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Editorial

Benefits of Angiotensin Receptor Blockade: Preventing Smooth Muscle Cell Senescence and Beyond

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Conflict of Interest
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Cellular senescence indicates an irreversible arrest of cell proliferation that occurs when cells receive different types of stress such as oncogenic stimulation, epigenomic perturbations, increased reactive oxygen species (ROS) and aging.[1] Numerous studies have shown that the p53-p21 and $p16^{INK4a}$-pRb pathways play a crucial role in the occurrence of senescence and growth arrest. Eventually, senescent cells undergo significant changes in chromatin organization and morphology that are accompanied with the expression of $p16^{INK4a}$ and senescence-associated β-galactosidase (SA β-gal).[2][3] Although cellular senescence is an important tumor-suppressive mechanism that prevents malignant transformation, accumulating reports suggest that senescent cells induce deleterious effects on the tissue microenvironment by increasing senescence-associated secretory phenotypes.[4] Especially, age-associated senescence programs in cardiac muscle, endothelial, and vascular smooth muscle cells contribute to the development of atherosclerosis and cardiovascular diseases. Previous study showed that these age-related pathophysiologic phenotypes were largely decreased when the formation of senescent cells was inhibited by inactivation of $p16^{INK4a}$, an effector molecule of senescence.[5] Therefore, inhibition of senescence is a good strategy for alleviating vascular aging and cardiovascular diseases. Interestingly, many publications suggest that age-related dysregulation of the renin-angiotensin-aldosterone system may contribute to cellular senescence and metabolic syndromes.[6][7]

In this issue of the *Korean Circulation Journal*, Kim et al.[8] reported a key role of angiotensin II in the senescence of human coronary artery smooth muscle cells (hCSMCs). Angiotensin II, the active end peptide of the renin-angiotensin system, regulates blood pressure, aldosterone biosynthesis and renal actions through binding to angiotensin II type 1 receptor (AT1R). Similar to the previous study, which was done with vascular smooth muscle cells and *ApoE* knockout mice,[9] angiotensin II treatment significantly increased the levels of a senescence marker (SA-β-gal) and regulators (p53 and $p16^{INK4a}$) in hCSMCs. Kim and colleagues[8] have examined the effects of a recently developed AT1R antagonist, fimasartan, on angiotensin II-induced vascular senescence. Fimasartan markedly suppressed the expression of cysteine-rich angiogenic inducer 61 (CYR61), an important downstream molecule of AT1R. This result indicates that fimasartan efficiently suppresses angiotensin II-induced cellular senescence in hCSMCs. In addition, the authors clearly demonstrated that molecules involved in Angiotensin II-induced hCSMCs, such as CYR61, P53, and $p16^{INK4a}$, are activated through

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different signaling pathways. Expression of CYR61 and p53 is mediated by the ERK1/2 pathway, whereas that of $p16^{INK4a}$ is affected by the p38 MAPK pathway.

Although angiotensin II-mediated activation of ERK1/2 and p38 kinases is associated with the senescence of various cell types including hCSMCs, further investigation is needed to clarify the molecular mechanism involved in angiotensin-II induced senescence. For example, in endothelial cells, angiotensin II increases ROS and inflammation,[10] which are known to be implicated in the development of aging-related or stress-induced premature senescence. Thus, the roles of ROS or inflammation in the vascular senescence need to be explored. In addition, it is necessary to confirm the potential therapeutic intervention of fimasartan *in vivo* against the renin-angiotensin system-induced vascular senescence in the near future.

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