Minireview

Paraoxonases function as unique protectors against cardiovascular diseases and diabetes: Updated experimental and clinical data

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Abstract

Paraoxonase (PON) refers to a family of three enzymes, namely PON1, PON2, and PON3. PON1 and PON3 are found in circulation bound to high-density lipoprotein, whereas PON2 is an intracellular protein. PON1 was first discovered as an enzyme to hydrolyze the organophosphate pesticide paraoxon, an activity that both PON2 and PON3 lack. All three PON enzymes are able to degrade oxidized lipids and protect against oxidative stress. PON enzymes also act to suppress inflammation. Animal studies show a critical role for PON enzymes, especially PON1 in protecting against cardiovascular diseases and related disorders, including diabetes and metabolic syndrome. In line with the findings in experimental animals, accumulating evidence from clinical research also indicates that PON enzymes function as potential protectors in human cardiovascular diseases and related disorders. Identification of PON enzymes as important players in cardiovascular health will facilitate the development of novel preventive and therapeutic modalities targeting PON enzymes to combat cardiovascular diseases and related disorders, which collectively constitute the chief contributors to the global burden of disease. This review describes the biochemical properties and molecular regulation of PON and summarizes the major recent findings on the functions of PON in protecting against cardiovascular diseases and related disorders.

Keywords: Paraoxonase, pon enzymes, cardioprotection, cardiovascular diseases, diabetes, experimental animals

***Experimental Biology and Medicine* 2014; 239: 899–906. DOI: 10.1177/1535370214535897**

Introduction

Paraoxonase (PON) refers to a family of enzymes that includes three members in mammals, namely PON1, PON2, and PON3. PON1 was first identified by W.N. Aldridge in 1953 as an enzyme to hydrolyze paraoxon.[1,2] PON was thus named for its ability to metabolize paraoxon, the primary metabolite of the insecticide parathion. Upon identification in the mid 1990s of two closely related enzymes, the original PON became PON1, while the two additional enzymes were named PON2 and PON3. In contrast to PON1, neither PON2 nor PON3 exhibits any significant ability to hydrolyze paraoxon.

PON1 (43 kDa) is synthesized and secreted by the liver and is primarily associated with high-density lipoprotein (HDL) in plasma. PON1 catalyzes the breakdown of oxidized lipids and blocks oxidation of HDL as well as low-density lipoprotein (LDL). PON2 is an intracellular protein that is widely distributed in mammalian tissues. Similar to PON1, PON2 with a molecular mass of 44 kDa acts as an antioxidant to protect against oxidative stress. PON3 (40 kDa) is primarily expressed in liver and associated with HDL in plasma. Like other members of the PON gene family, PON3 has significant antioxidant activity in protecting both HDL and LDL from oxidation.

Biochemistry

Since its discovery, mammalian PON1 has been extensively studied with respect to its role in metabolizing pesticides, lipid peroxides, as well as a number of other substrates. In contrast, not much is known about PON2 and PON3.

This section focuses on the biochemistry of PON1 along with a description of recent findings on the biochemical properties of PON2 and PON3.

Biochemistry of PON1

PON1 is an excellent example of a multitasking protein, displaying at least two important biochemical functions: (1) hydrolysis of organophosphates (pesticides and nerve agents), and (2) protection of lipoprotein oxidation by catalyzing degradation of oxidized lipids. PON1 effectively hydrolyzes a variety of organophosphate pesticides and nerve agents, including paraoxon, diazoxon, chlorpyrifos-oxon, sarin, and soman.[3] Hydrolysis of these organophosphates by PON1 leads to their detoxification. Figure 1 illustrates the chemical reaction of PON1-catalyzed hydrolysis of paraoxon, an organophosphate pesticide.

Since paraoxon and other organophosphate toxicants are not present in the human body under normal conditions, other molecules would need to be the physiological substrates of PON1. Indeed, extensive studies have demonstrated that PON1 protects LDL and HDL from lipid peroxidation by catalyzing the degradation of oxidized lipids contained in the oxidized lipoproteins.[4] Notably, cysteine 284 is required for the enzyme's ability to hydrolyze oxidized lipids, but not for its activity against organophosphates. This suggests that different mechanisms of hydrolysis may operate toward organophosphates and oxidized lipids.[5] It is shown that PON1 can be inactivated by S-glutathionylation,[6] a redox mechanism characterized by formation of a mixed disulfide bridge between a protein sulfhydryl and the oxidized form of glutathione (GSSG).

