Statins in Asthma: A Closer Look into the Pharmacological Mechanism of Action

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Key Words

Asthma · Statins · 3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors · Isoprenylation · Animal model of asthma · Subepithelial fibrosis · Eosinophils

Abstract

The effect of statins in asthma is mediated through targeting several signaling molecules that are involved in the development of asthma phenotype. In vitro and in vivo studies revealed that statins reduce airway smooth muscle cells proliferation and inflammatory mediators' release. Statins reduce chemokine release and mucus production from airway epithelial cells besides attenuating subepithelial fibrosis and eosinophils recruitment. In acute and chronic allergen driven animal models of asthma, statins reduce airway hyper-responsiveness, inflammation and remodeling. However, the effectiveness of statins in clinical trials results in contradictory conclusions based on study design and treatment protocol. Therefore, more clinical trials are needed to evaluate their role in asthma patients.

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Introduction

Asthma is a chronic airway inflammatory disorder [1, 2] that is characterized by airway hyper-responsiveness (AHR), airway obstruction, airway inflammation and

mucus metaplasia. Worldwide, asthma affects 300 million people and the number is growing dramatically to reach 400 million by year 2025 [3, 4].

The inflammatory profile of asthma is characterized by an amplified T-helper-2 (T_H2) response at the expense of T_H1. The elevated levels of T_H2 cytokines (interleukin (IL)-4, IL-5 and IL-13) play a major role in orchestrating asthma inflammation and hence mediate airway remodeling [5].

Different inflammatory cells are recruited to the airways and participate in airway remodeling and disease progression. Asthma is characterized by eosinophilic type of inflammation [6]. Eosinophils release several granular proteins and cytokines that mediate epithelial damage and recruitment of further inflammatory cells, respectively [7]. β_2 -Adrenoceptor (β_2 -AR) agonists and inhaled corticosteroids (ICSs) are the most commonly used medications that target bronchoconstriction and inflammation of asthma, respectively. ICSs, especially at high doses in severe persistent asthma, result in serious systemic side effects such as growth impairment in children [8] and reduction in bone density [9]. Chronic use of β_2 -AR agonists is also associated with serious consequences such as increased risk of severe asthma exacerbations and possible death [10, 11]. The fear of long-term side effects of ICS and β_2 -AR agonists creates a subset of patients who have uncontrolled disease. Additionally, another subset of asthmatic patients, (~5–10%), are not responsive to conventional treatment approaches and exhibit severe

disease manifestations [12]. Thus, more research is required to improve the pharmacological approaches in asthma treatment. Statins are among the investigated agents for the treatment of asthma.

Statins

Statins are the most commonly used anti-hyperlipidemic agents for decades. Statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase enzyme [13] and thus inhibit the conversion of HMG-CoA to L-mevalonic acid, a rate limiting step in cholesterol synthesis. Of note, the mevalonate pathway is involved in the formation of membrane-raft microdomains, which is essential for immune system signaling and localization of major histocompatibility complex class II [14] on antigen presenting cells [15].

Not only is the synthesis of cholesterol reduced by statins, but also the production of numerous isoprenoid metabolites such as geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) [16, 17]. FPP and GGPP are involved in the process of protein prenylation which is an essential post-translational modification for several proteins such as Ras, Rab and protein kinases among others [18]. These modifications are essential for membrane association [19]. Knowing that isoprenylated proteins control several intracellular signaling and responses, it is expected that statins would have additional effects beside their lipid lowering mechanism.

Pharmacological Targets of Statins in Asthma

Both in vivo and in vitro evidence points toward the potential role of statins in attenuating the asthma phenotype. An elegant study conducted by Takeda et al. [20] showed normal human bronchial smooth muscle cells (SMCs) that were treated with simvastatin resulted in reduction of cell proliferation and DNA synthesis induced by fetal bovine serum. This inhibitory effect was due to inhibition of RhoA geranylgeranylation and not by inhibition of Ras farnesylation [20]. Increased airway SMC (ASMC) proliferation is a hallmark of asthma [21] and it has been found that there is increased proliferative capacity of cultured ASMCs from asthma patients as compared to ASMCs from healthy individuals [22]. Contraction of ASMCs results in airway narrowing in response to nonspecific stimuli or pharmacological ago-

nists. Because of this, ASMCs are the predominant cell type studied for control of AHR.

