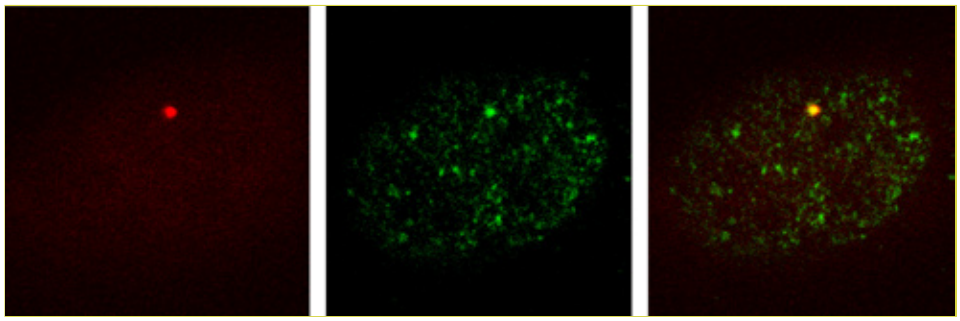
The Cell's Sophisticated Army to Defend Against Assaults on DNA

The maintenance of genome integrity and function is essential for the survival of cells and organisms. Any damage to our genetic material must be immediately sensed and repaired to preserve a cell's functional integrity. Cells are constantly faced with the challenge of protecting their DNA from assaults by damaging chemicals and ultraviolet light. DNA damage that escapes repair can lead to a variety of genetic disorders and diseases, particularly cancer. To avoid this catastrophe, the cell employs an army of DNA repair factors that "rush to the scene" and initiate a cascade of events to repair the damage. Exactly how different repair factors sense DNA damage and orchestrate their concerted response is not well understood.

As reported in a recent issue of *Science*, researchers Evi Soutoglou, Ph.D., and Tom Misteli, Ph.D., of CCR's Laboratory of Receptor Biology and Gene Expression, set out to examine how DNA repair factors sense DNA damage and form a multi-protein complex to elicit a cell's DNA damage response (DDR). To address this question, the researchers targeted individual DNA repair components to chromatin—the complex of DNA and protein that makes up the chromosome—in living cells and assessed their contribution to DDR.



The protein NBS1, expressed here as a red fluorescent fusion protein in mouse cells, plays a role in DNA repair. In this cell, most of the protein localizes in a prominent spot inside the nucleus. When researchers add an antibody conjugated with green fluorescence that stains phosphorylated H2AX (γ-H2AX), a yellow color appears. γ-H2AX is a marker for sites where DNA damage exists, so the appearance of yellow shows that NBS1 and γ-H2AX colocalize to sites of DNA damage.

Surprisingly, the researchers found that DDR could be activated by the experimental forced binding of NBS1 or MRE11, two early components of the DNA damage sensor complex, to chromatin. The authors could detect DDR by monitoring chemical changes in specific proteins (e.g., phosphorylated H2AX [γ-H2AX]) that served as hallmarks of DDR activation. Remarkably, activation of DDR occurred even in the absence of DNA damage, overthrowing the widely accepted dogma that DDR is only activated by a DNA lesion.

Further, the researchers discovered that some DNA repair factors could recruit proteins that are direct interaction partners as well as proteins that are downstream or upstream in the DDR cascade. These findings bring to light a complicated but well-coordinated interplay of components to trigger, amplify, and maintain DDR and protect the cell against genome damage and disease. The new experimental system developed by the researchers will now enable detailed analysis of the cancer-preventing response of proteins on damaged DNA.

Reference

Soutoglou E, Misteli T. Activation of the cellular DNA damage response in the absence of DNA lesions. *Science* 2008 [Epub ahead of print].