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Epigenetic Effects Of Ionizing Radiation

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ABSTRACT

Data generated during the last three decades provide evidence of Epigenetic Effects that are induced by ionizing radiation particularly those of high LET values and low level dose exposures.

Epigenesis is defined as the stepwise process by which genetic information, as modified by environmental influences, is translated into the substance and behavior of cells, tissues, and organism.

The epigenetic effects cited in the literature are essentially classified into several types depending on the nature of the effect induced.

The most accepted postulation, for the occurrence of these epigenetic effects is a radiation induced bioelectric disturbances in the environment of the non-irradiated cellular volume. This will trigger signals that will induce effects in the unirradiated cell populatiobs.

The epigenetic effects referenced in the literature up to date are five types; namely, Genomic Instability, Bystander. Effects, Clastogenic Plasma Factors, Abscopal Effects, and Transgenerational Effects.

The demonstration of Epigenetic Effects associated with exposure to ionizing radiation indicates the need to re- examine the concept of radiation dose and target size. Also an improved understanding of qualifying and quantifying radiation risk estimates may be attained. Also, a more logical means to understand the underling mechanisms of radiation induced carcinogenic transformation of cells.

Experimental evidence of the existence of Epigenetic Effects of radiation pose definite challenges in the evaluation of risk associated with exposure to ionizing radiation.

GENOMIC INSTABILITY.

This condition indicates that delayed effects of radiation become manifested in the progeny of irradiated cells multiple generations after the initial irradiation. This indicates an increased acquisition of alteration in the genome. Radiation induced instability is observed in cells at delayed times after cellular exposure to ionizing radiation, and manifests in the progeny of irradiated cells multiple generations after the initial radiation insult.

Genomic instability is measured as chromosomal rearrangements, aberrations, changes in ploidy, micronuclei formation, gene mutations, microsatellite instabilities, and decreased plating efficiency. Multiple pathways appear to be involved in initiating and perpetuating induced instability depending upon the genetic background of the initial target cell.

Genomic instability may represent the first critical step in the genesis of radiation induced cancer transformation; a postulation that is critical in the risk assessment of radiation exposures, and also in determining the role of genomic instability in radiation carcinogenesis. Chromosomal duplications or partial trisomies are significant to the processes associated with malignant transformation. Recent data indicate that polymorphism in genes induces genomic instability.

The molecular, biochemical, and cellular events that initiate and perpetuate instability in the progeny of irradiated cells remain unknown. The changes in gene expression and disturbances in the extra cellular homeostatic processes are likely to be involved, rather than directly induced DNA damage. The target and target size for induced instability indicate that the nucleus is probably the ultimate target. Other lines of evidence point to the role of epigenetic effects in perpetuating radiation – induced genomic instability.

In conclusion, radiation – induced genomic instability has an epigenetic component. Signals from irradiated cells can stimulate chromosomal rearrangements in cells not present at time of irradiation. This has major implications for the fate of cells surviving radiation exposure, and indicates that even cells outside the radiation environment may be susceptible to signals from irradiated cells and manifest detrimental effects.

BYSTANDER EFFECTS.

The tern "Bystander Effects" refers to the effects induced in non- targeted cell populations due to the manifestations of damage caused to other cells that are initially targeted. This means that cells that were not traversed by radiations, but were bystanders at time of irradiation; elicit similar effects as those of the irradiated cells. Alternatively, "Bystander Effects" are observed when non-irradiated bystander cells are cultured in a medium from irradiated cells and then display several detrimental effects associated with irradiation.

Experiments performed on cytoplasm membrane irradiation indicated that the target for genetic effects of irradiation is larger than the nucleus; and that cytoplasmic transversal by radiation (α particles) is potentially more effective than nuclear transversal; because increased mutagenicity occurred with negligible killing of the target cells. The most convincing demonstration of the bystander effects came from studies using charged particle micro beams. The micro beam is capable of delivering a predefined exact number of α - particles through a specific sub-cellular compartment of a defined number of cells in a particular radiation environment. Bystander effects induced mutations, oncogenic transformation and increased micronuclei frequency. Other experiments using α - particle beam showed increased mutation frequency in the non-exposed bystander cells four times that of background frequency.

Bystander effects can also be induced by transfer of medium from irradiated cells; this was first demonstrated in 1997. Significant reduction in plating efficiency in unirradiated normal and malignant cell lines had received medium from irradiated cultures. This bystander effect suggested that irradiated cells secreted substances into the culture medium which was capable of killing the unirradiated cells when that medium was transferred onto them. However, not all cells responded to the secreted signal. The majority of medium transfer experiments utilized low LET X or γ-rays. Also, Bystander Effects were also demonstrated in vivo in animal experiments using internally deposited plutonium emitting α - particles in the liver.

