BRIT1 allows DNA repair teams access to damaged sites

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Like a mechanic popping the hood of a car to get at a faulty engine, a tumor-suppressing protein allows cellular repair mechanisms to pounce on damaged DNA by overcoming a barrier to DNA access.

Reporting online at Nature Cell Biology this week, a research team led by scientists at The University of Texas M. D. Anderson Cancer Center shows that BRIT1 connects with another protein complex to relax DNA's tight packaging at the site of the damage.

"Relaxing this barrier allows two different DNA repair pathways greater access to the damage, preventing flawed DNA from being passed on as the cell divides, which causes genomic instability leading to cancer," said senior author Shiaw-Yih Lin, Ph.D., assistant professor in M. D. Anderson's Department of Systems Biology.

BRIT1 is under-expressed in human ovarian, breast and prostate cancer cell lines. Lin and colleagues previously showed that the protein plays a key role in early detection of DNA damage.

Chromosomes are made of DNA that is tightly intertwined with proteins called histones to form chromatin. Chromatin is a very condensed structure that forms a natural barrier inhibiting access to genes, said first author Guang Peng, Ph.D., a post-doctoral fellow in Systems Biology. ATP-dependent chromatin remodeling is a fundamental mechanism used by cells to relax chromatin in DNA repair, but the detailed molecular mechanism by which it is recruited to DNA lesions in response to

damage signaling has been largely unknown.

BRIT1 summons help

"Our studies demonstrate a novel mechanism by which BRIT1 recruits chromatin remodeling factors to DNA lesions to facilitate chromatin relaxation and DNA repair," Peng said.

A series of lab experiments showed that BRIT1 accomplishes this by enhanced binding to a known chromatin remodeling complex called SWI-SNF when a specific site on the complex is phosphorylated. BRIT1 also maintains the relaxation factor at the damage site.

The team showed that normal BRIT1 aids repair of double-stranded DNA breaks by allowing access to two repair pathways: homologous recombination (HR) and non-homologous end-joining (NHEC).

DNA repair efficiency dropped by between 40 and 60 percent in cells with BRIT1 knocked down that were then exposed to ionizing radiation, allowing many damaged cells to divide and pass on their genetic defects.

Potential for cancer treatment

Having shown that BRIT1 deficiency impairs HR repair, Peng said one solution the team is examining is to treat cancer cells lacking BRIT1 with PARP inhibitors, drugs that specifically kill HR-deficient cancer cells.

BRIT1 mutations are known to cause a neurological condition called primary microcephaly, in which the brain develops to only one third of normal size. The team showed that in experiments using cells derived from primary microcephaly patients that BRIT1 dysfunction may specifically contribute to development of the neurological disease by

failing to bind to SWI-SNF to relax chromatin.

Source: University of Texas M. D. Anderson Cancer Center (news : web)