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Radiation Induced Genomic Instability

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Abstract

Radiation induced genomic instability can be observed in the progeny of irradiated cells multiple generations after irradiation of parental cells. The phenotype is well established both *in vivo* (Morgan 2003) and *in vitro* (Morgan 2003), and may be critical in radiation carcinogenesis (Little 2000, Huang et al. 2003). Instability can be induced by both the deposition of energy in irradiated cells as well as by signals transmitted by irradiated (targeted) cells to non-irradiated (non-targeted) cells (Kadhim et al. 1992, Lorimore et al. 1998). Thus both targeted and non-targeted cells can pass on the legacy of radiation to their progeny. However the radiation induced events and cellular processes that respond to both targeted and non-targeted radiation effects that lead to the unstable phenotype remain elusive.

Keywords

Low dose; genomic instability; chromosome

The cell system we have used to study radiation induced genomic instability utilizes human hamster GM10115 cells. These cells have a single copy of human chromosome 4 in a background of hamster chromosomes. Instability is evaluated in the clonal progeny of irradiated cells and a clone is considered unstable if it contains three or more metaphase sub-populations involving unique rearrangements of the human chromosome (Marder and Morgan 1993). Many of these unstable clones have been maintained in culture for many years and have been extensively characterized. As initially described by Clutton et al., (Clutton et al. 1996) many of our unstable clones exhibit persistently elevated levels of reactive oxygen species (Limoli et al. 2003), which appear to be due dysfunctional mitochondria (Kim et al. 2006, Kim et al. 2006). Interestingly, but perhaps not surprisingly, our unstable clones do not demonstrate a “mutator phenotype” (Limoli et al. 1997), but they do continue to rearrange their genomes for many years. The limiting factor with this system is the target – the human chromosome. While some clones demonstrate amplification of this chromosome and thus lend themselves to prolonged study, many tend to eliminate or rearrange the target chromosome until it is too small for further rearrangement.

The observed frequency of induced instability by low and high linear-energy-transfer radiations greatly exceeds that observed for nuclear gene mutations at similar doses; hence, mutation of a gene or gene family is unlikely to be the initiating mechanism. Once initiated however, there is evidence in the GM10115 model system that it can be perpetuated over time by dicentric chromosome formation followed by bridge breakage fusion cycles (Marder and Morgan 1993), as well as recombinational events involving interstitial telomere like repeat sequences (Day et al. 1998). There is also increasing evidence that inflammatory type

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reactions (Lorimore et al. 2001, Lorimore and Wright 2003), presumably involving reactive oxygen and nitrogen species as well as cytokines and chemokines might be involved in driving the ustable phenotype (Liaikis et al. 2007, Hei et al. 2008). To this end there is very convincing evidence for such reactions being involved in another non-targeted effect associated with ionizing radiation, the bystander effect (Hei et al. 2008). Clearly the link between induced instability and bystander effects suggests common processes and inflammatory type reactions will likely be the subject of future investigation.

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