Accumulation of mutations in cancer cells is often leading to impaired metabolic pathways that can lead to impaired abilities to produce certain metabolites. If these metabolites are required for cell growth or survival, the cells need to acquire them (or the corresponding precursors that they would be able to metabolize) exogenously. Such dependence on a specific exogenous supply is called auxotrophy. For instance, cancer cells that cannot synthesize cholesterol de novo, strongly depend on cholesterol uptake via LDL receptors (LDLRs) for their survival. This was reported to be the case for cells of the glioblastoma multiforme (GBM), the most aggressive malignant tumor of the brain [1*], for which targeting cholesterol metabolism might represent an effective pharmacological treatment [2].

Garcia-Bermudez et al. [3] now show that cholesterol auxotrophy might be a promising metabolic target also in ALK⁺ anaplastic large cell lymphoma (ALCL), in which cholesterol metabolism is impaired because of strong downregulation of squalene epoxidase (SQLE). SQLE is a rate-limiting enzyme that converts squalene, a \( \text{C}_{30}\text{H}_{50} \) lipophilic metabolite, into squalene 2,3-epoxide, the loss of which prevents cholesterol formation [4,5**]. As a result of their defective SQLE activity, ALK⁺ ALCL cells are thus characterized by remarkable accumulation of squalene. Such abnormal accumulation, otherwise undetectable in most cancer cells, confers protection against a form of lipid oxidation-induced cell death called ferroptosis. Blocking squalene build-up by knocking out the squalene synthase enzyme \( \text{FDFT1} \) or by overexpressing SQLE in ALK⁺ ALCL cells rendered ALK⁺ ALCL cells extremely sensitive to pharmacologically induced ferroptosis, both in vitro and in tumor xenografts in vivo.

Although these findings suggest the squalene accumulation might prevent death induced by oxidative damage, at least in ALK⁺ lymphomas, other recent evidence points toward a toxic role for the same metabolite. Indeed, Mahoney et al. [6**] identified, through a chemical biology screen, a subset of cancer cells, mostly of small cell lung cancer (SCLC) origin, that were sensitive to SQLE inhibition. As expected, treatment of SCLC with NB-598, a compound that specifically inhibits SQLE, was associated with squalene accumulation and inhibition of cholesterol biosynthesis. In this case, intracellular accumulation of squalene was toxic in the sensitive tumor cell lines, a clinically relevant finding as the corresponding tumor xenografts displayed considerable sensitivity to NB-598.

In both studies, squalene was reported to accumulate in lipid droplets. Of note, abrogation of lipid droplets formation in NB-598-resistant cells rendered them sensitive to the drug. This suggests that lipid droplets fulfill important protective functions against squalene accumulation in cells.

These two studies provide evidence that squalene exerts its effects on cellular growth and survival through distinct mechanisms, which most likely vary according to the subset of cancer cells considered. In some cancers, squalene accumulation is beneficial whereas in others, it is detrimental. Understanding the molecular basis of nutrient dependency and selective vulnerability of tumor cells is, therefore, indispensable for designing targeted drugs, and it remains one of the major challenges in the field. In this context, it would be interesting to assess the role of statins that inhibit the cholesterol biosynthetic pathway upstream of squalene synthesis and that could, therefore, either promote or inhibit the development of tumors depending on the role played by squalene in these malignancies.

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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

   This work shows that survival of glioblastoma cells relies on exogenous cholesterol uptake. Depletion of cholesterol in glioblastoma multiforme cells through a synthetic agonist of the liver X receptor was effective in slowing the growth of GBM xenografts.


   This article shows that some cancer cells rely on squalene to protect them against ferroptosis but this comes at the expense of rendering them auxotrophic for cholesterol.

   This work, in striking contrast with ref. [5••], provides evidence that squalene accumulation through the use of squalene monooxygenase (squalene epoxidase) inhibitors is very efficient in blocking the growth of certain tumors. Ref. [5••] and [6••] highlight the Janus faces in cancer of squalene, a metabolite in the cholesterol biosynthetic pathways, exemplifying how important target therapy must be developed in the future to treat given types of cancer.