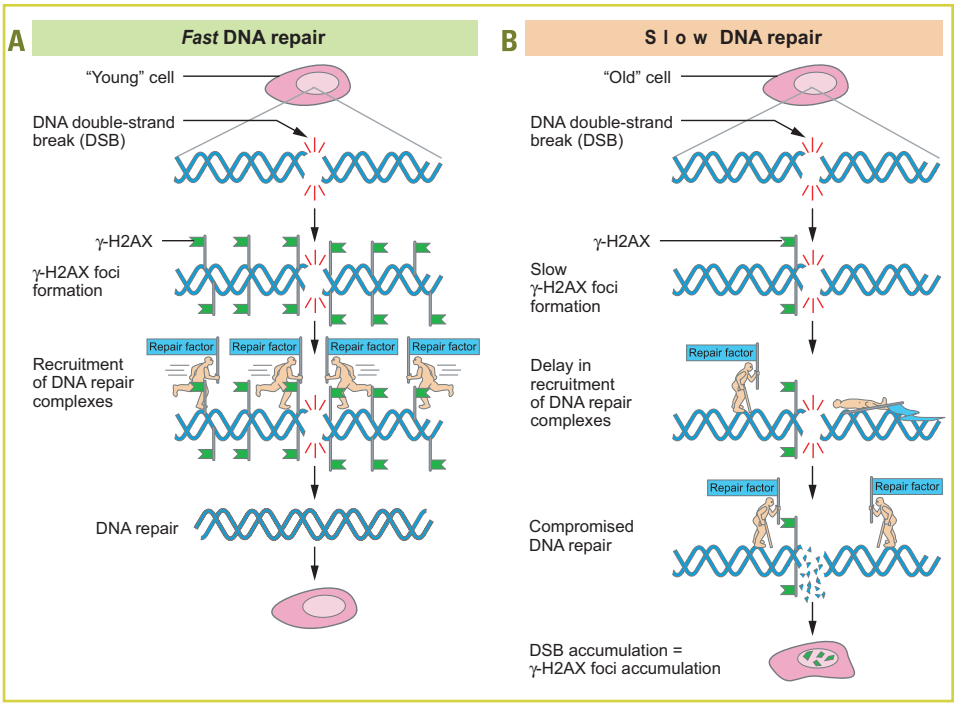
Efficient DNA Repair: A Cell's Fountain of Youth?

Given the central importance of the genome to a cell's function, it is not surprising that there are a number of proteins devoted to sensing and repairing DNA damage. But what happens when these repair proteins do not work properly? Cancer is one possible outcome, and a growing body of evidence also indicates that the cellular response to DNA damage plays a key role in the aging process. This concept is supported by the fact that many premature aging syndromes are caused by mutations in DNA repair proteins.

William Bonner, Ph.D., who leads the Genome Integrity Group in CCR's Laboratory of Molecular Pharmacology, is interested in the relationship between DNA damage repair and aging. He and a group of CCR scientists recently studied the response to one type of DNA damage—double-stranded DNA breaks—in cells from healthy people of different ages and in patients with Werner syndrome, a rare disorder associated with premature aging. Staff Scientist Olga Sedelnikova, Ph.D., served as lead author of the resulting paper, published in the January 2008 issue of *Aging Cell*.

The study focused on a protein called H2AX, a member of a family of proteins called histones, which package and organize DNA into chromatin.



As shown in photo sequence A, high numbers of γ-H2AX foci are visible soon after irradiation at the sites of double-stranded DNA breaks in the chromosomes of cells from younger healthy donors. Several DNA repair proteins appear in the foci shortly thereafter, and within a few minutes, a DNA repair complex assembles itself. In contrast, as shown in photo sequence B, at double-stranded DNA break sites in the chromosomes of cells from older healthy donors, fewer numbers of γ-H2AX foci are visible, and the DNA repair complex forms substantially more slowly.

γ-H2AX, the phosphorylated form of H2AX, accumulates at sites of double-stranded DNA breaks and recruits other components of the DNA repair machinery. Break sites in cells can be detected using microscopy and a fluorescence-labeled antibody to γ-H2AX.

Dr. Bonner and his colleagues analyzed γ-H2AX foci in cells from healthy donors of different ages and in cells from patients with Werner syndrome. The researchers found that cells from older healthy donors contained higher numbers of γ-H2AX foci than those from younger donors. Furthermore, cells from Werner syndrome patients exhibited more γ-H2AX foci than cells from healthy patients of similar ages. These data suggest that both normal and pathological aging are associated with the accumulation of DNA damage.

Subsequent experiments assessed how quickly the cells could assemble DNA repair complexes following induction of double-stranded DNA breaks with ionizing radiation. γ-H2AX foci were visible in cells from healthy younger donors soon after irradiation, and other DNA repair proteins, such as Rad50 and Mre11, appeared in the foci shortly thereafter. In contrast, the complexes formed substantially more slowly in cells from older healthy donors and even more slowly in cells from Werner syndrome patients. Cells from younger Werner syndrome patients recruited DNA repair proteins to γ-H2AX foci at rates similar to older healthy donors.

These results suggest that age-associated decline in the integrity of the genome may be due, at least in part, to the decreased speed with which aging cells can assemble DNA repair machinery at a damage-induced site. One possible consequence of slower foci formation is that the machinery is more likely to make mistakes, producing cells more prone to cancer. Shedding light on aberrant DNA repair processes in aging cells also may provide insight into how DNA damage contributes to tumor formation, possibly opening the door for new types of preventive and therapeutic interventions for both cancer and premature aging syndromes.

Reference

Sedelnikova OA, Horikawa I, Redon C, Nakamura A, Zimonjic DB, Popescu NC, Bonner WM. Delayed kinetics of DNA double-strand break processing in normal and pathological aging. *Aging Cell* 7(1): 89–100, 2008.