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Mast cells in airway diseases and interstitial lung disease

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Abstract

Mast cells are major effector cells of inflammation and there is strong evidence that mast cells play a significant role in asthma pathophysiology. There is also a growing body of evidence that mast cells contribute to other inflammatory and fibrotic lung diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. This review discusses the role that mast cells play in airway diseases and highlights how mast cell microlocalisation within specific lung compartments and their cellular interactions are likely to be critical for their effector function in disease.

Keywords

Mast cell; asthma; airway diseases; interstitial lung disease

1. Introduction

Mast cells are highly specialised granulocytes that contribute towards innate and adaptive immunity (Echtenacher et al., 1996) as well as tissue repair and revascularisation (Heissig et al., 2005; Iba et al., 2004; Weller et al., 2006). Mast cells perform the majority of their functions by releasing preformed and/or newly generated pleiotropic mediators in response to diverse activation signals to trigger a programmed inflammatory response. Mast cells are present in all vascularised tissues and are particularly abundant at sites of the environmental interface, such as the skin, gastrointestinal tract and the pulmonary epithelia. Thus mast cells are well equipped to respond to their environment where they can trigger an inflammatory response against a perceived tissue insult. Indeed, mast cells appear to be able to “sense” their environment by extending membranous projections into the lumen of blood vessels, which can sensitise the cells to respond to antigen (Cheng et al., 2013). However, in many disease states such as asthma, chronic inflammation may be due to inappropriate mast cell

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activation and/or redistribution of mast cells to specific structures that could drive detrimental tissue remodelling processes contributing to disease progression. In fact, mast cells are found to be in an “activated” state in asthmatic airways (for review see (Bradding et al., 2006)) suggesting that either the tissue microenvironment is supporting chronic mast cell activation or mast cells in asthmatic airways are intrinsically hyper-secretory. Despite asthma being associated with atopy, the role of allergen exposure in chronic asthma may be overstated and the disease can become self-perpetuating once established. Indeed, mast cells may also play roles in other respiratory diseases that are not associated with atopy, such as chronic obstructive pulmonary disease (COPD) and interstitial lung diseases, where the drivers of mast cell involvement are often idiopathic, but unlikely to be allergens. In this review, we will discuss current opinion on the role that mast cells play in airway diseases with particular emphasis on asthma where the role of mast cells is more understood.

2. Mast cell heterogeneity

Mast cells are long-lived tissue-resident cells derived from haematopoietic stem cells that leave the bone marrow as mast cell-committed, but undifferentiated $CD34^+$ progenitor cells. Mast cell precursors are recruited into tissues where they become resident and then mature and differentiate under the influence of the local cytokine milieu (for review see (Gurish and Boyce, 2006)). Therefore, mast cells represent heterogeneous populations depending upon the tissue where they reside and the local cytokine environment. For example, human lung mast cells can be discriminated from mast cells isolated from other tissues based on their profile of released mediators and surface expression of chemokine receptors (Bradding et al., 1995; Brightling et al., 2005b; Irani et al., 1991; Oskeritzian et al., 2005; Saito et al., 2006; Weidner and Austen, 1993). This heterogeneity also extends to the microlocalisation of mast cells within distinct tissue compartments (Bradding, 2009). Thus, human mast cells from different lung compartments contain granules with distinct protease content, which can be classified as mast cells containing either tryptase only (MC_T), chymase only (MC_C) or both tryptase and chymase (MC_{TC}) in their granules (Balzar et al., 2005; Bradding et al., 1995; Weidner and Austen, 1993).

The MC_T subtype is smaller and contains less histamine than the MC_{TC} subtype (Oskeritzian et al., 2005; Schulman et al., 1983; Schulman et al., 1990) and it is possible that MC_{TC} development from MC_T cells may be a step in maturation. However, it is clear that mast cells can change subtype in response to their environment and that changes in subtype can occur in both directions. For example, MC_{TC} cells cultured with human airway epithelial cells convert to an MC_T phenotype *in vitro* (Hsieh et al., 2005), whereas MC_T cells cultured with endothelial cells transform into an MC_{TC} phenotype (Mierke et al., 2000). This phenomenon most likely also occurs *in vivo* since the MC_T subtype predominates in the lung parenchyma, bronchial lamina propria and bronchial epithelium, while the MC_{TC} subtype surrounds pulmonary blood vessels with close proximity to the vascular endothelial cells (Andersson et al., 2009; Bradding et al., 1995; Irani et al., 1989; Irani et al., 1991). The significance and consequences of microlocalisation of mast cell subtypes is not yet clear and the factors that drive the development of each subtype are largely unknown and most likely multifactorial. However, these observations demonstrate the complexity of the mast cell

compartment and the heterogeneity of mast cell populations that can adapt to a changing environment.

3. Mechanisms that support mast cell growth and function

Many canonical mast cell functions are regulated by two distinct, but interconnected receptor-mediated signalling pathways. Mast cells regulate adaptive immune responses when they encounter antigen that crosslinks immunoglobulin E (IgE) bound to the high affinity IgE receptor, FcεRI (for review see (Rivera and Gilfillan, 2006)). Aggregation of FcεRI triggers a number of signalling pathways that lead to the release of Ca^{2+} from intracellular stores, influx of extracellular Ca^{2+} and reorganization of the cytoskeleton that are all critical processes for the release of pre-stored and newly generated mediators (Allen et al., 2009; Cruse et al., 2013; Draber et al., 2012; Gilfillan and Beaven, 2011; Gilfillan and Tkaczyk, 2006; Hajkova et al., 2011; Rivera and Gilfillan, 2006). Mast cells can also respond to a variety of alternative stimuli that may inhibit or augment FcεRI-dependent responses. One of the most important crosstalk interactions between receptors may be the synergism between FcεRI and KIT, the receptor tyrosine kinase for stem cell factor (SCF) encoded by the proto-oncogene *c-KIT* (for reviews see (Cruse et al., 2014; Gilfillan and Tkaczyk, 2006; Lennartsson and Ronnstrand, 2012)). SCF is the major growth and survival factor for mast cells and is absolutely required for mast cell survival (Jensen et al., 2007; Okayama and Kawakami, 2006). In addition, SCF is a chemoattractant for mast cells (Halova et al., 2012; Okayama and Kawakami, 2006) and synergistically enhances antigen-induced degranulation, cytokine production and migration (reviewed in (Gilfillan and Tkaczyk, 2006)). Therefore, increased concentrations of SCF in tissues may not only promote mast cell recruitment, survival and differentiation, but could also result in increased mast cell responsiveness. As will be discussed below, SCF expression in the airways of patients with asthma has been reported to be increased compared to control subjects (Al-Muhsen et al., 2004; Da Silva et al., 2006) and therefore may play an important role in asthma pathogenesis and contribute to low-level chronic activation of mast cells. Indeed, under certain circumstances where either the actin cytoskeleton (Smrz et al., 2013) or inhibitory molecules such as SH2 domain containing inositol-5-phosphatase-1 (SHIP-1) that interact with the actin cytoskeleton (Gimborn et al., 2005; Lesourne et al., 2005) are perturbed, SCF does not simply potentiate mast cell degranulation, but can directly induce degranulation (Huber et al., 1998; Smrz et al., 2013).

