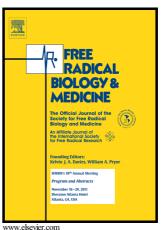
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Salazar et al.

Zinc Regulates Nox1 Expression Through a NF-κB and Mitochondrial ROS Dependent Mechanism to Induce Senescence of Vascular Smooth Muscle Cells

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Abstract

Aims

The role of oxidative stress and inflammation in the development and progression of cardiovascular diseases (CVD) is well established. Increases in oxidative stress can further exacerbate the inflammatory response and lead to cellular senescence. We previously reported that angiotensin II (Ang II) and zinc increase reactive oxygen species (ROS) and cause senescence of vascular smooth muscle cells (VSMCs) and that senescence induced by Ang II is a zinc-dependent process. Zinc stimulated NADPH oxidase (Nox) activity; however, the role of Nox isoforms in zinc effects was not determined.

Results

Here, we show that downregulation of Nox1, but not Nox4, by siRNA prevented both Ang II- and zinc-induced senescence in VSMCs. On the other hand, overexpression of Nox1 induced senescence, which was associated with reduced proliferation, reduced expression of telomerase and increased DNA damage. Zinc increased Nox1 protein expression, which was inhibited by chelation of zinc with TPEN and by overexpression of the zinc exporters ZnT3 and ZnT10. These transporters work to reduce

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