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Review

Insights into mast cell functions in asthma using mouse models

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ABSTRACT

Therapeutics targeting specific mechanisms of asthma have shown promising results in mouse models of asthma. However, these successes have not transferred well to the clinic or to the treatment of asthma sufferers. We suggest a reason for this incongruity is that mast cell-dependent responses, which may play an important role in the pathogenesis of both atopic and non-atopic asthma, are not a key component in most of the current asthma mouse models. Two reasons for this are that wild type mice have, in contrast to humans, a negligible number of mast cells localized in the smaller airways and in the parenchyma, and that only specific protocols show mast cell-dependent reactions. The development of mast cell-deficient mice and the reconstitution of mast cells within these mice have opened up the possibility to generate mouse models of asthma with a marked role of mast cells. In addition, mast cell-deficient mice engrafted with mast cells have a distribution of mast cells more similar to humans. In this article we review and highlight the mast cell-dependent and -independent responses with respect to airway hyperresponsiveness and inflammation in asthma models using mast cell-deficient and mast cell-engrafted mice.

1. Introduction

Asthma is a chronic inflammatory airway disease characterized by recurring incidents of wheezing, breathlessness, chest tightness and coughing. It is a complex disease consisting of multiple phenotypes and with airway hyperresponsiveness (AHR) occurring in response to a range of different triggers [1]. Mast cells are implicated as important players in the pathobiology of, in particular, allergic or intrinsic asthma, but also extrinsic phenotypes such as exercise-induced asthma and non-Th2-mediated asthma [2]. Mast cells synthesize, store, and upon stimulation, release a plethora of bioactive mediators. In patients with allergic asthma, airborne allergens binds to specific IgE attached to FcεRI at the membrane of mast cells which causes cross-linking of the FcεRI and subsequent mast cell activation. This activation induces a rapid release of mediators such as histamine, proteases, cysteinyl-leukotrienes (CysLTs) and prostaglandins, which can be detected in increased concentrations in the broncho-alveloar lavage of allergen-challenged patients [3]. Following the rapid release of mediators from mast cells, cytokines, chemokines and growth factors are synthesized and subsequently also released from the mast cells (Fig. 1). The mediators induce bronchoconstriction, leukocyte infiltration and activation, and tissue remodeling, with an important role in both the early- and late-phase allergic responses, as well as with chronic inflammation [4,5]. Given the profound role of mast cells in the pathobiology of asthma, mast cells and mast cell mediators are attractive targets for developing new anti-asthma drugs [6,7]. In light of this, the role for mast cells in the pathobiology of the various asthma phenotypes must be clarified.

To study the mechanisms underlying the development of asthma, a variety of mouse models have been employed. However, there has been a marked discrepancy between the results obtained using allergic asthma models in mice and those obtained from clinical trials [8]. One reason for this can be the lack of a proper mast cell response in mouse models. Thus, to identify relevant mouse models with a significant role of mast cells in asthma pathobiology would be an important development in experimental asthma research.

2. Phenotypes and localization of mast cells in human

Mast cells originate from pluripotent hematopoietic stem cells, which circulate as $CD34^+$ precursors until they migrate into tissues where they mature into long lived effector cells [9]. They are especially numerous at the barrier between self and the environment (e.g. in the skin and the mucosa of respiratory, genitourinary and gastrointestinal tracts), but they are also found in most vascularized tissues, including the lymphoid organ [10]. In tissues,

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mast cells localize close to capillaries and lymphatic vessels, and are often in close contact to the nervous system through proximity to nerve terminals [11,12].

Two phenotypes of human mast cells can be identified by immunohistochemical techniques in skin, lung, and small intestine based on their protease content [13]. One type contains only tryptase and is termed MC_T. The second type contains tryptase, chymases and carboxypeptidase A, and is termed MC_{TC}. In human bronchus and lung, MC_T is the predominant phenotype, except in proximity to pulmonary vessels where MC_T and MC_{TC} are present in similar numbers [14].

3. Appearance, localization and phenotype of mast cells in asthma

Asthma leads to an alteration in the number, localization and phenotype of mast cells. For example, there have been reports describing how the numbers of mast cells are increased in patients with mild asthma [15] or decreased in patients with fatal asthma compared to healthy individuals [16]. When considering mast cells with respect to phenotype, MC_{TC} has been shown to be the predominant mast cell phenotype within the airway submucosa and epithelium in cases of severe asthma with higher numbers compared to individuals with mild asthma [17]. Atopic uncontrolled asthma leads to an increased alveolar parenchymal infiltration of both MC_T and MC_{TC} populations, with a higher expression of FcεRI and surface-bound IgE compared to non-atopic control subjects [18]. From a study of fatal asthma cases, the ratio of degranulated to intact mast cells was significantly increased in the smooth muscle and outer airway wall in short-duration cases compared with long-duration cases, though the total number of tryptase-positive mast cells was found to be similar [19]. Given that airway smooth muscle cells are the effector cells of bronchoconstriction, it is of special interest that the number of mast cells in the airway smooth muscle bundles from subjects with asthma is substantially increased compared to healthy subjects [20]. It has also been found that patients using inhaled corticosteroids possess significantly lower numbers of mast cells within their respiratory epithelium and smooth muscle compared to those not treated with inhaled corticosteroids [21]. These latter studies indicate a positive correlation between the number of mast cells and AHR. Also, in non-atopic asthma, such as exercise-induced asthma, the release of mast cell mediators [22], mast cell infiltration of the airways, and increased expression of mast cell genes including tryptase and carboxypeptidase A have been observed [23].

