Outline

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Redox Dysregulation in Vascular Pathobiology

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Abstract

Oxidation-reduction (redox) reactions comprise a subset of fundamental biochemical reactions found throughout biological systems. While redox reactions are involved in many normal cellular functions, excess oxidative potential, or oxidative stress, can lead to cellular dysfunction and injury. Multiple protective antioxidant systems have evolved to guard against the adverse consequences of oxidant stress and injury. These systems include low-molecular-weight antioxidants, such as the glutathione-glutathione disulfide redox couple; the thiol proteome, whose various oxidation states can serve as a global redox buffer; and antioxidant enzymes, such as the superoxide dismutases, catalase, peroxidredoxins, and the glutathione peroxidases.

pathobiology in the vasculature is glutathione peroxidase-3 (GPx-3), the principal antioxidant enzyme in the extracellular compartment. This enzyme catalyzes the reduction of hydrogen and lipid peroxides to water and lipid alcohols, respectively, and does so using reducing equivalents provided by glutathione. As a selenoprotein, it requires unique translational machinery for its expression, as well as adequate selenium stores; its primary site of synthesis is the renal tubule, although all nucleated cells can express low levels of the enzyme. We have previously demonstrated that a deficiency of GPx-3 leads to enhanced platelet activation, and is an independent risk factor for acute ischemic stroke in the young. We recently developed a GPx-3-deficient mouse model, and demonstrated endothelial dysfunction as well as increased platelet-dependent thrombosis in an acute ischemic stroke model. Importantly, platelet inhibitors or small-molecule superoxide and hydrogen peroxide scavengers greatly attenuated the size of the ischemic stroke and its functional consequences in this model. These data support the importance of GPx-3 as a key antioxidant enzyme that functions to limit arterial thrombosis in the setting of increased oxidant stress and endothelial dysfunction.

A second example of an essential antioxidant enzyme whose deficiency contributes to pathobiology in the vasculature is glutathione peroxidase-1 (GPx-1), a central intracellular antioxidant. In our efforts to uncover a mechanism for the oxidative stress of hyperhomocysteinemia, we found that elevated levels of this amino acid is associated with a decrease in the expression and activity of GPx-1 in endothelial cells. This change in expression was found to be post-translational, and we recently demonstrated that it is a consequence of hypomethylation of selenocysteine (Sec)-charged tRNA. This modification is essential for appropriate incorporation of Sec into the selenoprotein GPx-1's active site during translation. Changes in Sec-tRNA methylation are brought about by increased S-adenosylhomocysteine, which inhibits the methyltransferase required to methylate Sec-tRNA to the Um34 form. These data suggest a unique mechanism for impaired GPx-1 expression in hyperhomocysteinemic states that directly relates to impaired cellular methylation potential caused by increased S-adenosylhomocysteine accumulation.

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