Review Article

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A critical review on human serum Paraoxonase-1 in the literature: truths and misconceptions

İnsan serum Paraoksonaz-1 enzimi ile ilgili yayınların eleştirel olarak gözden geçirilmesi: gerçekler ve kavram yanılgıları

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Abstract: Human serum paraoxonase 1 (PON1) appears to play an important role in the development of a large variety of diseases with an inflammatory component including heart disease, diabetes, rheumatic diseases, neurological diseases and cancer. As such PON1 research is rapidly expanding into new biomedical fields. Unfortunately, this rapid expansion has resulted in a number of problems due to poor experimental design and the spreading of misconceptions in the literature. This review seeks to describe the basic properties of PON1 and the problems and misconceptions that have arisen.

Keywords: hastalık; lactonase; paraoxonase; polymorphisms.

Öz: İnsan serum paraoksonaz -1 (PON1) enzimi, kalp hastalığı, diyabetes mellitus, romatizmal hastalıklar, nörolojik hastalıklar ve kanser dahil olmak üzere inflamatuvar bileşeni olan çok çeşitli hastalıkların gelişiminde önemli bir rol oynamaktadır. Bu nedenle PON1 araştırmaları hızla yeni biyomedikal alanlara doğru genişlemektedir. Maalesef bu hızlı genişleme, deneysel tasarımın zayıf olması ve yanlış anlamaların literatürde yaygınlaşması gibi bir takım sorunlara yol açmıştır.

Bu eleştirel inceleme, PON1'in temel özelliklerini ve yayınlarda gözlenen sorunları ve yanılgıları açıklamayı amaçlamaktadır.

Anahtar kelimeler: hastalık; laktonaz; paraoksonaz; polimorfizmler.

Introduction

The paraoxonase (PON) multi-gene family consists of three enzymes: PON1, PON2 and PON3. The genes for which are located adjacent to each other on human chromosome 7 (q21.22). All share the considerable similarity in the amino-acid sequence. All three members of the PON family are able to retard lipid (per)oxidation in lipoproteins and cell membranes and are believed to be important in the development of diseases with an inflammatory component such as cardiovascular diseases, rheumatic diseases and cancer [1]. Since PON1 has the capability to hydrolyse various substrates (including lactones, thiolactones, organophosphorus triester pesticides and nerve gases, arylesters, oestrogen-esters, cyclic carbamates and glucuronide drugs) [1–3], it may have varied physiological roles in many diseases (inflammation, organophosphate intoxication, drug metabolism, cardiovascular disease, etc.,). So, PON1 activity has been extensively studied in many diseases since 1986. In this review, we searched the literature in PubMed between 1982 and 2020, with the search term "paraoxonase + arylesterase" and limiting the search to clinical trials, randomised controlled trials and clinical studies. A total of 775 results were found and evaluated.

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With the number of investigations in the literature rapidly increasing, some misconceptions have arisen. This review seeks to point out potential problems and pitfalls in the hope that they will be addressed and avoided.

PON1: Structure, genetics and substrate specificity

Human serum paraoxonase1 (PON1) is the best-known member of the paraoxonase multi-gene family which also includes PON2 and PON3. PON1 is a circulating Ca^{2+}-dependent enzyme with a molecular mass of 43 kDa and containing 354 amino acids [1–3], which is classified as an aryldialkylphosphatase (EC 3.1.8.1) [1]. PON1 is mainly synthesized by the liver and then secreted into the bloodstream, where it is tightly bound to high-density lipoprotein (HDL) particles [4]. PON2 appears to be the ancestral family member [5, 6]. The term paraoxonase is originally derived from the enzyme's ability to hydrolyse paraoxon (diethyl p-nitrophenyl phosphate), which is the active metabolite of the insecticide parathion [1, 7].

The structure of PON1 is a six-bladed beta-propeller with a central tunnel containing two calcium ions. One of these calcium ions is structural and therefore essential for the conformational stability of the enzyme while the second ion is catalytic [8, 9]. The removal of calcium from PON1 by the addition of EDTA results in the inactivation of Ca^{2+}-dependent activities, including paraoxon and phenyl acetate hydrolysis, however, it does not affect the ability of PON1 to protect low-density lipoprotein (LDL) from oxidation. Different active sites may therefore exist on PON1 for Ca^{2+}- dependent activities and for protecting LDL from oxidation [10]. The amino terminal end of the protein contains hydrophobic amino acid residues that play a role in its binding to HDL and to other proteins such as apoA1 and also in its self-aggregation [11]. According to recent findings, modulating the active site hydrophobicity of PON1 is a key factor that could affect the organophosphatase activity of the enzyme [9].

A histidine–histidine (His) catalytic dyad is proposed to be involved in the catalytic mechanism of PON1 in which His-115 acts as a general base to deprotonate a single water molecule while His-134 increases His-115 basicity via a proton shuttle mechanism [12]. However, Grunkemeyer et al. based on His-dyad mutagenesis data recently reported that the dyad likely does not participate directly in catalysis, but may play an important role in substrate binding or orientation [13].

