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Giuseppe Poli, Fiorella Biasi

Department of Clinical and Biological Sciences, University of Torino, Torino, Italy

Corresponding Giuseppe Poli

Department of Clinical and Biological Sciences, at San Luigi Hospital, University of Torino,

10043 Orbassano, Turin, Italy.

Tel.: +39 0116705422; fax: +39 0112365422.

e-mail giuseppe.poli@unito.it

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Abstract

At least with regard to promotion and progression of cancer, oxysterols actually appear as typical Janus molecules, by inducing early inflammatory reaction against cancer expansion and apoptotic death of cancer cells, but on the other hand sustaining a complex survival signaling pathway that eventually turns in favor of the neoplastic process itself.

The protumoral and anti-tumoral properties of this class of compounds is mediated by both LXRdependent and independent mechanisms. The extent of oxidative redox imbalance, moderate or extensive, likely plays a key role in determining the actual effects operated by oxysterols along the various steps of carcinogenesis.

The hypothesis that certain oxysterols might favor tumor growth and progression was put forward just a few years ago (for a review, see Traversari and Russo, 2012). The review concentrated on oxysterols generated by the enzymatic oxidation of cholesterol's side chain, known therefore as side-chain oxysterols.

Several members of this sub-set of oxysterols have attracted particular interest for their active involvement in carcinogenesis: they can trigger the transcription of a number of cell regulatory and protective genes, and are the natural endogenous ligands of liver X receptors (LXRs).

Oxysterols recognized as primary LXR ligands have been shown to play a crucial role in the clearance of apoptotic cells by dendritic cells and macrophages, as well as in the negative regulation of lymphocyte proliferation (Bensinger et al., 2008) and differentiation (Cui et al., 2011). 22(R)-hydroxycholesterol and 27-hydroxycholesterol (27HC) have been found to markedly inhibit the expression of CC chemokine receptor-7 (CCR7) on human dendritic cells, through an LXRα-dependent mechanism; in a mouse model this inhibition hampered the migration of these cells to lymphoid tissues (Villablanca et al., 2010).

In several animal models, 27-hydroxycholesterol has been demonstrated to enhance the growth of estrogen receptor (ER) positive breast cancers; this effect was considered primarily dependent on the oxysterol's strong affinity for ER, although involvement of an LXR-dependent mechanism cannot be excluded. Indeed, 27HC significantly increased the metastatic potential of ER-negative and LXR-positive breast cancer cells (Nelson et al., 2013).

Consistently, two marketed anti-breast-cancer drugs have been recognized to inhibit cytochrome P27A1 activity, namely the enzyme generating 27HC (Mast et al., 2015). Notably, various oxysterols have been shown to activate several intracellular receptors and transcription factors other than LXR (for a review see Vurusaner et al. 2016, in this issue of MAM);in other words, oxysterols may also trigger signal transduction in LXR-independent ways. In this connection, a growing bulk of evidence points to side chain oxysterols as promoting rather than inhibiting cancer progression,

including independently of their binding to LXRs: in a number of tumors transplanted into mice, the chemotactic attraction of neutrophils, considered to favor cancer growth, has been shown to be exerted by 22(R)- hydroxycholesterol and 27HC through the LXR-independent activation of the G protein-coupled receptor CXCR2 (Raccosta et al., 2013).

In this issue, 27HC is reported to trigger very marked survival signaling in a promonocytic cell line, essentially involving Nrf2 transcription factor (see Vuruzaner et al., this issue). Conversely, several experimental reports point to the anti-proliferative action of both synthetic and natural LXR agonists, the latter being represented by certain oxysterols, including 24(S)-hydroxycholesterol and 22(R)- hydroxycholesterol (see Chuu and Lin, 2010; Chuu, 2011, Lin et al., 2013).

Consistent with the conclusions drawn by these studies is the evidence of an antiangiogenic effect exerted by synthetic LXR ligands (T0901317, GW3965) on human umbilical vein endothelial cells, by impairing vascular endothelial growth factor receptor-2-mediated signaling (Noghero et al., 2012). In addition, 5–6 cholesterol epoxides have been shown to contribute to part of the antiproliferative effect of tamoxifen in the hormonotherapy of breast cancer (Segala et al., 2013).

On the basis of these and other studies, a possible role of oxysterols as promising molecules in cancer therapy has been suggested. However, the observed opposing activities of LXR in cancer must unquestionably be carefully addressed (De Boussac et al., 2013).

It remains to be fully elucidated how the signaling transduction driven by oxysterols might overwhelm and/or bypass their binding to LXR, with its consequent activation. The different tissue distribution pattern of LXR isoform α (mainly limited to liver, adipose tissue and macrophages) and LXR isoform β (ubiquitous) (Repa and Mangelsdorf, 2000) could play a role, in terms of higher or lower LXR receptor availability in the various organs.

Another player is probably the polymorphism in the genes encoding for cholesterol hydroxylases, an emerging aspect of oxysterol activity that deserves deeper investigation. In our opinion, a moderate but consistent switch of cell and tissue redox equilibrium toward oxidation might be a major factor favoring LXR-independent reactions driven by oxysterols. Such a switch

needs not be a marked oxidative state (oxidative stress) of pathological significance, rather a pathophysiological increase of reactive oxygen species (ROS), a typical and common example of which is that promoted by inflammation. This process mainly involves oxysterols of non-enzymatic origin, which are not LXR ligands and have been suggested to be associated with an increased risk of developing cancer for their strong proinflammatory, pro-oxidant, and mutagenic effects (Jusakul et al., 2011).

If this hypothesis is correct, in all chronic disease processes sustained by inflammatory reactions, quantitatively relevant amounts of oxysterols would activate LXR-independent rather than LXR-dependent pathways. This context would make this class of sterols, otherwise very active in a variety of important physiological conditions, decidedly harmful. In other words, oxysterols and chronic inflammation could be considered as dangerous partners in crime.

Finally, with regard to the apparent discrepancy in the available literature about the pro-tumoral or anti-tumoral effects of this family of compounds, the chronic inflammatory environment that characterizes the advanced progression of several malignant tumors certainly provides a number of cells (like type II macrophages) and molecules (e.g. metalloproteases, pro-angiogenic factors) that play in favor of the neoplasia and against the host, and oxysterols arewell represented in this context.

Thus, without ruling out the possibility that cholesterol oxides might, in principle, exert certain beneficial effects against cancer cell growth, mainly LXR-dependent ones, in the long run their excessive accumulation, as in chronic inflammatory foci and lesions, appears to be detrimental.

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