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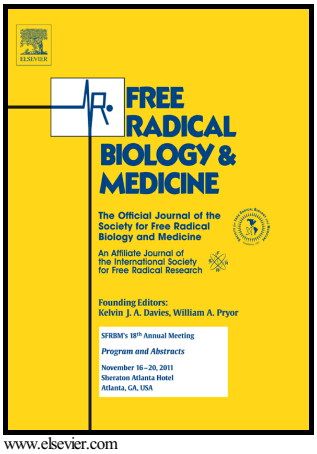

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Metformin treatment prevents SREBP2-mediated cholesterol uptake and improves lipid homeostasis during oxidative stress-induced atherosclerosis

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Abstract

Lipids are responsible for the atheromatous plaque formation during atherosclerosis by their deposition in the subendothelial intima of the aorta, leading to infarction. Sterol regulatory element-binding protein 2 (SREBP2), regulating cholesterol homeostasis, is suggested to play a pivotal role during the early incidence of atherosclerosis through dysregulation of lipid homeostasis. Here we demonstrate that oxidative stress stimulates SREBP2-mediated cholesterol uptake via low density lipoprotein receptor (LDLR), rather than cholesterol synthesis, in mouse vascular aortic smooth muscle cells (MOVAS) and THP-1 monocytes. The enhancement of mature form of SREBP2 (SREBP2-M) during oxidative stress was associated with the inhibition of AMP-activated protein kinase (AMPK) activation. In contrast, inhibition of either SREBP2 by fatostatin or LDLR by siLDLR resulted in decreased cholesterol levels during oxidative stress. Thereby confirming the role of SREBP2 in cholesterol regulation via LDLR. Metformin-mediated activation of AMPK was able to significantly abrogate cholesterol uptake by inhibiting SREBP2-M. Interestingly, although metformin administration attenuated angiotensin (Ang)-II-impaired lipid homeostasis in both aorta and liver tissues of $ApoE^{-/-}$ mice, the results indicate that SREBP2 through LDLR regulates lipid homeostasis in aorta but not in liver tissue. Taken together, AMPK activation inhibits oxidative stress-mediated SREBP2-dependent cholesterol uptake, and moreover,