Clinical Biochemistry 73 (2019) 1–10

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

The epigenetic regulation of paraoxonase 1 (PON1) as an important enzyme in HDL function: The missing link between environmental and genetic regulation

Abdolkarim Mahrooz[a,*], Mike Mackness[b], Abouzar Bagheri[a], Maryam Ghaffari-Cherati[c], Parisa Masoumi[d]

[a] Molecular and Cell Biology Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[b] Division of Cardiovascular Sciences, University of Manchester, Manchester, UK
[c] Department of Clinical Biochemistry and Genetics, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[d] Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

ARTICLE INFO

Keywords:
PON1
Epigenetics
Cardiovascular diseases
Antioxidants
Gene expression regulation

ABSTRACT

Background: Paraoxonase 1 (PON1) is an important antiatherogenic and antioxidant enzyme in the circulation that has been associated with adverse health outcomes particularly cardiovascular disease (CVD) and other metabolic disorders. PON1 is a highly promiscuous enzyme and can hydrolyse a large variety of substrates, however, detailed structure/function studies have concluded that the natural substrates for PON1 are lipophilic lactones. The interindividual variability in PON1 activity has been mainly attributed to genetic determinants; however, it appears that the contribution of epigenetics has been ignored as a result of the lack of adequate research.

Content: Epigenetic processes, including the histone modifications in the PON1 gene, the methylation of CpG sites in the promoter region of the PON1 gene and the microRNA modulation of PON1 expression can be responsible for the under researched gap between the environmental and genetic regulation of PON1. Environmental factors, including diet, pollution and lifestyle-related factors widely differ between individuals and populations and can cause large differences in the distribution of PON1 and it is important to note that their effects may be exerted through the epigenetic processes. This review discusses and emphasizes the importance of the epigenetic regulation of PON1 as a less-studied subject to highlight future research landscapes.

Summary: Epigenetic regulation is known as an important contributor to the pathogenesis of human diseases, particularly multifactorial diseases such as CVD, which is life-threatening. Due to the importance of PON1 in the functionality of high-density lipoprotein (HDL) and its association with CVD, further explorations of its epigenetic regulation using advanced methods such as Methyl-Seq may lead to the identification of new epigenetic contributors that in turn may lead to targeted therapies.

1. Introduction

Human paraoxonase1 (PON1) is a circulating Ca^{2+}-dependent esterase/lactonase with an approximate molecular mass of 43 kDa and 354 amino acids [1,2]. This enzyme is classified as an aryldialkylphosphatase (EC 3.1.8.1) by the Enzyme Commission of the International Union of Biochemistry and Molecular Biology [3]. 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]. PON1 is the best-known member of the family of paraoxonases that has two other members, namely PON2 and PON3, which share considerable structural homology with PON1 [5,6]. The term paraoxonase is originally derived from the enzyme's ability to hydrolyze paraoxon (diethyl *p*-nitrophenyl phosphate), which is an active metabolite of the insecticide parathion [4,7]. From among the numerous physiological functions of PON1, in particular, its capacity to degrade lipid peroxides, has led many researchers to examine the relationship between this enzyme and various human diseases particularly cardiovascular disease (CVD). PON1 inhibits lipid oxidation in low-density lipoprotein (LDL), thereby reducing levels of oxidized lipids that are critical for the

* Corresponding author at: Department of Clinical Biochemistry and Genetics, Faculty of Medicine, Mazandaran University of Medical Sciences, Km 17 Khazarabad Road, Sari, Iran.
E-mail address: amahrooz@mazums.ac.ir (A. Mahrooz).

https://doi.org/10.1016/j.clinbiochem.2019.07.010
Received 15 June 2019; Received in revised form 22 July 2019; Accepted 24 July 2019
Available online 25 July 2019

initiation and propagation of atherosclerosis [3]. This enzyme can be an important determinant of HDL dysfunctionality [8]. In addition, there is a growing evidence that PON1 may exert its atheroprotective effect through regulating cholesterol efflux from macrophages and maintaining cholesterol homeostasis [9].

The various studies have demonstrated the association of PON1 status (phenotype and genotype) with CVD. In 2012, Zhao et al. [10] reviewed 43 studies to investigate the association between PON1 activity and the susceptibility for CHD and concluded that a decreased PON1 activity is a risk factor for an increased CHD susceptibility. A more recent meta-analysis by Kunutsor et al. [11] on six prospective studies reported an approximately log-linear inverse association between PON1 activity and CVD. Based on the transgenic or adenovirus mediated expression of human PON1 in various mouse models of atherosclerosis, PON1 has been demonstrated to retard or reverse atherosclerosis through mechanisms which include a reduction in oxidized-LDL (ox-LDL) levels, which is a key molecule in the formation of atherosclerotic plaques. The studies of macrophages in cell culture have shown that PON1 potentially contribute to atheroprotective properties such as reducing macrophage oxidative stress and the ability of macrophages to oxidize LDL. The putative mechanisms explaining pleiotropic roles of PON1 in the prevention and improvement of atherosclerosis, including prevention of LDL and cell membrane oxidation, prevention of LDL glycation, reduction of macrophage oxidative stress, contribution to the metabolism of homocysteine thiolactones, prevention of the oxidative inactivation of lecithin cholesterol acyltransferase, and reduction of monocyte macrophage inflammatory response have been reviewed by Mackness et al. [3]. In addition to atherosclerosis, PON1 activity and or mass and as well as its genotype have been associated with various human diseases, including diabetes mellitus, obesity, cancers, aging, and several neurological disorders. The association between PON1 and some diseases such as diabetes mellitus seem to be reciprocal so that the disorder significantly decreases PON1 concentrations, and in turn, PON1 genotype contributes to modulating the risk of susceptibility to diabetes mellitus [12]. For more information, Camps et al. [13] have reviewed the involvement of PON1 in the various human diseases.

Several studies have investigated the effects of drugs, particularly lipid modulating therapy on PON1 status (activity and gene expression). Human, animal and in vitro studies have shown that statin therapy increase PON1 expression and/or activity; however, the results are inconsistent. For example, whereas some studies such as Harangi et al. [14] have indicated an increase in PON1 activity in response to statin therapy, other studies such as Dullaart et al. [15] did not find any changes in serum PON1 activity following short-term administration of simvastatin and bezafibrate (even when combined) in type 2 diabetes. It seems that the effect of statins on PON1 expression may be mediated by activation of the transcription factor Sp1 (specificity protein 1) and sterol regulatory element binding protein 2 (SREBP2), as confirmed by Deakin et al. [16].

Since PON1 has a potential for use as a therapeutic molecule, researchers are struggling to develop purified or recombinant PON1s with therapeutic capabilities. For example, Stevens et al. generated a highly-purified engineered recombinant human PON1 (rHuPON1) through a single amino acid substitution at the position 192, the injection of which into mice lacking PON1 ($PON1^{-/-}$ mice) provides a good protection against diazinon/diazoxon and chlorpyrifos/chlorpyrifos-oxon exposure [17]. Efforts should be made to produce nontoxic rHuPON1s that are more human-like and have a minimal immunological response and to engineer rHuPON1s that have a high catalytic efficiency with enough half-life and are as close as possible to the native human sequence [18]. These and other experiments on PON1 gene transfer [19] and generating fusion proteins such as IgG-PON1 [20] are promising for important therapeutic perspectives. The researchers hope that this data can be used in treating individuals with vascular disease or PON1-related diseases.

Further understanding and identifying the factors involved in the modulation of PON1 can be of clinical importance and may contribute to therapeutic strategies for vascular diseases and other diseases in the development of which PON1 could play a role. As one of the most essential regulatory systems in cells, epigenetic regulation plays a key role in the pathogenesis of human diseases, including CVD [21,22]; however, the epigenetic control of PON1 as a known antiatherogenic and antioxidant enzyme has been less addressed. The interindividual variability in PON1 activity has been mainly attributed to genetic determinants; however, it appears that the contribution of epigenetics has been ignored as a result of the lack of adequate research. This review study therefore discusses and emphasizes the importance of the epigenetic regulation of PON1 as a less-studied subject.

2. Biochemistry and genetics of PON1

2.1. Enzymatic activities

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 [23]. 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 [8]. The experiments through PON1 knockout mice have been indicated that PON1 absence leads to an increase in endothelial adhesion molecules and oxidative stress, which can confirm the role of this enzyme in preventing the onset of atherosclerosis [6]. In addition to the protective role against the toxicity of organophosphate exposure, the possible role of PON1 has been addressed in the defense against air pollutant exposures [24]. Some studies have presented PON1 as a potential target of toxic environmental exposures particularly during fetal development and childhood [25]. For more information on the physiological roles and actions of PON1, see Mackness et al. [3] and Précourt et al. [6].

Paraoxonase activity (POXase activity with paraoxon as the substrate) and arylesterase activity (AREase activity with phenyl acetate as the substrate) are usually used to measure PON1 activity. However, AREase activity is recommended for evaluating the enzyme activity because it is minimally affected by genetic polymorphisms and so would have minor interindividual variability and also there is a strong correlation between this activity and the concentration of PON1 (confirmed by western blot and ELISA assays) [8,26].

2.1.1. Lactonase activity and its importance

Detailed structure/function studies have concluded that the natural substrates for PON1 are lactones and lipophylic lactones form the primary substrates [13,27]. The aromatic nature of amino acids in active site of PON1 could explain why the enzyme prefers lipophilic substrates [28]. PON1 is able to hydrolyze a wide range of lactones. All 3 members of the PON family (PON1, PON2 and PON3) share this property of being lactonases, albeit with distinct substrate specificities [7]. A decreased serum lactonase activity would be accompanied by the delayed catabolism of oxidized phospholipids in LDL and oxidized macrophages, and with greater protein homocysteinylation, which can play a role in accelerating atherosclerosis [29]. Deakin et al. showed that PON1 can be transferred into cell membranes and retain its enzymatic activities including lactonase activity. They suggested that PON1 can exert its protective functions on oxidative stress outside the HDL environment [30].

