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## DNA Repair

**Major finding:** The proteasomal shuttle factor UBQLN4 represses homologous recombination–mediated DNA repair (HRR).

**Mechanism:** UBQLN4 is recruited to DSBs and suppresses HRR by facilitating degradation of ubiquitinated MRE11.

**Impact:** Reduced HRR usage in UBQLN4-overexpressing tumors may confer sensitivity to PARP inhibition.

### UBQLN4 REGULATES DNA REPAIR PATHWAY CHOICE

The DNA damage response (DDR) is a signaling cascade primarily activated following induction of DNA double strand breaks (DSB) by the protein kinase ATM, which phosphorylates multiple substrates to activate the different branches of this vast network. In addition to protein phosphorylation, ubiquitination also occurs at DSB sites, but few ubiquitinated proteins have been identified and the role of this post-translational modification in the DDR is less clear. Jachimowicz and colleagues identified a homozygous germline mutation in ubiquilin 4 (*UBQLN4*), a gene encoding a protein that shuttles ubiquitinated proteins to the proteasome for degradation, in families with an autosomal recessive syndrome with similar clinical manifestations as disorders caused by mutations in DDR genes, suggesting that UBQLN4 may play a role in this process. Consistent with this possibility, UBQLN4-mutant and UBQLN4-deficient cells were hypersensitive to genotoxic agents, and UBQLN4 loss significantly delayed clearance nuclear foci representing unrepaired DSBs. Furthermore, UBQLN4 was shown to be an ATM substrate, and ATM-dependent phosphorylation of UBQLN4 was required for proper DSB repair. Following DSB induction, UBQLN4 interacted with the nuclease MRE11, which normally initiates DSB repair by binding and resecting DSB ends. UBQLN4 bound ubiquitinated MRE11 and promoted its removal from damaged chromatin. The presence of UBQLN4 dictated whether cells used homologous recombination-mediated DNA repair (HRR) or non-homologous end-joining (NHEJ) to repair DSBs, as loss of UBQLN4 increased HRR pathway usage in response to DNA damage and UBQLN4 overexpression led to a significant increase in NHEJ usage relative to HRR. HRR deficiency is a known biomarker of sensitivity to PARP inhibition, and UBQLN4 overexpression, which is observed in a number of human cancers and associated with poor outcome, conferred sensitivity to the PARP inhibitor olaparib *in vitro*. HRR deficiency caused by UBQLN4 overexpression and increased MRE11 turnover may therefore be actionable and potentially expand the number of tumors for which PARP inhibitors might be effective. ■

*Jachimowicz RD, Beleggia F, Isensee J, Bhavana Velpula B, Goergens J, Bustos MA, et al. UBQLN4 represses homologous recombination and is overexpressed in aggressive tumors. Cell 2019 Jan 3 [Epub ahead of print].*

## Translation

**Major finding:** Methylation of eEF1A by METTL13 is required for KRAS-driven pancreatic and lung tumorigenesis.

**Mechanism:** METTL13-driven dimethylation of eEF1AK55 increases protein synthesis and cancer cell proliferation.

**Impact:** METTL13 depletion inhibits tumor growth and sensitizes cancer cells to PI3K/mTOR inhibitors.

### KRAS-DRIVEN CANCERS ARE DEPENDENT ON METTL13-MEDIATED eEF1A METHYLATION

Upregulation of protein translation is a hallmark of many oncogene-driven tumors and is essential to sustain neoplastic growth. However, the mechanisms underlying this increase in protein synthesis and whether it represents a potential therapeutic vulnerability remain incompletely understood. Liu, Hausmann, and colleagues found that the eukaryotic elongation factor 1α (eEF1A), a GTPase that is a nonribosomal component of the translational machinery, is dimethylated at lysine 55 (eEF1AK55me2) by the lysine methyltransferase METTL13. *In vitro* methylation assays and quantitative proteomics analysis defined methylation of eEF1AK55 as the primary physiologic activity of METTL13. METTL13-mediated methylation of eEF1AK55 enhanced the basal GTPase activity of eEF1A, leading to an increase in global protein synthesis in pancreatic and lung cancer cells. Expression of METTL13 and methylation of eEF1AK55 were increased in human pancreatic and lung cancer samples and correlated with poor patient survival, suggesting a role for METTL13-driven modification of eEF1A in tumorigenesis. Consistent with this idea, depletion of METTL13 or eEF1A inhibited pancreatic cancer cell proliferation, and this effect could be rescued by expression of wild-type METTL13 or eEF1A, but not catalytically inactive METTL13 or eEF1A with a mutation at K55. In addition, deletion of METTL13 and subsequent loss of eEF1AK55me2 suppressed the growth of KRAS-driven tumors in mice and primary human pancreatic and lung cancer patient-derived xenografts (PDX). Furthermore, depletion of METTL13 increased the sensitivity of cancer cells to drugs targeting growth signaling via the PI3K–mTOR and MAPK pathways; combined deletion of METTL13 and treatment with a dual pan-PI3K/mTOR inhibitor significantly inhibited pancreatic and lung PDX tumor growth. These findings identify METTL13-catalyzed methylation of eEF1AK55 as a critical mechanism by which KRAS-driven tumors sustain increased protein synthesis to promote tumorigenesis and suggest the METTL13–eEF1AK55me2 axis as a potential therapeutic target. ■

*Liu S, Hausmann S, Carlson SM, Fuentes ME, Francis JW, Pillai R, et al. METTL13 methylation of eEF1A increases translational output to promote tumorigenesis. Cell 2018 Dec 28 [Epub ahead of print].*

AACR American Association for Cancer Research

CANCER DISCOVERY

# KRAS-Driven Cancers Are Dependent on METTL13-Mediated eEF1A Methylation

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