4. Mast cells in the lungs of mice, rats and guinea pigs

In contrast to humans where mast cells are found around the airways and vessels from proximal to distal sites and in the parenchyma, mast cells in mice are primarily located in the trachea and in the larger airways in close proximity to the bronchial smooth muscle (Fig. 2) [14,24]. Mast cells are extremely rare in the mouse lung parenchyma and essentially absent in the alveoli. By comparison, there is a wider distribution of mast cells in both the rat and guinea pig lung [25]. After IgE activation, both mouse and human mast cells secrete Cys-LTs and prostaglandins. Mouse and rat mast cells preferentially secrete 5-hydroxythryptamine (5-HT) compared to histamine in contrast to guinea pig and human mast cells which both secrete histamine in response to IgE activation (Fig. 1) [26]. With early-phase allergic reactions in mice, the smooth muscle activity is due to the secretion of 5-HT which causes the release of neuronal an/or epithelial acetylcholine and the resultant smooth muscle contraction through binding of acetylcholine to muscarinic M_3 receptors on the airway smooth muscle [27,28] (Fig. 2). This differs from both the guinea pig and human condition where the IgE activation of mast cells and subsequent release of histamine, Cys-LTs and prostaglandins induce smooth muscle contraction through the direct activation of these mediators on the airway smooth muscle [29–31]. Guinea pigs exhibit a higher density of mast cells in the peripheral airways and in the interalveolar septa compared to rats [25]. In fact, guinea pigs share similarities to humans in terms of the anatomy and physiology of the airway and lungs, including the release of histamine and Cys-LTs from mast cells, and the presence of early and late asthmatic responses [32,33]. Rat models of asthma also have some features of airway inflammation and pulmonary reactivity that are

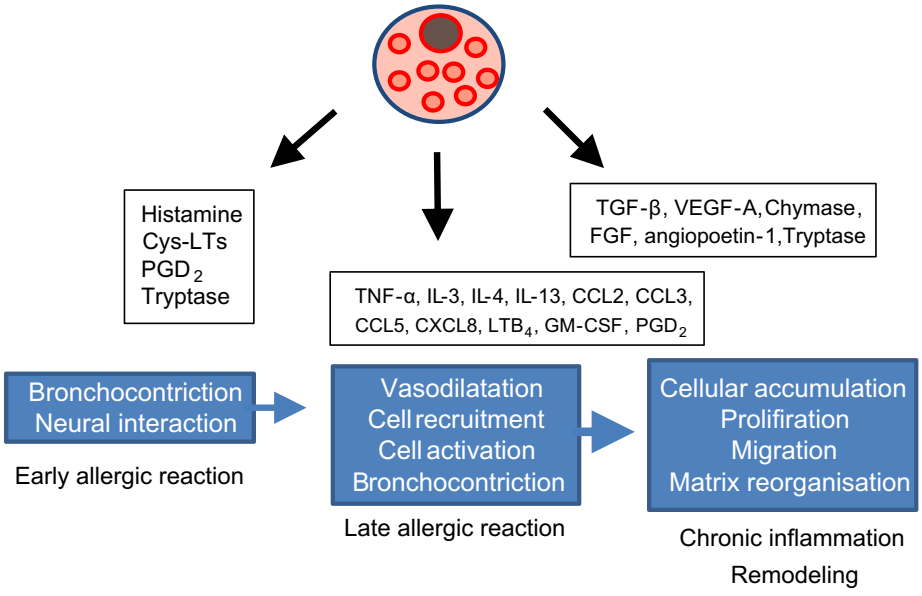

Fig. 1. Upon stimulation, mast cells release a range of different mediators that have the potential to induce several pathophysiological effects in asthma patients. Early- and late-phase allergic reactions are clearly defined, but due to the diversity of mediators, mast cells can also be involved in the development and perpetuation of chronic inflammation and tissue remodeling; Cys-LTs (cysteinyl-leukotrienes), PGD_2 (prostaglandin D_2), TNF-α (tumour necrosis factor α), IL (interleukin), LTB_4 (leukotriene B_4), GM-CSF (granulocyte-macrophage colony-stimulating factor), TGF-β (transforming growth factor β), VEGF-A (vascular endothelial growth factor A), FGF (fibroblast growth factor).