Medical Hypotheses 81 (2013) 1041–1045

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

# Intrinsic radio-sensitivity of tumours to low let radiations: A mathematical model in LQ formalism

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ARTICLE INFO

*Article history:*
Received 24 June 2013
Accepted 26 September 2013

ABSTRACT

Intrinsic radio-sensitivity is the determinant of differential response of tumours to low LET ionising radiations. The probabilistic DNA fibril both model shows intrinsic radio-sensitivity factor [I] as function of nuclear diameter (Nd) and intra cellular hydrogen ion concentration [$H^+$]. Linking probabilities of lethal and sub-lethal events to [I] further results in equations which show the LQ parameters namely alpha and beta are functions of (Nd), [$H^+$] and repair constant ($\mu$) mu. This model is able to explain radiobiological phenomena of OER and Do value of lymphocytes.



## Introduction

Ionising radiation deposits energy in random and discrete manner during its passage through absorbing medium. Three to several dozens of ions constitutes a cluster. The rate at which energy gets deposited per unit length is defined as linear energy transfer (LET). Sparsely ionising X-rays and gamma rays belong to low LET whereas heavy particles like protons, neutrons and charged nuclei constitute high LET. Low LET particles damage intra cellular target molecules mostly indirect through reactive radicals generated from radiolysis of water. Out of variety of reactive radicals generated, hydroxyl ($OH^*$) is most reactive due to its very short half-life of $10^{-9}$ s and contributes maximum towards radiation damage. High LET particles do the same job but through direct ionisation within target molecules. Although hydroxyl radical can attack any molecule coming within mean range of 100 Å, the macromolecule most critical for cell death is DNA. The prerequisite for DNA hit is that it has to be accessible and within the range.

The mechanism of hydroxyl radical induced DNA damage is shown below,

$$OH^* + DNA \longrightarrow DNA^* + H_2O$$

This radical form of DNA can happen at anywhere along the macromolecule leading to rupture of bonds and result in one of the lesions alone or in combination such as: (1) alteration or deletion of a base, (2) deletion of a nucleotide, (3) single strand break, (4) double strand break, (5) DNA–DNA cross-link and (6) DNA–protein cross link [1–3]. The hydroxyl radical can also add up to any C≡C or C≡N double bond within purine or pyrimidine nuclei leading to formation of molecules like Thymine glycol and 8-Hydroxyguanine. However, at present it is believed that a double strand break whether from a single event or from two sequential events is minimum essential for cell death. According to cluster hypothesis because the initial energy deposition events are discrete and clustered, the free radicals generated are also clustered. Therefore multiple damages are produced in a highly localised area through multiple chemical reactions. The type of DNA lesions produced is not different for normal and cancer cells. However, the dose-quantity relationship differs between normal cells of different histology, so also for cancer cells. This differential response is said to be determined by intrinsic radio-sensitivity the molecular basis of which is yet to be revealed.

The exponential relationship between absorbed dose ($D$) and surviving fraction (SF) is represented now-a-days in the most popular linear–quadratic equations as following,

$$-\ln\ SF = \alpha D + \beta D^2 \quad (1)$$

Here the parameters alpha and beta stand for coefficient of lethal and sub-lethal events, respectively.

Differential response could only come from variation in any of the values of alpha and beta. Thus the so called intrinsic radio-sensitivity factor [I] has be the determinant of these two parameters. The mysterious factor [I] quite dominant in response of tumours to low LET irradiations gradually disappears with rise in LET and becomes non-entity for particles of very high LET. The radiation induced damage while mostly direct for high LET particles it is indirect from reactive radicals generated within nuclear volume for low LET. Thus the factors influencing the access of reactive radicals to genome and ultimate concentration of reactive radicals just before hit must constitute the elusive intrinsic radio-sensitivity factor [I].

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0306-9877/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mehy.2013.09.031

Metabolic environment though equivalent for all normal cells, is different for cancer cells. While normal cells derive most of their energy need from oxidative phosphorylation, cancer cells adopt glycolysis for the same purpose. As to differential access, organisation of DNA inside chromosome will explain.

As shown in Fig. 1 organisation of DNA starts with formation of 'nucleosome', where a unit length of 146 base pairs wrap around a spheroid histone–protein complex comprising two units each of H2A, H2B, H3, and H4. Whereas the intervening 50–54 base pairs bound only to H1 histone, serve as linkers. The DNA double helix makes around 1.8 turn around histone complex and one molecule of H1 brings both ends close to each other. Tension arising from formation of nucleosome makes six of them to twist around to form a 30 nm loop. Further six loops twist to form a rosette and 30 rosettes organise into a solenoid. The loops are held together in a rosette by central scaffold containing Topoisomerase II and abundant H1 histones. Thirty solenoids organise ultimately into a chromosome. All this organisation together leads 10,000 fold compaction of DNA inside a chromosome!