N-acylhomoserine γ-lactones (AHL) are produced by gram negative

bacteria and regulate bacterial virulence and biofilm formation. All 3 PONs hydrolyse AHL with PON2 having the greatest efficacy, the resulting metabolites are inactive therefore the PON family could be important in preventing bacterial infections [31].

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 3 PONs. PON1 has the greatest hydrolytic efficacy followed by PON3 with PON2 having little activity toward this substrate [32]. PON3 has by far the highest activity toward 2 other eicosanoids, cycloepoxycyclopentenone (cycloEC) and 5,6 dihydroxy-eicosatrienoic acid lactone (5,6-DHTL) followed by PON1 again with PON2 having little or no activity toward these substrates [32,33]. 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. The lactonase activity in the endothelium can influence vascular dilation. In this context, Gilad et al. [34] recently showed that PON1 penetrates endothelial cells and is able to reduce 5,6-DHTL-dependent vasodilation through lactonase activity. In addition, it has been demonstrated that the absence of PON1 in mice is associated with vascular changes, including enhanced oxidative stress, thrombogenicity, and expression of adhesion molecules [35], which highlights the role of this enzyme in vascular health.

2.2. Protein structure

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 [5,36]. The removal of calcium from PON1 or the addition of EDTA result in the inactivation of Ca^{2+}-dependent activities, including POXase activity and AREase activity (with phenyl acetate as the substrate); 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 [37]. 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 [38]. According to recent findings, modulating the active site hydrophobicity of PON1 is a key factor that could affect the organophosphatase activity of the enzyme [36].

According to Harel et al. a histidine–histidine (His) catalytic dyad is 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 [5]. However, recently Grunkemeyer et al. [39] based on His-dyad mutagenesis data reported that the dyad likely does not participate directly in catalysis, but may play an important role in substrate binding or orientation. Therefore, it seems that previously proposed mechanisms should be reviewed. PON1 contains three cysteine residues; one of the residues at the position 284 is free, while the other two (Cys42 and Cys353) form an intramolecular disulphide bridge. Cys284, common to all paraoxonases, has been proposed to play an important role in the ability of PONs to protect LDL from oxidation and to consequently decrease atherosclerosis [5,37].

PON1 is known to have four potential N-linked glycosylation sites at asparagine residues (Asn227, Asn253, Asp270 and Asn324). Asn253 and Asn324, which are structurally located on the surface of the protein, are most likely the glycosylation sites in PON1. Glycosylation is not necessary for the hydrolytic activities of paraoxonases, however, it may be important in elevating their solubility and stability or in stopping non-specific binding to cell membranes [5].

2.3. Gene structure and molecular polymorphisms

The paraoxonase gene family is clustered in tandem on the long arm of human chromosome 7 (q21.22). The PON1 gene covers approximately 26 kb and its coding sequence contains nine exons. The fourth intron of the PON1 gene (out of eight) contains a CA repeat with a polymorphic length [3,40]. The PON1 promoter contains an essential regulatory region. According to reporter gene assays, deleting the approximately 200-bp region including the −108 and −162 polymorphisms eliminates promoter activity completely [41]. The -108C/T polymorphism is found in the center of a consensus binding site for the transcription factor Sp1. Binding of Sp1 to this site is weaker in the presence of the T allele than the C allele. Also, the −162A/G polymorphism is located in a potential NF-1 (nuclear factor-1) binding site. Changes at −108 and −162 affect PON1 gene expression and lead to different serum activities [3,41]. There is a region at the proximal end of the promoter containing the −108 polymorphism that is necessary for the modulation of the PON1 promoter by the transcription factor SREBP2. SREBP2 is closely related to cholesterol metabolism and binds to sequences that have a similarity with sterol regulatory element (SRE). Two of these sequences (−104 to −95 and −138 to −130), with a similarity of 70%, are located in the statin-sensitive region of the PON1 promoter, and SREBP2 putatively upregulates PON1 in the presence of statins. It should be noted that SREBP2 was able to bind to the PON1 promoter in interaction with Sp1, which is a known co-activator of SREPB2. Since the −108 polymorphism is located in the Sp1 site, it is important in the modulation of the PON1 promoter via the interaction between SREBP2 and Sp1 [41,42].

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 [3,43]. They may affect splicing and polyadenylation efficiency, message stability or transcription factor binding [44]. Four functional SNPs have been established, two are located in the coding region [PON1-Q192R (rs662) and PON1-L55 M (rs854560)] and two in the promoter region [−108 (rs705379) and −162 (rs705381)] [45].

The Q192R polymorphism is located in the active site and is an important functional site, because it is a major determinant of variations in catalytic activity toward substrates such as paraoxon, but not toward phenylacetate [3,46]. The 192R allozyme is more efficient at hydrolyzing the substrates paraoxon and chlorpyrifos-oxon, while phenylacetate is hydrolyzed with the same efficiency by both allozymes [46,47]. Salt influences the R allozyme much more than it does the Q allozyme [48]. The 192Q allozyme has a higher efficiency (1.5 to 3.5 times) in hydrolyzing diazoxon and the nerve agents sarin and soman [41,49]. The hydrolysis of lactones depends on their structure so that the R allozyme has a higher activity toward homocysteine thiolactone, whereas δ-valerolactone and 2-coumaranone are more rapidly hydrolyzed by the Q allozyme. These allozymes have also different impacts on oxidation of LDL. People carrying the Q allozyme have better protection against LDL oxidation compared to people with the R allozyme [46,47]. Gaidukov et al. [50] found that the position 192 contributes to HDL binding. The researchers carried out in-vitro and sera tests and showed that the affinity of the Q allozyme for HDL binding is three times lower than that of the R allozyme.

The L55 M polymorphism is a functional variant that may affect the risk of CVD and diabetes mellitus [51]. Although the polymorphism does not seem to directly affect the catalytic activity of PON1, it does affect plasma PON1 protein concentrations; some studies attribute this role to its linkage disequilibrium with the −108 promoter region polymorphism [47], although this association cannot fully explain the

effect of L55M. The effects of this polymorphism on PON1 protein structure may explain part of its contribution to PON1 concentrations. L55M may affect the stability of the enzyme protein, as reported by Leviev et al. [52]. According to Leviev et al., the 55M allozyme has a lower stability, which makes it more susceptible to proteolysis [52]. Harel et al. also studied the crystalline structure of the enzyme and showed that the 55L allozyme plays a key role in the packing of the PON1 protein [5]. Additionally, the L55M polymorphism is located in the vicinity of two crucial amino acids (Glu52 and Asp53), which were among the eight amino acids required for PON1 activity based on the site-directed mutagenesis and this was found to affect the functionality of PON1 protein [53].

Several SNPs have been identified in the promoter region, including -909C/G, -832A/G, -162A/G, -126C/G and -108C/T, among which -108C/T appears to be the main contributor to the regulation of PON1 expression [41,54]. The −108 is located within the consensus sequence GGCGGG (the polymorphic site underlined) in a way that the mutations in the position affect the promoter activity since it is the binding site for Sp1 [55], as previously noted. According to Kim et al. [56], the −108 polymorphism is responsible for at least 12% of the variations in PON1 activity even when considering other dietary factors.

2.4. Misconceptions about PON1 in the literature

In recent years a number of misconceptions about PON1 have arisen in the literature. The first is that the PON1 gene contains a limited number of SNPs. In fact, to date, over 400 SNPs have been identified in the PON1 gene [3,57]. For a comprehensive list see *http://pga.gs.washington.edu*. The second misconception is that PON1 is causally involved in the bioactivation of the antithrombotic drug 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 oxidative opening of the thiolactone ring. A paper by Bouman et al. [58] first suggested that PON1 was responsible for the second step to form the active thiol metabolite [3]. Unfortunately, there were many methodological problems related to this study and many experts in PON1 research demonstrated that their conclusion was incorrect [59–61]. 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 [3]. Unfortunately, some studies still refer to Bouman et al. [58], which must be considered by authors and reviewers of related articles.

The third and perhaps most pernicious is that human serum (blood) contains separate enzymes, one with POXase activity and another with AREase activity. Nothing could be further from the truth! Although several vertebrate species have an arylesterase activity independent of PON1, human serum contains a single enzyme (one gene product) responsible for the hydrolysis of both paraoxon (PON) and phenylacetate (ARE), as elegantly described by Karen Gan and Bert La Du in 1991 who purified PON1 from human serum and found it hydrolysed both PON and ARE and accounted for all the serum hydrolysis of ARE [62]. Further detailed investigations by the same group involved expressing rHuPON1. The purified rPON1 hydrolysed both PON and ARE in the same ratio as did human serum proving one enzyme was responsible for both activities [63]. These results have subsequently been confirmed at the biochemical, molecular biological and molecular genetic levels [3] and reconfirmed in detailed biochemical studies conducted by Li et al. [64]. This enzyme is paraoxonase 1 (PON1), which used to be called serum POXase/AREase to illustrate the fact that a single enzyme was responsible for the hydrolysis of both substrates. Interested readers are referred to Chapters 1 in references 56 and 57 by Professors La Du and Furlong respectively, on the historical context of this controversy and how it was resolved [65,66].

These basic facts about PON1 have been known for over 20 years. That the misconceptions described here still persist in today's literature is very worrying and we urge all reviewers to be vigilant and correct these misconceptions in manuscripts before they are published to prevent their spread to a new generation of researchers.

