Lysyl Oxidase
New Looks on LOX
Ruud A. Bank, Victor W.M. van Hinsbergh

The extracellular matrix proteins collagen and elastin determine, to a large extent, the biomechanical properties of the vessel wall. Both molecules are secreted as monomers, but are posttranslationally modified in the extracellular space in order to generate stable polymers. A critical feature of collagen and elastin fibers is the degree of cross-linking. The first step in cross-linking is the oxidative deamination of the \( \epsilon \)-amino group of certain peptidyl (hydroxy)lysyl residues, resulting in the aldehyde (hydroxy)aldehydes. In collagen, (hydroxy)lysyl residues are restricted to the C- and N-telopeptide. The aldehyde reacts with a lysyl (Lys) or hydroxylysyl (Hyl) residue in the triple helix, resulting in a variety of cross-links. In elastin, the oxidative deamination of Lys (Hyl is absent in elastin) is less restrictive, resulting in modification of most of the Lys residues. Well known elastin cross-links are lysinonorleucine and the pyridiniums desmosine and isodesmosine. The cross-links in collagen are responsible for the stiffness of collagen fibers, whereas the cross-links in elastin are important for the rubber-like properties of elastin fibers.

See page 1409

The enzyme responsible for the oxidative deamination of the \( \epsilon \)-amino groups is lysyl oxidase (LOX), a copper-dependent amine oxidase. Reduced activity levels of this enzyme result in decreased degree of cross-linking, affecting the biomechanical properties of extracellular matrices as well as the susceptibility of collagen and elastin to degradation by proteinases.

In this issue, Rodríguez et al describe the downregulation of LOX expression in porcine endothelial cells subjected to atherogenic levels of LDL. The authors hypothesize that this results in a decreased degree of elastin and/or collagen cross-linking, which leads to alterations in the integrity of the extracellular matrix and thereby enhances endothelial permeability. This is an interesting hypothesis that points to the intimate interaction between the cell matrix and cell functioning. It shows resemblance with the increased endothelial permeability found in diabetic vessels, which is also accompanied by alterations in the extracellular matrix. This attractive idea asks for further testing. For example, apart from LOX, four more LOX-like genes have recently been cloned (LOX1 to 4). The substrate specificity of these enzymes in vivo is hardly known, as is the expression in endothelial cells. It is likely that at least some of them are involved in cross-linking, and at this stage, it cannot be excluded that they are able to compensate for the decrease of LOX expression levels in the model described by Rodríguez et al. Multiple novel biological functions have recently been attributed to LOX, such as suppressing the \( \text{ras} \) oncogene, being a stimulator of collagen type III promotor activity, playing a role in cell adhesion and growth control, and acting intracellularly. It is therefore possible that the increased endothelial permeability is due to a phenomenon other than cross-linking or to a reduced cross-linking of other proteins. The fact that addition of \( \beta \)-aminopropionitrile (BAPN), a LOX inhibitor, also results in increased endothelial permeability, seems to be in favor of the cross-link hypothesis. This effect was observed at 22 hours after BAPN administration. Changes in the composition of the extracellular matrix within such a period of time may well reflect other proteins than collagen and elastin, because cross-linked elastin shows little turnover, and cross-linked collagen is generally believed to be a long-lived protein. Nevertheless, even a partial inhibition of cross-linking process in collagen, without affecting elastin, already results in destabilization of the aortic wall with subsequent increased aortic diameters and reduced strength and stiffness.

The induction of LOX by high concentrations of LDL is interesting. It is known that LDLs affect the sensitivity of platelets for various agonists. At physiological and higher concentrations, LDLs induce changes in platelet cell shape and aggregation, activate integrin \( \alpha_{\text{myosin}} \)-mediated signaling, and triggered the PKC-dependent phosphorylation of pleckstrin. The data of Rodríguez et al indicate that also endothelial cells respond to LDL at physiological and higher concentrations. At present, it is unknown how the LDL particle transduces its signal into the cell. While several agents are presently known to induce an increase in LOX mRNA, LDL reduces LOX in vascular cells, an effect only observed to a limited degree in vascular smooth muscle cells after exposure to interferon-\( \gamma \). Induction of LOX has been observed in endothelial cells after exposure to shear forces. In smooth muscle cells PDGF, TGF-\( \beta 1 \), angiotensin II, adenosine, and serum increase LOX expression. PDGF signals via the PKC-MEK-MAPK-dependent pathways and adenosine via cAMP. The effect of LDL may require binding to the B,E-(LDL)-receptor or may be caused by the presence of small amounts of minimally oxidized LDL or other components, such as lyosphospholids. Even if binding to the B,E-receptor is required, as appears the case in...
platelets,26 the possibility remains that binding to a cellular receptor facilitates the exchange of cell-activating moieties. Rodríguez et al also show that, in aorta of diet-induced hypercholesterolemic pigs, the overall concentration of LOX mRNA is markedly reduced. Consequently, if it reflects an intrinsic property of the vessel wall, a reduced LOX activity not only affects the distensibility and elasticity of the vessel wall, but it would also increase the vulnerability of the fibrous cap of plaques to rupture. Interestingly, not only a decrease but also an increase in LOX has been reported to play a role in atherosclerosis. Rabbids fed on an atherogenic diet of rabbit chow supplemented with 8% peanut oil and 2% cholesterol but also an increase in LOX has been reported to play a role in the intrinsic property of the vessel wall, a reduced LOX activity mRNA is markedly reduced. Consequently, if it reflects an arterial pig of diet-induced atherosclerosis. The article by Rodríguez et al29 also shows that hypertension results in increased LOX levels and subsequently in increased aortic collagen content. Administration of BAPN to rats before the induction of hypertension decreased LOX activity and aortic collagen content, and concomitant with this reduction, atherosclerotic changes were partially prevented.28 Similar to the LOX increase in hypertension, the cholesterol-induced increase in LOX may reflect a compensatory mechanism to vessel injury. Chvapil et al29 observed an increase in LOX in cholesterol-fed animals only after endothelial dysfunction and lipid accumulation, probably as a tissue response to enforce the connective tissue in the vessel wall. Future localization studies in human vulnerable and stable plaques should clarify a possible role of LOX in plaque integrity.

These latter studies on atherosclerosis were published more than 20 years ago; remarkably, little has been published in the last two decades about the direct relationship between LOX and atherosclerosis. The article by Rodríguez et al29 and the newly cloned LOXs provide a new look on LOX, offering new insight and perspectives on this interesting enzyme.

References

Lysyl Oxidase: New Looks on LOX
Ruud A. Bank and Victor W.M. van Hinsbergh

doi: 10.1161/01.ATV.0000033935.66786.DE
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/22/9/1365

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/