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Review

Paraoxonases and infectious diseases

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ABSTRACT

The paraoxonases (PON1, PON2 and PON3) are an enzyme family with a high structural homology. All of them have lactonase activity and degrade lipid peroxides in lipoproteins and cells. As such, they play a role in protection against oxidation and inflammation. Infectious diseases are often associated with oxidative stress and an inflammatory response. Infection and inflammation trigger a cascade of reactions in the host, known as the acute-phase response. This response is associated with dramatic changes in serum proteins and lipoproteins, including a decrease in serum PON1 activity. These alterations have clinical consequences for the infected patient, including an increased risk for cardiovascular diseases, and an impaired protection against the formation of antibiotic-resistant bacterial biofilms. Several studies have investigated the value of serum PON1 measurement as a biomarker of the infection process. Low serum PON1 activities are associated with poor survival in patients with severe sepsis. In addition, preliminary studies suggest that serum PON1 concentration and/or enzyme activity may be useful as markers of acute concomitant infection in patients with an indwelling central venous catheter. Investigating the associations between paraoxonases and infectious diseases is a recent, and productive, line of research.

1. Paraoxonases have a role in the innate immune system

The paraoxonases (PON1, PON2 and PON3) are the protein products of a gene family that evolved *via* duplication of a common precursor. They have high structural homology with each other (approximately 60% in the amino acid sequence and 70% in nucleotide) [1] and the three genes are located in adjacent positions of chromosome 7 (7q21.3) [2]. PON1 is a lactonase and ester hydrolase which catalyzes the hydrolysis of thiolactones and some xenobiotics such as organophosphate esters, unsaturated aliphatic esters, aromatic carboxylic esters and carbamates [3–5]. PON2 and PON3 do not degrade xenobiotics, but have lactonase activity [6]. All three PON enzymes degrade lipid peroxides in low-density lipoproteins (LDL) and high-density lipoproteins (HDL) [6]. In addition, PON2 reduces intracellular oxidative stress and decreases apoptosis [7]. In humans, *PON1* and *PON3* genes are mainly expressed in the kidney and liver, and the enzymes are found in blood bound to HDL particles [3,8–10]. Conversely, the *PON2* gene expression is almost ubiquitous, and its protein product is an intracellular enzyme that is not found in the circulation [11].

Paraoxonases are polymorphic enzymes. Playfer et al. [12] were the first to report that PON1 activity was determined by a single autosomal locus with two possible alleles. In 1983, Eckerson et al. [13] reported that two isoenzymes (termed Q and R) differed in a particular property: the R allozyme having a greater ability to hydrolyze paraoxon than the Q allozyme. Later, this group sequenced the coding region of PON1, and two polymorphic sites were identified: Leu/Met in position 55 (polymorphism $PON1_{55}$) and Arg/Gln in position 192 (polymorphism $PON1_{192}$). Polymorphism $PON1_{192}$ clearly correlated with phenotypes Q and R described above: individuals with the Gln variant at position 192 belonging to the phenotype Q, while those with the Arg at position 192 exhibited the phenotype R [14]. In 1997, Blatter-Garin et al. [15] studied the influence of the $PON1_{55}$ genotype on the enzyme's activity and concentration in serum of diabetic patients, and observed significant differences with respect to the different isoforms *i.e.* individuals who had a Leu at position 55 (L isoform) had higher concentrations of PON1 than carriers of a Met (M isoform), and these increases in paraoxonase concentrations correlated with parallel increases in enzyme activity. More recently, several other polymorphic sites in the

Abbreviations: AHL, *N*-acyl homoserine lactones; APR, acute-phase response; CCL2, chemokine (C—C motif) ligand 2; CRP, C-reactive protein; CVC, central venous catheter; HDL, high-density lipoproteins; HIV, human immunodeficiency virus; LDL, low-density lipoproteins; PON, paraoxonase; PPAR γ, peroxisome proliferator-activated receptor-γ; SOFA, Sequential Organ Failure Assessment

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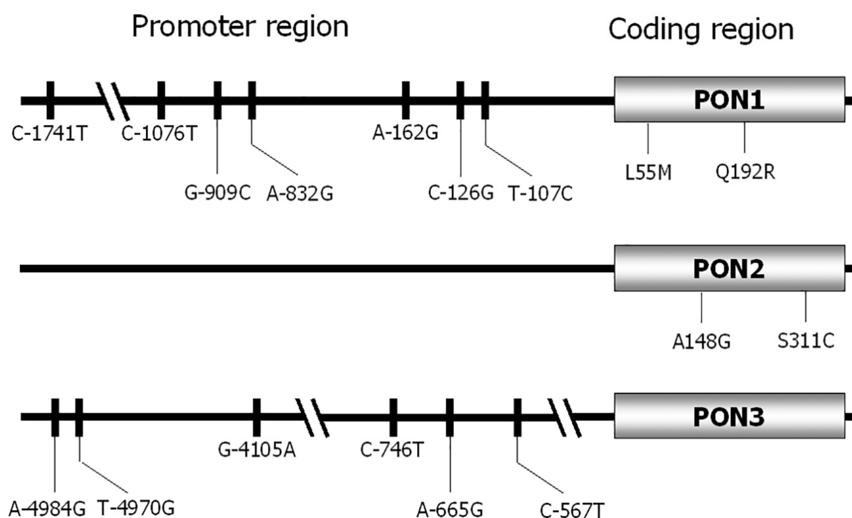