Of interest, Rho plays a critical role in regulating ASMC contraction through its effect on myosin light chain (MLC), one of the major proteins that regulate muscle contraction. MLC is activated by MLC kinase (MLCK) and inactivated by MLC phosphatase (MLCP) resulting in smooth muscle contraction and relaxation, respectively [23]. Of interest, MLC is also phosphorylated by Rho kinase [24], a downstream signaling molecule of Rho [25]. Rho kinase phosphorylates ser-19 residue of MLC, which is same site phosphorylated by MLCK [24] and hence leads to smooth muscle contraction. Rho kinase also phosphorylates other proteins that are involved in smooth muscle contraction, such as CPI-17, that inhibits MLCP [26] and calponin [27]. Calponin is a specific protein of SMCs that is involved in regulating SMCs contraction [28].

ASMCs release inflammatory mediators [22, 29] and undergo hypertrophy and hyperplasia in the asthma patient's airways [30]. Several factors were found to be involved in ASMC proliferation including ILs (such as IL-6 and IL-1 β), growth factors (such as insulin-like growth factors) and contractile agents acting through a Ras/ERK/phosphatidylinositol 3-kinase pathway [31]. Eicosanoid agents are also inducers of ASMC proliferation. It has been found that treating cultured human ASMCs with rosvastatin inhibited cell growth, as measured by [3 H] thymidine nuclear incorporation, in response to eicosanoid agents [32]. Of interest, it has been suggested that inhibition of both geranylgeranylated and farnesylated proteins are involved in the effect of rosvastatin [32].

The role of airway epithelial cells, the second most predominant parenchymal lung cell, in asthma has been the subject of less intense investigation and initially considered primarily as mechanical barrier. However, several recent studies have shown an emerging role for epithelium as a tissue orchestrating a sophisticated set of responses. These include a critical role in initiating the immune response to inhaled allergens [33] and polarizing the response toward T_H2 [34]. Moreover, airway epithelial cells, through producing mucus to form mucus plugs, cause airway obstruction. Mucous plugs, together with AHR, are the cause of death in almost all asthma-related fatalities [35]. Treating primary mouse tracheal epithelial cells with atorvastatin attenuated IL-13 induced expression of several chemokines such as eotaxin-1 (an eosinophil attractant) and chemokines MCP-1, MCP-2 and MCP-3 [36].

Statins affect mucus overproduction by airway epithelial cells. Simvastatin reduced the expression of the *MUC5AC* gene, the main mucin-producing gene in gob-

let cells [37, 38], in response to acrolein in cultured NCI-H292 cells [39]. Oral administration of lovastatin attenuates Muc5ac expression in the allergen-driven murine model of asthma [40]. Rosuvastatin also reduced mucus metaplasia in the chronic murine model of asthma [41]. Of interest, rosuvastatin's effect is mediated through regulating the expression of gamma-aminobutyric acid type A receptor (GABA_AR) [41]. Mice lungs and human airway epithelial cell lines express GABA_AR [42]. The increased levels of IL-13, directly or mediated by allergen exposure, enhances the release of GABA and hence activation of GABA_ARs and results in chloride efflux and mucus overproduction that is observed in asthma [42].

Decreasing airway eosinophil recruitment is another proposed anti-inflammatory effect of statins. Fluvastatin and lovastatin inhibited the adhesion of human eosinophils to recombinant human intercellular adhesion molecule-1, and this effect was reversed by the addition of mevalonate [43]. In addition, pravastatin and fluvastatin reduced the expression of intercellular adhesion molecule-1 and the release of TNF- α , IFN- γ and IL-12 from cultured human peripheral blood mononuclear cells [43]. In recent years, it has been suggested that the accumulation of eosinophils in asthma could be due to their prolonged survival and defective apoptosis [44, 45]. Hence, strategies to induce eosinophil apoptosis in asthma are an appealing area of research. Of interest, IL-13 and IL-5 are among the cytokines that inhibit eosinophil apoptosis [44]. Nuclear factor-kappa B (NF- κ B) is a transcription factor that plays a major role in asthma pathogenesis [46, 47], and inhibition of the NF- κ B signaling pathway enhances eosinophil apoptosis [48]. Simvastatin reduces the level of activated NF- κ B in inflammatory cells and lung tissues as well as airway eosinophils recruitment in ovalbumin (OVA) induced allergic airway inflammation [49].

