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Concepts needed to understand potential health effects of chronic low-level radiation exposures: Role of adult stem cells and modulated cell–cell communication

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Abstract. To understand the extremely relevant, but complex, process of potential low-level ionizing radiation-induced health effects, particularly, cancer, both research-derived factual results and theoretical concepts must be generated and tested. To date, due to the difficulties of (a) generating epidemiological statistically rigorous and unambiguous data at extremely low levels; (b) deriving any mechanistic understanding from epidemiological data; (c) doing enough animal experiments due to cost and even relevancy of results to human beings; (d) using dubious molecular, biochemical, cellular in vitro assays, due to limitations, artifacts and misinterpretation of results; and (e) potently lack of appropriate paradigms and concepts needed to interpret results of chronic low-level exposures, the usual default tactic to assume extrapolation down from high-level exposures, using a non-threshold, linear model seems to defy facts and concepts that are known about carcinogenesis to date. The objective of this short analysis is to point out that several important concepts, namely, the role of adult stem cells as the "target" cells for carcinogenesis, the role of cell–cell communication, and oxidative stress as an intra-cellular signal transducer must be considered in the risk assessment of chronic low-level radiation exposure. In fact, the relatively new concepts of the "adaptive response," the "bystander effects" and "genomic instability" must be carefully integrated with the stem cell, cell–cell communication and oxidative stress-signaling concepts.

Keywords: Adult stem cell; Gap junctional intercellular communication; Epigenetic mechanism; Oxidative stress-signaling; Stem cell theory of carcinogenesis

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> Unfortunately, the inherent limitations of epidemiology make it extremely difficult to directly quantify health risks from these exposures (<0.2 Gy)…Interactions between radiation epidemiologists and radiation biologists will become increasingly important as the field focuses more on the effects of low doses of radiation. E. Ron [1].

1. Introduction: Challenge to the "linear, no threshold" paradigm of radiation carcinogenesis: how might acute or chronic low-dose radiation exposure contribute to carcinogenesis?

Given that cancer is one of the major concerns of radiation exposure, as well as one of the easiest measured health end points, this short review will focus on trying to integrate current understanding of radiation biology with that of the mechanisms of carcinogenesis. It is almost universally accepted that carcinogenesis is a multi-step, multiple mechanism process, consisting, conceptually, of the operational steps of "initiation," "promotion" and "progression" [2,3]. It has been hypothesized that the underlying mechanism of *initiation* involves an irreversible or stable change in the genome of one cell and which can be explained by the induction of DNA damage that, if not repaired in an error-free manner, can lead to a mutation in a critical gene related to the carcinogenic process, namely an "oncogene" or a "tumor suppressor gene" which could contribute to the universal expression of the "hallmarks of cancer" [4]. Although the cells within a tumor demonstrate phenotypic or even genotypic differences, they are all derived from a single cell [5,6]. *Promotion*, on the other hand, is the operational concept to explain the process by which this single "initiated" cell is clonally expanded by (a) a mitogenic stimulation (caused by growth factors, wounding, compensatory hyperplasia after cell death, inflammatory stimulation [7–9], and (b) the inhibition of apoptosis of the initiated cells [10,11]. The hypothesis to explain both how promotion is accomplished by both mitogenesis and apoptosis is the reversible inhibition of gap junctional intercellular communication [12], which is triggered by intracellular signaling [13]. *Progression*, operationally, is the concept that one of the many cells in the promoted population of "initiated" cells finally acquires enough of the genotypic/phenotypic changes or "hallmarks" needed to become invasive of the surrounding tissue cells and to metastasize to a distal site [14].

From this description of the operational definitions of the multi-stage process of carcinogenesis, "initiation" infers that a normal, "mortal" cell must be "immortalized" in order to proliferate indefinitely to accrue all the "hallmarks" needed to become a metastatic cell. That has been one of the prevailing paradigms of the cancer field [15]. Moreover, this "initiated" cell must be able to resist apoptosis, as it has been shown with chemical carcinogenesis, that is, once a cell in tissue has been initiated, it can remain quiescent for months prior to being promoted. This infers, again, that during this pre-promotion period, the initiated cell does not die.

Clearly, within this prevailing paradigm, it is generally assumed that, since tumors appear in experimental animals and in epidemiological studies after high-dose exposures, and since ionizing radiation can induce DNA lesions, chromosomal mutations and deletion mutations in molecular in vitro assays to detect genotoxic events, it is easy to accept this assumption that ionizing radiation "caused" the mutations found in the oncogenes and tumor suppressor genes in cells within the tumors. Within this paradigm, it generally assumed that the