In addition to hydrolyzing organophosphates, PON1 also hydrolyzes aromatic esters, preferably those of acetic acid. Indeed, phenyl acetate is one of the most commonly used substrates for assaying the enzymatic activity of PON1 in serum. More recently, PON1 has been reported to catalyze the hydrolysis of a variety of aromatic and aliphatic lactones as well as the reverse reaction, lactonization, of gamma- and delta-hydroxycarboxylic acids.7 PON1 is suggested to act as a lactonase or lactonizing enzyme. PON1, PON2, and PON3 can efficiently metabolize 5-hydroxy-eicosatetraenoic acid 1,5-lactone and 4-hydroxy-docosahexaenoic acid. 5-hydroxy-eicosatetraenoic acid 1,5-lactone and 4-hydroxy-docosahexaenoic acid are products of oxidation of arachidonic acid and docosahexaenoic acid, respectively. These compounds may represent the PON enzymes' endogenous substrates. PON1 may also possess other biochemical activities, such as metabolizing estrogen esters as well as certain drugs.

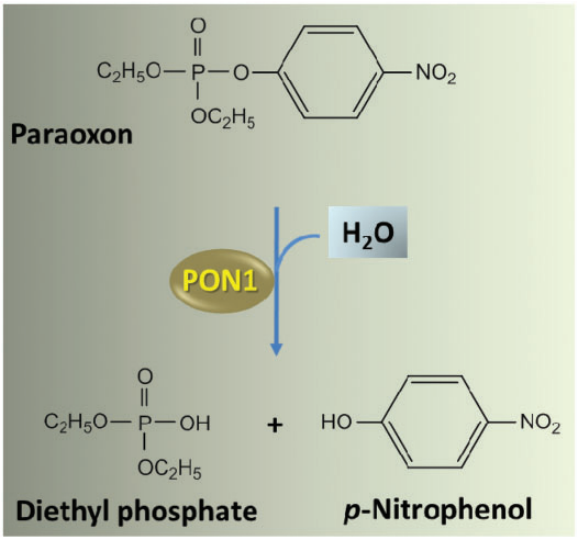

Figure 1 Hydrolysis of paraoxon by paraoxonase 1 (PON1). As illustrated, PON1-catalyzed hydrolysis of paraoxon forms diethyl phosphate and p-nitrophenol. (A color version of this figure is available in the online journal.)

Biochemistry of PON2 and PON3

As noted earlier, PON2 and PON3 lack the ability to hydrolyze organophosphates. However, PON2 and PON3 effectively hydrolyze lactones, and as such also act as lactonases. Of particular note is the ability of PON enzymes, especially PON2 to hydrolyze and thereby inactivate acrylhomoserine lactones, which are quorum-sensing signals of pathogenic bacteria.[8] PON3 has been shown to hydrolyze bulky drug substrates, such as lovastatin and spironolactone. Lavastatin is one of the seven available statin drugs for treating dyslipidemia. Spirinolactone is a selective antagonist of aldosterone receptors and has been used as an effective drug in the management of congestive heart failure.

Less is known regarding the detailed activities of PON2 and PON3 in metabolizing oxidized lipids. Similar to PON1, purified PON2 and PON3 are shown to inhibit lipid peroxidation of LDL *in vitro*. Since PON2 is an intracellular protein and not present in plasma, it is suggested to act as a protector against cellular oxidative stress. Indeed, intracellular overexpression of PON2 attenuates oxidative stress in vascular cells and protects against cell-mediated oxidation of LDL.[9,10]

Molecular regulation

In humans, PON1, PON2, and PON3 are localized next to each other on chromosome 7q21.3-22.1. Among the three members of the mammalian PON family, PON1 has been most extensively studied with regard to the regulation of gene expression. Multiple regulatory mechanisms and signaling pathways have been implicated in the regulation of PON1 gene expression. For instance, PON1 expression is inducible by various agents or biomolecules, including phenolic compounds,[11–13] aspirin,[14] statin drugs,[15] alcohol,[16] glucose,[17] and interleukin-6.[18] Conversely, several compounds such as bile acids, interleukin-1β, and tumor necrosis factor-α are found to suppress PON1 gene expression.[18,19]

