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DNA Double-Strand Break–Capturing Nuclear Envelope Tubules Drive DNA Repair

Authors : Mitra Shokrollahi, Mia Stanic, Anisha Hundal, Janet N. Y. Chan, Defne Urman, Chris A. Jordan, Anne Hakem, Roderic Espin, Jun Hao, Rehna Krishnan, Philipp G. Maass, Brendan C. Dickson, Manoor P. Hande, Miquel A. Pujana, Razqallah Hakem, Karim Mekhail

Abstract : Current models suggest that DNA double-strand breaks (DSBs) can move to the nuclear periphery for repair. It is unclear to what extent human DSBs display such repositioning. Here we show that the human nuclear envelope localizes to DSBs in a manner depending on DNA damage response (DDR) kinases and cytoplasmic microtubules acetylated by α-tubulin acetyltransferase-1 (ATAT1). These factors collaborate with the linker of nucleoskeleton and cytoskeleton complex (LINC), nuclear pore complex (NPC) protein NUP153, the nuclear lamina and kinesins KIF5B and KIF13B to generate DSB-capturing nuclear envelope tubules (dsbNETs). dsbNETs are partly supported by nuclear actin filaments and the circadian factor PER1 and reversed by kinesin KIFC3. Although dsbNETs promote repair and survival, they are also co-opted during poly (ADP-ribose) polymerase (PARP) inhibition to restrain BRCA1-deficient breast cancer cells and are hyper-induced in cells expressing the aging-linked lamin A mutant progerin. In summary, our results advance understanding of nuclear structure-function relationships, uncover a nuclear-cytoplasmic DDR and identify dsbNETs as critical factors in genome organization and stability.

Keywords : DNA damage response, genome stability, nuclear envelope, cancer, age-related disorders
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