3. Epigenetics and PON1

Epigenetics is the study of heritable changes in gene expression without changing the underlying genetic sequence [67]. Epigenetic mechanisms connect genes and the environment, mediated by DNA methylation, histone modification and microRNA alterations, which, collectively, enable the cells to quickly respond to environmental stimuli. Epigenetic processes contribute to describing how a number of cells with the same genome can be differentiated into distinct cell types with different phenotypes [68]. The comparison and analysis of the genome and epigenome of healthy and diseased cells is essential for understanding how multifactorial diseases and traits form and develop. The increasing knowledge of epigenetics is changing our understanding of biology, medicine and human diseases [67,69]. The hypothesis is that epigenetics can help explain the main early-life origins of adult diseases [70]. Epigenetics can create a new framework contributing to the search for etiological factors in complex traits and diseases and could therefore lead to targeted interventions and therapies [22,69]. In this context, DNA methylation can be of particular importance because the tissue-specific patterns of this epigenetic process established during differentiation are stably maintained throughout life. According to studies, nutrition and exposure to environmental contaminants such as bisphenol A during early life can affect the establishment of DNA methylation at specific loci, leading to persistent alterations in related phenotypes, which in turn may affect susceptibility to chronic diseases including cardiovascular disease, type 2 diabetes and obesity [71].

The core histones in the nucleosomes (building blocks of chromatin) are densely packed; however, their tails can be modified by histone-modifying enzymes [Fig. 1(A)]. Modifications including methylation, acetylation, phosphorylation, ubiquitination or sumoylation, along with DNA methylation, are able to alter the accessibility of chromatin to transcription machinery and also to replication, recombination, and chromosomal organization [68,72]. The counterbalancing functions of various enzymes make epigenetic modifications reversible. The enzymes such as histone acetyltransferases [HATs or lysine acetyltransferases (KATs)] are counteracted by histone deacetylases [HDACs or lysine deacetylases (KDACs)] and histone methyltransferases [HMTs or lysine methyltransferases (KMTs)] are counteracted by histone demethylases [HDMs or lysine demethylases (KDMs)] are responsible for maintaining the epigenome [21,72]. A review of literature showed that PON1-related histone modifications have attracted very little attention; however, in one study on rats, Strakovsky et al. [73] examined the fetal hepatic epigenome by focusing on PON1 as a model for studying histone modifications in a gene that had a gender-specific pattern. Their results showed that the acetylation of histone H4 and the methylation of histone H3 at lysine residue 4 can affect PON1 gene expression in response to a high-fat maternal diet. The researchers concluded that the in utero exposure to a high-fat diet influences hepatic metabolism in the neonate in a gender-specific manner, and the epigenetic modification of histones in the antioxidant genes such as PON1, may contribute to the known gender differences in oxidative balance.

The reversibility of epigenetic processes increases their importance as excellent therapeutic targets. The majority of studies conducted on the inhibitors of chromatin-modifying enzymes have been in the field of cancer. For instance, 5-Azacytidine, Decitabine and SGI-110 are three FDA-approved nucleoside analogs capable of inhibiting DNA methylation after incorporation into DNA [74]. Additionally, trichostatin A, trapoxin and vorinostat can also inhibit HDAC and the FDA has already approved their use in cancer therapy [75,76]. Curcumin (an enhancer of PON1 levels) is also a HAT inhibitor that can decrease LDL concentrations and increase HDL significantly in healthy people [21].

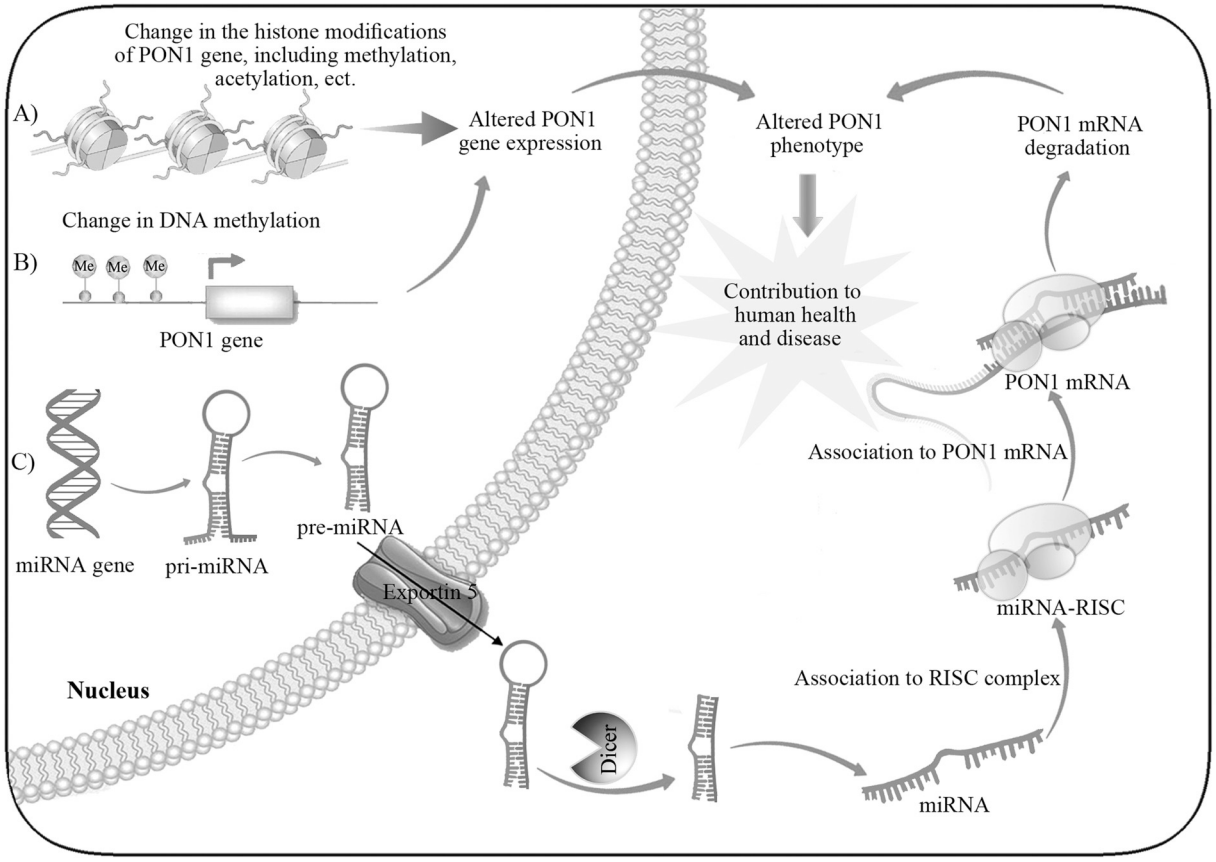

Fig. 1. Schematic representation of epigenetic processes that can affect PON1 phenotype through (A) Changes in the histone modifications of the PON1 gene; (B) Changes in DNA methylation; and (C) micro RNAs. In the nucleus, miRNA genes are transcribed into primary miRNAs (pri-miRNAs). Pre-miRNAs are generated after the cleavage of pri-miRNAs. The pre-miRNAs are then exported from the nucleus into the cytoplasm (by a process involving Exportin-5) where they are cleaved by the RNase Dicer to generate miRNA duplexes. One strand of the miRNA duplex can associate to the RNA-induced silencing complex (RISC) and guide to silence target mRNAs such as PON1 mRNA through mRNA cleavage.

Overall, it seems that the modification of the epigenome using targeted therapies may be an ongoing tool for the management of human diseases.

Epigenetics, along with environmental and genetic factors, can play a fundamental role in understanding the pathogenesis of diseases, particularly multifactorial disorders such as CVD, which, despite the advances in their prevention and management, remain a leading cause of mortality worldwide [72,77]. The relationship between epigenetics and the risk factors of CVD has been studied in several comprehensive reviews; however, the role of epigenetics in the pathogenesis of CVD is still an unexplored area [72,78]. According to studies, the risk factors of CVD, such as smoking, poor nutrition, pollution, stress and a poor circadian rhythm, are some of the modulators of epigenetic marks [72]. Many of these risk factors contribute to PON1 regulation [6]. The epigenetic regulation of PON1 becomes more apparent when noting that the antioxidant properties of HDL as an important cardioprotective lipoprotein for preventing the oxidation of lipoproteins, particularly LDL, are attributed mostly to this enzyme among all the HDL-associated proteins [8]. Epigenetic processes may play a role when the variability of PON1 levels are not fully explained by genetic variations. It should be noted that the processes can also mediate genetic variation.

According to studies, aging and atherosclerosis work simultaneously to affect the cardiovascular system [79]. The relationship between aging and CVD has attracted a lot of attention in geriatric medicine [80,81]. Epigenetic modulators are critically involved in the formation of atherosclerotic lesions. Different cell types contribute to atherosclerotic plaque formation, and the activity of these cells in turn depends on the expression of the different genes in which epigenetic processes play an essential role [21]. As an important epigenetic alteration, DNA methylation can be a key player, because age-related methylation can elevate the incidence of atherosclerosis among the elderly by upregulating atherosclerosis-susceptibility genes and downregulating atherosclerosis-protective genes [79]. Based on studies, the increased susceptibility of HDL to lipid peroxidation, which occurs in aging, is mainly due to an age-related reduction in PON1 activity [81,82]. Due to the role of PON1 in aging-related atherosclerosis, further understanding PON1 regulation, particularly its epigenetic regulation as a less-identified process, could shed light on some obscure issues in the etiology of aging and atherosclerosis.