A study in a cultured human liver cell line demonstrates a critical role for SP-1 and protein kinase C in the positive regulation of PON1 gene transcription.[20] The transcription factor SP-1 as well as sterol regulatory element-binding protein-2 is involved in statin-induced activation of PON1 gene expression in human liver and kidney cell lines.[15,21] SP-1 is also implicated in glucose-induced PON1 gene expression in cultured liver cells.[17] On the other hand, induction of

PON1 gene expression by dietary polyphenols, such as resveratrol and quercetin occurs via an aryl hydrocarbon receptor-dependent mechanism.[12,22] Nucleotide sequence analysis reveals a xenobiotic resPON enzymes element (XRE)-like sequence within the PON1 promoter, and this XRE-like sequence mediates the induction of PON1 gene transcription by phenolic compounds. In addition, evidence suggests regulation of PON1 by Nrf2 signaling, but to a lower extent, as compared with other antioxidant enzymes, such as heme oxygenase-1.[23] A more recent study reports a role for peroxisome proliferator-activated receptor gamma (PPARγ) pathway in regulating increased expression of PON1 gene by polyphenols in hepatocytes.[13]

PON2 is also inducible by polyphenols. In macrophages, induction of PON2 by polyphenols is shown to occur via PPARγ and activator protein 1 (AP-1) dependent mechanisms.[24] PON2 gene expression is upregulated by unesterified cholesterol and dexamethasone. Induction of PON2 expression by unesterified cholesterol occurs through activation of the phosphatidylinositol 3-kinase pathway.[25] A putative glucocorticoid resPON enzymes element in the promoter region of PON2 is suggested to mediate the activation of PON2 gene expression by glucocorticoid drugs.[26] The *in vivo* biological relevance of these two regulatory mechanisms of PON2 expression remains to be determined. Currently, the molecular regulation of PON3 gene expression is largely unknown. Nevertheless, the inducibility of PON enzymes, especially PON1 and PON2 by phenolic compounds may render them as key molecular targets for developing natural compound-based modalities to upregulate these enzymes for disease protection.

PON enzymes as protectors against cardiovascular diseases and diabetes: Animal studies

Animal experimental approaches

Both transgenic overexpression and gene knockout mouse models have been created to investigate the biological functions of PON isozymes in health and disease. In addition, recombinant PON proteins have been made available for studying the protective role of PON enzymes in disease conditions in experimental animals. Mice with homozygous knockout of PON1 or PON2 are born and reproduced adeptly, indicating neither of these two PON enzymes is essential for murine embryonic development. To date, PON3-null mouse model has not been reported in the literature. Viral vector-mediated gene transfer and siRNA-mediated gene knockdown have also been utilized to elucidate the biological functions of PON enzymes in various experimental models.

Selective chemical inhibitors of PON enzymes would be useful tools for studying the biological activities of PON enzymes. In this context, 2-hydroxyquinoline was claimed to be a selective inhibitor of PON1[27]; however, its usefulness as a specific inhibitor of PON1 in biological systems remains to be determined. Recently, a high throughput PON1 assay has been developed for discovery of small molecule modulators of PON1 activity.[28] With using this assay, a potent inhibitor of PON1, designated as BAS03551158, has been identified, which is 10-fold more potent than 2-hydroxyquinoline in inhibiting purified PON1.[28] However, this compound is less potent in inhibiting serum PON1 than 2-hydroxyquinoline. There are also studies showing selective inhibition of PON1 by negatively charged lipids.[29] However, as noted earlier for 2-hydroxyquinonline, the value of these PON1 inhibitors in biological systems remains unclear. As discussed later, PON enzymes play an important role in cardiovascular diseases and related disorders. Hence, there is a great need to develop selective and potent inhibitors of PON isozymes, which can be used in biological systems, including animal models to further delineate the molecular basis of protection as well as other novel biological activities of these fascinating proteins.[29]

