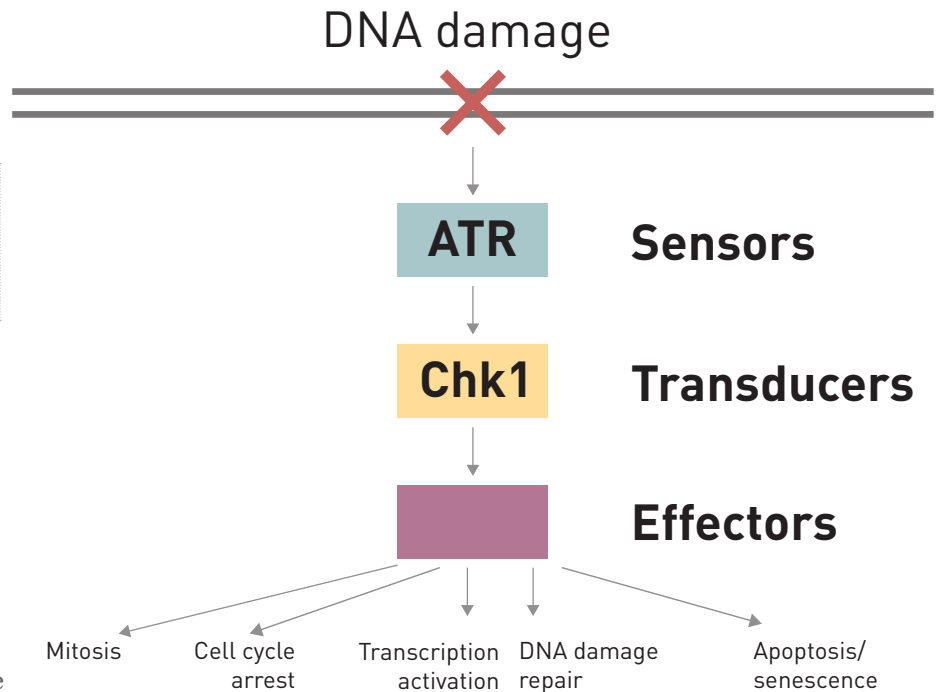


## ATR Inhibition in Tumor Cells

*Can a discovery about mitosis lead to a novel treatment pathway?*

Several genes, and the proteins they produce, play essential roles in maintaining the integrity of DNA in the genome during replication. One of these proteins, the ATR enzyme, controls a signal transduction pathway that protects the genome when cells are duplicating. The ATR checkpoint controls DNA repair, replication and many other cellular processes that keep the genome stable during that process (Figure 1).<sup>1</sup>

An accumulation of genetic mutations in ATR can result in cancer development. Without functional ATR, cells are unable to cope with insults to the genome that result in DNA breaks or mutations. But targeting ATR may, paradoxically, also turn out to be a promising strategy in cancer therapy, according to Lee Zou, PhD, associate scientific director of the Massachusetts General Hospital Cancer Center. Dr. Zou and his colleagues have found unexpected activity of ATR during mitosis, when duplicated chromosomes segregate into new cells.



### DNA Damage Checkpoint Signaling

Figure 1. Sensing DNA damage or replication stress, ATR responds by phosphorylating downstream transducers such as Chk1 (checkpoint kinase 1). Activated Chk1 leads to several downstream effects, including cell cycle arrest, transcription repression or activation, DNA damage repair, and apoptosis or senescence (cell death).

In a paper published in *Science*<sup>2</sup> in January 2018, Dr. Zou and colleagues discovered that when ATR was inhibited in cells undergoing mitosis, the chromosomes did not move properly into these new cells (Figure 2). While researchers have known for some time that ATR is important in protecting the genome during genome replication, the discovery of this ATR activity during mitosis is a milestone. “Others have detected problems in mitosis in the absence of ATR, but they thought it was

an indirect problem occurring when the chromosomes are multiplying,” says Dr. Zou.