3.1. The role of DNA methylation in the regulation of PON1

DNA methylation is the addition of methyl groups to the C5 position of cytosine residues in CpG dinucleotides. These epigenetic marks can change the connection of the DNA-binding proteins that work through alterations in the major groove of DNA. Nearly 70% of CpG dinucleotides in the mammalian genome are constitutively methylated. These areas are responsible for silencing large amounts of non-coding DNA existing in the mammalian genome, including introns, repetitive elements and potentially-active transposable elements [79,82]. In contrast to these constitutively-methylated regions, there are short interspersed DNA sequences that diverge significantly from the average genomic pattern by being GC-rich (60–70%), CpG-rich (a CpG:GpC ratio of at least 0.6) and predominantly non-methylated, namely the CpG islands. CpG islands are responsible for 1–2% of the genome and their position is primarily in the 5′ regulatory region of all housekeeping genes, a

Table 1
Summary of studies related to the importance of epigenetic regulation of PON1.

Epigenetic mechanism	Findings	Refs.
Histone modification	Curcumin (an enhancer of PON1 levels) is a histone acetyltransferase inhibitor that can decrease LDL concentrations and increase HDL significantly in healthy people	[21]
Histone modification	The acetylation of histone H4 and the methylation of histone H3 at lysine residue 4 can affect PON1 gene expression in response to a high-fat maternal diet	[73]
DNA methylation and/or, histone modification and/or microRNA alteration	The risk factors of CVD, such as smoking, poor nutrition, pollution, stress and a poor circadian rhythm, are some of the modulators of epigenetic marks. Many of these risk factors contribute to PON1 regulation.	[6,72]
DNA methylation and/or, histone modification and/or microRNA alteration	The increased susceptibility of HDL to lipid peroxidation, which occurs in aging, is mainly due to an age-related reduction in PON1 activity; therefore, further understanding PON1 regulation, particularly its epigenetic regulation could shed light on some obscure issues in the etiology of aging and atherosclerosis	[81,82]
DNA methylation	The conflicting data about the association of PON1 activity with PON1-related diseases, particularly CVD, may be partly explained by the alterations in the methylation of CpG sites in the promoter region of PON1 gene	[86]
DNA methylation	According to blood samples collected from children (umbilical cord blood representing fetal blood), there are a total of 287 CpG sites in the PON1 gene, including 19 CpG sites located in one CpG island in the promoter region. The analyses based on arylesterase (AREase) activity of PON1 as a marker of gene expression at the protein level showed that methylation at Block 1 (surrounding the promoter region) CpG sites can act as a mediator of the -108C/T for this activity and the relationship was age-related	[86]
DNA methylation	The methylation of CpG sites in the paraoxonase promoter (in DNA extracted from blood cells) is associated with weight, waist circumference and energy intake in people with no history of stroke. Also, higher methylation can lead to a lower expression of paraoxonas in adult obese patients	[87]
DNA methylation	Analysis of whole blood DNA methylation patterns in children showed that the DNA methylation (in genes other than the PON1 gene) may be related to an adverse cardio-metabolic risk in prenatally pesticide-exposed children carrying the PON1 192R allele	[88]
DNA methylation	There is an inverse relationship between methylation at CpG sites and AREase activity in white blood cells obtained from obese adults	[89]
DNA methylation	DNA methylation of PON1 CpG sites might affect obesity risk	[87,89]
DNA methylation	The polymorphism -108C/T (rs705379) as an effective SNP in serum PON1 protein concentrations and transcript levels was associated with increase in the methylation of nine CpG sites in its vicinity and with a reduction in the expression of PON1 in the liver samples	[90]
DNA methylation	DNA methylation (in cord blood DNA samples) at the PON1 locus could regulate the association between prenatal mercury exposure, cognitive development and other health outcomes in children	[25]
DNA methylation	Homocysteine is the biomarker most directly involved in epigenetic mechanisms related to CVD, and the homocysteine-induced alterations in the DNA methylation of vascular smooth muscle cells are contributed to atherogenesis. PON1 as one of the genes involved in the modulation of homocysteine concentrations can contribute to the process	[72,92]
DNA methylation and histone modification	Methionine synthase activity is inhibited by oxidative stress, and DNA and histone methylation therefore decreases in oxidative stress and causes epigenetic modification. The reduction of methionine synthase activity under oxidative stress also leads to an increase in the production of homocysteine thiolactone –a toxic molecule in whose detoxification PON1 plays an important role	[91,95]
DNA methylation and/or, histone modification and/or microRNA alteration	The role of many phytochemicals that are commonly found in the diet and have a beneficial effect on health in the epigenetic changes of the gene expression of antioxidant enzymes such as PON1 is a subject that merits further studies	[99,100]
microRNA alteration	There are 25 putative miRNA binding sites in the 3′ UTR of PON1 that the majority of these miRNAs have not been functionally validated with PON1	[70]
microRNA alteration	Serum PON1 activity correlates negatively with miR-92a, miR-486 and miR-122 levels in CAD patients	[108]
microRNA alteration	The decreased miR-486 as a result of exercise may play a role in the increased PON1 activity, since PON1 activity was found to have increased right after exercise	[109,110]
microRNA alteration	Epigenetics along with PON1 functional polymorphisms could affect PON1 levels	[111,112]
microRNA alteration	PON1 is a target gene of miR-616	[112–115]
microRNA alteration	The variant rs3735590 as an SNP located at the binding site of miR-616 can affect the genetic expression of PON1. The expression of miR-616 increases in vascular smooth muscle cells and may play a role in the susceptibility to ischemic stroke and atherosclerosis	[112]
microRNA alteration	The minor allele of rs3735590 affect the binding of miR-616 to the 3'-UTR of PON1	[115]
microRNA alteration	The variant rs3735590 as an SNP located at the binding site of miR-616 is associated with CAD, calcific aortic valve stenosis and chronic obstructive pulmonary disease	[113–115]

portion of tissue-specific genes and developmental regulatory genes [79,83]. DNA methylation is catalyzed by the activity of DNA methyltransferases (DNMTs). Two important classes of DNMTs process methylation in mammalian cells. DNMT1 methylates CpG dinucleotides in newly-synthesized strands during replication, which is required for maintaining the methylation. Two members of the second class (DNMT3a and DNMT3b) are accountable for de novo methylation during embryonic development [21,68].

The risk factors of diseases such as CVD can impose aberrant DNA methylation patterns, which in turn modify the methylation pattern in sequences that are normally hyper-, hypo or un-methylated [84,85]. DNA methylation may be important for regulating PON1 concentrations (Fig. 1(B) and Table 1). According to studies, the conflicting data about the association of AREase activity or PON1 activity in general with PON1-related diseases, particularly CVD, may be partly explained by the alterations in the methylation of CpG sites in the promoter region of PON1 gene [86]. The analysis of 22 CpG sites from the paraoxonase promoter (in DNA extracted from blood cells) by Gómez-Uriz et al. [87] showed that, in some of these CpGs, methylation is associated with weight, waist circumference and energy intake in people with no history of stroke. They concluded that higher paraoxonase promoter methylation can lead to a lower expression of paraoxonase in adult obese patients. In another study, Declerck et al. [88] analyzed whole blood DNA methylation patterns in children, whose mothers were occupationally unexposed or exposed to pesticides early in pregnancy. They concluded that DNA methylation (in genes other than the PON1 gene) may be related to an adverse cardio-metabolic risk in prenatally pesticide-exposed children carrying the PON1 192R allele. However, it is unclear whether this DNA methylation pattern is unique to pesticide exposure or is shared by other adverse prenatal environmental factors

that should be revealed in future research.

In a study conducted on blood samples collected from children (umbilical cord blood representing fetal blood), Huen et al. [86] used PON1 as a model for the integration of genetic and epigenetic data and identified a total of 287 CpG sites in the PON1 gene, including 19 CpG sites located in one CpG island in the promoter region. The analyses based on the promoter polymorphism at the position -108C/T showed that this site can be most strongly associated with methylation. The researchers found that children with the CC and TT genotypes had the lowest and highest levels of methylation, respectively, and the CT genotype children had intermediate levels of methylation. In addition, methylation in Block 1 (surrounding the promoter region) CpG sites was associated with additional SNPs in the promoter region that were in strong linkage disequilibrium with -108C/T. Their analyses based on the AREase activity of PON1 as a marker of gene expression at the protein level showed that methylation at Block 1 CpG sites can act as a mediator of the -108C/T for this activity and the relationship was age-related [86]. Similarly, de la Iglesia et al. [89] found an inverse relationship between methylation at CpG sites and AREase activity in white blood cells obtained from obese adults. It seems that the study of de la Iglesia et al. [89] and Gómez-Uriz et al. [87] providing further reasons that the DNA methylation of PON1 CpG sites might affect obesity risk. Bonder et al. [90] also reported that DNA methylation is responsible for a larger part of the variation in PON1 gene expression compared to SNPs. They reported that the -108C/T (rs705379) as an effective SNP in serum PON1 protein concentrations and transcript levels was associated with increase in the methylation of nine CpG sites in its vicinity and with a reduction in the expression of PON1 in the liver samples.

In a study, Cardenas et al. [25] analyzed associations of maternal prenatal mercury exposure with epigenome-wide DNA methylation in cord blood DNA samples, and examined if these epigenetic modifications persist in blood through early and mid-childhood. According to their findings, DNA methylation at the PON1 locus could regulate the association between prenatal mercury exposure, cognitive development and other health outcomes in children. The researchers expressed that the persistent epigenetic disruption of the PON1 gene might serve as a biomarker of mercury exposure and disease susceptibility. They linked these results to that the epigenetic modifications may help describe conflicting results observed for prenatal mercury exposure and cognitive development in different populations.

