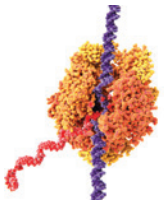
Transcription

Major Finding: NUAK1 inhibition caused buildup of nonproductive stalled transcription complexes in high-MYC cells.

Concept: Phosphorylation of the PP1 interactor PNUTS by NUAK1 on chromatin promoted spliceosome activity.

Impact: This study shows why high-MYC cells require NUAK1, revealing a potentially exploitable pathway.

HIGH-MYC CELLS DEPEND ON NUAK1 TO PREVENT STALLED TRANSCRIPTION



For unknown reasons, tumors with high levels of MYC exhibit dependency on NUAK1 (also known as ARK5), an AMPK-related serine/threonine protein kinase that regulates the activity of the serine/threonine phosphatase 1 (PP1). Cossa and colleagues observed that NUAK1 bound chromatin and colocalized with proteins that interact with PP1, including a PP1 regulatory subunit, protein phosphatase 1 nuclear-targeting subunit (PNUTS), and further experiments revealed evidence of NUAK1-dependent phosphorylation of PNUTS at S313. Deeper investigation demonstrated that nascent RNA binding was essential for PNUTS's chromatin binding, an interaction that promoted spliceosome activity by inhibiting PP1 downstream of the transcription start sites of actively transcribed genes. NUAK1's role in the process was multifaceted and appeared to be related to its phosphorylation of PNUTS at S313, which increased PNUTS's association with chromatin by stabilizing the PNUTS–nascent RNA interaction. Additionally, NUAK1 promoted transcriptional termination genome-wide and enhanced splicing of nascent RNAs encoding members of the transcription machinery. Notably, NUAK1 inhibition caused accumulation of R-loops (DNA–RNA hybrids that can stall transcription) along with recruitment of members of complexes that decap mRNAs (which makes them more susceptible to degradation). However, in cells with high levels of MYC, transcriptional termination did not occur at these sites; rather, RNA polymerase II appeared to remain stalled at the first transcription pause sites and intron–exon boundaries of NUAK1-regulated genes. Thus, in cells with high MYC levels, NUAK1 inhibition resulted in accumulation of nonproductive, stalled transcription complexes, explaining the requirement for NUAK1 in this context. Collectively, this work provides an in-depth molecular look into the role of an essential dependency in high-MYC cells, which represent a substantial portion of tumor cells, uncovering a pathway that may be targetable. ■

Cossa G, Roeschert I, Prinz F, Baluapuri A, Vidal RS, Schülein-Völk C, et al. Localized inhibition of protein phosphatase 1 by NUAK1 promotes spliceosome activity and reveals a MYC-sensitive feedback control of transcription. Molec Cell 2020 Jan 31 [Epub ahead of print].

Cell Death

Major Finding: In response to glucose starvation, AMPK inhibited lipid peroxidation–associated ferroptosis.

Mechanism: AMPK's phosphorylation of ACC1/2 reduced levels of polyunsaturated fatty acid–containing lipids.

Impact: Whether AMPK-mediated ferroptosis inhibition is linked to AMPK's tumorigenic effects is of interest.

ENERGY STRESS INHIBITS FERROPTOTIC CELL DEATH VIA AMPK ACTIVATION

Dysregulation of ferroptosis, a form of programmed cell death in which cells accumulate lipid peroxides in an iron-dependent fashion, has been linked to cancer and other pathologies. Despite the fact that glucose starvation is associated with increases in levels of reactive oxygen species, which could generate lipid peroxides, Lee, Zandkarimi, and colleagues unexpectedly found that energy stress protected cells against ferroptosis. The mechanism of ferroptosis inhibition appeared to be dependent on AMP-activated protein kinase (AMPK), and, correspondingly, further investigation revealed that inactivation of *AMPK* in a normally ferroptosis-resistant cancer cell line rendered cells sensitive to ferroptosis. Mechanistically, additional experiments suggested this ferroptosis inhibition was dependent on phosphorylation of acetyl-CoA carboxylase 1 and 2 (ACC1/2) by AMPK, which prevents ACC1/2-mediated promotion of fatty-acid synthesis and inhibition of fatty-acid oxidation. Activation of AMPK was also associated with reduced levels of polyunsaturated fatty acid–containing lipids, which may also contribute to the modulation of ferroptosis sensitivity by AMPK. In a mouse model of renal ischemia–reperfusion injury (IRI), which has been associated with ferroptosis in previous studies, treatment with an inhibitor of ferroptosis reduced the pathologic effects of renal IRI, as did AMPK activation triggered by energy stress. Collectively, these results establish AMPK as a key regulator of ferroptosis *in vitro* and *in vivo*. Interestingly, the function of AMPK in cancer appears to vary depending on several factors; for example, AMPK can act as a tumor suppressor by blocking biosynthesis of proteins or fatty acids, but it can also enhance tumor growth by preventing cell death during energy stress, and *AMPK* overexpression or amplification has been observed in some cancers. Whether AMPK-mediated ferroptosis inhibition contributes to its tumor-promoting effects in some circumstances would be an intriguing topic for further research. ■

Lee H, Zandkarimi F, Zhang Y, Meena JK, Kim J, Zhuang L, et al. Energy-stress-mediated AMPK activation inhibits ferroptosis. Nat Cell Biol 2020;22:225–34.