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## Melanoma

**Major finding:** FAK inhibition confers synthetic lethality in GNAQ-activated uveal melanoma.

**Mechanism:** Phosphorylation of MOB1A by FAK inhibits Hippo signaling and activates YAP transcriptional activity.

**Impact:** FAK represents a potential therapeutic target in uveal melanoma and other Gαq-driven cancers.

### FAK IS A CRITICAL MEDIATOR OF GNAQ-DRIVEN UVEAL MELANOMA

Uveal melanoma (UM) is characterized by gain-of-function mutations in *GNAQ* or *GNA11*, which encode Gαq G proteins. However, the molecular mechanisms underlying Gαq-mediated cancer cell growth remain unknown, and there are currently no effective therapies for UM. Feng, Arang, and colleagues utilized an integrated bioinformatics pipeline to identify *PTK2*, which encodes focal adhesion kinase (FAK), as a clinically actionable synthetic lethal gene target in GNAQ-activated UM. Although *PTK2* is not mutated in UM, expression of *PTK2* inversely correlated with overall patient survival. Overexpression of an active Gαq mutant or activation of an inducible Gαq in UM cells resulted in increased active phosphorylation of FAK; conversely, knockdown or inhibition of Gαq diminished FAK activation, indicating that FAK acts downstream of Gαq. This activation occurred via the noncanonical TRIO-dependent signaling pathway and resulted in RhoA activation and subsequent changes to the cytoskeletion and actomyosin-initiated cell signaling. Inhibition of FAK (FAKi) with either of two chemically distinct FAK inhibitors revealed a dose-dependent sensitivity to FAKi and abolished colony-forming capacity in UM *in vitro*. FAKi resulted in a significant reduction of nuclear accumulation of the YES-associated protein (YAP) transcription factor and downregulation of YAP target genes. Similarly, knockdown or inhibition of Gαq or FAK reduced active YAP phosphorylation and increased repressive YAP phosphorylation, suggesting that the cellular effects of FAKi in UM are mediated by reduced YAP activity. Phosphorylation of MOB kinase activator 1A (MOB1A) by FAK resulted in dissociation of YAP from the Hippo repressor complex and increased YAP transcriptional activity. *In vivo*, treatment with FAK inhibitors reduced UM tumor size and cell proliferation and increased cytoplasmic retention of YAP. Taken together, these results indicate that pharmacologic inhibition of FAK deactivates oncogenic signaling pathways and may be a viable therapeutic strategy in patients with UM. ■

*Feng X, Arang N, Rigiracciolo DC, Lee JS, Yeerna H, Wang Z, et al. A platform of synthetic lethal gene interaction networks reveals that the GNAQ uveal melanoma oncogene controls the Hippo pathway through FAK. Cancer Cell 2019 Feb 14 [Epub ahead of print].*

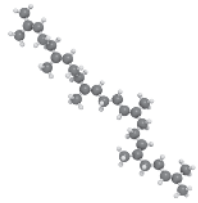
## Metabolism

**Major finding:** *SQLE* loss in ALK$^+$ lymphomas results in cholesterol auxotrophy and resistance to oxidative cell death.

**Approach:** Cholesterol dependencies were assessed by lentiviral barcoding of a panel of cancer cell lines.

**Impact:** Therapeutic inhibition of cholesterol uptake may be a potential therapy for patients with ALK$^+$ ALCL.

### ALK$^+$ LYMPHOMAS HARBOR A TARGETABLE DEPENDENCY ON EXOGENOUS CHOLESTEROL



Changes in the expression of metabolic genes promote nutrient dependencies and may affect nonmetabolic processes in cancer cells that can be therapeutically exploited. To systematically identify cancer type–specific cholesterol auxotrophy, Garcia-Bermudez and colleagues performed a competitive proliferation assay with a pooled collection of 28 cancer cell lines that had been individually transduced with a lentiviral barcode library and grown in either lipoprotein-replete or lipoprotein-depleted medium. A subset of cell lines, representing a variety of cancer types, exhibited strong cholesterol dependencies but no mutations in cholesterol biosynthesis genes; analysis of the Cancer Cell Line Encyclopedia (CCLE) revealed that the cholesterol biosynthesis enzyme squalene monooxygenase (*SQLE*) was not expressed in the SNU-1 cell line, resulting in increased squalene accumulation in SNU-1 cells. Further examination of the CCLE identified nine additional cell lines, six of which were ALK$^+$ anaplastic large cell lymphoma (ALCL) cell lines, that simultaneously lacked SQLE mRNA and protein, were sensitive to cholesterol depletion, and exhibited increased squalene accumulation. Similarly, ALK$^+$ ALCL patient-derived xenografts (PDX) and primary samples exhibited decreased SQLE mRNA and protein expression compared with ALK$^-$ ALCLs and other lymphomas. A CRISPR/Cas9 screen identified LDLR as critical for ALK$^+$ ALCL cell line growth *in vitro* and ALK$^+$ ALCL cell line xenograft and PDX growth *in vivo*. Genetic ablation of squalene synthase (*FDFT1*), which drives squalene synthesis, in ALK$^+$ ALCL cells resulted in wild-type–like squalene levels and decreased growth *in vivo*. Given that squalene is lipophilic and accumulates in cellular membranes, genetic or pharmacologic inhibition of *FDFT1* sensitized ALK$^+$ ALCL cells to ferroptosis; treatment with an antioxidant or inhibition of polyunsaturated fatty acid incorporation into the membrane blocked ferroptosis in *FDFT1*-ablated ALK$^+$ ALCL cells. These findings show that cholesterol dependency represents a therapeutic target in ALK$^+$ ALCL, characterize the antioxidant-like properties of a metabolite, and describe a systematic approach to identify nutrient auxotrophies. ■

*Garcia-Bermudez J, Baudrier L, Bayraktar EC, Shen Y, La K, Guarecuco R, et al. Squalene accumulation in cholesterol auxotrophic lymphomas prevents oxidative cell death. Nature 2019;567:118–22.*

AACR American Association for Cancer Research

CANCER DISCOVERY

# FAK Is a Critical Mediator of GNAQ-Driven Uveal Melanoma

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