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Oxysterols and mechanisms of survival signaling

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ABSTRACT

Oxysterols, a family of oxidation products of cholesterol, are increasingly drawing attention of scientists to their multifaceted biochemical properties, several of them of clear relevance to human pathophysiology. Taken up by cells through both vesicular and non-vesicular ways or often generated intracellularly, oxysterols contribute to modulate not only the inflammatory and immunological response but also cell viability, metabolism and function by modulating several signaling pathways. Moreover, they have been recognized as elective ligands for the most important nuclear receptors. The outcome of such a complex network of intracellular reactions promoted by these cholesterol oxidation products appears to be largely dependent not only on the type of cells, the dynamic conditions of the cellular and tissue environment but also on the concentration of the oxysterols. Here focus has been given to the cascade of molecular events exerted by relatively low concentrations of certain oxysterols that elicit survival and functional signals in the cells, with the aim to contribute to further expand the knowledge about the biological and physiological potential of the biochemical reactions triggered and modulated by oxysterols.

Abbreviations: 5,6-S, 5,6-secosterol; 24OH, 24-hydroxycholesterol; 25OH, 25-hydroxycholesterol; 27OH, 27-hydroxycholesterol; 7K, 7-ketocholesterol; 7βOH, 7β-hydroxycholesterol; AGE, advanced glycation end products; AMPK, AMP-activated protein kinase; AP-1, activator protein-1; ARE, antioxidant response element; ASK, apoptosis signal-regulating kinase; ATF, activating transcription factor; Aβ, amyloid-β; CHOP, CEBP-homologous protein; CREB, cyclic AMP response element binding protein; DAG, diacylglycerol; DAPK, death associated protein kinase; EGF, epidermal growth factor; EIF2α, eukaryotic translation initiation factor 2α; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; GRP78, glucose-regulated protein 78; GSK3, glycogen synthase kinase 3; HNE, 4-hydroxynonenal; HO-1, heme oxygenase 1; HUVEC, human umbilical-vein endothelial cell; ICAM-1, intercellular adhesion molecule 1; IGFBP1, insulin-like growth factor-binding protein 1; IKK, inhibitory κB kinase; IL, interleukin; IP3, inositol 1,4,5-triphosphate; IRE1, inositol requiring protein-1; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; LOX-1, lectin-like oxLDL scavenger receptor 1; LXR, liver X receptor; MAPK, mitogen-activated protein kinase; MAPKK, MAPK kinase; MAPKKK, MAPK kinase kinase; MCP-1, monocyte chemotactic protein 1; MEK, mitogen-activated protein kinase ERK kinase; Mnk, MAPK interacting kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; NOX, NADPH oxidase; NQO-1, NADPH:quinone oxidoreductase 1; Nrf2, nuclear erythroid 2-related factor 2; OSBP, oxysterol-binding protein; oxLDL, oxidized low density lipoprotein; oxPAPC, oxidized 1-palmitoyl-2-arachidonyl-sn-glycerol-3-phosphocholine; PDGF, platelet-derived growth factor; PDK, 3-phosphoinositide-dependent protein kinase; PERK, protein kinase RNA-like ER kinase; PI3K, phosphatidylinositol 3-kinase; PIP2, PIP3, phosphatidyl inositol di/triphosphate; PK, protein kinase; PLC, phospholipase C; PM, plasma membrane; PP2A, protein phosphatase 2A; PPAR, peroxisome proliferator-activated receptor; RNS, reactive nitrogen species; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; RXR, retinoid X receptor; SCAP, SREBP cleavage activating protein; SMC, smooth muscle cell; Smo, Smoothened transducer; S1P, sphingosine 1-phosphate; SREBP, sterol regulatory element binding protein; TLR, Toll like receptor; Triol, cholestan-3β,5α,6β-triol; UPR, unfolded protein response; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; XBP1, X-box-binding protein 1.

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Contents

1. Introduction

Cholesterol is undoubtedly a molecule of key biological importance, being the structural core of estrogens and androgens, starting the synthesis of vitamin D and biliary acids and playing a primary role in stabilization and function of membrane lipid rafts, but its "popularity" is biased by the fact that hypercholesterolemia represents a main risk factor of cardiovascular disease, neurodegeneration, inflammatory bowel disease and cancer.

Going a bit deeper in evaluating the pathophysiological impact of cholesterol, it appears clear that this powerful molecule exerts a number of effects not simply *per se* but mainly through the biochemical properties exerted by its metabolites. Among cholesterol metabolites, an increasing attention is drawn by the family of cholesterol oxidation products termed oxysterols. Oxysterols are 27-carbon molecules that, unlike cholesterol, have an epoxide or ketone or an additional hydroxyl group in the sterol nucleus and/or a hydroxyl group in the side chain. Within this family of compounds there are components that are from 10 to 100 more chemically reactive than cholesterol, thus suggesting their involvement in many of the biochemical and biological effects ascribed to cholesterol (Leonarduzzi et al., 2002; Schroepfer, 2000). In Fig. 1, the oxidation sites in the cholesterol molecule are depicted, and Table 1 reports on the most representative oxysterols of non-enzymatic and enzymatic origin.

In the last years oxysterols have been mainly investigated for their physiological role played in the synthesis of bile acids and steroid hormones, in the sterol transport and metabolism, and in gene regulation. Evaluating the effects of cholesterol oxidation products, it appeared quite evident the strong pro-inflammatory, pro-apoptotic and pro-fibrogenic properties of some of them (Sottero et al., 2009). In particular, the molecular aspects of their pro-inflammatory effects have been well deepened, and a growing bulk of experimental findings points to a significant contribution paid by these cholesterol derivatives to the progression of inflammatory-based chronic pathologies, such as vascular aging, atherosclerosis, Alzheimer's disease, multiple sclerosis, inflammatory bowel disease and colorectal cancer, non-alcoholic liver disease, retinopathies, diabetes mellitus (Biasi et al., 2013; Gamba et al., 2012, 2015; Gargiulo et al., 2015; Poli et al., 2013).

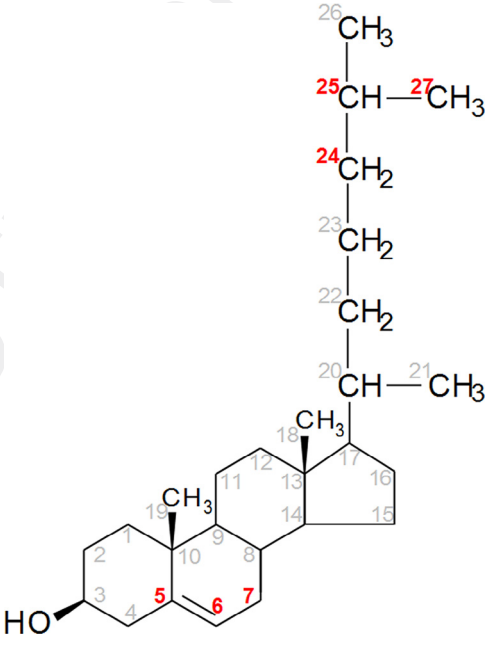

Fig. 1. Cholesterol structure and its main oxidation sites (in red).

Nowadays, new emphasis to the beneficial effects exerted by at least certain oxysterols has been given by the largely proven evidence that side-chain cholesterol oxides like 24-, 25- and 27-hydroxycholesterol (24OH, 25OH and 27OH) are among the best ligands of a variety of physiologically important nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs), and by this way could modulate not only the inflammatory and immunological response but also cell viability, metabo-

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