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Targeting mast cells in inflammatory diseases

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ABSTRACT

Although mast cells have long been known to play a critical role in anaphylaxis and other allergic diseases, they also participate in some innate immune responses and may even have some protective functions. Data from the study of mast cell-deficient mice have facilitated our understanding of some of the molecular mechanisms driving mast cell functions during both innate and adaptive immune responses. This review presents an overview of the biology of mast cells and their potential involvement in various inflammatory diseases. We then discuss some of the current pharmacological approaches used to target mast cells and their products in several diseases associated with mast cell activation.

Contents

1. Introduction

Mast cells (MCs) originate from progenitor cells in the bone marrow that express both CD34 (cluster of differentiation 34) (Rottem et al., 1994) and the stem cell factor (SCF) receptor c-KIT (CD117) (Catlett et al., 1991; Rottem et al., 1994). These progenitors migrate via the circulation to tissues where they undergo maturation under the influence of local factors (Kitamura, 1989). MCs reside in most tissues, but are especially rich in those exposed to the external environment, including the airways, the skin, and the gastrointestinal tract. For this reason, MCs are likely to be one of the first inflammatory cells, along with dendritic cells, to encounter allergens, pathogens, and other proinflammatory and toxic agents (Galli et al., 2005).

SCF is the main MC growth and survival factor (Oliveira & Lukacs, 2003; Reber et al., 2006), but various mediators can also modulate MC proliferation, differentiation, and survival; these include interleukin (IL)-3 (Razin et al., 1984), IL-4 (Sillaber et al., 1991; Valent et al., 1991; Toru et al., 1996, 1998), IL-9 (Mwamtemi et al., 2001; Matsuzawa

Abbreviations: AHR, airway hyperresponsiveness; BAL, bronchoalveolar lavage; BMCMC, bone marrow-derived cultured mast cell; CLP, cecal ligation and puncture; CPA, carboxypeptidase; DT, diphtheria toxin; DTR, diphtheria toxin receptor; EAE, experimental allergic encephalomyelitis; ER, endoplasmic reticulum; HDC, histidine decarboxylase; Ig, immunoglobulin; IL, interleukin; MC, mast cell; MCPT, mast cell protease; MS, multiple sclerosis; PAF, platelet-activating factor; PCA, passive cutaneous anaphylaxis; PSA, passive systemic anaphylaxis; RA, rheumatoid arthritis; SCF, stem cell factor; TLR, toll-like receptor; TNF, tumor necrosis factor; WT, wild type.

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et al., 2003), CXCL12 (also named stromal cell-derived factor-1, or SDF-1) (Lin et al., 2000; Godot et al., 2007), and nerve growth factor (NGF) (Matsuda et al., 1991).

MCs are often classified according to their location or protease content. In mice, MCs can be classified into two subpopulations: mucosal type MCs and connective tissue-type MCs (Bienenstock et al., 1982; Galli et al., 1984). In humans, MCs are subcategorized into MC_T, which express high levels of the MC-specific protease tryptase but not of chymase, and MC_{TC}, which express both tryptase and chymase (Irani et al., 1989; Li et al., 1996).

While the numbers and activation of MCs increase in many human diseases, proof of MC involvement in these diseases has been derived mostly from animal models developed in various strains of MC-deficient mice (Grimbaldeston et al., 2005; Tsai et al., 2005; Reber et al., 2012; Rodewald & Feyerabend, 2012). Studies in these animal models suggest that MCs play important roles in a variety of immune and inflammatory reactions, including a central role in allergies, defense against some pathogens, resistance to venoms, and development or exacerbation of certain autoimmune diseases (Galli et al., 2005, 2008a, 2008b; Rodewald & Feyerabend, 2012).

This review presents an overview of MC biology and the potential roles that MCs play in various inflammatory diseases. We will then discuss some of the current pharmacologic approaches used to target MCs and their products in several diseases thought to be associated with MC activation.

2. Analyzing mast cell functions in vivo

2.1. Mice with kit and stem cell factor mutations

Animals with genetic MC deficiencies have been widely used to analyze MC functions in vivo. Kitamura et al. first reported that $Kit^{W/W\text{-}v}$ and Sl/Sl^{d} mice are deficient in MCs and that this deficiency can be restored by adoptive transfer of bone marrow cells from WT mice (Kitamura et al., 1978; Kitamura & Go, 1979; Kitamura et al., 1981). $Kit^{W/W\text{-}v}$ mice have mutations in the c-*kit* gene (the *white spotting W* locus) that lead to reduced c-KIT tyrosine kinase-dependent signaling (Kitamura et al., 1978; Nocka et al., 1990). As a result, $Kit^{W/W\text{-}v}$ mice are profoundly MC-deficient (adult mice have less than 1% of the total number of MCs found in WT mice) (Kitamura et al., 1978, 1981). This reduced c-KIT activity also causes several other phenotypic abnormalities, including anemia, sterility, lack of skin pigmentation, and neutropenia (Chervenick & Boggs, 1969; Grimbaldeston et al., 2005; Zhou et al., 2007; Nigrovic et al., 2008; Piliponsky et al., 2010; Feyerabend et al., 2011). Sl/Sl^{d} mice have a deletion in the transmembrane domain of the *scf* gene (*steel Sl* locus) (Chabot et al., 1988) and consequently do not express the membrane form of SCF but do have normal levels of soluble SCF (Kapur et al., 1999). Like $Kit^{W/W\text{-}v}$ mice, these mice are profoundly MC-deficient and have many phenotypic abnormalities, including sterility, anemia, and lack of skin pigmentation (Kitamura & Go, 1979).

More recently, $Kit^{W\text{-}sh/W\text{-}sh}$ mice have also been used as a model to study the role of MCs in vivo (Lyon & Glenister, 1982; Grimbaldeston et al., 2005; Wolters et al., 2005). These mice have an inversion mutation of 72 kb in a transcriptional regulatory element upstream of the c-*kit* transcription start site (Duttlinger et al., 1993; Berrozpe et al., 1999). As a result, they lack c-KIT activity in most tissues and are profoundly MC-deficient (Grimbaldeston et al., 2005). Besides this MC deficiency, they also develop several phenotypic abnormalities, including mild neutrophilia and impaired skin pigmentation, but they are not anemic or sterile (Grimbaldeston et al., 2005; Zhou et al., 2007; Nigrovic et al., 2008; Piliponsky et al., 2010).

Differences between WT and *Kit* mutant mice can be attributed to MC- or other c-*kit*-related phenotypic abnormalities. The specific role of MCs must therefore be ascertained by grafting $Kit^{W/W\text{-}v}$ or $Kit^{W\text{-}sh/W\text{-}sh}$ mice with MCs derived in vitro from bone marrow (that is, with bone marrow-derived cultured MCs, BMCMCs) or embryonic stem cells (Nakano et al., 1985; Tsai et al., 2000; Grimbaldeston et al., 2005; Wolters et al., 2005).

2.2. New transgenic models

Several groups have recently generated new transgenic mice expressing Cre recombinase under the control of promoters for MC proteases, such as those for carboxypeptidase A3 (*Cpa3*) and MC protease 5 (*Mcpt5*) (Musch et al., 2008; Scholten et al., 2008; Dudeck et al., 2011; Feyerabend et al., 2011; Lilla et al., 2011; Otsuka et al., 2011) (for review, see Reber et al., 2012; Rodewald & Feyerabend, 2012). Such mice can be crossed with mice in which genes of interest have been "floxed" to delete expression of these gene products in the MCs (Dudeck et al., 2011; Furumoto et al., 2011). However, Cre expression in these transgenic mice must be assessed carefully. For example, *Cpa3*-Cre mice express Cre in MCs but also in some basophils (Feyerabend et al., 2011; Lilla et al., 2011) and T cells (Feyerabend et al., 2009).

Lilla et al. mated *Cpa3*-Cre mice with mice expressing the floxed survival factor *Mcl-1*: the resulting *Cpa3-Cre*; $Mcl\text{-}1^{fl/fl}$ mice were severely deficient in MCs and markedly deficient in basophils (Lilla et al., 2011). Consistent with these findings, Feyerabend et al. reported Cre-mediated cytotoxicity that led to MC ablation and reduced basophil numbers in a different line of *Cpa3-Cre* mice (Feyerabend et al., 2011). *Mcpt5-Cre* mice, which express Cre in connective tissue-type MCs but not mucosal MCs (Scholten et al., 2008; Dudeck et al., 2011), were mated with transgenic mice expressing Cre inducible diphtheria toxin A (DT-A) or diphtheria toxin receptor (iDTR) genes to achieve constitutive (in *Mcpt5-Cre*; DTA^{+} mice) or inducible (after DT injection in *Mcpt5-Cre*; $iDTR^{+}$ mice) ablation of connective tissue-type MCs (Dudeck et al., 2011). Otsuka et al. and Sawaguchi et al. generated 'Mas-TRECK' (for mast cell-specific enhancer-mediated toxin receptor-mediated conditional cell knockout) mice that expressed the human DTR dependent on an intronic enhancer element of the *Il-4* gene (Otsuka et al., 2011; Sawaguchi et al., 2012). Repeated injections of DT in these mice deplete MCs in multiple organs but also lead to transient depletion of blood basophils. A more recent report describes mice expressing a tamoxifen-inducible Cre recombinase ($CreER^{T2}$) dependent on the c-*kit* promoter (Heger et al., 2013). The authors inserted an internal ribosome entry site (IRES) directly after the $CreER^{T2}$ sequence, in an attempt to enable Cre expression under endogenous control of the c-*kit* gene locus and simultaneously sustain c-KIT expression levels. However, adult mice carrying one $CreER^{T2}$ allele ($Kit^{CreERT2/+}$) showed a reduction in both c-KIT expression and the number of peritoneal MCs as well as a coat-color pigmentation phenotype reminiscent of mice heterozygous for c-*kit* loss-of-function mutations. Moreover, embryos homozygous for $Kit^{CreERT2/CreERT2}$ died in utero, and fetal liver-derived MCs from them showed a total lack of c-KIT expression (Heger et al., 2013).

Since residual MCs or defects in other cell populations or both are found in most of these new transgenic models, conclusions about the involvement (or lack of involvement) of MCs in disease models should ideally be derived from multiple model systems (Reber et al., 2012).

3. Mast cell-derived mediators

MCs produce several families of mediators: preformed products that are stored in MC granules and rapidly liberated upon degranulation, de novo synthesized lipid mediators, and many cytokines, chemokines, and growth factors.

