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Viewpoint

Macrophage Foam Cell Formation During Early Atherogenesis Is Determined by the Balance Between Pro-Oxidants and Anti-Oxidants in Arterial Cells and Blood Lipoproteins

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ABSTRACT

Atherosclerosis is a multifactorial disease, where more than one mechanism, along more than one step, contributes to macrophage cholesterol accumulation and foam cell formation, the hallmark of early atherogenesis. Arterial macrophages take up oxidized low-density lipoproteins (Ox-LDL), leading to cellular accumulation of cholesterol and oxysterols. Atherogenic modifications of LDL include, in addition to oxidation, retention and aggregation. Intervention to inhibit LDL oxidation can affect the above additional LDL modifications. Indeed, we have demonstrated in the atherosclerotic apolipoprotein E-deficient mice that consumption of vitamin E or of flavonoids from red wine or licorice decreased LDL oxidation, LDL retention, and LDL aggregation and attenuated macrophage foam cell formation and atherosclerosis. The balance between pro-oxidants and anti-oxidants in the LDL particle (such as cholesteryl ester vs. vitamin E), as well as in arterial wall macrophages (such as NADPH oxidase vs. glutathione), determines the extent of LDL oxidation. Antioxidants can protect LDL from oxidation not only by their binding to the lipoprotein, but also following their accumulation in cells of the arterial wall. Whereas antioxidants can prevent the formation of Ox-LDL, human serum paraoxonase (PON 1), an HDL-associated esterase that hydrolyzes organophosphates, can eliminate oxidized LDL (by hydrolysis of its lipid peroxides), which is formed when antioxidant protection is not sufficient. Ox-LDL, in turn, can inactivate paraoxonase activity. Thus, the combination of antioxidants together with active paraoxonase decreases the formation of Ox-LDL and preserves PON1's ability to hydrolyze this atherogenic lipoprotein and hence, to attenuate atherosclerosis. Antiox. Redox Signal. 1, 585–594.

INTRODUCTION

THIS VIEWPOINT SUMMARIZES our current understanding of the causal relationship between oxidative stress and atherosclerosis. Atherosclerosis is a multifactorial disease and low-density lipoprotein (LDL) oxidation can be induced by all major cells of the aterial wall along the progression of atherogenesis, via several different mechanisms. An appropriate balance between processes that stimulate or inhibit oxidative stress, LDL oxidation, and additional LDL atherogenic modifications (which are related to lipids peroxidation) determines the progression rate of atherogenesis. The originality of the viewpoint is in its emphasis on the role in atherosclerosis, of pro-oxidants versus anti-oxidants, which are either bound to

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LDL or accumulated in arterial cells. Intervention means to attenuate atherosclerosis should thus take into consideration the balance between stimulators and inhibitors of oxidative stress.

LDL RETENTION, OXIDATION, AND AGGREGATION DURING ATHEROGENESIS

Monocyte-derived macrophages in the arterial wall play a major role at the early stage of atherogenesis. Arterial macrophages take up modified forms of LDL and accumulate cholesterol and oxysterols (Brown and Jessup, 1999). At later stages, smooth muscle cell proliferation, migration, and secretion of cytokines and growth factors, as well as thrombotic and inflammatory processes, take place. The major theories on the pathogenesis of atherosclerosis (Steinberg *et al.*, 1989; Aviram, 1993, 1995a,b, 1996, 1999b; Berliner *et al.*, 1995; Williams and Tabas, 1995; Ross, 1999; Berliner and Heinecke, 1996; Uyemura *et al.*, 1996; Aviram and Fuhrman, 1998a; Heinecke, 1998; Witztum and Berliner, 1998) involve endothelial dysfunction, platelet activation, and LDL modifications. All of these processes are affected by oxidative stress (FitzGerald *et al.*, 1997; Ruef *et al.*, 1997; Welch *et al.*, 1997; Aviram and Fuhrman, 1998a; Aviram, 1999b). LDL modifications include its retention (by extracellular matrix proteoglycans), its oxidation (by arterial wall cells and by blood cells), and its aggregation (by arterial wall sphingomyelinase and proteoglycans, and also as a result of its oxidation).

Intimal proteoglycans interact specifically with apo B lipoproteins and contribute to their retention (Camejo *et al.*, 1997). This could provide the residence time and the initial alterations of the lipoproteins that favor their further modifications by oxidative processes and by hydrolytic enzymes (Williams and Tabas, 1995; Hurt-Camejo *et al.*, 1997). Lipoprotein lipase (LPL) was shown to enhance the interaction of plasma LDL with arterial chondroitin sulfate proteoglycan and with dermatan sulfate proteoglycan, and thus facilitates LDL retention in the artery wall (Edwards *et al.*, 1993).

Treatment of LDL with sphingomyelinase (SMase) and phospholipase A_2 (PLA_2) generated modified LDL particles, which bind to human aortic proteoglycans with increased strength. SMase- and PLA_2-induced aggregation and fusion of LDL are potential mechanisms that lead to focal retention of extracellular lipids in the arterial wall (Oorni *et al.*, 1998; Maor and Aviram, 1999). Prominent features of atheroma include smooth muscle cells, cholesteryl ester-loaded macrophage foam cells, extracellular matrix, extracellularly trapped and aggregated lipoproteins, and also LPL and SMase (Schissel *et al.*, 1996, 1998; Hurt-Camejo *et al.* 1997; Maor *et al.*, 1999). Incubation of bovine aortic smooth muscle cells with LDL in the presence of LPL and SMase led to a massive aggregation of LDL on the surface of the cells (Tabas *et al.*, 1993). The relevance of these *in vitro* observation to the *in vivo* situation is not yet fully understood.

The above processes can occur during atherogenesis consecutively or in parallel. Lipoprotein retention can lead to its oxidation, followed by its subsequent aggregation (Maor *et al.*, 1997), and oxidative stress can significantly enhance these modifications of LDL (Fig. 1). In the atherosclerotic lesion, modified forms of LDL such as oxidized LDL and aggregated LDL were shown (Aviram, 1996a). Lipid peroxides, isoprostanes (metabolites of arachidonic acid oxidation), and oxysterols were demonstrated in lesions from atherosclerotic mice and humans both in arterial lipoproteins and in cells (Steinberg *et al.*, 1989; Berliner *et al.*, 1995; Aviram, 1996, 1999b). The beneficial antiatherosclerotic effect of LDL oxidation may be obtained under mild conditions of oxidative stress, such as moderate physical activity (Parthasarathy *et al.*, 1998). Under mild oxidation conditions, the conversion of native LDL into mildly oxidized LDL can provide an appropriate means to remove excess LDL from the circulation, and to prevent extracellular accumulation of atherogenic oxidized LDL (Aviram, 1993).

