Targeted Therapy

Major finding: Disruption of the menin–MLL interaction inhibits MLL leukemia without affecting normal hematopoiesis.

Concept: Menin is a required cofactor for MLL fusion protein–driven leukemic transformation.

Impact: Small-molecule inhibition of menin–MLL may be a viable therapeutic approach for acute MLL leukemias.

TARGETING THE MENIN–MLL INTERACTION BLOCKS ACUTE LEUKEMIA PROGRESSION

Chromosomal translocations of the mixed-lineage leukemia (*MLL*) gene frequently occur in aggressive acute leukemias affecting both children and adults. All MLL fusion proteins retain the N-terminal fragment of MLL that binds menin, a necessary cofactor for MLL fusion protein–induced oncogenic transformation, but not normal hematopoiesis. Genetic deletion of *Men1* (which encodes menin) suppresses acute leukemia development, suggesting that the menin–MLL interaction may be an attractive therapeutic target. Borkin, He, Miao, and colleagues developed two small-molecule inhibitors that bound menin with low nanomolar affinity, potently blocked the menin–MLL interaction, and exhibited favorable pharmacokinetic profiles. These pharmacologic inhibitors showed selective, on-target activity in MLL leukemia cells, but not leukemia cells lacking *MLL* translocations, resulting in growth suppression and induction of differentiation *in vitro*. Analysis of global gene expression profiles showed that inhibitor treatment downregulated MLL target genes implicated in leukemogenesis, such as homeobox genes, and upregulated genes associated with myeloid differentiation. Furthermore, single-agent treatment with menin–MLL inhibitors significantly reduced tumor volume, delayed leukemia progression, and increased survival in both xenograft and xenotransplantation mouse models of MLL leukemia. Consistent with these findings, menin–MLL inhibitors reduced the clonogenic growth of patient-derived MLL leukemia samples, but had little effect on primary acute myelogenous leukemia patient samples without *MLL* translocations. Importantly, prolonged administration of menin–MLL inhibitors did not induce toxicity or impair normal hematopoiesis *in vivo*, supporting a therapeutic window for these compounds. Together, these studies highlight small-molecule inhibition of the menin–MLL interaction as a viable therapeutic approach for acute *MLL*-rearranged leukemia and support further optimization to identify clinical lead compounds. ■

Borkin D, He S, Miao H, Kempinska K, Pollock J, Chase J, et al. Pharmacologic inhibition of the menin-MLL interaction blocks progression of MLL leukemia in vivo. Cancer Cell 2015 Mar 26 [Epub ahead of print].

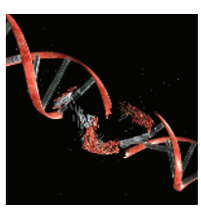
DNA Repair

Major finding: MAD2L2 promotes NHEJ at exposed DNA ends by inhibiting CTIP-dependent 5′ end resection.

Clinical relevance: Restoration of HR via MAD2L2 loss may drive PARP inhibitor resistance in BRCA1-deficient cancers.

Impact: MAD2L2 regulates DNA repair choices downstream of 53BP1 and RIF1 and independent of DNA Polζ.

MAD2L2 PROMOTES NHEJ AT DSBs AND TELOMERES VIA 5′ END RESECTION INHIBITION



Proper regulation of error-free homologous recombination (HR)–mediated repair at DNA double-strand breaks (DSB) and telomeres is required for genomic stability and is orchestrated by a complex network of proteins including BRCA1. Defects in HR activity fuel the acquisition of genomic alterations and confer dependency on parallel DNA repair pathways that have been targeted using PARP1 inhibitors. To identify regulators of telomere-induced genomic instability and nonhomologous end-joining (NHEJ)–dependent repair of uncapped telomeres, Boersma, Moatti, and colleagues performed a functional genetic screen. Suppression of mitotic arrest deficient-like 2 (MAD2L2, also known as REV7) prevented telomere fusion and enhanced cell survival. Mechanistically, MAD2L2 was recruited to exposed telomeres and sites of irradiation-induced DSBs and promoted NHEJ activity in multiple contexts by inhibiting CtBP-interacting protein (CTIP)–dependent and exonuclease 1–dependent 5′ DNA end resection independent of PAX-interacting protein 1 and the other components of DNA polymerase ζ (Polζ), REV1 and REV3. In a parallel study, Xu, Chapman, Brandsma, and colleagues identified MAD2L2 suppression as a mediator of resistance to the PARP1 inhibitor olaparib in BRCA1-deficient tumor cells both *in vitro* and *in vivo*. MAD2L2 depletion promoted olaparib resistance by increasing CTIP-dependent DNA end resection, restoring HR activity in BRCA1-deficient cells independent of the Polζ-associated function in translesion synthesis. Importantly, both groups found that MAD2L2 recruitment to DSBs was dependent on ATM kinase activity, histone H2AX, mediator of DNA damage checkpoint 1, ring finger protein 8 (RNF8), RNF168, and p53-binding protein 1 (53BP1), with Boersma, Moatti, and colleagues also showing dependence on RAP-interacting factor 1 (RIF1). In addition, both groups found that MAD2L2 loss inhibited NHEJ activity and decreased class switch recombination, similar to the effects of 53BP1 ablation. Together, these data highlight a critical role for MAD2L2 in the regulation of DNA repair pathway decisions downstream of 53BP1 and suggest that MAD2L2 loss may compromise genomic integrity. ■

Boersma V, Moatti N, Segura-Bayona S, Peuscher MH, van der Torre J, Wevers BA, et al. MAD2L2 controls DNA repair at telomeres and DNA breaks by inhibiting 5′ end resection. Nature 2015 Mar 23 [Epub ahead of print].

Xu G, Chapman JR, Brandsma I, Yuan J, Mistrik M, Bouwman P, et al. REV7 counteracts DNA double-strand break resection and affects PARP inhibition. Nature 2015 Mar 23 [Epub ahead of print].