It is clear that SCF has the capacity to regulate most mast cell functions, which highlights the importance of understanding the signalling mechanisms that control specific functional responses to SCF. The mechanisms that regulate whether mast cells will differentiate or proliferate in response to SCF, for example, are not well understood. It is possible that the concentration of SCF and/or differential phosphorylation of specific tyrosine residues in KIT may play roles in dictating responses, although studies to specifically address these possibilities are needed. SCF also plays important roles in mast cell adhesion to structural cells where SCF exists as a membrane bound form (Hollins et al., 2008; Koma et al., 2005; Wygrecka et al., 2013). Most studies of SCF function in mast cells have been performed with the soluble form of SCF, which would be expected to undergo endocytosis more rapidly than a membrane tethered ligand. While studies on the membrane form of SCF have been

limited by technical difficulties, it has been suggested that transmembrane SCF on fibroblasts, or SCF immobilised onto culture plates increases histamine release and eotaxin production in mast cells, but the soluble SCF induced little or no eotaxin production (Hogaboam et al., 1998). In addition, the mechanism of KIT endocytosis and trafficking affects signaling and functional responses in human mast cells, which may be due to altered signaling at the plasma membrane or within intracellular compartments (Cruse et al., 2015). Therefore, it is attractive to hypothesise that a soluble version of SCF would result in different signals than a membrane tethered version of SCF that would act to tether mast cells in tissues and presumably sustain signalling events at the plasma membrane.

4. Mast cells in asthma

Asthma is characterised by the presence of airway obstruction that is reversible, at least in part, either with pharmacological intervention or spontaneously. Asthma usually presents with symptoms of wheeze, dyspnoea, cough and tightness in the chest. Asthma symptoms can be triggered by many different stimuli depending in part upon whether the disease is atopic, non-atopic (intrinsic), or occupational. Common triggers for symptoms include allergen exposure, viral infection, inhaled irritants, exercise and drugs. With respect to acute allergen exposure, the immediate effects are classified as the early asthmatic reaction and include airflow obstruction caused by bronchoconstriction, mucosal oedema due to increased vascular permeability and mucus hypersecretion. This early asthmatic reaction is then followed by the late asthmatic reaction in about 50% of subjects, which includes aggravation of underlying airway inflammation due to an influx of activated inflammatory cells and increased airway hyperresponsiveness. The mechanisms driving the late asthmatic reaction were thought for many years to be representative of the factors promoting chronic inflammatory changes in the airways in day-to-day asthma. In addition, it has been proposed that these events may lead to tissue damage and if the inflammation is chronic, airway remodelling can ensue. However, this is an over simplification, and there is increasing evidence that airway inflammation and airway remodelling may occur independently.

There is strong evidence that mast cells play an important role in the early asthmatic reaction following allergen exposure. Mast cell-derived mediators induce the classical features of the early asthmatic reaction *in vivo*, inducing bronchoconstriction, mucus secretion and mucosal oedema (for reviews see (Bradding and Cruse, 2008; Bradding et al., 2006; Brightling et al., 2003a; Moiseeva and Bradding, 2011)). For example, several studies have identified an increase in histamine, prostaglandin D_2 (PGD_2) and leukotriene C_4 (LTC_4) in the BAL fluid of asthma subjects following bronchial allergen challenge (Casale et al., 1987; Liu et al., 1991; Murray et al., 1986; Sedgwick et al., 1991; Wenzel et al., 1988; Wenzel et al., 1990; Wenzel et al., 1991) and that the early asthmatic reaction is significantly alleviated with the administration of potent selective inhibitors of histamine, LTC_4 and to a lesser extent PGD_2 (Beasley et al., 1987; Curzen et al., 1987; Findlay et al., 1992; Rafferty et al., 1987; Taylor et al., 1991). These mediators are most likely derived from mast cells in the bronchial mucosa because histamine, PGD_2 and LTC_4 are all released from human lung mast cells *in vitro* with remarkably similar kinetics to the allergen challenge studies (Schleimer et al., 1986). In addition, evidence for mast cell degranulation comes from the mast cell-specific protease tryptase being recovered at increased levels from the BAL fluid after allergen challenge

(Sedgwick et al., 1991; Wenzel et al., 1988). Furthermore, the early asthmatic reaction can be significantly attenuated with neutralizing anti-IgE (Omalizumab) pretreatment demonstrating that IgE-dependent signalling is required (Boulet et al., 1997; Fahy et al., 1997).

Mast cells also synthesise and release a vast array of proinflammatory cytokines and chemokines that act to recruit inflammatory cells such as eosinophils, activated macrophages and lymphocytes (Bentley et al., 1993; De Monchy et al., 1985; Diaz et al., 1989; Metzger et al., 1987; Montefort et al., 1994; Tonnel et al., 1983) that participate in the late asthmatic reaction (for reviews see (Bradding and Cruse, 2008; Bradding and Holgate, 1999; Moiseeva and Bradding, 2011)). The late asthmatic reaction is associated with the infiltration of inflammatory cells including eosinophils, which were believed to contribute to airway obstruction and the development of airway hyperresponsiveness. However, anti-IL-5 therapy effectively inhibits eosinophil recruitment after allergen challenge but has no effect on the allergen-induced increase in airflow obstruction or airway hyperresponsiveness suggesting that other factors mediate this (Haldar et al., 2009). Elucidating roles for mast cells in the late asthmatic reaction is more difficult than the early asthmatic reaction. Indeed, it has been suggested that many of the features of the late asthmatic reaction are likely to be driven by the infiltrating cells rather than mast cells because levels of tryptase are reduced in the late asthmatic reaction (Sedgwick et al., 1991). However, a decline in tryptase levels during the late asthmatic reaction may be an indicator that the initial release of preformed mast cell mediators has subsided, but it does not necessarily mean that there is no longer mast cell involvement. Development of the late asthmatic reaction can be alleviated with anti-IgE (Omalizumab) therapy (Fahy et al., 1997) providing strong evidence that mast cell-driven events are a pre-requisite for the development of the late asthmatic reaction.