OXIDIZED LDL AND MACROPHAGE FOAM CELL FORMATION

Macrophage cholesterol accumulation and foam cell formation are the hallmarks of early

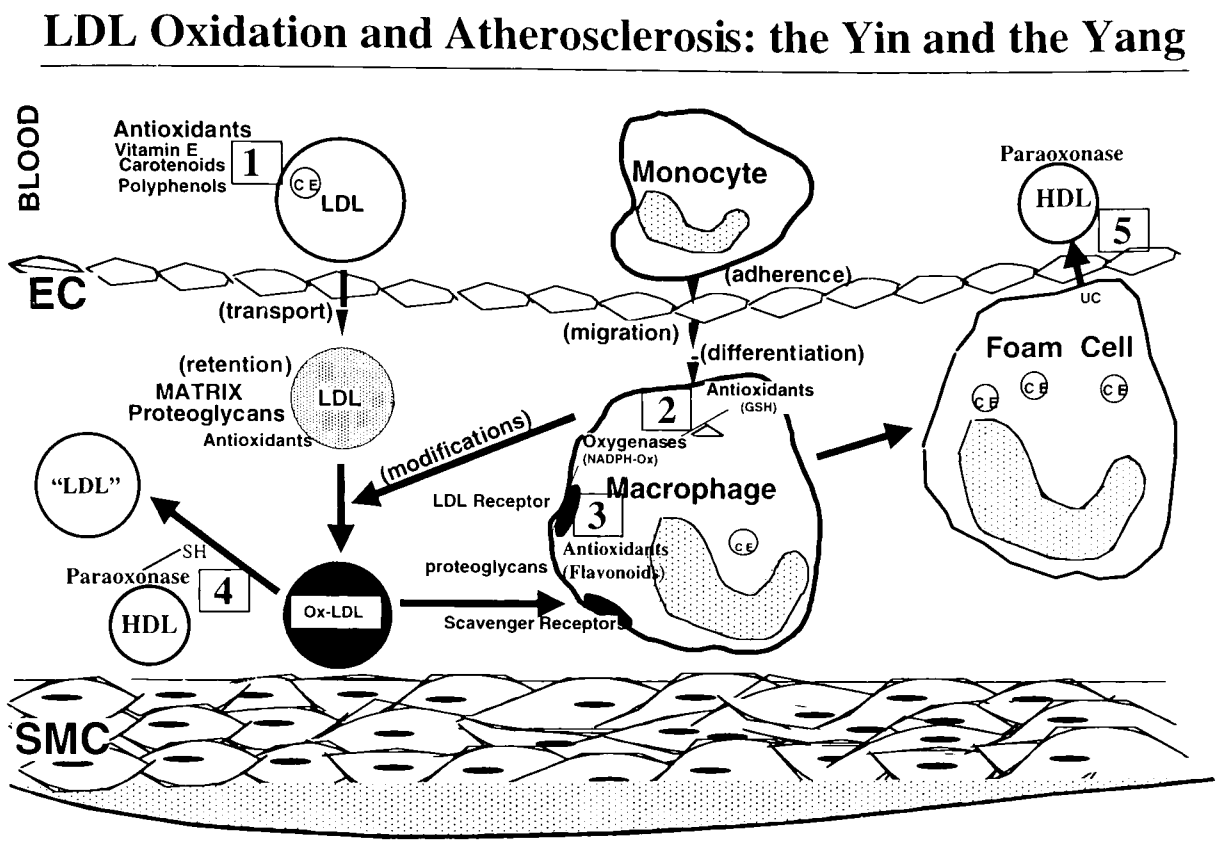

FIG. 1. Oxidative stress and macrophage foam cell formation: a dual approach. Under oxidative stress, both plasma LDL and blood monocytes invade the arterial wall. LDL binds to extracellular matrix proteoglycans and can be oxidized by arterial wall macrophages. The extent of LDL oxidation is determined by the balance between LDL-associated cholesteryl ester (CE), the major LDL substrate for oxidation, and by vitamin E, β-carotene, lycopene, and some polyphenols, which are associated with the LDL (#1). The macrophage oxidative state also determines the extent of LDL oxidation, and is the result of the balance between cellular oxygenases, such as NADPH oxidase, and antioxidants, such as glutathione (#2). Potent nutritional antioxidants such as flavonoids, are not only associated with the LDL particle (#1), but they can also accumulate in arterial cells, including macrophages. Accumulation of dietary antioxidants in macrophages can inhibit cell-mediated oxidation of LDL by their scavenging capacity of reactive oxygen species (ROS), as well as by their effects on cellular oxygenases and antioxidants (#3). Finally, if oxidized LDL (Ox-LDL) is formed in the arterial wall under excessive oxidative stress, HDL-associated paraoxonase can hydrolyze specific lipid peroxides in Ox-LDL and convert this atherogenic lipoprotein into a nonatherogenic "LDL"-like particle (#4). Oxidized lipids in Ox-LDL inactivate paraoxonase, and thus antioxidants, which reduce Ox-LDL lipid peroxides content, can preserve paraoxonase activity (#4). Macrophage uptake of Ox-LDL leads to cellular accumulation of cholesterol and oxysterols. Reversal of this process can be obtained by reverse cholesterol transport (RCT), which can be induced by intact HDL (#5). As paraoxonase protects HDL from oxidation, it promotes HDL-mediated cholesterol efflux from macrophage foam cells (#5). The yin and the yang in this figure thus represent factors that contribute to stimulation and inhibition of foam cell formation, respectively.

atherosclerosis (Navab *et al.*, 1995; Aviram and Fuhrman, 1998a). Macrophages can oxidize LDL, and the formed oxidized (Ox) LDL possesses several atherogenic properties, including its cytotoxicity to arterial cells, its pro-inflammatory and pro-thrombotic characteristics, and its enhanced cellular uptake by macrophages via scavenger receptors (Krieger, 1997). Oxidized LDL consists of heterogenous populations of lipoproteins with specific oxidized lipids and protein moieties.

Cell-surface receptors for oxidized LDL are thought to be multifunctional because they interact with several structurally different ligands, and accordingly have been termed scavenger receptors (Steinbrecher, 1999). LDL that was modified with lipid peroxides is rapidly degraded by cultured macrophages through the scavenger receptor pathway (Steinbrecher *et al.*, 1989). It was demonstrated that LDL oxidation is accompanied by a marked decrease in amino group reactivity, that leads to its

recognition by the "acetyl LDL receptor" (Steinbrecher *et al.*, 1987). Oxidation of LDL is accompanied by derivatization of lysine epsilon-amino groups by lipid products, and these adducts are important in the interaction of Ox-LDL with the acetyl LDL receptor (Steinbrecher, 1987). It was suggested that oxidized LDL is rather a marker of coronary atherosclerosis, whereas malondialdehyde-modified LDL is a marker of plaque instability and atherothrombosis (Holvoet, 1998). Both LDL lipids and protein moieties are affected by oxidative stress and antioxidants such as vitamin E or flavonoids can protect both of these LDL moieties against oxidation. Not only the protein moiety of Ox-LDL is involved in its binding to the cell's surface lipoprotein receptors (Steinbrecher, 1999), but the Ox-LDL lipid moieties are also involved (Nicholson *et al.*, 1995; Steinberg, 1999). The protein component of Ox-LDL and its lipid moieties (oxidized fatty acid products, oxidized phospholipids, lysolecithin, aldehydes, and oxysterols) were all shown to be associated with various pro-atherogenic effects on arterial wall cells and on blood cells (Parthasarathy *et al.*, 1998). Oxidized lipids were shown to stimulate a monocyte–endothelial cells interaction (Watson *et al.*, 1997; Honda *et al.*, 1999), an initial step during atherogenesis. The extent of LDL oxidation depends on the balance between the lipoprotein substrates for lipid peroxidation (mainly the cholesterol and the polyunsaturated fatty acids in its core cholesteryl ester moiety), and antioxidants that are bound to LDL (mainly the lipophylic vitamin E and carotenoids), or present in the plasma environment (the hydrophylic vitamin C) as shown in Fig. 1, #1.

