HHS Public Access

Author manuscript

Drug Metab Lett. Author manuscript; available in PMC 2018 August 08.

Published in final edited form as:

Drug Metab Lett. 2011 January ; 5(1): 40–44.

Statin Drugs, Metabolic Pathways, and Asthma: A Therapeutic Opportunity Needing Further Research

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Abstract

The chance discovery of *hydroxymethylglutaryl (HMG)-CoA reductase* inhibitors has revolutionized the care of patients with cardiovascular disease. The unexpected finding that these cholesterol-lowering drugs (or 'statins') also posses pleiotropic immunomodulatory properties, has opened a new area of research which investigates the anti-inflammatory and anti-proliferative properties of statins. In this brief commentary, we discuss the potential application of these drugs in asthma, where metabolic pathways pertinent to lung inflammation, in addition to the mevalonate cascade, may be targeted. We review mechanisms of action, discuss the potential therapeutic use of statins in asthma, share some preliminary data from our laboratory, discuss results from recent clinical trials in asthma, and propose a new target asthma subpopulation that could potentially benefit. We conclude our essay by highlighting the mevalonate-dependent and –independent pathways that may be modulated by statins, including the emerging area of cholesterol, sphingolipid, and lipid raft biology in lung disease. In this is an opportunity to develop new treatments for asthma, where innovative therapies are urgently needed to prevent acute exacerbations and alter disease progression.

Keywords

Statins; asthma; mevalonate; metabolic; novel therapy; HMG-CoA reductase; anti-inflammatory; immunomodulatory; eotaxin; obese asthmatic; lipid

A GROUNDBREAKING DISCOVERY

The discovery of compactin (now known as mevastatin) by Dr. Akira Endo in 1973, led to the development of the 'statin' class of drugs. In the last two decades these medications have revolutionized the care of patients with cardiovascular disease. Endo's work on cholesterol metabolism in fungi revealed that *Penicillium citrinum* can produce organic molecules, i.e. the statins, which naturally inhibit *hydroxymethylglutaryl (HMG)-CoA reductase (HMGR)* via competitive inhibition. Subsequent studies on cholesterol homeostasis and the low

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density lipoprotein (LDL) receptor by Drs. Joseph L. Goldstein and Michael S. Brown garnered them the Nobel Prize in 1985 and lay the foundation for the use of statins in clinical trials. The relatively recent realization that statins also have anti-inflammatory and immunomodulatory properties has resulted in a new and intriguing avenue of research relevant to lung diseases such as asthma and chronic obstructive pulmonary disease (COPD).

MECHANISMS AND BIOLOGICAL IMPLICATIONS

The statins directly inhibit HMGR, the rate-limiting step in the cholesterol biosynthesis pathway in the mevalonate (MA) cascade (Fig. 1). Depletion of MA by statins affects critical downstream intermediates, such as the isoprenoids farnesyl- and geranylgeranylpyrophosphate (FPP and GGPP). These lipid metabolites post-translationally modify the small guanosine triphosphatases (GTPases) Rho, Ras, Rac, and Cdc42, which can then associate with the cell membrane leading to intracellular signal transduction [1, 2]. These GTPases are important in a variety of key biological activities that include recruitment of inflammatory cells, cellular proliferation and transmigration, vesicular trafficking, cytoskeletal dynamics, apoptosis and phagocytosis, antigen uptake and processing, and cell cycle regulation [3]. Thus, the MA cascade is a major metabolic pathway that regulates manifold cellular processes important to many diseases beyond cardiovascular disease [4]. The statins modulate this pathway in different cell types which has created an opportunity for novel and innovative investigations in several fields outside of cardiovascular medicine.

THERAPEUTIC POTENTIAL

We are interested in the therapeutic potential of statins in lung disease, in particular inflammatory airway diseases such as asthma and COPD. We and others have demonstrated that simvastatin in the allergic mouse model attenuates eosinophilic airway inflammation [5, 6] via inhibition of HMGR in the MA pathway [7]. Interestingly, improvements in airway hyperreactivity (AHR) and lung compliance appeared to be MA- or HMGR-*independent* [7]. This suggests other statin targets exist beyond the HMGR enzyme (Fig. 1).

Although systemic treatment with simvastatin has a known potent anti-inflammatory effect in our asthma model (Fig. 2), additional work in our lab will explore lung-targeted modalities of delivering statins. Beyond the asthma model, simvastatin also attenuates the production of cytokines important in neutrophilic recruitment and airway remodeling [8]. Ongoing studies will test the anti-inflammatory and anti-remodeling effects of simvastatin and lovastatin in a rat model of cigarette smoke-induced inflammation. Our preliminary data lead us to believe that statins affect a profound inhibition of Th1/Th2/Th17 cytokine and chemokine expression in both mouse and human airway epithelial cells (Fig. 3), where the epithelium is known to play a central role in asthma mucosal immunity [9].

