One Step Beyond
Glutathione Peroxidase and Endothelial Dysfunction

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Much evidence supports the role of increased levels of reactive oxygen species (ROS) in the pathogenesis of cardiovascular diseases, including hypertension. The increased activity and expression of the reduced nicotinamide-adenine dinucleotide phosphate oxidase observed in hypertensive populations have implicated the superoxide anion as one of the main species responsible. This view has been supported by studies demonstrating vascular-protective effects of the superoxide dismutase family, enzymes that remove superoxide anion thereby protecting the bioavailability of NO. Despite this, it has proven particularly difficult to identify those genetic and environmental factors, relating to ROS metabolism, that contribute to the development of vascular dysfunction. The article by Chrissobolis et al in this issue of Hypertension serves to remind us that we need to look one step beyond those mechanisms directly involving superoxide anion and superoxide dismutase. Indeed, hydrogen peroxide (H$_2$O$_2$), the end product of the superoxide anion and superoxide dismutase, has been shown to have vascular reactive properties and can impair NO-mediated signaling in blood vessels by a variety of mechanisms. Looking beyond superoxide dismutase will undoubtedly help us to more comprehensively understand the roles of ROS in vascular function and disease. Perhaps this will assist in the identification of those elusive genes suspected, but so far undefined, in the pathogenesis of high blood pressure.

Chrissobolis et al explored the effects of modulating the activity of glutathione peroxidase-1 (GPX1), an enzyme that catalyzes the conversion of H$_2$O$_2$ to water, on vascular function in mice. The authors demonstrated impaired endothelial function in carotid arteries from mice genetically engineered to be deficient in GPX1. This study showed that isolated carotid arteries, from Gpx1$^{-/-}$ mice, demonstrated similar vascular responses to acetylcholine under basal conditions but were unable to cope with the increased levels of oxidative stress induced by incubation with angiotensin II. Interestingly, a dose dependency of GPX1 expression was observed. The heterozygote Gpx1$^{+/−}$ mice showed a reduced response to acetylcholine only after incubation with angiotensin II, whereas the homozygote Gpx1$^{-/-}$ had diminished responses even under basal conditions. This haplinsufficiency suggests that relatively small changes in GPX1 activity can have profound effects on vascular function. This idea is supported by the data showing that transgenic mice, overexpressing GPX1, have a better vascular response to acetylcholine than wild-type mice under conditions of high angiotensin II.

The study by Chrissobolis et al is not the only study implicating alterations in GPX1 in the development and/or maintenance of oxidative stress and vascular dysfunction. Fortepiani and Reckelhoff demonstrated that spontaneously hypertensive rats were unable to increase the renal levels of GPX1 in the same way that the genetically normotensive Wistar-Kyoto rats did in response to molsidomine. Mutations in the Gpx1 promoter and untranslated regions have been associated with increased intima-media thickness of carotid arteries and risk of cardiovascular and peripheral disease in type 2 diabetic patients.

So, moderate changes in GPX1 expression can profoundly affect vascular function. Why might this be important in our efforts to elucidate the mechanisms underlying essential hypertension? Taking a look at the roles, activities, and regulation if GPX1 is very revealing. The GPX family of selenocysteine containing enzymes function in the detoxification of H$_2$O$_2$ to water and in the reduction of lipid hydroperoxides to their corresponding alcohols. Each of the several isozymes is encoded by different genes, which vary in cellular location and substrate specificity. GPX1, the most abundant version, is found in the cytoplasm of nearly all mammalian tissues and preferentially detoxifies H$_2$O$_2$. The activity of this enzyme is subject to a unique repertoire of genetic and environmental control with gender, dietary supplementation, and smoking all being implicated. The human gene for GPX1 is located on chromosome 3p21.3, contains 2 exons, and has several common polymorphisms. Some of these genotypes have been shown to have effects on enzymatic activity. For examples, Bastaki et al, investigating the effects of the functional single nucleotide polymorphism (C593T Pro197Leu) on GPX1 enzyme activity, found a 6-fold range with the TT males having the lowest GPX1 activity of any group. At least part of the gender-based effect may be related to the need for the selenocysteine residue. This residue is encoded for by the UGA codon, which normally codes for a termination signal. A specialized mechanism, involving regions within the 3’-untranslated region, results in the incorporation of selenocysteine only when selenium levels are high enough. Selenium is also believed to stabilize the mRNA. Reduced selenium in the diet would, therefore, result in reduced GPX1 activity. Based on this, the suggestion has been made that preferential consumption of selenium-rich...
foods by a female population may account for the gender-based increase in activity. Although the present study reports no differences in GPX1 activity between male and female mice, the diet was the same in both. The effects of selenium supplementation on the vascular function of haploinsufficient mice would be of great interest.

Expression of the GPX1 gene is also subject to epistatic control. Hyperhomocysteinemia, a known risk factor for cardiovascular disease, results as a consequence of mutations in the genes encoding cystathionine β-synthase7 and 5,10-methylenetetrahydrofolate reductase (MTHFR). Elevated levels of homocysteine have been clearly shown to contribute to endothelial dysfunction with at least some of the effects mediated via an accumulation of ROS.8 How does this relate to expression of GPX1? Elegant studies from Handy et al9 demonstrated that high levels of homocysteine downregulate the translation of Gpx1. Indeed, it has been reported recently that both GPX1 immunodetectable protein levels and enzymatic activity are reduced by increases in homocysteine levels without any effect on the levels of GPX-1 mRNA. It is, therefore, not surprising to find that the relatively common C667T single nucleotide polymorphism in the MTHFR gene has been associated with coronary artery disease.10

In summary, the activity and expression of GPX1, an enzyme with a role in modulating the levels of ROS, redox state, and oxidative stress, are subject to a unique repertoire of control acting at the levels of transcription and translation (shown in Figure). The well-designed demonstration that moderate changes in GPX1 activity result in major effects on vascular function suggests that this enzyme may be one of those as-yet-undefined enzymes that contribute to the development of hypertension. The complex array of factors influencing the activity of GPX1 means that future studies investigating this gene as a candidate need to be carefully controlled.

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References
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