Radiation-Induced Cancer from Low Doses of Ionizing Radiation : Risk Analysis Using the Cell Dose Concept*

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ABSTRACT

High doses of ionizing radiations are known to bear the risk of cancer to the exposed individual. In order to appreciate potential carcinogenesis from low 'doses also, the action of ionizing radiation in the human body has to be considered in holistic approach: energy depositions to individual cells trigger effects within a hierachical structure of interacting levels of biological systems, consisting consecutively of atoms, molecules, cells and organ tissue.

The present paper describes the cell dose concept which is an essential factor in assessing the risk due to the ionizing radiation to the cells and tissues. Low dose of ionizing radiation induces adaptive response in individual cells which could be linked to the action of molecular radicals. Enzyme activities in bone marrow cells and bilayer lipid membranes and radicals are directly related to radiation effects. Temporary improvements of the detoxification of molecular radicals also improve the cellular defence. The risk analysis calls for more attention as it is important for radiation protection and other beneficial effects due to low doses of irradiation.

1. THE CELL, ELEMENTAL UNIT OF LIFE

The perturbations introduced by ionizing radiation primarily at the atomic-molecular level of organisation may be transferred to higher levels of organisation. Yet, this promotion of perturbation appears to be inhibited or blocked by mechanisms for protection. Cells have enzymes which defend against potentially toxic agents, such as molecular radicals including oxygen contianing free radicals that

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are produced in the course of normal metabolism. Other enzymes take care of the repair of damaged molecules, such as DNA, and of the replacement of damaged or lost structures as long as information for replacement through functional DNA remains available. At the organ-tissue level, mechanisms of defence, repair and replacement operate through the immune system and the control of proliferation, differentiation and maturation of cells. For all these responses, the cell is the crucial element of tissue, i.e., the elemental unit of life.

2. THE RADIATION DOSE TO CELLS

In correspondence with the practice in radiation protection, the average mass of the cell, 1 ng, or of its cell nucleus,' 270 pg, is proposed to be taken as the gross sensitive volume (GSV) in assessing the evolution of radiation effects[1-4]. Even though the cell nucleus is known to be more radiosensitive than the cytoplasm regarding effects on DNA which is the most crucial molecule for cellular function, the multitude of intracellular metabolic interactions make the cell a functional entity to be viewed individually as a whole. In the following calculations, the cell is taken to constitute a spherical volume having an average mass of 1 ng.

With respect to the intercellular matrix, radiation effects are considered to be negligible as long as they do not interfere with cellular functions, for example, through attacks of toxic substances, such as molecular radicals adjacent to a cell,. If there is an interaction of extracellular radicals with a cell, the cell is considered to have experienced an energy deposition. Other types of intercellular toxic interactions are comparatively rare and are not considered further.

The amount of energy that is deposited per radiation absorption event per GSV is conventionally termed as specific energy. Since the GSV here is the cell, the specific energy is specifically defined as the elemental dose, δ[5]. It is demonstrated that the number of δs per unit conventional dose of absorbed energy,, D, is inversely related to the linear energy transfer (LET)[6-8]. In fact, D is equal to the product of the mean elemental dose, δ, the number of such elemental doses, N, and the fraction of cells affected by such doses, F.

$$D = \delta.N,F \tag{1}$$

with $1 \leqslant N < \infty$ and $0 < F \leqslant 1$.

Below a given level of absorbed dose of a given radiation quality with its corresponding probability distribution of δs, Nremains 1 and Fis small against 1, and so

$$D = \delta.N.F = 6.F \tag{2}$$

for $D \ll \delta$ and thus $N = 1$ and $F \ll 1$.

Thus it is only F that changes and determines the magnitude of the effect with changing D at the tissue level. For 'low dose' in this sense, i.e., for $D \ll \delta$, the fraction of GSVs is small against 1, i.e., $F \ll 1$. Hence, in the low dose region, most of the GSVs are not affected by radiation and F is equal to the probability of being hit, a probability which is small against 1.

For the better understanding of radiation risk, absorbed dose rate, D' is also to be considered besides absorbed dose. Dose rate determines the mean time interval, t, between two consecutive δs in a given GSV[5].

$$t = \delta/D' \tag{3}$$

If this mean time interval is larger than the period needed by the biological system for complete repair and recovery, then the two radiation events cannot interact. The risk involved with the second event is independent of the experience of a first event. This is the case, for example, with the background radiation of about 1.5 mGy per year, corresponding to around one δ per GSV per year.

With professionally exposed people, the time interval between two δs may be in the order of hours and thus be comparable to repair and recovery periods. This is then of particular importance because stimulation of the cellular defence system, induced by the first radiation absorption event, may reduce the effect of the second event to almost zero, as will be shown in this paper.

3. THE RISK TO CELLS FROM RADIATION

The cell dose concept, as described above, is essential for overcoming common difficulties in risk assessment. Risk to tissue is eventually based on three risks to the cell: (a) the risk of being hit by an elemental dose, δ; (b) the risk of experiencing a given size of δ when hit; and (c) the risk of a defined biological effect in response to δ. The first two risks are physical in nature. With a given spectrum of δs for a defined radiation field, the probability of a cell being hit in terms of F, rises linearly with radiation fluence, i.e., with D. The third risk depends on the biological property of the individual cell.

