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Interaction between allergic asthma and atherosclerosis

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Abstract

Prior studies have established an essential role of mast cells in allergic asthma and atherosclerosis. Mast cell deficiency or inactivation protects mice from allergen-induced airway hyper-responsiveness and diet-induced atherosclerosis, suggesting that mast cells share pathologic activities in both diseases. Allergic asthma and atherosclerosis are inflammatory diseases that contain similar sets of elevated numbers of inflammatory cells in addition to mast cells in the airway and arterial wall, such as macrophages, monocytes, T cells, eosinophils, and smooth muscle cells. Emerging evidence from experimental models and human studies points to a potential interaction between the two seemingly unrelated diseases. Patients or mice with allergic asthma have a high risk of developing atherosclerosis or *vice versa*, despite the fact that asthma is a Th2-oriented disease, whereas Th1 immunity promotes atherosclerosis. In addition to the preferred Th1/Th2 responses that may differentiate the two diseases, mast cells and many other inflammatory cells also contribute to their pathogenesis by much more than just T cell immunity. Here we summarize the different roles of airway and arterial wall inflammatory cells and vascular cells in asthma and atherosclerosis, and propose an interaction between the two diseases, although limited investigations are available to delineate the molecular and cellular mechanisms by which one disease increases the risk of the other. Results from mouse allergic asthma and atherosclerosis models and from human population studies lead to the hypothesis that patients with atherosclerosis may benefit from anti-asthmatic medications, or that the therapeutic regimens targeting atherosclerosis may also alleviate allergic asthma.

Keywords

Allergic asthma; atherosclerosis; mast cell; risk factor; inflammatory cells

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INTRODUCTION

Asthma is an inflammatory disease of the airways and characterized by severe airway inflammation, bronchial hyper-responsiveness, and airway remodeling.^{1,2} Among patients with either symptomatic or asymptomatic asthma, airway accumulation of inflammatory cells is probably the most common signature. These cells include mast cells, macrophages, lymphocytes, and eosinophils, which are frequently increased in the alveoli, alveolus, and the bronchoalveolar lavage (BAL) fluid.¹ These cells then elaborate cytokines and chemokines to activate bronchial vascular cells and to promote subsequent inflammatory cell infiltration.³ However, all of these cells in the inflamed bronchoalveolar also play pathogenic roles in atherosclerosis.

Atherosclerosis is a chronic inflammatory disease of the arterial wall.⁴ Atherosclerotic lesions often exhibit asymmetric focal thickenings of the arterial intima,⁵ which is also rich in inflammatory cells,⁶ including macrophages, monocytes, lymphocytes, neutrophils, and mast cells.^{7,8} The presence of the same sets of inflammatory cells in both the asthmatic bronchoalveolar and atherosclerotic aortic wall suggest that these cells share similar activities in both diseases. Therefore, asthma may serve as a risk factor of atherosclerosis, or *vice versa*. Among those bronchoalveolar and aortic wall inflammatory cells, macrophages and lymphocytes are probably among the best-studied cell types in both asthma and atherosclerosis.^{2,9-13} Mast cells are considered the signature cells in asthmatic lungs and play detrimental roles in allergic responses after activation by allergen-induced IgE, followed by the release of histamine and other inflammatory mediators in the airway.^{14,15} Both antihistamine and anti-IgE therapies are among the most popular anti-asthmatic medications.^{16,17}

Since the original detection of mast cells from human atherosclerotic lesions,¹⁸ accumulating evidence from *in vitro* and *in vivo* studies and from human clinical studies has proven a direct participation of mast cells in atherosclerosis. By releasing chymase, mast cells modify low-density lipoprotein (LDL) to promote foam cell formation,¹⁹ degrade high-density lipoprotein (HDL) to block foam cell cholesterol efflux,²⁰ and activate matrix metalloproteinases for arterial wall remodeling.²¹ By releasing histamine, mast cells induce vascular cell expression of tissue factor to activate thrombin formation and coagulation pathway.²² By releasing leukotrienes and histamine, mast cells elicit vascular permeability and increase the entry of circulating LDL and inflammatory cells to the aortic intima.^{23,24} Mast cells also produce chymase, TNF- α , and histamine to induce vascular cell apoptosis.²⁴⁻²⁶ In atherosclerosis-prone LDL receptor-deficient (*Ldlr*^{-/-}) mice, mast cell deficiency or pharmacological stabilization prevents mice from atherosclerosis.²⁷⁻²⁹ In apolipoprotein E-deficient (*ApoE*^{-/-}) mice, mast cell activation or overexpression of mast cell tryptase increases intraplaque hemorrhage, lesion inflammation, angiogenesis, and plaque vulnerability,^{24,30,31} whereas chymase inhibition in these mice reduces atherosclerosis.³² Mast cell numbers in human carotid atherosclerotic plaques correlate with atheromatous inflammation, angiogenesis, and intraplaque hemorrhage.³³ Atherosclerotic lesion mast cell protease contents correlate positively with lesion collagen content and lipid deposition.³⁴ Serum tryptase levels predict cardiovascular events and complexity.^{33,35}

As in asthmatic patients or animals, plasma IgE levels were also elevated in patients and mice with atherosclerosis.³⁶ IgE contributes to both asthma and atherosclerosis by activating mast cells. In the absence of IgE high affinity receptor FcεR1 expression, mice were fully protected from both asthma and atherosclerosis,^{36,37} suggesting an interaction between these two inflammatory diseases. This hypothesis has recently been tested in *Apoe*^{-/-} mice. Mice with ovalbumin (OVA)-induced allergic asthma had enlarged atherosclerosis in the aortic roots, along with increased Th2 and Th17 cells in the spleen.³⁸ In this review, we will discuss the activities of each major cell type that remain important contributors of asthma and atherosclerosis, including mast cells, monocyte and macrophages, T cells, eosinophils, and smooth muscle cells (SMCs) (Figure 1).

Prevalence of atherosclerosis in asthmatic patients

Asthma and atherosclerosis share several common pathological events, including inflammatory cell migration and accumulation at site of injury, increased plasma and *in situ* IgE levels and associated activation of mast cells and SMCs, and inflammatory cell production of cytokines and chemokines. Therefore, patients with asthma may be prone to developing atherosclerosis, or atherosclerosis remains a risk factor of asthma.

