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Molecular dissection of the interplay between SIRT1, LKB1 and HERC2: linkage implication in endothelial senescence and vascular remodeling
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Endothelial senescence is one of the earliest events during vascular aging and contributes to vascular remodeling. Sirtuin-1 (SIRT1) elicits its anti-senescent functions in part by mediating proteasome-mediated degradation of LKB1, a pro-senescent protein kinase [1, 2]. The present study was designed to investigate the molecular mechanisms underlying SIRT1-regulated LKB1 degradation by focusing on an E3 ligase, HERC2 (HECT domain and RLD 2 protein). In primary porcine aortic endothelial cells (PAECs), LKB1 degradation was significantly blocked by MG132. Western blotting revealed that LKB1 was ubiquitinated and degraded in nucleus. HERC2 was identified as the E3 ligase of LKB1. Knockdown of HERC2 enhanced the protein accumulation of LKB1 in nucleus and promoted endothelial senescence. Site-directed mutagenesis revealed that acetylation of lysine 64 was involved in the interactions between LKB1 and SIRT1 and the latter facilitated the protein complex formation between acetylated LKB1 and HERC2 . Compared to wild type LKB1, mutation of lysine 64 to glutamine (K64Q) enhanced, whereas replacing this residue with arginine (K64R) attenuated the ubiquitination, nuclear degradation and pro-senescent functions of LKB1. In arteries of eNOS knockout (eNOS-/-) mice, increased LKB1 expression contributed to the abnormal vascular remodeling process. Endothelial overexpression of SIRT1 decreased pressure-wall thickness, reduced circumferential to axial stretch ratios and collagen accumulation in arteries of eNOS-/- mice. These beneficial effects of SIRT1 were attenuated by lentivirus-mediated knocking down of HERC2. In conclusion, SIRT1 prevents endothelial senescence and vascular remodeling by promoting HERC2-mediated ubiquitination and degradation of LKB1.
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1. Zu et al. Circ Res, 2010. 106(8): 1384-93.
2. Bai et al. Circulation, 2012. 126(6): 729-40.