It has to be noted that the methylation capacity of DNA and histones is highly dependent on the activity of a folate- and vitamin B12-dependent enzyme, namely methionine synthase, which catalyzes homocysteine to methionine conversion [91]. Homocysteine is the biomarker most directly involved in epigenetic mechanisms related to CVD, and the homocysteine-induced alterations in the DNA methylation of vascular smooth muscle cells are contributed to atherogenesis [72]. According to studies, there is a negative correlation between plasma PON1 activity and homocysteine concentrations, and PON1 is one of the genes involved in the modulation of homocysteine concentrations [91,92]. Since the methylation of DNA and histones is a pivotal process in the epigenetic regulation of gene expression, homocysteine metabolism should be considered important in epigenetics. Therefore, PON1 may contribute to the epigenetic alteration of gene expression, since it contributes to homocysteine metabolism.

3.2. PON1 and oxidative stress-regulated epigenetic processes

Oxidative stress can be considered a gene expression modulator. According to studies, oxidative stress-regulated epigenetic processes could be prominent players in the pathology of certain diseases and powering antioxidant defense systems is therefore important for combating oxidant production and oxidative stress. In one study, Hedman et al. [93] used the analyses of genome-wide DNA methylation and showed that DNA methylation is associated with markers of oxidative stress and may therefore play a role in the development of type-2 diabetes. DNA methylation also contributed to tumor development by repressing the antioxidant enzymes involved in the metabolism of reactive oxygen species [93,94]. According to studies, methionine synthase activity is inhibited by oxidative stress, and DNA and histone methylation therefore decreases in oxidative stress and causes epigenetic modification [91]. The reduction of methionine synthase activity under oxidative stress also leads to an increase in the production of homocysteine thiolactone [91]–a toxic molecule in whose detoxification PON1 plays an important role [95].

Phenolic antioxidants such as flavonoids and nonflavonoid phenols could be potent modulators of mammalian epigenetic-regulated gene expression that exert their effects on the epigenome by alterations in DNA methylation and histone modifications. They could act as drugs in the treatment of human diseases such as cancer and CVD [96]. The protective effects of polyphenols in CVD, particularly the vascular endothelial cells, are carried out by their antioxidant activity and also their ability in increasing the expression of several protective proteins, including PON1 [96,97]. Estrada-Luna et al. [98] recently showed that polyphenol-rich pomegranate juice can potentially control the adverse effects of a high-fat diet through the enhancement of PON1 gene expression and activity. A recent review study by Martini et al. [99] examined the potential effects of polyphenols and polyphenol-rich foods on both PON1 activity and its gene expression. Many phytochemicals that are commonly found in the diet and have a beneficial effect on health can be able to modify aberrant epigenome changes and may play a role in the prevention/treatment of human diseases such as cancer [100]. The role of epigenetic processes in the altered gene expression of antioxidant enzymes such as PON1 by these compounds is a subject that merits further studies.

3.3. The role of microRNAs in the regulation of PON1

microRNAs (miRNAs, miRs) are a class of small (21–23 nucleotides), noncoding, endogenous, and single-strand RNA molecules that regulate both physiological and pathological pathways [101,102]. These gene regulators work by post-transcriptionally inhibiting the expression of a large number of target genes, which occurs through complementary binding to the 3'-UTR and occasionally to the 5'-UTR or the coding regions of target mRNAs [103]. miRNAs can be key controllers in a variety of biological processes including differentiation, proliferation, and metabolism [104]. Furthermore, these small molecules transmitted through meiosis can play a role in restoring the state of the epigenome in zygotes [67]. Based on the latest release of the miRBase database (v22), the human genome encodes 1917 miRNA precursors, producing up to 2654 mature miRNAs [105]. Each of these miRNAs are potentially capable of controlling the expression of a variety of genes. Although new miRs are being identified every day, the target binding sites of many of them is still unknown.

According to research, miRNAs are detectable in a variety of biological samples, including plasma, serum, urine, saliva, tear and sputum. These small RNAs are very stable and resistant to endogenous and exogenous RNase activity, extreme temperatures and pH, long-term storage in frozen conditions and repeated freeze/thaw cycles. The biomarker role of miRNAs becomes more apparent when noting how they are sometimes detectable several years before the disease appears [106,107]. These features make miRNAs excellent targets for different aspects of biological and medical studies.

miRNAs may be important in the modulation of PON1 (Fig. 1 (C) and Table 1). Holland et al. [70] used miRanda software and identified 25 putative miRNA binding sites in the 3′ UTR of PON1. The in silico analyses identified miRNAs such as miR-616, miR-19a, miR-26a, miR-505, miR-495, miR-153, and miR-185. It should be mentioned that the majority of these miRNAs have not been functionally validated with PON1. In one study, Niculescu et al. [108] found that serum PON1 activity correlates negatively with miR-92a, miR-486 and miR-122

levels in coronary artery disease (CAD) patients. In another study, Aoi et al. [109] concluded that circulating miR-486 decreased significantly by way of intense continuous exercise. The decreased miR-486 as a result of exercise may play a role in the increased PON1 activity, since PON1 activity was found to have increased right after exercise [110]. The link between genetics and epigenetics should also be considered. For example, Tomas et al. [111] reported that the effects of exercise on PON1 activity are modulated by the polymorphism PON1-Q192R. In other words, epigenetics along with PON1 functional polymorphisms may affect PON1 levels.

Liu et al. [112] used bioinformatics analysis, a miRNA array and luciferase reporter assays and showed that PON1 is a direct target gene of miR-616 and rs3735590 as an SNP located at the binding site of this miRNA and can affect the genetic expression of PON1. The researchers showed that the expression of miR-616 increases in vascular smooth muscle cells and may play a role in the susceptibility to ischemic stroke and atherosclerosis. These findings have recently been confirmed by Zhang et al. [113], Wang et al. [114] and Lv et al. [115], who showed that PON1 is a potential target gene of miR-616. The minor allele of rs3735590 has been shown to affect the binding of miR-616 to the 3'-UTR of PON1 [115]. These studies also showed that this SNP is associated with CAD [113], calcific aortic valve stenosis [114] and chronic obstructive pulmonary disease [115]. These results could highlight the importance of this miRNA in PON1 metabolism and the development of atherosclerosis.

4. Conclusion and future perspectives

Due to the importance of PON1 in the functionality of HDL and its association with CVD, further explorations of its epigenetic regulation may lead to the identification of new epigenetic contributors that may in turn help improve the prevention and diagnosis of these diseases and may also lead to targeted therapies based on epigenetic mechanisms. The role of many phytochemicals that are commonly found in the diet and have a beneficial effect on health in the epigenetic changes of the altered gene expression of PON1 is a subject that merits further studies. Also, the role of epigenetics in the in vivo effects of environmental factors on the hydrolysis of lipid substrates such as δ-lactone eicosanoids by PON1 may be considered in future research. In addition, the analysis of DNA methylation, miRNA alteration and histone modifications in the antioxidant genes such as PON1 in response to environmental factors may help to elucidate the known differences in oxidative balance. There are still many unknown issues about the interaction between DNA methylation, miRNAs and genetics; however, miRNAs have the potential to be used in clinical practice. Further understanding the interactions between the genetics and epigenetics of PON1 may help design therapeutic approaches for PON1-related diseases, particularly CVD, which is life-threatening.

Declaration of Competing Interests

The authors declare no conflicts of interest.

References

[1] P. Durrington, B. Mackness, M. Mackness, Paraoxonase and atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 21 (4) (2001) 473–480.

[2] H. Tavori, M. Aviram, S. Khatib, R. Musa, D. Mannheim, R. Karmeli, J. Vaya, Human carotid lesion linoleic acid hydroperoxide inhibits paraoxonase 1 (PON1) activity via reaction with PON1 free sulfhydryl cysteine 284, Free Radic. Biol. Med. 50 (1) (2011) 148–156.

[3] M. Mackness, B. Mackness, Human paraoxonase-1 (PON1): gene structure and expression, promiscuous activities and multiple physiological roles, Gene 567 (1) (2015) 12–21.

[4] C.E. Furlong, J. Marsillach, G.P. Jarvik, L.G. Costa, Paraoxonases-1,-2 and-3: what are their functions? Chem. Biol. Interact. 259 (2016) 51–62.

[5] M. Harel, A. Aharoni, L. Gaidukov, B. Brumshtein, O. Khersonsky, R. Meged, H. Dvir, R.B. Ravelli, A. McCarthy, L. Toker, Structure and evolution of the serum paraoxonase family of detoxifying and anti-atherosclerotic enzymes, Nat. Struct. Mol. Biol. 11 (5) (2004) 412.

[6] L.-P. Précourt, D. Amre, M.-C. Denis, J.-C. Lavoie, E. Delvin, E. Seidman, E. Levy, The three-gene paraoxonase family: physiologic roles, actions and regulation, Atherosclerosis 214 (1) (2011) 20–36.

[7] D.I. Draganov, J.F. Teiber, A. Speelman, Y. Osawa, R. Sunahara, B.N. La Du, Human paraoxonases (PON1, PON2, and PON3) are lactonases with overlapping and distinct substrate specificities, J. Lipid Res. 46 (6) (2005) 1239–1247.

[8] A. Variji, Y. Shokri, S. Fallahpour, M. Zargari, B. Bagheri, S. Abediankenari, A. Alizadeh, A. Mahrooz, The combined utility of myeloperoxidase (MPO) and paraoxonase 1 (PON1) as two important HDL-associated enzymes in coronary artery disease: which has a stronger predictive role? Atherosclerosis 280 (2019) 7–13.

[9] H. Berrougui, S. Loued, A. Khalil, Purified human paraoxonase-1 interacts with plasma membrane lipid rafts and mediates cholesterol efflux from macrophages, Free Radic. Biol. Med. 52 (8) (2012) 1372–1381.