In a survey of 759 consecutive asthmatic patients from North Carolina, Mississippi, Minnesota, and Maryland, adult-onset asthmatics had significantly higher mean carotid artery intima-media thickness (IMT) compared to non-asthmatics among women (0.688 mm vs 0.656 mm, $P = 0.0096$), suggesting that adult-onset asthma associates with increased risk of carotid artery atherosclerosis.³⁹ In a study of random samples of all inhabitants of Bruneck, Italy, patients with allergic disorders (allergic rhinitis and asthma) were at increased risk for atherosclerosis (odds ratio (OR): 3.8; 95% confidence interval (CI): 1.4-10.2; $P = 0.007$).⁴⁰ In a cross-sectional evaluation of 141 men aged 17 to 18 years in Innsbruck, Austria, participants with the same allergic disorders were at a higher risk of having large IMT (OR, 2.5; 95% CI, 1.1-5.5; $P = 0.03$).⁴⁰ In a cohort of 70,047 men and 81,573 women enrolled in a large managed care organization in Northern California, asthma associated with a 1.22-fold (95% CI: 1.14-1.31) increased hazard of coronary heart disease (CHD) both in never and ever smoking women, and in younger and older women after a median follow-up time of 27 years, before ($P < 0.0001$) and after ($P < 0.0001$) adjusting for age, race/ethnicity, education level, smoking status, alcohol consumption, body mass index, serum total cholesterol, white blood cell count, hypertension, diabetes, and history of occupational exposures.⁴¹ More recently, from a study of 34 asthma patients and 68 subjects in 2 control groups, it was reported that target-to-background-ratio (TBR, ratio of the average arterial to blood axial slice SUV_{max})⁴² in the aorta was higher in asthmatics vs non-asthmatic Framingham risk scores (FRS)-matched controls both before and after adjusting traditional cardiovascular risk factors ($P < 0.001$), indicating augmented vascular inflammation and hence cardiovascular risks exist in asthmatic patients.⁴³

Differing from these discussed studies, a biracial cohort of 13,501 adults aged 45-64 years old allowed for the examination of the association of self-reported, doctor-diagnosed asthma and cardiovascular disease incidence, after 14 years of follow up. Ever, former, and current asthma did not associate with the incidence of CHD in this mid-aged population, and the

duration of asthma also did not associate with CHD.⁴⁴ Therefore, it remains uncertain whether the mutual risk association between asthma and atherosclerosis applies to all race populations. For example, from the Centers for Disease Control and Prevention's 2009-2010 Behavioral Risk Factor Surveillance System database of 869,519 adult respondents, African Americans (10.0%, 95% C.I. 9.6-10.5%) had higher risks of having asthma than Caucasians (8.6%, 95% C.I. 8.5-8.8%). Asians and Pacific Islanders (4.8%, 95% C.I. 4.2-5.5%) had a lower risk of asthma than Hispanics (6.7%, 95% C.I. 6.3-7.1%).⁴⁵ In contrast, African Americans had significantly lower prevalence of coronary artery calcification (84% vs. 62%, $P < 0.001$) and greater than 50% angiographic stenosis (71% vs. 49%, $P < 0.001$) than Caucasians from a study of 782 symptomatic subjects.⁴⁶ Table 1 summarized most of the published reports of asthma coexisting with atherosclerosis in both children and adults.

Mast cells in asthma and atherosclerosis

Mast cells are nearly absent in normal lungs (Figure 2A, left), but accumulate in allergen-challenged asthmatic lungs (Figure 2B, left). These cells are probably the best-known effector cells of allergic asthma and activated *via* the binding of IgE to the high-affinity IgE receptors (FcεRI) on cell surface and many other mechanisms,^{11,47} followed by degranulation and release of granules that contain histamine, leukotrienes, and cytokines to mediate the development of asthma.⁴⁸ Using genetically manipulated mice and mast cell inhibitors, translational studies have been focusing on the potential therapeutic value of targeting mast cells in asthma. House dust mite (HDM)-induced bronchoconstriction in C57BL/6J mice contain significantly more airway and lung connective tissue mast cells than those from saline-treated mice, while no evidence of HDM-induced bronchoconstriction was found in sensitized mast cell-deficient mice *Kit^{W-sh/W-sh}* mice.⁴⁹ Hong et al.⁵⁰ found that the expression of CD1d, a nonpolymorphic MHC I-like molecule, from mast cell surface was enhanced after IgE activation; mast cells from CD1d-deficient (*Cd1d^{-/-}*) mice, however, showed reduced activation of signaling molecules (Ras, Rac1/2, PLA₂, COX-2, NF-κB/AP-1), mediator release (histamines, leukotrienes and cytokines/chemokines), and total IgE levels. *Cd1d^{-/-}* mice also had lower total and OVA-specific serum IgE levels, and fewer BAL fluid mast cells and inflammatory cell recruiting molecules (CCR2/CCL2, VCAM-1, PECAM-1), compared with those from the corresponding wild-type (WT) control mice, suggesting that CD1d-expressed mast cells exacerbate airway inflammation and remodeling through up-regulating IgE production and mediator release in mast cells of OVA-challenged mice. The study also showed that IgE or IgA, produced by surface molecule interactions between B cells and mast cells (CD40–CD40L or OX40–OX40L), may re-activate their corresponding receptors (FcεRI and FcαRI) on mast cell surfaces, followed by the release of various mediators (histamine, leukotrienes, and cytokines).⁵¹ Therefore, antibody targeting of these mast cell activation molecules might offer a potential therapy for allergic asthma.

Besides histamine, leukotrienes, and cytokines, mast cells also release proteases, including their cell type-specific tryptase and chymase that participate in allergic airway inflammation. In humans, those carrying two copies of the α-tryptase allele had significantly higher serum levels of total and HDM-specific IgE and greater atopy severity scores, compared to those carrying one copy of the α-tryptase allele.⁵² Mouse mast cell protease-6 (mMCP-6) is a human β-tryptase ortholog of mice.⁵³ mMCP-6-deficient (*Mcpt6^{-/-}*) mice had reduced

allergic airway hyper-responsiveness, lung inflammation, plasma IgE, and Th2 responses upon OVA sensitization and challenge, although such activity of mMCP-6 depended on the MHC haplotype.⁵⁴ In fact, chymase inhibitor blocked OVA-induced airway hyperresponsiveness.⁵⁵

Few mast cells may appear in the adventitia of normal aortas (Figure 2A, middle and right), but tend to accumulate in the intima and adventitia during atherosclerotic plaque formation and progression (Figure 2B, middle and right). These cells can be activated by pro-inflammatory stimuli, including IgE, cytokines, hypercholesterolemia, and hyperglycemia, and release pro-inflammatory mediators, such as arachidonic acid metabolites, histamine, cytokines (IFN- γ , TNF- α , and IL-4, -5, -6, and -13), chemokines (MCP-1, IL-8, RANTES), platelet activating factor (PAF), and proteolytic enzymes (chymase, tryptase, matrix metalloproteinases, and cysteinyl cathepsins), all of which may participate in the progression and rupture of atherosclerotic plaques.

