SREBPs through N-glycosylation of SCAP. Moreover, pharmaceutical agents that target SCAP in glioblastoma cells, such as glucose, are known to upregulate the SCAP protein, and SCAP knockdown reduces SREBP activation during sterol deprivation. N-acetylglucosamine (GlcNAc) was also shown to be indispensable for SREBP activation during sterol deprivation. Glucose-mediated activation of SREBPs was accompanied by upregulation of SCAP protein, and SCAP knockdown reduced SREBP activation. N-acetylgalactosamine (GlcNac) was also shown to be effective in increasing SCAP protein levels and activating SREBPs, suggesting that glucose enhances SCAP and activates SREBPs through N-glycosylation of SCAP. Moreover, pharmacologic inhibition of N-glycosylation, but not O-glycosylation, reduced SCAP N-glycosylation and its protein levels, and suppressed SREBP activation, which was rescued by GlcNAc addition. Mechanistically, glucose-driven N-glycosylation of SCAP enhanced its stability by preventing proteasomal degradation. Additionally, glucose-mediated N-glycosylation of SCAP reduced its binding to INSIG1, directing the trafficking of SCAP/SREBP to the Golgi for SREBP activation. Increased glucose uptake driven by EGFR signaling led to the downstream activation of SREBP1 via upregulation of SCAP N-glycosylation. Genetic knockdown of SCAP or mutation of SCAP N-glycosylation sites significantly suppressed EGFR-mediated glioblastoma tumor growth. Together, these findings indicate that the N-glycosylation of SCAP is critical for SCAP/SREBP trafficking and SREBP activation. These results reveal an important link between glucose and lipid metabolism in tumors, and suggest that targeting SCAP N-glycosylation may be an effective strategy to disrupt lipid metabolism in cancer.

Major finding: Glucose activates SCAP/SREBP trafficking and SREBP N-glycosylation is critical for SCAP/SREBP trafficking from ER to the Golgi.

Mechanism: Glucose-mediated N-glycosylation directs SCAP/SREBP trafficking from ER to the Golgi.

Impact: Blocking SCAP N-glycosylation is a promising strategy to target cancer.

Tumors are commonly characterized by increased lipogenesis and glucose utilization, and elevated glucose consumption is frequently correlated with increased lipogenesis. However, the mechanism connecting tumor glucose metabolism with lipid metabolism remains elusive. Lipogenesis is regulated by a family of transcription factors, the sterol regulatory element-binding proteins (SREBP), which regulate the expression of genes involved in the uptake and synthesis of cholesterol, fatty acids, and phospholipids. When cholesterol concentrations are high, the complex of SREBP and SREBP cleavage-activating protein (SCAP) is blocked in the ER membrane by binding to the ER-anchored protein insulin-induced gene 1 (INSIG1). Cheng and colleagues showed that, in glioblastoma cells, glucose was indispensable for SREBP activation during sterol deprivation. Glucose-mediated activation of SREBPs was accompanied by upregulation of SCAP protein, and SCAP knockdown reduced SREBP activation. N-acetylgalactosamine (GlcNac) was also shown to be effective in increasing SCAP protein levels and activating SREBPs, suggesting that glucose enhances SCAP and activates SREBPs through N-glycosylation of SCAP. Moreover, pharmacologic inhibition of N-glycosylation, but not O-glycosylation, reduced SCAP N-glycosylation and its protein levels, and suppressed SREBP activation, which was rescued by GlcNAc addition. Mechanistically, glucose-driven N-glycosylation of SCAP enhanced its stability by preventing proteasomal degradation. Additionally, glucose-mediated N-glycosylation of SCAP reduced its binding to INSIG1, directing the trafficking of SCAP/SREBP to the Golgi for SREBP activation. Increased glucose uptake driven by EGFR signaling led to the downstream activation of SREBP1 via upregulation of SCAP N-glycosylation. Genetic knockdown of SCAP or mutation of SCAP N-glycosylation sites significantly suppressed EGFR-driven glioblastoma tumor growth. Together, these findings indicate that the N-glycosylation of SCAP is critical for SCAP/SREBP trafficking and SREBP activation. These results reveal an important link between glucose and lipid metabolism in tumors, and suggest that targeting SCAP N-glycosylation may be an effective strategy to disrupt lipid metabolism in cancer.

**Mechanism:** PARP inhibitors reduce DNA break repair, leading to cell death and differentiation in the absence of HOXA9.

**Impact:** PARP inhibitors may be effective in treating AML, and HOXA9 inhibition may potentiate their effects.

**Major finding:** PARP inhibitors can suppress acute myeloid leukemias harboring AML1–ETO and PML–RARα.

**PARP INHIBITORS SUPPRESS AML1–ETO- AND PML–RARα-POSITIVE LEUKEMIA**

Acute myeloid leukemia (AML) is characterized by transcription factor fusion proteins, including runt-related transcription factor 1 (RUNX1)–RUNX1T1 (also known as AML1–ETO), promyelocytic leukemia (PML)–retinoic acid receptor α (RARα), and lymphoma (K)-specific methyltransferase 2A (KMT2A, also known as mixed lineage leukemia (MLL)) fusions, which function as oncogenic drivers. However, there are no targeted therapies against these fusions, and AML treatment is generally limited to toxic chemotherapy. In an effort to identify synthetic lethal therapeutic approaches for AML, Esposito and colleagues treated primary mouse hematopoietic cells transformed by leukemia-associated transcription factors with PARP inhibitors. PARP inhibition or knockdown reduced colony formation in cells expressing AML1–ETO or PML–RARα, but not MLL–Af9 or E2A–Pbx. Similar results were observed in patient-derived leukemia cell lines and in mouse xenografts. Additionally, PARP inhibition induced differentiation into mononuclear and granulocytic lineages, G1 cell-cycle arrest, and senescence in AML1–ETO- and PML–RARα-transformed cells, but not MLL–Af9- or E2A–Pbx-transformed cells. AML cells exhibited DNA damage or replication stress marked by high levels of γH2AX DNA damage foci, which were further induced by PARP inhibition. However, in contrast to E2A–Pbx- and MLL–Af9-transformed cells, AML1–ETO and PML–RARα cells did not efficiently recruit RAD51, indicating a defect in homologous recombination (HR)-mediated double-strand break repair. MLL–Af9-transformed cells induced expression of HOXA9, which promoted resistance to PARP inhibition; HOXA9 deletion or suppression of HOXA9 function via inhibition of glycogen synthase kinase 3 sensitized MLL leukemic cells to PARP inhibition and impaired MLL leukemia growth. Conversely, HOXA9 overexpression in AML1–ETO- and PML–RARα-positive cells increased RAD51 recruitment to DNA damage foci, enhanced HR efficiency, and reduced sensitivity to PARP inhibition. Together, these data indicate that PARP inhibitors effectively target AML1–ETO- and PML–RARα-positive leukemia, and suggest that HOXA9 inhibition may sensitize AML cells to PARP inhibitors.

**Major finding:** PARP inhibition can suppress acute myeloid leukemias harboring AML1–ETO and PML–RARα.

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