**Metabolism**

**Major Finding:** TAZ-mediated mitochondrial phospholipid production regulates AML cell stemness and clonogenicity.

**Mechanism:** TAZ suppresses intracellular levels of phosphatidylserine, which in turn suppresses TLR activity.

**Impact:** Inhibition of mitochondrial phospholipid production could be therapeutically efficacious in AML.

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**Pancreatic Cancer**

**Major finding:** *Egfr* and *Raf1* ablation results in regression of a subset of mouse PDACs and inhibits proliferation of PDXs.

**Concept:** Ablation of *Egfr* and *Raf1* strongly inhibits tumor growth without affecting MAPK and PI3K signaling.

**Impact:** Combined inhibition of EGFR and CRAF may represent a high-efficacy, low-toxicity strategy for targeting PDAC.

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**COMBINED EGFR AND CRAF INHIBITION INDUCES COMPLETE PDAC REGRESSION IN MICE**

Current therapeutic strategies for pancreatic ductal adenocarcinoma (PDAC) suffer from low antitumor efficacy and high toxicity. Although mutations in *KRAS* are the most common driving event for PDAC, secondary mutations in genes such as *TP53* contribute to tumor progression. Blasco, Navas, and colleagues show in *Kras*/Trp53-mutant (KPC) PDAC that combined inhibition of EGFR and CRAF leads to complete tumor regression. In a modified murine KPC model of PDAC where mutant *Kras* is expressed only in the acinar cell compartment, individual ablation of *Egfr* or *Raf1* (encoding CRAF) led to a modest increase or no change in median survival, respectively. By contrast, combined ablation of *Egfr* and *Raf1* during tumor initiation completely prevented PDAC development to 2 years of age, with no indication of PanIN lesions or metaplasias. Targeted deletion of *Egfr* and *Raf1* had no effect on MAPK and PI3K signaling, thus preventing major toxicities. Indeed, only minor alterations to skin cells, such as hyperplasia, inflammation, hair loss, ulceration, and scabbing, were observed due to lack of EGFR expression. In advanced PDAC, ablation of *Egfr* and *Raf1* resulted in apoptosis of tumor cells, regression of tumor volume, extended survival, and reversion to normal tissue architecture within the pancreas. Transcriptional profiling of tumor-derived cell lines revealed significant changes in metabolic signaling pathways, and mice nonresponsive to *Egfr/*Raf1 ablation exhibited increased phosphorylation of STAT3 and multiple pro-proliferative gene signatures, suggesting these alternative pathways promote tumor growth independently of EGFR/CRAF signaling. In patient-derived PDAC xenografts (PDX), combined pharmacologic inhibition of EGFR and knockdown of CRAF inhibited proliferation in cells derived from 9 out of 10 tumors. Collectively, these results demonstrate that inhibition of EGFR and CRAF signaling exerts significant antitumor effects with low toxicity and may be a viable therapeutic strategy for patients with PDAC.


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**MITOCHONDRIAL PHOSPHOLIPID PRODUCTION REGULATES AML SURVIVAL**

Acute myeloid leukemia (AML) cells possess unique mitochondrial and metabolic features, including an increased reliance on oxidative phosphorylation. Seneviratne, Xu, and colleagues sought to exploit this distinguishing feature of AML cells, and thus performed a genome-wide CRISPR knock-out screen to identify mitochondrial genes that are required for AML cell growth and viability. Among the top depleted genes was *Taz*, which encodes a mitochondrial transacylase that is required for the production of the mitochondrial phospholipid cardiolipin under physiologic conditions. TAZ depletion in leukemia cell lines was associated with an increase in genes associated with myeloid differentiation and a concomitant decrease in stem/progenitor cell–associated genes. Furthermore, TAZ knockdown reduced the clonogenic growth of AML cells *in vitro*. No discernible effect of TAZ depletion on normal steady-state hematopoiesis and stem-cell function was observed, indicating that the consequences of TAZ loss are leukemia cell–specific, but reduced numbers of hematopoietic stem cells were observed after 5-FU–induced cellular stress. In addition to cardiolipin, TAZ knockdown in AML cells also altered levels of intracellular phospholipids, and led to increased levels of phosphatidylserine (PS). Increased intracellular PS or TAZ knockdown increased AML differentiation and reduced clonogenic growth and engraftment *in vivo* in association with increased Toll-like receptor (TLR) activity. Moreover, inhibition of PS decarboxylase, which converts PS to phosphatidylethanolamine in the inner mitochondrial membrane and also binds cardiolipin, reduced clonogenic growth of AML cells. This work collectively uncovers the therapeutic potential of exploiting phospholipid metabolism in AML.

Mitochondrial Phospholipid Production Regulates AML Survival

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