EMERGING CLINICAL TRIAL DATA

Recent observational studies have linked statin use with improvements in lung health (e.g. exacerbations, COPD mortality, and decline in *forced expiratory volume in the first second* (FEV1)), the largest studies being done in COPD and asthma [10–13]. A recent large

retrospective study found that statin exposure in patients with asthma using inhaled corticosteroids (ICS) was independently associated with a significant reduction in asthma-related hospitalizations and emergency room events over 12 months [14]. However, no human randomized clinical trials have definitively reproduced the benefits seen in animal models.

Several ongoing clinical trials are investigating exacerbation rates, lung function, inflammatory markers, and quality of life in asthmatics treated with statins compared to placebo (www.clinicaltrials.gov). So far, four small clinical trials in asthma have been reported, three using simvastatin [15–17] and one using atorvastatin [18]. Overall, the results are mixed where in one study an anti-inflammatory effect (as measured by sputum markers, e.g. macrophage count and leukotriene B4) was observed absent clinical benefit [18]. And in another study, despite a lack of a steroid-sparing effect, there were some improvements in asthmatic symptoms, lung function (as measured by FEV1), and the number of sputum eosinophils (in those who reached the 0 μg/day inhaled corticosteroid dose) [16]. However, in a recent double-blinded study, simvastatin (10 mg daily for 8 weeks) was given as add-on therapy to low-dose inhaled budesonide (200 μg) in patients with mild asthma. Simvastatin enhanced the anti-inflammatory effect of budesonide where sputum eosinophil counts were significantly reduced by the combined therapy (budesonide and simvastatin) compared to the control group (budesonide and placebo) ($p=0.02$) [17]. Although the study was not powered to detect changes in lung function, there was a trend toward higher FEV_1 in the budesonide and simvastatin group compared to the control population. A major limitation of these trials is that these were small, relatively short-term studies (4-8 weeks [15, 17, 18]), and 3 months [16]) where the subpopulation of asthmatics was not defined beyond allergic asthma.

It is important to remain cautious with these results given no definitive improvement in clinical outcomes as of yet. However, the observation that statins attenuate airway inflammation in asthma as measured by sputum markers is noteworthy. Whether this translates into reduced exacerbations and improved lung function remains an open and worthwhile research question. It also raises the following question: What would happen if the statin was given for a longer period of time and/or at a higher dose? This has implications for an aspect of severe asthma that remains without a viable treatment – irreversible airway remodeling.

Thus, the hypothesis that the statins may have benefit in a subpopulation of asthmatics has not been adequately tested in clinical trials of longer-term duration, where effects on asthma pathogenesis (e.g. chronic inflammation and remodeling) and clinical outcomes (e.g. acute exacerbations) require additional evaluation.

PROPOSED TARGET ASTHMA POPULATION

Why is asthma a potential disease target for statins? Asthma being a heterogeneous disease presents particular difficulties for clinical trials designed to test novel therapies. However, in this limitation is a hidden opportunity. Although one can propose many different arguments for why statins could benefit patients with asthma, we choose to focus on a subpopulation that may be underappreciated.

Epidemiologic studies have linked obesity with asthma [19–22]. Obesity is also strongly associated with metabolic syndrome, where a link to asthma is also emerging [23]. Using multidimensional cluster analyses, an obese subgroup of female asthmatics has been described [24]. The Severe Asthma Research Program has also described a cluster of older obese women with late onset non-atopic asthma [25]. Obesity being linked to systemic inflammation [26, 27], dyslipidemia, and metabolic syndrome [28] (where statins may be indicated) [29, 30], presents a unique opportunity for those with the obese-asthma phenotype. This subpopulation of asthmatics could potentially benefit from statins – a safe and widely used treatment that would also treat other comorbidities (e.g. cardiovascular disease, dyslipidemia). Adding to this complexity, emerging epidemiologic data link serum cholesterol levels with asthma risk in U.S. populations [31].

Thus, we believe that future clinical trials to assess the potential therapeutic use of statins in asthma should focus on the obese asthmatic as one target subpopulation or phenotype that could potentially benefit. Albeit the underling mechanisms in this specific population have not yet been fully described, we feel that parallel work in animal models and humans may accelerate the application of this innovative therapy.

