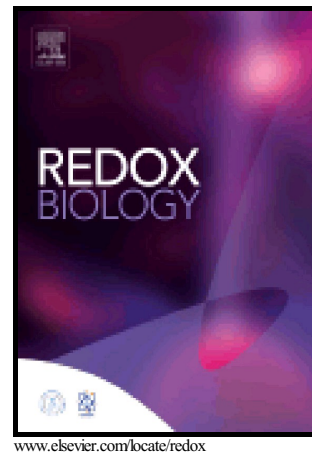


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Homocysteine causes vascular endothelial dysfunction by disrupting endoplasmic reticulum redox homeostasis

Xun Wu^{a,b}, Lihui Zhang^{a,b}, Yütong Miao^c, Juan Yang^c, Xian Wang^c, Chih-chen Wang^{a,b}, Juan Feng^{c,*}, Lei Wang^{a,b,*}

^a National Laboratory of Biomacromolecules, CAS Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China

^b College of Life Sciences, University of Chinese Academy of Sciences, Beijing 100049, China

^c Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Peking University Health Science Center, Key Laboratory of Molecular Cardiovascular Science, Ministry of Education, Beijing 100191, China

* Correspondence: juanfeng@bjmu.edu.cn or wanglei@moon.ibp.ac.cn

Abstract

Endothelial dysfunction induced by hyperhomocysteinemia (HHcy) plays a critical role in vascular pathology. However, little is known about the role of endoplasmic reticulum (ER) redox homeostasis in HHcy-induced endothelial dysfunction. Here, we show that Hcy induces ER oxidoreductin-1 α (Ero1 α) expression with ER stress and inflammation in human umbilical vein endothelial cells and in the arteries of HHcy mice. Hcy upregulates Ero1 α expression by promoting binding of hypoxia-inducible factor 1 α to the *ERO1A* promoter. Notably, Hcy rather than other thiol agents markedly increases the GSH/GSSG ratio in the ER, therefore allosterically activating Ero1 α to produce H₂O₂ and trigger ER oxidative stress. By contrast, the antioxidant pathway mediated by ER glutathione peroxidase 7 (GPx7) is downregulated in HHcy mice. Ero1 α knockdown and GPx7 overexpression protect the endothelium from HHcy-induced ER oxidative stress and inflammation. Our work suggests that targeting ER redox homeostasis could be used as an intervention for HHcy-related vascular diseases.

Keywords: endothelial cells, endoplasmic reticulum, Ero1 α , GPx7, homocysteine, redox homeostasis

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