A Role of Impaired Superoxide Dismutase Activity for Vascular Constrictive Remodeling After Angioplasty

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Lumen loss by constrictive remodeling is a mechanistically still incompletely understood, clinically important problem frequently arising after balloon angioplasty. The arterial trauma, potentially in combination with the destruction of the vascular endothelium, gives rise to a fundamental reorganization of the extracellular matrix. This process is mediated by vascular fibrosis and subsequent condensation of the matrix, ultimately leading to shrinkage of the scar and of the vessel. Several elements contribute to remodeling, including smooth muscle cells and adventitial fibroblasts, resulting in the expression and secretion of matrix proteins such as collagen and of matrix-degrading metalloproteinases (MMPs). Furthermore, cellular proliferation, migration, apoptosis, and vascular spasm are involved in the process.1

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Reactive oxygen and nitrogen species play a central role in the regulation of the activity state of vascular cells. Several studies have demonstrated that oxidative as well as nitrosative stress occurs after balloon injury of arteries.2 The pathophysiological role of redox stress for constrictive remodeling, however, is still obscure. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Leite et al3 communicate an elegant study that provides insights into the complicated interplay of reactive oxygen and nitrogen species after balloon angioplasty finally leading to constrictive remodeling. Their observation of an attenuation of vascular superoxide dismutase (SOD) activity after angioplasty in conjunction with the demonstration that delayed systemic application of extracellular SOD (ecSOD) prevents vascular shrinkage after angioplasty is intriguing and could give rise to a reassessment of our current doctrines of angioplasty-induced redox stress.

SOD, as the only enzyme catalyzing the reaction of superoxide anions (O$_2^-$) to hydrogen peroxide (H$_2$O$_2$) is a central element in the maintenance of the vascular redox balance. If O$_2^-$ is not detoxified by SOD, it rapidly reacts with nitric oxide (NO) to form peroxynitrite (ONOO$^-$). Therefore O$_2^-$ is the main limiting factor for vascular NO bioavailability, and consequently, SOD, via its action on O$_2^-$, is central for controlling NO levels (Figure).4 Such that a complicated network of reactions is indeed functional in the setting of angioplasty is impressively demonstrated by the study by Leite et al4: Balloon injury led to a marked induction of the inducible NO synthase (iNOS) in the rabbit femoral artery, but this process was not associated with an increased formation of nitrate, the end-product of NO bioconversion, but with an enhancement of protein tyrosine nitration, the footprint marker of peroxynitrite. Application of human recombinant ecSOD attenuated tyrosine nitration and dramatically enhanced nitrate formation.5 This observation clearly demonstrated that, after angioplasty, NO, which is excessively produced by iNOS, is instantaneously scavenged by O$_2^-$, which therefore has to be present in excess. Several studies have demonstrated that the formation of O$_2^-$ is increased after balloon injury, and vascular NADPH oxidases have been identified to contribute to O$_2^-$ production in this setting (for examples, see Szocs et al6 and Jacobson et al6). Based on the observations made by Leite et al,7 the lack of vascular SOD activity has to be acknowledged as an important mechanism resulting in high O$_2^-$ levels after angioplasty. An unsolved issue of the study, however, is why the high level of SOD proteins found after angioplasty do not translate into activity and therefore which mechanisms underlie SOD inactivation after angioplasty.

SOD has already been suggested to be beneficial in preventing development of restenosis.8 However, the observation of the study by Leite et al9 that even a delayed treatment with ecSOD attenuated vascular collagen accumulation and prevented constrictive remodeling is unexpected and clinically appealing. What could be the mechanism underlying the beneficial effects of SOD? It is generally accepted that oxygen-derived radicals have the potential to activate several transcription factors involved in cellular activation.9 NO, in contrast, rather “calms down” smooth muscle cells and fibroblasts and may even induce apoptosis in these cells. It is certainly difficult to judge whether the beneficial effects of ecSOD treatment arise from the withdrawal of O$_2^-$ or the enhancement of NO bioavailability, but several aspects speak in favor of a dominant role of NO: O$_2^-$ itself is relative stable and, with a few exceptions, most of its effects can be attributed to the action of H$_2$O$_2$, the product of the reaction catalyzed by SOD. It is conceivable that in a setting of concomitant oxidative and nitrosative stress, such as angioplasty, SOD treatment increases the H$_2$O$_2$ level. The reasons why the enhanced formation of H$_2$O$_2$ does not result in the anticipated effects could be based on the concomitant reduction of ONOO$^-$ level. ONOO$^-$ is a much stronger...
oxidizing agent than \( \text{H}_2\text{O}_2 \), which activates transcription factors similar to \( \text{H}_2\text{O}_2 \). Indeed, in the setting of inflammation, \( \text{ONOO}^- \) activates NF-\( \kappa \)B and mediates E-selectin expression in vitro\(^9\) and in vivo.\(^{10} \) Alternatively, the inhibitory action of NO on remodeling is more potent than the stimulus elicited by \( \text{H}_2\text{O}_2 \). Indeed, catalase, which decomposes \( \text{H}_2\text{O}_2 \), had no effect on vascular spasms occurring after angioplasty.\(^{11} \) Finally, \( \text{H}_2\text{O}_2 \) and \( \text{ONOO}^- \) are certainly only two of a multitude of activating factors generated after balloon injury. The type of vascular remodeling after angioplasty is not necessarily constrictive, and the fate of this process is mainly controlled by NO. To allow outward remodeling, degradation of extracellular matrix is required. NO induces the expression of MMPs,\(^{12} \) and the NO-mediated outward remodeling in response to endothelial shear stress\(^{13} \) is mediated by MMP-2 and MMP-9.\(^{14} \)

An alternative effector to NO could be the group of transforming growth factors (TGF). TGF-\( \beta \) has been shown to be involved in remodeling and influences matrix formation and scarring,\(^{15} \) and there is a tight link among redox stress, TGF-\( \beta \), and matrix generation. In the study by Leite et al.,\(^3 \) ecSOD application resulted in a reduced collagen accumulation. Indeed, liposomal SOD has previously been shown to reduce the expression of TGF-\( \beta \) and collagen in dermal myofibroblasts,\(^{16} \) and TGF-\( \beta \) expression is induced by oxidative stress. Interestingly, TGF-\( \beta \) itself activates NADPH oxidases in cultured fibroblasts\(^{17} \) and inhibits induction of iNOS.\(^{18} \)

In conclusion, vascular remodeling is influenced by a tight interaction of redox-modulated pathways at several levels of cellular signaling cascades. SOD is the central switch between inward and outward remodeling by determining not only the bioavailability of \( \text{O}_2^- \) but also that of \( \text{ONOO}^- \) and NO.

**References**

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