



## Review

## Oxysterols in cancer cell proliferation and death



Jan de Weille\*, Christine Fabre, Norbert Bakalara

Institut des Neurosciences de Montpellier, U1051 INSERM, 80 rue Augustin Fliche, 34295 Montpellier Cedex 05, France

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## ABSTRACT

Oxysterols have been shown to interfere with proliferation and cause the death of many cancer cell types, such as leukaemia, glioblastoma, colon, breast and prostate cancer cells, while they have little or no effect on senescent cells. The mechanisms by which oxysterols may influence proliferation are manifold: they control the transcription and the turnover of the key enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl CoA reductase, by binding to Insig-1, Insig-2 and liver X receptors. Oxysterols are thought to be generated in proportion to the rate of cholesterol synthesis. Although there is no consensus about the mechanism by which these oxysterols are generated *in vivo*, it clearly has to be ubiquitous. The 25- and the 27-cholesterol hydroxylases, present in almost all tissues, are possible candidates. Cholesterol uptake from lipoproteins, intracellular vesicle transport and lipid transfer are also modified by oxysterols. Oxysterols interfere with ERK, hedgehog and wnt pathways of proliferation and differentiation. When administered *in vitro* to cancer cell lines, oxysterols invariably both slow down proliferation and provoke cell death. Perhaps it is sufficient to stop proliferation of a cancer to provoke its eradication. Therefore, the two facets of oxysterol action that seem important for cancer treatment, cytostaticity and cytotoxicity, will be discussed.

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## 1. Introduction

Proliferation, especially that of cancers, requires energy and proliferative signals to maintain cellular division and building materials to create daughter cells. For the creation of daughter cells, cholesterol, fatty acids and phospholipids are needed in large quantities. In order to satisfy this need, cholesterol synthesis is upregulated and glucose metabolites, normally used for ATP production, are redirected *via* the pentose pathways for use in lipid (and nucleotide) synthesis. This use of glucose is known as the

Warburg effect [1], a glycolytic regime that is also dominating during embryogenesis [2]. Upregulation of cholesterol and lipid synthesis is controlled by sterol regulatory element binding proteins (SREBPs). These transcription factors are sensitive to (oxy)sterols. Intracellular transport, in particular that of cholesterol and lipids, has also been found to be under the control of (oxy)sterols [3] and its dysfunction leads to Niemann-Pick's disease [4].

This paper reviews concisely the oxysterol-sensitive mechanisms that are important for (cancer cell) proliferation on the one hand and the oxysterols that cause cancer cell death on the other. These mechanisms and pathways include cholesterol homeostasis, intracellular lipid transfer and the transmission of intra- and extra-cellular signals. As it turns out, apart from 25-hydroxycholesterol (25-HC) and perhaps 7-ketocholesterol (7-KC), the physiological roles of oxysterols are still far from established. At non-physiologically elevated doses, many effects have been reported, but since these were observed in cells that were already well under way to meet their end, the importance to understand the mechanisms of oxysterol action is limited. Nevertheless, oxysterols appear to become important weapons to fight cancer as they pair toxicity to cancer with innocuousness to healthy tissue.

## 2. Cholesterol homeostasis

Cholesterol synthesis starts with two molecules of acetyl CoA, which in two steps form one molecule of 3-hydroxy-3-methyl-

**Abbreviations:** 7-KC, 7 ketocholesterol; ACAT, acyl-CoA cholesterol acyl transferase; CHEH, cholesterol-5-6-epoxide hydrolase; CNS, central nervous system; CT, cholestane 3 $\beta$ -5 $\alpha$ -6 $\beta$  triol; EC, epoxycholesterol; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERK, extracellular signal regulated kinase; GSK3 $\beta$ , glycogen synthase kinase 3 $\beta$ ; HC, hydroxycholesterol; HDL, high density lipoprotein; HMGCR, 3-hydroxy-3-methyl-glutaryl CoA reductase; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; HT, serotonin receptor; Insig, Insulin-induced gene; LD<sub>50</sub>, lethal dose of a drug, killing 50% of the cells; LDL, low density lipoprotein; LEF, lymphocyte enhancer factor; LXR, liver X receptor; NPC, Niemann-Pick Type C disease; OCDO, 6-oxo-cholestan-3 $\beta$ -5 $\alpha$ -diol; ORP, OSBP-related protein; OSBP, oxysterol binding protein; PDGF, platelet-derived growth factor; PKM, muscular pyruvate kinase; ROS, reactive oxygen species; SCAP, SREBP cleavage activating protein; Smo, smoothened; SREBP, sterol regulatory element binding protein; SSTR, somatostatin receptor; SuFu, suppressor of Fu; TCF, T-cell factor.

