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Relationship Between Protein Oxidation Markers and Oxidative Stress Biomarkers

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1. Introduction

There is a general agreement (belief) that lipids are the pivotal element in inflammatory disease. One of the most studied topics is the connection between lipid oxidation and cardiovascular disease. In a very recent review, the introductory paragraphs states, after resuming the elements of the inflammatory response starting with stimulated endothelium displaying adhesive molecules for circulating leucocytes, lipid oxidation products formed by virtually every vascular cell type participate in orchestrating these processes and the inflammatory process is actively limited by activation of a resolution phase, often via generation of structurally specific oxidized lipids whose function is to orchestrate resolution of inflammation (McIntyre & Hazen 2010).

Most of the knowledge involving lipid oxidation comes from "in vitro" studies and on supplementation trials with antioxidants like vitamins and anti-inflammatory drugs. Vitamins E and C are considered dietary antioxidants although mostly ex vivo measurements of lipid peroxidation have been performed (Hillstrom et al. 2003; Heinecke 2001). Quantifying "in vivo" lipid oxidation is not easy and several biomarkers of lipid peroxidation has been used like F2-isoprostanes, considered the most accurate way to measure oxidative stress "in vivo", and as a risk factor for atherosclerosis and other diseases (Lawson et al. 1999).

The secondary products of lipid peroxidation (LPO) the reactive carbonyl compounds, modify biologically essential molecules such as proteins and DNA bases (Yuan et al. 2006). Thus lipid oxidation processes in biological tissues may be more complicated since they contain a plethora of carbohydrates, proteins and lipids forming a complex matrix. In tissues, lipid oxidation can cause protein oxidation due to close interactions between lipids and proteins. LPO "in vivo" has been implicated as the underlying mechanisms in numerous disorders and diseases such as cardiovascular diseases, cancer, neurological disorders, and aging.

Thus, when oxidative stress biomarkers are evaluated protein oxidation deserves consideration.

2. Protein oxidation

In the next paragraphs I will analyze several works about protein oxidation "in vitro" (incubation in test tubes, cells systems, perfusion, foods) and "in vivo" (disease epidemiology and animal models mostly) with the intention of stressing similarities and differences between them. The next table is an outline of the literature reviewed in points 2.1 and 2.2.

Protein oxidation "in vitro"	Characteristis of the model employed	Main observation
(Batthyány et al. 2000)	Copper binding to apolipoprotein B-100 is necessary for oxidation	Formation of protein-tryptophanyl radicals
(Yang et al. 1997)	LDL treated with HOCL	Selective process of modification of apoB-100 by HOCL
(Hedrick et al. 2000)	Incubation of HDL under hyperglycaemic conditions	Changes in HDL caused by hyperglycaemia contribute to accelerated atherosclerosis
(Chantepie et al. 2009)	HDL treated with HOCL	Small, dense HDL less susceptible to oxidative modification
(Sigalov & Stern 2001)	Reconstituted HDL containing oxidized apo A-I	Destabilization of the oxidized protein to denaturation
(Chen et al. 2007)	Polyphenolics in the Cu(2+)-induced generation of conjugated dienes of LDL	Polyphenolics reduce oxidation of apoB-100
(Arai & Nakamura 2004)	VLDL oxidation induced by peroxyl radicals and peroxynitrite	Ascorbic acid protects apolipoprotein E of oxidation
(Jedidi et al. 2003)	LDL oxidation was mediated by water gamma radiolysis	(*)OH initiate oxidation leading to apob carbonylation in presence of aminoguanidine
(Roland et al. 2001)	LDL and Cu(2+)	Flavonoids myricetin, quercetin, and catechin decreased copper binding to LDL
(Patterson et al. 2003)	LDL, human serum ultrafiltrate of Mr below 500 and hydroperoxide or Cu(2+)	Low Cu(2+) inhibit tocopherol induced oxidation in LDL, promote breakdown of lipid hydroperoxides into radicals
(Makedou et al. 2009)	Copper-induced Low-density lipoprotein (LDL) oxidizability	Progeny with a positive family history for hyperlipidemia have increased LDL susceptibility to oxidation
(Hockerstedt et al. 2004)	Copper-induced oxidation of purified HDL	LCAT causes estradiol esterification and thus provide antioxidant protection to HDL
(Moreno & Fuster 2004)	LDL oxidation susceptibility to Cu(2+)	Apolipoprotein E polymorphism partially explain differences in individual responses to diet
(Popa et al. 2009)	HDL ability to inhibit copper-induced oxidation of low-density lipoprotein (LDL)	Infliximab has beneficial effects on lipids through changes in HDL antioxidative capacity
(Deakin et al. 2002)	Transfection of CHO cells, did not co-secretate apo A-I and lipids leading to formation of	Accumulation of PON1 in cell membrane was not influenced by the ability of the cell to co-secrete of apoA-I

