RESEARCH WATCH

DNA Repair

**Major finding:** H3K36me3 interacts with MSH6 to recruit the MutSα mismatch repair (MMR) complex to chromatin.

**Concept:** Loss of the H3K36me3 methyltransferase SETD2 causes microsatellite instability and hypermutability.

**Impact:** Microsatellite instability-positive cancers without mutations in MMR genes may lack SETD2/H3K36me3.

**HISTONE H3 K36 TRIMETHYLATION IS REQUIRED FOR MISMATCH REPAIR**

Mismatch repair (MMR) proteins correct base mispairs caused by incorrect nucleotide incorporation or small insertions and deletions during DNA replication. Loss of MMR gene expression induces a mutator phenotype marked by increased microsatellite instability (MSI) and mutational frequency that predisposes to cancer. However, a subset of MSI-positive cancers express normal levels of MMR genes and appear to be MMR proficient, indicating that other mechanisms underlying MSI remain to be identified. As most MMR studies have been performed in vitro with naked DNA, additional MMR factors are likely needed in vivo in the context of chromatin. Because the MutS homolog 6 (MSH6) subunit of the MutSα MMR complex has a Pro-Trp-Trp-Pro (PWWP) domain capable of recognizing the histone H3 Lys36 trimethylation mark (H3K36me3), Li and colleagues hypothesized that H3K36me3 might play a role in recruiting MutSα to chromatin. Indeed, the MSH6 PWWP domain specifically bound H3K36me3 and was required for formation of MSH6 nuclear foci in cells even though it was not required for MMR in vitro. The majority of MSH6 foci colocalized with H3K36me3, which peaked in abundance in early S-phase, consistent with a role of H3K36me3 in MMR during DNA replication. Knockdown of the H3K36me3 methyltransferase SET domain containing 2 (SETD2) depleted H3K36me3 and significantly reduced MSH6 foci. Moreover, SETD2/H3K36me3-depleted cells showed a significant increase in MSI and mutation frequency, indicating that loss of SETD2 or H3K36me3 confers a mutator phenotype. Notably, several human cancer cell lines with MSI but no known MMR gene mutations or MMR defect in vitro were found to have inactivating SETD2 mutations, H3K36me3 depletion, and diminished S-phase MSH6 foci formation. These findings thus not only provide insight into how MSI occurs in vivo but also offer an explanation for how MSI can occur in the absence of MMR gene mutation.


Targeted Therapy

**Major finding:** Disruption of IQGAP1 scaffold function inhibits oncogenic ERK signaling without toxicity.

**Clinical relevance:** An IQGAP1 peptide reduces RAS/RAF-driven tumor growth and bypasses vemurafenib resistance.

**Impact:** Blockade of scaffold-kinase interactions can complement direct kinase inhibition.

**SCAFFOLD BLOCKADE INHIBITS ONCOGENIC KINASE SIGNALING**

The clinical effectiveness of mitogen-activated protein kinase (MAPK) pathway kinase inhibitors is often limited by acquired resistance and by toxicities caused by inhibition of essential kinases in normal cells. Jameson and colleagues hypothesized that disruption of IQ motif-containing GTPase activating protein 1 (IQGAP1), an intracellular scaffold protein that binds and facilitates interactions among RAF, MAP-ERK kinase (MEK), and ERK, might represent an alternative approach to suppress MAPK signaling and may circumvent resistance mechanisms associated with direct kinase inhibition. Furthermore, because Igqap1-null mice are viable and fertile, IQGAP1 may likely be safely targetable in human cells. Consistent with a role for IQGAP1 in tumorigenesis, Igqap1 was required for Hras-driven tumor formation in mice. IQGAP1 depletion also suppressed basement membrane degradation and invasion in RAS-transformed human epidermal tissue but did not cause the hypoplastic tissue collapse seen with ERK inhibition, likely because depletion of IQGAP1 did not completely eliminate ERK kinase activity. Blockade of the IQGAP1–ERK interaction through lentiviral expression of the IQGAP1 WW domain required for ERK binding or use of a cell-permeable IQGAP1 WW peptide blocked IQGAP1 from binding to ERK, suppressed ERK activation, and specifically impaired proliferation and invasion in cancer cell lines with MAPK activation caused by KRAS or BRAF mutation. IQGAP1 blockade also inhibited growth of established MAPK pathway–mutant tumors, and systemic WW peptide delivery significantly slowed progression of murine tumor models without detectable morbidity. Importantly, BRAF-mutant melanoma cell lines with acquired resistance to the kinase inhibitor vemurafenib retained sensitivity to the IQGAP1 WW peptide, providing further evidence that scaffold and direct kinase inhibition are non-redundant. Together, these findings support clinical development of inhibitors of IQGAP1 scaffold activity and provide proof-of-principle that targeting scaffold-kinase interactions can complement existing approaches to inhibit oncogenic kinase signaling.

Histone H3 K36 Trimethylation Is Required for Mismatch Repair

Cancer Discovery 2013;3:600. Published OnlineFirst May 2, 2013.

Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-RW2013-092

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