The metabolic program of cancer cells is significant different from the normal cells, which makes it possible to develop novel strategies targeting cancer cells. Mevalonate pathway and its rate-limiting enzyme HMG-CoA reductase (HMGCR) have shown important roles in the progression of several cancer types.

HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase, officially abbreviated HMGCR) is the rate-controlling enzyme (NADH-dependent, EC 1.1.1.88; NADPH-dependent, EC 1.1.1.34) of the mevalonate pathway, the metabolic pathway that produces cholesterol and other isoprenoids. Normally in mammalian cells this enzyme is suppressed by cholesterol derived from the internalization and degradation of low density lipoprotein (LDL) via the LDL receptor as well as oxidized species of cholesterol. Competitive inhibitors of the reductase induce the expression of LDL receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol, an important determinant of atherosclerosis.

This enzyme is thus the target of the widely available cholesterol-lowering drugs known collectively as the statins. HMG-CoA reductase is anchored in the membrane of the endoplasmic reticulum, and was long regarded as having seven transmembrane domains, with the active site located in a long carboxyl terminal domain in the cytosol. More recent evidence shows it to contain eight transmembrane domains.

Forced expression of HMGCR promoted the growth and migration of U251 and U373 cells, while knocking down the expression of HMGCR inhibited the growth, migration and metastasis of glioblastoma cells. Molecular mechanism studies revealed that HMGCR positively regulated the expression of TAZ, an important mediator of Hippo pathway, and the downstream target gene connective tissue growth factor (CTGF), suggesting HMGCR might activate Hippo pathway in glioblastoma cells. Taken together, our study demonstrated the oncogenic roles of HMGCR in glioblastoma cells and HMGCR might be a promising therapeutic target [1].

1)
Qiu Z, Yuan W, Chen T, Zhou C, Liu C, Huang Y, Han D, Huang Q. HMGCR positively regulated the growth and migration of glioblastoma cells. Gene. 2016 Jan 15;576(1 Pt 1):22-7. doi: 10.1016/j.gene.2015.09.067. Epub 2015 Sep 30. PubMed PMID: 26432005.