We have shown that in cultured macrophages binding of LDL to the macrophage LDL receptor, in the presence of copper ions, is required for cell-mediated oxidation of LDL (Aviram and Rosenblat, 1994). Unlike the above results with cultured macrophages, activated human monocytes oxidized LDL irrespective of the binding of LDL to cell-surface LDL receptor (Cathcart *et al.*, 1995). Similarly, the ability of resident peritoneal macrophages derived from LDL receptor-deficient ($LDLR^{-/-}$) mice to oxidize LDL was not different from that of resident peritoneal macrophages from C57B6 control mice (Steinberg, 1999). In the LDL-R mice, however, additional factors could be responsible for the observed results (Tangirala *et al.*, 1996).

The major known sources for LDL oxidation include several cellular oxygenases, which are present in arterial wall macrophages, endothelial cells and smooth muscle cells. These arterial cells are modified during different stages of atherogenesis, and probably by more than one mechanism (Aviram and Fuhrman, 1998a; Heinecke, 1998; Aviram *et al.*, 1999a; Aviram, 1999b). Evidence exists for the involvement of arterial cells in LDL oxidation, and continuous presence of the cells together with the LDL is essential. The role of arterial cells in LDL oxidation is probably to generate reactive oxygen and nitrogen species (ROS and NOS, respectively), to provide substrates that generate extracellular oxidants (thiols?), to participate in the propagation of LDL oxidation (secreted peroxidases?) and/or to deplete the LDL from its antioxidants (Parthasarathy *et al.*, 1998).

Oxygenases involved in cell-mediated oxidation of LDL include NADPH oxidase, lipoxygenases, xantin oxidase, myeloperoxidase, cytochrome P-450, and the mitochondrial electron transport system (Steinberg *et al.*, 1989; Aviram, 1995a, 1999b; Aviram *et al.*, 1996a, 1999b; Aviram and Fuhrman, 1998a; Aviram *et al.*, 1999a; Steinberg, 1999; Cyrus *et al.*, 1999; Podrez *et al.*, 1999).

Cellular nitric oxide (NO), a potent inhibitor of oxidative stress can be converted, in the presence of NADPH oxidase-derived superoxides, into peroxynitrite, which is a potent oxidant. Additional sources for LDL oxidation include transition metal ions such as copper or ferrous ions and their corresponding proteins, ceruloplasmin and myoglobin, respectively.

Cellular antioxidants such as superoxide dismutase (SOD), catalase, reduced glutathione (GSH), and glutathione -peroxidase, -reductase, and -transferase also play a role in cell-mediated oxidation of LDL. Cellular glutathione peroxidase (GPx) activity is significantly affected in atherosclerosis (Lapenna *et al.*, 1998), and upon increasing macrophages GPx activity cell-mediated oxidation of LDL was inhibited (Rosenblat and Aviram, 1998; see Fig. 1,#2). Oxidized lipids in the atherosclerotic lesion are

probably derived not only from oxidized lipoproteins, but also from phospholipids and cholesterol in arterial wall cells. Thus, we hypothesized that lipid peroxides in arterial macrophages can also induce LDL oxidation. LDL oxidation by arterial cells is affected not only by the lipoprotein oxidative state, but also by the oxidative state in the cells (Aviram and Fuhrman, 1998a). Lipid peroxidation in macrophages could be induced by cell incubation with angiotensin II or with ferrous ions (Fuhrman *et al.*, 1997a). Angiotensin-converting enzyme inhibitors and angiotensin antagonists are potent inhibitors of cellular lipid peroxidation, of macrophage-mediated oxidation of LDL and of atherosclerosis, as we have recently shown in the apo E-deficient mice (Keidar *et al.*, 1995; Aviram *et al.*, 1999b). Macrophages isolated from human coronary or carotid lesions, or from the aortas of the atherosclerotic apo E-deficient mice, were shown to contain oxidized lipids (lipid peroxides and oxysterols). These "lipid peroxidized" cells can oxidize LDL, even in the absence of transition metal ions (Fuhrman *et al.*, 1994, 1997a; Keidar *et al.*, 1995). Macrophages that contain oxidized lipids may be easily converted into foam cells as a result of increased cholesterol biosynthesis, and/or increased uptake of atherogenic lipoproteins, due to a progressive oxidative modification of LDL by the oxidized lipids-enriched macrophages.

In the case of iron-loaded cells, iron can be released from the cells and then it can enhance oxidative stress and LDL oxidation in its microenvironment (Van Lenten *et al.*, 1995; Yuan *et al.*, 1995, 1996).

ANTIOXIDANTS AGAINST LDL OXIDATION AND ATHEROSCLEROSIS

Antioxidants, which are bound to LDL (vitamin E, carotenoids, and some flavonoids) or those present in the plasma environment (vitamin C, some flavonoids) can inhibit LDL oxidation. Antioxidants, which accumulate in arterial cells, including macrophages, can also block cell-mediated oxidation of LDL (Frei *et al.*, 1990, 1998; Stocker *et al.*, 1991; Halliwell, 1996; Maor *et al.*, 1997; Rosenblat *et al.*, 1999).

Antioxidants, such as vitamin E (Upston *et al.*, 1999), as well as the licorice-derived isoflavan glabridin (Belinky *et al.*, 1998a), can act under certain conditions as pro-oxidants. Possibly, glabridin, like vitamin E, exhibits the ability to reduce copper ion (Cu^{2+}) to the cuprous ion (Cu^{+}), which, in turn, produces highly reactive alkoxyl radicals ($RO^{\cdot}$) from lipid hydroperoxides (ROOH), or it may initiate lipid peroxidation by its phenoxyl radical. Cellular thiols are important contributors for maintaining a reductive environment, and hence they efficiently protect cells against lipid peroxidation (Lapenna *et al.*, 1998; Rosenblat and Aviram, 1998). Under certain conditions, however (in the presence of transition metals or of some other pro-oxidants), thiols can also be converted into potent radicals, which can enhance LDL oxidation (Graham, 1998).

Combination of several different antioxidants was suggested to prevent pro-oxidant activity of some pure antioxidants. Vitamin E supplementation together with other antioxidants, rather then alone, ameliorated lipoprotein lipid peroxidation in the artery wall (Fuhrman *et al.*, 1997c; Upston *et al.*, 1999). We and others have demonstrated the antiatherogenicity of vitamin E in the atherosclerotic apo E-deficient mice (Maor *et al.*, 1997; Pratico *et al.*, 1999; Witting *et al.*, 1999). The antioxidative and antiatherosclerotic effects of β-carotene and lycopene, unlike vitamin E or some flavonoids, were not always significant. However, on using a combination of vitamin E and carotenoids, a synergistic effect was obtained (Fuhrman *et al.*, 1997c).

Some polyphenolic flavonoids, such as those found in red wine, in pomegranate, or in licorice, are more efficient inhibitors of LDL oxidation and of atherosclerosis than vitmain E, vitamin C, or carotenoids (Fuhrman *et al.*, 1995; Van Acker *et al.*, 1996; Hayek *et al.*, 1997; Aviram and Fuhrman, 1998b; Aviram *et al.*, in press [a]), and an inverse relationship exists between flavonoids consumption and coronary heart diseases (Hertog *et al.*, 1993). The extent to which a potent antioxidant binds to LDL, and also the extent to which it accumulates in arterial wall macrophages, determines the rate of cell-mediated oxidation of the lipoprotein. Thus, we hypothesized that binding of flav-

onoids to LDL and cellular accumulation of flavonoids can possibly decrease macrophage cholesterol accumulation and foam cell formation, secondary to the inhibition of LDL and macrophage lipid peroxidation, and blocking of cell-mediated oxidation of LDL. In addition, accumulation of flavonoids in macrophages can possibly affect cholesterol biosynthesis and cellular uptake of atherogenic Ox-LDL. Polyphenolic flavonoids, such as those found in red wine or in licorice, significantly inhibited LDL oxidation both *in vitro* and *in vivo*. These antioxidants also decreased macrophage foam cell formation and attenuated atherosclerosis (Fuhrman *et al.*, 1995, 1997b; Hayek *et al.*, 1997; Aviram and Fuhrman, 1998a,b).

