Dual action: RNA binding protein also binds DNA and acts as a damage sensor across the genome

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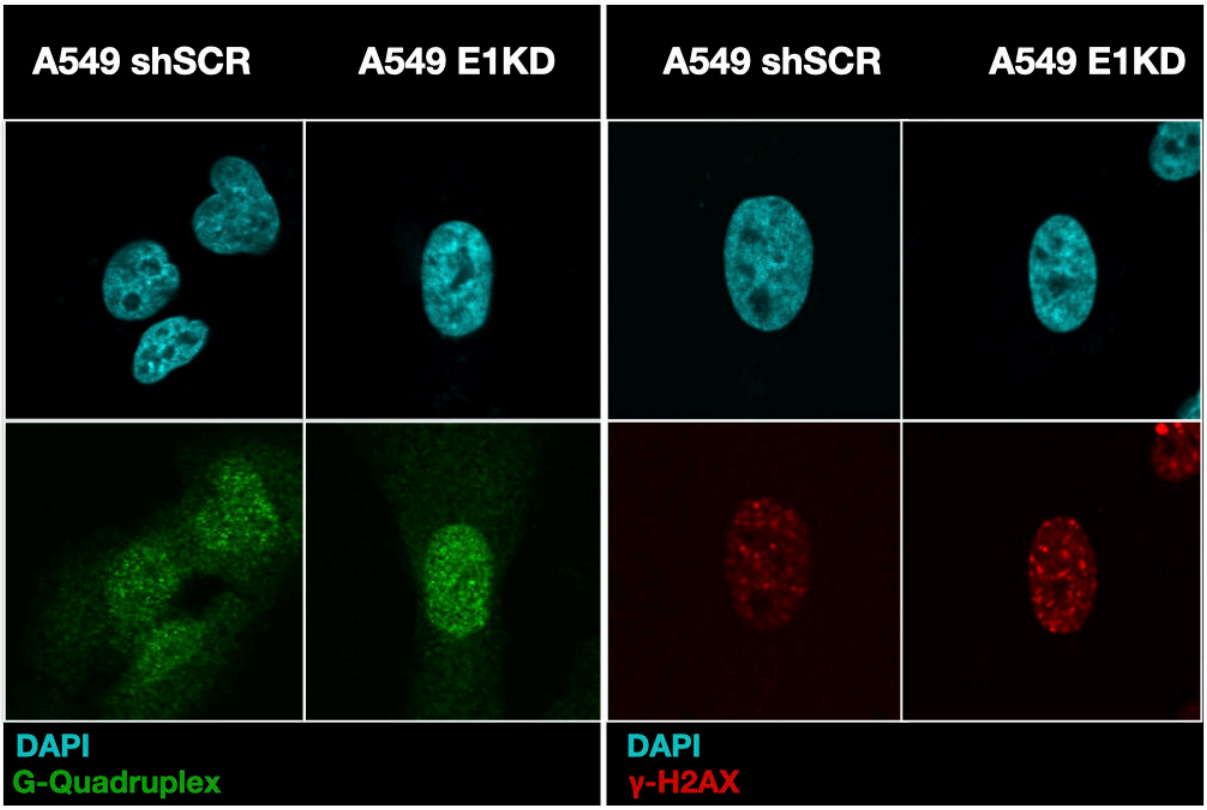

G-Quadruplexes (green) and the histone marker gamm-H2AX (red) localize to the nucleus in cells with or without hnRNP E1. Credit: MUSC / Dr. Bidyut Mohanty and Joseph Karam.

Cancer is a devastating disease and is the second leading cause of death in the U.S. One of the hallmarks of cancer is genomic instability, or the tendency to accumulate mutations and damage to the DNA that leads to genome alterations during cell division. DNA mutations can arise from exposure to ultraviolet or X-ray radiation or from certain chemicals known as carcinogens; however, our cells have developed mechanisms to monitor and repair damaged DNA.

Stability of the genome can also be threatened by the translation of certain messenger RNAs (mRNA). mRNA, copied from DNA, serves as the genetic code for the building of proteins. Certain mRNAs are known to be associated with cancer metastasis. To counteract this threat, a specific protein, heterogenous nuclear ribonucleoprotein E1 (hnRNP E1), binds these mRNAs and prevents them from making proteins. Researchers at the Medical University of South Carolina have previously demonstrated how hnRNP E1 binds to metastatic-associated RNAs to inhibit their translation. The hnRNP E1 binds RNA in the cytoplasm of the cell, but the protein can also be found in the cell's nucleus. This led researchers to hypothesize that hnRNP E1 might also interact with DNA. Their results, published online on July 16 in the journal *Life Science Alliance*, describe a novel role for hnRNP E1 in binding DNA in the nucleus.

"We found that this RNA binding protein not only has broad RNA binding function, but that it also binds to similar sequences on the DNA," said Bidyut K. Mohanty, Ph.D., lead author and assistant professor in the College of Medicine at Medical University of South Carolina . "The protein binds DNA in a sequence- and structure-specific manner to maintain genome integrity and sense or prevent DNA damage."

How hnRNP E1 binds and interacts with RNA has been extensively studied, but Mohanty's finding that hnRNP E1 also binds DNA has

opened up new research avenues to explore. hnRNP E1's DNA binding is not limited to a few sites, but rather the protein has a plethora of potential binding sites on the genome, enabling it to sense or prevent DNA damage throughout the genome.

The group also found that hnRNP E1 binds to a specific structure that can form on DNA, known as an I-motif. I-motifs form in regions enriched in the nucleotide cytosine and act as regulators of gene expression. Because DNA is formed of specific bonds between nucleotides, known as base-pairings, numerous guanine bases are found opposite of the cytosine rich I-motifs. These guanine rich regions have the potential to form their own structure known as G-quadruplexes (G4). G4s are present at the beginning of several oncogenes (genes that contribute to the formation of tumor cells). However, it is unknown if I-motifs and G4s can exist at the same time or whether they are mutually exclusive. Thus, hnRNP binding to I-motif regions might suppress the formation of G4 structures in order to protect the cell.

Mohanty hypothesized that hnRNP E1 would protect against genomic instability by maintaining I-motifs and suppressing G4s. Indeed, experiments using cells that don't have hnRNP E1 displayed a decrease in I-motifs while simultaneously showing increases in G4s, DNA damage signals and mutations. Treating these cells with additional DNA damaging agents, such as UV and hydroxyurea (a carcinogen), resulted in an intensified DNA damage response from the cells, which led them to stop progressing through the cell cycle.

"This protein, involved in prevention of metastasis, may also have a role as a DNA damage sensing protein. This is a great launching point for future studies," said Joseph Karam, second author and graduate student in the Biochemistry Department.

These findings have great relevance to the field of genetics and cancer

biology. For decades now, researchers have been studying the contribution of G4s to cancer biology. Due to its association with oncogenes, these regions have been the target for drug design and anticancer therapies. Understanding the protein-DNA interactions occurring at the sites opposite G4s can contribute to the efficacy of these drugs, thereby facilitating better drug targeting and specificity.

More information: Bidyut K Mohanty et al, Heterogeneous nuclear ribonucleoprotein E1 binds polycytosine DNA and monitors genome integrity, *Life Science Alliance* (2021). DOI: 10.26508/lsa.202000995

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