Clinical Pathology and Treatment of Renin-Angiotensin System

3. Atherosclerosis and the Renin-Angiotensin System

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Atherosclerosis and Angiotensin II

Atherosclerosis is an inflammatory disease characterized by endothelial dysfunction, thereby leading to the accumulation of macrophage-derived foam cells in the vessel wall. Endothelial cells, intimal smooth muscle cells, and leukocytes produce a wide range of inflammatory cytokines, chemokines, and growth factors in the multifactorial process of atherosclerosis. Angiotensin II (Ang II) has been shown to amplify this inflammatory process by exaggerating the production of reactive oxygen species, inflammatory cytokines, and adhesion molecules, which further facilitate monocyte/macrophage recruitment, enhancing oxidative stress, and activating various signaling pathways and gene expressions involved in atherogenesis. Accumulated evidence has demonstrated that Ang II receptor blocker (ARB) reduces lesion formation in atherosclerosis-prone animals, and improves endothelial dysfunction in humans.

Two major Ang II receptor subtypes have been characterized, Ang II type 1 (AT1) and type 2 (AT2) receptor. Recent studies clearly demonstrated that atherosclerotic lesion development is markedly attenuated in AT1 receptor/apolipoprotein E-deficient (apoE-KO) mice and AT1/LDL receptor-deficient mice. These findings indicate that AT1 receptor exerts a pro-atherogenic action by augmentation of vascular oxidative stress and/or hypercholesteremia-induced stimulation of angiotensin peptide production.

The Role of AT2 Receptor in Atherosclerosis

The AT2 receptor expression is known to be restricted in the adult cardiovascular system; however it is upregulated in various pathological conditions. Recently, AT2 receptor has been shown to be expressed in muscular media in the aorta as well as in the endothelial cells of resistant arteries, and subsequently it is increased in the aorta from apoE-KO mice after an atherogenic diet. We previously generated AT2 transgenic (AT2-Tg) mice with targeted overexpressed AT2 in vascular smooth muscle cells (VSMCs), and revealed that AT2 in VSMCs promotes intracellular acidosis by blocking the amiloride-sensitive Na+/H+ exchanger, leading to kininogense activation followed by bradykinin release (from VSMCs) that causes endothelial NO-dependent vasodilation and anti-pressor response to Ang II. To elucidate this AT2-mediated signaling pathway in the development of atherosclerosis, we generated AT2-overexpressed apoE-KO (AT2-Tg/apoE-KO) mice. A subpressor dose of Ang II infusion significantly accelerated atherosclerosis in apoE-KO mice, whereas the lesion formation was markedly reduced in AT2-Tg/apoE-KO mice (Fig. 1). Inhibitors for nitric oxide (NO) synthase (L-NAME) or bradykinin type 2 receptor (icatibant) significantly attenuated such AT2-mediated anti-atherogenic action. Ang II infusion markedly reduced superoxide products and VCAM-1 expression (48% and 73%, respectively, P<0.01) in the aorta from AT2-Tg/apoE-KO mice, concomitant with a significant decrease in monocyte/macrophage accumulation (38%, P<0.05). Stimulation of aortic AT2 exerts anti-atherogenic action through inhibition of oxidative stress, in which AT2-mediated activation of the bradykinin-NO system plays a major role, suggesting that selective stimulation of AT2 by AT2 antagonists has an inhibitory effect on the development of atherosclerosis.

Atherosclerosis and Bone Marrow RAS

The main focus in cardiovascular research has been on the vessel wall, in particular, endothelial cells and vascular smooth muscle cells and their interactions with the blood flow. Recently, hematopoietic bone marrow-derived cells have been reported to contribute to the development of atherosclerosis. However, the role of bone marrow RAS in the development of cardiovascular diseases remains poorly de-
AT₂ overexpression inhibits atherosclerotic formation in apoE-KO mice. A subpressor dose of Ang II infusion markedly increased the atherosclerotic lesion size in apoE-KO mice (from 5.3±1.1 to 16.7±4.8%, p<0.001), whereas the lesion formation was markedly attenuated in AT₂-Tg/apoE-KO mice (from 5.7±0.6 to 6.9±1.9 %, p=n.s.).

Absence of AT₁a receptor in bone marrow-derived cells attenuates atherosclerosis. Eight weeks after the initiation of Western diet and Ang II infusion, the development of atherosclerosis in the aortic root was evaluated. The atherosclerotic lesion area was markedly reduced by 60% (p<0.05) in bone marrow-AT₁a receptor-deficient mice compared with apoE-KO control mice. The accumulation of monocyte/macrophages and T lymphocytes was reduced by 55% and 87%, respectively in bone marrow-AT₁a receptor-deficient mice. Furthermore, the number of macrophage colony-forming units stimulated by M-CSF was markedly reduced by 82% (p<0.01) in bone marrow-AT₁a receptor-deficient mice compared with apoE-KO control mice, suggesting that bone marrow-AT₁a receptors are closely involved in the differentiation and/or self-renewal activity of macrophage progenitors.
The field of cardiovascular medicine is moving rapidly towards the clinical detection of rupture-prone plaques, which precipitates the life-threatening clinical events such as acute coronary syndromes and stroke. Autopsy studies have demonstrated prominent macrophage accumulation in ruptured atherosclerotic lesions. The treatment with ARB has also been reported to attenuate macrophage accumulation within the plaque and reduced plaque disruption in the atherogenic-prone animal. Furthermore, plaques from patients with symptomatic carotid artery stenosis had fewer macrophages and T lymphocytes after ARB treatment. Therefore, the study of the bone marrow RAS is imperative to further understand the mechanism of plaque rupture and it could be useful for the new development of a therapeutic strategy targeting the bone marrow-derived progenitor cells and/or circulating inflammatory cells.

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