A most potent flavonoid antioxidant was recently isolated from the licorice root. This lipophylic flavonoid, the isoflavan glabridin, binds to LDL and inhibits its subsequent induced oxidation (Fuhrman *et al.*, 1997b; Vaya *et al.*, 1997; Belinky *et al.*, 1998b). FIavonoids can be internalized by macrophages, as we have recently shown for the licorice-derived isoflavan glabridin, both *in vitro* and *in vivo* in studies performed on the atherosclerotic, apo E-deficient mice (Rosenblat *et al.*, 1999). Glabridin, which is taken up by macrophages, can scavenge free radicals, but can also affect signal transduction pathways. We have recently shown indeed that glabridin can be accumulated in macrophages where it decreases cellular NADPH oxidase activity via the inhibition of macrophage protein kinase C (Rosenblat *et al.*, 1999). The oxidation of LDL by glabridin-enriched cells was substantially inhibited in comparison to control cells. Glabridin can also interact with lipoprotein receptors on the macrophage surface, such as the LDL receptor and the scavenger receptors. These effects can contribute to a reduction in macrophage uptake of lipoproteins, and, thus, to inhibition of cellular cholesterol accumulation and foam cell formation (Fig. 1, #3).

PARAOXONASE, LDL OXIDATION, AND ANTIOXIDANTS

Human serum paraoxonase (PON 1) is an HDL-associated esterase that can hydrolyze organophosphates, such as paraoxon, and arylesters, such as phenyl acetate. Because such substrates are not present in the human body, research is focused to identify other substrates of physiopathological relevance to atherosclerosis. PON 1 activity in serum is inversely related to the risk for cardiovascular diseases, and hence it might be that the antiatherogenic properties of HDL are related to its associated PON 1 (Machness *et al.*, 1998; Aviram, 1999a). PON 1 protects lipoproteins from oxidation induced by either copper ion or by a free radical-generating system (Watson *et al.*, 1995; Navab *et al.*, 1996, 1998; Aviram *et al.*, 1998a,b, 1999a; Mackness *et al.*, 1998). PON 1's protection against LDL oxidation (which is different from its arylesterase/paraoxonase activities) utilizes its free sulfhydryl group on cysteine-284 (Aviram *et al.*, 1998b).

Upon removal of calcium ions, PON 1 arylesterase activity is substantially decreased. Despite possessing a five-fold lower PON 1 arylesterase activity, HDL isolated from plasma (where calcium ions were chelated) or from serum was equally effective in protecting LDL from oxidation by THP-1 macrophages. However, we have recently shown (Aviram *et al.*, 1998b) that the PON 1-induced protection of LDL against oxidation, unlike its arylesterase activity, does not require calcium ions. The protection of PON 1 against LDL oxidation is not related to an antioxidant effect of PON 1, but it is associated with PON1's ability to hydrolyze specific lipid peroxides in the cholesteryl ester and in the phospholipid moieties of oxidized LDL (Aviram *et al.*, 1998a,b; Navab *et al.*, 1998) and convert Ox-LDL into a non-atherogenic lipoprotein (LDL, Fig. 1, #4). While PON 1 protects LDL from oxidation, lipid peroxides in Ox-LDL, in turn, inactivate PON 1 via an interaction with PON1's free sulfhydryl group (Aviram *et al.*, 1999b; Fig. 1, #4). Taken together the effects of paraoxonase on "neutralization" of Ox-LDL from its oxidized lipids, and that of Ox-LDL on paraoxonase inactivation, the combination of active PON 1 with potent antioxidants against LDL oxidation can preserve PON 1's ability to protect lipoproteins from oxidation, and hence, to reduce oxidative stress. Because PON 1 can hydrolyze and eliminate oxidized lipids from Ox-LDL, we hy-

pothesize that PON 1 may also hydrolyze specific atherogenic oxidized lipids in atherosclerotic lesions (arterial macrophages and lipoproteins) and thus can possibly contribute to regression of atherosclerosis. Indeed, studies from our laboratory identified active PON 1 in human coronary and carotid lesions (Aviram et al., in press). Furthermore, PON 1 acted on lesion's oxidized lipids and significantly reduced the oxidative stress that exists in lesions (Aviram *et al.*, in press [b]). Finally, protection of HDL from oxidation by PON 1 is associated with preservation of HDL capacity to enhance macrophage cholesterol efflux (Aviram *et al.*, 1998a). Thus, increased PON 1 activity can prevent Ox-LDL-induced cellular cholesterol accumulation and foam cell formation (Fig. 1, #5).

In summary, we suggest that elevation in activity of nutritional antioxidants over the damaging effects of pro-oxidants (both in LDL and in arterial cells), together with overexpression of PON 1, have the potential to reduce oxidative stress, to inhibit foam cell formation, and to attenuate atherosclerosis, the major cause of morbidity and mortality in the western world.

ABBREVIATIONS

CE, Cholesteryl ester; GPx, glutathione peroxidase; GSH, glutathione (reduced form); HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; NADPH, nicotine amid adenine dinucleotide phosphate (reduced form); NOS, reactive nitrogen species; Ox-LDL, oxidized low-density lipoprotein; PLA_2, phospholipase A_2; PON, paraoxonase; RCT, reverse cholesterol transport; ROS, reactive oxygen species; SMase, sphingomyelinase; SOD, superoxide dismutase.

REFERENCES

AVIRAM, M. (1993). Modified forms of low density lipoprotein and atherosclerosis. Atherosclerosis **98,** 1–9.

AVIRAM, M. (1995a). Oxidative modification of low density lipoprotein and atherosclerosis. Isr. J. Med. Sci. **31,** 241–249.

AVIRAM, M. (1995b). LDL-platelet interaction under oxidative stress induces macrophage foam cell formation. Thromb. Haemost. **74,** 560–564.

AVIRAM, M. (1996). Oxidized low density lipoprotein interaction with macrophages in atherosclerosis and the antiatherogenicity of antioxidants. Eur. J. Clin. Chem. Clin. Biochem. **34,** 599–608.

AVIRAM, M. (1999a). Does paraoxonase play a role in susceptibility to cardiovascular disease? Mol. Med. Today **5,** 381–386.

AVIRAM, M. (1999b). Antioxidants in restenosis and atherosclerosis. Curr. Intervent. Cardiol. Rep. **1,** 77–78.

AVIRAM, M., and ROSENBLAT, M. (1994). Macrophage-mediated oxidation of extra-cellular low density lipoprotein requires an initial binding of the lipoprotein to its receptor. J. Lipid. Res. **35,** 385–398.

AVIRAM, M., and FUHRMAN, B. (1998a). LDL oxidation by arterial wall macrophages depends on the oxidative status in the lipoprotein and in the cells: role of prooxidants vs. antioxidants. Mol. Cell. Biochem. **188,** 149–159.

AVIRAM, M., and FUHRMAN, B. (1998b). Polyphenolic flavonoids inhibit macrophage-mediated oxidation of LDL and attenuate atherogenesis. Atherosclerosis **137,** S45–S50.

