Background

Chronic inflammation and airway smooth muscle dysfunction are consistent features of asthma responsible for disease progression and airway remodeling [1]. The increase in bronchial smooth muscle, both hypertrophy [2] and hyperplasia [3], plays a critical role in the development of airway hyperreactivity (AHR), the hallmark of asthma. Airway smooth muscle cells (ASMC) may also play a secretory or immunomodulatory role by producing pro-inflammatory cytokines, chemokines, polypeptide growth factors, extracellular matrix proteins, cell adhesion receptors, and co-stimulatory molecules, which perpetuate submucosal inflammation [4,5]. These mediators may act on the ASM itself in an autocrine manner as well to further contribute to the asthma phenotype [6]. Therefore, smooth muscle itself may be capable of initiating and maintaining airway inflammation. Also, ASMC have been shown to undergo cell migration, which could contribute to airway remodeling [7]. Thus, regulation of airway smooth muscle hypertrophy and migration may be a new target for treatment of asthma [7,8].

It is well known that IgE plays a critical role in the pathogenesis of asthma in the early and late phases by interacting with its two receptors, the high affinity receptor (FcεRI) and the low affinity receptor (FcεRII) [9]. IgE plays a key role in bronchial hyperresponsiveness and smooth muscle hyperreactivity [8]. Crosslinking of the high affinity IgE receptor (FcεRI) on mast cells leads to cellular degranulation and the release of various proinflammatory mediators and cytokines contributing to bronchoconstriction. The low affinity IgE receptor (CD23) (FcεRII) has been identified on B cells, monocytes, follicular dendritic cells, Langerhan's cells, eosinophils, and platelets [10]. Upregulation of the CD23 receptor is thought to increase allergic responses in the bronchial mucosa through the enhancement of antigen uptake and presentation [8]. The receptor has two isoforms that differ only in their cytoplasmic domains [11]. CD23a is constitutively expressed on B cells and is associated with endocytosis of IgE coated particles, and CD23b is induced by IL-4 and is also found on non- B cells such as T cells, Langerhan's cells, monocytes, macrophages, platelets, and eosinophils [12,13]. IL-4 causes CD23 induction on B cells through CD40 [12]. CD23b mediates phagocytosis of soluble IgE complexes. An autocatalytic process involving cleavage of membrane bound CD23 by a matrix metalloprotease yields a series of soluble elements (sCD23) which increase IgE production via the CD21 receptor on B cells [13,14].

The CD23 receptor has been shown to be upregulated on monocytes and alveolar macrophages in a T helper cell type 2 (TH2) environment and may contribute to chronic inflammation in asthma through this mechanism [15]. It has been shown that IL-4 and GM-CSF induce CD23 expression on monocytes, and GM-CSF primes monocytes for cellular activation and secretion of IL-1 upon subsequent exposure to IgE-containing immune complexes [8]. CD23 is also involved in antigen presentation to B cells as well as cellular interactions between B and T cells [12].

In previous studies, Hakonarson et al. [16] demonstrated the expression of CD23 (FcεRII) messages and a low level of the protein in airway smooth muscle cells. In two patients who died of status asthmaticus, CD23 expression was also markedly upregulated on ASMC. The CD23 expression was inducible with human atopic sera or IgE immune complexes in naïve (control) ASMC, and this upregulation was blocked when pretreated with anti-CD23 blocking antibody. The authors concluded that IgE coupled activation of CD23 contributes largely to its upregulation [5,14]. In a corresponding experiment with rabbit ASMC subjected to control and atopic serum, they were able to demonstrate, through Western blot analysis, a markedly enhanced expression of CD23 in the ASMC sensitized with atopic serum or IgE immune complexes. They were able to achieve significant inhibition of upregulation by pretreatment with anti-CD23 mAb. They hypothesized that IgE was responsible for the upregulation of the low affinity IgE receptor [17]. Hakonarson, et al. have also demonstrated that ASMC in vitro exposed to human atopic sera results in an initial increase in TH2 cytokines including IL-5 and GM-CSF followed hours later by production of IL-1 and TH1 cytokines [18,19]. Recently, phase I trials have been completed on IDEC-152, an IgG1 anti-CD23 antibody, for patients with mild to moderate persistent asthma. The drug was well tolerated by participants, and a dose-dependent decrease in mean IgE values was reported [20].

T helper cell type 2 (TH2) mediated inflammatory cytokines, such as IL-4, IL-13, and IL-5, as well as other enzymes and chemokines are active in the asthmatic patient. GM-CSF has been shown to be involved in asthma pathogenesis and in vivo can induce TH2 differentiation independent of IL-4 [21]. Tryptase and prostagladin D2 (PGD2) were chosen as major mast cell mediators, and more recently the PGD2 receptor gene (PTGDR) has been shown to be an asthma susceptibility gene [22-24]. It is possible that many factors are responsible for the upregulation of the low affinity IgE receptor in addition to and independent of IgE. The purpose of this study was to identify specific mediators released in the asthmatic patient that are responsible for the upregulation of CD23 on human airway smooth muscle cells independent of IgE.