PON1 is a highly promiscuous enzyme and will hydrolyse a large variety of substrates including lactones, thiolactones, organophosphorus triester pesticides and nerve gases (paraoxon, diazoxon, sarin and soman to name a few), arylesters, oestrogen-esters, cyclic carbamates and glucuronide drugs [1, 14]. Due to these various enzymatic activities, the role of PON1 in detoxifying organophosphate compounds, drug metabolism, cardiovascular disease, and other diseases, has been extensively studied. These activities possibly explain the varied physiological roles of this enzyme. PON1 has been closely linked to the reduction of oxidative stress and inflammation, which are important features that can markedly affect the development of atherosclerotic plaques and cardiovascular events [1, 15]. Experiments with PON1 knockout mice have indicated that PON1 absence leads to an increase in endothelial adhesion molecules and oxidative stress, confirming the role of this enzyme in preventing the onset of atherosclerosis [16, 17].

Detailed structure/function studies have concluded that the natural substrates for PON1 are lactones and lipophylic lactones form the primary substrates [7, 18, 19]. The aromatic nature of amino acids in the active site of PON1 could explain why the enzyme prefers lipophilic substrates [20]. PON1 is able to hydrolyse a wide range of lactones. All three members of the PON family (PON1, PON2 and PON3) share this property of being lactonases, albeit with distinct substrate specificities [7].

N-acylhomoserine γ-lactones (AHL) are produced by gram negative bacteria and regulate bacterial virulence and biofilm formation. All three PONs hydrolyse AHL (a process known as quorum quenching) with PON2 having the greatest efficacy, the resulting metabolites are inactive therefore the PON family could be important in preventing bacterial infections [21].

In recent years attention has turned to δ-lactone eicosanoids as PON substrates. These compounds are metabolites of arachidonic acid and mediate a number of metabolic processes *in vivo*. 5-hydroxy-eicosatetraenoic acid 1,5 lactone (5-HL) is a substrate for all three PONs. PON1 has the greatest hydrolytic efficacy followed by PON3 with PON2 having little activity towards this substrate [22]. PON3 has by far the highest activity towards two other eicosanoids, cycloepoxycyclopentenone (cyclo-EC) and 5,6 dihydroxy-eicosatrienoic acid lactone (5,6-DHTL) followed by PON1 again with PON2 having little or no activity towards these substrates [22, 23]. Interestingly, this order of hydrolytic efficacy also applies to the hydrolysis of oestrogen esters by the PON family indicating a preference of PON3 for bulky cyclic groups. Lactonase activity in the endothelium can influence vascular dilation. In this context, Gilad et al. [24] recently showed that PON1 penetrates endothelial cells and is able to reduce 5,6-DHTL-dependent vasodilation through its lactonase activity.

PON1 inhibits lipid oxidation in LDL, thereby reducing levels of oxidized lipids that are critical for the initiation and propagation of atherosclerosis and is believed to play a central role in the antioxidant activity of HDL [1]. PON1 is also an important determinant of HDL dysfunctionality [15]. In addition, there is growing evidence that PON1 may exert part of its atheroprotective effect through regulating cholesterol efflux from macrophages and maintaining cholesterol homeostasis [25].

The PON1 gene is highly polymorphic in human populations and more than 400 single-nucleotide polymorphisms (SNPs) have been identified in the coding region, introns and regulatory regions. Although the effects of many of these SNPs on PON1 activity or concentration remain unidentified for those that have been identified, their greatest effect has been observed on PON1 activities. The effects of these SNPs can lead to differences in PON1 activity of up to 40 times and differences in PON1 concentration of 15 times between people [1, 26]. The SNPs may affect splicing and polyadenylation efficiency, message stability or transcription factor binding [26]. Four functional SNPs have been established, two are located in the coding region (PON1-Q192R (rs662) and PON1-L55M (rs854560)) and two in the promoter region (–108 (rs0705379) and –162 (rs705381)) [27]. The effects of these SNPs on PON1 activity and concentration have been the subject of many excellent reviews and will not be dealt with here. Interested readers are referred to the following references [1–3, 14, 15, 28, 29]. PON1 is also subject to epigenetic regulation via DNA-methylation and microRNA binding, which, again has been the subject of extensive recent reviews [30–32] and not repeated here.

Problems and misconceptions

Methodological problems

Lack of a physiologically relevant substrate

The lack of a physiologically relevant PON1 substrate for high throughput analysis of clinical studies, hampers the discovery of clinically relevant pathways and mechanisms by which PON1 may be involved in disease development. This also means that a variety of substrates are used to measure PON1 activity such as paraoxon, diazoxon, phenyl-acetate, homocysteine thiolactone etc., These do not necessarily reflect the physiological activity of PON1, make comparisons between studies using different substrates difficult and generally add to some of the misconceptions surrounding PON1 (see later).

