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Review

Cholesterol oxidation products in the vascular remodeling due to atherosclerosis

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ABSTRACT

Like the other oxidation products of the lipid moiety of plasma low density lipoproteins (LDL), cholesterol oxidation products are consistently found within the characteristic lesions of atherosclerosis, both in experimental animals and in man. A growing bulk of evidence suggests that oxysterols make a significant contribution to the vascular remodeling that occurs in atherosclerosis, being involved in various key steps of this complex process: endothelial cell dysfunction, adhesion of circulating blood cells, foam cell and fibrous cap formation, modulation of the extracellular matrix (ECM), vascular cell apoptosis and plaque's instability. Moreover, oxysterols have been demonstrated to be at least one or two orders of magnitude more reactive than unoxidized cholesterol in exerting pro-inflammatory, pro-apoptotic, and pro-fibrogenic effects. Thus, a pathological level of cholesterol oxidation in the vasculature may be the missing molecular link between hypercholesterolemia and the formation of atherosclerotic lesions.

Contents

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Abbreviations: 5-OVC, 5-oxovaleroyl cholesterol; 7α-OH, 7α-hydroxycholesterol; 7β-OH, 7β-hydroxycholesterol; 7β-OOH, 7β-hydroperoxycholesterol; 7-K, 7-ketocholesterol; 9-ONC, 9-oxononanoyl cholesterol; 24-OH, 24-hydroxycholesterol; 25-OH, 25-hydroxycholesterol; AP-1, activator protein-1; apoB-100, apolipoprotein B-100; EC, endothelial cell; ECM, extracellular matrix; α-EPOX, α-epoxycholesterol; β-EPOX, β-epoxycholesterol; ERK1/2, extracellular signal-regulated kinase 1/2; HAEC, human aortic endothelial cell; HDL, high density lipoprotein; HUVEC, human umbilical vein endothelial cell; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IL-18R, interleukin-18 receptor; JNK, c-Jun N-terminal kinase; LDL, low density lipoprotein; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MEK, mitogen-activated protein kinase kinase; MIP-1β, macrophage inflammatory protein-1β; MMP, metalloproteinase; NF-kB, nuclear factor-kB; oxLDL, oxidized LDL; PPARγ, peroxisome proliferator-activated receptor γ; PKC, protein kinase C; ROS, reactive oxygen species; SMC, smooth muscle cell; TF, tissue factor; TGFβ1, transforming growth factor-β1; TIMP-1, tissue inhibitor of metalloproteinase-1; TRIOL, cholestan-3β,5α,6β-triol; uPAR, urokinase-type plasminogen activator receptor; VCAM-1, vascular cell adhesion molecule-1.

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1. Cholesterol oxidation products potentially implicated in atherosclerosis-dependent vascular remodeling

Two types of cholesterol oxidation products appear of interest in the pathogenesis of atherosclerosis: (1) those generated by oxidative modification either of the ring structure or of the side chain of cholesterol in its free form, termed oxysterols, and (2) those derived from partial oxidative breakdown of the fatty acids esterified to cholesterol, known as the core-aldehydes.

Oxysterols may derive from foodstuffs that contain cholesterol, especially after long storage and cooking, or may be formed in the body, through either enzymatic or non-enzymatic reactions (Smith and Johnson, 1989; Schroepfer, 2000; Leonarduzzi et al., 2002, 2005a). Oxidation of the side chain is an enzymatic process, while oxidation of the sterol nucleus, with the single exception of 7α-hydroxycholesterol production, is commonly a non-enzymatic one. Among side-chain cholesterol oxidized compounds, 27-hydroxycholesterol (27-OH) appears by far the most likely to be implicated in the pathogenesis of atherosclerosis. Besides 7α-hydroxycholesterol (7α-OH), other oxysterols deriving from sterol nucleus oxidation are thought to have pro-atherogenic potential, namely 7-ketocholesterol (7-K), 7β-hydroxycholesterol (7β-OH), 5α,6α- and 5β,6β-epoxycholesterol (α-EPOX and β-EPOX), and cholestan-3β,5α,6β-triol (TRIOL) (Schroepfer, 2000).

