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Targeting mast cells in inflammatory diseases

Laurent L. Reber [a,*], Nelly Frossard [b]

[a] Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA
[b] Laboratoire d'Innovation Thérapeutique, UMR 7200 CNRS-Université de Strasbourg, Faculté de Pharmacie, France

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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.

* Corresponding author at: Department of Pathology, Stanford University, 269 Campus Drive CCSR, Stanford, CA 94305, USA. Tel.: 650 736 0069; fax: 650 736 0073.
E-mail address: lreber@stanford.edu (L.L. Reber).

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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