	HDL-like complexes	
(Allen & Jandeleit-Dahm 2005)	Review	Recognised metabolic abnormalities upregulation of advanced glycation endproducts, renin-angiotensin system, oxidative stress associated with diabetes
(Shao et al. 2010)	Revision	Biochemical studies implicated tyrosine chlorination and methionine oxygenation in the loss of ABCA1 and LCAT activity by oxidized apoA-I
(Obama et al. 2007)	Copper-induced oxLDL	Histidine residue modified by 4-hydroxynonenal, a major lipid peroxidation product, oxidized histidine and tryptophan residues
(Suc et al. 2003)	Tyrosylation of high-density lipoprotein	HDLT competes with oxidized and acetylated LDL, ligands of scavenger receptor class B type I/II
(Zarev et al. 2002)	LDL oxidation induced in vitro by copper and *OH/O*(2)(-) free radicals generated by gamma-radiolysis	Apolipoprotein B carbonylated fragmentation not detected during the lag phase of copper-oxidized LDL but detected during the propagation phase
(Edelstein et al. 2001)	Oxidation of LDL by Cu(2)+ or the combined phospholipase A2 and lipoxygenase system	Apo[a] but not apoB-100 resists oxidative fragmentation, apoB-100 can be degraded by enzymes and oxidation
(Gao et al. 2008)	Copper and hypochlorite (prefer´-entially oxidize lipids or proteins, respectively) oxidation of HDL	Mild oxidation favor HDL remodeling due to diminished apolipoprotein affinity for lipids due to oxidation of methionine and aromatic residues
(Gomes et al. 2002)	Beta 2-Glycoprotein I (beta 2 GPI), macrophage uptake of particles with phosphatidylserine containing surfaces, and unilamellar vesicles	Particle uptake in the presence of beta 2 GPI is coupled to an inhibition of reactive species production by liver macrophagest
(Jolivalt et al. 2000)	Myeloperoxidase oxidative system	Oxidation of apo E decreases its incorporation into phospholipid discs by approximately 50%
(Van Antwerpen et al. 2006; Van Antwerpen et al. 2005)	LDL oxidation by myeloperoxidase	Thiol-containing molecules such as glutathione, captopril, and N-acetylcysteine (NAC) and its lysinate salt (NAL)
Protein oxidation "in vivo"	**Characteristis of the model employed**	**Main observation**
(Hershfield et al. 2010)	Erythrocytes	Urate is not a major factor controlling oxidative stress in vivo
(Janatuinen et al.	Young adults with Type 1	Pravastatin decreased LDL oxidation;

2004)	Diabetes	without improvement in myocardial perfusion
(Zhang et al. 2002)	A model of inflammation (peritonitis) with MPO knockout mice (MPO−/−)	MPO-dependent formation of NO-derived oxidants, and not tyrosyl radical, serve as a preferred pathway for initiating lipid peroxidation.
(Seshadri et al. 2002)	Transfected HepG2	Insulin functions as a bidirectional, condition-dependent regulator of hepatic cell Ceruloplasmin expression, reflecting its dual roles in inflammation
(Yoshida & Kisugi 2010)	Review	Several pathways are involved in the promotion of LDL oxidation in vitro and in vivo, but the physiologically relevant mechanisms of LDL oxidation are still imperfectly understood
(Allen & Jandeleit-Dahm 2005)	Review	Glycation endproducts, renin-angiotensin system, oxidative stress and increased expression of growth factors and cytokines have been observed in the setting of diabetes
(Erciyas et al. 2004)	Children with type 1 diabetes mellitus	Relationship between the lipid profile and oxidative stress
(Candore et al. 2010)	Review	Cholesterol, oxidative stress and related therapeutic possibilities, i.e., nonsteroidal antiinflammatory drugs, immunotherapy, diet, and curcumin
(Bassett & Montine 2003)	Review	ApoE isoforms may specifically influence the cellular distribution of lipid peroxidation products in brain
(Shao et al. 2008)	Incubation of oxidized HDL and LCAT	Oxidation of a single Met in apoa-I in impaired LCAT activation, a critical early step in reverse cholesterol transport
(Haberland et al. 1988)	Watanabe heritable hyperlipidemic rabbits	Presence of protein modified by malondialdehyde which colocalizes with the extracellular deposition of apolipoprotein B-100
(Palinski et al. 1989)	Rabbit and human	Autoantibodies against malondialdehyde-LDL (titers from 512 to greater than 4096) can be demonstrated in sera
(Artola et al. 1997)	Hypercholesterolemic chickens	HDL from treated animals was more peroxidized, had higher amount of oligomeric apoA-I, than that of control

		animals
(Ónody et al. 2003)	Rat experimental hyperlipidemia	Induced hyperlipidemia leads to an increase in cardiac ONOO− formation and a decrease of NO and deterioration of cardiac performance
(Ueno et al. 2002)	Diabetic Akita mice	Hyperglycemia induced oxidative stress
(Wiggin et al. 2008)	Streptozotocin-treated DBA/2J mice	Rosiglitazone treatment did not affect hyperglycemia but did reduce oxidative stress and prevented the development of thermal hypoalgesia

Table 1. Bibliography reviewed about protein oxidation "in vitro" and "in vivo".