In a human study of a total of 270 randomly selected patients who suffered from carotid artery stenosis and underwent carotid endarterectomy with a follow-up of 3 years, patients entering the study with symptoms such as transient ischemic attack were found to contain significantly more mast cells in their carotid atherosclerotic plaques compared with those from asymptomatic patients. Further, patients with high numbers of intraplaque mast cells had increased cardiovascular events during the follow-up.³³ Our previous results established the direct participation of mast cells and mast cell-derived IL-6 and IFN- γ in mouse atherogenesis²⁷ and demonstrated that mast cell stabilization with cromolyn reduces lesion inflammation and ameliorates plasma lipid profiles.²⁸ Similarly, the direct involvement of mast cells in the progression of atherosclerosis was also demonstrated by the observation that lower serum levels of total cholesterol and LDL, lower circulating levels of IL-6 and IL-10, and a marked reduction of plaque coverage were found in mast cell-deficient *Kit^{W-sh/W-sh}Apoe^{-/-}* mice than *Apoe^{-/-}* control mice. Also, atherosclerotic lesions from *Kit^{W-sh/W-sh}Apoe^{-/-}* mice contained less T-lymphocytes and macrophage infiltration than those from *Apoe^{-/-}* control mice after maintaining a high-fat diet for 6 months.⁵⁶ Oral administration of the mast cell chymase inhibitor RO5066852 to *Apoe^{-/-}* mice inhibited spontaneous atherosclerotic plaque progression in the thoracic aorta, increased plaque collagen content, reduced necrotic core size, and reduced the incidence and size of mast cell-induced intraplaque haemorrhage, suggesting that chymase inhibition serves as a potential therapeutic modality for atherosclerotic plaque stabilization.³²

In summary, activation of mast cells in asthma might exacerbate the inflammatory response, thereby increasing the risk of severe symptoms of atherosclerosis. In contrast, pharmacological inhibition of mast cell activity might hold a promise for future therapeutic strategies in atherosclerotic plaque progression among asthmatic patients. This hypothesis has recently been tested indirectly in obese and diabetic patients. Patients who received 2 mg/day of the mast cell inhibitor ketotifen had significantly reduced plasma IgE, total cholesterol, LDL, and triglyceride levels, but increased plasma HDL levels.⁵⁷ Although direct use of such mast cell inhibitors among atherosclerotic patients has not been reported, an improved lipid profile after receiving the mast cell inhibitor may mitigate atherosclerosis and associated complications.

Monocytes and macrophages in asthma and atherosclerosis

As Figure 1 illustrates, other major cell types that play a pathogenic role in both asthma and atherosclerosis are monocytes or macrophages. Alveolar macrophages are the key component of pulmonary immune responses. When exposed to allergens, the epithelial barrier and alveolar macrophages are the first line cells that come into contact with inhaled antigens.⁵⁸ Using soluble CD163 (sCD163) as a marker for macrophage activation to investigate the role of macrophages in obese and non-obese children and adults with asthma, elevated serum sCD163 was found in obese asthmatic children. Greater numbers of this macrophage activation marker were revealed in obese female children than in those from obese female adults and male children, demonstrating an age- and sex-specific effect of macrophage activation in asthma from an obese population.⁵⁹ In a dust mite (*Dermatophyoides farina*), ragweed, and *Aspergillus sp.* (DRA) triple-allergen-induced allergic asthma model, bronchial epithelial-derived monocyte chemoattractant protein (MCP-1)/CCL2 expression was found prominently in BAL fluid, concomitant with a rapid appearance of a monocyte-derived population of alveolar macrophages. This suggests that bronchial allergen challenge induces the recruitment of blood monocytes along with chemotactic gradients generated by bronchial epithelial cells.⁶⁰

Macrophage polarization plays an important role in airway inflammatory response. Two main subsets of macrophages have been investigated. These include the pro-inflammatory macrophages as classically activated macrophages (often called M1 macrophages) and anti-inflammatory macrophages as alternatively activated macrophages (also known as M2 macrophages).⁶¹ Previous studies have demonstrated that lipopolysaccharide (LPS) pre-exposition modified the local bronchioalveolar microenvironment by promoting features of M1 macrophages that express nitric oxide, while avoiding M2 macrophage expression of arginase-1 and reducing local factors that drive Th2 type responses, thereby suppressing allergic inflammation.⁶² By quantifying the lung macrophage populations in two established murine models of allergic and non-allergic lung inflammation, data showed that M2 macrophages predominantly localized in the lungs in allergic asthma, while M1-dominant macrophages were more prevalent in non-allergic inflammation, which may contribute to Th1/Th17 responses *via* the transcription factor interferon-regulatory factor 5 (IRF5). Thus, interfering with this polarization may potentially lead to the treatment of different types of lung inflammation.⁶³

Other studies have identified a suppressive role for airway resident macrophages in asthma. Using HDM and OVA murine models of asthma, increased levels of typical allergic asthma-associated cytokines such as interleukin (IL)-4, IL-5, and IL-13, increased eosinophil numbers in BAL fluid, and augmented histologic evidence of inflammatory cell infiltration were detected after depleting resident alveolar macrophages. By contrast, clodronate depletion of circulating monocytes attenuated parameters of allergic inflammation, demonstrating that resident alveolar macrophages suppress, whereas circulating monocytes promote, allergic lung inflammation in murine models of asthma.⁶⁴ It was also noted that the maintenance of the alveolar macrophage pool in the early stages of asthmatic inflammation primarily depended on local proliferation, but not recruitment of precursor blood

monocytes.⁶⁴ Therefore, the function of macrophages in asthma depends on their nature of origin and polarization.

It remains widely accepted that atherosclerosis is an inflammatory disorder in which macrophages play a central role. Studies have been focusing on the influence of gene expression on macrophage functions in experimental atherosclerosis. To investigate the function of glycogen synthase kinase (GSK)-3 α/β in atherosclerosis in *Ldlr*^{-/-} mice, GSK3 α or GSK3 β expression was ablated in hepatic or myeloid cells of *Ldlr*^{-/-} mice. After feeding these mice with a Western diet for 10 weeks, only mice lacking GSK3 α in myeloid cells showed reduced atherosclerotic lesion volume and lesion complexity. Macrophages within atherosclerotic lesions of myeloid GSK3 α -deficient mice, but not of GSK3 β -deficient mice, displayed enhanced expression of the M2 markers and reduced expression of markers associated with M1 macrophage polarization; meanwhile GSK3 α deletion, but not GSK3 β deletion, attenuated the expression of genes associated with M1 polarization while promoting the expression of genes associated with M2 polarization by modulating STAT3 and STAT6 activation in bone marrow-derived macrophages, suggesting that the deletion of myeloid GSK3 α attenuates the progression of atherosclerosis by promoting an M2 macrophage phenotype.⁶⁵ Also, to assess the role of Fc γ receptor IIb (Fc γ R IIb)-signaling in atherosclerosis, apolipoprotein E (ApoE) and Fc γ RIIb double knockout mice congenic to the C57BL/6 background (*ApoE*^{-/-}*Fc γ RIIb*_{B6}^{-/-}) were generated. These mice had smaller atherosclerotic lesions in the aortic root than those of *ApoE*^{-/-} control mice. Macrophages from *ApoE*^{-/-}*Fc γ RIIb*_{B6}^{-/-} mice produced high levels of IL-10, but reduced IL-6, providing a possible mechanism of reduced atherosclerosis in *ApoE*^{-/-}*Fc γ RIIb*_{B6}^{-/-} mice.⁶⁶ Therefore, Fc γ RIIb deficiency may change macrophage phenotypes under this congenic C57BL/6 background.