Oral administration or intraperitoneal injection of simvastatin decreased the level of total inflammatory cells and eosinophils in chicken egg OVA-driven murine models of acute [50] and chronic asthma [51]. Additionally, simvastatin reduced bronchoalveolar lavage fluid levels of IL-4 and IL-5 as well as the extent of inflammatory cell infiltration in the lungs [50]. It has been found that the effect of simvastatin on AHR and airway inflammation attenuation is through a mevalonate independent mechanism [52]. Several small G proteins of Rho family, such as Rho, Rac1, Rac2, Ras and cdc42, were inactivated by simvastatin in lung tissues of mice that were sensitized and challenged with OVA [49]. Additionally, simvastatin inhibited the level of activated mitogen-activated protein kinases (MAPKs) – ERK, JNK and p38 – in inflammatory cells and

lung tissues [49]. MAPKs play a major role in inflammation [53], asthma pathogenesis and airway remodeling [54].

Imamura et al. [55] found that pravastatin inhibited T_H2 proliferation and the release of T_H2 cytokines and IL-17 when administered during the sensitization period in allergen driven murine model of asthma. IL-17 is involved in mediating several asthma responses, such as secretion of mucus and accumulation of neutrophils [56].

Subepithelial fibrosis, important for airway remodeling, occurs due to the accumulation of extracellular matrix proteins and enhanced fibroblast-myofibroblast transition [57]. Fibronectin is among these extracellular matrix proteins [58] and it has been found that asthmatic human bronchial epithelial cells are intrinsically more capable of producing higher levels of fibronectin [59]. Of interest, fibronectin stimulates the proliferation of human bronchial epithelial cells and the release of inflammatory mediators from epithelium [59]. Treating primary human fibroblast cells from asthma patients with simvastatin and lovastatin reduced fibronectin release [60] and myofibroblast differentiation, respectively, in response to transforming growth factor beta 1 [61]. The inhibitory effect of lovastatin is mediated by decreasing the intracellular cholesterol content and not through suppression of prenylation or reactive oxygen species production [61]. The effect of simvastatin on early airway remodeling markers in an acute model of asthma was through inhibiting the expression of arginase-1 and arginase activity [62]. The increased level and activity of arginase in asthma result in reduction of the released nitric oxide, which has anti-inflammatory and bronchodilator effect, and L-ornithine [63].

Clinical Evidence of the Role of Statins in Asthma

The clinical role of statins in asthma has been the focus of several clinical studies for years and has resulted in contradictory findings. It has been found that simvastatin administration did not reduce airway resistance [64], blood eosinophil levels or improve lung function [65] in asthma patients with mild-moderate disease. However, a double-blinded placebo control study found that the level of sputum eosinophils was significantly reduced by simvastatin and inhaled budesonide as compared to patients who received inhaled budesonide only [66]. It has been suggested that this anti-inflammatory effect of simvastatin is through enhancing indoleamine 2,3-dioxygenase [66], an important T-cell immunomodulator [67]. These inconclusive clinical findings on the role of statins in asthma could be due to differences in study design and

treatment duration. Therefore, multicenter clinical trials with larger number of asthma patients with different disease stages and longer treatment period are recommended to critically elucidate the role of statins in asthma.

The safety of statins received a lot of attention during the past years. Myalgia received widely perceived attention as a side effect of statins [68]. Rhabdomyolysis, a rare condition of severe myopathy that causes the release of myoglobin and eventually risk of renal failure, has increased among patients who are taking intensive statin therapy [69]. In 2012, the United States Food and Drug Administration modified the labeling of statins to include a warning regarding the potential negative effect on cognition and glucose level [70]. A recent comprehensive meta-analysis of 25 randomized controlled trials reported on the cognitive effect in 46,836 subjects revealing that statin use is not associated with cognitive decline [71]. In addition, a recent meta-analysis review revealed that statins use is associated with a slight increase in the risk of developing diabetes [72], particularly with more intensive statin therapy [72].

In clinical practice, statins are safe and well tolerated [73] and their benefits outweigh their risk of side effects.

Conclusion

In vitro and in vivo studies revealed that statins reduce ASMCs proliferation and inflammatory mediators' release. Statins reduce chemokine release and mucus production from airway epithelial cells besides attenuating subepithelial fibrosis and eosinophil recruitment. In acute and chronic allergen-driven animal models of asthma, statins reduce AHR, inflammation and remodeling. The effect of statins in asthma is mediated through their effect on several small G proteins, inducing cell apoptosis, inhibiting eosinophils adhesion, attenuating fibronectin release and modulating the activation of transcription factors.

Statins are relatively safe and well tolerated; however, more multi-centered clinical trials are needed to evaluate the effect of statins on asthma phenotype of different disease stages.

Disclosure Statement

There is no financial or other relationship that could lead to conflict of interest.

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