5. Chronic mast cell activation in asthma

The contribution of mast cells to the pathophysiology of asthma probably arises from the maladaptation of their protective roles in wound healing, defence against bacterial and parasitic infections and their important contribution to innate and adaptive immunity (for reviews see (Bradding and Cruse, 2008; Bradding and Holgate, 1999; Moiseeva and Bradding, 2011)). The role that mast cells play in these “healthy” responses is to elicit an inflammatory and/or immune response by releasing a number of proinflammatory mediators. In homeostatic mast cell responses, mast cells are usually protective and trigger inflammatory reactions that quickly resolve. However, in diseases such as asthma, mast cells within the asthmatic airways appear to be present in a chronically activated state with evidence of ongoing mediator secretion. There are increased numbers of mast cells in the bronchoalveolar lavage (BAL) fluid of patients with stable asthma when compared to control volunteers (Broide et al., 1991; Flint et al., 1985; Kirby et al., 1987) and increased levels of the mast cell mediators histamine and tryptase (Broide et al., 1991; Casale et al., 1987; Wenzel et al., 1988) suggesting on-going degranulation. It could be that the increase in mast cell mediators in BAL fluid of asthmatic subjects is due to an increase in mast cell numbers rather than mast cell hypersecretion. However, mast cells from the BAL fluid of symptomatic asthmatic subjects demonstrate an increase in both IgE-dependent degranulation and constitutive mediator release when compared to non-asthmatic controls

(Broide et al., 1991; Flint et al., 1985). In addition, mast cell morphology assessed by microscopy suggests that mast cells within key structures such as the airway smooth muscle are present in an activated state in the airways in asthma (Beasley et al., 1989; Begueret et al., 2007; Djukanovic et al., 1992; Laitinen et al., 1993). In addition, there is evidence of increased Th2 cytokine mRNA expression in mast cells in the airway wall in asthma, again providing evidence of activation (Ying et al., 1995). Bearing in mind the biological profile of mast cell autacoids, proteases and cytokines summarized in (Tables 1 and 2), it is easy to envisage how mast cell products could contribute to the development and propagation of airway inflammation, remodeling, bronchoconstriction, bronchial hyperresponsiveness, and mucus hypersecretion (Figure 1).

The studies discussed above provide strong evidence for mast cells in the airways of atopic asthma patients being present in an activated secretory state. Given the high incidence of atopy in asthmatic subjects under the age of 30, the role that pollen plays in exacerbating asthma (Newson et al., 1997, 1998), and the therapeutic efficacy of Omalizumab, it appears as though allergen-driven processes contribute to the pathophysiology of allergic asthma and the associated hypersecretory phenotype of mast cells. However, the precise role that allergens play in chronic asthma is not clear cut, and it is also evident that mast cells in both non-atopic asthma, and occupational asthma are also present in an activated state (Chan-Yeung et al., 1989; Di Stefano et al., 1993; Frew et al., 1993; Humbert et al., 1996; Saetta et al., 1992; Ying et al., 1997). In addition, while anti-IgE therapy with Omalizumab markedly reduces airway inflammation (Djukanovic et al., 2004), symptoms often persist at a lower level. In established asthma, the disease may become self-perpetuating and the on-going mast cell hypersecretion may arise from factors that activate mast cells independently of IgE, or that synergistically amplify very low level IgE signals. As is discussed elsewhere in this issue, mast cells can be activated by both IgE-dependent and IgE-independent mechanisms to release a plethora of autacoid mediators, proteases and cytokines (for additional reviews see (Gilfillan and Beaven, 2011; Gilfillan and Tkaczyk, 2006)). The maximum degranulation with different stimuli *in vitro* are often comparable and signalling triggered by various receptors share common pathways with co-stimulation often having synergistic effects (for reviews see (Gilfillan and Beaven, 2011; Gilfillan and Tkaczyk, 2006)).

6. Mast cell activation by microorganisms

Synergistic crosstalk between FcεRI and other receptors may play an important role in activation of mast cells by microorganisms such as bacteria and viruses that could exacerbate chronic asthma. Human mast cells express toll-like receptors (TLR)-1, -2, -3, -4, -5, -7 and -9 (Kulka et al., 2004; Kulka and Metcalfe, 2006), which can activate mast cells following binding of the relevant ligand. Respiratory viruses are a common cause of asthma exacerbations and thus TLR-3, which recognises double stranded RNA (viral RNA), is of particular relevance. Activation of mast cells with a synthetic activator of TLR-3, Poly I:C, induces the specific release of interferon α (IFNα), which reflects the responses to both respiratory syncytial virus (RSV) and the influenza virus (Kulka et al., 2004) suggesting a potential role for TLR-3 in virus-induced mast cell activation within the lung.

Mast cells can also be activated by bacterial products such as lipopolysaccharide (LPS) that acts through TLR-4. Addition of LPS to mast cell cultures *in vitro* augments IL-5 and IL-13 production as well as mRNA levels for IL-4, IL-5 and IL-13 in mouse bone marrow-derived mast cells activated with IgE/Ag (Nigo et al., 2006). These results were reinforced with *in vivo* studies that demonstrated a dramatic increase in ovalbumin-induced eosinophilia in the lung with LPS treatment in wild-type mice, which was ablated in TLR-4-deficient mice (Nigo et al., 2006). In addition, mast cell-deficient mice ($Kit^{W/Wv}$) adoptively transferred with wild-type bone marrow-derived mast cells restored the synergistic effect of LPS on ovalbumin-induced airway eosinophilia, but TLR-$4^{-/-}$ bone marrow-derived mast cells did not (Nigo et al., 2006). Furthermore, inhalation of LPS into the lungs of mice increased IL-5 production by mast cells and exacerbated airway inflammation in a mouse model of asthma (Murakami et al., 2007). Taken together, these studies demonstrate that mast cell responsiveness and airway inflammation can be augmented by both viruses and bacteria and thus could contribute to deteriorating lung physiology in asthma during asthma exacerbations.