When a particular gene needs to be activated, a chromosome has to open in reverse direction of supercoiling until the desired segment is accessible and free of histones. This process of unfolding creates a lot of dead space which gets filled up with water. This extra volume of water is responsible for expansion of nuclear compartment. Thus nuclear diameter is proportional to number of genes activated. Further, formation of supercoil leaves little or no space for water to get in for which neither reactive radicals are generated inside nor they are able to penetrate from outside. Thus most of the DNA segments being buried inside major folds are immune to reactive radicals. Those free segments and some within few adjacent nucleosomes are only vulnerable. More the number of genes activated more the length of DNA accessible to hydroxyl radicals. This logic applies both to normal and cancer transformed cells.

As said earlier for low LET radiations intracellular metabolic environment is also one of the determinants of quantity of DNA damage. While for normal cells the metabolic environment is equivalent it is more acidic for cancer cells due to the fact that they get their energy supply almost from glycolysis compared to normal cells, from oxidative phosphorylation. And accumulated protons ($H^+$) act as scavengers of hydroxyl radicals.

Accessibility, intracellular pH and expansion of nuclear volume all together constitute intrinsic radio-sensitivity factor [I] and that needs to be quantified mathematically.

Dale [9] well back in 1985, derived the dose-effect equations for acute and protracted irradiations in LQ format applying Roesch method of reasoning as following,

Total type A (lethal) damage produced in time $T$ independent of dose rate

$$R = p \times D = \alpha D \tag{2}$$

Here the probability per unit absorbed dose that one lethal target is hit in infinitesimally small time dt is $p$ and that equals alpha. However, for type B (repairable) damage it is function of other variables besides probability $p$ as shown below,

$$\text{Total type } \beta \text{ damage} = \beta D^2 = 2n\epsilon\rho^2 \times R^2 \times 1/\mu[T - 1/\mu\{1 - \exp(-\mu T)\}]$$

$$\text{Therefore } \beta = 2n\epsilon\rho^2 \times R^2 \times 1/\mu[T - 1/\mu\{1 - \exp(-\mu T)\}]$$

Here $n$ = total number of sub-lethal target pairs. $\varepsilon$ (epsilon) = probability that two sub-lethally damaged target pairs interact to produce a lethal event. $p$ = probability per unit absorbed dose that one target of a pair is damaged. mu ($\mu$) = sub-lethal damage repair constant.

While the values of mu ($\mu$) being already known and that of quantities $\eta$ *and* $\varepsilon$ been fixed for any cell, the remaining probability factors: lethal and sub-lethal determine variable radio-sensitivity. The intrinsic radio-sensitivity factor [I] as of now the determinant of differential response to ionising radiations has to be connected to those two variables. The whole exercise in this paper goes towards quantifying [I] taking various morphological as well as biochemical changes that happens to a cancer transformed cell, into consideration besides probabilistic aspect of radiation events.

## Materials and methods

Let the probability of lethal and sub-lethal events be designated separately as $P_L$ and $P_S$ respectively for unit absorbed dose. These two quantities are once again proportional to total of all probable DNA hits. In this paper the total of all probable DNA hits is defined as intrinsic radio-sensitivity factor [I]

$$\text{Thus,} \quad P_L\alpha[I] \tag{3}$$

$$P_S\alpha[I] \tag{4}$$

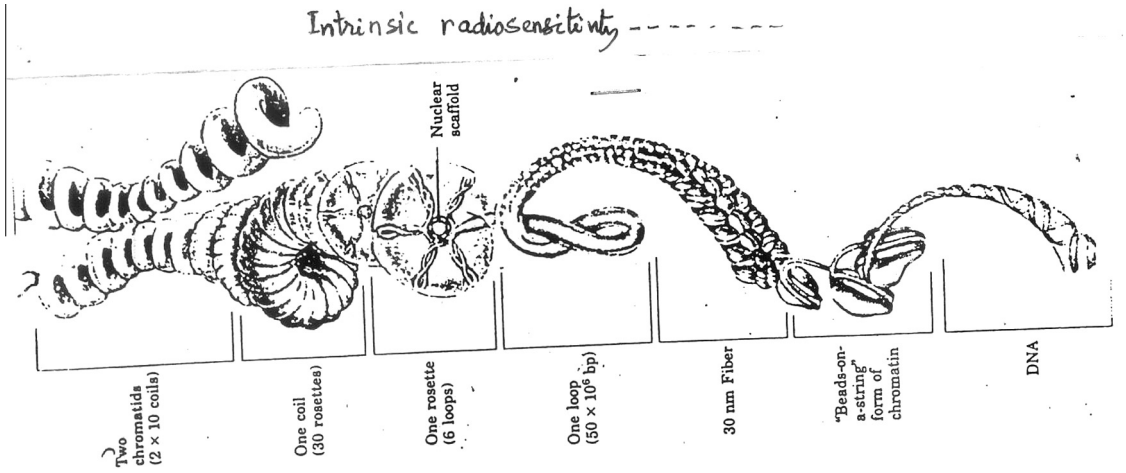


**Fig. 1.** Schematic diagram of DNA-histone complex organized into a super-coil in a eukaryote chromosome.