2.1 "In vitro" protein oxidation

The oxidation of lipoproteins has been studied in diverse "in vitro" systems using several experimental approaches i.e.; cupric ion (Batthyány et al. 2000), HOCl (Yang et al. 1997) or glycation mimicking diabetic conditions (Hedrick et al. 2000). More complex systems using "in vitro" cells systems had also been used.

Protein becomes modified during oxidation, resulting in a change in the protein conformation and degradation of amino acids, e.g., tryptophan and tyrosine (Batthyány et al. 2000), or amine groups (Chantepie et al. 2009) or methionine (Sigalov & Stern 2001). Different subclasses of lipoproteins, which differ in size or charge, have been shown to display different susceptibility to "in vitro" oxidation (Chantepie et al. 2009; Chen et al. 2007). Both apolipoprotein-B and apolipoprotein-A has been subjected to several oxidation processes and structural, chemical and biological functions alterations reported. Also, the effect of several antioxidants such as vitamins (Arai & Nakamura 2004), polyphenolic compounds (Chen et al. 2007) and inhibitors of glycation (Jedidi et al. 2003) has been reported.

Copper has been often used to oxidize LDL (low density lipoprotein) in experiments "in vitro" and was proposed as a candidate for oxidizing LDL in atherosclerotic lesions. Copper ions bind to LDL being the copper-binding capacity progressively and markedly higher when LDL is increasingly oxidized. It was assessed that the flavonoids myricetin, quercetin, and catechin (but not epicatechin, kaempferol, or morin), at concentrations equimolar to the copper present significantly decreased copper binding to LDL (Roland, Patterson, & Leake 2001). Later, the same group proposed uric acid as both antioxidant and prooxidant for LDL. They suggested that reduction of Cu^{+2} to Cu^+ was behind the effects observed since the decreased concentration of Cu^{+2} would inhibit tocopherol-mediated peroxidation in native LDL, and the generation of Cu^+ would promote the rapid breakdown of lipid hydroperoxides in mildly oxidized LDL into lipid radicals (Patterson, Horsley, & Leake 2003). These, other "in vitro" observations and the high plasma urate concentration, related to loss of urate oxidase in evolution, are postulated to protect humans from oxidative injury. This hypothesis has broad clinical relevance, but support rests largely on "in vitro" data and epidemiologic associations. Recently, "in vivo" evidence seems to deny such a physiological or pathological role. Therapy with infusion of PEGylated recombinant porcine urate oxidase generates H_2O_2 while depleting urate. Oxidative stress was monitored with F2-Isoprostanes (F2-IsoPs) and protein carbonyls (PC), products of arachidonic acid and protein oxidation, in plasma of 26 refractory gout patients receiving infusions of the enzyme. At baseline, urate was markedly elevated in all patients, and plasma F2-IsoP concentration was elevated in

most. Treatment rapidly lowered urate in all patients, but did not correlate with isoprostanes or protein carbonyls. The authors conclude that urate is not a major factor controlling oxidative stress "in vivo" (Hershfield et al. 2010).

Another interesting aspect of research is the one that deals with the susceptibility of lipoprotein taken from atherosclerotic lesions or from patients receiving pharmacological treatment with anti-inflammatory or hypolipemic drug therapy. For example, it has been found that descendants with a positive family history for cardiovascular disease (CVD) or hyperlipidemia have an atherogenic lipid profile and increased LDL susceptibility to oxidation (Makedou et al. 2009).

Also it has been suggested that endogenous estrogens protect against atherosclerosis by inhibition of lipoprotein oxidation. To act as antioxidants, estrogens need to be converted to lipophilic estrogen fatty acyl esters in a reaction catalyzed by lecithin: cholesterol acyltransferase (LCAT) (Hockerstedt, Jauhiainen, & Tikkanen 2004). Another hint linking LDL oxidative status and disease is the association between apolipoprotein E gene promoter polymorphism (–219G→T) has been with increased risk of myocardial infarction, premature coronary artery disease, and decreased plasma apolipoprotein E concentrations. The presence of the T allele in the apolipoproteinE –219G→T polymorphism increases the susceptibility of plasma LDL to oxidative modifications and enhances the response of apolipoprotein B and LDL cholesterol to the presence of saturated fat in the diet of healthy men (Moreno et al. 2004).

In Rheumatoid Arthritis (RA) patients, another disease of inflammatory etiology, effects of tumor necrosis factor (TNF) on the antioxidative capacity of HDL has been investigated and it was observed that has beneficial effects on lipids through changes in HDL (high density lipoprotein) antioxidative capacity, which might be clinically relevant and contribute to the reported protective effect of anti-TNF on cardiovascular morbidity in Rheumatoid Arthritis (Popa et al. 2009). This observation emphasizes the importance of HDL antiatherogenic capacity for cardiovascular risk in chronic inflammatory conditions.