The radiological bystander effects are well established. This means that in addition to the damage directly induced by the deposition of radiation energy in the irradiated cells; consideration must now be given to the indirect bystander effects of radiation. An irradiated cell can send out a signal to induce a response in a cell whose nucleus was not hit by irradiation. Therefore, a detrimental bystander effect e.g. micronuclei, oncogenic transformation, or cell killing, amplifies the biological effect of a given radiation dose. This bystander effects appears to predominate at very low doses of radiation. At radiation doses greater than 0.5 Gy, cell death is the result of the direct effect of radiation as well as the dose-independent bystander effect.

Bystander signals can be mediated via cell to cell gap junction communications, as well as by processes involving induced signals released into the extracelluar space medium. It is suggested that the induction and the reception of the bystander signals are separate processes. It is concluded that Bystander Effects indicate that the relevant target for radiation effects is larger than the cell nucleus.

This could have significant implications in terms of extrapolating radiation risk of low dose exposures. Although our knowledge of bystander effects is still in its infancy, the significance of the data available, particularly at low doses, certainly affects the estimates of low dose radiation risk to human health.

CLASTOGENIC PLASMA FACTORS.

There is a growing body of evidence that plasma from irradiated mammals (including humans), contains factors that are capable of inducing detrimental effects in unexposed cells cultured in that plasma. These factors have been termed "Clastogenic Plasma Factors". These are distinct from Bystander Effects. Several observations have demonstrated that culturing normal human lymphocytes in medium containing plasma obtained from accidentally or therapeutically irradiated individuals, resulted in significantly more chromosomal aberrations than lymphocytes cultured in medium with plasma from non-irradiated individuals.

Clastogenic factors have been described in plasma of atomic bomb survivors, Chernobyl accident emergency workers, also in humans and experimental animals after therapeutic or experimental irradiation. Formations of clastogenic factors occur 15 minutes after irradiation, and persisted for 10 weeks as reported in rats, and 7 – 10 years in humans, and 30 years in atomic bomb survivors.

Clastogenic factors represent products secreted (or excreted) by cellular elements as a result of irradiation. Radiation doses as low as 0.2 Gy can induce clastogenic factors in vivo. The precise nature of clastogenic factors is unknown; however, factors as endogenous viruses, interference with DNA repair and / or increased production of free radicals have been implicated. At present, the biologic significance of clastogenic plasma factors remains unclear. The role of clastogenic factors in creating a cellular environment that is predisposed to genomic instability and ultimately neoplastic transformation should be borne in mind.

It should be mentioned that clastogenic factors are not unique to radiation exposure; transferable clastogenic factors have been detected after whole stress conditions, hepatitis, Crohn's disease, and scleroderma.

ABSCOPAL EFFECTS.

These effects are defined as significant tissue response to irradiation in tissues definitely separate from the volume exposed to radiation. The response must be measurable, and the possible effects of scattered radiation must be ruled out. These abscopal effects are common in patients with malignant lymphoma treated by irradiation of liver and spleen. Experimental animal data demonstrate the presence of high count of micronuclei in unirradiated volumes of lung tissue as compared to control animals. Abscopal effects, however, require more quantitative data for verification, also the exact biochemical mechanisms involved in their production, and processes of action. Abscopal effects together with other epigenetic effects of radiation appear to gain a place in the consideration of the overall risk of exposure to ionizing radiation.

TRANGENERATIONAL EFFECTS.

These are defined as the effects that can manifest themselves in the progeny of irradiated humans and animals. Most Transgenerational studies use "Minisatellite Loci" for quantification of Transgenerational effects. Minisatellite sequences consist of medium-sized repeat units of 10-60 base pairs which are widely distributed in several mammalian species. Some minisatellites in humans are highly unstable and undergo frequent length change mutation in germ cells.

Minisatellite mutations were first described in 1993 in experimental animals. Later in 1996, they were described in humans living in areas heavily contaminated with caesium-137 after Chernobyl accident. A positive correlation between radiation dose and mutation rate was observed over multiple loci. Other studies failed to reproduce these positive findings. The reasons for such discrepancy are not obvious, except that irradiation modalities are not similar. Furthermore, the minisatellite profiling was conducted at different time periods after irradiation.

The biological significance and ultimate consequences of radiation induced changes in minisatellite mutation rates are unknown. However, the minisatellite system provides a system for efficient monitoring of germ cell line mutations. It is unlikely that the minisatellite loci themselves are the direct targets of the radiation.

CONCLUSION

The demonstration of in vitro and vivo Epigenetic Effects associated with exposure to ionizing radiation indicate that there is need to examine the concept of radiation dose, and target size. Grouped together, the epigenetic effects argue convincingly that the target for radiation induced effects may be much greater than the precise target volume irradiated. This would have important implications on human health. The human being is exposed to natural radiation, and to man made radiation in several aspects of life. The adverse effects of human exposure to ionizing radiation presumably occur through a combination of direct targeted induced damage and non- targeted epigenetic effects. These non-targeted epigenetic effects have been found to occur after low level radiation dose exposures. Understanding the complex multitude of multicellular responses to radiation may provide an improved basis for radiation risk estimates, and some logical means of intervening in the development of radiation- induced malignant transformation of cells.

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