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Translation

Major finding: METTL3 interacts with eIF3h to enhance the translation efficiency of target mRNAs including BRD4.

Concept: METTL3 is upregulated in human lung tumors, and METTL3 depletion suppressed tumor growth *in vivo*.

Impact: The METTL3–eIF3h interaction enhances oncogene translation, making it a potential therapeutic target.

METTL3 PROMOTES mRNA TRANSLATION TO DRIVE TUMORIGENESIS

The mRNA modification N^6-methyladenosine (m^6A) is catalyzed by the METTL3 enzyme, and m^6A is enriched in the 3′ untranslated region (3′UTR) of mRNAs near the stop codon. METTL3 has been shown to enhance translation, but the mechanism by which this occurs has not been determined. Choe, Lin, and colleagues found that METTL3 promoted translation only when bound to the 3′UTR near a stop codon. Mechanistically, METTL3 interacted with the eukaryotic translation initiation factor 3 subunit h (eIF3h) to promote translation of target mRNAs, suggesting an mRNA looping mechanism to facilitate ribosome recycling and translational control. Electron microscopy further supported this model, indicating that METTL3 bound to mRNA ribonucleoprotein complexes termed polyribosomes in close proximity to 5′ cap-binding proteins. METTL3 depletion reduced the translation efficiency of a large subset of mRNAs. These identified METTL3 targets tended to have longer 3′UTRs and, as expected, exhibited reduced protein expression. One of the target proteins depleted by eIF3h knockdown was BRD4, and METTL3 knockdown was sufficient to rescue BRD4 expression. Further, METTL3 depletion reduced expression of BRD4 in lung cancer cells, rendering them more sensitive to a BRD4 inhibitor. The METTL3–eIF3h interaction was required for enhanced mRNA translation. The METTL3 A155P mutation disrupted the eIF3h interaction, without altering its mRNA association, thereby blocking METTL3-mediated enhancement of mRNA translation. The METTL3–eIF3h interaction promoted translation by altering the polyribosome conformation, with wild-type METTL3 resulting in more densely packed polyribosomes than the A155P mutant. METTL3 was upregulated in primary human lung adenocarcinomas compared with adjacent normal tissue, and, *in vivo*, METTL3 depletion suppressed the growth of lung cancer xenografts. Conversely, ectopic expression of METTL3 promoted tumor growth *in vivo*. Collectively, these findings suggest that METTL3 promotes oncogenic translation by interacting with eIF3h, facilitating an mRNA looping to increase target protein expression and drive tumorigenesis. ■

Choe J, Lin S, Zhang W, Liu Q, Wang L, Ramirez-Moya J, et al. mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis. Nature 2018;561:556–60.

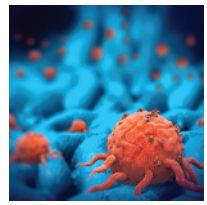
Inflammation

Major finding: Inflammation-induced neutrophil extracellular traps (NET) awaken dormant cells to promote metastasis.

Mechanism: NETs act as laminin-cleaving protease scaffolds to enable proteolytic remodeling and integrin activation.

Impact: Inflammation may trigger metastatic disease via NETs, suggesting their potential as therapeutic targets.

NEUTROPHIL EXTRACELLULAR TRAPS TRIGGER DORMANT TUMOR CELL PROLIFERATION



Cancer cells disseminated from the primary tumor can remain dormant at distant tissue sites for years before developing into metastatic cancer. However, the mechanisms by which dormant disseminated tumor cells resume proliferation remain unclear. Smoking-induced chronic lung inflammation has been linked to an increased risk of lung metastasis, suggesting a potential role for neutrophils, which mediate inflammation and have been linked to cancer cell awaking in experimental models. Neutrophils can kill microorganisms through the formation of neutrophil extracellular traps (NET), which are DNA scaffolds with associated cytotoxic enzymes and proteases that are released into the extracellular space. Albrengues and colleagues sought to determine whether NETs facilitate metastasis after dormancy. In mouse models of tumor dormancy, inflammation induced by lipopolysaccharide (LPS) or tobacco smoke exposure was sufficient to trigger aggressive lung metastases that were associated with NET formation. Blocking NET formation or digesting the NET DNA scaffold suppressed the conversion of disseminated cancer cells to active metastases, indicating that NET formation during inflammation promotes the awakening of dormant cancer cells. Mechanistically, the NET DNA acted as a proteolysis scaffold, binding to the extracellular matrix component laminin and facilitating laminin cleavage by the NET-associated proteases neutrophil elastase and matrix metalloproteinase 9. This laminin remodeling triggered α3β1 integrin activation and downstream FAK/ERK/MLCK/YAP signaling to promote the proliferation of dormant tumor cells. Consistent with these findings, antibody-mediated blockade of NET-remodeled laminin prevented LPS or smoke-induced inflammation from converting dormant cancer cells to metastases *in vivo*. In addition to elucidating a mechanism by which inflammation promotes NET-mediated laminin remodeling to awaken dormant cancer cells, these findings suggest the potential for therapeutic targeting of NETs to prevent metastasis in patients with dormant cancer. ■

Albrengues J, Shields MA, Ng D, Park CG, Ambrico A, Poindexter ME, et al. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. Science 2018;361:eaao4227.

AACR American Association for Cancer Research

CANCER DISCOVERY

METTL3 Promotes mRNA Translation to Drive Tumorigenesis

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