3.1. Preformed mediators

MC granules contain a variety of preformed mediators. MCs are the major source of preformed histamine, which is well known for promoting bronchoconstriction and vasodilatation (Riley, 1953; Razin et al., 1983). However, several other cell types can also produce and release

histamine, including basophils (Windelborg Nielsen et al., 1990) and neutrophils (Ghosh et al., 2002; Xu et al., 2006b). MC granules also contain heparin and, in rodents, serotonin (Razin et al., 1983).

Proteases, including tryptase, chymase, and carboxypeptidase A (CPA), are the most abundant proteins stored in MC granules (Irani et al., 1986; Compton et al., 1998; Huang et al., 1998; Algermissen et al., 1999; Compton et al., 2000; Pejler et al., 2007, 2010; Caughey, 2011). Protease content varies in human and mouse MCs according to the tissue location. Several forms of tryptase are found in human MCs; the active forms are βI-, βII-, βIII-, and γ-tryptase. Similarly, mouse MCs express different forms of tryptase, including MCPT6 and MCPT7 (although C57BL/6 mice are unable to express MCPT7 because of a point mutation in the exon/intron 2 splice of the *Mcpt7* gene (Hunt et al., 1996)). While humans only express one MC-specific chymase, there are 13 known mouse chymase genes (Gallwitz et al., 2006). Based on tissue distribution, heparin-binding properties, and substrate and cleavage specificity, the β-chymase MC protease 4 (MCPT4) appears to be the main homologue of human chymase (Tchougounova et al., 2003; Andersson et al., 2008). Finally, both human and mouse MCs contain CPA3 (for review, see (Pejler et al., 2010; Caughey, 2011)).

3.2. Lipid-derived mediators

Upon activation of MCs by various stimuli including IgE and antigen, various lipid mediators are synthesized de novo. Arachidonic acid is released from the perinuclear membrane and endoplasmic reticulum and processed into several eicosanoids (Gurish & Austen, 2001; Austen, 2005). Among these are prostaglandin D2 (PGD_2) (the major prostanoid product in MCs), prostaglandin E_2 (PGE_2) (Schmauder-Chock & Chock, 1989), and the leukotrienes LTC_4 and LTB_4 (Razin et al., 1982; Freeland et al., 1988). Leukotriene C4 synthase (LTC_4S) mediates the biosynthesis of LTC_4 (Lam & Austen, 2002), which appears to play an important role in allergic inflammation and MC proliferation, as demonstrated by the reduced Th2 cytokine generation and airway inflammation in $LTC_4S^{-/-}$ mouse models of asthma (Kim et al., 2006; Barrett et al., 2011). IL-4-mediated MC expansion is also reduced in $LTC_4S^{-/-}$ mice (Jiang et al., 2006). These mice are also partially protected in a MC-dependent IgE-mediated passive cutaneous anaphylaxis (PCA) model (Kanaoka et al., 2001).

3.3. Cytokines, chemokines, and growth factors

MCs can produce TNF-α on stimulation by many factors, including IgE, antigen, and bacterial products (Gordon & Galli, 1994; Malaviya et al., 1996; Dreskin & Abraham, 1999). Preformed tumor necrosis factor (TNF)-α can also be found in MC granules and is liberated upon MC degranulation in both humans (Walsh et al., 1991; Frangogiannis et al., 1998) and mice (Gordon & Galli, 1990; Kunder et al., 2009). Upon activation, peripheral MCs release stable heparin-based particles containing preformed TNF-α and other proteins. These complexes, by trafficking to the draining lymph nodes where they can deliver TNF-α, enable communication between peripheral sites of inflammation and secondary lymphoid tissues (Kunder et al., 2009). Studies in mice have shown that MC-derived TNF-α can promote neutrophil recruitment (Nakae et al., 2007b) and dendritic cell migration (Suto et al., 2006). It can also promote bacterial clearance in sepsis models (Malaviya et al., 1996, 1999; Piliponsky et al., 2010), as well as airway hyperresponsiveness (AHR), lung inflammation, and Th2 cytokine production in an asthma model (Nakae et al., 2007a).

Both human (Hagaman et al., 2001; Lin et al., 2002) and mouse (Burd et al., 1989; Nigrovic et al., 2007; Mrabet-Dahbi et al., 2009; Guma et al., 2010) MCs can also produce IL-1. Mouse MC-derived IL-1 has been found to mediate inflammation in a model of arthritis (Nigrovic et al., 2007), and human MCs can mediate neutrophil migration ex vivo through production of IL-1 upon activation by *Pseudomonas aeruginosa* (Lin et al., 2002). More recently, skin MCs have been reported to be a major source of IL-1 in patients with cryopyrin-associated periodic syndrome (CAPS), a rare inherited disease caused by gain-of-function mutations in nucleotide-binding oligomerization domain-leucine-rich repeats containing pyrin domain 3 (NLRP3) (Nakamura et al., 2009). MC-derived IL-1 also plays an important role in a mouse model of CAPS (Nakamura et al., 2012).

MCs can produce IL-6 in vitro (Burd et al., 1989) and in vivo (J. Liu et al., 2009; Oldford et al., 2010). MC-derived IL-6 plays a substantial role in toll-like receptor (TLR)-2-mediated inhibition of tumor growth in mice (Oldford et al., 2010). MC-derived IL-6 and IFN-γ can also mediate diet-induced obesity and diabetes in mice (Liu et al., 2009).

Mouse and human MCs can also secrete IL-17 (Mrabet-Dahbi et al., 2009; Buckland, 2010; Hueber et al., 2010). Interestingly, MCs are the major source of this cytokine in the inflamed synovial tissue from patients with various forms of arthritis (Buckland, 2010; Hueber et al., 2010; Suurmond et al., 2011; Noordenbos et al., 2012; Kenna & Brown, 2013).

MCs can also produce Th2 cytokines, including IL-4, IL-5, and IL-13 (Smith et al., 1994; Williams & Coleman, 1995; Stassen et al., 2001), as well as Th1 cytokines, including IFN-γ and IL-12 (Burd et al., 1989; Plaut et al., 1989; Gordon et al., 1990; Smith et al., 1994; Williams & Coleman, 1995).

In vitro studies show that MCs from both the human lung (Ishizuka et al., 1999a,b) and mice (Grimbaldeston et al., 2007; Song et al., 2012) can secrete IL-10. MC-derived IL-10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B in mice (Grimbaldeston et al., 2007). More recently, MC-derived IL-2 was also found to induce suppression of chronic allergic dermatitis in mice by promoting maturation of regulatory T cells (Hershko et al., 2011).

MCs can also produce some chemokines, including CCL5 (RANTES) (Jia et al., 1996; Rajakulasingam et al., 1997) and CXCL8 (IL-8) (King et al., 2002). Moreover, they are important sources of growth factors, including vascular endothelial growth factor (VEGF) (Boesiger et al., 1998), granulocyte macrophage-colony stimulating factor (GM-CSF) (Wodnar-Filipowicz et al., 1989), and SCF (Zhang et al., 1998; de Paulis et al., 1999).

4. Mast cell activation

The most frequently studied activation pathway by which MCs mediate allergic responses involves the binding of antigens to IgE prebound to FcεRI (Abramson & Pecht, 2007; Kalesnikoff & Galli, 2008; Galli & Tsai, 2012). Such antigen- and IgE-dependent activation of MCs is however only one of many activation pathways by which MCs can be activated in response to a variety of stimuli. For example, SCF can mediate MC activation through binding to its receptor c-KIT (Oliveira & Lukacs, 2003; Reber et al., 2006). MCs can also mediate responses to various pathogens though activation of TLRs, including TLR-2 and TLR-4 (Supajatura et al., 2002; Abraham & St John, 2010) or certain peptides found in venoms (Metz et al., 2006; Schneider et al., 2007; Akahoshi et al., 2011), or can be activated indirectly by various complement proteins (Ali, 2010; Schafer et al., 2013).

4.1. Activation through the high affinity immunoglobulin E receptor

Antigen-induced crosslinking of IgE bound to its high affinity receptor, FcεRI, on the MC surface activates multiple signaling pathways that lead to MC degranulation and inflammatory mediator production (Fig. 1). The FcεRI receptor belongs to the multichain immune recognition receptor (MIRR) family. Both human and mouse FcεRI are expressed on MC surfaces as αβγ2 tetramers. The α subunit is involved in IgE binding, while the β and γ subunits are involved in signal transduction (Garman et al., 1998).

The extracellular part of the α subunit contains two Ig-like domains that bind to the Fc domain of monomeric IgE with high affinity (Ortega et al., 1991). In mice, FcεRIα is essential for IgE-dependent MC activation,