7. Potential mechanisms of chronic mast cell activation

The mechanism(s) underlying chronic mast cell activation in asthma are not understood, but *in vitro* studies highlight several possible candidates that are relevant to the asthmatic airway. The first of these is IgE, which appears obvious because of the well-defined role of the high affinity IgE receptor, FcεRI, in mast cell degranulation. However, IgE may have roles in mast cell activation and function beyond that of recognising antigen. Monomeric IgE alone activates mouse mast cells leading to the release of cytokines but not degranulation, and this production of cytokines can promote mast cell survival in an autocrine or paracrine manner (Kalesnikoff et al., 2001; Kitaura et al., 2003; Oka et al., 2004; Pandey et al., 2004). When IgE is added to human lung mast cells in the presence of SCF, it induces a dose-dependent increase in the release of histamine, LTC_4 and IL-8 (Cruse et al., 2005). In addition, monomeric IgE in the absence of SCF promotes human lung mast cell survival through the autocrine production of IL-6 (Cruse et al., 2008). Signalling from monomeric IgE is maintained provided that there is free IgE in the medium suggesting that binding of IgE to FcεRI may heighten mast cell responsiveness and could account for the observation that there is a reproducible correlation between serum IgE levels, airway hyperresponsiveness and asthma (Burrows et al., 1989; Sears et al., 1991; Sunyer et al., 1996; Sunyer et al., 1995). Furthermore, IgE binding to FcεRI increases surface FcεRI expression on mast cells by stabilising the FcεRI complex at the plasma membrane (Yamaguchi et al., 1997). Moreover, sensitisation of mast cells with IgE markedly increases the expression of the FcεRI receptor β subunit and a smaller splice variant of FcεRIβ (Brenzovich et al., 2009).

FcεRIβ is encoded by the membrane spanning 4A gene family member 2 (*MS4A2*). This is of interest because human linkage analyses identified that the gene loci 11q12-q13 are linked to allergy and asthma susceptibility (Cookson and Hopkin, 1988; Cookson et al., 1989; Sandford et al., 1993; Stafford et al., 1994) and the MS4A family are clustered in these regions (Liang et al., 2001; Liang and Tedder, 2001). *MS4A1* (CD20) and *MS4A2* (FcεRIβ) are associated with the activation and proliferation of B cells (Tedder and Engel,

1994) and mast cells (Cruse et al., 2013; Cruse et al., 2010a; Gilfillan and Tkaczyk, 2006) respectively. FcεRIβ contributes to IgE-dependent mast cell signalling by trafficking FcεRI to the cell surface and amplifying FcεRI-induced signalling. The first transmembrane domain of FcεRIβ is required for trafficking the receptor complex (Singleton et al., 2009), whilst the C-terminal immunoreceptor tyrosine-based activation motif (ITAM) amplifies signalling (On et al., 2004). FcεRI signalling plays an important role in atopic asthma. Thus a report that polymorphisms in *MS4A2* were associated with asthma gained interest (Laprise et al., 2000). Studies into the functional consequence of mutations in FcεRIβ did not affect the function of FcεRIβ (Donnadieu et al., 2000). However, we have identified expression of a novel truncated isoform of FcεRIβ (t-FcεRIβ) in human mast cells with a naturally occurring truncation of exon 3 that encodes the first two transmembrane domains of FcεRIβ (Cruse et al., 2010a). Since the first transmembrane domain of full length FcεRIβ is responsible for the formation of the FcεRI complex (Singleton et al., 2009), t-FcεRIβ consequently appears not to associate with the FcεRI complex. However, t-FcεRIβ retains the signalling ITAM motif and thus has the capacity to signal. While full-length FcεRIβ functions at the plasma membrane, t-FcεRIβ displays cytosolic and juxta-nuclear localisation, where it appears to bind calmodulin and traffic adaptor molecules and kinases to the peri-centrosome in response to Ca^{2+} signals, triggering microtubule formation and degranulation (Cruse et al., 2013). In addition, another truncation of full-length FcεRIβ has been reported that contains an inclusion of intron 5 and as a result loses the signaling ITAM, but retains the first two transmembrane domains and thus the ability to associate with the FcεRI complex (Donnadieu et al., 2003). This isoform of FcεRIβ acts to downregulate FcεRI expression by targeting the FcεRI complex for proteasomal degradation (Donnadieu et al., 2003).

These observations could be particularly important because the linkage of *MS4A2* with asthma susceptibility could be much more complex than the function of a single FcεRIβ isoform and may be related to differences in expression levels of alternative splice forms. Indeed, polymorphisms have been reported to be linked to asthma susceptibility in the promoter region of *MS4A2*, which could affect expression levels of FcεRIβ (Sharma et al., 2009). In addition, mutations within regions recognised by the spliceosome could differentially affect isoform expression. However, reports of linkage of *MS4A2* with asthma are conflicting and require more in-depth study before any conclusions can be drawn. With these caveats in mind, overexpression of full-length FcεRIβ actually inhibits mast cell degranulation (Cruse et al., 2013; Okayama et al., 2014), while overexpression of t-FcεRIβ potentiates degranulation (Cruse et al., 2013). One possible mechanism for inhibition of mast cell degranulation is that incorporation of FcεRIβ into the FcεRI complex is limited by the availability of the FcεRIβ and FcεRIβ subunits. Therefore, full-length FcεRIβ that is not incorporated into FcεRI could compete with either full-length FcεRIβ that is in complex with FcεRI for binding to Lyn kinase (Okayama et al., 2014) restricting the availability of the kinase for recruitment into lipid rafts, or possibly competition with t-FcεRIβ for binding Fyn or Gab2 (Cruse et al., 2013). Either way, it is likely that FcεRIβ isoforms have competitive actions that sequester kinases and adaptor proteins to distinct subcellular localisations that can alter spatio-temporal signalling dynamics.

