

Figure S1. Integrated ubiquitin-m⁶A crosstalk networks in the PI3K/AKT signaling pathway. This schematic illustrates the bidirectional interplay between ubiquitination and m⁶A RNA methylation that converges to hyperactivate the PI3K/AKT axis in cancer. The left portion of the network depicts the ubiquitin-mediated regulation of the m⁶A machinery, where the E3 ligase TRIM17 catalyzes the polyubiquitination and subsequent proteasomal degradation of the m⁶A eraser FTO. This depletion of FTO activity leads to an accumulation of m⁶A marks on the PDK1 transcript, enhancing its mRNA stability and resulting in elevated PDK1 protein levels that facilitate phosphorylation-dependent AKT activation. Reciprocally, the right portion illustrates m⁶A-mediated regulation of the ubiquitination machinery, in which the m⁶A writer METTL3 modifies the mRNA of the ubiquitin-conjugating enzyme UBE2C to upregulate its expression, which further stimulates PI3K/AKT signaling activity. Together, these mechanisms form an intricate regulatory loop where post-translational and epitranscriptomic modifications mutually control the abundance of each other's components, collectively fine-tuning the amplitude of oncogenic signaling and promoting malignant phenotypes. Figure generated using online illustrations generating software Biorender (<https://app.biorender.com/>). TRIM17, tripartite motif-containing 17; FTO, fat mass and obesity-associated protein; m⁶A, N⁶-methyladenosine; Ub, ubiquitin; PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B (also known as AKT serine/threonine kinase); METTL3, methyltransferase-like 3; UBE2CU, ubiquitin-conjugating enzyme E2 C.