Recent studies tested the association between MMP7⁺S100A8⁺CD68⁺ M4 macrophages, which is a specific phenotype of macrophage promoted by the platelet chemokine CXCL4,⁶⁷ and atherosclerotic plaque destabilization. Unlike M1 or M2 macrophages that express unique sets of signature cytokines, M4 macrophages do not specifically express M1 or M2 cytokines, and their genes that link to atherogenesis were not consistently up- or down-regulated.⁶⁷ These macrophages can be found reproducibly in coronary artery atherosclerotic plaques, and their prevalence associates with advanced atherosclerosis and indexes of plaque instability,⁶⁸ serving as a surrogate marker of arterial wall inflammation and target for vulnerable plaque therapy.

Therefore, the study of the role of macrophages may advance our understanding of the immunological mechanisms in asthma and identify potential targets for therapeutic manipulation in patients who bear high risk of atherosclerosis. Further studies are needed to elucidate the molecular correlations involved in macrophage-dependent pathobiology and to test whether the modulation of macrophage phenotypes can mitigate asthmatic responses and plaque stabilization.

T lymphocytes in asthma and atherosclerosis

A typical characteristic of asthma is the aberrant accumulation, differentiation, or function of memory CD4⁺ T cells that produce type 2 cytokines (T-helper(Th) 2 cells) including IL-4,

IL-5 and IL-13,⁶⁹ whereas the atherosclerotic lesion contains cytokines that promote a Th1 response rather than a Th2 response.⁷⁰ Therefore, asthma and atherosclerosis may represent different directions of CD4⁺ T-cell differentiation and inflammatory responses.

A number of observations from human studies raise the hypothesis that asthmatic inflammation results from the Th2-mediated pathway. In a study of 12 patients with poorly controlled asthma by inhaled corticosteroids (asthma control test (ACT) score < 20), 12 patients with well-controlled asthma (ACT score ≥ 20), and 8 healthy controls, the expression of Th2 cells was significantly higher in patients with poorly controlled asthma than in those with well-controlled asthma ($P < 0.01$) in the alveolar parenchyma. Furthermore, the alveolar Th2-score (calculated as the logarithmic value of the ratio between Th2 cells/mm² and Th1 cells/mm²) was significantly higher in patients with poorly controlled asthma than in the well-controlled patients and correlated significantly with ACT score, revealing an alveolar Th2-skewed inflammation specifically in asthmatic patients poorly controlled with inhaled corticosteroids.⁷¹ By mapping genome-wide histone modification profiles for subsets of T cells isolated from peripheral blood of healthy and asthmatic individuals, evidence revealed that enhancers in T cells that gained the histone H3 Lys4 dimethyl (H3K4me2) mark during Th2 cell development showed the highest enrichment for asthma-associated single nucleotide polymorphisms (SNPs), supporting a predominant role for Th2 cells in the pathogenesis of asthma.⁷² In a randomized, double-blind, placebo-controlled, multicenter clinical trial of SB010, a novel DNA enzyme that can cleave and inactivate GATA3 (an important transcription factor of the Th2 pathway) messenger RNA, patients with allergic asthma showed significantly attenuated both late and early asthmatic responses and an attenuation of Th2-regulated inflammatory responses in a biomarker analysis of SB010 treatment.⁷³ However, evidence of non-atopic systemic inflammation, with Th1 polarization and monocyte activation, associated with insulin resistance and low HDL among obese urban adolescents with asthma, underlying the association of metabolic abnormalities with pulmonary function.⁷⁴ Therefore, although the imbalance between Th1 and Th2 cells contributes greatly to the initiation and progression of asthma, it remains too simple to classify asthma as a Th2-mediated inflammatory disease.

Accumulating evidence suggests that other subsets of CD4⁺ T cells also contribute to the pathogenesis of asthma. Increased numbers of dual-positive Th2/Th17 cells in BAL fluid from asthmatic patients associated with elevated airway hyper-reactivity, airway obstruction, and relative steroid resistance.⁷⁵ DNA methylation analysis determined the changes in Th17 and regulatory T cell (Treg) counts in the peripheral blood of mild allergic asthmatic patients undergoing allergen inhalation challenge, and the blood Th17/Treg ratio increased significantly after allergen challenge compared to pre-challenge, suggesting the participation of Th17 cells in the development of the late phase inflammatory phenotype.⁷⁶ A cross-sectional study showed that reduced risk of allergic disease among 149 children who had prenatal and postnatal exposure to farm milk relative to the 149 age-matched reference children was due to their increased Treg cell numbers. Peripheral CD4⁺CD25⁺Foxp3⁺ Treg cell numbers associated with doctor-diagnosed asthma and perennial IgE, suggesting a protective effect of Treg cells for the development of childhood allergic asthma.⁷⁷ In a mouse model of chronic allergic asthma, allergen-specific immunotherapy ameliorated airway hyper-responsiveness and airway inflammation by inducing Th1 cells, Foxp3⁺ Treg

cell responses, and IL-10 production. Detailed analyses showed that thymic Treg cells contribute to the effectiveness of immunotherapy by promoting IL-10 production in Foxp3-negative T cells, suggesting that IL-10-producing CD4⁺ T cells are pivotal for the effectiveness of allergen-specific immunotherapy.⁷⁸ However, studies failed to show the significant function of Th17 cells in asthma. In a study of 60 mild-to-severe asthmatic patients and 24 control subjects, reduced numbers of CD3⁺CD4⁺Foxp3⁺ Treg cells were identified in patients with severe asthma and no evidence of dysregulation of the Th17 response was found during cold-induced asthma exacerbations.⁷⁹

Switching in T cell phenotypes caused by the immune response of asthma might affect the progression of atherosclerosis. Numerous studies have focused on the possible relationship between asthma and atherosclerosis by exploring the changes of CD4⁺ T cell subsets. Accelerated atherosclerosis induced by allergic asthma accompanied increased Th2 and Th17 cells but not Th1 cells in the spleen. Further, lesion areas in the aortic root of asthmatic *Apoe*^{-/-} mice was markedly decreased after 8 weeks of treatment with the neutralizing antibodies of IL-4 or IL-17A, which are typical Th2 and Th17 biomarkers.³⁸