As regards the effective oxysterol content of human fibrotic plaques, data available thus far appear somewhat inconsistent, due to several variables: stage of lesion development, great variability of fat deposition in different plaques from the same individual, and differing sensitivities of the analytical procedures employed. However, despite quantitative discrepancies, all studies show the same trend pointing to 27-OH, 7-K and 7β-OH as the most abundant oxysterols in human atheromas (see Leonarduzzi et al., 2007, for a review of relevant recent analyses). In order to directly check the accumulation of cholesterol oxidation products in human atherosclerotic lesions and related features, our laboratory recently analyzed fibrotic plaques removed from human carotids. As expected, all the oxysterols commonly found in plasma from hypercholesterolemic patients were recovered in the 10 atheromas examined, but the finding of most interest was the strong direct correlation between the total oxysterols recovered from each atheroma and the total amount of cholesterol detected in the same plaque (Fig. 1). This finding further points to cholesterol oxidation as an important or even crucial event in vascular remodeling due to atherosclerosis.

Acyl chain oxidation of cholesteryl esters leads to the generation of the corresponding lipid hydroperoxides, which then undergo carbon–carbon cleavage, with the production of aldehydes still esterified to the parental lipid (Leitinger, 2003). *In vitro* oxidation of low density lipoprotein (LDL) and high density lipoprotein (HDL) micelles, or of isolated cholesteryl esters, by copper or tert-butyl hydroperoxide, has been shown to yield two major core-aldehydes, namely 5-oxovaleroyl cholesterol (5-OVC) and 9-oxononanoyl cholesterol (9-ONC), deriving from the oxidation respectively of cholesteryl arachidonate and of cholesteryl linoleate (Kamido et al., 1993). Further, when phorbol ester-treated J774 murine macrophages were incubated with LDL, approximately 5% of cholesterol linoleate and 4% of cholesterol arachidonate were converted to 9-ONC and to 5-OVC, respectively (Karten et al., 1998). However, 9-ONC was the most abundant core-aldehyde found in human atherosclerotic lesions (Hoppe et al., 1997; Karten et al., 1998). Indeed, plaques contain about 1.5 times as much Ch18:2 as Ch20:4, with approximately 20–30% of the fatty acid moiety of cholesteryl linoleate being present in oxidized forms (Suarna et al., 1995).

Indeed, 9-ONC has been detected in oxidized LDL (oxLDL) and in human atherosclerotic plaques (Kamido et al., 1993,1995; Hoppe et al., 1997; Karten et al., 1998; Kawai et al., 2006). With regard to quantitative data, on average 30 μmol of 9-ONC per mol of cholesterol may be found in advanced human atherosclerotic lesions (Karten et al, 1998). This core-aldehyde binds to serum proteins (Hoppe et al., 1997) and apolipoprotein B-100 (apoB-100) (Kawai et al., 2003), being detectable as 9-ONC-lysine Schiff base adduct. Notably, 9-ONC addition products with apoB-100 have mainly been found in foam cells and in the thickening neointima of the arterial wall (Kawai et al., 2003).

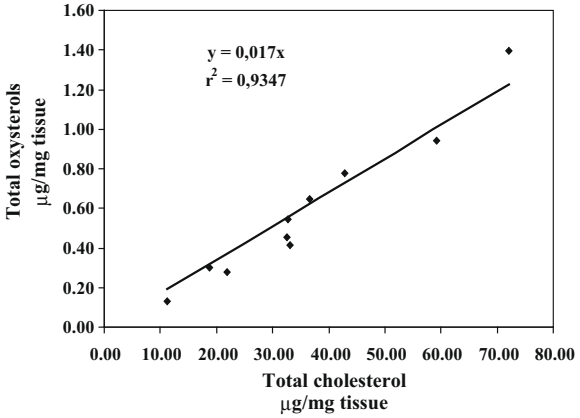

Fig. 1. Correlation between total oxysterols and total cholesterol detected in 10 advanced human carotid atherosclerotic lesions.