[10] Y. Zhao, Y. Ma, Y. Fang, L. Liu, S. Wu, D. Fu, X. Wang, Association between PON1 activity and coronary heart disease risk: a meta-analysis based on 43 studies, Mol. Genet. Metab. 105 (1) (2012) 141–148.

[11] S.K. Kunutsor, S.J.L. Bakker, R.W. James, R.P.F. Dullaart, Serum paraoxonase-1 activity and risk of incident cardiovascular disease: the prevend study and meta-analysis of prospective population studies, Atherosclerosis 245 (2016) 143–154.

[12] D. Farbstein, A.P. Levy, The genetics of vascular complications in diabetes mellitus, Cardiol. Clin. 28 (3) (2010) 477–496.

[13] J. Camps, J. Marsillach, J. Joven, The paraoxonases: role in human diseases and methodological difficulties in measurement, Crit. Rev. Clin. Lab. Sci. 46 (2) (2009) 83–106.

[14] M. Harangi, H.Z. Mirdamadi, I. Seres, F. Sztanek, M. Molnár, A. Kassai, Z. Derdák, L. Illyés, G. Paragh, Atorvastatin effect on the distribution of high-density lipoprotein subfractions and human paraoxonase activity, Transl. Res. 153 (4) (2009) 190–198.

[15] R.P.F. Dullaart, R. De Vries, H.A.M. Voorbij, W.J. Sluiter, A. Van Tol, Serum paraoxonase-I activity is unaffected by short-term administration of simvastatin, bezafibrate, and their combination in type 2 diabetes mellitus, Eur. J. Clin. Investig. 39 (3) (2009) 200–203.

[16] S. Deakin, S. Guernier, R.W. James, Pharmacogenetic interaction between paraoxonase-1 gene promoter polymorphism C-107T and statin, Pharmacogenet. Genomics 17 (6) (2007) 451–457.

[17] R.C. Stevens, S.M. Suzuki, T.B. Cole, S.S. Park, R.J. Richter, C.E. Furlong, Engineered recombinant human paraoxonase 1 (rHuPON1) purified from *Escherichia coli* protects against organophosphate poisoning, Proc. Natl. Acad. Sci. 105 (35) (2008) 12780–12784.

[18] D.S. Kim, J. Marsillach, C.E. Furlong, G.P. Jarvik, Pharmacogenetics of paraoxonase activity: elucidating the role of high-density lipoprotein in disease, Pharmacogenomics 14 (12) (2013) 1495–1515.

[19] P.J. Guns, T. Van Assche, W. Verreth, P. Fransen, B. Mackness, M. Mackness, P. Holvoet, H. Bult, Paraoxonase 1 gene transfer lowers vascular oxidative stress and improves vasomotor function in apolipoprotein E-deficient mice with pre-existing atherosclerosis, Br. J. Pharmacol. 153 (3) (2008) 508–516.

[20] R.J. Boado, Y. Zhang, Y. Zhang, Y. Wang, W.M. Pardridge, IgG-Paraoxonase-1 fusion protein for targeted drug delivery across the human blood− brain barrier, Mol. Pharm. 5 (6) (2008) 1037–1043.

[21] R.J. Wierda, S.B. Geutskens, J.W. Jukema, P.H. Quax, P.J. van den Elsen, Epigenetics in atherosclerosis and inflammation, J. Cell. Mol. Med. 14 (6a) (2010) 1225–1240.

[22] A.P. Feinberg, Phenotypic plasticity and the epigenetics of human disease, Nature 447 (7143) (2007) 433.

[23] M. Grdic Rajkovic, L. Rumora, K. Barisic, The paraoxonase 1, 2 and 3 in humans, Biochem. Med. 21 (2) (2011) 122–130.

[24] R.J. Delfino, N. Staimer, N.D. Vaziri, Air pollution and circulating biomarkers of oxidative stress, Air Qual. Atmos. Health 4 (1) (2011) 37–52.

[25] A. Cardenas, S.L. Rifas-Shiman, G. Agha, M.-F. Hivert, A.A. Litonjua, D.L. DeMeo, X. Lin, C.J. Amarasiriwardena, E. Oken, M.W. Gillman, A.A. Baccarelli, Persistent DNA methylation changes associated with prenatal mercury exposure and cognitive performance during childhood, Sci. Rep. 7 (1) (2017) 288.

[26] K. Huen, R. Richter, C. Furlong, B. Eskenazi, N. Holland, Validation of PON1 enzyme activity assays for longitudinal studies, Clin. Chim. Acta 402 (1–2) (2009) 67–74.

[27] O. Khersonsky, D.S. Tawfik, Structure− reactivity studies of serum paraoxonase PON1 suggest that its native activity is lactonase, Biochemistry 44 (16) (2005) 6371–6382.

[28] R.S. Bargota, M. Akhtar, K. Biggadike, D. Gani, R.K. Allemann, Structure–activity relationship on human serum paraoxonase (PON1) using substrate analogues and inhibitors, Bioorg. Med. Chem. Lett. 13 (10) (2003) 1623–1626.

[29] A. Gugliucci, E. Kinugasa, K. Kotani, R. Caccavello, S. Kimura, Serum paraoxonase 1 (PON1) lactonase activity is lower in end-stage renal disease patients than in healthy control subjects and increases after hemodialysis, Clin. Chem. Lab. Med. 49 (1) (2011) 61–67.

[30] S.P. Deakin, S. Bioletto, M.-L. Bochaton-Piallat, R.W. James, HDL-associated paraoxonase-1 can redistribute to cell membranes and influence sensitivity to oxidative stress, Free Radic. Biol. Med. 50 (1) (2011) 102–109.

[31] J.F. Teiber, S. Horke, D.C. Haines, P.K. Chowdhary, J. Xiao, G.L. Kramer, R.W. Haley, D.I. Draganov, Dominant role of paraoxonases in inactivation of the *Pseudomonas aeruginosa* quorum-sensing signal N-(3-oxododecanoyl)-L-homoserine lactone, Infect. Immun. 76 (6) (2008) 2512–2519.

[32] J.F. Teiber, J. Xiao, G.L. Kramer, S. Ogawa, C. Ebner, H. Wolleb, E.M. Carreira, D.M. Shih, R.W. Haley, Identification of biologically active δ-lactone eicosanoids