Fig. 1. Polymorphisms in the promoter and coding regions of paraoxonases (PON) 1, 2, and 3.

promoter region of the human *PON1* gene have been described at − 107, − 126, − 162, − 832, − 909, − 1076, and − 1741 positions [16,17]. Among these polymorphisms, T (− 107) C appears to be associated with variations in concentration and activity of PON1 in serum. Indeed, the effect of $PON1_{55}$ on serum PON1 concentrations appears to be due to $PON1_{-107}$ polymorphism, with which it is in strong linkage disequilibrium. More recent studies demonstrated that PON2 and PON3 are also polymorphic enzymes, and that $PON2_{148}$, $PON2_{311}$, and six different *PON3* polymorphisms are in linkage disequilibrium, and co-segregate together [18]. The effects on the function of these enzymes are similar [18–20] (Fig. 1).

PON1 degrades oxidized lipids in LDL and HDL and inhibits the synthesis of the pro-inflammatory chemokine (C—C motif) ligand 2 (CCL2) [21]. Watson et al. [22] demonstrated that treatment of oxidized LDL with purified PON1 significantly reduces the ability of this lipoprotein to induce interactions between monocyte and endothelial cells, and that this effect was associated with a decrease in the amount of oxidized phospholipids present in the LDL particles (especially oxidized 1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphoryl choline). These authors suggested that the physiological function of PON1 was to protect against induction of inflammatory responses by hydrolyzing the pro-inflammatory oxidized phospholipids in LDL. A subsequent study [23] demonstrated that, in addition to LDL particles, PON1 also protects HDL from oxidation. These *in vitro* experiments were confirmed in experimental animals when Shih et al. [24] reported that HDL particles obtained from mice deficient of the *PON1* gene lacked the ability to protect LDL from peroxidation. The same research group later showed that mice double-deficient for *PON1* and *apolipoprotein E* genes have higher levels of *in vivo* lipid peroxidation products than the animals that were deficient in apolipoprotein-E alone [25]. Schweikert et al. [26] showed that PON2 and PON3 protect several human cell lines against *Pseudomonas aeruginosa* infection. In addition, other investigators found that PON2-deficient mice have a higher sensitivity to bacterial infections than wild-type mice [27,28]. Several studies suggest that PON1 participates in the protection conferred by HDL against different infectious agents, including bacteria [29,30] and viruses [31,32]. Overall, these results indicate that the enzyme proteins of the PON family can be considered part of the innate immunity system [33].

2. Paraoxonases are potential anti-biofilm agents

The extensive use of catheters and the implantation of artificial prostheses is one of the greatest progresses in Medicine. However, an important side effect of these maneuvers is the susceptibility to infections which are difficult to treat because bacteria develop biofilms at the site of the intervention, and are becoming resistant to antibiotics currently available. Biofilms are evolutionary adaptations by bacteria which enables them to survive in hostile environments, and to colonize new ecological niches [34,35]. A biofilm is an aggregation of bacteria, often composed of millions of microorganisms, embedded within a self-generated matrix composed of extracellular proteins, DNA, and polysaccharides. Bacteria present in biofilms have high resistance to antimicrobial agents. Polysaccharides in biofilms are composed, mainly, of *O*- or *N*-acylated monosaccharides. The most common extracellular polysaccharides are poly-β-1,6-*N*-acetylglucosamine, cellulose, and alginate. The bacteria within the biofilms can develop specialized and coordinated phenotypes. These include antibiotic resistance and nutrient utilization together with expression of virulence factors and surface molecules [36–41]. A major concept in bacterial biofilm formation is that of quorum sensing. This phenomenon is defined as the coordination of the bacterial behavior *via* the accumulation of signaling molecules. Quorum sensing relies on the phenomenon of signaling molecule concentrations reaching a critical threshold resulting in the modulation of certain target genes triggering biofilm formation [42]. In Gram-negative bacteria, *N*-acyl homoserine lactones (AHL) have been identified as the major signaling molecules in this communication system [43,44]. In spite the high number of Gram-negative species, only a few varieties of AHL are involved in quorum sensing (Table 1). The first reported quorum sensing AHL was identified from *Vibrio fischeri* as *N*-(3′-oxohexanoyl)-L-homoserine lactone (3-oxo-C_6-AHL) that is synthesized by the LuxI protein [45,46]. Probably the most well documented bacteria in relation to quorum sensing is *P. aeruginosa*. This bacterium colonizes the lungs of patients with cystic fibrosis, and forms a biofilm on the epithelial cells of the airways [47].

Table 1
Quorum sensing-related acyl homoserine lactones (AHL) employed by several Gram-negative bacteria.

Organism	Molecule
Aeromonas hydrophila	*N*-butanoyl-AHL
Aeromonas salmonicida	*N*-butanoyl-AHL
Agrobacterium tumefaciens	*N*-(3-oxo-C_8)-AHL
Burkholderia cepacia	*N*-C_8-AHL
Erwinia carotovora	*N*-(3-oxo-C_6)-AHL
Pseudomonas aeruginosa	*N*-(3-oxo-C_{12})-AHL
	N-C_4-AHL
Pseudomonas chlororaphis	*N*-C_6-AHL
Rhodobacter spheroides	7,8-*cis*-*N*-C_{14}-AHL
Vibrio fischeri	3-oxo-C_6-AHL

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