### TREATMENT THROUGH PARTIAL ATR INHIBITION

Specifically, interfering with ATR affects the spindle apparatus, a cellular structure that pulls newly duplicated chromosomes to separate daughter cells. “Normally, spindles find the centromere in the middle of a chromosome and pull them in different directions,” says Dr. Zou. When ATR is inhibited, spindles cannot attach to the

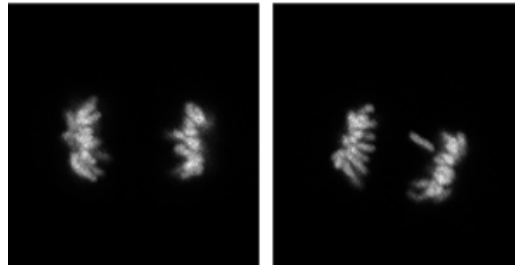
centromere on the chromosome properly. The new daughter cells lack the correct number of chromosomes and do not survive, suggesting that the ATR pathway acts on the centromeres to promote faithful chromosome segregation.

Some cancer cells are innately prone to replication errors during chromosome replication and mitosis, and are therefore more dependent on ATR than normal cells. This raises a new treatment possibility: If cancer cells have difficulties with replication and mitosis, inhibiting ATR may impair these processes even further, leading to the cells' demise.

"The idea is that you do not have to completely take out ATR," explains Dr. Zou. "Even partially inhibiting ATR is sufficient to kill cancer cells. And normal cells can tolerate this partial inhibition." To pursue this theory, his laboratory is investigating several cancer types with known mutations that are sensitive to ATR inhibition. "Right now, we are looking at cancers with mutations of one or more DNA repair or tumor suppressor genes, including ATM, BRCA1 and BRCA2," says Dr. Zou, with a goal of selectively killing cancer cells by ATR inhibition.

### NEXT STEPS FOR ATR TREATMENTS

ATR inhibition has been investigated previously as a cancer



### Lagging Chromosomes Following ATR Inhibition

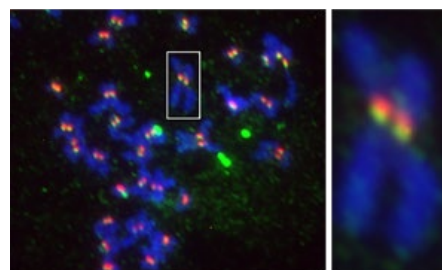
Figure 2. Image on left shows healthy control cells following mitosis. Chromosomes are split equally between daughter cells. Image on right shows a lagging chromosome following ATR inhibition during mitosis.

therapy targeting the chromosome replication cell-cycle phase, but not during mitosis. Some research teams are using ATR inhibitors in combination therapy clinical trials. These trials involve a chemotherapy drug or radiotherapy to induce DNA damage in cancer cells, along with an ATR inhibitor to block DNA repair.

"Now we have discovered a potentially new therapeutic approach: Identify cancer cells that have problems during mitosis, and see if ATR can specifically kill those cancer cells," says Dr. Zou, who is working with other

Cancer Center colleagues to establish clinical trials to test an ATR inhibitor in patients. These trials would use an ATR inhibitor as a single drug to exploit the intrinsic vulnerabilities in cancer cells, without additional agents to induce DNA damage.

"The idea is that if there are cancer cells with problems in both DNA replication and mitosis, an ATR inhibitor may be the best drug to target it," said Dr. Zou. His team is hopeful that they can find biomarkers for these kinds of cancer cells. "That would be a magical combination," he says.



### ATR Centromere Staining

Through fluorescent imaging, Dr. Zou's team also found evidence of ATR located on the centromere, the regions in mitotic chromosomes that control their movements to daughter cells.

<sup>1</sup>Yazinski SA, Zou L. Functions, regulation, and therapeutic implications of the ATR checkpoint pathway. *Annu Rev Genet.* 2016; 50:155-173.

<sup>2</sup>Kabeche L, Nguyen HD, Buisson R, Zou L. A mitosis-specific and R loop-driven ATR pathway promotes faithful chromosome segregation. *Science.* 2018; 359(6371): 108-114.

*(continued from page 2)*



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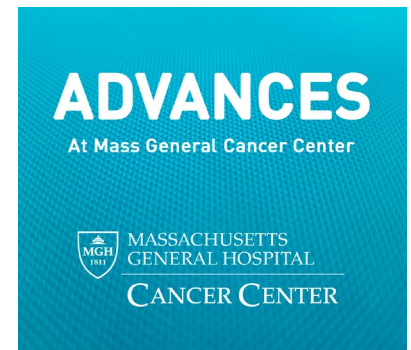
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