Paper published in *Genes and Environment* [§]

"Progerin, the protein responsible for the Hutchinson-Gilford Progeria Syndrome, increases the unrepaired DNA damages following exposure to ionizing radiation"

Asao Noda, Shuji Mishima, Yuko Hirai, Kanya Hamasaki, Reid D. Landes, Hiroshi Mitani, Kei Haga, Tohru Kiyono, Nori Nakamura, Yoshiaki Kodama

Genes and Environment 2015 (October); 37(13):1-12
(doi: 10.1186/s41021-015-0018-4)

Study Findings

We conducted a model-based investigation to test the hypothesis that genomic damage induced by radiation contributes to abnormal cell nuclear morphology and premature aging. We identified advanced nuclear envelope abnormalities and the expression of markers of premature aging in cells with unrepaired DNA double strand breaks (DSBs) induced by radiation exposure. We also found increased numbers of unrepaired DSBs in cells from patients with progeria, a genetic disease associated with rapid aging. Such cells express progerin, a mutant form of lamin A protein responsible for progeria in humans, and feature abnormal nuclear envelope structure. We concluded that nuclear lamin A, a protein thought to cause age-associated changes in nuclear envelope structure, is related to the formation of radiation-induced unrepaired DSBs.

Explanation

We attempted to measure unrepaired DSBs as a new biomarker for detecting tissues previously exposed to radiation and for estimating the radiation doses to which such tissues were exposed. In our research, we noticed that cells with unrepaired DSBs developed abnormal nuclear envelope morphology, with signs of premature aging. This led us to investigate whether nuclear lamin A could be involved in DSB repair. Hutchinson-Gilford progeria syndrome (HGPS) is an extreme example of aging caused by abnormal nuclear envelope structure. Cells of HGPS patients express progerin and have a nuclear envelope that is stiffer and more fragile than normal.

1. Objectives

The objectives were to evaluate whether nuclear lamin A, a structural protein in the meshwork of the nuclear envelope, is involved in repairing radiation-induced DSBs and whether the protein acts as a site for repairing or anchoring DSBs that are particularly resistant to repair.

2. Methods

Radiation-induced unrepaired DSBs and structural changes in the nuclear envelope were measured in cells from healthy humans and HGPS patients. Effects of farnesyl transferase

inhibitor (FTI), a new class of cancer drug, were also measured, because FTI suppresses the changes in nuclear envelope structure caused by progerin. Finally, unrepaired DSBs and nuclear envelope changes were assessed following telomerase gene induction, as telomerase gene induction has been implicated in rejuvenating cells and making cells immortal.

3. Results

(1) About 1% of radiation-induced DSBs persist in the cell nucleus as unrepaired DSBs (Noda et al., J Cell Science 125:5280, 2012). Unrepaired DSBs inhibit cell division, indefinitely arresting growth and causing premature aging. The numbers of unrepaired DSBs induced by radiation were at least two-fold higher in HGPS cells than in healthy cells. The numbers were even higher in cells with abnormal nuclear envelope structure.

(2) FTI treatment suppressed the anchoring of progerin to the nuclear membrane, thereby improving the nuclear structure in HGPS cells. The number of unrepaired DSBs consequently decreased. Nuclear structure improved and unrepaired DSBs decreased in HGPS cells with cell division capability restored by telomerase induction. The forced expression of telomerase suppressed progerin expression and induced the expression of nuclear lamin B1, a cousin of lamin A. This expression profile is characteristic of young and undifferentiated cells.

(3) Structural changes in the nuclear envelope and the numbers of unrepaired DSBs were also found to be correlated with radiation-induced premature aging in normal cells.

Study Significance

Previous studies indicated that cells bearing unrepaired DSBs underwent premature senescence, even though this finding was not directly linked to physiological changes in humans. In this study we show that the occurrence and anchoring of unrepaired DSBs caused by radiation exposure depend on nuclear envelope structure.

The Radiation Effects Research Foundation has studied A-bomb survivors and their offspring in Hiroshima and Nagasaki for more than 60 years. RERF's research achievements are considered the principal scientific basis for radiation risk assessment by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and for recommendations regarding radiation protection standards by the International Commission on Radiological Protection (ICRP). RERF expresses its profound gratitude to the A-bomb survivors and survivors' offspring for their cooperation in our studies.