Study design

Because of the over 40 fold variation in PON1 activity between individuals which has a large genetic (and epigenetic) component due, as far as is currently understood, largely to the Q192R, L55M and C-108T SNPs, case-control studies require accurate matching by PON1 genotype (and preferably haplotype) to prove any relationship between PON1 and disease. Most studies in the literature lack any genetic matching, giving a high probability of a type II statistical error i.e. any findings are more than likely completely accidental [28].

There is also a very large variation in the distribution of PON1 SNPs between ethnic groups and particularly between Caucasians and Eastern Asians (Chinese, Japanese and Thais etc.,) [1] which also needs to be controlled in clinical studies.

Use of EDTA treated samples

Despite Erdos and Boggs first showing in 1961 that EDTA inhibited PON1 [33] some researchers persist in publishing using EDTA treated samples. In the case of activity measurements, these authors are actually measuring the hydrolysis of paraoxon by serum albumin [34]. Studies measuring PON1 protein levels by immunological methods are also inaccurate when using EDTA treated samples due to the instability and loss of immunoreactivity caused to the PON1 protein by EDTA [35]. The use of EDTA treated samples for PON1 measurement should be actively discouraged.

Misconceptions

PON1 is an esterase

PON1 was historically classified as an esterase. However, advances in the last 10 years have indicated that PON1 is a lipolactonase with a number of promiscuous activities including ester hydrolysis, as described in the introduction.

PON1 has a few SNPs

It is quite common to see in the literature the phrase "PON1 has 2 (or 3) SNPs" thus there is the misconception that the PON1 gene contains a limited number of SNPs. In fact, as previously described to date, over 400 SNPs have been identified in the PON1 gene [36]. A comprehensive list of PON1 SNPs has been compiled by the University of Washington and is available online at http://pga.gs.washington.edu.

PON1 metabolises clopidogrel

Another misconception is that PON1 is causally involved in the bioactivation of the antithrombotic prodrug clopidogrel that inhibits ADP binding to the ADP receptor P2Y12 on the surface of platelets. Clopidogrel as a prodrug requires two steps in its bioactivation process. It is firstly converted to 2-oxo-clopidogrel by CYP450 and then to the pharmacologically active thiol metabolite by the oxidative opening of the thiolactone ring. A paper by Bouman et al. first suggested that PON1 was responsible for the second step to form the active thiol metabolite [37]. Unfortunately, there were many methodological problems related to this study and many experts in PON1 research demonstrated that their conclusion was incorrect [38, 39]. Subsequent clinical studies have also failed to confirm these findings. In fact, detailed biochemical investigations have shown that PON1 metabolises clopidogrel to its pharmacologically inactive endothiol metabolite [40]. Unfortunately, some studies still refer to the data of Bouman et al. as being proven fact, that it is not should be considered by authors and reviewers of related articles.

Human serum paraoxonase and arylesterase are different enzymes

The last and perhaps most pernicious is that human serum (blood) contains separate enzymes, one with paraoxonase activity and another with arylesterase activity. Nothing could be further from the truth! Although several vertebrate species have an arylesterase activity independent of PON1, the human serum contains a single enzyme (one gene product) responsible for the hydrolysis of both paraoxon and phenylacetate, as elegantly described by Karen Gan and Bert La Du in 1991 who purified PON1 from human serum and found it hydrolysed both paraoxon and phenylacetate and accounted for all the serum hydrolysis of phenylacetate [41]. Further detailed investigations by the same group involved expressing rHuPON1. The purified rPON1 hydrolysed both paraoxon and phenylacetate in the same ratio as did human serum proving one enzyme was responsible for both activities [11]. These results have subsequently been confirmed at the biochemical, molecular biological and molecular genetic levels [1] and reconfirmed in detailed biochemical studies conducted by Li et al. [42]. This enzyme is paraoxonase 1 (PON1), which used to be called serum paraoxonase/arylesterase to illustrate the fact that a single enzyme was responsible for the hydrolysis of both substrates. Interested readers are invited to review the Proceedings of the 2nd and 3rd International Conferences on Paraoxonases specifically Chapters one by Professors La Du and Furlong respectively, on the historical context of this controversy and how it was resolved [43, 44].

Concluding remarks

These basic facts about PON1 which were explained in this critical review have been known for over 20 years. Interestingly, the misconceptions and the problems described here still persist in today's literature. The main misconceptions probably arise from authors either using old literature information (PON-1 is an esterase and PON-1 SNPs) or a lack of knowledge of PON-1 activity methods which use several different substrates to determine PON-1 activity. In addition, commercially available kits to determine PON1 activity fall into two categories, those measuring the arylesterase activity of PON1 and those measuring its paraoxonase activity leading authors to treat them as if they are different enzymes. It is very important to follow the recent literature and to discuss the data with an expert before publishing in order to avoid these misconceptions and also to correct methodological problems.

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