Lipoproteins are very heterogeneous particles that contain several active enzymes and interact with other circulating proteins. Several of the these intrinsic or interacting enzymes have oxidative or antioxidative functions, e. g., paraoxonase-1 (Deakin et al. 2002), renin-angiotensin system (Allen & Jandeleit-Dahm 2005), or myeloperoxidase (Shao et al. 2010). Most interestingly, changes in the interaction between apolipoprotein and shell lipids has been shown to occur when HDL or LDL were subject to oxidation "in vitro" (Obama et al. 2007; Suc et al. 2003; Zarev et al. 2002). These changes in lipid protein interaction seem to be of importance for the biological function and receptor binding (Edelstein et al. 2001; Gao, Jayaraman, & Gursky 2008; Gomes et al. 2002; Hedrick et al. 2000). One example of the alteration in lipid-protein interaction was obtained using the myeloperoxidase (MPO) oxidative system. The researchers reported that oxidation of the three recombinant apolipoprotein E isoforms was differential, with apolipoprotein E4 being more susceptible than apolipoprotein E3, which in turn is much more susceptible than apolipoprotein E2 and that oxidation of apolipoprotein E decreases its incorporation into phospholipid discs (Jolivalt et al. 2000). LDL was also modified by MPO "in vitro" and by thiol-containing molecules as glutathione, captopril, and N-acetylcysteine has been shown to act as antioxidants (Van Antwerpen et al. 2005; Van Antwerpen et al. 2006). The ability of MPO to initiate lipid peroxidation "in vivo" and its role in generating bioactive eicosanoids during inflammation has been explored using a model of inflammation (peritonitis) with MPO

knockout mice (MPO−/−). Peritonitis-triggered formation of F2-isoprostanes, a marker of oxidant stress "in vivo" and was reduced by 85% in the MPO−/− mice. Parallel analyses of peritoneal lavage proteins for protein dityrosine and nitrotyrosine, molecular markers for oxidative modification by tyrosyl radical and $\cdot NO_2$, respectively, revealed marked reductions in the content of nitrotyrosine, but not dityrosine, in MPO−/−samples. Thus, MPO serves as a major enzymatic catalyst of lipid peroxidation at sites of inflammation. Moreover, MPO-dependent formation of $\cdot NO^-$ derived oxidants, and not tyrosyl radical, appears to serve as a preferred pathway for initiating lipid peroxidation and promoting oxidant stress "in vivo" (Zhang et al. 2002). These findings indicate that the proposed role of MPO in dityrosine cross-linking were erroneous and suggest that alternative mechanisms participate in dityrosine formation in this model, such as protein-bound redox active transition metal ions, and ceruloplasmin (Seshadri, Fox, & Mukhopadhyay 2002).

2.2 "In vivo" protein oxidation

There are many reports that relate diseases caused by oxidative imbalance with characteristic features of oxidized protein "in vivo". Many lines of evidence suggest that oxidized LDL is implicated in the pathogenesis of atherosclerotic vascular diseases (Yoshida & Kisugi 2010), in diabetes (Allen & Jandeleit-Dahm 2005; Erciyas et al. 2004), Alzheimer (Candore et al. 2010; Bassett & Montine 2003) .

Recently, it has been demonstrated that HDL isolated from patients with established cardiovascular disease contains elevated levels of 3-chlorotyrosine and 3-nitrotyrosine, two characteristic products of MPO. When apolipoprotein A-I, the major HDL protein, was oxidized by MPO, its ability to promote cellular cholesterol was impaired. Moreover, oxidized apolipoprotein A-I was unable to activate LCAT, which rapidly converts free cholesterol to cholesteryl ester, a critical step in HDL maturation (Shao et al. 2010). Biochemical studies implicated tyrosine chlorination and methionine oxygenation in the loss of ability to promote cellular cholesterol efflux and LCAT activity by oxidized apolipoproteinA-I (Shao et al. 2008).

In animal studies, the existence of oxidized apolipoproteins has been described under several experimental models, i.e. in Watanabe heritable hyperlipidemic rabbits the occurrence of malondialdehyde-LDL and of autoantibodies against malondialdehyde-LDL has been reported (Haberland, Fong, & Cheng 1988; Palinski et al. 1989). HDL from hypercholesterolemic chickens bear peroxidized oligomeric apolipoprotein A-I consequence of "in vivo" oxidation process (Artola et al. 1997). Interestingly, the oligomerization of apolipoprotein A-I implied dityrosine crosslink formation.

It was found that high-cholesterol diet increases formation of a potential marker of cardiac ONOO−, dityrosine in the perfusate, demonstrating that hyperlipidemia increases ONOO− formation in the heart (Ónody et al. 2003). In contrast to dityrosine, perfusate nitrotyrosine was not statistically significantly increased in the study. This can be explained by results showing that at relatively low level of ONOO−, nitrotyrosine formation is suppressed in favor of dityrosine (Ónody et al. 2003).

