Editorials

Is Paraoxonase-3 Another HDL-Associated Protein Protective Against Atherosclerosis?

Bert N. La Du

The article by Reddy et al. in the present issue of Arteriosclerosis, Thrombosis, and Vascular Biology is the first report of expression of human paraoxonase-3 (PON3) and its ability to prevent the formation of mildly oxidized LDL and also to inactivate preformed mildly oxidized LDL.

Investigations on mammalian serum paraoxonase (PON), now called PON1, started nearly 50 years ago by Aldridge. There are 3 PON genes closely aligned on human chromosome 7 and mouse chromosome 6.

Research efforts on possible physiological functions of the PON family of enzymes have probably been hindered to some degree by their inappropriate designation as PONs (PON1, PON2, and PON3) and by the fact that most of our present knowledge of this homologous group of proteins has been limited to PON1, which does involve PON and arylesterase activities (reviewed by Durrington et al. in the present issue of Arteriosclerosis, Thrombosis, and Vascular Biology). However, other members of the PON family (PON2 and PON3) from human and rabbit sources have recently been examined in our laboratory (Draganov et al.; D.I. Draganov, personal communication), and these all completely lack PON activity and have very little, if any, arylesterase activity. Thus, PON activity of PON1 appears to be a distinctive marker of its more recent evolutionary origin than the other PONs, but this eliminates PON activity as being a common enzymatic feature shared generally by members of the PON family.

Kobayashi et al. pointed out that a fungal lactonase of Fusarium oxysporum has appreciable structural homology with human PON1. The fungal lactonase was earlier shown by this same group to hydrolyze aldonate lactones, α-pantoyl lactone, dihydrocoumarin, and homogentisic acid but not paraaxon.

Recently, the lactonase activities of purified human serum PON1 Q and R isozymes were investigated in our laboratory. Both PON1 isozymes can hydrolyze many aliphatic and several aromatic lactones, including 2-coumaranone, dihydrocoumarin, and homogentisic acid lactone. In addition, human PON1 hydrolyzes a number of the statin drugs (eg, lovastatin and simvastatin) as well as spironolactone and γ-hydroxybutyric acid lactone. Some of these new lactone substrates have been used in purifying and characterizing PON3 from rabbit serum, which has unusually high lactonase activity with lovastatin.

Of further cardiovascular interest is the finding that rabbit serum PON3 is closely associated with the HDL fraction, and it is even more effective than rabbit PON1 in protecting LDL from copper-induced oxidation. The human serum PON3 enzyme was also been found to be closely associated with the HDL fraction by Reddy et al. Thus, several common features have recently emerged suggesting that the hydrolytic capacity and the ability to protect against oxidative damage by LDL may be important clues involving some common physiological functions of the PON proteins.

Interestingly, the lactonase activity and the protection against oxidative damage of LDL require the free cysteine at position 284, but this residue is not essential for either PON or arylesterase activity. So far, lactonase activity with several of the lactone substrates tested does not directly predict the degree of protection against oxidative damage, but the 2 activities are clearly related. It may turn out that the mechanism by which protection is achieved is the hydrolysis of a potentially toxic endogenous lactone that would otherwise produce vascular damage. Unfortunately, neither arylesterase activity nor PON activity has predictive value concerning the degree of protection against oxidative damage. In any case, lactonase activity appears, at this time, to be a common property shared by the evolved PON enzymes.

The observations by Shih et al. that knockout mice lacking PON1 develop atherosclerosis only when fed an atherogenic diet suggest that this enzyme is a protector but perhaps not a major protector against this disease. An alternative explanation, however, is that the other PONs still present in the knockout mice are able to compensate to some degree for the PON1 deficiency, and this redundancy accounts for the less than expected clinical effect. The other PON enzymes have tissue levels and distributions different from those of PON1, and possibly different substrate specificity, but they may also be important protectors against tissue damage from oxidized HDL and LDL and may be able to inactivate chemical mediators of cardiovascular damage. As we learn more about the properties of these other PON proteins in the future, these questions will be answered, and the relationship between the PON family of enzymes and cardiovascular disease should become clear.

References

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