

IN THE SPOTLIGHT

Nuclear Receptor LXR as a Novel Therapeutic Antitumoral Target in Glioblastoma

Antonio Moschetta

Summary: Both primary and transformed cells need cholesterol for their growth. Guo and colleagues unraveled the connection between epidermal growth factor receptor mutations in glioblastoma and increased cholesterol influx via sterol regulatory element-binding protein 1 and low-density lipoprotein receptor (LDLR) increase. They propose the activation of the liver X receptor–inducible degrader of LDLR–LDLR axis as a therapeutic approach to reduce intracellular cholesterol, block tumor growth, and induce cell death. *Cancer Discovery*; 1(5): 381–2. ©2011 AACR.

Commentary on Guo et al., p. 442 (8).

A large body of evidence suggests a possible central role for cholesterol in cell proliferation and tumor growth. Indeed, rapidly growing tissues, such as the brains of newborn rats, synthesize cholesterol in a faster and more active way than tissues that demonstrate little cellular turnover (1). In addition, alterations in the synthesis, uptake, and membrane content of cholesterol have been observed in a variety of experimental tumor models as well as in human tumors. These changes include a high rate of cholesterol biosynthesis linked to an increase in the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis (2). In line with this, treatment with compactin, a very potent competitive inhibitor of HMG-CoA reductase, prevented cell proliferation (3, 4). Interestingly, proliferating cells' requirement for increased cholesterol can also be satisfied by the up-regulation of low-density lipoprotein receptor (LDLR) and the subsequent increase of cholesterol influx (3, 4). In most of these studies, a synchronism between increase in cholesterol synthesis and influx with the proliferative process has been observed. *In vivo* experiments provide evidence that tumor-unrelated cell proliferation, such as proliferating T cells (5) and regenerating liver after partial hepatectomy (6), as well as tumor-related hyper-proliferation status (7), are closely associated with changes in cholesterol homeostasis. Strategies aimed at affecting cholesterol homeostasis are thus emerging as putative therapies against cancer or other hyperproliferative-related disorders.

Guo and colleagues (8) now present a novel pathway that provides increased cholesterol content to drive proliferation in glioblastoma cells. Glioblastoma is the most common malignant and lethal tumor in the brain. Highly proliferating glioblastoma cells are characterized by epidermal growth

factor receptor (EGFR) mutation and loss of the PTEN tumor suppressor protein. Both events lead to activation of the phosphoinositide 3-kinase (PI3K) signaling pathway that potentiates malignant cell growth. The authors elegantly show that the EGFR–PI3K axis up-regulates LDLR expression via activation of the sterol regulatory element-binding protein 1 (SREBP-1) system. The final consequence of this cascade is a turbo boost in cholesterol influx, which guarantees the sterol needs of a proliferating malignant cell (Fig. 1). The translational relevance of the present study is supported by the use of cell lines and clinical samples from patients treated with the EGFR tyrosine kinase inhibitor lapatinib.

The nuclear receptor liver X receptor (LXR) is one of the main transcriptional regulators of cholesterol metabolism. Nuclear receptors are a large family of transcription factors that act as transcriptional regulators after being activated by specific ligands. LXRs respond to physiological concentrations of oxysterols (9) and enhance transcription of genes whose encoded products are involved in regulating cholesterol metabolism. LXRs are putative pharmacological targets in atherosclerosis (10) because they are able to decrease intracellular cholesterol by up-regulation of cholesterol efflux (via induction of the target gene *ABCA1*) and down-regulation of cholesterol influx [via induction of the target gene *IDOL* (inducible degrader of LDLR), which blocks LDLR via ubiquitination]. Interestingly, these properties of LXRs led several investigators to propose specific synthetic ligand therapies to inhibit cellular proliferation.

This study by Guo and colleagues (8), which uses cell and xenograft growth curves with a combination of chemical and genetic gain and loss-of-function approaches, shows that LXR synthetic ligands are able to decrease cell growth and to induce significant tumor cell death *in vivo*. This event is achieved by repression of LDLR protein expression via *IDOL* activation and induction of *ABCA1* (Fig. 1). However, one of the main LXR transcriptional activities relates to driving and sustaining fatty acid synthesis. This lipogenic role of LXR, especially in the liver, leads to systemic hypertriglyceridemia, which today represents a limitation for a putative LXR-targeting therapeutic strategy. Also, one cannot exclude that fatty acid synthase activity might be increased by LXR in the same glioblastoma cell, whose proliferation is indeed

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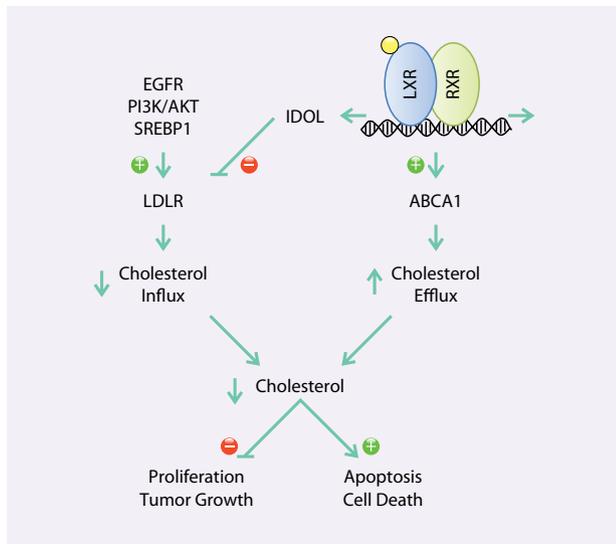


Figure 1. EGFR mutation in glioblastoma together with loss of PTEN leads to activation of SREBP1 and subsequent induction of LDLR expression. The final outcome is increased cholesterol influx, fulfilling the requirements of proliferating transformed cells. Activation of LXR via synthetic ligands induces (i) overexpression of IDOL, which down-regulates LDLR protein expression via ubiquitination and (ii) overexpression of ABCA1. These molecular events drive decreased cholesterol influx and increased cholesterol efflux with the aim of reducing intracellular cholesterol levels, blocking cellular proliferation and tumor growth, and inducing cell death via apoptosis.

additionally blocked when LXR ligands are administered together with fatty acid synthesis inhibitors. Overall, this elegant study will truly open new avenues for LXR synthetic ligands as a novel therapeutic approach in glioblastoma. The antitumoral LXR strategy will soon be definitively tested in other tumors. Subtype-, tissue-, and promoter-specific

scenarios will then be urgently required to avoid proliopogenic effects of LXR.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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