論 文 要 旨

Association of Lectin-like Oxidized Low-density Lipoprotein Receptor-1
With Angiotensin II Type 1 Receptor Impacts Mitochondrial Quality Control
, Offering Promise for the Treatment of Vascular Senescence

（Lectin-like Oxidized Low-density Lipoprotein Receptor-1 (LOX-1)と
AngiotensinⅡ type 1 Receptor (AT1R)の受容体連関に伴う
ミトコンドリアダイナミクス及びマイトファジーは血管老化に重要な役割を果たす）

内門 義博

Lectin-like oxidized low-density lipoprotein (ox-LDL) causes vascular senescence and atherosclerosis. It has been reported that ox-LDL scavenger receptor-1 (LOX-1) is associated with the angiotensin II type 1 receptor (AT1R). While mitochondria play a crucial role in the development of vascular senescence and atherosclerosis, they also undergo quality control through mitochondrial dynamics and autophagy. The aim of this study was to investigate 1) whether LOX-1 associates with AT1R, 2) if this regulates mitochondrial quality control, and 3) whether AT1R inhibition using Candesartan might ameliorate ox-LDL-induced vascular senescence. We performed in vitro and in vivo experiments using vascular smooth muscle cells (VSMCs), and C57BL/6 and apolipoprotein E-deficient (ApoE KO) mice. Administration of oxidized low-density lipoprotein (ox-LDL) to VSMCs induced mitochondrial dysfunction and cellular senescence accompanied by excessive mitochondrial fission, due to the activation of fission factor Drp1, which was derived from the activation of the Raf/MEK/ERK pathway. Administration of either Drp1 inhibitor, mdivi-1, or AT1R blocker candesartan attenuated these alterations. Electron microscopy and immunohistochemistry of the co-localization of LAMP2 with TOMM20 signal showed that AT1R inhibition also increased mitochondrial autophagy, but this was not affected by Atg7 deficiency. Conversely, AT1R inhibition increased the co-localization of LAMP2 with Rab9 signal. Moreover, AT1R inhibition-induced mitochondrial autophagy was abolished by Rab9 deficiency, suggesting that AT1R signaling modulated mitochondrial autophagy derived from Rab9-dependent alternative autophagy. Inhibition of the Raf/MEK/ERK pathway also decreased the excessive mitochondrial fission, and Rab9-dependent mitochondrial autophagy, suggesting that AT1R signaling followed the Raf/MEK/ERK axis modulated both mitochondrial dynamics and autophagy. The degree of mitochondrial dysfunction, reactive oxygen species production, vascular senescence, atherosclerosis, and the number of fragmented mitochondria accompanied by Drp1 activation were all higher in ApoE KO mice than in C57BL/6 mice. These detrimental alterations were successfully restored, and mitochondrial autophagy was upregulated with the administration of candesartan to ApoE KO mice. The association of LOX-1 with AT1R was found to play a crucial role in regulating mitochondrial quality control, as cellular/vascular senescence is induced by ox-LDL, and AT1R inhibition improves the adverse effects of ox-LDL.

（ Frontiers in Cardiovascular Medicine [IN PRESS] ）