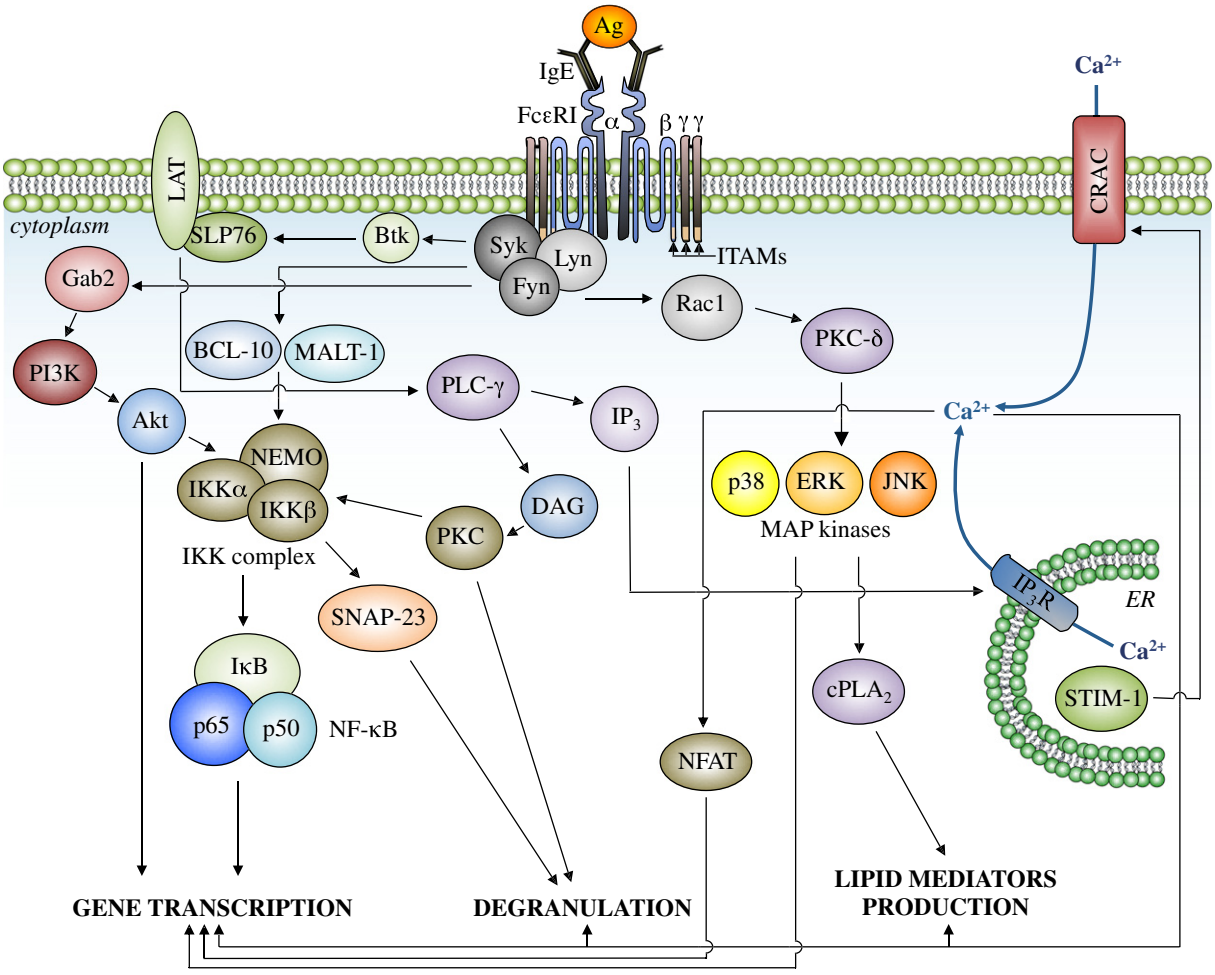

Fig. 1. Simplified overview of FcεRI-mediated signal transduction. Antigen (Ag)-induced crosslinking of IgE bound to its high affinity receptor FcεRI on the MC surface activates multiple signaling pathways leading to MC degranulation, lipid mediator production, and gene transcription. BCL-10: B cell lymphoma 10; Btk: Bruton's tyrosine kinase; cPLA2: cytosolic phospholipase A_2; CRAC: calcium release-activated calcium channel; DAG: diacylglycerol; ER: endoplasmic reticulum; ERK: extracellular signal-regulated kinase; IκB: Inhibitor of κB; IKK: IκB kinase; IP_3: inositol-1,4,5-trisphosphate; IP_3R: IP_3 receptor; ITAM: immunoreceptor tyrosine-based activation motifs; LAT: linker for activation of T cells; MALT-1: mucosa-associated lymphoid tissue 1; MAP kinase: mitogen-activated protein kinase; NFAT: nuclear factor of activated T cells; NF-κB: nuclear factor-κB; PI3K: phosphatidylinositol-3 kinase; PKC-δ: protein kinase C (PKC)-δ; PLC-γ: phospholipase C-γ; SLP76: SH2-domain-containing leukocyte protein of 76 kDa.

for *FcεRIα*$^{-/-}$ mice are fully resistant to both IgE-mediated PCA and passive systemic anaphylaxis (PSA) (Dombrowicz et al., 1993). Monomeric IgE binding to FcεRI has long been considered to cause sensitization but not to induce MC activation in the absence of antigen. However, several reports now indicate that such binding can induce MC survival and cytokine production and enhance FcεRI expression in vitro, even in the absence of antigen (Asai et al., 2001; Kalesnikoff et al., 2001; Matsuda et al., 2005). Such antigen-independent effects of monomeric IgE have also been observed in vivo in a mouse model of contact hypersensitivity (CHS) (Bryce et al., 2004): *IgE*$^{-/-}$ mice developed less hypersensitivity to various chemical haptens than WT mice did, and this hypersensitivity was restored by the transfer of hapten-irrelevant IgE before sensitization in these *IgE*$^{-/-}$ mice (Bryce et al., 2004).

The cytoplasmic tails of the β and γ subunits of FcεRI contain domains of immunoreceptor tyrosine-based activation motifs (ITAM) that can serve as docking sites for several members of the Src kinase family, such as Lyn and Fyn, as well as the kinase Syk (Eiseman & Bolen, 1992). Lyn is constitutively associated with FcεRI in resting MCs (Vonakis et al., 1997, 2001). Antigen-specific IgE binding to FcεRI and the subsequent aggregation of this IgE by antigens lead to the rapid activation of Lyn, which can in turn phosphorylate ITAM motifs in the β and γ subunits (Paolini et al., 1991; Eiseman & Bolen, 1992; Pribluda et al., 1994). Once phosphorylated, these ITAMs can recruit Syk (Kihara & Siraganian, 1994) and Fyn (Parravicini et al., 2002). The subsequent phosphorylation by Fyn of the adaptor protein Gab2 leads to activation of phosphatidylinositol-3 kinase (PI3K) (Yu et al., 2006a). Syk and Lyn activate various substrates such as the SH2-domain-containing leukocyte protein of 76 kDa (SLP76) (Pivniouk et al., 1999), the linker for activation of T cells (LAT) (Saitoh et al., 2000, 2003), and Bruton's tyrosine kinase (Btk) (Kawakami et al., 1994), all of which contribute to the activation of phospholipase C-γ (PLC-γ) (Nadler et al., 2000). It was recently shown that the SH3-binding protein 2 (3BP2) adaptor protein is essential for optimal Syk and PLC-γ activation and for release of IL-8 and GM-CSF after stimulation with antigen and IgE in the LAD2 human MC line (Ainsua-Enrich et al., 2012).

When activated, PLC-γ catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate ($PI(4,5)P_2$) into inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) (Turner & Kinet, 1999; Gilfillan & Tkaczyk, 2006; Kraft & Kinet, 2007; Kalesnikoff & Galli, 2008). IP_3 binds to its receptor in the endoplasmic reticulum (ER) membrane and thereby causes a rapid but transient release of Ca^{2+} from the ER stores. The transmembrane protein STIM1 is located in the ER and plays a crucial role in this release (Liou et al., 2005; Roos et al., 2005). Loss of STIM1 impairs FcεRI-dependent Ca^{2+} influx, degranulation, and production of NF-κB- and NFAT-regulated pro-inflammatory cytokines (IL-6, TNF, and IL-13) in mouse MCs; in vivo, it inhibits IgE- and antigen-mediated PCA reactions (Baba et al., 2008). The release of Ca^{2+} from

the ER stores leads to activation of Ca^{2+} channels in the plasma membrane, which in turn promotes the influx of extracellular Ca^{2+}. This process, called store-operated Ca^{2+} (SOC) influx, is mediated by calcium release-activated calcium (CRAC) channels (Hoth & Penner, 1992; Parekh & Penner, 1997; Parekh & Putney, 2005). The plasma membrane protein Orai1 (also called CRACM1) plays an essential role in SOC entry (Feske et al., 2006; Vig et al., 2006; Zhang et al., 2006). Vig et al. showed that in *CRACM1*$^{-/-}$ MCs, FcεRI-dependent degranulation, lipid mediator synthesis, and cytokine release are all reduced in vitro, as is IgE-dependent PCA in vivo (Vig et al., 2008).

IgE- and antigen-dependent MC activation leads to rapid generation of eicosanoids (leukotriene (LT)C_4, prostaglandin (PG)D_2, and LTB_4) (MacGlashan et al., 1982; Boyce, 2007). These eicosanoids are de novo products of arachidonic acid, a fatty acid that is liberated from nuclear membrane phospholipids by cytosolic phospholipase A_2 (cPLA$_2$) (Clark et al., 1991; Boyce, 2007). The necessity of cPLA$_2$ for eicosanoid generation was demonstrated by showing that *cPLA*$_2^{-/-}$ MCs cannot synthesize the eicosanoids LTC_4, LTB_4, 6-*trans*-LTB_4, or $_5$-hydroxyeicosatetranoic acid ($_5$-HETE) on FcεRI ligation (Fujishima et al., 1999). The small guanosine triphosphatase Rac1 activates protein kinase C (PKC)-δ after FcεRI-dependent stimulation, which leads to the activation of the MAP kinase kinase MEK-1 and subsequent activation of extracellular signal-regulated kinase (ERK). ERK can then phosphorylate cPLA$_2$, which then becomes active and liberates arachidonic acid to promote synthesis of all types of eicosanoids (Cho et al., 2004).

FcεRI-dependent production of inflammatory cytokines such as TNF-α or IL-6 in MCs is controlled by two transcription factors, nuclear factor-κB (NF-κB) and nuclear factor of activated T-cells (NFAT) (Hutchinson & McCloskey, 1995; Jeong et al., 2002; Monticelli et al., 2004; Peng et al., 2005; Klein et al., 2006; Klemm et al., 2006; Chen et al., 2007). In MCs, the predominant NF-κB dimer is a p50/p65 heterodimer (Kalesnikoff et al., 2002). NF-κB activity is tightly controlled by inhibitor of κB (IκB) proteins that bind to NF-κB dimers and retain them in an inactive state in the cytoplasm. Upon stimulation by many factors, including crosslinked IgE and antigens, the IκB kinase (IKK) phosphorylates IκB proteins to target them for ubiquitin-dependent degradation. Free NF-κB dimers translocate into the nucleus where they promote the expression of many inflammatory genes (Hayden & Ghosh, 2008; Oeckinghaus et al., 2011; Hayden & Ghosh, 2012).

B-cell lymphoma 10 (Bcl10), a caspase recruitment domain protein, and mucosa-associated lymphoid tissue 1 (Malt1), a paracaspase, are key regulators of FcεRI-dependent IKK activation and the subsequent activation of NF-κB in MCs. After they showed that BMCMCs from *Bcl10*$^{-/-}$ or *Malt1*$^{-/-}$ mice do not produce TNF-α or IL-6 in response to FcεRI stimulation, despite normal capacity for leukotriene production and degranulation, Klemm et al. proposed that Bcl10 and Malt1 are crucial regulators of FcεRI-dependent NF-κB activation and can selectively uncouple pro-inflammatory cytokine production from degranulation and lipid mediator synthesis (Klemm et al., 2006). Beside its role in NF-κB activation, IKKβ (also termed IKK2), one of two catalytically active subunits of the IKK complex, can phosphorylate SNAP23, a soluble N-ethylmaleimide-sensitive fusion factor (NSF) attachment protein receptor (SNARE) protein that regulates exocytosis in MCs (Guo et al., 1998; Suzuki & Verma, 2008). This phosphorylation of SNAP23 enhances FcεRI-induced MC degranulation independently of NF-κB (Suzuki & Verma, 2008).

