CHAPTER 8

PON1 GENOTYPES AND CORONARY HEART DISEASE

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Abstract: Paraoxonase type 1 (PON1) have emerged as predictor of coronary heart disease (CHD). To date it is not known if PON1 is a causal determinant of atherosclerosis. In mouse models and in vitro it has been shown that PON1 is functionally involved in atherosclerosis, as it inhibits both LDL-oxidation and atherosclerosis progression. In humans, it turned out to be more difficult to find evidence for causality, because epidemiological studies on PON1 levels and/or activity are sensitive methodological bias and confounding variables and do not distinguish between cause or consequence. PON1 genotype is fixed at conception and therefore not subject to most forms of bias, not affected by confounding variables and not a consequence of CHD. Therefore, a relationship between PON1 genotype and CHD would support causal involvement of PON1 in CHD.

In the past decades there have been a large number of studies on PON1 Q192R, L55M and C-107T genotype and CHD. A meta analysis of those studies showed no convincing relationship, indicating that there is currently no strong genetic support for causal involvement of PON1 in CHD.

Keywords: PON1, genotype, Coronary Heart Disease

The last decades a multitude of risk factors for coronary heart disease (CHD) have been established. Among these risk factors, low levels of high density lipoprotein (HDL) have emerged as one of the strongest (Gordon et al., 1989). There does not appear to be a single explanation for this protective role of HDL in CHD, but it is obvious that the proteins on HDL, which determine the function of the particle, play a major role in the protection against CHD. The cardioprotective effects of HDL have been attributed to enhanced cholesterol efflux and reversed cholesterol transport (RCT) from peripheral cells to the liver (Lewis and Rader, 2005). More recently, it has become apparent that HDL attenuates the bioavailability of a number of pro-oxidant species that have been implicated in the propagation of atherogenesis and inhibits the oxidative modification of LDL and therefore preventing the detrimental effects of this lipoprotein on the arterial wall (Navab et al., 1996). Paraoxonase type 1 (PON1), which is physically associated with the high-density lipoprotein (HDL) particle, plays a prominent role in those antioxidative and anti-inflammatory properties of HDL (Mackness et al., 1991).
The human paraoxonase family consists of three members; PON1, PON2 and PON3, which are aligned next to each other on chromosome 7 (Primo-Parmo et al., 1996). PON1 is the best characterized member of this family, whereas the main functions and properties of PON2 and PON3 remain to be elucidated. The current chapter will focus on PON1 genotypes and CHD.

PON1 is primarily a lactonase that hydrolyses aromatic and long chain aliphatic lactones, but is also capable of hydrolysing a variety of other substrates, including pesticides, nerve agents and phenylacetate (Costa et al., 1999). Furthermore, it has been suggested that PON1 may be able to prevent or limit oxidation of low-density lipoprotein (LDL) and therefore protect against atherosclerosis (Mackness et al., 1991). This latter hypothesis was proposed for the first time by Mackness in the early 1990s and resulted in an exponential gain in the number of studies to the role of PON-1 in CHD. More recently, it has been shown that PON-1 is also capable to hydrolyse the oxidised lipid derivates hydroy-docosahexaenoic acid (5-HETEL) and 4-hydroxy-docosahexaeonic acid (4-HDoHE), which are derivates of the oxidised fatty acids arachidonic acid and docosahexaenoic acid, respectively (Draganov et al., 2005; Khersonsky and Tawfik, 2005). Those oxidised lipid derivates are potent triggers of an inflammatory response and therefore determinants of atherosclerotic disease.

1. PON1 AND CHD: MOUSE MODELS

The most convincing evidence for causal involvement of PON1 in CHD is derived from studies in PON-1 null mice. Those PON1 null mice exhibited no detectable plasma paraoxonase activity, whereas their heterozygous counterparts exhibited 50% lower plasma paraoxonase activity compared with wild-type mice (Shih et al., 2000). PON1 null mice were unable to protect LDL against oxidation in a culture model of the artery wall and when fed a high-fat, high-cholesterol, cholate-containing diet, PON1 null mice developed significantly larger lesions than their wild-type and heterozygous littermates (Shih et al., 2000). Furthermore, when PON1 null mice were crossed with apoE null mice, PON1/apoE null mice developed significantly larger lesions than apoE null mice (Shih et al., 2000). LDL freshly isolated from PON1/apoE null mice had higher levels of biologically active phospholipids relative to LDL from apoE null mice, suggesting higher levels of oxidative stress in the double knockout mice. Similar to PON1 null mice, HDL from PON1/apoE null mice failed to protect LDL against oxidation. Taken together, these loss of function studies corroborate the hypothesis that PON1 protects against atherogenesis and is an important contributor to HDL’s antioxidant capacity.

In a model of PON-1 over-expressing mice it has been shown that their HDL is more resistant to lipid peroxidation than HDL from their control littermates (Oda et al., 2002). In a PON-1 over-expressing mouse model it was shown that PON1 transgenic mice exhibited enhanced abilities to protect LDL against oxidation and developed significantly smaller lesions than their non-transgenic littermates (Oda et al., 2002).