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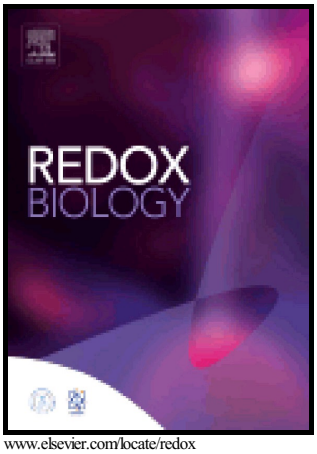


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PII: S2213-2317(18)30658-X
DOI: https://doi.org/10.1016/j.redox.2018.09.021
Reference: REDOX1014

To appear in: *Redox Biology*

Received date: 27 July 2018
Revised date: 18 September 2018
Accepted date: 26 September 2018

Cite this article as: Xun Wu, Lihui Zhang, Yütong Miao, Juan Yang, Xian Wang, Chih-chen Wang, Juan Feng and Lei Wang, Homocysteine causes vascular endothelial dysfunction by disrupting endoplasmic reticulum redox homeostasis, *Redox Biology,* https://doi.org/10.1016/j.redox.2018.09.021

# Homocysteine causes vascular endothelial dysfunction by disrupting endoplasmic reticulum redox homeostasis

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**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-1α (Ero1α) expression with ER stress and inflammation in human umbilical vein endothelial cells and in the arteries of HHcy mice. Hcy upregulates Ero1α expression by promoting binding of hypoxia-inducible factor 1α to the *ERO1A* promoter. Notably, Hcy rather than other thiol agents markedly increases the GSH/GSSG ratio in the ER, therefore allosterically activating Ero1α to produce $H_2O_2$ and trigger ER oxidative stress. By contrast, the antioxidant pathway mediated by ER glutathione peroxidase 7 (GPx7) is downregulated in HHcy mice. Ero1α 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, Ero1α, GPx7, homocysteine, redox homeostasis