Fine-tuning of IgE- and antigen-dependent MC activation is controlled by several negative regulators of FcεRI signaling. Some studies indicate that Lyn can act as a negative regulator of FcεRI-dependent MC activation. BMCMCs from *Lyn*$^{-/-}$ mice show enhanced FcεRI-mediated activation (Parravicini et al., 2002; Hernandez-Hansen et al., 2004), although these data are controversial in view of the conflicting results from different groups (Nishizumi & Yamamoto, 1997; Kawakami et al., 2000). Other negative regulators of FcεRI-dependent signaling in MCs include: the Src homology 2-containing inositol phosphatases (SHIP)-1 (Huber et al., 1998) and SHIP-2 (Leung & Bolland, 2007), PKCδ (Leitges et al., 2002), allergin-1, an immunoglobulin-like receptor (Hitomi et al., 2010), and the guanine nucleotide exchange factor RabGEF1 (Tam et al., 2004; Kalesnikoff et al., 2007). RabGEF1 activates the small GTPase Rab5 that regulates early endocytic events. Several other Rab proteins, including Rab3a, Rab27a, and Rab27b, have also been implicated in both positive and negative regulation of IgE- and antigen-dependent MC activation through regulation of IgE- and antigen-dependent endocytosis, exocytosis, granule size, and fusion (Oberhauser et al., 1992; Mizuno et al., 2007; Kageyama-Yahara et al., 2011; Azouz et al., 2012).

4.2. Activation through the stem cell factor receptor c-KIT

Binding stem cell factor (SCF) homodimers to the c-KIT receptor on MC surfaces induces homodimerization and transphosphorylation of the receptor on several tyrosine residues; these in turn create docking sites for various signaling molecules and induce pathways essential for MC development, survival, proliferation, chemotaxis, and adhesion (for review, see Oliveira & Lukacs, 2003; L. Reber et al., 2006) (Fig. 2).

Growth factor receptor-bound protein-2 (Grb2) is an adaptor protein that can bind to phosphorylated Y703 and Y936 of c-KIT (Thommes et al., 1999). Grb2 associates with the son-of-sevenless (sos) gene set, which promotes activation of the small G-protein Ras (Duronio et al., 1992) and then of Raf-1 (Miyazawa et al., 1991) and the MAP kinases: p38 (Ishizuka et al., 1998, 1999a), ERK (Miyazawa et al., 1991; Hallek et al., 1992; Ishizuka et al., 1999a), and JNK (Ishizuka et al., 1998).

The p85α regulatory subunit of phosphatidyl-inositol-3 kinase (PI3K) interacts with phosphorylated Y721 of c-KIT (Serve et al., 1994) to promote the activation of Akt and the subsequent phosphorylation of the pro-apoptotic factor Bad. This phosphorylation inhibits Bad activity, thereby promoting cell survival (Blume-Jensen et al., 1998). PI3K can also mediate SCF-induced MC proliferation by activating the Rac1, a small guanosine-triphosphate (GTP)-binding protein, and JNK pathways (Timokhina et al., 1998; Fukao et al., 2002). This activation of the Rac1/JNK pathway also depends on the scaffolding adapter Gab2, which associates with c-KIT Y567 upon SCF stimulation (Yu et al., 2006a).

SCF also induces the activation of the Janus kinase (JAK) and signal transducer and activators of transcription (STAT) pathways. JAK2 associates with c-KIT and is phosphorylated upon SCF stimulation (Brizzi et al., 1994; Weiler et al., 1996), which in turn leads to the phosphorylation of STAT (Gotoh et al., 1996; Weiler et al., 1996; Deberry et al., 1997; Ryan et al., 1997; Brizzi et al., 1999).

SCF induces the activation of multiple Src family members, including Src, Tec, Lyn, and Fyn (Blume-Jensen et al., 1994; Tang et al., 1994; Linnekin et al., 1997), and Src family kinases associate with phosphorylated Y568 and Y570 in the juxtamembrane domain of c-KIT (Price et al., 1997; Ueda et al., 2002). Levels of SCF-dependent activation of Rac1, Rac2, and p38 MAP kinase and of filamentous actin polymerization and chemotaxis are lower in *Fyn*$^{-/-}$ MCs than in WT (Samayawardhena et al., 2006, 2007). SCF-induced recruitment of Src and PI3K to c-KIT leads to activation of Rac1 and JNK, thereby promoting MC proliferation (Linnekin et al., 1997; Timokhina et al., 1998). Lyn deficiency in MCs impairs SCF-dependent proliferation (O'Laughlin-Bunner et al., 2001). SCF-induced activation of members of the Src family kinases also leads to gene transcription through activation of the Ras/MAP kinase pathway (Lennartsson et al., 1999; Bondzi et al., 2000).

As in FcεRI-induced signaling, many negative regulators control the strength of SCF-mediated MC activation; these include the guanine nucleotide exchange factor, RabGEF1 (Kalesnikoff et al., 2006), the sprouty-related Ena/VASP homology-1 domain-containing (Spred1) protein, and microRNA-126 (miR126), its upstream suppressor (Ishizaki et al., 2011), and the adaptor protein Lnk, which binds c-KIT at Y567 (Simon et al., 2008). MCs deficient for the p85α subunit of PI3K show

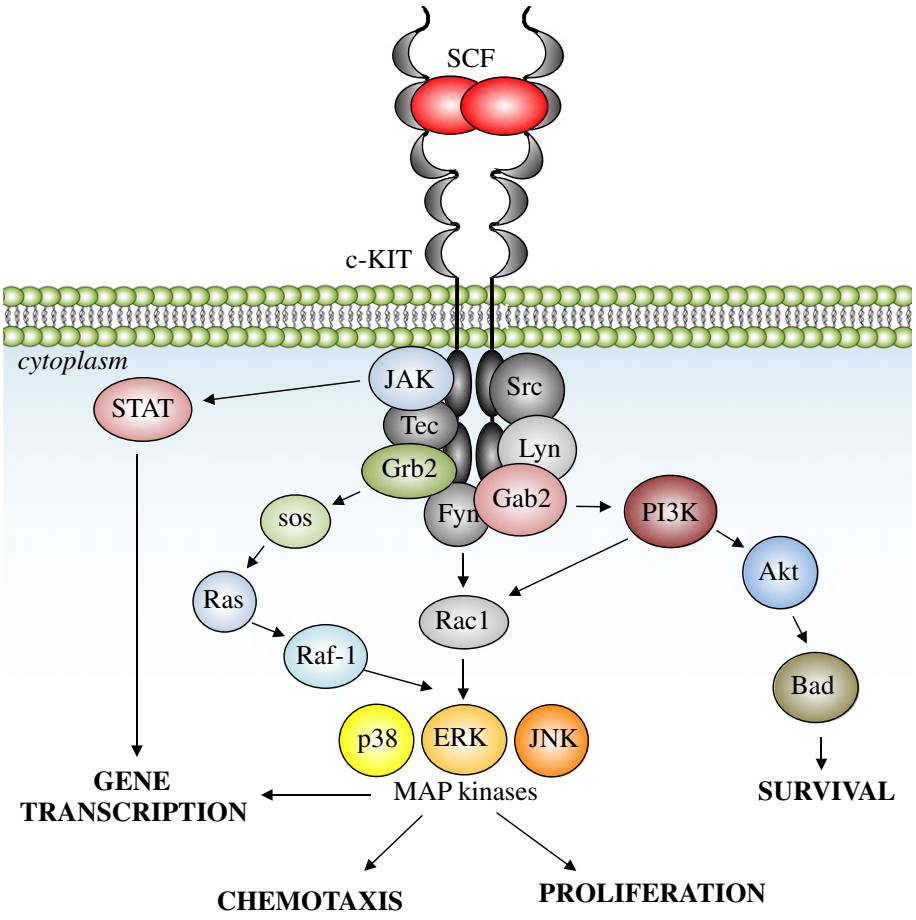

Fig. 2. Simplified overview of c-KIT-mediated signal transduction. Binding of SCF homodimers induces dimerization and transphosphorylation of the c-KIT receptor, creating docking sites for a number of signaling molecules, including some Src family members, JAK, and Gab2. Activation of these pathways leads to MC survival, proliferation, chemotaxis, and gene transcription. ERK: extracellular signal-regulated kinase; Grb2: growth factor receptor-bound protein-2; JAK: Janus kinase; MAP kinase: mitogen-activated protein kinase; PI3K: phosphatidylinositol-3 kinase; SCF: stem cell factor; sos; son-of-sevenless; STAT: signal transducers and activators of transcription.

reduced SCF-induced growth and maturation in vitro, while these effects are enhanced in *p85β* MCs (Krishnan et al., 2012a, 2012b).

SCF is one of several endogenous agents known to potentiate IgE- and antigen-mediated MC activation (Hill et al., 1996; Hundley et al., 2004; Tkaczyk et al., 2004). Nonetheless, repetitive subcutaneous injection of SCF into mice over a period of 21 days is reported to protect them against fatal PSA reactions (Ando et al., 1993). It was recently proposed that this hyporesponsive phenotype of MCs exposed to prolonged treatment with SCF results from SCF-induced ineffective cytoskeletal reorganization that potentially decreases expression of the Src kinase Hck (Ito et al., 2012).

5. Mast cells in allergic diseases

The role of MCs in allergic diseases has been discussed in many reviews (for examples, see Galli et al., 2008a, 2008b; Galli & Tsai, 2010, 2012). Observations in both human and animal models suggest that IgE-dependent MC degranulation is a key effector step in initiating acute allergic reactions, most probably through release of preformed histamine. However, other allergy pathways have now been described, as discussed below for food anaphylaxis and asthma.

5.1. Food allergy and anaphylaxis

Food allergies are acquired immune responses to food proteins with adverse effects (Sicherer & Sampson, 2009). Their prevalence is increasing: food allergies now affect ~6% of children and 3–4% of adults in developed countries (Sicherer & Sampson, 2009). The manifestations of food allergy can range from mild to severe, with the most severe form being anaphylaxis, an acute and potentially life-threatening multi-system reaction to allergen exposure.

MCs play an essential role in a murine model of oral allergen-induced intestinal inflammation (Brandt et al., 2003). In this model, exposure of ovalbumin (OVA)/alum-sensitized mice to repeated doses of intragastric OVA induced acute diarrhea associated with increased numbers of mucosal MCs and their increased degranulation (Brandt et al., 2003). By depleting MCs with anti-c-KIT monoclonal antibodies, Brandt et al. demonstrated that MCs play a critical role in mediating allergic diarrhea in this model (Brandt et al., 2003). Wang et al. also showed that a peanut-induced intestinal allergy in mice is mediated through a MC-dependent IgE-FcεRI-IL-13 pathway (Wang et al., 2010).