AVIRAM, M., ROSENBLAT, M., ETZIONI, A., and LAVY, R. (1996). Activation of NADPH oxidase is required for macrophage-mediated oxidation of low density lipoprotein. Metabolism, **45,** 1069–1079.

AVIRAM, M., ROSENBLAT, M., BISGAIER, C.L., NEWTON, R.S., PRIMO-PARMO, S.L., and LA DU, B.N. (1998a). Paraoxonase inhibits high density lipoprotein (HDL) oxidation and preserves its functions: A possible peroxidative role for paraoxonase. J. Clin. Invest. **101,** 1581–1590.

AVIRAM, M., BILLECKE, S., SORENSON, R., BISGAIER, C., NEWTON, R., ROSENBLAT, M., EROGUL, J., DUNLOP, C., and LA DU, B.N. (1998b). Paraoxonase active site required for protection against LDL oxidation involves its free sulfhydryl group and is different than that required for its arylesterase/paraoxonase activities: selective action of human paraoxonase allozymes Q and R. Arterioscler. Thromb. Vasc. Biol. **18,** 1617–1624.

AVIRAM, M., KENT, U.M., and HOLLENBERG, P.F. (1999a). Microsomal cytochrome P450 catalyze the oxidation of low density lipoprotein. Atherosclerosis **143,** 253–260.

AVIRAM, M., ROSENBLAT, M., BILLECKE, S., EROGUL, J., SORENSON, R., BISGAIER, C.L., NEWTON, R.S., and LA DU, B.N. (1999b). Human serum paraoxonase (PON 1) is inactivated by oxidized low density lipoprotein and preserved by antioxidants. Free Radic. Biol. Med. **26,** 892–904.

AVIRAM, M., DORNFELD, L., ROSENBLAT, M., VOLKOVA, N., KAPLAN, M., HAYEK, T., PRESSER, D., and FUHRMAN, B. Pomegranate juice consumption reduces oxidative stress, low density lipoprotein modifications and platelet aggregation: studies in the atherosclerotic apolipoprotein E deficient mice and in humans. Am. J. Clin. Nutr., in press (a).

AVIRAM, M., HARDAK, E., VAYA, J., MAHMOOD, S., MILO, S., HOFFMAN, A., BILLIKE, S., DRAGONOV,

D., LA DU, B., and ROSENBLAT, M. Human serum paroaoxnases (PON 1) Q and R selectively decrease lipid peroxides in coronary and carotid atherosclerotic lesions: PON 1 esterase- and peroxidase-like activities. Circulation, in press (b).

BELINKY, P.A., AVIRAM, M., FUHRMAN, B., ROSENBLAT, M., and VAYA, J. (1998a). The antioxidative effects of the isoflavan glabridin on endogenous constituents of LDL during its oxidation. Atherosclerosis **137,** 49–61.

BELINKY, P.A., AVIRAM, M., MAHMOOD, S., and VAYA, J. (1998b). Structural aspects of the inhibitory effect of glabridin on LDL oxidation. Free. Radic. Biol. Med. **24,** 1419–1429.

BERLINER, J.A., NAVAB, M., FOGELMAN, A.M., FRANK, J.S., DEMER, L.L., EDWARDS, P.A., WATSON, A.D., and LUSIS, A.J. (1995). Atherosclerosis. Basic mechanisms oxidation, inflammation, and genetics. Circulation **91,** 2488–2498.

BERLINER, J.A., and HEINECKE, J.W. (1996). The role of oxidized lipoproteins in atherogenesis. Free Radic. Biol. Med. **20,** 707–727.

BROWN, A.J., and JESSUP, W. (1999). Oxysterols and atherosclerosis. Atherosclerosis **142,** 1–28.

CAMEJO, E., OLSSON, U., WIKLUND, O., BONDJERS, G., and CAMEJO, G. (1997). Cellular consequences of the association of apo B lipoproteins with protegolycans. Potential contribution to atherogenesis. Arterioscler. Thromb. Vasc. Biol. **17,** 1011–1017.

CATHCART, M.K., LI, Q., and CHISOLM, G.M. (1995). Lipoprotein receptor interactions are not required for monocyte oxidation of LDL. J. Lipid Res. **36,** 1857–1865.

CYRUS, T., WITZTUM, J.L., RADER, D.J., TANGIRALA, R., FAZIO, Z., LINTON, M.F., and FUNK, C.D. (1999). Disruption of the 12/15-lipoxygeanse gene diminishes atherosclerosis in apo E-deficient mice. J. Clin. Invest. **103,** 1597–1604.

EDWARDS, I.J., GOLDBERG, I.J., PARKS, J.S., ZU, H., and WAGNER, W.D. (1993). Lipoprotein lipase enhances the interaction of low density lipoproteins with artery-derived extracellular matrix proteoglycans. J Lipid Res. **34,** 1155–1163.

FITZGERALD, G.A., TIGGES, J., BARRY, P., and LAWSON, J.A. (1997). Markers of platelet activation and oxidant stress in atherothrombotic disease. Thromb. Haemost. **1,** 280–284.

FREI, B., STOCKER, R., and AMES, B.N. (1998). Antioxidant defenses and lipid peroxidation in human blood plasma. Proc. Natl. Acad. Sci. USA **85,** 9748–9752.

FREI, B., STOCKER, R., ENGLAND, L., and AMES, B.N. (1990). Ascorbate: the most effective antioxidant in human blood plasma. Adv. Exp. Med. Biol. **264,** 155–163.

FUHRMAN, B., OIKNINE, J., and AVIRAM, M. (1994). Iron induced lipid peroxidation in cultured macrophages increases their ability to oxidatively modify LDL and affect their secretory properties. Atherosclerosis **111,** 65–78.

FUHRMAN, B., LAVY, A., and AVIRAM, M. (1995). Consumption of red wine with meal reduces the susceptibility of human plasma and LDL to undergo lipid peroxidation Am. J. Clin. Nutr. **61,** 549–554.

FUHRMAN, B., OIKNINE, J., KEIDAR, S., BEN-YAISH, L., KAPLAN, M., and AVIRAM, M. (1997a). Increased uptake of LDL by oxidized macrophages is the result of an initial enhanced LDL receptor activity and of further progressive LDL oxidation. Free Radic. Biol. Med. **23,** 34–46.

FUHRMAN, B., BUCH, S., VAYA, J., BELINKY, P.A., COLEMAN, R., HAYEK, T., and AVIRAM, M. (1997b). Licorice ethanolic extract and its major polyphenol glabridin protect LDL against lipid peroxidation: in vitro and ex-vivo studies in humans and in the atherosclerotic apolipoprotein E deficient mice. Am. J. Clin. Nutr. **66,** 10–19.

FUHRMAN, B., BEN-YAISH, L., ATTIAS, J., HAYEK, T., and AVIRAM, M. (1997c). Tomato's lycopene and β-carotene inhibit low density lipoprotein oxidation and this effect depends on the lipoprotein vitamin E content. Nutr. Metab. Cardiovasc. Dis. **7,** 433–443.

GRAHAM, A. (1998). Cellular thiol production and oxidation of low-density lipoprotein. Free Radic. Res. **28,** 611–621.

GRAHAM, A., HASSAL, D.G., RAFIQUE, S., and OWEN, J.S. (1997). Evidence for a paraoxonase-independent inhibition of low-density lipoprotein oxidation by high-density lipoprotein. Atherosclerosis. **135,** 193–204.