Th17 and Th1 cells increased in the spleens of atherosclerotic *Apoe*^{-/-} mice compared with non-atherosclerotic WT littermates. Increased Th17 and Th1 cells associated with the area of atherosclerotic plaque in *Apoe*^{-/-} mice. Treatment with a IL-17-specific antibody markedly suppressed the development of atherosclerotic plaques, whereas treatment with exogenous IL-17 exacerbated plaque formation in *Apoe*^{-/-} mice, indicating a critical role of Th17 in the development of atherosclerosis.⁸⁰ When ApoE-Fc γ -chain double-knockout (DKO) mice were used to investigate the role of activating Fc γ R in the progression of atherosclerosis, reduced atherosclerotic lesions in DKO mice was thought because of reduced Th17 cells and increased Tregs, rather than a Th1/Th2 imbalance. A Th17/Treg shift might be caused by reduced IL-6 production from antigen-presenting cells and impaired STAT3 phosphorylation in these mice.⁸¹ To understand the functions of diverse CD4⁺ lymphocyte subsets in atherosclerotic plaque rupture, a murine model of plaque rupture using a Western diet and collar placement on the carotid artery of *Apoe*^{-/-} mice was established, and plaque rupture was triggered by short-term stimulation with a combination of LPS, phenylephrine injection, and cold temperature. This study suggested that increased Th17 cells and IL-17, rather than Th1 cells and Treg cells, are involved in the disruption of vulnerable plaques triggered by short-term stimulation.⁸² Recently, IL-2/anti-IL-2 neutralizing monoclonal antibody (IL-2/anti-IL-2 mAb) complex has been shown to attenuate the progression of established atherosclerosis *via* selective Treg cell expansion and the suppression of cytokine secretion from CD4⁺ Th1, Th2, and Th17 cells in *Apoe*^{-/-} mice.⁸³ These data suggest that CD4⁺ T cell-mediated immune responses contribute to the development of atherosclerotic plaque.

In conclusion, these previous studies seem to suggest that enhanced Th2, Th17 cells, and decreased Th1 and Treg responses in asthma participate in the development of atherosclerotic plaques, but the potential mechanisms connecting these cell types are not fully understood. Phenotypic switching of peripheral airway CD4⁺ T cell subsets towards pro-atherosclerotic activation may exert beneficial effects among asthmatic patients.

Eosinophils in asthma and atherosclerosis

The unique pathologic features of asthma are the lack of neutrophils and the dominance of eosinophils in the exudative phase.¹ Recruitment of eosinophils from the peripheral blood to the airway following allergen exposure is believed to exacerbate asthma,⁸⁴ and the mechanisms underlying eosinophil recruitment to the lungs mainly involve coordinate actions of vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells,^{85,86} integrin activation,⁸⁷ the chemokine eotaxin, and T cell-derived cytokines such as IL-5.⁸⁸ A genome-wide association scan (GWAS) detected sequence variants associated with the number of blood eosinophils from 9,392 Icelanders. Three asthma and one myocardial infarction susceptibility loci were identified, including SNPs at WDR36, IL-33, and MYB that associated with atopic asthma, and a nonsynonymous SNP at 12q24 in SH2B3 that associated with myocardial infarction.⁸⁹ These observations pointed to the possible association of sequence variants that may affect the eosinophil counts in human asthmatic lungs. Several studies have proven the diagnostic and prognostic value of blood eosinophil counts in asthma. An annual cross-sectional survey of 3,162 patients with asthma showed that patients with higher blood eosinophil counts (400 cells or more per μ l blood) reported more asthma attacks than those with lower eosinophil counts (200 cells or fewer per μ l blood), and the difference was more pronounced in children than in adults.⁹⁰ To determine the association of blood eosinophil counts and asthma events, 12,408 subjects aged 6 to 80 years were selected from the National Health and Nutrition Examination Survey. The intermediate (between 300 to 500 cells per mm^3 of blood) and high (more than 500 cells per mm^3 of blood) blood eosinophil counts associated independently with asthma, asthma attacks, and asthma-related emergency department visits within a 12-month frame, suggesting that phenotyping and individualized treatment with regard to both local and systemic eosinophilic inflammation should be determined in asthmatic patients.⁹¹ Therefore, targeting eosinophilic airway inflammation could be an advantageous strategy for asthmatic intervention. Indeed, treatment for sputum eosinophil count normalization reduced asthma exacerbations and hospital admissions.⁹² In a multicenter, double-blind, placebo-controlled trial to test the efficacy and patient characteristics associated with the response to mepolizumab, a selective inhibitor of eosinophilic airway inflammation, the rate of clinically significant exacerbations was reduced in response to different doses of mepolizumab compared with the placebo group, indicating that mepolizumab significantly reduced the number of asthma exacerbations in patients with severe eosinophilic asthma.⁹³ To assess the efficacy and safety of reslizumab, a humanized anti-IL-5 monoclonal antibody that disrupts eosinophil maturation and promotes programmed cell death in patients with inadequately controlled, moderate-to-severe asthma, two duplicate, multicentre, double-blind, parallel-group, randomized, placebo-controlled phase 3 trials were carried out and the results showed that patients who received reslizumab had a significant reduction in the frequency of asthma exacerbations, compared with those who received the placebo. These findings support the use of reslizumab in patients with asthma and elevated blood eosinophil counts who were inadequately controlled on inhaled corticosteroid-based therapy.⁹⁴

Eosinophils are multifunctional leukocytes implicated in the pathogenesis of numerous inflammatory processes, which also includes atherosclerosis. Though rarely present in human atherosclerotic tissue,⁹⁵ eosinophils may contribute to the progression of plaques in

coronary arteries leading to myocardial infarction by releasing from their granules mediators including many potent inducers of inflammatory and immune responses.⁹⁶ Eosinophils serve as novel biomarkers for risk stratification of patients with atherosclerosis and related coronary artery diseases (CAD). High peripheral eosinophil counts ($0.29 \times 10^9 \sim 0.43 \times 10^9$ cell per liter of blood) before percutaneous coronary intervention (PCI) associated with improved outcomes within the first 6 months, but there was an increased risk of mortality after this period.⁹⁷ Positive correlation was detected between blood eosinophil counts and mean IMT of the common carotid artery, an indicator of carotid atherosclerosis and CAD.⁹⁸ A cohort of 3,742 patients undergoing non-urgent coronary angiography were included to investigate the relationship between blood absolute eosinophil counts and the prevalence and extent of CAD. Among this population, high absolute eosinophil counts (more than 200 cell per μ l blood) correlated to several established cardiovascular risk factors, including hypertension, smoking, renal failure, and lipid and glycemic profiles, but did not independently associate with the prevalence and extent of CAD.⁹⁹ Moreover, eosinophilic cationic protein (ECP), a sensitive marker of eosinophil activation,¹⁰⁰ associated with overall major adverse cardiac event rate, including hard endpoints such as cardiac death and myocardial infarction after bare metal stent implantation, suggesting that an allergy-mediated inflammation against the metal explains some of the adverse reactions that occur after coronary stenting.¹⁰¹

These studies suggest that high blood eosinophil counts constitute an independent predictor of adverse outcomes in patients with CAD and lead to the identification of novel targets for treatments. Therefore, therapies that target eosinophilic disorders may help control asthma and atherosclerosis.

