Sensing of DNA Damage, Replication Stress, and Transcription Problems

ATM and ATR are two master checkpoint kinases in human cells. In particular, ATR is the key responder to a broad spectrum of DNA damage and DNA replication problems. To understand how ATR is activated, we sought to identify the key DNA structural elements and sensor proteins that activate ATR. We have developed unique biochemical and cell biological assays to dissect the process of ATR activation. Our recent studies have revealed that ATR is important not only for sensing DNA damage and replication stress, but also for problems associated with transcription. R loops, which arise from stable DNA:RNA hybrids during transcription, are a major source of genomic instability. We found that ATR is activated by R loops and plays a key role in suppressing R loop-induced genomic instability, thus, uncovering a new function of ATR in safeguarding the genome.

Checkpoint, DNA Replication, DNA Repair, Telomeres, Centromeres and the Cell Cycle

The ATR checkpoint plays a key role in regulating and coordinating DNA replication, DNA repair, and cell cycle transitions. During the past few years, our studies have identified a number of novel roles that ATR plays in protecting the genome, such as: suppressing single-stranded DNA (ssDNA) accumulation during DNA replication, regulating homologous recombination (HR), and promoting alternative lengthening of telomeres (ALT). Recently, we have discovered a surprising function of ATR in mitosis. We have shown that ATR is localized to centromeres in mitosis, where it is activated by centromeric R loops. The activation of ATR at centromeres is critical for faithful chromosome segregation, thus revealing the unexpected importance of ATR in suppressing chromosomal instability (CIN).

RNA, DNA repair and Genomic Integrity

Non-coding RNAs are important components and regulators of chromatin. We are interested in understanding how non-coding RNAs affect DNA repair and genomic stability in specific chromosomal regions.
For example, the telomere non-coding RNA TERRA is upregulated in ALT-positive tumors, and may regulate the lengthening of telomeres through a unique DNA repair pathway. Moreover, centromeric RNAs form R loops in mitotic cells, promoting ATR activation and accurate chromosomal segregation. In addition to non-coding RNAs, our recent studies also suggest that even coding RNA transcripts may directly participate in the repair of DNA breaks, revealing another function of RNA in the regulation of genomic integrity.

**Cancer Genomics, Tumor evolution and Targeted Cancer Therapy**

During the evolution of tumors, cancer cells acquire mutations through a variety of mechanisms. We recently discovered that APOBEC3A/B proteins, two cytidine deaminases that are aberrantly expressed in multiple types of cancers, induce DNA replication stress and render cancer cells susceptible to ATR inhibition. Working with the team of Dr. Michael Lawrence, we find that APOBEC3A prefers substrate sites in DNA hairpins, leading to the discovery of passenger hotspot mutations in cancer. Furthermore, in collaboration with Dr. Tim Graubert, we find that the splicing factor mutations associated with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) induce R loops and trigger an ATR response. Cells that express these splicing factor mutants are sensitive to ATR inhibitors, providing a new strategy for the treatment of MDS and possibly other malignancies associated with RNA splicing defects.

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Selected Publications:


*Co-corresponding authors