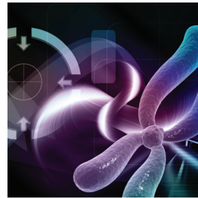
Cell Cycle

Major finding: Inhibiting assembly of the BRCA1–PALB2–BRCA2 complex suppresses homologous recombination in G1 phase.

Mechanism: Ubiquitylation of PALB2 by CRL3–KEAP1 blocks its interaction with BRCA1, and is reversed by USP11.

Impact: Inducing homologous recombination in G1 cells might allow for gene targeting in nondividing cells.

CELL-CYCLE REGULATION OF BRCA1 INHIBITS HOMOLOGOUS RECOMBINATION IN G1



The tumor suppressors BRCA1, partner and localizer of BRCA2 (PALB2), and BRCA2 form a complex that promotes DNA double-strand break (DSB) repair by homologous recombination, which is repressed in G1 cells; however, the mechanism by which homologous recombination is suppressed is unknown. Orthwein, Noordermeer, and colleagues showed that recruiting BRCA1 to DSBs during G1 by mutating tumor protein p53 binding protein1 (53BP1) did not result in the recruitment of BRCA2 or PALB2. PALB2 interacted with BRCA2 throughout the cell cycle, but interacted with BRCA1 only during S phase, suggesting that the cell cycle controls the assembly of the BRCA1–PALB2–BRCA2 complex and prevents BRCA2 from localizing to DSBs outside of the S/G2 phases. The domain of PALB2 that interacts with kelch-like ECH-associated protein 1 (KEAP1) was required for the cell-cycle–dependent regulation of the BRCA1–PALB2 interaction. KEAP1, a substrate adaptor for a cullin 3–RING ubiquitin ligase (CRL3), was found to ubiquitylate lysine residues 20, 25, and 30 in the N-terminus of PALB2, which blocked its interaction with BRCA1 and prevented the assembly of the BRCA1–PALB2–BRCA2 complex in G1 phase. Ubiquitin specific peptidase 11 (USP11) removed ubiquitin from PALB2, promoting BRCA1–PALB2–BRCA2 complex formation. USP11 rapidly turned over in G1 cells, consistent with the loss of the BRCA1–PALB2–BRCA2 complex. Homologous recombination could be triggered in G1 cells, but required both activation of DNA-end resection and BRCA2 recruitment to DSBs. These findings reveal that the assembly of the BRCA1–PALB2–BRCA2 complex is an essential step in controlling the cell-cycle regulation of homologous recombination, and indicate that suppression of homologous recombination during G1 phase is reversible, which may have implications for therapeutic gene targeting in nondividing cells. ■

Orthwein A, Noordermeer SM, Wilson MD, Landry S, Enchev RI, Sherker A, et al. A mechanism for the suppression of homologous recombination in G1 cells. Nature 2015;528:422–6.

Glioma

Major finding: Disrupted CTCF binding at the *PDGFRA* boundary element enhances its expression, promoting glioma growth.

Mechanism: *IDH* mutations disrupt insulator elements by promoting CTCF binding site hypermethylation.

Impact: Activation of oncogenes by the disruption of chromosomal topology may occur in other tumor settings.

IDH MUTATIONS PROMOTE GLIOMA THROUGH EPIGENETIC INSULATOR DISRUPTION

Gain-of-function mutations in isocitrate dehydrogenase (*IDH*) lead to the production of 2-hydroxyglutarate, which disrupts the activity of the TET family DNA demethylases and thus can contribute to CpG island hypermethylation. However, the functional relevance of enhanced CpG methylation in glioma is not well understood. CCCTC-binding factor (CTCF) is a methylation-sensitive insulator protein involved in creating chromatin boundaries. To determine if IDH-dependent hypermethylation altered CTCF binding, Flavahan, Drier, and colleagues performed CTCF chromatin immunoprecipitation sequencing (ChIP-seq) of gliomas, and obtained DNA methylation profiles from The Cancer Genome Atlas. CTCF occupancy was reduced at more sites than it was increased in *IDH*-mutant gliomas, and the CTCF-deficient sites had higher GC content and increased DNA methylation than *IDH*–wild-type gliomas. Based on constitutive domain boundaries and RNA-seq data, *IDH* mutant gliomas had an increased correlation between genes normally insulated from each other by topological domain boundaries. The increased correlation raised the possibility that reduced CTCF binding in *IDH*-mutant gliomas may disrupt topological domain boundaries. Approximately 200 domain boundaries disrupted by *IDH* mutation were identified, and genes located adjacent to these boundaries showing increased expression in *IDH*-mutant gliomas included known glioma oncogenes such as *PDGFRA*. In *IDH*-mutant gliomas, *PDGFRA* expression was correlated with expression of *FIP1L1*, a housekeeping gene normally located in a distinct domain separated from *PDGFRA* by a CTCF-bound constitutive boundary. In *IDH*-mutant gliomas, CTCF occupancy at this boundary was reduced, and the *PDGFRA* promoter interacted with the *FIP1L1* enhancer instead of its cognate enhancer as in *IDH*–wild-type glioma. Treatment with the DNA methyltransferase inhibitor 5-azacytidine reduced methylation of the CTCF motif, increased CTCF binding, and downregulated *PDGFRA*. Conversely, CRISPR-mediated disruption of the CTCF boundary element also increased *PDGFRA* expression, and promoted glioma cell growth. Altogether, these findings demonstrate that *IDH* mutations can promote glioma growth through disruption of boundary elements and impaired oncogene insulation. ■

Flavahan WA, Drier Y, Liau BB, Gillespie SM, Venteicher AS, Stemmer-Rachamimov AO, et al. Insulator dysfunction and oncogene activation in IDH *mutant gliomas. Nature 2016;529:110–4.*

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