Biological activities of PON enzymes in animal models

As stated earlier, PON enzymes hydrolyze oxidized lipids and protect against lipid peroxidation as well as cellular oxidative stress. In addition, these enzymes possess other novel biological functions, including anti-inflammation and stimulation of macrophage cholesterol efflux.[30,31] These findings implicate that PON enzymes may potentially affect a variety of disease processes involving oxidative stress and inflammation, such as atherosclerosis, diabetes and metabolic syndrome, hepatic injury, and infectious diseases. Furthermore, PON1 efficiently hydrolyzes various organophosphates, including pesticides and nerve agents,[3] implicating that this PON enzyme may also act as an important defense against organophosphate poisoning. The following sections discuss the role of PON enzymes in cardiovascular diseases as well as diabetes and metabolic syndromes in animal models.

PON enzymes as protectors in cardiovascular diseases in experimental animals

The best characterized biological activity of PON enzymes, especially PON1 in experimental animals is the protection against atherogenesis. There is substantial evidence for an important role of all three PON enzymes in protecting against experimental atherosclerosis, vascular inflammation, and oxidative stress.[32,33] In this regard, targeted disruption of PON1 markedly augments high-fat diet-induced vascular inflammation, oxidative stress, and atherosclerosis. Conversely, either transgenic overexpression of PON1 or viral vector-mediated PON1 gene transfer greatly attenuates the above detrimental effects caused by high-fat diet.[34–37] Furthermore, HDL isolated from the PON1-deficient animals is unable to protect LDL from lipid peroxidation, suggesting that PON1 mediates the antioxidant activities of HDL.[34] Recently, PON1 gene transfer is found to also attenuate vascular oxidative stress and improve vasomotor function in apolipoprotein E-deficient mice with pre-existing atherosclerosis, pointing to a therapeutic role for PON1 in atherogenesis.[38]

The protective effects of both PON2 and PON3 in experimental atherosclerosis have been recently demonstrated. Despite lower levels of very-low density lipoprotein and LDL cholesterol, mice deficient in PON2 develop

significantly larger atherosclerotic lesions compared with their wild-type counterparts.[39] Three potential mechanisms may account for the enhanced atherosclerotic lesions in PON2-deficient mice. They are: (1) enhanced inflammatory properties of LDL, (2) diminished antiatherogenic capacity of HDL, and (3) a heightened state of oxidative stress coupled with an exacerbated inflammatory PON enzymes from PON2-deficient macrophages.[39] In line with these findings, adenovirus-mediated expression of PON2 protects against the development of atherosclerosis in apolipoprotein E-deficient mice.[40] Similarly, adenovirus-mediated gene transfer of human PON3 augments HDL antioxidant effects against lipid peroxidation of LDL and protects against the progression of atherosclerosis in apolipoprotein E-deficient mice.[41] Transgenic overexpression of human PON3 in mice also attenuates atherosclerosis lesion and vascular inflammation in both wild-type mice fed atherogenic diet and in LDL receptor-deficient mice.[42] Notably, a recent study demonstrates that transgenic overexpression of a human PON gene cluster containing PON1, PON2, and PON3 not only represses atherosclerosis, but also promotes atherosclerotic plaque stability in apolipoprotein E-deficient mice.[43] In summary, there is substantial evidence from studies in animal models supporting a critical role for PON enzymes in protecting against atherosclerosis. However, it remains unknown if PON enzymes also play a protective role in other forms of cardiovascular disorders.

PON enzymes as protectors in diabetes and metabolic syndrome in experimental animals

Diabetes is characterized by increased inflammation and oxidative stress, and by decreased PON1 activity.[44] Transgenic overexpression of PON1 attenuates diabetes-induced macrophage oxidative stress, represses diabetes development, and decreases mortality in mice treated with streptozotocin.[30,45,46] Conversely, mice lacking PON1 are more susceptible to streptozotocin-induced diabetes and oxidative stress.[45] Streptozotocin is a commonly used chemical model for inducing type 1 diabetes in experimental animals. It has been suggested that pharmacological and nutritional intervention directed toward increasing PON1 activity may be beneficial in arresting diabetes development and its cardiovascular complications.[45] Recently, the potential role of PON2 in diabetes has been studied in cellular systems under diabetic conditions. It is shown that PON2 decreases high glucose-induced macrophage triglyceride accumulation and oxidative stress by inhibiting NADPH oxidase and diacylglycerol acyltransferase-1.[47] Hypertriglyceridemia is an independent factor for atherosclerosis and is also associated with diabetes. As such, accumulation of triglycerides by macrophages under diabetic conditions may promote foam cell formation and contribute to diabetic vascular complications. Thus, use of appropriate means to augment macrophage PON2 expression might attenuate macrophage atherogenicity and foam cell formation and the resulting vascular complications in diabetes.

