

3-5 A Study to Reveal the Mechanism of Radiobiological Effects — DNA Damage Induces Aberrations in Normal Chromosomes in a Living Cell —

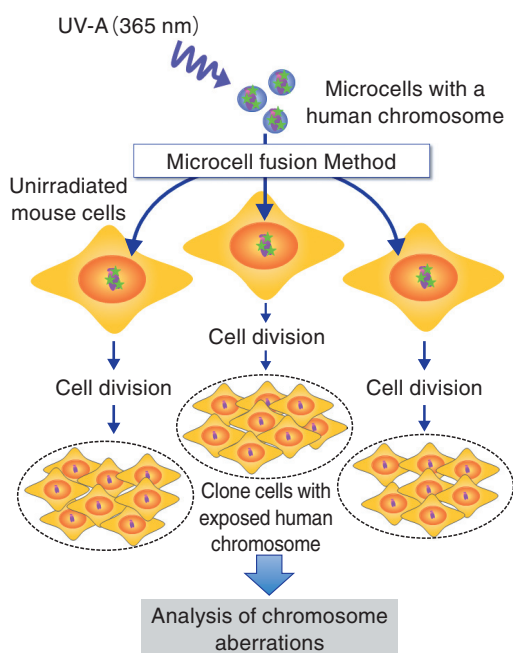


Fig.3-10 Transfer of damaged DNA by a microcell fusion method

Microcells containing a human chromosome were exposed to UV-A, and then transferred to unirradiated mouse cells. The cells were cultured, and many clones with a stable cell division function were selected. The resulting chromosome aberrations were microscopically observed in the cells and analyzed.

As one of the genetic effects through multiple repetitions of cell division, chromosome aberrations are occasionally induced in the progeny cells after ionizing irradiation. This is known to be “genetic instability,” which is strongly involved in the induction of late radiation effects, such as carcinogenesis. The detailed mechanism behind it, however, has not yet been fully understood.

In this study, we focused on DNA damage as a trigger of the instability, particularly DNA base damage, which might persist even after repeated cell divisions. The bases normally work as elementary units of genetic code in DNA, and their alteration is thought to raise mutation frequencies. In addition to DNA damage, irradiation could also induce damage to cytoplasmic organelles. To exclude the cytoplasmic effects, we applied a microcell fusion method to observe genetic instabilities induced only by DNA base damage.

Sub-cellular small structures called microcells, including one human chromosome, were irradiated and then transferred into unirradiated normal mouse cells (Fig.3-10). The human chromosome is considerably different from those of the mouse cell, such that the exposed human chromosome was easily distinguished from unirradiated mouse chromosomes by means of microscopic observations. It was confirmed beforehand that normal chromosome transfer did not induce any genetic

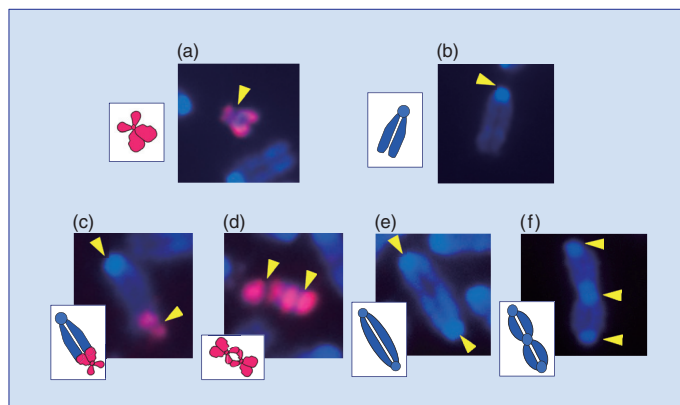


Fig.3-11 Typical chromosome aberrations microscopically observed

Human and mouse chromosomes are indicated in red and blue, respectively. Yellow arrows show pieces of apparatus, the so-called “centromere,” used to pull the chromosomes into both daughter cells during cell division. Normal human (a) and mouse (b) chromosomes are shown in the upper panels. The abnormal chromosomes comprise a mouse chromosome and a human chromosome (c), two human chromosomes (d), and two (e) and three (f) mouse chromosomes, which are shown in the lower panels.

instabilities. Ultraviolet light (wavelength: 365 nm), known as UV-A, was used as the source of the irradiation, because it has been known to preferentially induce the same sort of DNA base lesions that are induced by ionizing radiation. After the chromosome transfer, the cells were cultured for 20 days or a month to obtain various clonal cell lines that stably undergo cell division.

The analysis of the chromosomes in the clones revealed that certain types of aberrations, such as fusions between normal mouse chromosomes, were frequently induced, in addition to fusions between the human chromosomes, or between human and mouse chromosomes (Fig.3-11). Furthermore, it was observed that the number of chromosomes in the clone cells abnormally increased from the normal number of 43 to twice that number or more.

These evidences indicate that a novel mechanism of signal transfer from damaged to normal chromosomes could result in the genetic instability in the unirradiated cells. Detailed investigation is expected to reveal the induction process of radiation carcinogenesis in the low dose region in the near future.

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Reference

Urushibara, A., Yokoya, A. et al., Induction of Genetic Instability by Transfer of a UV-A-Irradiated Chromosome, *Mutation Research*, vol.766, 2014, p.29-34.