5.1.1. Passive anaphylaxis models

Anaphylaxis in mice has been studied extensively with passive models, involving cutaneous (for PCA) or systemic (for PSA) sensitization with antigen-specific IgE or IgG, followed by a systemic challenge with antigen. These models have provided important information about the cellular and molecular mechanisms of anaphylaxis.

Studies with MC-deficient *Kit* mutant mice have demonstrated that IgE-mediated PCA and PSA depend highly on MCs. By contrast, MCs are not necessary for IgG_1-dependent PSA (Dombrowicz et al., 1997; Miyajima et al., 1997; Finkelman, 2007; Tsujimura et al., 2008). IgE-dependent PSA appears to depend on histamine release by MCs, since $HDC^{-/-}$ mice (which are deficient for the enzyme histidine decarboxylase, responsible for histamine production) are protected in this model, and injection of histamine can induce most features of PSA in WT

mice (Makabe-Kobayashi et al., 2002). The finding that MC-deficient *Cpa3*$^{Cre/+}$ mice, *Cpa3-Cre*; *Mcl-1*$^{fl/fl}$ mice, and DT-treated Mas-TRECK mice are all protected in IgE-dependent models of both PSA and PCA confirms the key role of MCs in these reactions (Feyerabend et al., 2011; Lilla et al., 2011; Sawaguchi et al., 2012). Moreover, engraftment of *Cpa3*$^{Cre/+}$ mice with BMCMCs restores IgE- and antigen-induced hypothermia to levels observed in WT mice (Feyerabend et al., 2011). Similarly, intradermal engraftment of *Cpa3-Cre*; *Mcl-1*$^{fl/fl}$ mice with BMCMCs restores IgE- and antigen-induced ear swelling to levels observed in WT mice (Lilla et al., 2011). Both *Cpa3-Cre*; *Mcl-1*$^{fl/fl}$, and DT-treated Mas-TRECK mice are also protected in models of basophil-dependent IgE-mediated chronic allergic inflammation; this finding confirms that these mice are also functionally deficient in basophils (Mukai et al., 2005; Obata et al., 2007; Lilla et al., 2011; Sawaguchi et al., 2012).

5.1.2. Active anaphylaxis models

Active models, in which mice are sensitized with the antigen in the presence of an adjuvant and then challenged by the antigen, produce a more complex picture of the cellular mechanisms of anaphylaxis, which involve several pathways.

Studies by Finkelman et al. have characterized two pathways of anaphylaxis in mice: a classical pathway consisting of antigens, IgE, FcεRI, MCs, and histamine, and an alternative pathway made up of IgG_1-antigen immune complexes, FcγRIII, macrophages, and platelet-activating factor (PAF) (Finkelman, 2007). Tsujimura et al. showed that basophil depletion can rescue MC-deficient *Kit*$^{W/W\text{-}v}$ and *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice from death in an active anaphylaxis model. The absence of this effect in WT mice suggests that both MCs and basophils contribute to the response in this model (Tsujimura et al., 2008). More recently, Jönsson et al. showed that neutrophils also contribute to certain models of active anaphylaxis in mice, through an IgG-FcγRIV-mediated pathway (Jönsson et al., 2011).

In the USA, most cases of food-induced fatal or near-fatal anaphylaxis are caused by peanuts or tree nuts (Bock et al., 2001, 2007). Several studies using *Kit*-mutant *Kit*$^{W/W\text{-}v}$ and *Kit*$^{W\text{-}sh/W\text{-}sh}$ MC-deficient mice have suggested that MCs can significantly contribute to peanut-induced active anaphylaxis (Sun et al., 2007; Arias et al., 2011; Smit et al., 2011). These results were recently confirmed in non-*Kit* mutant MC-deficient mice, by showing that selective ablation of connective tissue-type MCs (induced by DT injection in *Mcpt5-Cre*; *iDTR* mice) significantly reduced the hypothermia induced by peanut challenge in peanut-sensitized mice (Reber et al., 2013). This study also showed that selective ablation of basophils can reduce peanut-induced hypothermia. However, significant hypothermia still developed in the absence of both MCs and basophils (in *Cpa3-Cre*$^{+}$; *Mcl-1*$^{fl/fl}$ mice) in this active model, although at a lower level than in WT mice (Reber et al., 2013). Histamine production was abrogated in *Cpa3-Cre*$^{+}$; *Mcl-1*$^{fl/fl}$ mice. Small but significant increases in PAF were nonetheless detected in spleen specimens derived from peanut-sensitized, peanut-challenged *Cpa3-Cre*$^{+}$; *Mcl-1*$^{fl/fl}$ mice (Reber et al., 2013). Altogether, these findings confirm the involvement of both the classical and alternative pathways of anaphylaxis in this active anaphylaxis model (Reber et al., 2013).

In humans, several lines of evidence suggest that both MCs and basophils can contribute to systemic anaphylaxis, and measurement of serum levels of tryptase, which is specific for MCs, is a useful diagnostic tool for anaphylaxis (Schwartz, 2004; Galli, 2005). However, the alternative pathway is also likely to play an important role. Vadas et al. showed that serum PAF levels are directly correlated and that serum PAF acetylhydrolase activity is inversely correlated with the severity of anaphylaxis (Vadas et al., 2008). A follow-up study demonstrated that PAF levels are elevated in all patients with severe anaphylaxis, although neither histamine nor tryptase levels are (Vadas et al., 2013). Thus, while MCs likely play an important role in anaphylaxis, they are surely not the only cell type involved in this complex acute reaction.

5.2. Asthma

Even in the absence of allergen exposure, the airways of patients with asthma contain more MCs than those of individuals without asthma (Bradding et al., 1994; Koshino et al., 1996). MC numbers are higher in the bronchial mucosa, particularly in the bronchial epithelium (Laitinen et al., 1993; Bradding et al., 1994). After allergen exposure, the number of MCs rises still higher in the bronchial epithelium of patients with asthma (Crimi et al., 1991; Montefort et al., 1994) compared with healthy subjects. MC numbers correlate with bronchial hyperresponsiveness (Wardlaw et al., 1988; Ferguson et al., 1992). Moreover, concentrations of MC-derived mediators, such as histamine (Casale et al., 1987; Jarjour et al., 1991) and tryptase (Wenzel et al., 1988), are higher in bronchoalveolar lavage (BAL) from asthma patients after allergen challenges, than in subjects without asthma. Moreover, MC degranulation has been observed in bronchial biopsies of people with asthma (Djukanovic et al., 1992).

This evidence suggests that MCs play an important role in the acute airway response to allergens. Their role in chronic asthma, however, remains to be fully assessed. Moreover, various mouse models of allergic airway inflammation have yielded conflicting data on the role of MCs (reviewed in Reber et al., 2012).

Several studies using the MC knock-in model in both *Kit*$^{W/W\text{-}v}$ and *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice have shown that MCs can mediate AHR and airway inflammation in asthma models induced by systemic immunization of mice with OVA without adjuvant, followed by repeated intranasal challenge with OVA (Yu et al., 2006b, 2011; Nakae et al., 2007a). In these conditions, MC-derived TNF seems to play a major role in the development of both AHR and airway inflammation (Nakae et al., 2007a). Other reports, however, indicate that both WT and MC-deficient *Kit* mutant mice can develop similar levels of AHR and airway inflammation in models that use alum as an adjuvant during the sensitization phase (Egan et al., 1995; Kobayashi et al., 2000; Williams & Galli, 2000; Masuda et al., 2003). In addition, results in these models depend highly on the mouse background, since BALB/c-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice developed AHR and airway inflammation at the levels observed in WT BALB/c mice, while less airway reactivity and inflammation were observed in C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice in an adjuvant-free asthma model (Becker et al., 2011). More recently, Sawaguchi et al. showed in an adjuvant-free model of asthma that diphtheria toxin (DT)-mediated MC ablation in Mas-TRECK mice reduces AHR and histamine levels but has no effect on the number of inflammatory leukocytes in BAL fluid (Sawaguchi et al., 2012). Finally, the increased lung inflammation in *Mcpt4*$^{-/-}$ mice in the adjuvant-free model suggests that this protease might even play a protective role in this model (Waern et al., 2009).

6. Mast cells in innate immunity

Abundant evidence from mouse studies suggests that MCs have a central role in the innate response against invading pathogens, such as viruses and bacteria (Abraham & St John, 2010; Galli & Tsai, 2010; Kumar & Sharma, 2010). Because MCs reside at sites exposed to the external environment, such as the skin and the airways, they are likely to be among the first innate cells, along with macrophages and dendritic cells, to be activated by invading pathogens. Human and mouse MCs express TLRs, in particular TLR2 and TLR4 (McCurdy et al., 2001; Supajatura et al., 2001, 2002; McCurdy et al., 2003), and NOD-like receptors (NLRs), such as NOD2 and NLRP3 (Feng et al., 2007; Wu et al., 2007; Nakamura et al., 2009; Okumura et al., 2009; Nakamura et al., 2012); both types of receptors permit direct recognition of invading pathogens. MCs can also be activated indirectly by endogenous factors produced during innate immune response, such as endothelin-1 (Ehrenreich et al., 1992), substance P (Johnson & Krenger, 1992; Ferry et al., 2002), or products of complement activation (Nilsson et al., 1996).

6.1. Bacterial infections

Using the MC knock-in model in *Kit*$^{W/W\text{-}v}$ mice and anti-TNFα blocking antibodies, Echtenacher et al. demonstrated that MCs can mediate survival after cecal ligation and puncture (CLP), a model of polymicrobial sepsis; blocking TNFα inhibits this protection (Echtenacher et al., 1996). Follow-up studies using the MC knock-in system have confirmed the central role of MC-derived TNF in defense against bacteria by showing that TNF production by MCs promotes hypertrophy of draining lymph nodes during bacterial infections (McLachlan et al., 2003); TNF is also required for full development of MC-dependent features in the CLP model (Piliponsky et al., 2010). Treatment of WT mice with SCF increases MC numbers and improves survival in the CLP model (Maurer et al., 1998). These effects of SCF treatment reflect, at least in part, the actions of SCF on MCs, since SCF improves survival of *Kit*$^{W/W\text{-}v}$ mice in the CLP model only when these mice are engrafted with WT BMCMCs (Maurer et al., 1998).