\* Corresponding author. Tel.: +33 0499636032.

E-mail addresses: [Jan.de-Weille@INSERM.fr](mailto:Jan.de-Weille@INSERM.fr), [deweille@bram.org](mailto:deweille@bram.org) (J. de Weille).

glutaryl CoA (HMG-CoA) which is then transformed into mevalonate by the rate-limiting enzyme HMG-CoA reductase.

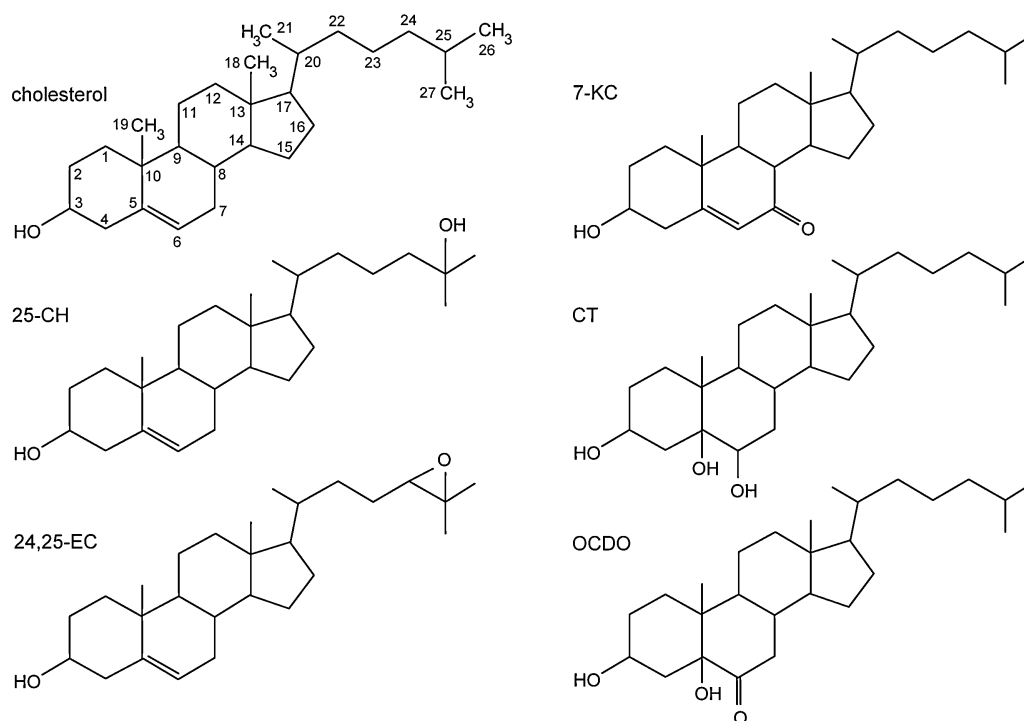
Since this enzyme plays a pivotal role in cholesterol synthesis, its activity is closely regulated by transcriptional and metabolic feedback loops in which oxysterols partake prominently [5–7]. The activity of HMG-CoA reductase is controlled transcriptionally via the sterol regulatory element binding protein (SREBP). Two SREBP genes exist: SREBP-1, of which there are two splice variants, and SREBP-2. The latter regulates the HMG-CoA reductase gene and other genes involved in cholesterol synthesis, while the former preferentially activates genes involved in lipid synthesis such as Acetyl-CoA carboxylase- $\alpha$  [8,9]. SREBP is an endoplasmic reticulum membrane-bound protein that may be cleaved by caspase-3 or SREBP cleavage activating protein (SCAP) [10,11]. SREBP cleavage is inhibited if SCAP binds cholesterol, 7-KC, or the membrane-bound oxysterol binding proteins Insig-1 and Insig-2. SCAP does not bind the side chain oxysterols 19-HC, 24-HC, 25-HC or 27-HC [12–14].

