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Review

Mitochondria and vascular pathology

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Abstract:
Functional and structural changes in mitochondria are caused by the opening of the mitochondrial permeability transition pore (PTP) and by the mitochondrial generation of reactive oxygen species (ROS). These two processes are linked in a vicious cycle that has been extensively documented in ischemia/reperfusion injuries of the heart, and the same processes likely contribute to vascular pathology. For instance, the opening of the PTP causes cell death in isolated endothelial and vascular smooth muscle cells. Indeed, atherosclerosis is exacerbated when mitochondrial antioxidant defenses are hampered, but a decrease in mitochondrial ROS formation reduces atherogenesis.
Determining the exact location of ROS generation in mitochondria is a relevant and still unanswered question. The respiratory chain is generally believed to be a main site of ROS formation. However, several other mitochondrial components likely contribute to ROS generation. Recent reports highlight the relevance of monoamine oxidases (MAO) and $p66^{Shc}$. For example, the absence of $p66^{Shc}$ in hypercholesterolemic mice has been reported to reduce the occurrence of foam cells and early atherogenic lesions. On the other hand, MAO inhibition has been shown to reduce oxidative stress in many cell types eliciting significant protection from myocardial ischemia. In conclusion, evidence will be presented to demonstrate that (i) mitochondria are major sites of ROS formation; (ii) an increase in mitochondrial ROS formation and/or a decrease in mitochondrial antioxidant defenses exacerbate atherosclerosis; and (iii) mitochondrial dysfunction is likely a relevant mechanism underlying several risk factors (i.e., diabetes, hyperlipidemia, hypertension) associated with atherosclerosis.

Key words: oxidative stress, mitochondria, $p66^{Shc}$, monoamine oxidase