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“Why genetic effects from radiation are observed in mice but not in humans”

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Study Findings

This paper examines the reasons why genetic effects from radiation have been observed in mice but not in humans. In summary, it seems likely that specific genes examined in mouse experiments happened to be sensitive to radiation, whereas it later turned out that most other genes are not. In contrast, such radiation-sensitive genes employed in the mouse experiments have not been found in humans, which may account for the difficulty in detecting the effects of radiation in humans.

Explanation

Research on the genetic effects of radiation in mice is mainly based on experiments of mutation induction at several types of selected loci. Mice with normal genotypes (wild-type mice) are irradiated. Homozygous mice bearing seven recessive marker genes, including those related to coat color, are used as a tester strain (white mice). The tester mice are mated with irradiated wild-type mice to obtain offspring (F1 generation). All the offspring are principally heterozygous for the seven specific loci: that is, they have inherited one mutant allele from the tester strain and one normal allele from the irradiated wild-type parent. Thus, phenotypically, the offspring are wild-type mice. If a mutation occurs at any of the seven selected loci, offspring bearing mutations are detected. That is, recessive mutational events are observed. In the case of humans, unlike mice, such marker genes have yet to be determined, making it only possible to detect mutational events in subsequent generations, such as congenital malformation, stillbirth, and chromosomal abnormalities (i.e., dominant mutations).

Recent mouse experiments suggest that a large difference exists in mutation-induction rates among genes. The previously mentioned coat-color genes of the tester strain are likely prone to spontaneous mutations, since those mice were used as pets in the 1940s. Furthermore, genes prone to spontaneous mutation have a tendency to be more responsive to radiation. That is, the seven genes selected in mice as likely representatives of a large number of genes mutate far more readily than average after irradiation. This analysis of deletions observed across the mouse genome revealed that the mean mutation rate of many other genes was only 1/50 to 1/100 of the mean mutation induction rate of the previously mentioned seven genes.

Research themes other than specific-gene mutation induction include the lifespan of offspring born to irradiated mice and the onset of tumors in this population. With regard to lifespan, no evidence was present to indicate that life was shortened. On the other hand, at least six reports were published regarding the onset of tumors, five of which did not indicate increased tumor frequencies. Even though the other paper reported that tumor frequencies in the F1 population had increased, the author suggested a possibility that the observed increase might have been limited to the mouse strain used in that specific experiment.

Study Significance

Small animals such as mice need a variety of coat colors to deceive predators and adapt to the environment. The survival of this acquired genetic diversity over the course of evolution may explain the difference in results between mouse experiments and human genetic studies. If mouse experiments had been conducted without utilization of coat-color-related genes, it would have been considerably more difficult to detect genetic effects; for that reason, the species differences between mice and humans should not be overanalyzed with regard to the discrepancy. Furthermore, recent human genome analyses reveal that a surprisingly large number of spontaneous mutations are accumulated in the DNA of individuals. (Such events are known as genetic polymorphisms.) This is the reason it is said that no one is perfect (namely, no one carries “normal” DNA). It is currently understood that genomic mutations do not immediately lead to health effects. Even though a large number of genes involving human recessive genetic diseases have been reported, a particular mutation affects only

homozygous individuals and not heterozygous individuals. In other words, a mutation occurring in just one copy of an allele (heterozygote) will have no actual impact. On the other hand, dominant mutations can occur even in the presence of one normal copy of an allele. However, it is still unknown what percentage of approximately 25,000 genes in humans falls into this category of “haploinsufficient” genes. If this issue can be elucidated, it will be possible to explain radiation’s genetic effects in a more understandable manner.

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 2016/2017: 2.539)