SCF may also play a major role in asthma as the expression of SCF is markedly increased in asthmatic airways (Al-Muhsen et al., 2004; Da Silva et al., 2006) and this expression is suppressed by glucocorticosteroids (Da Silva et al., 2006). Neutralising SCF in an animal model of asthma attenuates airway hyperresponsiveness, goblet cell hyperplasia and eosinophilia, which were accompanied by reduced IL-5 and TNFα production (Berlin et al., 2006; Berlin et al., 2004). This is particularly interesting because TNFα is strongly implicated in asthma pathophysiology. TNFα is expressed at higher levels in the asthmatic lung, particularly in mast cells, (Berry et al., 2006; Bradding et al., 1994; Howarth et al., 2005) and inhalation of TNFα induces airway hyperresponsiveness (Thomas and Heywood, 2002; Thomas et al., 1995). However, in spite of early promise, recent studies of anti-TNFα therapy in asthma have been disappointing (Brightling et al., 2008; Holgate et al., 2011). Another interesting aspect is that both SCF and IgE impact on the efficacy of β_2-adrenoceptor agonists, which are widely used as reliever medication in asthma. Administration of β_2-adrenoceptor agonists acutely *in vitro* inhibits IgE-dependent human lung mast cell degranulation in the absence of SCF. However, this inhibition is lost in the presence of SCF and furthermore, when IgE is also present, the β_2-adrenoceptor agonist salbutamol increases degranulation (Cruse et al., 2010b). This phenomenon may help to explain clinical observations where regular administration of the long acting β_2-adrenoceptor agonist salmeterol increases the magnitude of the early asthmatic reaction and accompanied mast cell mediator release is enhanced (Giannini et al., 1996; Swystun et al., 2000). It might also explain why the regular administration of short acting β_2-adrenoceptor agonists to asthmatic subjects has been associated with loss of asthma control (Taylor et al., 1993; Taylor et al., 1998).

8. Integration and crosstalk of adhesion and signalling

The involvement of SCF in mast cell responsiveness could also extend to roles in adhesion and related pathways. For example, mast cell progenitors in the blood would be likely to encounter soluble SCF, whereas mast cells in tissue would be exposed to membrane bound SCF expressed on structural cells. Recent evidence suggests that membrane bound SCF expressed on airway smooth muscle cells plays a critical role in the functional consequences of mast cell adhesion to airway smooth muscle cells. In collaboration with the mast cell-expressed cell adhesion molecule 1 (CADM1) and soluble IL-6, SCF promotes mast cell survival, proliferation and secretion (Hollins et al., 2008). The cooperative actions of SCF and CADM1 could be due to direct interactions between CADM1 and KIT in mast cells facilitating stable interactions between KIT and membrane bound SCF on airway smooth muscle cells (Hollins et al., 2008) and lung fibroblasts (Moiseeva et al., 2013b). CADM1 exists as several isoforms (Moiseeva et al., 2012, 2013a). The SP6 isoform is encoded by the full-length splice variant containing 12 exons. SP1 contains an internal in-frame truncation of exon 10. SP4 has exons 9 and 10 truncated in-frame, while SP3 is the shorter variant with truncations of exons 8, 9 and 10 (Moiseeva et al., 2013a). Differential expression of CADM1 splice variants affects both the adhesion of mast cells and their survival (Moiseeva et al., 2012, 2013a).

Downregulation of CADM1 expression reduced mast cell adhesion to airway smooth muscle and lung fibroblasts *in vitro* (Moiseeva et al., 2013b) and reduced mast cell viability

(Moiseeva et al., 2012). However, overexpression of the CADM1 SP4 splice variant, which is the dominantly expressed isoform in human mast cells, increased mast cell adhesion to human lung fibroblasts without affecting adhesion of mast cells to human airway smooth muscle cells (Moiseeva et al., 2013b). Conversely, overexpression of either SP1 or SP6 reduced adhesion of mast cells to lung fibroblasts and not airway smooth muscle cells (Moiseeva et al., 2013a). These results are intriguing since they provide potential mechanisms for targeted adhesion of mast cells to specific cell types, which could be regulated by alternative splicing of CADM1 in the spliceosome, possibly in response to environmental cues.

9. Mast cell microlocalisation in the asthmatic lung

In addition to the microenvironment affecting mast cell function, it also contributes to mast cell microlocalisation within the lung, which itself may regulate mast cell function through cell-cell contact and adhesion signals. Mast cells are present near blood vessels and throughout the lamina propria of healthy airways (Carroll et al., 2002a; de Magalhaes Simoes et al., 2005; Pesci et al., 1993b). Mast cells infiltrate three key sites in asthmatic airways that may be critical for the development and propagation of the pathophysiology. The first of these sites is the airway smooth muscle where mast cell infiltration is a characteristic and reproducible feature of asthma (Amin et al., 2005; Begueret et al., 2007; Berger et al., 2003; Brightling et al., 2005a; Brightling et al., 2002a; Chen et al., 2004; El-Shazly et al., 2006; Shikotra et al., 2012). It has long been considered that the disordered airway physiology and airway wall remodelling in asthma are a culmination of the effects of infiltrating eosinophils recruited to the lung by activated Th2 lymphocytes. However, the relationship between airway inflammation and airflow obstruction is weak.

A good example of this weak relationship was demonstrated by the study of eosinophilic bronchitis, which accounts for approximately 15% of patients referred to respiratory specialists for chronic cough (Brightling et al., 1999). Eosinophilic bronchitis is characterised by the presence of sputum eosinophilia without variable airflow obstruction or airway hyperresponsiveness (Brightling et al., 1999). Detailed comparisons between asthma and eosinophilic bronchitis reveal remarkable similarities between the two conditions. In terms of immunopathology, both asthma and eosinophilic bronchitis have identical mucosal inflammatory infiltration, subbasement membrane thickening and collagen deposition as well as comparable mucosal IL-4 and IL-5 expression (Berry et al., 2004; Brightling et al., 2002b; Brightling et al., 2003b; Brightling et al., 2000). In addition to the histological similarities of the lungs in these two diseases, the inflammation patterns also appear similar with comparable levels of the inflammatory mediators histamine and PGD_2 in induced sputum and BAL fluid as well as almost identical numbers of IL-4-expressing T cells (Brightling et al., 2002b; Brightling et al., 2000). Therefore, in eosinophilic bronchitis, it appears as though a seemingly identical pattern of inflammation as asthma exists without accompanied disordered airway physiology and airway hyperresponsiveness. This indicates that the Th2-related inflammation of the airways in asthma may not be fundamental to the pathogenesis of asthma. Instead, the picture that emerged was that the striking difference between asthma and eosinophilic bronchitis lay within the airway smooth muscle bundles.

