in the chronic inflammatory skin disease psoriasis [111]. In detail, the cytoplasmic phospholipase A2 (PLA2G4D) is expressed by MCs upon psoriasis and transferred within exosomes to neighboring CD1a-expressing Langerhans cells. The resulting presentation of neolipid antigens to lipid-specific CD1a-binding T cells induced the production of IL-22 and IL-17A, driving the skin inflammation [111].

**MC functions in B cell activation**

In contrast to the MC-T cell axis, there is much less knowledge regarding MC functions in regulating B cell numbers, activation or antibody responses. Due to the accumulation of MCs and MC-driven effects in B cell-mediated inflammatory disorders, including rheumatoid arthritis, a direct modulation of B cells by MCs was hypothesized. Moreover, the high levels of IL-6 release by MCs suggests a MC-B cell communication, for example in pulmonary hypertension [112]. In MC-deficient Kit mutant mice, an impaired protective humoral response to E. coli was observed, which led to the suggestion of pharmacologic MC activation as a new adjuvant principle in vaccination [72,113,114]. However, a non-redundant role for MCs in antibody production could not be confirmed in Kit independent novel mouse models of MC-deficiency [115].

*In vitro*, naïve, sensitized and activated MCs were shown to promote proliferation of naïve and B cell receptor-activated B cells [116-118], as well as both follicular and marginal zone B cells [115]. As indicated by the secretion of IgM and IgG by IgM+ B cells, MCs can induce class switch recombination [115]. Pucillo and colleagues further reported that the CD40/CD40L-mediated MC/B cell contact, together with IL-6 secretion by MCs differentiates B cells to CD138+ plasma cells and IgA secretion [114]. The same group demonstrated the MC/B cell crosstalk in the inflamed colon of inflammatory bowel disease (IBD) patients and by using MC depleted mice, confirmed *in vivo*, a role for MCs in the control of B cell distribution in the gut, and in the increased IgA production upon dextran sulfate sodium (DSS)-colitis [119]. *In vitro*, MCs regulated splenic B cells, while peritoneal B cells were unresponsive but skewed the MCs to increased IL33 receptor expression and TNF production [116]. The synthesis of IgE by B cells was found to be enhanced by adenosine-activated human MCs via IL-4 and IL-13 production, a process that might be implicated in asthma-associated amplification of allergic inflammatory responses [120]. In contrast, Kim et al. recently described an immunoregulatory function of MCs in the control of severe CHS. Here, MC production of IL-5 maintains the population of IL-10+ regulatory B cells in peripheral tissues, which in turn suppress the activation of IL-13 producing type 2 innate lymphoid cells in an IL-10 dependent manner [121].

**MCs orchestrate effector cell recruitment to inflamed tissues**

While MCs are known for their role in neutrophil recruitment, only few reports address, until now, the impact of MCs on effector T cell recruitment to peripheral tissues. This limited knowledge may arise from the restriction of cell dynamics and recruitment studies to *in vivo* mouse model investigation. On the other hand, MC effects on T cell recruitment are hard to discriminate from effects on T cell expansion and activation. Hence, the reduction of CD4+ and CD8+ T cell numbers infiltrating the ear skin upon allergic contact dermatitis, which we have observed in absence of MCs, may include MC effects on the recruitment process itself in addition to effects on LN-borne T cell expansion [18, 78]. Determining specific MC functions in effector T cell recruitment requires the uncoupling of T cell priming from T cell extravasation, for example by site-specific MC depletion (possible in the novel mouse models of diphtheria

toxin-induced MC depletion [18, 87, 122], or by adoptive transfer approaches. However, the vessel endothelium activation by MCs, in line with their capacity to produce the T cell chemoattractants CCL2 (MCP-1), CCL5 (RANTES), and CXCL10 (IP-10), indicates a contribution to the recruitment of effector T cells, once expanded in lymphoid organs, to the peripheral site of inflammation or infection [123-126]. MCs have been suggested as attractors of CD8^{+} effector T cells in two studies: In an early *in vitro* report, activated MCs induced the chemotaxis of effector, but not central memory, CD8^{+} T cells through production of leukotriene B4 (LTB4) [127]. *In vivo*, Ebert et al. showed that systemic infection with cytomegalovirus (CMV) induced MC degranulation, selectively in infected MCs, thereby eliciting a wave of CCL5 [128]. In MC-deficient mice, CD8^{+} T cells were recruited less efficiently to the lungs, which correlated with enhanced viral replication and delayed virus clearance [125].

## Concluding remarks

MC research of the last two decades has provided increasing evidence that MCs critically contribute to innate host defense and adaptive immunity. In peripheral tissues, MCs sense pathogen and danger associated patterns and initiate local innate responses. Beyond that, MCs affect the onset, kinetic and amplitude of adaptive immunity by (at least) four modes of action: (a) remote effects initiating draining LN hypertrophy, (b) promoting DC migration and functionality, (c) inducing or modulating T cell activation and polarization, and finally (d) orchestrating the homing of effector T cells to the site of inflammation or infection. Despite our current advances, future work is crucial to substantiate recent findings and indications with *in vivo* evidence, particularly using novel mouse models of MC deficiency or MC-specific gene inactivation, independent of Kit mutations. Moreover, due to their immobility, the capacity of MCs to link innate sensing to induction and fine-tuning of adaptive immune responses relies on cellular communication. Therefore, understanding MC communication with neighboring tissue resident immune cells and infiltrating effector cells should be the principal focus, in order to reveal future therapeutic targets to either intentionally boost or dampen adaptive immunity.

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