MBG FOCUS TALK

Hosted by Tinna Stevnsner

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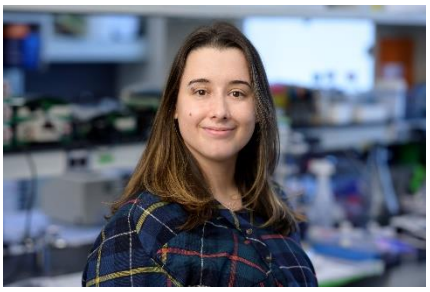
NUCLEUS (1871-120)



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The role of non-canonical double-strand break repair pathways in genome stability

DNA Double-strand breaks (DSB) are genotoxic lesions that contribute to genome instability, a driver of aging, cancer, and neurodegeneration. Cells have evolved various DSB repair pathways, including non-homologous end joining (NHEJ) and homologous recombination (HR). While NHEJ and HR are well-characterized, my research focuses on two non-canonical yet important pathways for genome stability: microhomology-mediated end joining (MMEJ) and RNA-mediated DSB repair.

MMEJ is a highly error-prone pathway driven by the key factor DNA Polymerase θ (*POLQ*). When canonical pathways of DSBs repair are absent, cells rely on MMEJ for survival. Given the synthetic lethality between MMEJ and HR, Polθ inhibitors are being tested in the clinical settings. My work reveals that MMEJ is the exclusive DSB repair pathway during mitosis, when canonical pathways are inactive. I uncovered a key role for RHINO in confining MMEJ activity to mitosis and showed that MMEJ repairs persistent DSBs that originate in the previous S phase. This finding provides new insights into the synthetic lethality between *POLQ*and HR factors *BRCA1/2* and supports the clinical exploration of Polθ and PARP inhibitors.

In a separate study, I found that human cells utilize RNA transcripts for DSB repair through reverse transcription (RT-DSBR), with translesion polymerase ζ acting as a reverse transcriptase. We developed a computational algorithm to identify RT-DSBR scars, specifically whole intron deletions (WIDs), in cancer genomes. Our findings suggest that RT-DSBR contributes to genomic instability in human tumors.

These studies highlight the critical roles of MMEJ and RT-DSBR in maintaining genome stability their potential implications in cancer therapy.

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