Both the levels of dityrosine and Nε-(hexanonyl)lysine were significantly elevated in the kidneys of diabetic Akita mice compared with the control mice without any accumulation of thiobarbituric acid reactive substances and 4-hydroxy-2-nonenal-modified protein (Ueno et al. 2002). These findings are consistent with previous works showing that diabetes increases oxidized lipids and protein. In another model of diabetic mice, increased levels of dityrosine

were found in the nerve of treated mice that had developed neuropathy respect to the control mice (Wiggin et al. 2008).

In one study, LDL oxidation and myocardial perfusion were measured in normocholesterolemic patients with type 1 diabetes before and after 4-month treatment with pravastatin or placebo. Pravastatin decreased LDL oxidation without improvement in myocardial perfusion reserve measured by positron emission tomography (Janatuinen et al. 2004).

2.2.1 Pharmacological treatments with antioxidant effects

The pathogenesis of chronic inflammatory diseases is regulated by modulation of the expression of redox-sensitive inflammatory genes including adhesion molecules, chemokines, cytokines and several receptors (Khatami 2009). The inflammation of vasculature produces reactive oxygen species (ROS) released both extracellularly from activated leukocytes as well as intracellularly in cells involved in the inflammatory reaction. ROS can be toxic and not only cause damage to biomolecules (DNA, proteins, lipids) but have been recognized as important intracellular signaling mediators (Nordberg & Arnér 2001).

Besides vasculature system, free radicals are constantly produced in the brain "in vivo". Because of its high ATP demand, the brain consumes oxygen rapidly, and is thus susceptible to interference with mitochondrial function, which can in turn lead to increased superoxide radical formation (Zorov et al. 2006). Free radicals in central nervous system arise by the leakage of electrons from the mitochondrial electron transport chain to generate superoxide radical and are generated for precise purposes, such as the role of nitric oxide in neurotransmission and the production of superoxide radical by activated microglia (Breckwoldt et al. 2008).

Increased levels of oxidative damage to DNA, lipids and proteins have been detected by a range of assays in post-mortem tissues from patients with Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis, and at least some of these changes may occur early in disease progression (Ursini et al. 2002; Paula-Lima et al. 2009). The accumulation and precipitation of proteins that occur in these diseases may be aggravated by oxidative damage, and may in turn cause more oxidative damage by interfering with the function of the proteasome (Cook & Petrucelli 2009). Indeed, it has been shown that proteasomal inhibition increases levels of oxidative damage to proteins and to other biomolecules. Hence, there are many attempts to develop antioxidants that can cross the blood-brain barrier and decrease oxidative damage (Halliwell 2007) and of biopharmaceuticals that can counteract protein oxidation and precipitation-aggregation (Wang 2005).

Aggregation of proteins is a common feature triggered by protein oxidation and it has been found "in vitro and "in vivo" being carbonylation a common feature (Mirzaei & Regnier 2008). Aggregation is manifest in globular proteins, because under stress conditions or proteolysis nonnative conformations can be adopted. Although it seems that most proteins are able to form aggregates when expressed at high concentrations "in vitro", they differ substantially in their intrinsic propensity to do so "in vivo". The major contributors to aggregation propensity have been identified as hydrophobicity, net charge and propensity to form beta-sheet instead of alpha-helical structures (Tartaglia & Caflisch 2007).

There is a large body of evidence demonstrating a role for ROS and oxidant stress in the pathogenesis of RA. Both preclinical and clinical studies have demonstrated relationship between oxidative stress biomarkers with disease progression and the potential beneficial

effects of antioxidant supplementation or therapy (Uchida 2008). Although a complete understanding of how oxidative stress participates in the pathogenesis of RA is lacking, there is evidence demonstrating that expression of several inflammatory genes that participate in RA is regulated by redox-sensitive signaling pathways (Filippin et al. 2008).

Other cells that have an important role in inflammation are lymphocytes. Distinct types of lymphocytes have divergent effects of inflammation. For example; Tr1-type regulatory immune response cells (CD4CD25 T-cells) reduces the development of experimental atherosclerosis, while the activation of T-lymphocytes contributes importantly to atherogenesis (Mallat et al. 2003). In human atheroma, CD4-positive cells, the major T-cell population, appear to promote atherosclerosis through elaboration of proinflammatory cytokines, such as interferon (IFN), tumor necrosis factors (TNFs), and interleukin (IL)-2 (Zhou et al. 2000). In fact, patients with atherosclerosis and acute coronary syndromes exhibit T-cell activation and increased IFN serum levels (Liuzzo et al. 1999) and there is evidence that fibrates, drugs that are PPAR agonists, are anti-inflammatory mediators because they limit inflammatory cytokine expression of T lymphocytes (Marx et al. 2002). Statins are currently the medical treatment of choice for hypercholesterolemia. In addition to attaining a decrease in serum cholesterol levels, statin therapy seems to promote other effects that are independent of changes in serum cholesterol. These ''pleiotropic'' effects include attenuation of vascular inflammation, improved endothelial cell function, stabilization of atherosclerotic plaque, decreased vascular smooth muscle cell migration and proliferation, and inhibition of platelet aggregation (Sadowitz et al. 2010) and increase the synthesis of apolipoprotein A-I and HDL biogenesis in the liver (Yamashita et al. 2010). Interestingly, statin therapy in dyslipidemic type 2 diabetic patients plays a protective role on the lipid and protein oxidative damage (Manfredini et al. 2010). We have tested the effect of a statin (atorvastatin) and of a fibrate (fenofibrate) on the activation of T lymphocytes in culture by an unspecific mitogen (concanavalin A). It was noted that upon activation with concanavalin A T-cells expressing IL-2 receptor (CD25, marker of activation) are augmented and that VLDL (very low density lipoprotein) inhibit the proportion of CD25+ CD4+ cells after 48 h of co-culturing. When lymphocytes were cultured with VLDL plus Atorvastatin CD25CD4 positive cells increased respect to cell culture with VLDL alone, suggesting that another anti-inflammatory effect of the statin (Forcato et al. 2007). In another study, it has been shown that the combined treatment of pravastatin with irbesartan reduced sPLA2-IIA-activity, sPLA2-IIA-protein concentration, and oxidized LDL in patients with CAD suggesting a novel anti-atherogenic effect by combining AT1-receptor blockade with statin treatment (Divchev et al. 2008).