HALLIWELL, B. (1996). Antioxidants in human health and disease. Annu. Rev. Nutr. **16,** 33–50.

HAYEK, T., FUHRMAN, B., VAYA, J., ROSENBLAT, M., BELINKY, P., COLEMAN, R., ELIS, A., and AVIRAM, M. (1997). Reduced progression of atherosclerosis in the apolipoprotein E-deficient mice following consumption of red wine, or its polyphenols quercetin, or catechin, is associated with reduced susceptibility of LDL to oxidation and aggregation. Arterioscler. Thromb. Vasc. Biol. **17,** 2744–2752.

HEINECKE, J.W. (1998). Oxidants and antioxidants in the pathogenesis of atherosclerosis: implications for the oxidized low density lipoprotein hypothesis. Atherosclerosis. **141,** 1–15.

HERTOG, M.G., FESKENS, E.J., HOLLMAN, P.C., KATAN, M.B., and KORMHOUT, D. (1993). Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen elderly study. Lancet **342,** 1007–1011.

HOLVOET, P. (1998). Oxidative modification of low-density lipoprotein in atherothrombosis. Acta. Cardiol. **53,** 253–260.

HONDA, H.M., LEITINGER, N., FRANKEL, M., GOLDHABER, J.L., NATARAJAN, R., NADLER, J.L., WEISS, J.N., and BERLINER, J.A. (1999). Induction of monocyte binding to endothelial cells by MM-LDL: role of lipoxygenase metabolites. Arterioscler. Thromb. Vasc. Biol. **19,** 680–686.

HURT-CAMEJO, F., OLSSON, U., WIKLUND, O., BONDJERS, G., and CAMEJO, G. (1997). Cellular consequences of the association of apo B lipoproteins with proteoglycans. Arterioscler. Thromb. Vasc. Biol. **17,** 1011–1017.

KEIDAR, S., KAPLAN, M., HOFFMAN, A., BROOK, J.G., and AVIRAM, M. (1995). Angiotensin II stimulates macrophage-mediated lipid peroxidation of low density lipoprotein. Atherosclerosis **115,** 201–215.

KRIEGER, M. (1997). The other side of scavenger receptors: pattern recognition for host defense. Curr. Opin. Lipidol. **8,** 275–280.

LAPENNA, D., DE GIOIA, S., CIOFANI, G., MEZZETTI, A., UCCHINO, S., CALAFIORE, A.M., NAPOLITANO, A.M., DI ILIO, C., and CUCCURULLO, F. (1998). Glutathione-related antioxidant defenses in human atherosclerotic plaques. Circulation **97,** 1930–1934.

MACKNESS, M.I., MACKNESS, B., DURRINGTON, P.N., FOGELMAN, A.M., BERLINER, J., LUSIS, A.J., NAVAB, M., SHIH, D., and FONAROW, G.C. (1998). Paraoxonase and coronary heart disease. Curr. Opin. Lipidol. **9,** 319–324.

MAOR, I., and AVIRAM, M. (1999). Macrophage released proteoglycans are involved in cell-mediated aggregation of LDL. Atherosclerosis **142,** 57–66.

MAOR, I., HAYEK, T., COLEMAN, R., and AVIRAM, M. (1997). Plasma LDL oxidation leads to its aggregation in the atherosclerotic apolipoprotein E deficient mice. Arterioscler. Thromb. Vasc. Biol. **17,** 2995–3005.

MAOR, I., HAYEK, T., HIRSH, M., IANCU, T.C., and AVIRAM, M. (1999). Macrophage released proteoglycans enhance LDL aggregation in the aorta of apolipoprotein E-deficient mice. Atherosclerosis (in press).

NAVAB, M., FOGELMAN, A.M., BERLINER, J.A., TERRITO, M.C., DEMER, L.L., FRANK, J.S., WATSON, A.D., EDWARDS, P.A., LUSIS, A.J. (1995). Pathogenesis of atherosclerosis. Am J. Cardiol. **28,** 18C–23C.

NAVAB, M., BERLINER, J.A., WATSON, A.D., HAMA, S.Y., TERRITO, M.C., LUSIS, A.J., SHIH, D.M., VAN LENTEN, B.J., FRANK, I.S., DEMER, L.L., EDWARDS, P.A., and FOGELMAN, A.M. (1996). The yin and yang of oxidation in the development of the fatty streak. A review based on the 1994 George Lyman Duff Memorial Lecture. Arterioscler. Thromb. Vasc. Biol. **16,** 831–842.

NAVAB, M., HAMA, S.Y., HOUGH, G.P., HEDRICK, C.C., SORENSON, R., LA DU, B.N., KOBASHIGAQA, J.A., FONAROW, G.C., BERLINER, J.A., and FOGELMAN, A.M. (1998). High density associated enzymes: their role in vascular biology. Curr. Opin Lipidol. **9,** 449–456.

NICHOLSON, A.C., FRIEDA, S., PEARCE, A., and SILVERSTEIN, R.L. (1995). Oxidized LDL binds to CD36 on human monocyte-derived macrophages and transfected lines: evidence implicating the lipid moiety of the lipoprotein as the binding site. Arterioscler. Thromb. Vasc. Biol. **15,** 269–275.

OORNI, K., HAKALA, J.K., ANNILA, A., ALA-KORPELA, M., and KOVANEN, P.T. (1998). Sphingomyelinase induces aggregation and fusion, but phospholipase A2 only aggregation, of low density lipoprotein (LDL) particles. Two distinct mechanisms leading to increased binding strength of LDL to human aortic proteoglycans. J. Biol. Chem. **273,** 29127–29134.

PARTHASARATHY, S., SANTANUM, N., and AUGE, N. (1998). Oxidized low-density lipoprotein: a two-faced Janus in coronary artery disease? Biochem. Pharm. **56,** 279–284.

PODREZ, E.A., SCHMITT, D., HOFF, H.F., and HAZEN, S.L. (1999). Myeloperoxidase-generated reactive nitrogen species convert LDL into an atherogenic form in vitro. J. Clin. Invest. **103,** 1547–1560.

PRATICO, D.T., IULIANO, L., MAURIELLO, A., SPAGNOLI, L., LAWSON, J.A., ROCKACH, J., MACLOUF, J., VIOLI, F., and FITZ GERALD, G.A. (1997). In vivo formation of distinct F_2-isoprostances in human atherosclerotic lesions. J. Clin. Invest. **100,** 2028–2034.

PRATICO, D.T., TANGIRALA, R.K., RADER, D.J., ROCKACH, J., and FITZGERALD, G.A. (1999). Vitamin E suppresses isoprostane generation in vivo and reduces atherosclerosis in apo E-deficient mice. Nature Med. **10,** 1189–1192.

ROSS, R. (1999). Atherosclerosis-an inflammatory disease. N. Engl. J. Med. **340,** 115–126.

ROSENBLAT, M., and AVIRAM, M. (1998). Macrophage glutathione content and glutathione peroxidase activity are inversely related to cell-mediated oxidation of LDL:in vitro and in vivo studies. Free. Radic. Biol. Med. **24,** 305–317.

ROSENBLAT, M., BELINKY, P., VAYA, J., LEVY, R., HAYEK, T., COLEMAN, R., MERCHAV, S., and AVIRAM, M. (1999). Macrophage enrichment with the isoflavan glabridin inhibits superoxide-induced cell-mediated oxidation of low density lipoprotein (LDL): A possible role for protein kinase C. J. Biol. Chem. **274,** 13790–13799.

