ORIGINAL ARTICLES

Allergic lung inflammation promotes atherosclerosis in apolipoprotein E-deficient mice

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Inflammation drives asthma and atherosclerosis. Clinical studies suggest that asthmatic patients have a high risk of atherosclerosis. Yet this hypothesis remains uncertain, given that Th2 imbalance causes asthma whereas Th1 immunity promotes atherosclerosis. In this study, chronic allergic lung inflammation (ALI) was induced in mice by ovalbumin sensitization and challenge. Acute ALI was induced in mice by ovalbumin and aluminum sensitization and ovalbumin challenge. Atherosclerosis was produced in apolipoprotein E-deficient (*Apoe*$^{-/-}$) mice with a Western diet. When chronic ALI and atherosclerosis were produced simultaneously, ALI increased atherosclerotic lesion size, lesion inflammatory cell content, elastin fragmentation, smooth muscle cell (SMC) loss, lesion cell proliferation, and apoptosis. Production of acute ALI before atherogenesis did not affect lesion size, but increased atherosclerotic lesion CD4^{+} T cells, lesion SMC loss, angiogenesis, and apoptosis. Production of acute ALI after atherogenesis also did not change atherosclerotic lesion area, but increased lesion elastin fragmentation, cell proliferation, and apoptosis. In mice with chronic ALI and diet-induced atherosclerosis, daily inhalation of a mast cell inhibitor or corticosteroid significantly reduced atherosclerotic lesion T-cell and mast cell contents, SMC loss, angiogenesis, and cell proliferation and apoptosis, although these drugs did not affect lesion area, compared with those that received vehicle treatment. In conclusion, both chronic and acute ALI promote atherogenesis or aortic lesion pathology, regardless whether ALI occurred before, after, or at the same time as atherogenesis. Antiasthmatic medication can efficiently mitigate atherosclerotic lesion pathology. (Translational Research 2016;171:1–16)

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Abbreviations: ALI = allergic lung inflammation; SBP = systolic blood pressure; DBP = diastolic blood pressure; Apoe = apolipoprotein E; SMC = smooth muscle cell; IMT = intima-media thickness; OR = odds ratio; CI = confidential interval; OVA = ovalbumin; MHC II = major histocompatibility complex class II; BALF = bronchoalveolar lavage fluid; MCP-1 = monocyte chemoattractant protein-1; LDL = low-density lipoproteins; HDL = high-density lipoprotein; CatS = cathepsin S; CatK = cathepsin K

AT A GLANCE COMMENTARY

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Background

Both atherosclerosis and asthma are chronic inflammatory diseases. Prior studies demonstrated that patients with allergic disorders, such as asthma have several folds higher risk of developing atherosclerosis, suggesting an interaction between the 2 human diseases. Using both chronic and acute allergic lung inflammation mouse models and atherogenic diet-induced atherosclerosis in apolipoprotein E-deficient mice, we demonstrated that production of allergic lung inflammation, before, after, or at the same time as atherosclerosis induction–enhanced mouse atherosclerotic lesion size or lesion pathologies. Many of these lesion characters can be efficiently improved after mice were given antiasthmatic medications, including mast cell inhibitor ketotifen and glucocorticoid budesonide.

Translational Significance

Antimast cell inhibitors, glucocorticoids, and other common antiasthmatic medications may be efficient in mitigating atherosclerosis in humans.

INTRODUCTION

Inflammation drives both asthma and atherosclerosis, diseases that share many pathologies. This includes the accumulation of inflammatory cells in the allergic lung airway and arterial wall, including macrophages, T cells, mast cells, eosinophils, or neutrophils.[1-5] These cells release various inflammatory cytokines to induce airway narrowing and arterial wall thickening, matrix protein catabolism, cell proliferation, or apoptosis.[4-7] In humans and mice, the development of allergic asthma associates with an increase of peripheral Th2 cytokines, including IL4, IL5, and IL13.[8,9] In contrast, patients with atherosclerosis often have reduced plasma IL4, IL5, and IL13, but increased circulating Th1 cytokines, such as IFN-γ, IL6, and TNF-α,[10,11] although patients with either asthma or atherosclerosis all have increased plasma IgE and chemokines, including monocyte chemoattractant protein-1 (MCP-1) and eotaxin, that mediate blood-borne leukocyte migration and accumulation at the site of injury.[12-19] These pathological differences and similarities suggest an interaction between these 2 common human inflammatory diseases.

Prior studies in a survey of patients from several U.S. states demonstrated that patients with adult-onset asthma had significantly larger carotid artery intima-media thickness than those of nonasthmatics.[20] Patients with allergic disorders, including allergic rhinitis and asthma selected from random samples from Bruneck, Italy, had several folds higher risk of atherosclerosis (odds ratio [OR]: 3.8; 95% confidential interval [CI]: 1.4–10.2, $P = 0.007$).[21] A small cross-sectional evaluation of 141 men aged 17–18 years in Innsbruck, Austria, showed that participants with the same allergic disorders have several folds higher risk of developing large intima-media thickness (OR: 2.5; 95% CI: 1.1–5.5; $P = 0.01$).[21] In a much larger cohort of 70,047 men and 81,573 women from Northern California, evidence again showed asthma as a significant risk factor (OR: 1.22, 95% CI: 1.14–1.31, $P < 0.001$) of coronary heart disease before or after adjusting for several common risk factors of atherosclerosis, including smoking, alcohol consumption, body mass index, plasma cholesterol levels, white blood cell count, hypertension, diabetes, and several others.[22] Yet a large biracial cohort of 13,501 middle-aged adults between 45 and 64 years old with 14 years of follow up study did not reveal an association between asthma and cardiovascular disease incidence.[23] It is possible that the varying risk of asthma or atherosclerosis among different races caused this insignificance.[24,25]

A recent study assessed the risk of allergic asthma in atherosclerosis-prone apolipoprotein E-deficient ($Apoe^{-/-}$) mice sensitized with ovalbumin (OVA) together with aluminum, followed by OVA nebulization 3 times a week. OVA-induced airway allergic inflammation increased atherosclerotic lesion sizes in the aortic root, along with increased lesion macrophages, increased splenic Th17 and Th2 cells, and reduced splenic regulatory T cells, without affecting splenic Th1 cell population.[26] Using OVA to sensitize $Apoe^{-/-}$ mice followed by OVA weekly nebulization to develop