Human hepatocyte cells in different cell cycle phases (G1 and G2/M) were analyzed using flow citometry techniques for VLDL receptor (VLDLR+). VLDLR+ cells belonged equally to cells in the quiescent and in the synthesis or mitosis phase of the cell cycle. Challenging them with lipopolysaccharide an increase in the percentage of VLDLR+ cells was produced. Gemfibrozil treatment decreased the number of resting VLDLR+ hepatocytes but increased significantly (more than twice) the number of VLDLR+ hepatocytes in phase G2/M (Forcato et al. 2007). These observations could explain why fenofibrate is particularly effective for reducing postprandial VLDL and LDL particle concentrations, and the increased oxidative stress and inflammatory response that occurs after a fatty meal (Rosenson 2008).

It is interesting to note that metabolites of statins and fenofibrate, but not the parent drugs, had been implied in protecting lipoproteins from oxidation "in vitro" suggesting that the antioxidant effects will be relevant "in vivo" (Aviram et al. 1998).

2.3 Oxidation of proteins in tissues and fluids, where there are good and bad neighbors

In this section I pretend to discuss some new insights about reactions that occur only in complex milieu as the appearance of acrylamide (Stadler et al. 2004), the antioxidant activity of Maillard products (Yilmaz & Toledo 2005) and discuss that some antioxidants produces oxidative modifications of proteins. Polyphenolic compounds have powerful antioxidant effects "in vitro" in many test systems, but can act as pro-oxidants in some others (Halliwell 2007). And it has been reported that tea catechins contribute to the formation of protein carbonyl in human serum albumin (HSA) (Ishii et al. 2010).

2.3.1 Acrylamide from food is absorbed in humans

The heating of free amino acids, in particular asparagine, and sugars during food processing (120–180°C) results in the formation of acrylamide (Stadler et al. 2002). Most of the acrylamide ingested with food (i.e. fried potatoes) is absorbed in humans. Acrylamide and its metabolite glycidamide have the capability to bind covalently to the −SH and −NH2 groups of proteins and nucleic acid nitrogens. Although both acrylamide and glycidamide DNA adducts are formed "in vitro", only glycidamide adducts have been found after the administration of acrylamide or glycidamide "in vivo"(Gamboa da Costa et al. 2003). Acrylamide and glycidamide adducts to the NH2-terminal valine of human hemoglobin are used as convenient biomarkers for external acrylamide and/or internal glycidamide exposure. Acrylamide and glycidamide are also able to form glutathione conjugates that have been found in human urine, these metabolites have been proposed as biomarkers for acrylamide and glycidamide exposure (Fuhr et al. 2006). It is important to stress that there is no report of acrylamide formation in humans.

2.3.2 Antioxidant activity of Maillard products

Nonenzymatic glycation of free amino groups on proteins and amino acids is a biochemical reaction known as the "Maillard reaction." It has been proposed that this is an evolutionary pathway for labeling of senescent cellular proteins for their recognition and ultimate degradation. The two traditional factors found to modulate the early glycation of proteins are the concentration of glucose and half life of the protein, so in both major forms of diabetes, persistent hyperglycemia and oxidative stress act to increase the formation of advanced glycation end products (Reddy et al. 2009). But evidences in the literature have documented an increased glycated protein levels in some non-diabetic pathological states. Recently it has been hypothesized that oxidative stress either via increasing reactive oxygen species or by depleting the antioxidants may modulate the genesis of early glycated proteins "in vivo". This hypothesis was sustained by the observations that a common denominator in all non-diabetic pathological conditions is oxidative stress and that malondialdehyde, reduced glutathione, vitamin C, vitamin E and drugs with antioxidant properties mitigate the process of protein glycation (Selvaraj et al. 2008). Maillard reactions occurring "in vivo" are associated with the chronic complications of diabetes mellitus and aging and age-related diseases by increases in oxidative chemical modification of lipids, DNA, and proteins. In particular, long-lived proteins such as lens, crystallines, collagens, and hemoglobin may react with reducing sugars to form advanced glycation end products and are biomarkers for detecting oxidative stress produced during Maillard reaction (Osawa & Kato 2005).