Both the fraction of affected cells, F, and the distribution of δ within the affected cells can be easily measured by a properly scaled microdosimeter. The risk of a definded biological effect in a cohort of defined cells in response to being hit by δ is expressed by an appropriate 'dose response function' or 'hit size effectiveness function' of involved cells'. If such dose response functions would be invariable, then linearity between dose to tissue and effects would be conclusive.

If there would be evidence of variability, then the concept of linearity would need correction". In fact, variability in terms of adaptive response was observed.

4. ADAPTIVE RESPONSES BY CELLS TO RADIATION

There is evidence that low doses of ionizing radiation, i.e., a single δ or few δs per cell, induce in the hit cells adaptive responses by which, for example, the detoxification of molecular radicals and repair of damaged DNA are stimulated.

Thus, from about 6 to 60 hours following an acute x- irradiation of human lymphocytes with priming doses of 5 or 10 mGy, the frequency of chromated aberrations that are induced by a high dose of x-rays of 1.5 Gy, was significantly reduced compared with non-primed controls"*".

An adaptive response could also be linked to the action of molecular radicals. In mouse bone marrow cells, the enzyme thymidine kinase reacts sensitively to changes

in intracellular radical concentration [13-15]. The enzyme was acutely and temporarily inhibited to a minimum activity of about 60 per cent at about 4 hours with complete recovery in about 10 hours after an acute gamma irradiation of the whole body with less than 10 mGy, i.e., in the range of single δs per cell[14]. When a second acute whole body irradiation with the same dose was given four hours after the first, the enzyme activity in the bone marrow cells returned quickly to normal level and remained there as if there had been no irradiation at all.

Concomitantly, at 4 hours, there was a significant increase in the concentration level of free glutathion in these cells indicative of an improved radical detoxification at that time[15,16].

This adaptive response has been elucidated further. When the mice immediately after the first radiation exposure, at a controlled body temperature of 27°C, were treated with a static magnetic field of 1.4 T, the radiation effect on the enzyme activity of the bone marrow cells was abolished[14]. Since bilayer lipid membranes and radicals are known to respond to strong static magnetic fields" and to be also directly related to radiation effects, the investigations indicate the involvement of these components in the observed adaptive response. The result, obviously, is a temporary resistance of the cellular thymidine kinase against potentially detrimental molecular radicals. This is a beneficial effect for the cells following hits by elemental doses. It may be assumed that protection is also afforded against such radicals, which are produced during normal metabolism and are comparable to those generated by ionizing radiation.

5. THE RISK TO TISSUE FROM THE FRACTION OF CELLS AFFECTED

The cell is the basic element of the tissue system. Transfer of damage from cells to tissue is governed by the tolerance level to which the tissue may experience perturbation, or loss of its cells, without breakdown of tissue structure and functions required for maintaining life. Crucially important is the fraction of cells that are hit by δ and respond detrimentally.

In the realm of low dose irradiation, as it is encountered mainly by environmental or occupational exposure or by accident, the number of cells being hit per unit tissue mass is of primary importance. It should perhaps be expressed in terms of a unit, the corresponding reference sample of this quantity[18]. Such a definition would improve clarity of the concept of low dose. The number of cells per unit tissue mass is easily measurable and may be applied to predicting effects from measured distribution of δs in a given radiation field when related response functions of involved cells are known'. Mode of exposure, then, would be expressed in terms of number of cells hit per unit tissue mass per unit time, with subsequent attention to the distribution of δs within the population of involved cells. This approach would be somewhat analogous to express radionuclide decay per unit time for which the unit is becquerel and which primarily does not attend to the quality of radiation that is emitted per decay.

A major conclusion of applying the cell dose concept is the recognition that for low dose irradiation of low ionisation density, there are adaptive responses in individual cells with the result of the risk of detriment to the individual cells from repeated

exposures being not generally additive, so that the linear extrapolation of risk to zero dose cannot be upheld valid. Moreover, when regarding the multitude of cells in tissue, and if in an irradiated tissue the sum of cells with temporary improvement of the radical detoxification system is larger than the sum of cells with radiation-induced detriment such as malignant transformation, the net result of low dose irradiation on tissue may well be beneficial. This is to be expected because temporary improvement of the radical detoxification system does improve the cellular defence not only against radiation-induced radicals but also against radicals produced by metabolism. Thus the effect of radiation-induced stimulation of the cellular defence system is amplified and the net effect may be positive.

Indeed, the risk to malignant transformation of a hit hemopoietic stem cell in man per δ is exceedingly small and is calculated to range at 10^{-13} for induction of lethal leukemia from 100 kV x-rays" whereas adaptive responses are easily measured at values of single δs.

6. CONCLUSION

The holistic approach to analysing tissue effects that are primarily initiated at the level of cells, the elements of the tissue system, thus leads to new questions in radiation biology, which still needs answering. Only with the starting help of the tools of microdosimetry at the level of cells can the sequence of biological responses perpetuating from the atomic-molecular level to the more complex levels of biological organisation be integrated into assessing risk to the whole organism. This is important for radiation. protection and uncovers the potential for beneficial effects also in terms of a reduced incidence of malignant diseases, following low dose irradiation.

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