ROLE OF THE MEVALONATE PATHWAY: FERTILE GROUND AND FUTURE DIRECTIONS

The MA pathway is important not only for its regulation of small GTPases, but also for the biosynthesis of cholesterol which is the precursor to many crucial metabolites and is a critical component of cell membranes. Numerous cholesterol products have emerging roles in asthma (and possibly other lung diseases), including vitamin D [32], steroid hormones, lipid rafts [33], and lipoproteins [34, 35]. Cholesterol itself may have a role in allergic lung inflammation [36] and lung host defense [37] which may be important in the pathogenesis of asthma.

Beyond this and given the pleiotropic effects of statins [38], an opportunity also exists to investigate HMGR- or MA-*independent* pathways thereby unraveling other important mechanisms. Emerging data suggest that statins can also inhibit LFA-1 [39], HDAC activity [40], and PKCα inactivation of PPARα [41], while potentially activating vitamin D receptors [42] or increasing serum vitamin D levels [43] (Fig. 1, see for Abbreviations). Omega-3 fatty acids may also inhibit HMGR [44] independently of statins, indicating crosstalk among different metabolic pathways with the attendant dietary considerations. This highlights the broad-ranging, pleiotropic statin effects and alternative metabolic pathways which may be relevant to asthma or other lung diseases.

Finally, the potential for statins to modulate cell signaling and subsequent immune responses by altering cholesterol content in lipid rafts [45] remains a relatively unexplored area in lung biology. Lipid raft trafficking and stabilization of receptor-to-ligand binding, a fundamental event in cellular inflammation and proliferation, is an area of intense exploration with direct relevance to asthma [46, 47]. In addition to cholesterol, the sphingolipids are also a key component of lipid rafts [48], where they may play a role in cigarette smoke-induced lung injury [49, 50] and asthma [51]. Thus, the statins, the pathways they affect, and cholesterol/

sphingolipid biology [52, 53] emerge as a fertile ground for investigation in lung diseases, particularly in asthma where targeted, novel, and innovative therapies are urgently needed.

Acknowledgments

We would like to thank Professor Reen Wu and Dr. Phil Thai for their technical input and insightful discussions regarding some of our *in vitro* experiments.

GRANT FUNDING

NIH (T32) HL07013, NCRR UL1 RR024146 (CTSC K30), HL-076415 (K08), ATS Fellows Career Development Award, CTSC K12 Award (KL2 RR 024144), and NIH-R01-HL066189.

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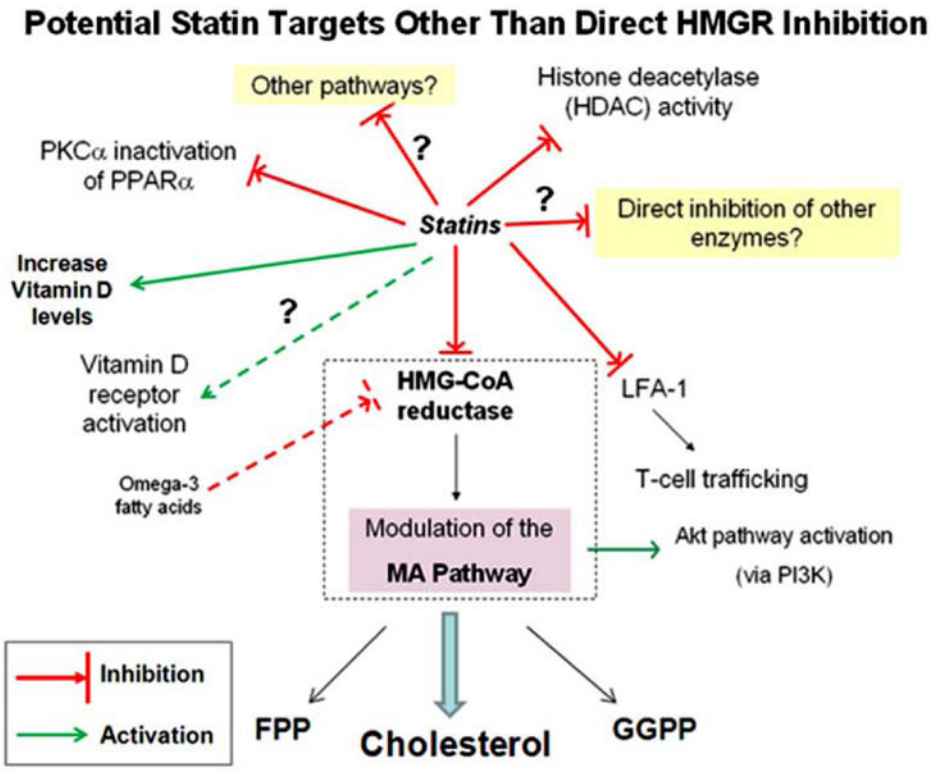

Fig. 1.