There is also evidence supporting a beneficial role for PON enzymes in metabolic syndrome and associated cardiovascular complications. For instance, transgenic overexpression of human PON3 in mice is shown to decrease adiposity and lower circulating leptin levels, implicating a critical role for PON3 in protecting against obesity.[42] In mice with combined leptin and LDL receptor deficiency, a model of metabolic syndrome, adenovirus-mediated overexpression of human PON1 significantly reduces the total atherosclerotic plaque volume, the volume of plaque macrophages, and the amount of plaque-associated oxidized LDL.[46]

PON enzymes as protectors against cardiovascular diseases and diabetes: Clinical research

Clinical study approaches and general considerations

Clinical research is involved in the patient-oriented research that is defined as research conducted with human subjects for which an investigator (or colleague) directly interacts with human subjects or with *in vitro* studies to utilize the materials of human origin such as tissues, specimens, and cognitive phenomena. The potential involvement of PON enzymes in human diseases has been extensively investigated in clinical research over the last decade. Numerous studies involve the evaluation of changes in the levels or activities of PON enzymes in sera of patients with various disease conditions.[48–50] Many others involve the epidemiological assessment of the association of PON gene polymorphisms with risk or incidence of particular diseases.[48–51] There are also studies aiming to link gene polymorphisms to changes in PON activities, and further, to risk of disease development. These studies in human subject have provided important information on the involvement of PON enzymes in disease processes[48–51]; however, they do not establish a casual role for PON enzymes in disease pathophysiology. Nevertheless, analysis of the data obtained from both experimental animal models and human studies has yielded important insights into the function of PON enzymes in human health and disease. The following sections begin with a description of common PON gene polymorphisms, followed by a summary of the major clinical and epidemiological findings on the involvement of PON enzymes in prevalent human diseases.

PON gene polymorphisms

Among the three members of human PON enzymes, PON1 gene polymorphisms and their influence on enzyme activity have received the most extensive studies.[52–57] PON1 gene has two well-studied polymorphisms in the coding region, which have been associated with various human diseases. Substitution of glutamine (Gln or Q) by arginine (Arg or R) at position 192 and methionine (Met or M) by leucine (Leu or L) at position 55 of the amino acid sequence of the protein independently influence the PON1 activity and constitute an important molecular basis for interindividual variability.[54–56] These two coding region polymorphisms of PON1 are designated as Gln192Arg (or Q192R) and Met55Leu (or M55L), respectively.

The Q192R polymorphism exhibits a striking substrate-specific difference in the hydrolytic activity of the enzyme. The 192 R alloenzyme shows greater activity toward paraoxon hydrolysis than the 192Q alloenzyme, whereas the 192Q alloenzyme provides greater protection against the accumulation of lipid peroxides on LDL than the R alloenzyme *in vitro*.[58,59] However, it should be noted that the *in vitro* effects of the PON alloenzymes on LDL oxidation may not be translated into corresponding *in vivo* activities in human subjects.

The M55L polymorphism also affects PON1 activity/concentration, though less than that of the Q192R polymorphism. Individuals carrying a leucine at position 55 (L alloenzyme) have a higher PON1 concentration than those with a methionine (M alloenzyme) at this position.[60] There are also five known polymorphisms located within the PON1 promoter region that have been shown to affect PON1 expression. However, their association with human diseases has not been clearly demonstrated.[33,61] Figure 2 illustrates the impact of Q192R and M55L polymorphisms on serum PON1 activity/concentration.

