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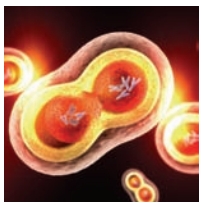
Mitosis

Major finding: ATR localized to centromeres to prevent lagging chromosomes independent of its role in replication stress.

Mechanism: ATR engages centromeric R loops in mitosis to activate Aurora B via CHK1 to prevent lagging chromosomes.

Impact: ATR may be a therapeutic target in cancer cells vulnerable to chromosomal instability and replication stress.

ATR PROMOTES FAITHFUL CHROMOSOME SEGREGATION IN MITOSIS



The ATR kinase is an essential component of the response to DNA damage and replication stress, and loss of ATR during DNA replication increases genomic instability in S phase. Thus, ATR is a master regulator of genome integrity. Unexpectedly, Kabeche and colleagues found that ATR localized to centromeres on mitotic chromosomes, suggesting a potential role for ATR in chromosome segregation. Inhibition of ATR increased the rate of lagging chromosomes in anaphase, indicating a role for ATR in promoting accurate whole-chromosome segregation separate from its S-phase functions. Mechanistically, ATR phosphorylated CHK1 at centromeres, which subsequently activated Aurora B to facilitate correction of erroneous microtubule attachments at kinetochores. ATR localization to the mitotic centromeres was dependent on Aurora A, CENP-F, and R loops (DNA–RNA hybrids with a displaced single-stranded DNA), and ATR colocalized with RPA, which serves as a sensor for ssDNA in R loops. RPA-coated R loops generated by RNA polymerase II–mediated transcription during mitosis were detected at centromeres in mitotic cells and promoted ATR activation. R-loop stabilization facilitated ATR-mediated Aurora B activation and faithful chromosome segregation. Collectively, these findings reveal a role for ATR in promoting faithful chromosome segregation in mitosis to maintain genomic stability that is independent of its S-phase role in the DNA damage response. Further, these results suggest that ATR may be an effective therapeutic target in cancer cells that are vulnerable to defects in both chromosomal instability and replication stress. ■

Kabeche L, Nguyen HD, Buisson R, Zou L. A mitosis-specific and R loop–driven ATR pathway promotes faithful chromosome segregation. Science 2017 Nov 23 [Epub ahead of print].

DNA Repair

Major finding: DNA mismatch repair in tumors promotes enhanced immune surveillance.

Concept: Loss of DNA mismatch repair drives hypermutation to increase the tumor neoantigen repertoire.

Impact: Inhibition of DNA repair processes is a potential adjuvant approach for immunotherapy.

LOSS OF DNA REPAIR DRIVES NEOANTIGEN RENEWAL AND INHIBITS TUMOR GROWTH

Mutations in genes associated with DNA mismatch repair (MMR), such as *MLH1*, result in a microsatellite instability (MSI) phenotype and promote tumor initiation and growth; however, MMR-deficient cancers are associated with favorable prognosis. It has recently been shown that immune checkpoint blockade is more efficacious in patients with MSI tumors than in patients with microsatellite stable (MSS) tumors. To elucidate the role of MMR in tumorigenesis and immunotherapy response, Germano and colleagues performed CRISPR/Cas9-mediated targeting of *Mlh1* in murine breast, colon cancer, and pancreatic ductal adenocarcinoma cells to generate isogenic sets of MMR-proficient and MMR-deficient cell lines. While both MMR-proficient and MMR-deficient cells grew at similar rates and rapidly formed tumors in immunocompromised mice, only MMR-proficient cells formed subcutaneous and orthotopic tumors in immune-competent syngeneic mice; however, transplantation of MMR-deficient tumors grown in immunocompromised mice to immune-competent mice resulted in tumor growth. Treatment with combined anti–PD-1 and anti-CTLA4 antibodies resulted in decreased growth of transplanted MMR-deficient tumors, but not MMR-proficient tumors, in immune-competent mice. Consistent with these findings, MMR-deficient cells formed tumors in immune-competent mice depleted of $CD8^+$ T cells. Longitudinal exome sequencing revealed that mutational load, the number of neoantigens, and T-cell receptor diversity increased over time in MMR-deficient, but not MMR-proficient, cells. Further, treatment with the genotoxic agent temozolomide inactivated MMR in MMR-proficient cancer cells, resulting in increases in mutational load and neoantigens and enhanced tumor immune surveillance *in vivo*. Similarly, decreased expression of the DNA repair enzyme MGMT in human cancer cells and tumors treated with temozolomide was associated with alterations in MMR genes and high tumor mutation burden and number of neoantigens. These findings show that MMR deficiency induces neoantigen production to promote durable immune surveillance and suggest that inactivation of DNA repair may enhance the immunogenicity of MSS tumors. ■

Germano G, Lamba S, Rospo G, Barault L, Magrì A, Maione F, et al. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. Nature 2017;552:116–20.

AACR American Association for Cancer Research

CANCER DISCOVERY

Loss of DNA Repair Drives Neoantigen Renewal and Inhibits Tumor Growth

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