The statins may inhibit *or* activate various other pathways beyond the MA cascade. Direct HMGR inhibition depletes cellular MA and downstream metabolites (cholesterol, FPP, and GGPP) – i.e. the classical target of statins, while HMGR-independent pathways represent novel statin targets. (Abbreviations: phosphatidylinositol 3-kinase (P13K), peroxisome proliferators-activated receptor (PPAR), protein kinase C (PKC)α, mevalonate (MA), hydroxymethylglutaryl (HMG)-CoA reductase (HMGR), histone deacetylase (HDAC), leukocyte function antigen-1 (LFA-1), farnesylpyrophosphate (FPP), geranygeranylpyrophosphate (GGPP)).

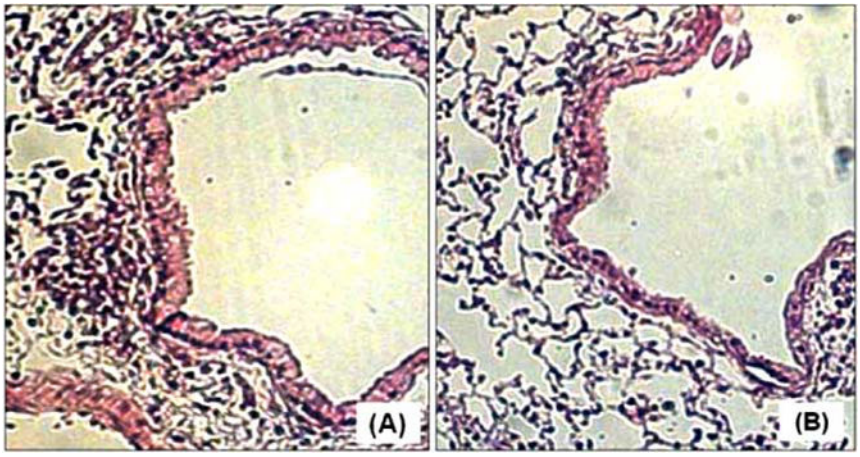

Fig. 2.

Lung histology of ovalbumin (OVA)-sensitized/exposed BALB/c mice (H&E statin at 100× magnification). Panel **(A)** shows the influx of peribronochiolar inflammatory cells in the OVA control group. Panel **(B)** shows a marked reduction of peribronchiolar inflammation in OVA mice treated with simvastatin (40 mg/kg) intraperitoneally.

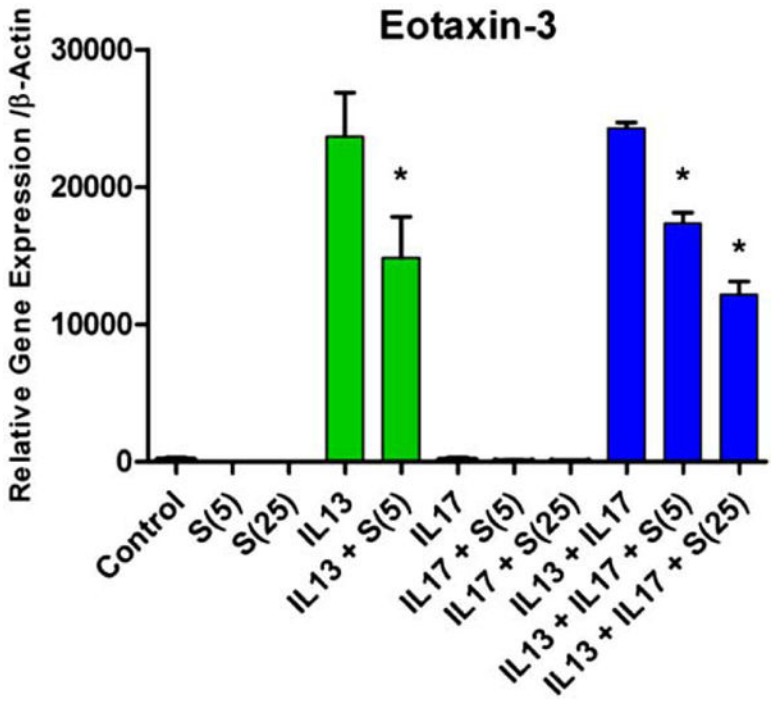

Fig. 3.

Eotaxin-3 expression in primary human airway epithelial cells. Simvastatin (5 uM and 25 uM, abbreviated as S(5) and S(25), respectively) attenuated IL-13-induced eotaxin-3-expression (IL-13 dose = 20 ng/mL) (*$p<0.05$). Co-stimulation with IL-17 did not alter the effect of IL-13 on eotaxin-3 gene expression.