as paraoxonase substrates, Biochem. Biophys. Res. Commun. 505 (1) (2018) 87–92.
[33] S. Eryanni-Levin, S. Khatib, R. Levy-Rosenzvig, S. Tamir, A. Szuchman-Sapir, 5, 6-δ-DHTL, a stable metabolite of arachidonic acid, is a potential substrate for paraoxonase 1, Biochim. Biophys. Acta (BBA)-Mol. Cell Biol. Lipids 1851 (9) (2015) 1118–1122.
[34] D. Gilad, S. Atiya, Z. Mozes-Autmazgin, R.S. Ben-Shushan, R. Ben-David, E. Amram, S. Tamir, D. Chuyun, A. Szuchman-Sapir, Paraoxonase 1 in endothelial cells impairs vasodilation induced by arachidonic acid lactone metabolite, Biochim. Biophys. Acta (BBA)-Mol. Cell Biol. Lipids 1864 (3) (2019) 386–393.
[35] D.S. Ng, T. Chu, B. Esposito, P. Hui, P.W. Connelly, P.L. Gross, Paraoxonase-1 deficiency in mice predisposes to vascular inflammation, oxidative stress, and thrombogenicity in the absence of hyperlipidemia, Cardiovasc. Pathol. 17 (4) (2008) 226–232.
[36] D. Blaha-Nelson, D.M. Krüger, K. Szeler, M. Ben-David, S.C.L. Kamerlin, Active site hydrophobicity and the convergent evolution of paraoxonase activity in structurally divergent enzymes: the case of serum paraoxonase 1, J. Am. Chem. Soc. 139 (3) (2017) 1155–1167.
[37] M. Aviram, S. Billecke, R. Sorenson, C. Bisgaier, R. Newton, M. Rosenblat, J. Erogul, C. Hsu, C. Dunlop, B. La Du, Paraoxonase active site required for protection against LDL oxidation involves its free sulfhydryl group and is different from that required for its arylesterase/paraoxonase activities: selective action of human paraoxonase allozymes Q and R, Arterioscler. Thromb. Vasc. Biol. 18 (10) (1998) 1617–1624.
[38] S.M. Ali, S.E. Chia, Interethnic variability of plasma Paraoxonase (PON1) activity towards organophosphates and PON1 polymorphisms among Asian populations—a short review, Ind. Health 46 (4) (2008) 309–317.
[39] T.J. Grunkemeyer, D.G. Mata, K. Doddapaneni, S. Murali, T.J. Magliery, Insights into the mechanism of paraoxonase-1: comparing the reactivity of the six-bladed β-propeller hydrolases, Biochemistry (2018), https://doi.org/10.1021/acs.biochem.8b01115.
[40] J.B. Clendenning, R. Humbert, E.D. Green, C. Wood, D. Traver, C.E. Furlong, Structural organization of the HumanPON1Gene, Genomics 35 (3) (1996) 586–589.
[41] S.P. Deakin, R.W. James, Genetic and environmental factors modulating serum concentrations and activities of the antioxidant enzyme paraoxonase-1, Clin. Sci. 107 (5) (2004) 435–447.
[42] S. Deakin, I. Leviev, S. Guernier, R.W. James, Simvastatin modulates expression of the PON1 gene and increases serum paraoxonase: a role for sterol regulatory element–binding protein-2, Arterioscler. Thromb. Vasc. Biol. 23 (11) (2003) 2083–2089.
[43] A. Mahrooz, Pharmacological interactions of paraoxonase 1 (PON1): a HDL-bound antiatherogenic enzyme, Curr. Clin. Pharmacol. 11 (4) (2016) 259–264.
[44] L.G. Costa, G. Giordano, T.B. Cole, J. Marsillach, C.E. Furlong, Paraoxonase 1 (PON1) as a genetic determinant of susceptibility to organophosphate toxicity, Toxicology 307 (2013) 115–122.
[45] D.S. Kim, A.A. Burt, D.R. Crosslin, P.D. Robertson, J.E. Ranchalis, E.J. Boyko, D.A. Nickerson, C.E. Furlong, G.P. Jarvik, Novel common and rare genetic determinants of paraoxonase activity: FTO, SERPINA12, and ITGAL, J. Lipid Res. 54 (2) (2013) 552–560.
[46] M. Zargari, F. Sharafeddin, A. Mahrooz, A. Alizadeh, P. Masoumi, The common variant Q192R at the paraoxonase 1 (PON1) gene and its activity are responsible for a portion of the altered antioxidant status in type 2 diabetes, Exp. Biol. Med. 241 (14) (2016) 1489–1496.
[47] B. Mackness, M.I. Mackness, S. Arrol, W. Turkie, P.N. Durrington, Effect of the human serum paraoxonase 55 and 192 genetic polymorphisms on the protection by high density lipoprotein against low density lipoprotein oxidative modification, FEBS Lett. 423 (1) (1998) 57–60.
[48] A. Mahrooz, A. Alizadeh, G. Gohari, The salt stimulation property of serum paraoxonase (PON1) could be a valuable factor in evaluating the enzyme status in ischemic stroke: the role of activity-determined PON1 192Q/R phenotypes, J. Neurol. Sci. 338 (1–2) (2014) 197–202.
[49] H.G. Davies, R.J. Richter, M. Keifer, C.A. Broomfield, J. Sowalla, C.E. Furlong, The effect of the human serum paraoxonase polymorphism is reversed with diazoxon, soman and sarin, Nat. Genet. 14 (3) (1996) 334.
[50] L. Gaidukov, M. Rosenblat, M. Aviram, D.S. Tawfik, The 192R/Q polymorphs of serum paraoxonase PON1 differ in HDL binding, lipolactonase stimulation, and cholesterol efflux, J. Lipid Res. 47 (11) (2006) 2492–2502.
[51] A. Mahrooz, M.B. Hashemi-Soteh, M. Heydari, R. Boorank, F. Ramazani, A. Mahmoudi, A. Kianmehr, A. Alizadeh, Paraoxonase 1 (PON1)-L55M among common variants in the coding region of the paraoxonase gene family may contribute to the glycemic control in type 2 diabetes, Clin. Chim. Acta 484 (2018) 40–46.
[52] I. Leviev, S. Deakin, R.W. James, Decreased stability of the M54 isoform of paraoxonase as a contributory factor to variations in human serum paraoxonase concentrations, J. Lipid Res. 42 (4) (2001) 528–535.
[53] K.C. Chiu, L.-M. Chuang, A. Chu, J. Lu, J. Hu, S. Fernando, Association of Paraoxonase 1 polymorphism with Beta-cell function: a case of molecular Heterosis, Pancreas 28 (4) (2004) e96–e103.
[54] J. Camps, S. Iftimie, A. García-Heredia, A. Castro, J. Joven, Paraoxonases and infectious diseases, Clin. Biochem. 50 (13) (2017) 804–811.
[55] F. Osaki, Y. Ikeda, T. Suehiro, K. Ota, S. Tsuzura, K. Arii, Y. Kumon, K. Hashimoto, Roles of Sp1 and protein kinase C in regulation of human serum paraoxonase 1 (PON1) gene transcription in HepG2 cells, Atherosclerosis 176 (2) (2004) 279–287.
[56] D.S. Kim, A.A. Burt, J.E. Ranchalis, R.J. Richter, J.K. Marshall, K.S. Nakayama, E.R. Jarvik, J.F. Eintracht, E.A. Rosenthal, C.E. Furlong, G.P. Jarvik, Dietary cholesterol increases paraoxonase 1 enzyme activity, J. Lipid Res. 53 (11) (2012) 2450–2458.
[57] D.S. Kim, A.A. Burt, J.E. Ranchalis, R.J. Richter, J.K. Marshall, J.F. Eintracht, E.A. Rosenthal, C.E. Furlong, G.P. Jarvik, Additional common Polymorphisms in the PON Gene Cluster Predict PON1 activity but not vascular Disease, J. Lipids 2012 (2012).
[58] H.J. Bouman, E. Schömig, J.W. Van Werkum, J. Velder, C.M. Hackeng, C. Hirschhäuser, C. Waldmann, H.-G. Schmalz, J.M. Ten Berg, D. Taubert, Paraoxonase-1 is a major determinant of clopidogrel efficacy, Nat. Med. 17 (1) (2011) 110.
[59] P.M. Dansette, J. Rosi, G. Bertho, D. Mansuy, Cytochromes P450 catalyze both steps of the major pathway of clopidogrel bioactivation, whereas paraoxonase catalyzes the formation of a minor thiol metabolite isomer, Chem. Res. Toxicol. 25 (2) (2011) 348–356.
[60] J. Camps, J. Joven, B. Mackness, M. Mackness, D. Tawfik, D. Draganov, L.G. Costa, G. Paragh, I. Seres, S. Horke, Paraoxonase-1 and clopidogrel efficacy, Nat. Med. 17 (9) (2011) 1041.
[61] P.M. Dansette, J. Rosi, G. Bertho, D. Mansuy, Paraoxonase-1 and clopidogrel efficacy, Nat. Med. 17 (9) (2011) 1040.
[62] K.N. Gan, A. Smolen, H.W. Eckerson, B.N. La Du, Purification of human serum paraoxonase/arylesterase. Evidence for one esterase catalyzing both activities, Drug Metab. Dispos. 19 (1) (1991) 100–106.
[63] R.C. Sorenson, S.L. Primo-Parmo, C.-L. Kuo, S. Adkins, O. Lockridge, B.N. La Du, Reconsideration of the catalytic center and mechanism of mammalian paraoxonase/arylesterase, Proc. Natl. Acad. Sci. 92 (16) (1995) 7187–7191.
[64] B. Li, M. Sedlacek, I. Manoharan, R. Boopathy, E.G. Duysen, P. Masson, O. Lockridge, Butyrylcholinesterase, paraoxonase, and albumin esterase, but not carboxylesterase, are present in human plasma, Biochem. Pharmacol. 70 (11) (2005) 1673–1684.
[65] L.G. Costa, C.E. Furlong, Paraoxonase (PON1) in Health and Disease: basic and Clinical Aspects, Springer Science & Business Media, 2002.
[66] B. Mackness, M. Mackness, M. Aviram, G. Paragh, The Paraoxonases: their Role in Disease Development and Xenobiotic Metabolism, Springer Science & Business Media, 2007.
[67] A.E. Handel, G.C. Ebers, S.V. Ramagopalan, Epigenetics: molecular mechanisms and implications for disease, Trends Mol. Med. 16 (1) (2010) 7–16.
[68] C. Ling, L. Groop, Epigenetics: a molecular link between environmental factors and type 2 diabetes, Diabetes 58 (12) (2009) 2718–2725.
[69] A. Petronis, Epigenetics as a unifying principle in the aetiology of complex traits and diseases, Nature 465 (7299) (2010) 721.
[70] N. Holland, D. Lizarraga, K. Huen, Recent progress in the genetics and epigenetics of paraoxonase: why it is relevant to children's environmental health, Curr. Opin. Pediatr. 27 (2) (2015) 240.
[71] R.A. Waterland, Is epigenetics an important link between early life events and adult disease? Hormone Res. Paediatr. 71 (Suppl. 1) (2009) 13–16.
[72] J.M. Ordovás, C.E. Smith, Epigenetics and cardiovascular disease, Nat. Rev. Cardiol. 7 (9) (2010) 510.
[73] R.S. Strakovsky, X. Zhang, D. Zhou, Y.-X. Pan, The regulation of hepatic Pon1 by a maternal high-fat diet is gender specific and may occur through promoter histone modifications in neonatal rats, J. Nutr. Biochem. 25 (2) (2014) 170–176.
[74] S.B. Baylin, P.A. Jones, Epigenetic determinants of cancer, Cold Spring Harb. Perspect. Biol. 8 (9) (2016) a019505.
[75] E. Seto, M. Yoshida, Erasers of histone acetylation: the histone deacetylase enzymes, Cold Spring Harb. Perspect. Biol. 6 (4) (2014) a018713.
[76] C.D. Allis, T. Jenuwein, The molecular hallmarks of epigenetic control, Nat. Rev. Genet. 17 (8) (2016) 487.
[77] P. Stenvinkel, M. Karimi, S. Johansson, J. Axelsson, M. Suliman, B. Lindholm, O. Heimbürger, P. Barany, A. Alvestrand, L. Nordfors, Impact of inflammation on epigenetic DNA methylation–a novel risk factor for cardiovascular disease? J. Intern. Med. 261 (5) (2007) 488–499.
[78] M.P. Turunen, E. Aavik, S. Ylä-Herttuala, Epigenetics and atherosclerosis, Biochim. Biophys. Acta (BBA)-Gen. Subjects 1790 (9) (2009) 886–891.
[79] C. Dong, W. Yoon, P.J. Goldschmidt-Clermont, DNA methylation and atherosclerosis, J. Nutr. 132 (8) (2002) 2406S–2409S.
[80] F. Lescai, F. Marchegiani, C. Franceschi, PON1 is a longevity gene: results of a meta-analysis, Ageing Res. Rev. 8 (4) (2009) 277–284.
[81] A. Khalil, O. Kamtchueng Simo, S. Ikhlef, H. Berrougui, The role of paraoxonase 1 in regulating HDL functionality during aging, Can. J. Physiol. Pharmacol. 95 (10) (2017) 1254–1262.
[82] F. Marchegiani, M. Marra, L. Spazzafumo, R.W. James, M. Boemi, F. Olivieri, M. Cardelli, L. Cavallone, A.R. Bonfigli, C. Franceschi, Paraoxonase activity and genotype predispose to successful aging, J. Gerontol. Ser. A Biol. Med. Sci. 61 (6) (2006) 541–546.
[83] A.M. Deaton, A. Bird, CpG islands and the regulation of transcription, Genes Dev. 25 (10) (2011) 1010–1022.
[84] G. Lund, S. Zaina, Atherosclerosis risk factors can impose aberrant DNA methylation patterns: a tale of traffic and homocysteine, Curr. Opin. Lipidol. 20 (5) (2009) 448–449.
[85] P.D. Gluckman, M.A. Hanson, T. Buklijas, F.M. Low, A.S. Beedle, Epigenetic mechanisms that underpin metabolic and cardiovascular diseases, Nat. Rev. Endocrinol. 5 (2009) 401.
[86] K. Huen, P. Yousefi, K. Street, B. Eskenazi, N. Holland, PON1 as a model for integration of genetic, epigenetic, and expression data on candidate susceptibility genes, Environ. Epigen. 1 (1) (2015).
[87] A. Gómez-Uriz, E. Goyenechea, J. Campión, A. De Arce, M. Martinez, B. Puchau,