MC-derived IL-12 (Nakano et al., 2007) and MC expression of dipeptidyl peptidase I (DPPI), a cysteinyl protease, and of the transcription factor Smad3 (a major TGFβ transducer) are also required for survival in the CLP model (Mallen-St Clair et al., 2004; Kanamaru et al., 2005). Moreover, MCs play a protective role in the CLP model through release of proteases that can degrade endogenous peptides such as endothelin-1 (a potent vasoconstrictor) (Maurer et al., 2004). Among these MC proteases, the mouse chymase MCPT4 appears central in promoting survival in the CLP model, possibly by degrading TNF and thus limiting the potentially toxic effects of high levels of this cytokine (Piliponsky et al., 2012).

Orinska et al. reported that IL-15 expression in MCs limits the antibacterial properties of these cells by suppressing chymase activity (Orinska et al., 2007). The protective role of MCs during bacterial infection has been challenged, however, by Piliponsky et al., who showed that the severity of the infection model and the strain of MC-deficient mice used govern the MC effect, which can be undetectable or opposite (that is, can promote or impede survival) (Piliponsky et al., 2010).

That, depending on the mouse strain background, the nature of the mutation resulting in a MC deficiency, and type and severity of bacterial infection, MCs can have either no detectable effect or opposite effects on survival during bacterial infections, e.g., promoting survival during moderately severe CLP associated with low mortality but, in C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice, increasing mortality during severe CLP or infection with *Salmonella typhimurium*.

MCs can also mediate neutrophil recruitment after intraperitoneal injection of *Klebsiella pneumoniae*, through their release of TNF (Malaviya et al., 1996), IL-6 (Sutherland et al., 2008), and the tryptase MCPT6 (Thakurdas et al., 2007). They also play a protective role in a mouse model of infection with *Mycoplasma pneumonia* (Xu et al., 2006a). Interestingly, histamine has a significant role in this model, but neutrophils rather than MCs have been shown to be its major source in the lungs of infected mice (Xu et al., 2006b). Finally, MCs are reported to play a protective role in mouse models of infection with *Escherichia coli* (Malaviya et al., 2001).

Beside their roles in promoting immediate innate immune responses to bacteria, MCs can also suppress adaptive immune responses in the bladder after infection with uropathogenic *E. coli* (UPEC); this immunosuppressive role is mediated by MC-derived IL-10 (Chan et al., 2013).

6.2. Viral infections

Although it is less extensive than for bacterial infections, there is evidence suggesting that MCs can mediate innate immunity to some viruses (Abraham & St John, 2010). The Sendai virus induces release of histamine from rat MCs (Sugiyama, 1977). Several other viruses and double-stranded RNA (dsRNA) (through activation of TLR3) can activate MCs in vitro and thereby promote production of type I interferons (Kulka et al., 2004; Orinska et al., 2005). In addition, several reports of experiments with the MC knock-in models now suggest that MCs can mediate innate responses to some viruses in vivo. For example, CD8$^+$ T-cell recruitment following intraperitoneal injection of dsRNA in mice depends on MCs (Orinska et al., 2005). They also participate in the acute inflammatory reaction that follows intraperitoneal infection with the encephalomyocarditis virus (Higuchi et al., 2008) and play a protective role in a mouse model of infection with vaccinia virus through release of antimicrobial peptides, such as cathelicidin, in the skin (Wang et al., 2012a, 2012b). Finally, MCs can also promote the recruitment of natural killer (NK) and NK T cells during dengue infection in mice (St John et al., 2011). Their role in HIV can be either positive or negative, protective or adverse: while in vitro experiments show that the gp120 envelope protein can induce human MCs to produce IL-4 and IL-5 (Kulka et al., 2004), another study reports that MCs can serve as a reservoir for latent virus (detrimental to the host) (Sundstrom et al., 2007).

7. Mast cells in autoimmune diseases

Repeated observations of increased numbers and higher activation of MCs at sites of inflammation in various autoimmune diseases suggest that MCs play an important role in these pathologies. Nonetheless, in vivo results are conflicting about the role of MCs in several models of autoimmune diseases, including rheumatoid arthritis (RA) and multiple sclerosis (MS).

7.1. Rheumatoid arthritis

MC numbers are higher in synovial tissue from affected joints of RA patients compared to normal synovial tissue (Crisp et al., 1984; Godfrey et al., 1984; Kopicky-Burd et al., 1988; Bridges et al., 1991; Gotis-Graham & McNeil, 1997; Ceponis et al., 1998). In addition, relatively high levels of histamine (Frewin et al., 1986; Malone et al., 1986; Buckley et al., 1997) and tryptase (Brodeur et al., 1991; Lavery & Lisse, 1994; Buckley et al., 1997) in synovial fluid from RA patients suggest that these synovial MCs in RA patients are locally activated. MCs produce several mediators implicated in the pathogenesis of RA. Double immunostaining has demonstrated MC production of TNF-α in rheumatoid tissue and fluid specimens (Woolley & Tetlow, 2000), and Hueber et al. showed that synovial MCs are the major IL-17A-expressing cells in human inflamed RA tissue (Hueber et al., 2010).

In mice, increased numbers of MCs and levels of MC degranulation have also been observed in various arthritis models (Lee et al., 2002; Shin et al., 2006), but the role of MCs in these experimental arthritis models remains controversial.

Lee et al. were the first to report that MC-deficient *Kit*$^{W/W\text{-}v}$ and *Sl*/*Sl*^{d} mice are resistant to the development of joint inflammation in the K/BxN serum-transfer arthritis model and that the disease can be restored to WT levels in *Kit*$^{W/W\text{-}v}$ mice after engraftment with BMCMCs (Lee et al., 2002). Several groups subsequently confirmed the protection of *Kit*$^{W/W\text{-}v}$ mice in this model (Nigrovic et al., 2007; Guma et al., 2010; Nigrovic et al., 2010; Elliott et al., 2011; Feyerabend et al., 2011; Mancardi et al., 2011) and found that it extends to arthritis models induced by injection of collagen or anti-collagen antibodies (Kneilling et al., 2007; Zhou et al., 2007; Xu et al., 2008). A study using the MC knock-in model in *Kit*$^{W/W\text{-}v}$ mice reported that full expression of arthritis in the K/BxN model requires MC-derived IL-1β (Nigrovic et al., 2007), as well as MC activation through the Fc-receptor common γ subunit (FcRγ) (Nigrovic et al., 2007) and complement receptor C5aR (Nigrovic et al., 2010).

In contrast, MC-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice developed severe arthritis in all these models despite the absence of MCs (Nigrovic et al., 2007; Zhou et al., 2007; Elliott et al., 2011; Mancardi et al., 2011; Pitman et al., 2011). Because of the important role of neutrophils in these experimental arthritis models (Wipke & Allen, 2001; Eyles et al., 2008;

Monach et al., 2010; Wang et al., 2012a, 2012c, 2012d), it has been suggested that these conflicting results might be attributed to the respective neutropenia vs neutrophilia of $Kit^{W/W\text{-}v}$ (Chervenick & Boggs, 1969; Zhou et al., 2007; Shin et al., 2009; Piliponsky et al., 2010) compared with $Kit^{W\text{-}sh/W\text{-}sh}$ mice (Shin et al., 2009; Piliponsky et al., 2010). Indeed, depletion of neutrophils by anti-Gr-1 antibodies abrogates arthritis induced by anti-collagen antibodies in the $Kit^{W\text{-}sh/W\text{-}sh}$ mice (Zhou et al., 2007).

Arguing in favor of a role for MCs in experimental arthritis in non-*Kit* mutant mice, Shin et al. showed that the development of joint inflammation is reduced in heparin-deficient *N*-deacetylase/*N*-sulfotransferase-2$^{-/-}$ (*NDST-2*$^{-/-}$) mice, which cannot synthesize sulfated heparin (Forsberg et al., 1999; Humphries et al., 1999). They also have fewer connective tissue-type MCs and lower levels of histamine and of several MC proteases (Forsberg et al., 1999; Humphries et al., 1999). Joint inflammation is also milder in mice deficient for MC protease-6 (*Mcpt6*$^{-/-}$) in the K/BxN arthritis model (Shin et al., 2009), and *Mcpt4*$^{-/-}$ mice develop lower levels of collagen-induced arthritis (Magnusson et al., 2009). On the other hand, Feyerabend et al. recently reported that they found no evidence of MC involvement in the K/BxN arthritis model with *Cpa3-Cre* mice, for which Cre recombinase-associated cytotoxicity produces a constitutive deficiency of MCs (and basophils), independent of c-*kit* (Feyerabend et al., 2011).

7.2. Multiple sclerosis

A growing body of evidence suggests that MCs are strongly involved in multiple sclerosis (MS) (reviewed in Brown et al., 2002; Walker et al., 2012). Increased numbers of MCs are observed at sites of demyelination in the central nervous system (CNS) of MS patients (Brown et al., 2002), who also have high levels of tryptase in their cerebrospinal fluid (Roznieckі et al., 1995).

Experimental autoimmune encephalomyelitis (EAE) is used to model MS in rodents. It is induced by immunization with different myelin peptides, such as myelin basic protein (MBP) or myelin oligodendrocyte glycoprotein (MOG), together with complete Freund's adjuvant (CFA) (Constantinescu et al., 2011). Increased numbers of MCs have been observed in EAE (Rouleau et al., 1997), and evidence of MC degranulation has been found in the brain (Bo et al., 1991). The first pharmacological evidence of MC implication in EAE came from the observation that proxicromil, a MC stabilizer related to cromolyn, reduces the severity of EAE in rats when administered just before the onset of clinical disease (Dietsch & Hinrichs, 1989). Secor et al. showed that the EAE severity and disease incidence induced by myelin oligodendrocyte glycoprotein are substantially lower in $Kit^{W/W\text{-}v}$ MC-deficient mice and can be restored to levels observed in WT mice by the adoptive transfer of BMCMCs, a finding that suggests that MCs are essential for full manifestation of the disease (Secor et al., 2000). Using the MC knock-in model in $Kit^{W/W\text{-}v}$ mice, this group also reported that full EAE development requires that the activating Fc-receptor FcγRIII be expressed on the MC surface and that this expression is negatively regulated by the presence of the inhibitory FcγRII on MCs (Robbie-Ryan et al., 2003). Intravenous injection of BMCMCs was used to reconstitute the MCs. The authors showed that this procedure did not produce effective engraftment in the CNS and thus concluded that MCs exert effects outside the CNS to influence the course of EAE (Tanzola et al., 2003). They later reported that MCs influence autoreactive T-cell responses in this model (Gregory et al., 2005), an effect they attributed to MC-derived IL-4 (Gregory et al., 2006).