RUEF, J., HU, Z.Y., YIN, L.Y., WU, Y., HANSON, S.R., KELLY, A.B., HARKER, L.A., RAO, G.N., RUNGE, M.S., and PATTERSON, C. (1997). Induction of vascular endothelial growth factor in baloon-injured baboon arteries. A novel role for reactive oxygen species in atherosclerosis. Circ. Res. 1, 24–33.

SCHISSEL, S.L., TWEEDIE-HARDMAN, J., RAPP, J.H., GRAHAM, G., WILLIAMS, K.J., and TABAS, I. (1996). Rabbit aorta and human atherosclerotic lesions hydrolyze the sphingomyelin of retained low-density lipoprotein. Proposed role for arterial-wall sphingomyelinase in subendothelial retention and aggregation of atherogenic lipoprotein. J. Clin. Invest. **15,** 1455–1464.

SCHISSEL, S.L., JIANG, X., TWEEDIE-HARDMAN, J., JEONG, T., CAMEJO, E.H., NAJIB, J., RAPP, J.H., WILLIAMS, K.J., and TABAS, I. (1998). Secretory sphingomyelinase, a product of the acid sphingomyelinase gene, can hydrolyze atherogenic lipoproteins at neutral pH. Implications for atherosclerotic lesion development. J. Biol. Chem. **273,** 2738–2746.

SMITH, C., MITCHINSON, M.J., ARUOMA, O.I., and HALLIWELL, B. (1992). Stimulation of lipid peroxidation and hydroxyl radical generation by the contents of human atherosclerotic lesions. Biochem. J. **286,** 901–905.

STEINBERG, D. (1999). At last, direct evidence that lipoxygenases play a role in atherogenesis. J. Clin. Invest. **103,** 1487–1488.

STEINBERG, D., PARTHASARATHY, S., CAREW, T.E., KHOO, J.C., and WITZTUM, J.L. (1989). Beyond cholesterol: modification of low-density lipoprotein that increase its atherogenicity. N. Engl. J. Med. 320, 915–924.

STEINBRECHER, U.P., (1987). Oxidation of human low density lipoprotein results in derivatization of lysine

residues of apolipoprotein B by lipid peroxide decomposition products. J. Biol. Chem. **262,** 3603–3608.

STEINBRECHER, U.P. (1999). Receptors for oxidized low density lipoprotein. Biochim. Biophys. Acta **1436,** 279–298.

STEINBRECHER, U.P., WITZTUM, J.L., PARTHASARATHY, S., and STEINBERG, D. (1987). Decrease in reactive amino groups during oxidation or endothelial cell modification of LDL. Correlation with changes in receptor-mediated catabolism. Arteriosclerosis **7,** 135–143.

STEINBRECHER, U.P., LOUGHEED, M., KWAN, W.C., and DIRKS, M. (1989). Recognition of oxidized low density lipoprotein by the scavenger receptor of macrophages results from derivatization of apolipoprotein B by products of fatty acid peroxidation. J. Biol. Chem. **264,** 15216–15223.

STOCKER, R., BOWRY, V.W., and FREI, B. (1991). Ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does alpha-tocopherol. Proc. Natl. Acad. Sci. USA **89,** 1646–1650.

TABAS, I., LI, Y., BROCIA, R.W., WX, S.W., SWENSON, T.L., and WILLIAMS, K.J. (1993). Lipoprotein lipase and sphingomyelinase synergistically enhance the association of atherogenic lipoproteins with smooth muscle cells and extracellular matrix. A possible mechanism for low density lipoprotein and lipoprotein (a) retention and macrophage foam cell formation. J. Biol. Chem. **268,** 20419–20432.

TANGIRALA, R.K., MOL, M.J., and STEINBERG, D. (1996). Macrophage oxidative modification of low density lipoprotein occurs independently of its binding to the LDL receptor. J. Lipid Res. **37,** 835–843.

UPSTON, J.M., TERENTIS, A.C., and STOCKER, R. (1999). Tocopherol-mediated peroxidation of lipoproteins: implications for vitamin E as a potential antiatherogenic supplement. FASEB J. **13,** 977–994.

UYEMURA, K., DEMER, L.L., CASTLE, S.C., JULLIEN, D., BERLINER, J.A., GATELY, M.K., WARRIER, R.R., PHAM, N., FOGELMAN, A.M., and MODLIN, R.L. (1996). Cross-regulatory roles of interleukin (IL)-12 and IL-10 in atherosclerosis. J. Clin. Invest. **97,** 2130–2138.

VAN ACKER, S.A., VAN DEN BERG, D.J., TROMP, M.N., GRIFFIOEN, D.H., VAN BENNEKOM, W.P., VAN DER VIJGH, W.J., and BAST, A. (1996). Structural aspects of antioxidant activity of flavonoids. Free. Radic. Biol. Med. **20,** 331–342.

VAN LENTEN, B.J., PRIEVE, J., NAVAB, M., HAMA, S., LUSIS, A.J., and FOGELMAN, A.M., (1995). Lipid-induced changes in intracellular iron homeostasis in vitro and in vivo. J. Clin. Invest. **95,** 2104–2110.

VAYA, J., BELINKI, P., and AVIRAM, M. (1997). Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity towards LDL oxidation. Free. Radic. Biol. Med. **23,** 302–312.

WATSON, A.D., BERLINER, J.A., HAMA, S.Y., LA DU, B.N., FAULL, K.F., FOGELMAN, A.M., and NAVAB, M. (1995). Protective effect of high density lipoprotein associated paraoxonase. Inhibition of the biological activity of minimally oxidized low density lipoprotein. J. Clin. Invest. **96,** 2882–2891.

WATSON, A.D., LEITINGER, N., NAVAB, M., FAULL, K.F., HORKKO, S., WITZTUM, J.L., PALINSKI, W., SCHWENKE, D., SALOMO, R.G., SHA, W., SUBBANAGOUNDER, G., FOGELMAN, A.M., and BERLINER, J.A. (1997). Structural identification by mass spectrometry of oxidized phospholipids in minimally oxidized low density lipoprotein that induced monocyte-endothelial interactions and evidence for their presence in vivo. J. Biol. Chem. **272,** 13597–13607.

WELCH, G.N., UPCHURCH, G.R., JR., and LOSCALZO, J. (1997). Homocysteine, oxidative stress, and vascular disease. Hosp. Pract. **32,** 88–92.

WILLIAMS, K.J., and TABAS, I. (1995). The response-to-retention hypothesis of early atherogenesis. Arterioscler. Thromb. Vasc. Biol. **15,** 551–561.

WITTING, P.K., PETTERSSON, K., OSTLUND-LINDQVIST, A.M., WESTERLUND, C., ERIKSSON, A.W., and STOCKER, R. (1999). Inhibition by a coantioxidant of aortic lipoprotein lipid peroxidation and atherosclerosis in apolipoprotein E and low density lipoprotein receptor gene double knockout mice. FASEB J. **13,** 667–675.

WITZTUM, J.L., and BERLINER, J.A. (1998). Oxidized phospholipids and isoprostanes in atherosclerosis. Curr. Opin. Lipidol. **9,** 441–448.

YUAN, X.M., BRUNK, U.T., and OLSSON, A.G. (1995). Effects of iron-and hemoglobin-loaded human monocyte-derived macrophages on oxidation and uptake of LDL. Arterioscler. Thromb. Vasc. Biol. **15,** 1345–1351.

YUAN, X.M., ANDERS, W.L., OLSSON, A.G., and BRUNK, U.T. (1996). Iron in human atheroma and LDL oxidation by macrophages following erythrophagocytosis. Atherosclerosis **124,** 61–73.

