

The Role and Mechanism of KLF4-mediated Regulation of PARK2-dependent Endothelial Mitophagy in Atherosclerosis

Ping Fan*

School of Medicine, Tongji University, Shanghai, China

Email address:

512991445@qq.com (Ping Fan)

*Corresponding author

Abstract

Objective: To investigate the regulatory role of KLF4 in endothelial mitophagy under atherosclerotic conditions, to elucidate its functional association with PARK2, and to evaluate the potential therapeutic value of PARK2-targeted intervention. **Methods:** Human umbilical vein endothelial cells were treated with oxidized low-density lipoprotein(ox-LDL) to establish an in vitro endothelial injury model. The expression levels of KLF4, PARK2, and mitophagy-related molecules were examined using quantitative PCR, Western blotting, and immunofluorescence staining. A KLF4-deficient model was constructed, and mitochondrial membrane potential, mitochondrial reactive oxygen species production, and mitophagic activity were assessed by JC-1 staining, MitoSOX detection, and mitochondrial colocalization analysis. Chromatin immunoprecipitation (ChIP) assays were performed to verify the transcriptional regulatory effect of KLF4 on the PARK2 promoter region. Furthermore, an endothelial-specific KLF4-deficient mouse model was established, followed by intervention with the PARK2 activator MTK458, to evaluate changes in carotid atherosclerotic lesions and related pathological indicators. **Results:** Following ox-LDL stimulation, the expression of KLF4 and PARK2 was markedly decreased in endothelial cells. Mitophagy-associated markers, including PINK1 and the LC3-II/I ratio, were reduced, whereas p62 accumulated abnormally. These changes were accompanied by mitochondrial membrane potential disruption and increased mitochondrial reactive oxygen species production. KLF4 deficiency further aggravated ox-LDL-induced mitochondrial dysfunction and mitophagy impairment, thereby promoting endothelial injury. Mechanistic analyses demonstrated that KLF4 could bind to the PARK2 promoter region and positively regulate its transcription. In vivo experiments showed that endothelial-specific KLF4 deletion exacerbated carotid atherosclerotic plaque formation. Activation of PARK2 by MTK458 partially restored mitophagic activity, ameliorated mitochondrial dysfunction, and attenuated the atherosclerotic phenotype induced by KLF4 deficiency. **Conclusion:** KLF4 serves as an important protective factor in maintaining endothelial mitochondrial homeostasis. It promotes mitophagy by transcriptionally activating PARK2, thereby reducing oxidative stress and endothelial injury and ultimately delaying the progression of atherosclerosis. The KLF4/PARK2 signaling axis may represent a promising potential target for the prevention and treatment of atherosclerosis.

Keywords

KLF4, PARK2, Mitophagy, Endothelial Cells, Atherosclerosis