Cancer is a complex disease driven by genetic and epigenetic alterations in the genome. To prevent these detrimental alterations, cells have evolved an intricate signaling network, called the DNA damage checkpoint, to detect and signal problems in the genome. During cancer development, the activation of oncogenes and loss of tumor suppressors leads to genomic instability, rendering cancer cells increasingly dependent upon specific DNA repair and checkpoint signaling proteins to survive. The Zou laboratory is particularly interested in understanding how the checkpoint detects DNA damage and genomic instability, and how the checkpoint can be targeted in cancer therapy. Our current studies are focused on understanding the molecular mechanisms by which different types of oncogenic events give rise to replication stress and genomic instability. Furthermore, we are developing new strategies to exploit the genomic instability and checkpoint addiction of different cancer cells in targeted cancer therapy.

Sensing of DNA Damage, Replication Stress, and Genomic Instability

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. We are especially interested in the mechanisms by which ATR is activated by replication stress and its functions in the replication stress response. Our recent studies have revealed that ATR plays an important role in the cellular responses to R loops, which arise from stable DNA:RNA hybrids during transcription. We found that ATR is activated by the collisions between replication forks and R loops, and it suppresses R loop-induced genomic instability through multiple mechanisms. We are extending our investigation to elucidate how ATR protects replication forks at R-loops and how ATR stabilizes the genome in response to aberrant R-loops.

Functions of ATR in regulating 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. 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). We have also developed new assays to understand how the alternative lengthening of telomere (ALT) pathway, which is regulated by ATR, is activated at telomeres. These new assays have helped us establish the framework of the ALT pathway for the first time, and uncovered the key mechanisms by which the ALT pathway is temporarily and spatially regulated during the cell cycle.
Selected Publications:


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, 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.

Functions of transcription and RNA in DNA repair

We are interested in the impacts of RNAs, including coding and non-coding RNAs, on genomic integrity. We recently discovered that RNA transcripts stimulate homologous recombination by forming a novel intermediate that contains both DNA:DNA and RNA:DNA hybrids. This intermediate, which we dubbed DR-loop, enhances the function of RAD51 in donor DNA. Our results demonstrate for the first time that RNA transcripts directly participate in DNA recombination, opening a new avenue to study the roles of RNA in DNA repair. These new findings will significantly change the current view of the functions of RNAs in DNA repair, providing new opportunities for cancer therapy.

Telomeric bridges in an ALT+ cancer cell lacking the BLM helicase. Alternative lengthening of telomere (ALT) is a recombination-based mechanism to extend telomeres in cancer cells. We find that the BLM helicase is critical for resolving telomere recombination intermediates in ALT+ cancer cells. In the absence of BLM, unresolved recombination intermediates at telomeres result in chromosomal bridges in mitosis. Green: telomeres; Red: the telomere-binding protein TRF1; Blue: DNA.

Images were generated by Dr. Jiamin Zhang in the Zou lab.