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1. Marielle Kaplan, Michael Aviram, Tony Hayek. 2012. Oxidative stress and macrophage foam cell formation during diabetes mellitus#induced atherogenesis: Role of insulin therapy. *Pharmacology & Therapeutics* **136**:2, 175-185. [CrossRef]
2. Xiu-Juan Fan, Jun Ren. 2012. Compensation: A Contemporary Regulatory Machinery in Cardiovascular Diseases?. *Cardiovascular Toxicology* . [CrossRef]
3. Hagai Tavori, Michael Aviram, Soliman Khatib, Ramadan Musa, Dalit Mannheim, Ron Karmeli, Jacob Vaya. 2011. Paraoxonase 1 protects macrophages from atherogenicity of a specific triglyceride isolated from human carotid lesion. *Free Radical Biology and Medicine* **51**:1, 234-242. [CrossRef]
4. Ho Joong Sung, Jeonghan Kim, Yoonseo Kim, Sung-Wuk Jang, Jesang Ko. 2011. N-acetyl cysteine suppresses the foam cell formation that is induced by oxidized low density lipoprotein via regulation of gene expression. *Molecular Biology Reports* . [CrossRef]
5. Giangiacomo Beretta, Giancarlo Aldini, Roberto Maffei FacinoAntioxidant Activity of Solid Olive Oil Residues from Olea europaea 'Coratina' Cultivar 943-949. [CrossRef]
6. M KOU, J YEN, J HONG, C WANG, C LIN, M WU. 2009. Cyphomandra betacea Sendt. phenolics protect LDL from oxidation and PC12 cells from oxidative stress. *LWT - Food Science and Technology* **42**:2, 458-463. [CrossRef]
7. Michal Efrat, Michael Aviram. 2008. Macrophage paraoxonase 1 (PON1) binding sites. *Biochemical and Biophysical Research Communications* **376**:1, 105-110. [CrossRef]
8. Tzi-Wei Lian, Lisu Wang, Ya-Hsuan Lo, I-Jen Huang, Ming-Jiuan Wu. 2008. Fisetin, morin and myricetin attenuate CD36 expression and oxLDL uptake in U937-derived macrophages. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **1781**:10, 601-609. [CrossRef]
9. Orit Rozenberg, Maayan Shiner, Michael Aviram, Tony Hayek. 2008. Paraoxonase 1 (PON1) attenuates diabetes development in mice through its antioxidative properties. *Free Radical Biology and Medicine* **44**:11, 1951-1959. [CrossRef]
10. Manuel Mayr, Anissa Sidibe, Anna Zampetaki. 2008. The Paradox of Hypoxic and Oxidative Stress in Atherosclerosis##Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology. *Journal of the American College of Cardiology* **51**:13, 1266-1267. [CrossRef]
11. Meixiang Xiang, Jian'an Wang. 2007. Management of atherosclerosis with antiallergic medicine: a lesson from the mouse model. *Future Cardiology* **3**:6, 595-599. [CrossRef]
12. M. Naruszewicz, M. Kozlowska-Wojciechowska. 2007. Plant sterols beyond low-density lipoprotein-cholesterol. *British Journal of Nutrition* **98**:03, 454. [CrossRef]
13. Toshio Hayashi, Packiasamy A.R. Juliet, Asaka Miyazaki, Louis J. Ignarro, Akihisa Iguchi. 2007. High glucose downregulates the number of caveolae in monocytes through oxidative stress from NADPH oxidase: Implications for atherosclerosis. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1772**:3, 364-372. [CrossRef]
14. B FUHRMAN, N VOLKOVA, M AVIRAM. 2006. Postprandial serum triacylglycerols and oxidative stress in mice after consumption of fish oil, soy oil or olive oil: Possible role for paraoxonase-1 triacylglycerol lipase-like activity. *Nutrition* **22**:9, 922-930. [CrossRef]
15. B FUHRMAN, N VOLKOVA, M AVIRAM. 2005. Pomegranate juice inhibits oxidized LDL uptake and cholesterol biosynthesis in macrophages. *The Journal of Nutritional Biochemistry* **16**:9, 570-576. [CrossRef]
16. Gloria Lena Vega. 2004. Management of atherogenic dyslipidemia of the metabolic syndrome: evolving rationale for combined drug therapy. *Endocrinology and Metabolism Clinics of North America* **33**:3, 525-544. [CrossRef]
17. Tatsuya TAGAWA, Yoshitoshi URABE, Yoshikuni KIMURA, Satoshi SUZUKI, Hiroki ONO, Kotaro TAKEDA. 2004. Long-Term Treatment with Probucol Improves Endothelial Function in Patients with Coronary Artery Disease. *Hypertension Research* **27**:5, 311-318. [CrossRef]
18. Mariarosaria Napolitano, Gabriella Rainaldi, Elena Bravo, Roberto Rivabene. 2003. Influence of thiol balance on micellar cholesterol handling by polarized Caco-2 intestinal cells. *FEBS Letters* **551**:1-3, 165-170. [CrossRef]

19. S Monier. 2003. Impairment of the cytotoxic and oxidative activities of 7#-hydroxycholesterol and 7-ketocholesterol by esterification with oleate. *Biochemical and Biophysical Research Communications* **303**:3, 814-824. [CrossRef]
20. V. Schettler, J. Krontal, A. Scheel, E. Wieland. 2003. No acute impact of lipid apheresis treatment on free radical scavenging enzyme gene expression in white blood cells. *European Journal of Clinical Investigation* **33**:2, 134-140. [CrossRef]
21. Bianca Fuhrman, Nina Volkova, Michael Aviram. 2002. Oxidative stress increases the expression of the CD36 scavenger receptor and the cellular uptake of oxidized low-density lipoprotein in macrophages from atherosclerotic mice: protective role of antioxidants and of paraoxonase. *Atherosclerosis* **161**:2, 307-316. [CrossRef]
22. B Fuhrman. 2002. Antiatherosclerotic effects of licorice extract supplementation on hypercholesterolemic patients: increased resistance of LDL to atherogenic modifications, reduced plasma lipid levels, and decreased systolic blood pressure. *Nutrition* **18**:3, 268-273. [CrossRef]
23. Y Yamaguchi. 2002. Fluvastatin reduces modification of low-density lipoprotein in hyperlipidemic rabbit loaded with oxidative stress. *European Journal of Pharmacology* **436**:1-2, 97-105. [CrossRef]
24. Mira Rosenblat, Michael Aviram. 2002. Oxysterol-induced activation of macrophage NADPH-oxidase enhances cell-mediated oxidation of LDL in the atherosclerotic apolipoprotein E deficient mouse: inhibitory role for vitamin E. *Atherosclerosis* **160**:1, 69-80. [CrossRef]
25. Jess Reed. 2002. Cranberry Flavonoids, Atherosclerosis and Cardiovascular Health. *Critical Reviews in Food Science and Nutrition* **42**, 301-316. [CrossRef]
26. Mandy L Porter, Christian G Krueger, Donald A Wiebe, David G Cunningham, Jess D Reed. 2001. Cranberry proanthocyanidins associate with low-density lipoprotein and inhibitin vitro Cu2+-induced oxidation. *Journal of the Science of Food and Agriculture* **81**:14, 1306-1313. [CrossRef]
27. Biana Fuhrman, Michael AviramPolyphenols and Flavonoids Protect LDL Against Atherogenic Modifications . [CrossRef]