Toward Understanding of Extracellular Superoxide Dismutase Regulation in Atherosclerosis: A Novel Role of Uric Acid?

Ulf Landmesser, Helmut Drexler

Superoxide dismutases (SODs) represent the major antioxidant defense system against superoxide anions (O$_2^-$). Three isoforms of superoxide dismutase have been identified in mammals: copper-zinc SOD (Cu, Zn-SOD), manganese SOD (Mn-SOD), and extracellular SOD (ecSOD). Cu, Zn- and Mn-SOD are localized intracellularly, whereas the last discovered SOD isoform, ecSOD, is secreted and bound to heparan sulfate on the cellular surface. The arterial wall contains exceptionally large amounts of ecSOD in the interstitium that are about 100 times higher compared with other tissues such as muscle or fat tissue, suggesting a special function of this SOD isoform within the vascular wall. An important function of ecSOD in the arterial wall may be the preservation of bioactivity against the detrimental effects of O$_2^-$.

Moreover, reduced vascular SOD activity induced by dietary copper restriction was substantially reduced compared with in normal aortas. In human atherosclerotic lesions of the aorta, ecSOD activity is substantially reduced compared with in normal aortas. Furthermore, in coronary arteries from patients with coronary artery disease (CAD), ecSOD activity is reduced by 50% compared with control subjects without CAD. Moreover, endothelium-bound ecSOD activity, ie, released from endothelium into plasma by heparin bolus injection, is dramatically reduced in patients with CAD as compared with healthy control subjects and is closely related to endothelium-dependent, NO-mediated vasodilation, suggesting that reduced ecSOD activity contributes to reduced vascular NO-availability in patients with CAD.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Hink et al add an important novel aspect in our understanding of the regulation of vascular ecSOD activity in atherosclerosis. The authors demonstrate that the peroxidase reaction of ecSOD, i.e., the reaction with hydrogen peroxide, results in a rapid inactivation of the enzyme. Furthermore, uric acid was identified as a small molecule that effectively prevented inactivation of ecSOD via its peroxidase reaction at concentrations close to physiological levels. Moreover, recombinant ecSOD was shown to be effective in protecting NO bioactivity against the detrimental effects of O$_2^-$.

Given these observations, several recent studies have focused on the regulation of vascular ecSOD expression and activity. Interestingly, NO$^-$ itself was identified as one of the major regulators of vascular ecSOD expression. NO$^-$ donors potently induced ecSOD expression in vascular smooth muscle cells, while lack of endothelial NO$^-$ production in eNOS knockout mice dramatically reduced vascular ecSOD levels. This could represent an important “feed-forward” mechanism whereby NO$^-$ enhances its biological effects. In addition, ecSOD expression in vascular smooth muscle cells was found to be downregulated by the inflammatory cytokine TNF-$\alpha$ and homocysteine.

In atherosclerotic aortas from apolipoprotein E (apoE)-deficient mice, the regular ecSOD transcript is downregulated over time as compared with wild-type mice; however, a truncated ecSOD transcript, likely derived from lipid-laden macrophages, is increased in apoE-deficient mice. In human atherosclerotic lesions of the aorta, ecSOD activity is substantially reduced compared with in normal aortas. Furthermore, in coronary arteries from patients with coronary artery disease (CAD), ecSOD activity is reduced by 50% compared with control subjects without CAD. Moreover, endothelium-bound ecSOD activity, ie, released from endothelium into plasma by heparin bolus injection, is dramatically reduced in patients with CAD as compared with healthy control subjects and is closely related to endothelium-dependent, NO-mediated vasodilation, suggesting that reduced ecSOD activity contributes to reduced vascular NO-availability in patients with CAD.

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There has been an intense debate whether serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans. Several recent studies, however, including an analysis from the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study, could not demonstrate that serum levels of uric acid are an independent risk factor for cardiovascular events and coronary disease in humans.
uric acid are an independent predictor of cardiovascular events. The results of Hink et al.\textsuperscript{17} are intriguing in this respect because they suggest a novel beneficial effect of uric acid. This may counteract other detrimental effects of uric acid, such as stimulation of vascular smooth muscle cell proliferation\textsuperscript{21} and could help explain why uric acid may not represent an independent cardiovascular risk factor.

References

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