Smooth muscle cells in asthma and atherosclerosis

Besides the known contribution of smooth muscle cells (SMCs) to increased airway thickening and narrowing during airway remodeling, airway SMCs also play a key role in asthmatic airways by virtue of the expression of cytokines, chemokines, proteases, and growth factors¹⁰² that exert essential function in orchestrating the inflammatory response within the bronchial wall.¹⁰³ For example, monocyte-derived fibrocytes promote airway SMC production of IL-8 and IL-6 in asthmatic subjects, indicating a pro-inflammatory role for fibrocytes in modulating the secretion of immunomodulatory factors of airway SMCs in asthmatic patients.¹⁰⁴ MicroRNAs (miRs) are post-transcriptional regulators of gene expression that have been linked to a number of pathologies including asthma. In airway SMCs, pro-inflammatory cytokines induce the expression of miR-146a and -146b, especially in cells from asthmatic patients. Both miR-146a and miR-146b negatively regulate COX-2 and IL-1 expression at pharmacological levels. Therefore, miR-146a and/or miR-146b contribute to the pathogenesis of asthma by modulating airway SMC inflammatory mediator expression and these miR-146 mimics may be attractive candidates for anti-inflammatory treatments of asthma.¹⁰⁵

In the arterial wall, phenotypic changes in vascular SMCs from the contractile type towards the pro-inflammatory type contribute to the progression of atherosclerosis. It was recently reported that myocardin, a powerful myogenic transcriptional co-activator, is a central negative regulator of vascular SMC inflammatory activation and promotes the onset of

vascular disease.¹⁰⁶ Cultured vascular SMCs from myocardin-heterozygous mice (*Myocd*^{+/-} mice) retained increased inflammatory activation potential, compared with those from WT control mice. Conversely, increased expression of myocardin in vascular SMCs suppressed the induction of an array of inflammatory cytokines and chemokines while it up-regulated anti-inflammatory mediators. This suggests that maintaining or increasing myocardin expression can protect aortic and coronary artery SMCs from entering dysfunctional programs of inflammatory activation. Lentiviral overexpression of neuron-derived orphan receptor-1 (NOR-1) also significantly reduced LPS (100 ng/ml, for 24 h)-induced expression of cytokines (IL-1 β , -6 and -8) and chemokines (MCP-1 and CCL20) in human vascular SMCs with a mechanism that NOR-1 impaired NF- κ B-mediated transcriptional activation and interfered NF- κ B signaling pathway in vascular SMCs, postulating a role for NOR-1 as a potentially relevant player in modulating vascular inflammation.¹⁰⁷

These studies suggest that the same mechanisms of SMC activation and phenotypic changes apply to both the airway and vasculature. Indeed, SMC migration and proliferation are common features of atherosclerotic lesion intima thickening and airway narrowing.^{108,109} Effective inhibition of SMC activation or proliferation may mitigate both these inflammatory diseases.

Leukotrienes in asthma and atherosclerosis

Leukotrienes are identified as a class of eicosanoids that are synthesized upon activation of 5-lipoxygenase (5-LO, encoded by ALOX5), which is expressed in bone marrow-derived cells such as neutrophils, monocytes, macrophages, dendritic cells, and mast cells, and catalyzes the transformation of arachidonic acid into leukotriene A4 (LTA4).¹¹⁰ LTA4 is subsequently converted into either LTB4 or LTC4 by the action of LTA4-hydrolase (LTA4-H) and LTC4-synthase (LTC4-S), respectively.¹¹¹ Leukotrienes are considered important mediators of bronchial asthma and leukotriene receptor antagonists are recommended as effective anti-asthmatic medications. The effects of prostaglandin D2 (PGD2), leukotriene E4 (LTE4), and their combination on human Th2 cells have been tested to enhance Th2 responses and marked production of diverse non-classical Th2 inflammatory mediators, including IL-22, IL-8, and GM-CSF. Combined inhibition of both PGD2 and LTE4 pathways might provide an effective therapeutic strategy for asthma.¹¹²

Recently, these findings have been extended to atherosclerosis and CAD. Several clinical trials demonstrated the protective role of leukotriene pathway inhibitors in atherosclerosis. A genetic association study of 5-LO activating protein (FLAP, encoded by ALOX5AP) and LTA4-H from the leukotriene biosynthesis pathway was performed in a family-based research of early onset CAD. Association of SNPs in ALOX5, the target of ALOX5AP, with CAD ($P < 0.05$) as well as statistical evidence for interactions among ALOX5, ALOX5AP, and LTA4-H with varying degrees of atherosclerosis were detected, pointing to the importance of modulating the leukotriene biosynthesis pathway in determining atherosclerosis.¹¹³ Genetic variations of the 5-LO/leukotriene pathways also correlate with the risk of atherosclerosis. The expression of FLAP and LTB4, at both mRNA and protein levels, was increased in poly-morphonuclear cells from 120 patients with obstructive sleep apnea compared with those from 33 healthy subjects, and associated with carotid luminal

diameter and IMT.¹¹⁴ Zhao et al.¹¹⁵ analyzed sequence variants within ALOX5AP and LTA4-H genes with 32 SNPs in 169 Caucasian twin pairs from the Vietnam Era Twin Registry, and identified a novel leukotriene haplotype in LTA4-H, which was designated HapE. This haplotype associated significantly with carotid IMT. Twins which carried HapE had significantly lower carotid IMT (742 m vs. 701 m, $P=0.0007$), suggesting a potential protective role of HapE toward subclinical atherosclerosis. Similarly, associations between polymorphisms in ALOX12, ALOX15, ALOX5, and ALOX5AP genes with subclinical measures of atherosclerosis (IMT, coronary, carotid and aortic calcified plaque) were detected in genotyping results from the European American diabetic ($n=828$) and nondiabetic ($n=170$) siblings.¹¹⁶ Furthermore, the expression of FLAP and LTA4-H exhibited significant genetic correlations with arterial thrombosis, indicating significant pleiotropy underlying the covariation between these phenotypes and risk of arterial thrombosis.¹¹⁷ By applying 5-LO inhibitor VIA-2291 (Atreleuton) in patients with recent acute coronary syndrome, a reduction in non-calcified plaque volume at 24 weeks was observed in VIA-2291-treated groups *versus* the placebo-treated group with a 64-slice coronary CT examination, suggesting that a reduction in leukotriene production reduced atherosclerosis complications.¹¹⁸

However, conflicting observations were also obtained from an experimental model system and from clinical trials. In atherosclerosis-prone *ApoE*^{-/-} mice, 5-LO deficiency or pharmacological inhibition did not affect atherosclerotic lesion development in the aortic root, brachiocephalic artery, and throughout the whole aorta.¹¹⁹ In a phase II, randomized, double-blind, parallel-group study of 52 patients with recent acute coronary syndrome assigned 1:1 to either 100 mg 5-LO inhibitor VIA-2291, or placebo for 24 weeks, 5-LO inhibition did not improve significantly the vascular inflammation as assessed by ¹⁸F fluorodeoxyglucose positron emission tomography (FDG-PET) or blood inflammatory marker C-reactive protein levels in these patients, despite the significant inhibition of chemo-attractant LTB₄ in both blood and urine.¹²⁰ It is possible that such negative observations may be due to the relative small sample limitation. Larger trials may be required to confirm these observations.