In response to cholesterol loading, cholesterol becomes oxygenated at positions on the side-chain (see Fig. 1). The oxygenation mechanisms involved in the context of cholesterol homeostasis have not been clearly identified yet. Cholesterol side-chain hydroxylases are present in CNS neurones (CYP46A1) and tissues such as the liver (CYP7A1, CYP8B), ovary (CYP7B1) and adrenals (CYP11A1) [15–18], where they are thought to serve specific goals different from signalling the level of cholesterol. These goals are steroid hormone synthesis in gonads, bile acid synthesis in the liver and, in the case of neurones, removal of excess cholesterol by means of 24-HC transport across the blood–brain barrier [19]. The mitochondrial 27-cholesterol hydrolase, CYP27, is quasi-ubiquitous and can produce, apart from 27-HC, smaller amounts of 25-HC and 24-HC [4]. 25-Cholesterol hydroxylase mRNA has been detected in most tissues [17]. Some oxysterols, most notably 7-KC and 7B-HC, are generated by reactive oxygen species [4,20]. Cholesterol

is easily oxidized when in contact with air, but the possible existence of cholesterol auto-oxidation *in vivo* is subject of increasing scepticism [4,16]. Side-chain oxysterols are thought to signal excess cholesterol by binding to Insig. Insig-2 has been shown to bind 25-HC with a half maximum concentration of 150 nM. 22(R)-HC, 24(S)-HC, 27-HC and 24-25-epoxycholesterol (24-25-EC) have almost identical affinities for Insig as 25-HC [21,22]. Binding of 7 $\alpha$ -HC, 7 $\beta$ -HC and 7-KC to Insig-2 is much weaker ( $>5 \mu\text{M}$ ) [22]. Insig-2 is suppressed by protein kinase Akt [23]. Given the large degree of sequence homology, Insig-1 is thought to have similar oxysterol binding properties as Insig-2 [13].

Side-chain oxysterols also bind to the liver X receptors (LXRs). The latter suppress SREBP transcription and up-regulate genes involved in degradation of cholesterol or its transfer to high density apolipoproteins (HDL) [24]. However, the LXR of mammals is maximally activated by another side product of cholesterol synthesis, 24(S)-25-EC [25]. In addition a number of other natural endogenous oxysterol ligands, namely 22(R)-HC, 20(S)-HC, 25-HC, 27-HC and an oxysterol present in food, 5-6 $\alpha$ -EC activate LXRs [26–29].

Besides through the relatively slow transcriptional regulation, HMGCoA reductase is also controlled by metabolic feedback loops, some of which implicate oxysterols. Lanosterol and 25-HC promote Insig binding to HMGCoA reductase [30] and its subsequent ubiquitination and degradation by proteasomes. Cholesterol degradation by mitochondrial 27-hydroxylase produces 27-HC which also stimulates HMGCoA reductase digestion [18], by the same mechanism [31]. By stimulating SCAP-Insig binding they inhibit the transport of SREBP from the ER to the Golgi system [32,33] and stimulate the transport of cholesterol to the ER. Once in the ER, cholesterol is esterified by acyl-CoA cholesterol acyl transferase (ACAT). It is then stored in the cytosol in the form of lipid droplets [24,34]. Two ACAT isoforms exist that are coded by



**Fig. 1.** Cholesterol and some of its oxygenated derivatives. Carbon numbering of cholesterol is shown at the upper left. The side-chain starts at position 20. 25-Hydroxycholesterol (25-HC) contains a hydroxyl group at position 25. 24-25-Epoxycholesterol (24-25-EC) contains an epoxy group formed by the carbons at position 24 and 25 and an oxygen atom. 7-Ketocholesterol (7-KC) has a double-bonded oxygen at position 7. Cholestane 3 $\beta$ -5 $\alpha$ -6 $\beta$  triol (CT) contains three hydroxyl groups and 6-oxocholestan-3 $\beta$ -5 $\alpha$ -diol (OCDO) an extra hydroxyl at position 5 and an oxygen at position 6. The other cholesterol derivatives mentioned in the text can be easily deduced from their number prefixes, e.g. 7 $\beta$ -HC has a hydroxyl at position 7.

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