THE RNA METHYLTRANSFERASE METTL3 PROMOTES ONCOGENE TRANSLATION

The METTL3 RNA methyltransferase is a “writer” protein responsible for the N6-methyladenosine (m6A) modification, and is involved in mRNA biogenesis, decay, and translation. Although m6A has been implicated in diverse biological processes, its mechanism of action remain unclear. In emerging models, m6A methyl reader proteins bind to m6A and mediate effects downstream of METTL3. However, Lin and colleagues identified a tumor-promoting role of METTL3 independent of m6A reader proteins and its methyltransferase activity. In lung cancer cells, global mRNA profiling by methylated RNA-immunoprecipitation sequencing revealed m6A peaks near the stop codon in mRNAs of multiple oncogenes including EGFR and TAZ, but not others such as MYC and HRAS, and cross-linking immunoprecipitation showed that METTL3 bound to the m6A peak within EGFR mRNA. Depletion of METTL3 had little effect on global mRNA levels, but specifically reduced protein levels of EGFR and TAZ, without affecting MYC and RAS levels. Further, METTL3 was detected in polysome fractions, and METTL3 knockdown altered the polysome profile. These findings suggest that METTL3 specifically regulates translation of a subset of m6A-containing mRNAs. Accordingly, METTL3 was located in the cytoplasm where protein translation occurs, whereas METTL3 interacting proteins were restricted to the nucleus, suggesting that METTL3 itself promotes translation independent of m6A reader proteins. Instead, METTL3 interacted with components of the eIF3 translation initiation complex to promote translation of target mRNAs. The METTL3-dependent increase in translation of several oncogenes suggested a role in cancer, and analysis of data from The Cancer Genome Atlas revealed that METTL3 mRNA was upregulated in lung and colon adenocarcinomas. Lung cancer cell lines exhibited elevated METTL3 protein expression, and METTL3 depletion reduced cell growth and invasive ability, and increased apoptosis. Altogether, these results describe a role for METTL3 in promoting translation of a subset of oncogenes and suggest that it might be a therapeutic target in cancer.


Pancreatic Cancer

Major finding: Mutant SMAD4 PDAC increases tumor cell tension to modulate fibrosis and increase malignancy. Mechanism: Activated STAT3 drives integrin-mediated mecanosignaling to increase tumor cell tension. Impact: Inhibition of genotype-associated tumor cell tension may enhance anti-stromal therapy.

GENOTYPE ADJUSTS FIBROTIC PHENOTYPE TO DRIVE PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC) is associated with pronounced fibrosis, which can either promote tumor progression by physically preventing chemotherapy drugs and immune cells from targeting tumor cells, or inhibit tumor progression by decreasing tumor cell invasion. Elucidation of the relationship between tumor genotype and fibrotic phenotype could identify the PDACs that would benefit from stroma-targeting therapies, such as mesenchymal-like PDACs, which are highly fibrotic, frequently exhibit compromised TGFβ signaling, and are more resistant to treatment than classic PDAC. Laklai and colleagues characterized the fibrotic phenotypes of different PDAC genotypes and found that collagen thickness may be associated with tumor cell tension, and that both were linked to PDAC progression. Similarly, PDACs that exhibited decreased TGFβ signaling or mutant SMAD4 had thickened collagen bundles, which were shown to be stiffer in PDACs harboring mutant SMAD4 by atomic force microscopy. Examination of transgenic mouse models of PDAC revealed that although PDACs driven by mutant Kras and either deletion of Tgfbr2 (KTC) or Tp53 (KPC) had similar levels of collagen and other stromal components, KTC tumors had thicker collagen bundles. KTC tumor cells exhibited Rho kinase 1 (ROCK1)-dependent tumor growth, increased tumor cell tension, and a stiffer fibrotic phenotype compared to KPC or mutant Kras (KC) tumors. Transgenic mouse models of increased b1-integin-driven cell tension exhibited enhanced STAT3 activation and increased PTK2-associated focal adhesion signaling, extracellular matrix (ECM) stiffening, and fibrosis in pancreatic epithelial cells of nontumor mice, and drove ECM remodeling and stiffening, increased fibrosis, and accelerated PDAC progression in KC mice. Consistent with these findings, constitutively activated STAT3 induced fibrosis and quickened PDAC progression. Inhibition of JAK or PTK2 reduced matricellular fibrosis, ECM stiffness, and PDAC development. Together, these results describe a positive feedback loop between tumor cell tension, driven by PDAC genotype-induced mecanosignaling, and fibrosis that promotes tumor progression and aggression.

Genotype Adjusts Fibrotic Phenotype to Drive Pancreatic Cancer

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