Nevertheless, genetic variations of the 5-LO/leukotriene pathway may partially explain the increased prevalence of atherosclerosis in patients with asthma. Pharmacological interruption of the 5-LO/leukotriene pathway may become a potential therapeutic approach for these patients.

Interaction between asthma and lipid metabolism

Studies from humans and animals indicated that dyslipidemia is a traditional risk factor of atherosclerosis, and intensive lipid-lowering therapies with statins reduce the progression of atherosclerosis.¹²¹ However, increasing evidence suggests a close association between dyslipidemia and asthma-associated morbidity.

Clinical investigations have provided important clues to the role of lipid metabolism in the pathogenesis of asthma. Studies from a total of 17,994 children, 4 to 12 years old, living in predominantly rural West Virginia and enrolled in kindergarten, second, or fifth grade showed that serum triglycerides significantly associated with asthma, regardless of body

mass index percentile and after controlling for sex and smoke exposure (log-transformed; $P = 0.011$).¹²² In a population of 150 asthmatic patients at the Miyatake Asthma Clinic (Osaka, Japan), a higher prevalence of dyslipidaemia was seen in patients with carotid atherosclerosis than in those without ($P = 0.003$), and the mean daily dose of inhaled corticosteroids was significantly lower for patients with carotid atherosclerosis than for those without ($P = 0.02$).¹²³ Another study explored the association between serum lipids among Cypriot children aged 11-12 years and the prevalence of asthma between the ages of 15-17 years. In 3,982 children, serum HDL-C at baseline was significantly lower in subjects who at follow-up had ever asthma and active asthma in comparison with those without asthma. Furthermore, after adjusting for age, gender, nationality, birth order, parental education, active smoking, passive smoking, ownership of animal(s) inside or in the yard of the house, BMI and fitness at baseline, serum HDL-C values <40 mg/dL conferred increased ORs for ever asthma (OR: 1.89; 95% CI, 1.19-3.00) and active asthma (OR: 1.89; 95% CI, 1.02-3.53), suggesting the potential role of HDL in the pathogenesis of pediatric asthma.¹²⁴

In addition to the aforementioned clinical studies, observations from experimental animals also suggest a possible relationship between hypercholesterolemia and asthma. Both *Ldlr*^{-/-} and *ApoE*^{-/-} mice are prone to hypercholesterolemia, especially after consuming a Western diet.⁵ In these mice, HDM challenge induced airway hyper-reactivity, goblet cell hyperplasia, eosinophilic airway inflammation, serum IgE production, and the expression of Th2 and Th17 cytokines. Administration of an ApoE(130-149) mimetic peptide alleviates these asthmatic phenotypes in *ApoE*^{-/-} mice, but not in *Ldlr*^{-/-} mice.¹²⁵ These observations suggest an ApoE-LDL receptor pathway as an endogenous negative regulator of airway hyper-reactivity in asthma. ApoE mimetic peptide may serve as a novel therapeutic regimen for asthma. The role of very low-density lipoprotein (VLDL) receptor in attenuating HDM-induced airway inflammation was also demonstrated in experimental murine asthma. In VLDL receptor-deficient mice, HDM-induced eosinophilic and lymphocytic airway inflammation, and serum Th2 cytokines, C-C chemokines, IgE production, and mucous cell metaplasia were all enhanced. Adoptive transfer of bone-marrow-derived dendritic cells from VLDL receptor-null mice to WT mice enhanced asthmatic phenotypes, proving the VLDL receptor as a negative regulator of dendritic cell-mediated adaptive immune responses in HDM-induced allergic airway inflammation.¹²⁶

Above observations from humans and mice suggest that statin application with lipid-lowering effect will also benefit patients with asthma. Indeed, statin use associated with decreased risk of hospitalization in patients with asthma in a nationwide population-based study of 11,808 patients.¹²⁷ In a murine model of allergic asthma, simvastatin displayed anti-inflammatory activity by reducing the total inflammatory cell infiltration, eosinophilia, and Th2 lymphocyte-related cytokines (IL-4 and IL-5) in BAL fluid.¹²⁸ However, different observations were made from a small and randomized double-blind crossover trial. Patients who had one month of treatment with simvastatin did not differ from those treated with a placebo in exhaled nitric oxide, methacholine hyper-responsiveness, and other inflammatory outcomes, lung volumes, or airway resistance.¹²⁹ It was explained that statin treatments may cause preferential switching of Th1 immunity towards Th2 immune responses.^{130,131} Therefore, ineffectiveness of simvastatin from this small population may not exclude a

pathogenic role of dyslipidemia in asthma. Different methods of lipid regulation other than statin may act as better medications for asthmatic patients.

Possible management approach for both asthma and atherosclerosis

The hypothesis that asthma is a risk factor of atherosclerosis offers new opportunities for the treatment of atherosclerosis. Pharmacotherapeutic studies have shown that the treatment of asthma may improve the outcomes of atherosclerosis. The notion that both asthma and atherosclerosis involve extensive inflammatory cell accumulation and interactions, although at a different site, leads to the possibility that anti-inflammatory drugs such as glucocorticoids might improve the outcomes of CAD in asthmatic patients. Systemic approaches such as immunotherapy may improve the treatment of both disease states simultaneously. Table 2 shows potential benefits of therapies for both asthma and atherosclerosis. Those include lipid lowering statins, 5-LO inhibitor VIA-2291, and various corticosteroids.^{118,123,127,128} Of note, differences in drug formulation and dosing methods may also affect efficacies when applied to different diseases. For example, current guidelines recommend inhaled corticosteroid treatment for the management of asthma,¹³² and trials using inhaled corticosteroid have also improved atherosclerosis. In a study of 150 non-hospitalized Japanese asthmatic patients, the use of inhaled corticosteroids correlated negatively to atherosclerosis (IMT) of the carotid arteries. Inhaled corticosteroid-treated patients had less atherosclerotic burden than the untreated group.¹²³ However, oral corticosteroids may increase the risk of acute myocardial infarction¹³³ while the inhaled corticosteroids may reduce the risk of acute myocardial infarction in a different study.¹³⁴