10. Mast cell infiltration into airway smooth muscle

Several studies have now demonstrated that mast cells infiltrate the airway smooth muscle bundles in asthma, but not in control subjects (Amin et al., 2005; Begueret et al., 2007; Berger et al., 2003; Brightling et al., 2005a; Brightling et al., 2002a; El-Shazly et al., 2006; Shikotra et al., 2012) or eosinophilic bronchitis patients (Brightling et al., 2002a). In addition, there is good correlation between the number of mast cells in the airway smooth muscle bundles and the severity of airway hyperresponsiveness (Brightling et al., 2002a). In contrast, we could not find T cells or eosinophils in the airway smooth muscle bundles of any of the subjects. Taken together, these studies suggest that mast cell infiltration into the airway smooth muscle bundles could be important for the development of airway hyperresponsiveness where direct interactions between mast cells and airway smooth muscle cells could be critical. Indeed, co-culture of human lung mast cells with human airway smooth muscle cells demonstrates that human airway smooth muscle promotes survival and proliferation of human lung mast cells and induces constitutive mast cell degranulation (Hollins et al., 2008). It is likely that the promotion of mast cell functional responses by interactions with airway smooth muscle cells is due to interactions with membrane bound SCF, possibly facilitated by the adhesion molecule CADM1 (Hollins et al., 2008). As described above, SCF primes mast cells for degranulation and under conditions that modulate the actin cytoskeleton, SCF can directly induce degranulation (Smrz et al., 2013). Reorganisation of the actin cytoskeleton would be expected to occur during adhesion and migration processes where low-level secretion of mediators would aid migration. Indeed, downregulation of CADM1 that plays an important role in mast cell adhesion to airway smooth muscle, alters filamentous actin dynamics (Moiseeva et al., 2014) and ultrastructural analysis of mast cells within the airway smooth muscle bundles of asthma patients show evidence of ongoing activation (Begueret et al., 2007).

The ability of airway smooth muscle cells to modulate human lung mast cell function is not one-directional, because mast cells can also alter airway smooth muscle responses. For example, the mast cell autacoid mediators histamine, PGD_2 and LTC_4 all potently induce bronchoconstriction and as discussed above, are all released during allergen provocation challenge. However, the effects of mast cells on airway smooth muscle may be more complex than this suggests. For example, mast cell-derived tryptase induces the production and release of transforming growth factor β (TGFβ) from human airway smooth muscle cells (Woodman et al., 2008). TGFβ then upregulates α-smooth muscle actin expression promoting differentiation of airway smooth muscle cells in an autocrine manner rendering the cells more responsive to histamine-induced contraction, thus acting as a positive feedback loop (Woodman et al., 2008). In addition, administration of tryptase to either dogs or sheep induces bronchoconstriction and airway hyperresponsiveness (Molinari et al., 1996; Sekizawa et al., 1989). Tryptase also increases the contractile response of sensitised bronchi to histamine *in vitro* and induces proliferation of human airway smooth muscle cells (Berger et al., 2001; Brown et al., 2002). However, co-culture of human lung mast cells with airway smooth muscle cells did not affect either proliferation or survival of airway smooth muscle cells even if they were activated with IgE and anti-IgE (Kaur et al., 2010) indicating that

other mechanisms are involved when mast cells are activated that may counteract the mitogenic actions of tryptase on airway smooth muscle cells.

11. Mast cell infiltration into airway epithelium and submucosal glands

Mast cells also infiltrate epithelial structures in asthmatic airways (Bradding et al., 1994; Laitinen et al., 1993; Pesci et al., 1993b). The microlocalisation of mast cells within the airway epithelium places them in an ideal environment to respond to stimuli such as aeroallergens and other noxious stimuli where mast cell-driven inflammatory and effector cell responses may be on-going. However, mast cells in the epithelium also have the capacity to suppress allergic inflammation. For example, mast cell activation by allergens and subsequent release of tryptase could act as a negative feedback signal since tryptase degrades respiratory allergens and IgE (Rauter et al., 2006; Rauter et al., 2008). Tryptase also stimulates epithelial proliferation as well as upregulation of IL-8 and intercellular adhesion molecule (ICAM1) expression (Cairns and Walls, 1996), thus promoting recruitment and adhesion of inflammatory cells. Indeed, mast cells adhere strongly to bronchial epithelial cells (Sanmugalingam et al., 2000). However, the interaction between mast cells and epithelial cells in health may actually keep mast cells “in check” since coculture experiments reveal that IgE-dependent degranulation of human lung mast cells is suppressed when cocultured with the bronchial epithelial cell line BEAS-2B or primary human epithelial cells (Martin et al., 2012; Yang et al., 2006). Therefore in healthy airways, mast cells adjacent to the epithelium may be suppressed by factors released by the epithelial cells, but in asthma where there is airway epithelial denudation and injury, this suppressive effect could be lost.

Mucus plugging is a feature of fatal asthma, but mucus hypersecretion is also present in milder disease (Cutz et al., 1978). Mast cells appear abundant in airway mucosal glands (Bradding et al., 1994). When comparing lung sections post-mortem from patients with fatal asthma, patients with asthma who died of unrelated causes (non-fatal asthma) and subjects without asthma, there was a significant increase in the number of mast cells within the mucosal gland stroma of fatal asthma and non-fatal asthma compared to control subjects, and there was evidence of mast cell degranulation in both non-fatal and fatal asthma (Carroll et al., 2002b). However, what was perhaps more striking was that the number of degranulated and intact mast cells within the mucous glands correlated strongly with the degree of mucus obstruction, suggesting that mast cells could be involved in the pathogenesis of fatal asthma.

12. Mast cells in chronic obstructive pulmonary disease (COPD)

In addition to the strong evidence presented for a role of mast cells in the pathophysiology of asthma, there is growing evidence that mast cells may also play roles in other diseases of the airways. COPD is characterised by fixed airflow obstruction that is usually progressive. The disease is strongly associated with noxious inhaled particles or smoke such as tobacco smoke and is the result of chronic inflammation that leads the development of emphysema, chronic airway inflammation, mucus gland hyperplasia and small airway wall fibrosis. Although the density of mast cells in the lung decreases in COPD, mast cell activation and

degranulation are increased with evidence of enhanced histamine release in advanced COPD (Andersson et al., 2010; Wessler et al., 2007). An increase in the density of mast cells of the MC_{TC} subtype has been reported in the alveolar parenchyma and airway smooth muscle in COPD (Andersson et al., 2010; Gosman et al., 2008). This could be important as CD88 (the receptor for the anaphylatoxin C5a) is expressed in the MC_{TC} subtype of human lung mast cells (Oskeritzian et al., 2005) and C5a expression is increased in COPD patients (Marc et al., 2004). In addition, CD88 expression is increased in both MC_{TC} and MC_T cells in COPD (Andersson et al., 2010) and thus may be a cause for chronic mast cell activation in the disease.

