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When the genetic material inside a cell's nucleus starts to fall apart, a protein called ATM takes charge and orchestrates the rescue mission. Surprisingly, for ATM to kick into full gear, the stretches of DNA flanking a chromosomal break are just as important as the damaged site itself, report scientists at the Salk Institute for Biological Studies.

Until now, it had been thought that only already activated ATM could be recruited to the DNA damage sites, but the Salk's team findings, which are reported in the Oct. 25 advanced online edition of *Nature Cell Biology*, show just the opposite.

"We found that efficient ATM activation occurs only when it has physical contact with areas flanking the DNA breaks," says postdoctoral researcher and lead author Zhongsheng You, Ph.D. "When we blocked access to the adjoining regions, ATM activation was severely reduced," he adds.

"Activating ATM 'on scene' ensures a strong local DNA repair response, while the extent of the global response will depend on the number of double strand breaks within the cell," according to senior author Tony Hunter, Ph.D., a professor in the Molecular and Cell Biology Laboratory.

Our genetic material or DNA is constantly damaged by both external sources such as the sun's ultraviolet rays, and internal sources such as reactive oxygen species. Fortunately, cells have developed elegant surveillance systems to detect and repair the damaged DNA.

In the event of the most dangerous form of DNA damage, double-strand breaks, ATM coordinates the cellular response. ATM functions as a kinase — an enzyme that can install phosphate molecules on its substrates — and activates a wide variety of DNA repair enzymes and cell-cycle regulators by phosphorylating them. As a result, the cell cycle is halted until DNA repair is completed to prevent cells from passing on damaged genetic material, which could lead to cancer-causing mutations. If the damage is beyond repair, cells undergo programmed cell death.

A lack or deficiency of functional ATM (ataxia-teleangiectasia, mutated) is the underlying cause for a debilitating human genetic disease called ataxia-teleangiectasia. It is characterized by a wide spectrum of defects including neurodegeneration leading to uncoordinated or ataxic movements, immune dysfunction, radiosensitivity and cancer predisposition.

A lot of work has centered on the downstream targets of ATM since its discovery more than a decade ago. But the precise mechanism by which damaged DNA activates ATM had remained unclear. To address this issue You took advantage of a unique property of cellular extracts prepared from unfertilized frog eggs. Adding linear DNA fragments to these extracts mimics DNA double-strand breaks in cellular DNA: ATM rapidly self-activates and slams the brake on the cell cycle machinery.

The Salk scientist happened to have DNA fragments of different lengths (80 bps to 10 kbps) at hand and just added the same number of molecules, assuming that it was the number of ends or “breaks” that mattered and not their size. Not so. “The longer, the better,” says You to describe what he found when he assessed the ability of the DNA fragments in activating ATM. “Efficient ATM activation critically depends on both the number of DNA breaks and the total length of damaged DNA molecules.”

This puzzling observation led him to ask what role the intact DNA neighborhood played in the activation process. His experiments, he says, suggest that ATM is cooperatively activated after being recruited to the regions flanking broken DNA ends. “This mechanism directly couples ATM activation with damaged DNA and ensures that ATM is rapidly activated in response to just a few DNA breaks,” he explains.

Adds Hunter: “Recruiting ATM not only to the break itself but to the flanking regions as well, amplifies the signal from a small number of breaks to generate robust cell cycle block and DNA repair responses.”

DNA is not just floating around inside a cell’s nucleus, instead it is tightly wound around proteins known as histones, which are lined up along the DNA molecule like beads on a string. The whole assembly is collectively known as chromatin. “Our findings suggest that an important signal eliciting the DNA damage response emanates from modified chromatin flanking the DNA breaks in addition to that generated by the primary DNA lesions themselves,” says Hunter.

Source: Salk Institute