A number of polymorphisms have been identified in PON2 gene. Among them substitution of cysteine by serine at position 311 of the amino acid sequence of the protein, designated as Cys311Ser (or C311S), has been extensively investigated. The C311S polymorphism has been found to affect PON2 activity (with the C variant showing impaired lactonase activity)[62] and to be associated with the development of certain human diseases.

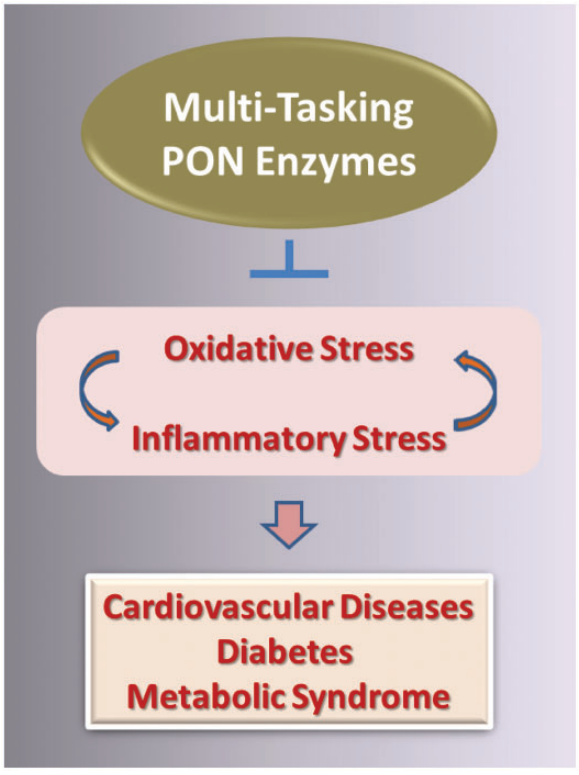

Figure 2 PON1 gene polymorphisms and their effects on serum PON1 activity or concentration. (A color version of this figure is available in the online journal.)

Much less is known about the gene polymorphisms of human PON3 and their association with diseases. A study in an Italian population has identified five point mutations in PON3 gene, with three being silent mutations and two being missense mutations. The two missense mutations give rise to amino acid substitutions at position 311 (S to T) and 324 (G to D).[63] Currently, the effects of the genetic variations on PON3 activity and their association with diseases remain unknown though a study shows an association of PON3 gene variation with PON1 activity.[64]

PON enzymes as potential protectors in human cardiovascular diseases

A beneficial role for PON enzymes in atherosclerosis is strongly supported by transgenic overexpression and gene knockout studies in experimental animals. There is also ample evidence supporting a protective role for PON enzymes, especially PON1 in human coronary heart disease. Many epidemiological studies suggest a correlation between low serum PON1 activity and coronary heart disease. Numerous gene polymorphism studies demonstrate an association between functional polymorphisms of PON1, such as Q192R and M55L, and the development of coronary heart disease; however, some studies report conflicting results.[33,65] In general, serum PON1 activity is a better predictor of risk for coronary heart disease than PON1 genotype. Therefore, it becomes necessary that when performing case–control studies, the observed differences in enzyme activities are matched by genotypes. In this context, a recent study demonstrates that PON1 genotype exhibits significant dose-dependent association (QQ192>QR192>RR192) with decreased levels of serum PON activity and increased levels of systemic oxidative stress.[66] Thus, among the three genotypes, QQ192 is associated with the lowest levels of PON1 activity and the highest levels of systemic oxidative stress, whereas RR192 exhibits the opposite. For individuals with either PON1 RR192 or QR192 genotype, those while with the QQ192 genotype have an increased risk of all-cause mortality and major adverse cardiac events. The incidence of major adverse cardiac events is significantly lower in individuals in the highest PON1 activity quartile compared to those in the lowest activity quartile.[66] These observations are consistent with findings in murine models and provide evidence for a cardiovascular protective function of PON1 in humans.