In addition to corticosteroids, statins, and 5-LO inhibitors that have been tested to treat atherosclerosis in humans (Table 2), we anticipate that the mast cell inhibitors ketotifen and cromolyn, or anti-IgE antibody omalizumab may comprise the next generation of anti-asthmatic drugs for patients with atherosclerosis. Both ketotifen and cromolyn are mast cell inhibitors that have been used to treat asthma.¹³⁵⁻¹³⁷ We have shown that intraperitoneal administration of cromolyn reduced atherosclerotic lesion growth in the aortic arch and thoracic-abdominal aorta by blocking mast cell activation.²⁸ Our recent unpublished data demonstrated that inhaled ketotifen acted the same as inhaled corticosteroid budesonide in reducing aortic arch atherosclerotic lesion T cell contents, mast cell numbers, lesion cell proliferation and apoptosis, and angiogenesis in mice with concurrent development of OVA-induced airway hyper-responsiveness and diet-induced atherosclerosis, although intima sizes in ketotifen- or budesonide-treated *Apoe*^{-/-} mice were not different from those of saline-treated *Apoe*^{-/-} mice. In this study, mice were nebulized with ketotifen at 70 mg in 5 mL saline for 3 months at 25 min per day. Topical application of ketotifen in the sinonasal tract and respiratory tract at this dose may not necessary affect efficiently the mast cells in the arterial wall, which may explain insignificant changes in atherosclerosis lesion area in these mice. It is possible that increased dose of ketotifen inhalation or direct administration *via* gavage or intravenous injection may exert different efficacies in alleviating atherosclerosis in these mice. Although there is no direct human trial to test whether these mast cell inhibitors are also effective among patients with atherosclerosis, recent studies showed that the oral administration of ketotifen at 2 mg/day significantly reduced body weight and fasting blood glucose, blood total cholesterol, LDL, and triglyceride levels, but increased significantly

blood HDL and adiponectin.⁵⁷ Therefore, it is possible that the activity of ketotifen in reducing LDL, triglyceride, and total cholesterol levels, and in increasing HDL may ameliorate atherosclerosis in humans. Administration of ketotifen or cromolyn, by inhalation or oral administration, may efficiently block atherogenesis.

IgE activates mast cells, macrophages, and T cells.¹⁴⁰ Anti-IgE antibodies, such as omalizumab (Xolair®) may demonstrate therapeutic efficacies not only among patients with allergy or asthma,^{141,142} but also those with atherosclerosis, although there is currently no direct evidence from human or experimental atherosclerosis to test this hypothesis. In *Apoe*^{-/-} mice, anti-IgE antibody prevented angiotensin II (Ang-II) infusion-induced abdominal aortic aneurysms (AAA).¹⁴⁰ We recently reported that the same antibody also blocked allergic lung inflammation-induced AAA in mice.¹⁴³ These experiments suggest indirectly that anti-IgE antibody also mitigates atherogenesis, but the US Food and Drug Administration's Adverse Event Reporting System (AERS) epidemiological study challenged this hypothesis. In the AERS study, the use of omalizumab associated with the risk of arterial thrombotic events.¹⁴⁴ In contrast, patients with severe asthma and cardiovascular complications showed significant improvement in plasma biomarkers of asthma and atherosclerosis after 20 months of medication,¹⁴⁵ although this study had fewer than 300 patients in total.

Pathophysiologically different from allergic asthma, which is induced after exposing to allergens, non-allergic asthma may be caused by anxiety, stress, exercise, cold air, dry air, hyperventilation, smoke, viruses or other irritants. These patients may be also at a high risk of atherosclerosis, yet a direct evidence is not available to prove this hypothesis. However, patients with non-allergic asthma also have elevated plasma high sensitivity C reactive protein (HsCRP) and IgE,^{146,147} all which are significant risk factors of atherosclerosis.^{140,148}

Conclusion and perspective

Although asthma and atherosclerosis both are chronic inflammatory diseases, they affect different organs with different immunological mechanisms of pathogenesis. While asthma remains prone to developing Th2 immune responses, Th2 immunity mitigates atherosclerosis. Based on this scenario, patients and animals with asthma should be protected from atherosclerosis. In fact, this has never been the case. In experimental models and in humans, subjects with asthma have a significantly higher chance of developing atherosclerosis or having larger IMT than those without asthma. Therefore, other inflammatory cells and mechanisms also participate importantly in the pathogenesis of both diseases. Indeed, emerging evidence suggests that one medication may hit the same target in both diseases, although asthma and atherosclerosis traditionally have been treated as separate diseases. It is possible that common drugs for atherosclerosis, such as statins, may come to be prescribed for asthmatic patients, and those for asthma, such as leukotriene inhibitors or mast cell stabilizers and anti-IgE antibodies, may be effective in treating atherosclerosis.

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Figure 1. Important players in asthmatic lung and atherosclerotic lesion and possible interaction between the two inflammatory diseases.

Figure 2.

Toluidine blue staining detected mouse tissue mast cells. **A.** Lung (left), aortic root (middle), and brachiocephalic trunk (right) from normal mice. **B.** Lung from OVA-induced airway hyper-responsiveness (left) and aortic root (middle) and brachiocephalic trunk (right) from Western diet-induced atherosclerosis from *Apoe*^{-/-} mice. Scale: 200 µm, inset: 50 µm.

Table 1

Studies reporting the co-existence of asthma and atherosclerosis.

Authors	Number of patients	Study name	Study type
Donohue KM, et al 2013 [138]	446 asthma cases and 2,925 participants without asthma	Multi-Ethnic Study of Atherosclerosis (MESA)	Multicenter cohort study
Vijayakumar J, et al 2013 [43]	34 patients with mild asthma and 68 matched non-asthmatic controls		Case-control study
Jaakkola U, et al 2012 [139]	1116 asthma cases and 2,925 participants without asthma	cardiovascular risk in young Finns study	Multicenter cohort study
Otsuki M, et al 2010 [123]	150 asthmatic patients and 150 matched non-asthmatic controls		Case-control study
Onufrak S, et al 2007 [39]	12868 participants without asthma and 759 asthma cases	Atherosclerosis Risk in Communities (ARIC)	Prospective population-based study
Schanen JG, et al 2005 [44]	709 asthma cases and 13088 participants without asthma	Atherosclerosis Risk In Communities (ARIC)	Multicenter prospective study
Knoflach M, et al 2005 [40]	436 non-AS subjects and 390 atherosclerosis subjects	Bruneck Study	Prospective population-based survey
Knoflach M, et al 2005 [40]	100 low intima-media thickness (IMT) subjects and 41 high IMT subjects	Atherosclerosis Risk Factors in Male Youngsters [ARMY] study	Prospective population-based survey
Iribarren C, et al 2004 [41]	13047 asthma cases and 138573 participants without asthma		Retrospective cohort study

Table 2

Potential benefits of therapies for both asthma and atherosclerosis.

Authors	Study name	Study type	Conclusion
Huang CC, et al 2011 [127]	Statin use in patients with asthma	A nationwide population-based study	Statin use is associated with reduced hospitalization in patients with asthma.
McKay, et al 2004 [128]	A Novel anti-inflammatory role of simvastatin in a murine model of allergic asthma	A murine model of allergic asthma	Simvastatin treatment is effective in allergic airways disease.
Otsuki , et al 2010 [123]	Reduced carotid atherosclerosis in asthmatic patients treated with inhaled corticosteroids	A case-control study	Inhaled corticosteroids may have protective effects against atherosclerosis.
Tardif, et al 2010 [118]	Treatment with 5-lipoxygenase inhibitor VIA-2291 (Atreleuton) in patients with recent acute coronary syndrome	A double-blinded study	Reduction in leukotriene production may influence atherosclerosis.