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242 Participation of ATM function in X-ray-induced delayed chromosomal instability

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Ataxia telangiectasia (AT) is an autosomal recessive disease characterized by hypersensitivity to ionizing radiation. The gene responsible for AT encodes ATM protein that is involved in recognition of DNA strand breaks. Therefore, ATM seems to be closely related to genetic instability, but it is not clear. In order to verify the above hypothesis, we examined delayed chromosomal instability in *Atm* wild-genotype (+/+), heterozygote (+/–) and knock out (–/–) mouse cell lines. The following results were obtained: There is no difference in the frequency of chromosomal aberrations among these three cell lines irradiated by the dosage that makes the survival rate to be 10%. However, incidence of telomeric instability (telomere loss and telomere segregation) increased in *Atm* (–/–) mouse cells. Here, we demonstrate that dysfunction of ATM protein results in elevated incidence of telomere instability. These results suggest that ATM protein play an important role in maintenance of telomere stability.

243 Instability of a Human Chromosome Exposed to Radiation in Unirradiated Mouse Cells

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Using a chromosome transfer technique, we previously investigated the stability of an irradiated human chromosome in unirradiated mouse cells and found that the irradiated chromosome showed the unstable nature mediated by telomeric instability. In the present study, to know the possibility that more damage may exist within the irradiated chromosome, we scored the foci of phosphorylated histone H2AX in the cells containing the irradiated chromosome. We failed to find a significant difference in the number of the foci between the cells containing the irradiated chromosome and the control cells. To know the nature of the irradiated chromosome further, we isolated colonies derived from a parental mouse cell line containing the irradiated human chromosome and investigated chromosomal instability. The result indicated that the irradiated chromosome formed a new common aberrant chromosome in seven clones examined, suggesting that instability of the irradiated chromosome might be a driving-force to promote genome rearrangement.

244 Delayed Induction of DNA Damage and Activation of p53 in X-ray Surviving Cells

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Ionizing radiation induces genomic instability, which is manifested by the expression of various delayed phenotypes. To examine the molecular mechanism underlying radiation-induced gemonic instability, we have established HTHyR clones, which harbor the reporter plasmid consists of p53 responsive elements and the bacterial beta-galactosidase gene. The cells were irradiated with 6 Gy of X-rays, and subjected to the primary colony formation. The formed colonies were collected to perform the secondary colony formation, and the secondary colonies were stained in situ by incubating colonies with X-gal. We found that significant number of surviving colonies contained beta-gal positive cells, indicating delayed activation of p53. They were also stained with the antibody recognizing phosphorylated histone H2AX, whose phosphorylation is induced by DNA double strand breaks, and the frequency of cells with phosphorylated H2AX foci was significantly higher in those surviving X-rays. These results indicate that radiation-induced genomic instability results from delayed DNA damage, and that delayed activation of p53 may eliminate cells that have potentially accumulated genomic alterations.

245 Involvement of reactive oxygen species (ROS) in the induction of genetic instability by radiation

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Radiation generates oxygen reactive species (ROS). These ROS may contribute to induction of genetic instability including delayed reproductive cell death. In the present study, we examined the effects of anti-ROS condition, such as treatment of ascorbic acid phosphate (AsAP) and hypoxic (2%) condition, on the induction of delayed reproductive cell death. Primary surviving colonies of mouse m5S cells irradiated with 6 Gy of X-rays were replated and allowed to secondary colony formation. The treatment of AsAP and hypoxic condition were applied either primary and secondary colony formation. Both anti-ROS conditions relieved X-ray-induced cell killing at a similar extent. These anti-ROS conditions also relieved delayed reproductive cell death when those conditions were applied at primary colony formation. However, no effect was observed when the conditions were applied at secondary colony formation. These results suggest that potential damage leading to the induction of genetic instability is mediated by ROS and fixed during two weeks after X-irradiation.

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