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"Radiation Effects on Human Heredity"

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Summary of paper

This paper, which offers a review of research results on the genetic effects of radiation, describes classic research using drosophila and mice, research with human subjects, and the influence of results of recent human genome sequencing studies. While clear genetic effects of radiation have been observed in animal experiments, no apparent effects have been observed in humans. This paper discusses possible reasons for the difference.

Explanation

This paper consists of the following sections: "Introduction," "Classic studies in laboratory animals," "Studies in humans," "Impact of the human genome study," and "Conclusion." The section "Studies in humans" discusses birth defects, chromosome aberrations, sex ratios, mutations at hypervariable minisatellite loci, cancer incidence, and mortality. It introduces research not only on A-bomb survivors but also on former patients who underwent radiation therapy for childhood cancer as well as workers of nuclear facilities and their families.

Why radiation effects are difficult to detect in studies of human subjects

1. Difference in radiation dose

Although mice are usually irradiated with 3 gray (Gy) or more, such heavy whole-body radiation exposure is extremely rare in humans. However, in the case of radiotherapy for childhood cancer, repetitive localized irradiation to cancer sites causes scattered radiation, which may give rise to gonadal irradiation of accumulated doses of up to 10 Gy or larger when nearby organs are treated.

2. Differences in effects on offspring

In mammalian male germ lines, stem cells continuously divide, with their daughter cells differentiating to become mature sperm. Fertilization occurring soon after radiation exposure is brought about by sperm cells that were irradiated, while fertilization occurring later is brought about by sperm that were irradiated at an immature, stem cell stage. Following exposure to the same radiation dose, the biologic effect on offspring is smaller when fertilization occurs later (i.e., derived from irradiated stem cells) as compared with fertilization that occurs sooner (i.e., from irradiated sperm). The major reason for the difference is thought to lie in the meiotic process (a unique cell-division system whereby chromosome number is reduced by half), which spermatogonia must undergo to differentiate into sperm. On the other hand, female mammals are born with a much larger number of eggs (immature eggs) than necessary in their lifetime, but the number of eggs continues to decrease naturally as they age, with most eggs remaining in an immature state without being released. Only a very limited number of eggs are released after absorbing nutrients in the maturation process. Because there are few examples of conception occurring immediately after radiation exposure, studies of human females focus on the effects of exposure on eggs at immature stages. Here too, the effects on eggs before meiosis are presumed to be small. Unfortunately, however, immature mouse eggs readily die due to apoptosis following exposure to low-dose radiation, and hence no conception is achieved at the higher doses used in studies of mutagenesis and no data are obtained. In contrast, immature human eggs are not susceptible to low-dose apoptosis, so mice cannot serve as a model for human females. In the immature eggs of hamsters, which are resistant to low-dose apoptosis, chromosome aberrations have not been detected in offspring after exposure to 1 Gy of radiation, and it is conceivable that the same applies to humans.

3. Impact of human genomic research

Recent studies reported that numerous "abnormalities" have already accumulated in the human genome. Comparison of two normal people selected randomly shows differences of one base in several million sites, and small deletions and duplications in several hundreds of thousands of sites. On the other hand, the probability that 1 Gy will cause mutation at any gene of a mouse spermatogonial cell is about 1/100,000. Both mice and humans have about 25,000 genes, and therefore the total number of genes in which mutation occurs is presumed to be 0.25 at the exposure level of 1 Gy. The average dose received by the parents in the studies on birth defects in the offspring of A-bomb survivors is about 0.3 Gy, so the number of genes with mutation is estimated to be 0.075 on average, based on the assumption that radiosensitivity in humans is the same as that in mice. This number, which is much smaller than the number of pre-existing "abnormalities," highlights just how difficult it is to detect radiation effects.

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.

[§]***Annual Review of Genetics***, a journal publishing review papers on various phenomena concerning genetics, deals with a wide variety of subjects in addition to radiation, from bacteria and viruses to animals (including humans) and plants. (Impact factor in 2012: 17.436)