A more recent study demonstrates that among symptomatic male coronary heart disease patients, carriership of the PON1 192Q or 55 M alleles is associated with an increase of the 10-year risk of myocardial infarction and mortality from ischemic heart disease.[67] Both 192Q and 55 M isotypes are associated with lower PON1 activity/concentration (Figure 2). The data thus support the notion that PON1 activity may predict the adverse coronary events and that PON1 may be a potential target of secondary prevention of coronary heart disease. In line with a protective role for PON1 in cardiovascular diseases as well as other aging-related disorders, a recent meta-analysis of studies involving a total of 5962 subjects reveal that subjects carrying PON1 192 RR and QR genotypes are favored in reaching

extreme ages, implicating that PON1 may be a longevity gene.[68]

Gene polymorphisms of PON2 are also associated with an increased risk of cardiovascular diseases. As noted earlier, the C311S polymorphism of PON2 affects PON2 activity, with the C isoform showing impaired lactonase activity.[62] A recent study in an Italian population reports that patients with at least one PON2 C allele represent a category of subjects at a higher risk for the development of acute myocardial infarction with a worse prognosis.[69] Similarly in a Polish population, the genotype with the C allele of the PON2 gene is also depicted as a risk factor for large vessel disease stroke, further supporting a vascular protective role for PON2 in humans.[70] These observations, however, contradict an early study showing S allele carriers of the PON2 C311S polymorphism at a higher risk of developing coronary heart disease.[71]

PON enzymes as potential protectors in human diabetes and metabolic syndrome

There are a number of clinical studies showing a significant decrease in serum PON1 activity in diabetic patients compared to control subjects. The decrease in serum PON1 activity is also associated with the development of diabetic complications. A more recent study demonstrates that lower serum PON1 activity is related to higher plasma C-reactive protein and obesity.[72] These observations indicate a potential protective role for PON1 in diabetes and metabolic syndrome, which is also in line with findings in animal models. However, epidemiological studies on the association of gene polymorphisms of PON1 with diabetes have produced inconsistent results. Some studies demonstrate that the PON1 genotypes causing decreased PON1 activity (e.g. PON1-192QQ and PON1-55MM) are associated with poorer diabetes control and complications.[73] In contrast, other studies report that the PON1-192 R allele causing increased PON activity can be an independent cardiovascular risk factor in type 2 diabetic patients.[74]

As a further line of supportive evidence for a beneficial role of PON1 in diabetes, the T allele of PON1 promoter polymorphism (−107 C>T) causing lower expression of PON1 is reportedly associated with lower serum levels of the enzyme and an increased risk for coronary heart disease in type 2 diabetic patients.[75] Moreover, the lower expression genotype of PON2 (–107TT) is also associated with higher blood glucose concentration in non-diabetic subjects, suggesting this polymorphism may predispose the individuals to insulin resistance.[76] Thus, majority of clinical and epidemiological studies support the view that PON1 may act as a potential protector in diabetes and its complications, as well as in metabolic syndrome.

Conclusion and perspectives

As illustrated in Figure 3, PON enzymes are multitasking antioxidant enzymes that have a beneficial role in a variety of oxidative stress- and inflammation-associated pathophysiological conditions, especially cardiovascular disorders, diabetes, and metabolic syndrome, in experimental animals. Substantial evidence from studies in human

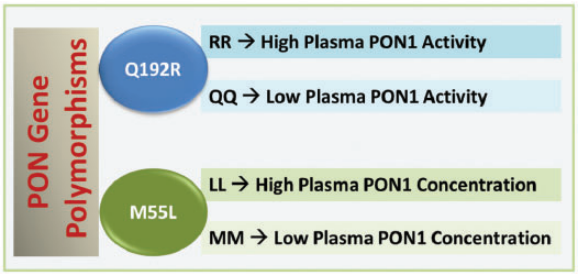

Figure 3 Multitasking PON enzymes in protecting against cardiovascular diseases, diabetes, and metabolic syndrome. (A color version of this figure is available in the online journal.)

subjects also suggests that PON enzymes act as protective factors in human atherosclerotic coronary heart disease, diabetes, and metabolic syndrome. Currently, there is a great need to translate the important discoveries on PON isozymes into effective interventional strategies, which involve a PON-dependent mechanism, to prevent and treat human cardiovascular diseases and related disorders.

Author contributions: All the authors participated in writing and review of the manuscript.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Institutes of Health (NIH) grants HL093557 (YR Li) and 7R15AT005372 (Z Jia).

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(Received February 24, 2014, Accepted March 25, 2014)