DNA Damage

**Major finding:** m^6^A RNA methylation rapidly recruits Pol κ to UV-induced damage sites to facilitate DNA repair.

**Concept:** UV damage-induced m^6^A methylation of poly(A)^+^ transcripts is added by METTL3 and removed by FTO.

**Impact:** An RNA-mediated response to UV-induced DNA damage promotes rapid DNA repair and cell survival.

### ULTRAVIOLET-INDUCED DNA DAMAGE PROMOTES RNA M^6^A METHYLATION

The DNA damage response (DDR) detects and repairs DNA damage and halts cell division until the DNA damage is repaired. Chromatin modifications render the damaged region accessible to repair machinery and prevent gene transcription using the damaged template. Xiang, Laurent, Hsu, and colleagues performed a screen to identify chromatin modifications and modifying factors involved in the DDR. DNA damage induced by UV radiation was associated with rapid accumulation of methylation at the 6 position of adenosine (m^6^A) in RNA at DNA damage sites. The m^6^A accumulation was specific to UV-induced damage, dose-dependent, and peaked two minutes after irradiation, with accumulation detectable on poly(A)^+^ RNA. The m^6^A methyltransferase METTL3 was responsible for RNA m^6^A methylation in response to UV-induced DNA damage, and the demethylase FTO opposed METTL3 to remove m^6^A at DNA damage sites. METTL3 catalytic activity enhanced the survival of cells after UV irradiation, and loss of METTL3 resulted in increased UV sensitivity. Mechanistically, METTL3 promoted immediate recruitment of the DNA polymerase Pol κ, which is involved in both nucleotide excision repair and trans-lesion synthesis pathways. Pol κ recruitment to damage sites is compromised by the loss of METTL3 catalytic activity and is associated with delayed removal of cyclobutane pyrimidine dimers, the main lesion induced by UV exposure. Notably, the METTL3/m^6^A-mediated recruitment of Pol κ occurred more rapidly than recruitment of the classic RAD18/PCNA components, suggesting that Pol κ might be acting through a noncanonical DNA repair pathway. Taken together, these results describe an unexpected role for RNA methylation in facilitating repair of UV-induced DNA lesions, thereby promoting resistance to UV damage and cell survival. ■


### Breast Cancer

**Major finding:** Targeting Pi3Kα enhances KMT2D methyltransferase activity to promote ER-mediated transcription.

**Mechanism:** Pi3Kα inhibition promotes KMT2D-mediated recruitment of ER, FOXA1, and PBX1 to chromatin.

**Impact:** Dual inhibition of PI3K and KMT2D may be more effective than PI3K inhibition alone in ER^+^ breast cancer.

### PI3K SIGNALING REGULATES ER ACTIVITY VIA KMT2D IN ER^+^ BREAST CANCER

Activating mutations in PIK3CA (encoding PI3Kα) occur frequently in estrogen receptor (ER)^+^ breast cancer, and PI3K signaling promotes breast tumorigenesis. PI3Kα inhibitors have antitumor activity in patients with PIK3CA-mutant ER^+^ breast cancer, but a compensatory increase in ER-mediated transcription limits the duration of response. Toska and colleagues investigated the mechanisms by which PI3Kα inhibitors promote ER signaling. Chromatin immunoprecipitation sequencing in breast cancer cells revealed that PI3Kα inhibition enhanced ER binding to chromatin and also promoted binding of the transcription factors FOXA1 and PBX1, which were required for PI3Kα inhibitor-mediated ER activation. In breast cancer xenografts, the antitumor activity of the PI3Kα inhibitor BYL719 was enhanced by the depletion of FOXA1 or PBX1, further demonstrating that FOXA1 and PBX1 promote ER activation in response to PI3Kα inhibition. PI3Kα inhibition remodeled the chromatin landscape, increasing chromatin accessibility and promoting ER-dependent transcription in BYL719-treated cells and tumor biopsies. BYL719-mediated ER activation was induced by the histone methyltransferase KMT2D, which mono- and dimethylated histone 3 lysine 4 (H3K4me1/2) to promote recruitment of FOXA1, PBX1, and ER to specific chromatin sites. Accordingly, KMT2D depletion reduced the ER, FOXA1, and PBX1 chromatin binding, and increased the antitumor activity of BYL719 in vitro and in vivo, indicating that KMT2D inhibitors might increase the sensitivity to PI3Kα inhibitors in patients with ER^+^ breast cancer. Mechanistically, PI3Kα inhibition relieved AKT-dependent phosphorylation of KMT2D at S1331, thereby activating KMT2D and enhancing ER activity. In addition to elucidating a mechanism by which PI3Kα inhibition promotes ER signaling, these findings suggest that KMT2D inhibition may enhance the efficacy of PI3Kα inhibition in patients with ER^+^ breast cancer. ■


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