Interaction between allergic asthma and atherosclerosis

CONG-LIN LIU, JIN-YING ZHANG, and GUO-PING SHI

ZHENGZHOU, CHINA AND BOSTON, MASS

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 2 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 T-helper (Th)2–oriented disease, whereas Th1 immunity promotes atherosclerosis. In addition to the preferred Th1/Th2 responses that may differentiate the 2 diseases, mast cells and many other inflammatory cells also contribute to their pathogenesis by 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 2 diseases, although limited investigations are available to delineate the molecular and cellular mechanisms by which 1 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 antiasthmatic medications or that the therapeutic regimens targeting atherosclerosis may also alleviate allergic asthma. (Translational Research 2016;174:5–22)

Abbreviations: BAL = bronchoalveolar lavage; LDL = low-density lipoprotein; SMC = smooth muscle cell; TNF- = tumor necrosis factor-; LDLr = LDL receptor; Apoe = apolipoprotein E; OVA = ovalbumin; IMT = intima-media thickness; SMCs = smooth muscle cells; CI = confidence interval; OR = odds ratio; SUVmax = maximum standardized uptake value; MHC-I = major histocompatibility complex class-I; CHD = coronary heart disease; HDM = House dust mite; mMCP-6 = Mouse mast cell protease-6; MCP-1 = monocyte chemoattractant protein-1; PLA2 = phospholipase A2; COX-2 = cyclooxygenase-2; NF-B = nuclear factor-B; AP-1 = activator protein-1; RANTES = regulated on activation, normal T cell expressed and secreted; CCR2/CCL2 = chemokine (C-C Motif) Receptor 2/chemokine (C-C motif) ligand 2; PECAM-1 = platelet endothelial cell adhesion molecule-1; MCP-1 = monocyte chemoattractant protein-1; DRA = dust mite (Dermatophagoides farinae), ragweed, and Aspergillus sp.; LPS = lipopolysaccharide; GSK = glycogen synthase kinase; STAT-3 = signal transducer and Activator of transcription-3; CXCL4 = CXC chemokine ligand 4; ACT = asthma control test; SNPs = single nucleotide polymorphisms; GATA3 = GATA binding protein 3; Treg = regulatory T cell; CADs = coronary artery diseases; miRs = MicroRNAs; NOR-1 = neuronderived orphan receptor-1; 5-

From the Department of Cardiology, Institute of Clinical Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass.

Submitted for publication August 2, 2015; revision submitted September 25, 2015; accepted for publication September 29, 2015.

Reprint requests: Guo-Ping Shi, Cardiovascular Medicine, Brigham and Women's Hospital, 77 Avenue Louis Pasteur, NRB-7, Boston, MA 02115; e-mail: gshi@rics.bwh.harvard.edu.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.09.009

LO = 5-lipoxygenase; LTA4 = leukotriene A4; GM-CSF = granulocyte-macrophage colony-stimulating factor; FLAP = 5-LO–activating protein; HDL-C = high-density lipoprotein cholesterol; VLDL = very low-density lipoprotein

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 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 suggests 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 as the signature cells in asthmatic lungs and play detrimental roles in allergic responses after activation by allergen-induced immunoglobulin E (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 antiasthmatic 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, tumor necrosis factor-α (TNF-α), and histamine to induce vascular cell apoptosis.[24-26] In atherosclerosis-prone LDL receptor–deficient ($Ldlr^{-/-}$) mice, mast cell deficiency or pharmacologic 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 2 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 T-helper (Th)2 and Th17 cells in the spleen.[38] In this review, we will discuss the activities of each major cell type that remain as important contributors of asthma and atherosclerosis, including mast cells, monocyte and macrophages, T cells, eosinophils, and smooth muscle cells (SMCs; Fig 1).

PREVALENCE OF ATHEROSCLEROSIS IN ASTHMATIC PATIENTS

Asthma and atherosclerosis share several common pathologic 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