The relationship between yin-yang and anti-oxidation-oxidation (Ou et al. 2003) seems also valid for Maillard reaction products since antioxidant activity of Maillard reaction products

has been demonstrated "in vitro" in foods. The existence of this relationship "in vivo" will be a subject of research in the future since a few studies have been reported exploring the antioxidant capacity of Maillard reaction products using "in vivo" systems (Chen & Kitts 2008).

2.3.3 Oxidant activity of antioxidants

Recent studies have reported that various polyphenolic compounds, including catechins, cause protein carbonyl formation in proteins via their pro-oxidant actions. The oxidation stability and binding affinity of catechins with proteins and with fatty acids bound to protein are responsible for the formation of protein carbonyl (Dufour et al. 2007). Polyphenol binding altered BSA conformation with a major reduction of alpha-helix and an increase in beta-sheet and turn structures, indicating a partial protein unfolding (Bourassa et al. 2007) that could increase BSA oxidation susceptibility. Some authors have claimed that antioxidants can stimulate oxidative damage "in vivo", especially ascorbate, alleged in several studies to increase oxidative DNA damage (Perron et al. 2011).

2.3.4 Aggregation and proteolysis are defense or repair mechanisms?

Moderately oxidized soluble cell proteins are selectively and rapidly degraded by the 20S proteasome, while harshly oxidized, aggregated, and crosslinked proteins are poor substrates and actually inhibit the proteasome (Davies & Shringarpure 2006). During aging, and in many age-related diseases/disorders, the proteasome is progressively inhibited by binding more protein aggregates. It has been postulated that an increase in the generation of reactive oxygen species as well as a decline in proteasome activity, results in the progressive accumulation of oxidatively damaged protein aggregates that eventually contribute to cellular dysfunction and senescence in senesce and disease (Davies & Shringarpure 2006).

Small endogenous peptides, such as peptide hormones and signaling peptides, have strong effects on human. This has prompted an increasing interest from academia and food industries where it is reasoned that certain dietary peptides could also be potentially used as bioactive ingredients in functional foods. Dietary proteins have sequences of peptides, partially similar to those found in endogenous peptides, with hormonal or neuronal functions, and it has been proposed to exert physiological effects by acting either agonistically or antagonistically on the same targets as their endogenous counterparts (Ahlman & Nilsson 2001). Scientists are currently exploring use of protein sources such as mammalian and fish meat, soybeans, chickpeas, almonds, etc. for production of bioactive peptides with different biological activities (Minkiewicz et al. 2011). Bioactive peptides can reduce free radicals and have antioxidant activity (Sarmadi & Ismail 2010).

During protein oxidation aggregation and proteolysis occur simultaneaously, so it can be presumed that the balance between protein aggregation and antioxidant peptide generation is important in modulating inflammation "in vivo".

2.4 Dityrosine and other markers of protein oxidative modification "in vivo"

Most of the oxidative modifications that occurs "in vivo" and "in vitro" are susceptible of reversion and thus it is necessary to discern stable markers (Davies et al. 1999). Dityrosine bound formation and protein polymerization seems to be less prone to "in vivo" reduction or repair (Artola et al. 1997; Nagy et al. 2010). Also protein carbonyls could be a marker of endogenous oxidative stress (D'Aguanno et al. 2010), taking in account that this could be a

better marker than dityrosine, when the oxidative stimulus is radiant energy (ultraviolet light) (Scheidegger et al. 2010).

3. Conclusion

3.1 Is there a relationship between oxidized apolipoprotein and health status?

Inflammation is associated with atherosclerosis. Human lipoproteins have been recognized to have proinflammatory or anti-inflammatory roles together with their receptors and the molecules involved in the interaction of lipoproteins with receptors. In example, it has been demonstrated that the inflammatory mediator IL-1ß disrupts cholesterol-mediated LDL receptor feedback regulation, permitting unregulated intracellular accumulation of unmodified LDL and causing foam cell formation. The authors suggest that this mechanism may contribute to the development of atherosclerosis in patients with chronic inflammation (Ruan et al. 2006).

On the other hand, the anti-atherogenic properties of HDL can be beneficial in metabolic diseases associated with accelerated atherosclerosis. Indeed, metabolic syndrome and type 2 diabetes are characterized by elevated cardiovascular risk and by low HDL-cholesterol (HDL-C) levels, but also by defective HDL function. Functional HDL deficiency is intimately associated with alterations in intravascular HDL metabolism and structure. Indeed, formation of HDL particles with attenuated antiatherogenic activity is mechanistically related to core lipid enrichment in triglycerides and cholesteryl ester depletion, altered apolipoprotein A-I conformation, replacement of apolipoprotein A-I by serum amyloid A, and covalent modification of HDL protein components by oxidation and glycation (Kontush & Chapman 2006, 2010). "In vivo" oxidation of apolipoprotein-I is equally consistent with the observation that HDL from hypercholesterolemic chickens contain higher amounts of oligomeric apolipoprotein-I and are more susceptible to "in vitro" oxidation than HDL from control animals (Artola et al. 1997).

