Signaling

Major Finding: The folate transporter SLC19A1 ferries charged cyclic dinucleotides (CDN) into human cells.

Concept: The presence of CDNs in the cytosol activates STING, triggering an immune response.

Impact: SLC19A1 may be involved in mechanisms behind cancer immunotherapy and immunopathology.

SLC19A1 TRANSPORTS STING-STIMULATING CYCLIC DINUCLEOTIDES INTO CELLS

The presence of the cyclic dinucleotide (CDN) 2′3′-cGAMP in the cytosol activates stimulator of interferon genes (STING), triggering a signaling cascade that culminates in an immune response. 2′3′-cGAMP is produced by cancer cells, and synthetic CDNs are used in cancer immunotherapy, but the mechanism by which these charged molecules are transported across cell membranes and into target cells is unclear. Using a genome-wide CRISPR-interference forward-genetic screen, Luteijn, Zaver, and colleagues identified the reduced-folate carrier SLC19A1 as the predominant transporter of CDNs in human cells. Validating this finding, *SLC19A1*-deficient cells exhibited reduced responses to stimulation by CDNs and reduced 2′3′-cGAMP uptake, whereas overexpression of *SLC19A1* led to a heightened response to CDNs and an increase in 2′3′-cGAMP uptake. In *SLC19A1*-depleted cells, STING function was restored upon direct introduction of CDNs into the cytosol, indicating that the role of SLC19A1 in this pathway is, indeed, to transport CDNs across the cell membrane. Experiments with other CDNs revealed that SLC19A1's transporter function is not specific to the phosphodiester linkage or base content of the CDN; thus, SLC19A1 appears to be a general CDN transporter. Pulldown experiments using His-tagged SLC19A1 supported a direct interaction between SLC19A1 and 2′3′-cGAMP, as would be predicted if SLC19A1 is a CDN transporter. Notably, the effects of CDN stimulation were not completely abolished in *SLC19A1*-null cells, implying that human cells possess another transporter capable, at least to some degree, of ferrying CDNs across the cell membrane. Collectively, these results establish the role of SLC19A1 in the STING pathway and suggest that SLC19A1 may be of interest in investigations of mechanisms behind cancer immunotherapy and immunopathology. ■

Luteijn RD, Zaver SA, Gowen BG, Wyman SK, Garelis NE, Onia L, et al. SLC19A1 transports immunoreactive cyclic dinucleotides. Nature 2019;573:434–8.

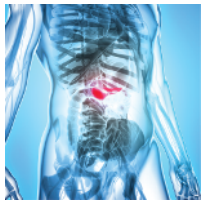
Pancreatic Cancer

Major Finding: Restoration of p53 led to an accumulation of αKG in mouse pancreatic cancer cells.

Mechanism: p53- and αKG-triggered changes in chromatin accessibility and gene expression overlapped.

Impact: This work establishes a previously unknown metabolic link between p53 and αKG in pancreatic cancer.

PANCREATIC CANCER CELL FATE IS MEDIATED BY A p53–α-KETOGLUTARATE LINK



Pancreatic ductal adenocarcinoma (PDAC) is often characterized by mutations affecting both *KRAS* and *TP53*. Oncogenic *KRAS* mutations have been demonstrated to have metabolic consequences in PDAC cells, but the potential effects of *TP53* mutations on PDAC metabolism have not been established. Morris, Yashinskie, and colleagues found that the restoration of wild-type p53 in a mouse PDAC model in which p53 had previously been inactivated led to accumulation of citrate and α-ketoglutarate (αKG), while the levels of glutamine-oxidation metabolites (including succinate, malate, and aspartate) decreased, increasing the ratio of αKG to succinate. The mechanism behind this metabolic shift is unclear, but the results of further experiments implied that alterations in the levels of several enzymes of the tricarboxylic acid (TCA) cycle triggered by the transcriptional functions of p53 may be involved. Treatment of the same PDAC cells used in the mouse model with αKG or restoration of p53 function led to increases in chromatin accessibility, with a large degree of overlap between the regions made accessible by p53 reactivation and αKG administration. Expression of genes specifically expressed in cells from premalignant pancreatic intraepithelial neoplasias were increased by p53 and αKG, whereas expression of genes selectively expressed in PDAC cells was decreased, indicating a potential connection to pancreatic cancer progression. In the mouse model, inhibition of oxoglutarate dehydrogenase (the TCA-cycle enzyme that converts αKG to succinyl-coenzyme A) led to a phenotype similar to that caused by p53 restoration, with promotion of cell differentiation and tumor suppression. Additionally, p53 status and the ratio of αKG to succinate determined the level of 5hmC, produced by the strictly αKG-dependent ten–eleven translocation enzymes, in the mouse PDAC model. Collectively, this work defines a previously unknown connection between p53 and metabolism in PDAC; further, this study suggests that it may be worth investigating therapies that increase αKG levels in p53-deficient tumors. ■

Morris JP IV, Yashinskie JJ, Koche R, Chandwani R, Tian S, Chen CC, et al. α-Ketoglutarate links p53 to cell fate during tumour suppression. Nature 2019;573:595–9.