Melanoma

Major finding: Fusions or truncations of *MAP3K8* occur in 33% of spitzoid melanomas and 1.5% of adult melanomas.

Clinical relevance: A patient with spitzoid melanoma with a *MAP3K8* fusion had a transient response to trametinib.

Impact: Alteration of *MAP3K8* may activate MAPK signaling in melanoma and predict response to MEK inhibition.

POTENTIALLY ACTIONABLE *MAP3K8* ALTERATIONS ARE COMMON IN SPITZOID MELANOMA

Spitzoid melanoma is a melanoma variant that primarily affects children and adolescents. Fusions of *ALK*, *RET*, *NTRK1*, *NTRK3*, *MET*, *ROS1*, and *BRAF* are known drivers of these tumors, but approximately half of spitzoid melanomas have no known genetic driver. Newman and colleagues report the case of a patient with recurrent, metastatic spitzoid melanoma who was enrolled on an institutional clinical genomics study. Comprehensive whole-genome, whole-exome, and whole-transcriptome analysis failed to identify any of the known oncogenic drivers of spitzoid melanoma but revealed an in-frame fusion affecting *MAP3K8* (also known as *COT*), which encodes a serine–threonine kinase that phosphorylates and activates MEK and has been implicated in BRAF inhibitor resistance. Immunohistochemistry confirmed that MEK1/2 was phosphorylated, and the patient was treated with the MEK inhibitor trametinib. Although the lesions initially were reduced in size and number based on examination and PET, treatment was discontinued due to cardiotoxicity and lack of sustained response. RNA sequencing (RNA-seq) of tumors from an additional 49 patients with spitzoid melanoma revealed that 16/49 (33%) tumors harbored either an in-frame fusion or C-terminal truncation of *MAP3K8*, making *MAP3K8* alterations the most common genetic event in this disease. All alterations led to loss of the final exon of *MAP3K8*, which encodes the autoinhibitory C-terminal domain, and were associated with MEK1/2 phosphorylation in paraffin-embedded tissue sections. Of note, locus-specific analysis of RNA-seq data from 472 adult melanoma samples in The Cancer Genome Atlas identified 7 samples (1.5%) with *MAP3K8* fusion or truncation, none of which had any other MAPK pathway mutation, suggesting that *MAP3K8* alterations may also be drivers in some adult melanomas. In addition to providing an example of how comprehensive sequencing of individual patients can lead to broader insights into tumor etiology, these findings suggest that *MAP3K8* alterations are more common than previously appreciated and may potentially be predictive of response to MEK inhibitors. ■

Newman S, Fan L, Pribnow A, Silkov A, Rice SV, Lee S, et al. Clinical genome sequencing uncovers potentially targetable truncations and fusions of MAP3K8 in spitzoid and other melanomas. Nat Med 2019;25:597–602.

Metabolism

Major finding: Pancreatic cancer cells alternatively activate macrophages to release pyrimidines.

Concept: The pyrimidine deoxycytidine competitively inhibits the intercellular activation of gemcitabine by DCK.

Impact: Therapeutically targeting TAMs may reduce gemcitabine resistance in patients with pancreatic cancer.

MACROPHAGE-DERIVED NUCLEOSIDES REDUCE THE EFFICACY OF GEMCITABINE

Pancreatic adenocarcinoma (PDAC) tumorigenesis is greatly influenced by an inflammatory response mediated significantly by immunosuppressive tumor-associated macrophages (TAM) in the tumor microenvironment (TME); conversely, the TME induces the metabolic reprogramming of TAMs. Recently, it has been shown that the presence of TAMs is associated with therapeutic response in patients with PDAC; thus, Halbrook and colleagues sought to ascertain whether therapeutic response of PDAC is influenced by metabolic cross-talk between PDAC and TAMs. Metabolomic profiling of macrophages polarized by PDAC cells *in vitro* (termed tumor-educated macrophages, or TEMs), classically activated macrophages (M1), and alternatively activated macrophages (M2) revealed that M2 and TEMs produced pyrimidine nucleosides and nucleobases, which were subsequently shown to be directly taken up by PDAC cells. Further, culturing PDAC cells in TEM-conditioned media (CM) resulted in reduced gemcitabine sensitivity, and a screen of individual pyrimidine nucleosides found in CM showed that deoxycytidine alone inhibited gemcitabine in PDAC cells *in vitro*. Metabolic flux and isotope tracing experiments demonstrated that M2 and TEMs, but not M1 macrophages, utilize glucose carbon for oxidative metabolism and pyrimidine biosynthesis.

Inhibition of glucose metabolism in TEMs through several methods that decreased deoxycytidine production, but did not affect TEM proliferation, increased gemcitabine sensitivity in PDAC cells grown in CM from glucose-depleted TEMs. Importantly, addition of exogenous deoxycytidine to these cultures restored gemcitabine resistance of PDAC cells. Deoxycytidine, which is structurally similar to gemcitabine, competed with gemcitabine for activation by the enzyme deoxycytidine kinase (DCK), which is required for the activation of gemcitabine; inhibition of gemcitabine incorporation into PDAC DNA prevented cell death. Depletion or pharmacologic inhibition of myeloid cells in murine models of PDAC enhanced the efficacy of gemcitabine treatment in an immune response–independent manner. These results demonstrate a mechanism of metabolic cross-talk between PDAC and macrophages and suggest targeting of TAMs may improve gemcitabine response in patients with PDAC. ■

Halbrook CJ, Pontious C, Kovalenko I, Lapienyte L, Dreyer S, Lee H-J, et al. Macrophage-released pyrimidines inhibit gemcitabine therapy in pancreatic cancer. Cell Metabolism 2019 Feb 28 [Epub ahead of print].