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Autophagy Promotes Vascular Smooth Muscle Cell Migration in vitro and in vivo

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Abstract : In response to proatherosclerotic factors such as oxidized lipids, or to therapeutic interventions such as angioplasty, stents, or bypass surgery, vascular smooth muscle cells (VSMCs) migrate from the media to the intima, resulting in intimal hyperplasia, restenosis, graft failure, or atherosclerosis. These proatherosclerotic factors also activate autophagy in VSMCs. However, the functional role of autophagy in vascular health and disease remains poorly understood. In the present study, we determined the role of autophagy in the regulation of VSMC migration. Autophagy activity in cultured human aortic smooth muscle cells (HASMCs) and mouse carotid arteries was measured by Western blot analysis of microtubule-associated protein 1 light chain 3 B (LC3B) and P62. The VSMC migration was determined by scratch wound assay and transwell migration assay. Ex vivo smooth muscle cell migration was determined using aortic ring assay. The in vivo SMC migration was examined by staining the carotid artery sections with smooth muscle alpha actin (alpha SMA) after carotid artery ligation. To examine the relationship between autophagy and neointimal hyperplasia, C57BL/6J mice were subjected to carotid artery ligation. Seven days after injury, protein levels of Atg5, Atg7, Beclin1, and LC3B drastically increased and remained higher in the injured arteries three weeks after the injury. In parallel with the activation of autophagy, vascular injury-induced neointimal hyperplasia as estimated by increased intima/media ratio. The en face staining of carotid artery showed that vascular injury enhanced alpha SMA staining in the intimal cells as compared with the sham operation. Treatment of HASMCs with platelet-derived growth factor (PDGF), one of the major factors for vascular remodeling in response to vascular injury, increased Atg7 and LC3 II protein levels and enhanced autophagosome formation. In addition, aortic ring assay demonstrated that PDGF treated aortic rings displayed an increase in neovessel formation compared with control rings. Whole mount staining for CD31 and alpha SMA in PDGF treated neovessels revealed that the neovessel structures were stained by alpha SMA but not CD31. In contrast, pharmacological and genetic suppression of autophagy inhibits VSMC migration. Especially, gene silencing of Atg7 inhibited VSMC migration induced by PDGF. Furthermore, three weeks after ligation, markedly decreased neointimal formation was found in mice treated with chloroquine, an inhibitor of autophagy. Quantitative morphometric analysis of the injured vessels revealed a marked reduction in the intima/media ratio in the mice treated with chloroquine. Conclusion: Autophagy activation increases VSMC migration while autophagy suppression inhibits VSMC migration. These findings suggest that autophagy suppression may be an important therapeutic strategy for atherosclerosis and intimal hyperplasia.

Keywords : autophagy, vascular smooth muscle cell, migration, neointimal formation
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