

Novel genomic targets in oxidant-induced vascular injury

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Abstract

To study the complex interaction between oxidative injury and the pathogenesis of vascular disease, vascular gene expression was examined in male Sprague–Dawley rats given 35 or 70 mg/kg allylamine, a synthetic amine converted to acrolein and hydrogen peroxide within the vascular wall. Vascular lesions and extensive vascular remodeling, coupled to increased production of 8-epi-PGF2 α , nuclear localization of NF κ B, and alterations in glutathione homeostasis, were observed in animals treated with allylamine for up to 20 days. Transcriptional profiling, immunohistochemistry, and in situ hybridization showed that genes involved in adhesion and extracellular matrix (ECM) (α_1 integrin, collagen), cytoskeletal rearrangements (α -smooth muscle actin, α -tropomyosin), and signal transduction (NF κ B, osteopontin, and LINE) were altered by oxidant treatment. To evaluate mechanisms of gene dysregulation, cultured aortic smooth muscle cells were challenged with allylamine or its metabolites and processed for molecular analysis. These agents increased formation of reactive oxygen species and elicited changes in gene expression similar to those observed in vivo. Oxidative stress and changes in gene expression were inhibited by *N*-acetyl cysteine, a precursor of glutathione. These results indicate that genes along the ECM–integrin–cytoskeletal axis, in addition to LINE, are molecular targets in oxidant-induced vascular injury.

Keywords: Functional genomics; Gene expression; Oxidative stress; Vascular injury