13. Mast cells in interstitial lung disease

Interstitial lung diseases are a group of diseases characterised by the presence of pulmonary fibrosis. The most commonly encountered interstitial lung disease is idiopathic pulmonary fibrosis (IPF) with a histological pattern of usual interstitial pneumonia. The development of IPF is not well understood, but most likely driven by on-going damage to the alveolar epithelium, basement membrane and capillary endothelium (for review see (Strieter, 2005)). Chronic tissue damage leads to dysregulated repair mechanisms and generation of fibroblastic foci with the production of profibrotic mediators such as transforming growth factor β (TGFβ), platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF). The key cell type in IPF is an intermediary between fibroblasts and smooth muscle, termed the myofibroblast, that expresses α-smooth muscle actin (αSMA) and exhibits contractility, but has the capability of producing and depositing a fibrotic matrix (Zhang et al., 1994). Extensive literature indicates that there are important bidirectional interactions between mast cells and myofibroblasts in fibrotic tissues that are also of likely relevance to airway wall matrix deposition in COPD and asthma.

Mast cell numbers in the lung of patients with fibrotic lung disease are increased compared to control subjects and correlate with the severity of fibrosis (Pesci et al., 1993a). In addition, histamine concentrations in the BAL fluid of patients with IPF are elevated about 10-fold that of control subjects (Casale et al., 1988; Rankin et al., 1987), and tryptase levels are increased in the lung tissue of IPF patients (Wygrecka et al., 2013). Mast cells present in pulmonary fibrosis show signs of on-going degranulation (Hunt et al., 1992; Kawanami et al., 1979) and coculture of human lung mast cells with human lung fibroblasts from IPF patients activates the mast cells to release tryptase (Wygrecka et al., 2013). Furthermore, infiltrating bFGF expressing cells are abundant in IPF and these cells have been identified as mast cells (Inoue et al., 2002; Inoue et al., 1996; Qu et al., 1995), which are surrounded by collagen, elastic fibres and smooth muscle cell/myofibroblast-like cells (Inoue et al., 2002; Wygrecka et al., 2013). SCF may again play an important role in interstitial lung disease since secretion of SCF by alveolar fibroblasts is increased in patients with diffuse interstitial fibrosis (Fireman et al., 1999). In addition, membrane bound SCF, but not soluble SCF, expression is increased in both lung tissue and in isolated lung fibroblasts in patients with IPF compared to control subjects (Wygrecka et al., 2013). Furthermore, coculture of isolated lung fibroblasts from IPF patients with mast cells enhanced SCF-driven survival and proliferation (Wygrecka et al., 2013) in a similar manner to human airway smooth muscle cells (Hollins et al., 2008). These observations suggest that interactions between mast cells

and smooth muscle and/or myofibroblasts may play a role in matrix deposition and fibrosis in interstitial lung diseases. Indeed, mast cell mediators such as histamine, bFGF and TGFβ promote fibroblast proliferation in humans (Boucek and Noble, 1973; Feghali et al., 1992; Hetzel et al., 2005; Jordana et al., 1988) and mast cells adhere strongly to fibroblasts in coculture (Moiseeva et al., 2013b; Trautmann et al., 1997; Wygrecka et al., 2013).

14. Concluding remarks

Mast cells play an important role in the pathogenesis of asthma and this role most likely depends upon the microlocalisation of mast cells, providing a niche to support mast cell growth, survival and activation through cell-to-cell contact. There is growing evidence that this may also be true for other airway diseases where direct interactions may also be critical for chronic mast cell activation. The factors that regulate the functional responses of mast cells and structural cells that interact with mast cells are not yet understood, but we are beginning to identify important mediators. One of the critical aspects may be that studying functional responses of soluble mediators in suspension cultures might not represent what is happening *in vivo* where cell-to-cell contact, formation of co-stimulatory and adhesion complexes and ligands tethered at the surface may drastically alter the signalling from receptors. This aspect could be critical for mast cells that mature within tissues where a complex milieu of soluble and membrane bound growth factors appear to be able to drive differentiation of the cells with a great deal of plasticity. Understanding the mechanisms that regulate mast cell activation by cellular crosstalk both in health and disease could lead to the identification of novel therapies that might be effective when administered chronically *in vivo*.

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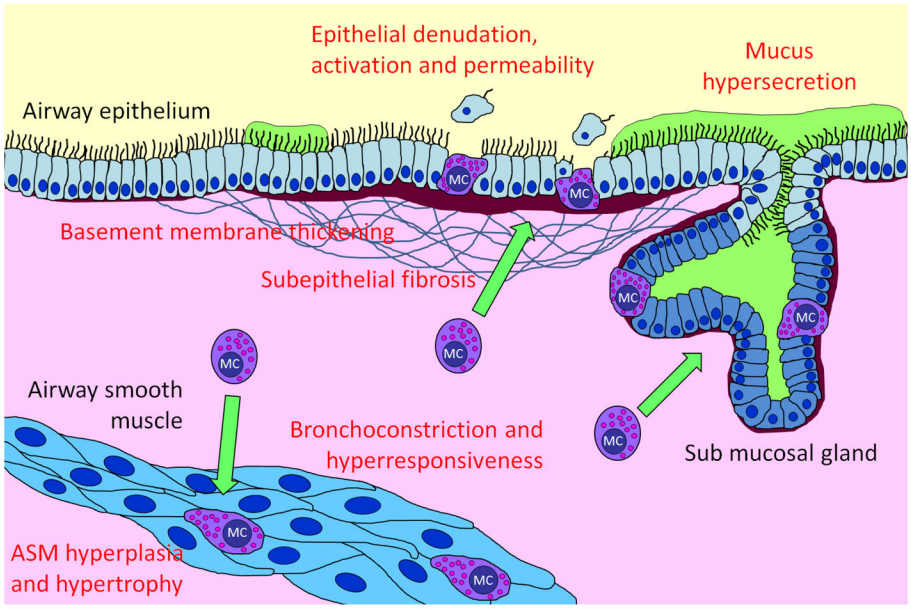

Figure 1.

