DNA double-strand breaks (DSB), one of the most toxic forms of DNA damage, are primarily repaired in eukaryotic cells by one of two mechanisms, homologous recombination (HR) or non-homologous end-joining (NHEJ), and faulty DSB repair in normal cells is a major driver of cancer. It has previously been shown that decreased fumarase (FH), which metabolizes fumarate, impairs DNA damage repair and promotes tumorigenesis; however, the mechanisms underlying FH-dependent DNA repair are unclear. Jiang and colleagues found that exposure to ionizing radiation (IR), the major exogenous cause of DSBs, resulted in increased binding of FH to histones, in particular the histone variant H2A.Z. Chromatin immunoprecipitation analyses revealed that H2A.Z promoted the recruitment of FH to DSBs, which was necessary for accumulation of the Ku70–Ku80 heterodimer, a central component of the DNA-dependent protein kinase (DNA-PK) holoenzyme that mediates NHEJ. IR induced DNA-PK-mediated phosphorylation of FH at Thr236, resulting in FH and DNA-PK complex binding specifically at DSBs and stimulation of NHEJ-dependent, but not HR-dependent, repair. Furthermore, FH-driven local generation of fumarate at DSBs inhibited lysine (K)-specific demethylase 2B (KDM2B)–mediated demethylation of dimethylated histone H3 Lys36 (H3K36me2), leading to increased association of Ku70 at DSBs, enhanced NHEJ, and increased cell survival in cell lines representing multiple tumor types. Taken together, these results delineate a feedback mechanism of reciprocal regulation between FH and DNA-PK that modulates histone methylation and promotes NHEJ-driven repair of DSBs and survival of cancer cells. In addition, these findings provide evidence of the critical roles of chromatin-localized FH and its metabolic product fumarate in cellular functions independent of metabolism.


**CHROMATIN-ASSOCIATED FUMARASE IS ESSENTIAL FOR DNA DSB REPAIR**

**Major finding:** Fumarase (FH) and DNA-PK regulate each other in a feedback manner to drive DNA DSB repair.

**Mechanism:** FH-generated fumarate inhibits KDM2B-mediated histone H3K36me2 demethylation to promote NHEJ repair.

**Impact:** Metabolic enzymes can respond to extracellular stimuli by regulating nonmetabolic cellular activities.

**YAP/TAZ ARE EFFECTORS OF ALTERNATIVE WNT SIGNALING**

WNT proteins regulate a variety of signaling pathways that control development and tissue homeostasis. Canonical WNT signaling utilizes β-catenin/TCF as transcription factors for downstream signal transduction, but effectors of alternative WNT signaling are less clearly defined. Park and colleagues characterized the YAP/TAZ transcriptional coactivators as downstream effectors of the alternative WNT signaling pathway. The WNT ligands WNT3A and WNT5A/B stabilized YAP/TAZ protein levels, induced their nuclear translocation, and resulted in YAP/TAZ target gene expression. Pharmacologic or genetic perturbation of canonical WNT/β-catenin signaling did not affect YAP/TAZ stability or activity, supporting the hypothesis that YAP/TAZ are exclusively activated via the alternative WNT signaling axis. Activation of YAP/TAZ was mediated by signaling of the Frizzled (FZD) receptor family and retinoic acid–related orphan receptors (ROR) via the G proteins Gα12,13 as depletion of Gα12,13 attenuated WNT3A-mediated YAP/TAZ activation. Similarly, mutation or inhibition of the RHO GTPases RHOA and RAC1 blocked WNT3A- and FZD-induced YAP/TAZ activation. Activated RHOA inhibited LATS1/2 kinases, which reduced their inhibitory phosphorylation of YAP/TAZ, demonstrating that FZD/ROR-driven activation of G-protein signaling promotes nuclear translocation and activation of YAP/TAZ. YAP/TAZ were required for alternative WNT–induced osteogenic differentiation and cell migration. Furthermore, activation of YAP/TAZ decreased the accumulation of β-catenin and β-catenin/TCF target gene expression; this inhibition was the result of YAP/TAZ–TEAD-mediated transcriptional upregulation of secreted factors known to block canonical WNT/β-catenin signaling, including WNT5A/B. Consistent with these findings, YAP/TAZ promoted adipogenesis by suppressing the anti-adipogenic effects of canonical WNT/β-catenin signaling, and YAP/TAZ–TEAD was required for WNT5A induction in PIK3CA-mutant cells. Overall, these data identify YAP/TAZ as transcriptional coactivators that mediate the biologic functions of the alternative WNT signaling axis and antagonize canonical WNT/β-catenin signaling.


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YAP/TAZ Are Effectors of Alternative WNT Signaling


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