F. Milagro, I. Abete, J. Martínez, A.L. de Munain, Epigenetic patterns of two gene promoters (TNF-α and PON) in stroke considering obesity condition and dietary intake, J. Physiol. Biochem. 70 (2) (2014) 603–614.
[88] K. Declerck, S. Remy, C. Wohlfahrt-Veje, K.M. Main, G. Van Camp, G. Schoeters, W.V. Berghe, H.R. Andersen, Interaction between prenatal pesticide exposure and a common polymorphism in the PON1 gene on DNA methylation in genes associated with cardio-metabolic disease risk—an exploratory study, Clin. Epigenetics 9 (1) (2017) 35.
[89] R. de la Iglesia, M.L. Mansego, F.J. Sánchez-Muniz, M.A. Zulet, J.A. Martinez, Arylesterase activity is associated with antioxidant intake and paraoxonase-1 (pon1) gene methylation in metabolic syndrome patients following an energy restricted diet, EXCLI J. 13 (2014) 416.
[90] M.J. Bonder, S. Kasela, M. Kals, R. Tamm, K. Lokk, I. Barragan, W.A. Buurman, P. Deelen, J.-W. Greve, M. Ivanov, Genetic and epigenetic regulation of gene expression in fetal and adult human livers, BMC Genomics 15 (1) (2014) 860.
[91] R. Dufault, W.J. Lukiw, R. Crider, R. Schnoll, D. Wallinga, R. Deth, A macroepigenetic approach to identify factors responsible for the autism epidemic in the United States, Clin. Epigenetics 4 (1) (2012) 6.
[92] P. Sharma, R. Senthilkumar, V. Brahmachari, E. Sundaramoorthy, A. Mahajan, A. Sharma, S. Sengupta, Mining literature for a comprehensive pathway analysis: a case study for retrieval of homocysteine related genes for genetic and epigenetic studies, Lipids Health Dis. 5 (1) (2006) 1.
[93] Å.K. Hedman, M. Zilmer, J. Sundström, L. Lind, E. Ingelsson, DNA methylation patterns associated with oxidative stress in an ageing population, BMC Med. Genet. 9 (1) (2016) 72.
[94] R. Franco, O. Schoneveld, A.G. Georgakilas, M.I. Panayiotidis, Oxidative stress DNA methylation and carcinogenesis, Cancer Lett. 266 (1) (2008) 6–11.
[95] J. Perła-Kaján, H. Jakubowski, Paraoxonase 1 protects against protein N-homocysteinylation in humans, FASEB J. 24 (3) (2010) 931–936.
[96] S. Malireddy, S.R. Kotha, J.D. Secor, T.O. Gurney, J.L. Abbott, G. Maulik, K.R. Maddipati, N.L. Parinandi, Phytochemical antioxidants modulate mammalian cellular epigenome: implications in health and disease, Antioxid. Redox Signal. 17 (2) (2012) 327–339.
[97] K. Yamagata, M. Tagami, Y. Yamori, Dietary polyphenols regulate endothelial function and prevent cardiovascular disease, Nutrition 31 (1) (2015) 28–37.
[98] D. Estrada-Luna, E. Martínez-Hinojosa, J. Cancino-Diaz, H. Belefant-Miller, G. López-Rodríguez, G. Betanzos-Cabrera, Daily supplementation with fresh pomegranate juice increases paraoxonase 1 expression and activity in mice fed a high-fat diet, Eur. J. Nutr. 57 (1) (2018) 383–389.
[99] D. Martini, C. Del Bo, M. Porrini, S. Ciappellano, P. Riso, Role of polyphenols and polyphenol-rich foods in the modulation of PON1 activity and expression, J. Nutr. Biochem. 48 (2017) 1–8.
[100] W. Li, Y. Guo, C. Zhang, R. Wu, A.Y. Yang, J. Gaspar, A.-N.T. Kong, Dietary phytochemicals and cancer chemoprevention: a perspective on oxidative stress, inflammation, and epigenetics, Chem. Res. Toxicol. 29 (12) (2016) 2071–2095.
[101] H. Zhu, S.W. Leung, Identification of microRNA Biomarkers in Type 2 Diabetes: A Meta-Analysis of Controlled Profiling Studies, Springer, 2015.
[102] S. Shantikumar, A. Caporali, C. Emanueli, Role of microRNAs in diabetes and its cardiovascular complications, Cardiovasc. Res. 93 (4) (2011) 583–593.
[103] A. Borghini, M.G. Andreassi, Genetic polymorphisms offer insight into the causal role of microrna in coronary artery disease, Atherosclerosis 269 (2018) 63–70.
[104] T. Xu, Q. Liu, J. Yao, Y. Dai, H. Wang, J. Xiao, Circulating microRNAs in response to exercise, Scand. J. Med. Sci. Sports 25 (2) (2015) e149–e154.
[105] A. Kozomara, M. Birgaoanu, S. Griffiths-Jones, miRBase: from microRNA sequences to function, Nucleic Acids Res. 47 (D1) (2018) D155–D162.
[106] C. Guay, R. Regazzi, Circulating microRNAs as novel biomarkers for diabetes mellitus, Nat. Rev. Endocrinol. 9 (9) (2013) 513.
[107] A. Bagheri, H.R.K. Khorshid, M. Tavallaie, S.J. Mowla, M. Sherafatian, M. Rashidi, M. Zargari, M.E. Boroujeni, S.M. Hosseini, A panel of noncoding RNAs in non–-small-cell lung cancer, J. Cell. Biochem. 120 (5) (2019) 8280–8290.
[108] L.S. Niculescu, N. Simionescu, G.M. Sanda, M.G. Carnuta, C.S. Stancu, A.C. Popescu, M.R. Popescu, A. Vlad, D.R. Dimulescu, M. Simionescu, MiR-486 and miR-92a identified in circulating HDL discriminate between stable and vulnerable coronary artery disease patients, PLoS ONE 10 (10) (2015) e0140958.
[109] W. Aoi, H. Ichikawa, K. Mune, Y. Tanimura, K. Mizushima, Y. Naito, T. Yoshikawa, Muscle-enriched microRNA miR-486 decreases in circulation in response to exercise in young men, Front. Physiol. 4 (2013) 80.
[110] A. Casella-Filho, A.C.P. Chagas, R.C. Maranhão, I.C. Trombetta, F.H. Cesena, V.M. Silva, J.E. Tanus-Santos, C.E. Negrão, P.L. da Luz, Effect of exercise training on plasma levels and functional properties of high-density lipoprotein cholesterol in the metabolic syndrome, Am. J. Cardiol. 107 (8) (2011) 1168–1172.
[111] M. Tomás, R. Elosua, M. Sentí, L. Molina, J. Vila, R. Anglada, M. Fitó, M.I. Covas, J. Marrugat, Paraoxonase1-192 polymorphism modulates the effects of regular and acute exercise on paraoxonase1 activity, J. Lipid Res. 43 (5) (2002) 713–720.
[112] M.-E. Liu, Y.-C. Liao, R.-T. Lin, Y.-S. Wang, E. Hsi, H.-F. Lin, K.-C. Chen, S.-H.H. Juo, A functional polymorphism of PON1 interferes with microRNA binding to increase the risk of ischemic stroke and carotid atherosclerosis, Atherosclerosis 228 (1) (2013) 161–167.
[113] Y. Zhang, S. Wang, Y. Li, C. Zhang, J. Xue, X. Wu, C. Wang, Relationship of microRNA 616 gene polymorphism with prognosis of patients with premature coronary artery disease, Int. J. Clin. Pharmacol. Ther. 54 (11) (2016) 899.
[114] Z. Wang, S. Chen, M. Zhu, W. Zhang, H. Zhang, H. Li, C. Zou, Functional SNP in the 3'UTR of PON1 is associated with the risk of calcific aortic valve stenosis via MiR-616, Cell. Physiol. Biochem. 45 (4) (2018) 1390–1398.
[115] M. Lv, D. Sun, L. Chen, Identification of prognostic value of Rs3735590 polymorphism in 3'-Untranslated region (3'-UTR) of Paraoxonase 1 (PON-1) in chronic obstructive pulmonary disease patients who received coronary artery bypass grafting (CABG), Cell. Physiol. Biochem. 47 (5) (2018) 1809–1818.