Paper published in *Radiation Research*[§]

"Genome-wide deletion screening with the array CGH method in mouse offspring derived from irradiated spermatogonia indicates that mutagenic responses are highly variable among genes"

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Radiat Res 2016 (December); 186(6):568-76
(doi: 10.1667/RR14402.1)

Study Findings

A majority of findings about the genetic effects of radiation have been generated from large-scale studies conducted using several specific genes as markers, including those involving variations in mouse coat color. Since radiation-induced mutation rates differed greatly depending on the target genes, however, it was unknown which gene(s) could be considered representative of the 20,000 or more genes on the genome. To solve this problem, we screened deletions at approximately one million sites on the genome with array CGH, using DNA from offspring born to irradiated male mice. The results indicated that deletion mutation rates observed on the genome were considerably lower (several tenths) than those estimated with several specific genes, including genes involving coat colors. The reasons for this difference include the possibility that deletion mutations may occur fairly evenly on the genome and that, since such deletions frequently involve haploid susceptibility genes,* mutant individuals may not be born alive. Another possibility is that radiation-induced DNA damage itself may not be evenly distributed over the genome. In either case, these findings suggest that genetic risks of radiation may have been overestimated.

*Haploid susceptibility gene: In a cell, each chromosome other than sex chromosomes (X and Y) has a pair of genes, one each from the father and the mother. In the majority of cases involving these chromosomes, dysfunction of one of the pair of genes will not cause disease; in cases in which both genes do not function, recessive mutation will occur. On the other hand, dysfunction of only one gene may cause dominant mutations called "haploid susceptibility genes."

Explanation

Approximately three billion base sequences have already been decoded in the human and mouse genomes. Based on these data, it is possible to prepare "probes" by printing on glass plates spots containing short DNA sequences (about 60 nucleotides) that are complementary to base sequences located at various sites on the genome. Then, target and control genomes, labeled with different fluorescent dyes (red and green), are mixed in a one-to-one ratio. The mixed DNAs are then hybridized slowly on the glass slides, and fluorescent-labeled DNA fragments are pulled and bound to their respective complementary probes in a selective manner. In cases where both target and control genomes are normal, the numbers of red and green DNA bound to probes are the same, with spots exhibiting a normal yellow color. However, in cases where partial deletions occur on target DNA (in red), copy numbers at deletion sites on target DNA decrease, so that a larger number of control DNA (in green) are bound to probes than are red target DNA, making spots yellow-green. By scanning such color differences in individual probes in an automated manner, it is possible to comprehensively examine deletion mutations on the genome.

Study Results

We examined 100 offspring (F1) derived from spermatogonia of male mice irradiated with 4 Gy and 100 offspring born to unexposed controls, and detected five deletions in the exposed group and one in the control group.

Study Significance

The mutation frequency in the exposed group (5%) minus that in the control group (1%) equals 4%, which is thought to be attributable to radiation of 4 Gy. On the assumption that mutations increase in direct proportion to radiation dose, the induction rate per Gy would be 1%. The mutation induction rate obtained from tests on specific genes, including those involving coat color variations, was 1×10^{-5} on average per gene. On the assumption that a majority of radiation-induced mutations are deletions, it follows that there are only 1,000 genes that exhibit mutations at a frequency of 1×10^{-5} ($1 \times 10^{-5} \times 1{,}000 = 1\%$). However, genome analyses results indicate the presence of approximately 25,000 genes, and therefore it can be concluded that a large number of genes do not readily develop mutations.

The Radiation Effects Research Foundation has studied A-bomb survivors and their offspring in Hiroshima and Nagasaki for around 70 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.

[§]***Radiation Research***, which is an official monthly journal of the Radiation Research Society, publishes original peer-reviewed papers and review articles on radiation effects and related issues in the fields of physics, chemistry, biology, and medicine. (Impact factor in 2015: 2.67)