In contrast to these results, two studies have reported no difference between WT and $Kit^{W/W\text{-}v}$ mice (Bennett et al., 2009; Feyerabend et al., 2011). Another study underlined the importance of the experimental protocol when it found that these mice are protected from EAE only when immunized with high, but not low, doses of antigen and adjuvant (Piconese et al., 2011). Two recent reports even show exacerbated EAE in $Kit^{W\text{-}sh/W\text{-}sh}$ MC-deficient mice (Li et al., 2011; Piconese et al., 2011). The reasons for these differences are not fully understood, but they cannot be attributed only to the difference in neutrophil populations between $Kit^{W/W\text{-}v}$ and $Kit^{W\text{-}sh/W\text{-}sh}$ mice, since $Kit^{W\text{-}sh/W\text{-}sh}$ mice develop exacerbated EAE even after neutrophil depletion (Piconese et al., 2011). More recently, Feyerabend et al. used a new model of *Kit*-independent MC-deficient *Cpa3-Cre* mice and reported no evidence of MC involvement in EAE (Feyerabend et al., 2011). Importantly, they also noted that the particular EAE experimental protocol used for this study resulted in similar levels of disease severity for WT and $Kit^{W/W\text{-}v}$ mice (Feyerabend et al., 2011; Brown et al., 2012).

8. Protective roles for mast cells

8.1. Immunosuppressive role

Some publications suggest that MCs may also participate in immunosuppression. Lu et al. first reported that MCs play a key role in skin graft tolerance (Lu et al., 2006). Using MC-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice, they showed that MCs are essential for the recruitment of $CD4^+CD25^+Foxp3^+$ regulatory T (T_{Reg}) cells, which in turn mediate immune suppression and prevent graft rejection (Lu et al., 2006). In a follow-up study, they reported that mice deficient for MCPT6, a MC-specific tryptase, do not develop tolerance to an allogeneic graft and that the graft rejection observed in these mice is similar to that in MC-deficient hosts (de Vries et al., 2010). They subsequently observed that in conditions favorable to the development of tolerance, MCs can produce granulocyte macrophage colony-stimulating factor (GM-CSF), which induces survival of graft-derived dendritic cells that migrate into the draining lymph nodes and suppresses T-cell responses to maintain peripheral tolerance (de Vries et al., 2011).

Using MC-deficient $Kit^{W/W\text{-}v}$ mice, Demeure et al. found that dermal MC activation is a necessary step in mosquito bite-induced extravasation and neutrophil recruitment (Demeure et al., 2005). They later showed that mosquito bites can down-regulate the magnitude of antigen (ovalbumin)-specific T-cell responses both MC- and IL-10-dependently (Depinay et al., 2006).

MCs were long thought to exacerbate dermatitis induced by chronic exposure to low-dose ultraviolet (UV)-B irradiation or haptens such as DNFB (1-fluoro-2,4-dinitrobenzene). Unexpectedly, however, Grimbaldeston et al. found that late responses to this exposure are actually higher in the MC-deficient $Kit^{W/W\text{-}v}$ and $Kit^{W\text{-}sh/W\text{-}sh}$ mice. They further found that IL-10 production by MCs contributes to the anti-inflammatory or immunosuppressive effects of MCs in these conditions (Grimbaldeston et al., 2007). They later reported that activation of MCs by vitamin D3 causes in vitro IL-10 production. Their adoptive transfer experiments showed that optimal MC-dependent suppression of the inflammation associated with chronic UV-B irradiation of the skin in $Kit^{W/W\text{-}v}$ mice requires expression of the vitamin D receptor (VDR) by the adoptively transferred MCs (Biggs et al., 2010). MC-derived IL-2 also contributes to recruitment of Tregs and suppression of chronic allergic dermatitis induced by repeated oxazolone challenges (Hershko et al., 2011).

These immunosuppressive properties of MCs, all identified in *Kit* mutant MC-deficient mice, have been called into question by the finding that increased contact hypersensitivity to DNFB does not occur either in *Kit*-independent MC deficient mice (both *Mcpt5-Cre*; *DTA*$^+$ and diphtheria toxin-treated *Mcpt5-Cre*; *iDTR*$^+$ mice) or in *Mcpt5-Cre*; *IL-10*$^{fl/fl}$ mice (which have no *Kit*-related phenotypic abnormalities but in which only MCs cannot produce IL-10) (Dudeck et al., 2011). However, Chan et al. recently confirmed that MCs can suppress adaptive immune responses in the bladder after infection with uropathogenic *E. coli* (UPEC) and that this immunosuppressive role for MCs is also mediated by MC-derived IL-10 (Chan et al., 2013). Importantly, the use of both *Kit* mutant MC-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice (engrafted with WT or *IL-10*$^{-/-}$ BMCMCs) and *Mcpt5-Cre*; *IL-10*$^{fl/fl}$ mice (Chan et al., 2013) for this

experiment strengthens the demonstration that MC-derived IL-10 plays a role in the immunoprotective properties of MCs.

8.2. Protection against toxins and venoms

Many animal venoms contain components that can induce MC degranulation, such as MC-degranulating peptide (MCD) in bumblebee venom (Gushchin et al., 1981) and mastoparan in wasp venom (Hirai et al., 1979), and these have been thought to contribute to the pathogenesis and mortality caused by envenomation. By contrast, studies in *Kit* mutant MC-deficient mice reveal that MC activation can actually reduce the pathology associated with exposure to various venoms, including the venoms of the Gila monster and of certain snakes, honeybees, and scorpions (Metz et al., 2006; Schneider et al., 2007; Akahoshi et al., 2011). Studies in mice deficient for the chymase MCPT4 or lacking CPA3 activity have identified a mechanism by which MCs protect against envenomation: these proteases can cleave various venoms or venom components, such as helodermin or sarafotoxin (Schneider et al., 2007; Akahoshi et al., 2011). MC proteases can also degrade some endogenous peptides produced during immune responses, such as endothelin-1 and neurotensin; this mechanism has been shown to play a protective role in a mouse model of sepsis (Maurer et al., 2004; Piliponsky et al., 2008).

9. Drugs targeting mast cells and mast cell-derived mediators

9.1. Mast cell stabilizers

MC stabilizers are drugs thought to prevent MC activation by stabilizing membranes. The most commonly used of these stabilizers are cromolyn sodium and nedocromil sodium (Howell & Altounyan, 1967; Lal et al., 1984), which have been shown to inhibit histamine release from primary human lung MCs in vitro (Leung et al., 1988) and have been used as antiasthma drugs for decades (Howell & Altounyan, 1967; Bernstein et al., 1972; Rainey, 1992; Edwards & Stevens, 1993). MC stabilizers have also been used for the treatment of other diseases thought to involve MC activation, including atopic dermatitis (Businco & Cantani, 1991), allergic rhinitis (Greiner & Meltzer, 2006), allergic conjunctivitis (Figus et al., 2010), and mastocytosis (Horan et al., 1990).

Cromolyn sodium has also been used extensively in rodents to attempt to elucidate MC functions in both allergic and non-allergic inflammatory disease models (Wyss et al., 2005; Kneilling et al., 2007; Soucek et al., 2007; Liu et al., 2009; Ramos et al., 2010; Kim et al., 2012). Cromolyn can, however, affect the functions of other types of cells as well, including granulocytes and B cells (Norris, 1996; Arumugam et al., 2006). Moreover, a recent report indicates that cromolyn inhibits the MC-dependent IgE-mediated PCA reaction in rats but not in mice (Oka et al., 2012). This article also reports that cromolyn can inhibit LPS-induced TNF production in both WT and MC-deficient mice and that this inhibition is thus MC-independent (Oka et al., 2012).

9.2. Mast cell activators

So-called MC activators comprise a family of structurally diverse cationic peptides and polymeric compounds that can induce MC degranulation in a Gi protein-dependent manner (Aridor et al., 1993; Ferry et al., 2002). This family includes compound 48/80 (c48/80) (Paton, 1951; Fawcett, 1954; Rothschild, 1970), and a variety of peptide toxins, such as MC-degranulating peptide (MCD), found in bumblebee venom (Gushchin et al., 1981), and mastoparan, found in wasp venom (Hirai et al., 1979). These MC activators have been widely used as tools to induce MC degranulation both in vitro and in vivo (Ferry et al., 2002).

More recently, they have been used as adjuvants (McLachlan et al., 2008). In mice, co-injection of c48/80 and recombinant anthrax protective antigen (PA) results in a robust production of IgG antibodies specific for PA. In MC-deficient $Kit^{W/W\text{-}v}$ mice, this effect falls to one tenth of that in WT but can be restored by reconstituting $Kit^{W/W\text{-}v}$ mice with MCs at the injection site (McLachlan et al., 2008). The potency of c48/80 is equal to that of other well-known adjuvants, such as CpG oligonucleotides and cholera toxin, when used intradermally; it promotes a balanced Th1/Th2/Th17 response without inducing production of PA-specific IgE (McGowen et al., 2009). In addition, c48/80 stimulates a strong mucosal response when applied nasally in mice (McLachlan et al., 2008) and rabbits (Staats et al., 2011; Wang et al., 2012b). However, c48/80 can also have a direct effect on other cell types, as recently demonstrated for excitation of cultured enteric neurons (Schemann et al., 2012).

9.3. Antihistamines

Histamine is an amine synthesized from L-histidine exclusively by histidine decarboxylase (HDC). Histamine exerts its biologic effects through activation of four G-protein-coupled receptors (GPCRs): H1-receptor (H1R), H2R, H3R, and H4R. Both the role of histamine in human health and disease and the expression of the histamine receptor have been extensively described elsewhere (for recent reviews, see O'Mahony et al., 2011; Ferstl et al., 2012).

That MCs contain histamine was demonstrated more than 60 years ago (Riley & West, 1952). However, although they are likely to be its major source in vivo, histamine cannot be considered to be specific to MCs, because several other types of cells can also produce and release it, including basophils (Windelborg Nielsen et al., 1990) and neutrophils (Ghosh et al., 2002; Xu et al., 2006b).

Histamine receptor inverse agonists are generally referred to as antihistamines. More than 40 inverse agonists of H1R (and some inverse agonists of H2R) have been approved for clinical use (for review, see Simons, 2004; Simons & Simons, 2011). Although no H3R and H4R inverse agonists have yet been approved for clinical use, some are now being used in clinical trials for allergic rhinitis and pruritus (Simons & Simons, 2011).