Fenofibrate is a PPAR-α agonist indicated for the treatment of hypertriglyceridemia and mixed dyslipidemia, lipid abnormalities commonly observed in patients at high risk of cardiovascular disease, including Type 2 diabetes and/or metabolic syndromes. Treatment with fenofibrate lowers triglycerides, raises HDL-cholesterol and decreases concentrations of small LDL-cholesterol particles and apolipoprotein B. Fenofibrate is effective for reducing postprandial VLDL and LDL particle concentrations that occurs after a fatty meal (Rosenson et al. 2007). This decrease in VLDL could be related to the increase in VLDL receptor cause by Gemfibrozil in spleen mononuclear cells, in human hepatocyte cells (HepG2) and in a human acute monocytic leukemia cell line (THP-1) cultured with the fibrate (Forcato 2008). Fibrate also produced an accumulation of apolipoprotein A-I in HepG2 (Forcato 2008). Thus it is probable that fibrates have several concurrent beneficial effects on hyperlipemia and oxidative imbalance.

The existence of oxidized lipids in pathological state is a common feature. Normal arteries contained similar levels of protein as atherosclerotic arteries, much less free cholesterol, and no detectable amounts of unoxidized or oxidized cholesteryl esters. It has been demonstrated the coexistence in human plaque of large amounts of oxidized cholesteryl esters with significant concentrations of ascorbate and vitamin E and that compared with healthy human arteries, advanced atherosclerotic plaques are not deficient in the antioxidant vitamins C and E, despite the occurrence of massive lipid oxidation (Suarna et al. 1995). On the contrary the removal of oxidized phospholipid in normal cells is the norm. Oxidized phospholipids within LDL can promote phagocyte recognition and engulfment, even when present at only a few molecules

per particle, by CD36, a prototypic member of the class B scavenger receptor family (Hazen 2008). The removal of oxidized lipids associated to lipoproteins or to membranes seems to grant a low level in physiological conditions.

3.2 Damaged proteins are biomarkers of oxidation imbalance

Damaged proteins are recognized by the proteolytic machinery for degradation to their constitutive amino acids; however, this process can be inefficient as is evidenced by their accumulation. Deposits of aggregated, misfolded, and oxidized proteins accumulate normally over time in cells and tissues, especially in postmitotic cells of the brain and heart, and are often present in increased amounts in a range of age-related disorders, such as atherosclerosis, neurodegeneration, and cataractogenesis (Dunlop et al. 2009; Dunlop Ra Fau - Rodgers et al. 2002).

Oxidatively modified proteins are usually considered degraded more or less exclusively by the proteasome system, although this would only apply to mildly oxidized proteins since substrates must be unfolded to enter the narrow catalytic chamber of the 20S core (Dunlop Ra Fau - Rodgers, Rodgers Kj Fau - Dean, & Dean 2002).

Altogether, these studies show that protein oxidation products may serve as biomarkers for oxidative free radical damage. The intracellular accumulation of oxidized forms of proteins is a complex function of prooxidant-antioxidant activities and the concentrations and activities of the proteases that degrade the oxidized forms of proteins (Stadtman & Levine 2000). However, measurements are performed in tissue or plasma that is invasively obtained samples. Therefore, future studies will have to be conducted to find techniques to determine these products in urine as well (de Zwart et al. 1999).

4. Acknowledgment

5. References

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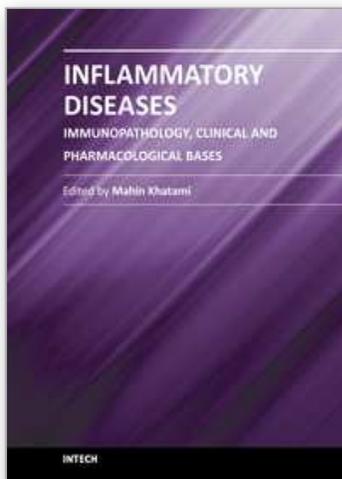
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This book is a collection of comprehensive reviews contributed by experts in the diverse fields of acute and chronic inflammatory diseases, with emphasis on current pharmacological and diagnostic options. Interested professionals are also encouraged to review the contributions made by experts in a second related book entitled "Inflammation, Chronic Diseases and Cancer"; it deals with immunobiology, clinical reviews, and perspectives of the mechanisms of immune inflammatory responses that are involved in alterations of immune dynamics during the genesis, progression and manifestation of a number of inflammatory diseases and cancers, as well as perspectives for diagnosis, and treatment or prevention of these disabling and potentially preventable diseases, particularly for the growing population of older adults around the globe.

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