DNA safeguard may be key in cancer treatment

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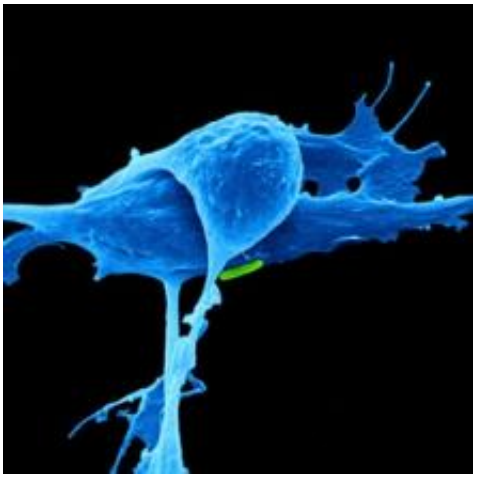

Cornell researchers have developed a new technique to understand the actions of key proteins required for cancer cells to proliferate.

The technique will help guide the development of drugs currently in clinical trials for anti-cancer treatments that inhibit this class of proteins, called kinases.

The study, published March 5 in the journal *Molecular Cell*, focuses on a few kinases – mainly ATR and ATM – that are involved in detecting and triggering responses to DNA damage in all human cells. Since our DNA may be replicated as many as 20 trillion times from fertilized egg

through adulthood, there are many occasions for error and the need for repair.

"The ATR protein is well-known to detect damage in our DNA and coordinate a response that ensures the efficient repair of the damage before the cell divides into two distinct cells," said Marcus Smolka, associate professor of molecular biology and genetics in the Weill Institute for Cell and Molecular Biology, and senior author of the paper. Francisco Meirelles Bastos de Oliveira, a former postdoctoral researcher, is the paper's first author, along with graduate student Dongsung Kim, both in Smolka's lab.

Damage that occurs during replication may be compared to a water pipe breaking in a municipality, said Smolka. "You need a system to detect when a water pipe breaks, and you need a group that makes and coordinates decisions to turn off the water, to notify people in the neighborhood, and to call a repair group," Smolka said. In this analogy, ATR and ATM function as the group that detects and signals other entities for an appropriate response.

In cancer cells, which reproduce very quickly, there is a great deal of DNA damage, as if "hundreds of water pipes are broken" at once, Smolka said. "Cancer cells highly depend on ATR to survive," he added.

Thus therapies that inhibit ATR may be effective in killing cancer cells, and, in fact, the first ATR inhibitors are entering early clinical trials.

The ATR kinase, which was discovered in the 1990s, was thought to be recruited only in the event of DNA damage, but Smolka and colleagues have discovered that ATR also acts pre-emptively to prevent DNA lesions that lead to cell disorders and cell death.

The work opens new opportunities to inhibit ATR and uncovers novel

pathways controlled by this kinase.

The new technique uses mass spectrometry to measure the mass of molecules with extremely high accuracy. Kinases signal actions by transferring phosphate groups to proteins. The transfer of a phosphate group regulates protein functions by activating and deactivating, changing location or degrading a protein, for example. The new technique uses exact mass measurements to detect these proteins (or substrates) and the transfer of phosphate groups.

The researchers also found evidence of proteins that turn ATR on to transfer phosphate groups to other proteins.

Though more than 500 kinases are known to exist, fewer than 100 are well-understood. The new technique offers a path for understanding the actions of all kinases in a highly quantitative way. Many kinases are involved centrally, not just in cancers, but also in diabetes and neurological disorders.

The study used yeast cells, which contain kinases that are homologous to ATR and ATM.

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