9.4. Anti-immunoglobulin E

Anti-IgE therapies have shown promise in the treatment of several allergic disorders, and the anti-IgE antibody omalizumab (rhuMAb-E25) has been approved for the treatment of allergic asthma. Omalizumab is a recombinant humanized monoclonal antibody that recognizes IgE at the same site as the high-affinity IgE receptor (FcεRI binding site) (Presta et al., 1993). Omalizumab can decrease serum levels of free IgE and has been shown to provide clinical benefits to patients with seasonal allergic rhinitis (Casale et al., 2001), asthma (Busse et al., 2001; Vignola et al., 2004), and chronic spontaneous urticaria (Kaplan et al., 2013; Maurer et al., 2013). Omalizumab has also been used successfully in some patients with food allergies, in combination with oral desensitization (Leung et al., 2003; Nadeau et al., 2011; Sampson et al., 2011).

IgE antibodies bind the high-affinity IgE Fc receptor (FcεRI), but also CD23 and some other receptors (for review, see Galli & Tsai, 2012). Cell types besides MCs that can express FcεRI include basophils (Kraft & Kinet, 2007), dendritic cells (Kraft & Kinet, 2007), monocytes (Kraft & Kinet, 2007), eosinophils (Kraft & Kinet, 2007; Porcherie et al., 2011), neutrophils (Gounni et al., 2001; Porcherie et al., 2011), and platelets (Joseph et al., 1997; Hasegawa et al., 1999). Thus, while anti-IgE appears to have great promise for allergic diseases, it is not yet fully clear whether these drugs mediate their action through inhibition of MC activation.

9.5. Inhibitors of stem cell factor/c-KIT

9.5.1. Anti-stem cell factor and anti-c-KIT antibodies

Blocking antibodies against SCF or c-KIT have been used in various animal models to try to block MC activation and functions. Lukacs et al. report that inhibiting SCF with an anti-SCF blocking antibody

leads to a significant reduction in histamine levels and eosinophil infiltration in a murine model of allergic asthma (Lukacs et al., 1996). Anti-SCF antibodies are reported to inhibit the allergic airway response in cockroach allergen-challenged mice by reducing AHR (Berlin et al., 2004, 2006). Repeated injection of a blocking anti-c-KIT antibody leads to depletion of MCs and reduces experimental oral allergen-induced diarrhea in mice (Brandt et al., 2003).

Treatment of rats with anti-SCF antibodies significantly reduces the number of jejunal mucosal MCs, the level of rat MC protease II, and the fecal egg counts in rats infected with the parasite *Nippostrongylus brasiliensis* (Newlands et al., 1995). By contrast, treating mice with anti-SCF or anti-c-KIT monoclonal antibodies, while it completely abrogates the MC hyperplasia generated by *Trichinella spiralis* infection, also delays worm expulsion in this model (Donaldson et al., 1996). These findings together indicate that MCs can act beneficially to defend against parasites.

9.5.2. Tyrosine kinase inhibitors

To date, the only drugs used clinically to inhibit c-KIT-dependent MC activation are tyrosine kinase inhibitors (for review, see Jensen et al., 2007; El-Agamy, 2012). Among these, imatinib (STI 571), the first c-KIT inhibitor described, inhibits growth and adhesion of human MCs in culture (Takeuchi et al., 2003). It also reduces disease intensity in a mouse model of experimental arthritis (Paniagua et al., 2006) and in rheumatoid arthritis in humans (Eklund & Joensuu, 2003; Juurikivi et al., 2005). Molecular remission and reversal of myelofibrosis have been reported in response to imatinib treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome (Klion et al., 2004). Imatinib also alleviates diarrhea in a mouse model of intestinal allergy (Vaali et al., 2012).

While imatinib is a potent inhibitor of c-KIT, it can also inhibit PDGFR c-abl, bcr-abl, and platelet-derived growth-factor receptor (PDGFR) tyrosine kinases (Heinrich et al., 2000). Moreover, it does not inhibit c-KIT bearing the D816V mutation found in some patients with mastocytosis, a rare disease characterized by the abnormal accumulation of aberrant MCs (Ma et al., 2002; Akin et al., 2003). For this reason, several other tyrosine kinase inhibitors have been developed, such as masitinib (AB1010) (Dubreuil et al., 2009), dasitinib (BMS-354825) (Schittenhelm et al., 2006; Shah et al., 2006), and EXEL-0862 (Pan et al., 2007); these show selectivity for both WT and mutant c-KIT proteins. These inhibitors show promise for the treatment of systemic mastocytosis (for review, see Horny et al., 2007; Metcalfe, 2008; Ustun et al., 2011).

Masitinib has greater activity and selectivity against WT c-KIT in vitro than imatinib and can inhibit mutant c-KIT proteins; it also potently inhibits PDGFR, the intracellular kinase Lyn, and to a lesser extent, fibroblast growth factor receptor 3. In contrast, masitinib inhibits ABL and c-Fms only weakly and is inactive against a variety of other tyrosine and serine/threonine kinases (Dubreuil et al., 2009). It has been proved to be an effective and mostly well-tolerated treatment of canine atopic dermatitis, including severe and refractory cases (Cadot et al., 2011). It also improves disease control in severe corticosteroid-dependent patients with asthma (Humbert et al., 2009) and is a promising treatment for indolent forms of mastocytosis with related disabilities (Paul et al., 2010). A randomized, placebo-controlled, phase 2 study showed that treatment with masitinib (administered as add-on therapy to standard care for 24 weeks) is associated with slower cognitive decline in Alzheimer's disease (Piette et al., 2011). In a multicenter, randomized, placebo-controlled, proof-of-concept trial, masitinib showed promising therapeutic benefits for patients with primary progressive multiple sclerosis (PPMS) and those with relapse-free secondary progressive multiple sclerosis (rfSPMS) (Vermersch et al., 2012).

9.6. Protease inhibitors

Tryptases and chymases are the major enzymes stored and secreted by MCs. Because these proteases are potentially implicated in many immune responses, including both allergic and non-allergic reactions, tryptases and chymases are promising therapeutic targets for many MC-dependent diseases (for review, see Caughey, 2007, 2011).

9.6.1. Tryptase inhibitors

Intranasal delivery of the MOL 6131 tryptase inhibitor decreases airway inflammation but not AHR in a mouse model of asthma (Oh et al., 2002). The β-tryptase inhibitor JNJ-27390467 also reduces airway inflammation when given orally in two models of asthma (in sheep and guinea pigs) (Costanzo et al., 2008).

In a single-center, randomized, double-blind study, Erin et al. assessed the effect of a single topical nasal dose (3 different doses tested) of RWJ-58643, a competitive inhibitor of both MC β-tryptase and pancreatic trypsin, or placebo, in a cohort of 16 men with grass pollen allergic rhinitis 30 min before a nasal allergen challenge. Significant reduction of symptoms, eosinophils, and IL-5 levels were found in the lowest-dose group. However, the higher doses caused a late eosinophilia, preceded by increases in IL-5, compared with placebo (Erin et al., 2006). This inhibitor was later discontinued from an allergic rhinitis phase IIa trial due to its taste (Liu & Hickey, 2008).

9.6.2. Chymase inhibitors

The peptidic chymotrypsin inhibitor chymostatin has been used as an inhibitor of MC chymase, but it can also inhibit several other proteases, including chymotrypsin, papain, chymotrypsin-like serine proteinases, and lysosomal cysteine proteinases such as cathepsins B, H, and L. Several small-molecule inhibitors of chymase have been developed, such as SUN-C8257, NK3201, and TY-51469; they show potent selectivity for chymase over other major proteases.

MC chymase can produce angiotensin II from angiotensin I (Urata et al., 1990; Takai et al., 1996). Angiotensin II is a potent vasoconstrictor peptide known to promote atherosclerosis (Wang et al., 2013). The chymase inhibitor SUN-C8257 suppresses the development of lipid accumulation in the hamster aorta induced by a high-cholesterol diet (Uehara et al., 2002), and oral administration of the chymase inhibitor RO5066852 reduces spontaneous atherosclerosis in the thoracic aorta of *apoE*$^{-/-}$ mice (Bot et al., 2011). In a model of aortic aneurysm induced by the application of elastase onto the abdominal aorta of hamsters, treatment with the compound NK3201 reduced both chymase activity and aortic diameter (Tsunemi et al., 2004).

Angiotensin I-converting enzyme (ACE) inhibitors are widely used to suppress the deleterious cardiac effects of angiotensin II by inhibiting locally generated angiotensin II (SOLVD Investigators, 1992). Combined chymase and ACE inhibition, compared with ACE inhibition alone, improved symptoms in a hamster model of myocardial infarction (Wei et al., 2010).

Increasing pharmacological evidence suggests that chymase inhibitors might be beneficial for the treatment of lung fibrosis. First, Tomimori et al. showed that administration of the chymase inhibitor SUN C8077 dose-dependently reverses bleomycin-induced lung fibrosis in mice (Tomimori et al., 2003). Sakaguchi et al. then showed that the chymase inhibitor NK3201, administered orally, can suppress bleomycin-induced pulmonary fibrosis in hamsters (Sakaguchi et al., 2004). Finally, Takato et al. demonstrated that the chymase inhibitor TY-51469 reduces silica-induced lung fibrosis in mice (Takato et al., 2011). Confirming the implication of MC chymase in lung fibrosis, we recently demonstrated that mice deficient for MCPT4 (the main homologue of human chymase (Tchougounova et al., 2003; Andersson et al., 2008)) develop reduced lung inflammation and injury at early times after bleomycin administration as compared to WT mice (Reber et al., 2014).

The chymase inhibitor ONO-WH-236 dose-dependently inhibits the induction of redness, edema, and scratching behavior in a guinea pig model of allergic conjunctivitis induced by cedar pollen (Nabe et al., 2013), while the oral administration of the chymase inhibitor

SUN13834 to mice reduces trinitrochlorobenzene (TNCB)-induced dermatitis (Ogata et al., 2011).

10. Concluding remarks

Taken together, the data presented in this review provide evidence that MCs play important functions in both innate and acquired immune responses. They may therefore be important therapeutic targets in a variety of inflammatory diseases, ranging from asthma to bacterial infections. Studies in animals and especially with MC-deficient mice have helped to define the mechanisms by which MCs mediate their functions in vivo. These animal models are also used to assess the effectiveness of potential drugs that target either MC activation or MC-derived products. Until now, these drugs have all sought to antagonize MC effects. As this review has also pointed out, however, many beneficial functions of MCs have now been identified in mice. If these beneficial functions also exist in human, the unwanted consequences of MC-targeted therapies must also be considered.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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