Genetic instability

239 Radiation-induced genomic instability caused by large deletion (position)

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There is accumulating evidence that genomic instability, manifested by the expression of delayed phenotypes, is induced by X-irradiation. However the mechanism of radiation-induced genomic instability has not been thoroughly explained. We have hypothesized that the point in which the chromosomal deletion of large size was generated becomes a cause of the genome instability. In this study, we examined whether gene deletion at the *HPRT* locus on chromosome X following X-irradiation would induce chromosome X instability. SV40-immortalized normal human fibroblasts, GM638, were irradiated with X-rays, and the *HPRT* mutants were isolated in the presence of 6-TG. By multiplex PCR and Whole Human Chromosome X Paint FISH (WCP FISH) analysis, only mutants with whole deletion of *HPRT* locus showed structural aberration in X-chromosome. These results indicate that large deletion may be involved in an induction of radiation-induced genomic instability.

240 The Role of DNA-PKcs Function on Induction of Genetic Instability by Radiation

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We previously demonstrated that *scid* mouse cells that were deficient in DNA-PKcs function showed high susceptibility to radiation-induced delayed reproductive cell death and chromosomal instability. To know a role of DNA-PKcs function on induction of genetic instability by radiation, we established *scid* mouse cells that expressed human DNA-PKcs by the introduction of a human chromosome 8. The hypersensitivity to acute lethality by radiation in *scid* mouse cells was normalized by the expression of human DNA-PKcs. Similarly, high susceptibility to delayed reproductive cell death by radiation in *scid* mouse cells was reduced to a normal level by the expression of human DNA-PKcs. This result indicates that DNA-PKcs plays a crucial role to suppress the induction of genetic instability by radiation.

241 Characterization of a Duplicated Segment of the ATM Gene Located on Human Chromosome 7 Possibly Generated by LINE-1-Mediated Retrotransposition

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A case of segmental duplication of the *ATM* gene which is akin to exon shuffling was studied. The *ATM* -like sequences on human chromosome 7 was initially revealed by Southern blots of a panel of human/rodent hybrids using *ATM* cDNA probe. A phage clone containing a 5.44-kb insert that hybridizes with the probe was obtained from chromosome 7-specific genomic library (LA07NS01), and its nucleotide sequences were determined. A 1.14-kb region corresponding to a single *ATM* exon and flanking introns was included in this insert. Genomic BLAST search indicated this segment is located within the intron of an another gene. The inserted segment was associated with tandem site duplications, poly A stretches, and partial inversion, suggesting the involvement of LINE-1 retrotransposition. There found no LINE-1 element around the original *ATM* exon. The duplicated *ATM* segments were present in the genome of *Pan* or *Gorilla* , but not in *Pongo* . The preservation of intact intron-exon structure in this transposed segment was possibly caused by the usage of antisense transcript as the substrate for LINE-1 reverse transcriptase.