Schematic representation of mast cell infiltration into important structures of the airways in asthma and the functional consequences. For information on key mediators of these events see Tables 1 and 2.

Table 1

Human mast cell mediators and their effects in airways.

Mediator	Biological effects in airways	References
Preformed (stored) mediators		
Histamine	Bronchoconstriction Mucus hypersecretion Collagen synthesis Promotes tissue oedema Fibroblast and endothelial cell proliferation Dendritic cell activation	Caron, et al., 2001; Dunford & Holgate, 2010; Garbuzenko, et al., 2002; Hargreave, et al., 1981; Hirota, et al., 2012; Jordana, et al., 1988; Marks, et al., 1986; Tamaoki, et al., 1997
Heparin	Anticoagulant Storage matrix for mast cell mediators Protects growth factors from degradation Potentiates growth factors action Fibroblast activation Endothelial cell migration	Caughey, 1989; Gao & Goldfarb, 1995; Lloyd, et al., 1967; Metcalfe & Austen, 1979; Moiseeva & Bradding, 2011; Nieto, et al., 2013; Spivak-Kroizman, et al., 1994; Terranova, et al., 1985
Tryptase	Potentiates MC histamine release Increases airway hyperresponsiveness Generates C3a and bradykinin Activates epithelial cells Promotes fibroblast growth and collagen synthesis Indirectly activates collagenase	Cairns & Walls, 1996; Cairns & Walls, 1997; Caughey, 1989; Garbuzenko, et al., 2002; He & Walls, 1997; Johnson, et al., 1997; Kozik, et al., 1998; Moiseeva & Bradding, 2011; Ruoss, et al., 1991; Schwartz, et al., 1983
Chymase	Mucus secretion Extracellular matrix degradation Converts angiotensin I to angiotensin II Activates IL-1β Releases membrane bound SCF Cleaves IL-33 to a more active form	Caughey, 1989; Fukami, et al., 1998; He & Zheng, 2004; Lefrançais, et al., 2014; Longley, et al., 1997; Mizutani, et al., 1991; Moiseeva & Bradding, 2011
Newly generated mediators		
Prostaglandin D_2	Bronchoconstriction Mucus secretion Promotes tissue oedema Dendritic cell activation Chemotaxis of eosinophils Chemotaxis of Th2 T cells and basophils	Gosset, et al., 2003; Hardy, et al., 1984; Hirai, et al., 2001; Matsuoka, et al., 2000; Moiseeva & Bradding, 2011; Stebbins, et al., 2010
Cysteinyl leukotrienes (LTC_4/LTD_4)	Bronchoconstriction Mucus secretion Promotes tissue oedema Dendritic cell maturation and migration Tissue fibrosis Enhances IL-13-dependent ASM proliferation Promotes IL-4 secretion from eosinophils Promotes IL-5, IL-8 and TNFα release from MC	Bandeira-Melo, et al., 2002; Busse, 1998; Dahlén et al., 1980; Dannull, et al., 2012; Espinosa, et al., 2003; Marom, et al., 1982; Mellor, et al., 2002; Moiseeva & Bradding, 2011; Perng, et al., 2006

Table 2

Mast cell cytokines and their effects in airways.

Cytokine	Biological effects in airways	References
IL-4	Allergic sensitisation Eosinophilic inflammation Allergen-specific IgE production Upregulation of IgE receptor expression Airway inflammation Airway hyperresponsiveness Airway remodelling Th2 cell polarisation	Brusselle, et al., 1994; Brusselle, et al., 1995; Chatila, et al., 2004; Lewis, et al., 2009; Maes, et al., 2012; Moiseeva & Bradding, 2011; Perkins, et al., 2006; Saito, et al., 2003; Xia, et al., 1997
IL-3/IL-5	Eosinophilic inflammation Eosinophil activation Airway inflammation Airway remodelling	Cho, et al., 2004; Lopez, et al., 1988; Moiseeva & Bradding, 2011; Takatsu & Nakajima, 2008
IL-6	Mast cell survival Mucus secretion T cell activation Airway inflammation	Cruse, et al., 2008; Moiseeva & Bradding, 2011; Neveu, et al., 2009; Yanagida, et al., 1996
IL-13	Goblet cell hyperplasia Mucus hypersecretion Airway remodelling Airway hyperresponsiveness Promotes eosinophilia IgE synthesis Airway inflammation	Chatila, et al., 2004; Grunig, et al., 1998; Lewis, et al., 2009; Maes, et al., 2012; Moiseeva & Bradding, 2011; Saito, et al., 2003; Wills-Karp, et al., 1998
TNFα	Mucus production Enhanced eosinophil activity Promotes eosinophil adhesion to airway epithelium Enhanced neutrophil activity Enhanced mast cell activity Airway inflammation	Chen, et al., 2003; Godding, et al., 1995; Lee, et al., 2008; Moiseeva & Bradding, 2011; Ohno, et al., 1990; Roubin, et al., 1987; Shalaby, et al., 1985; Zhang, et al., 1997
SCF	Enhances mast cell growth, survival and differentiation Promotes mast cell recruitment Enhances mast cell degranulation	Cruse, et al., 2014; Galli, et al., 1993; Gilfillan and Tkaczyk, 2006; Halova et al., 2012; Jensen et al., 2007; Moiseeva & Bradding, 2011; Nocka, et al., 1990; Okayama and Kawakami, 2006; Williams, et al., 1990
NGF	Enhances mast cell activation Promotes proliferation of inflammatory cells Airway inflammation Airway hyperresponsiveness	Braun, et al., 1998; De Vries, et al., 1999; Friberg, et al., 2001; Frossard, et al., 2005; Frossard, et al., 2004
TGFβ	Airway remodelling Tissue fibrosis Angiogenesis Airway hyperresponsiveness Airway inflammation	Bossé, et al., 2006; Kim, et al., 2005; Makinde, et al., 2007; Sagara, et al., 2002; Yang, et al., 2012
bFGF	Airway remodelling Airway smooth muscle proliferation	Bossé, et al., 2006; Moiseeva & Bradding, 2011; Redington, et al., 2001