

Abstract

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Reduced antioxidant capacity and diet-induced atherosclerosis in uncoupling protein-2-deficient mice.

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BACKGROUND AND OBJECTIVE: Vascular dysfunction in response to reactive oxygen species (ROS) plays an important role in the development and progression of atherosclerotic lesions. In most cells, mitochondria are the major source of cellular ROS during aerobic respiration. Under most conditions the rates of ROS formation and elimination are balanced through mechanisms that sense relative ROS levels. However, a chronic imbalance in redox homeostasis is believed to contribute to various chronic diseases, including atherosclerosis. Uncoupling protein-2 (UCP2) is a mitochondrial inner membrane protein shown to be a negative regulator of macrophage ROS production.

RESULTS: In response to a cholesterol-containing atherogenic diet, C57BL/6J mice significantly increased expression of UCP2 in the aorta, while mice lacking UCP2 - in the absence of any other genetic modification - displayed significant endothelial dysfunction following the atherogenic diet. Compared to wild-type mice, Ucp2^{-/-} mice had decreased endothelial nitric oxide synthase, an increase in vascular cell adhesion molecule-1 expression, increased ROS production and an impaired ability to increase total antioxidant capacity. These changes in Ucp2^{-/-} mice were associated with increased aortic macrophage infiltration and more numerous and larger atherosclerotic lesions.

CONCLUSION: These data establish that in the vasculature UCP2 functions as an adaptive antioxidant defense to protect against the development of atherosclerosis in response to a fat and cholesterol diet.

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