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 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 the activation of ATR and ATM, the master sensor kinases of two major checkpoint pathways. Furthermore, we are developing new strategies to exploit the genomic instability and checkpoint addiction of different cancer cells in targeted cancer therapy.

Sensing and Signaling of DNA Damage

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. Using both proteomic and genomic approaches, we have identified a number of regulators of the ATR checkpoint and novel functions of this pathway. We are currently investigating the regulation of ATR in different physiological, pathological and therapeutic contexts, such as in response to oncogenic stress, in radiation and drug resistant cancer cells, and during cellular aging.

Checkpoint Signaling, Non-Coding RNA, and Epigenetic Regulation

The signaling of DNA damage through the checkpoint pathway is generally viewed as a cascade of protein phosphorylation events. However, recent studies by us and others have revealed that many types of modifications of proteins and chromatin—such as ubiquitylation, SUMOylation, methylation and acetylation—also contribute to DNA damage signaling. Furthermore, noncoding RNAs have also been implicated in this process. We are currently investigating how this network of
regulatory events is integrated to the DNA damage response.

**Checkpoint Inhibitors and Targeted Cancer Therapy**

While the checkpoint is often compromised in cancers, certain checkpoint proteins are uniquely required for the survival of cancer cells because of the oncogenic events within them. We recently found that BRCA1/2 deficient cancer cells became resistant to PARP inhibitors through bypassing the functions of BRCA1/2 in homologous recombination (HR) and protection of stalled replication forks. Remarkably, inhibition of ATR disrupts the rewired HR and fork protection pathways in resistant cells, resensitizing them to PARP inhibitors. Our findings may bring about a new strategy to overcome the resistance of BRCA deficient tumors to PARP inhibitors.

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**Selected Publications:**


