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REVISITING LOW DOSE RADIOBIOLOGY: MECHANISTIC INSIGHTS AND FUTURE DIRECTIONS

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Abstract:

Low-dose radiobiology focuses on the biological effects of ionizing radiation at absorbed doses that are less than about 100 mGy or low dose rates (less than 10 mGy/h -1). These exposures are common, and they include the diagnostic imaging, nuclear medicine, radiotherapy scatter, occupational and environmental exposures, radon exposures and space travel. Although widespread, the biological effects of low dose radiation (LDR) have not been fully defined and they persistently troubles the current radiation risk assessment systems. Linear no-threshold (LNT) radiation protection has been the basis upon which radiation protection has depended over decades, wherein a proportional relationship exists between dose and stochastic risk and there exists no safe dose. Despite the fact that LNT has offered a conservative and practical regulatory foundation, increasing experimental and mechanistic information suggests that it is not sufficiently comprehensive of biological responses in the low-dose area. Recent developments in the field of molecular biology, epigenetics, microdosimetry, and systems biology show that LDR can trigger adaptive signaling, non-targeted, and long-lasting epigenetic reprogramming without causing a corresponding DNA damage. The responses tend to be qualitative as opposed to high-dose effects being extended in a linear manner. This is a critical review of the empirical and biological basis of the LNT paradigm against modern mechanistic data, a comparison with currently evolving non-linear dose response models, and epigenetic regulation as the key determinant of low dose effects. Combining historical information with the current experimental and clinical data, we will seek to answer the current controversies, and provide a way forward in terms of biologically informed but pragmatically feasible models of low-dose radiation risk assessment.

Keywords: Low-Dose Radiation, Radiobiology, Linear No-Threshold Model, Adaptive Response, Epigenetics, Radiation Risk Assessment

1. Introduction

Ionizing radiation was known as a strong biological agent, which has detrimental but also therapeutic effects since the discovery of X-rays by Wilhelm Conrad Röntgen in 1895. The initial radiobiological studies inherently concerned moderate-to-high radiation doses, at which the following effects were easily noticed; tissue injury, cell death, and carcinogenesis. Conversely, low-dose area has not been researched relatively, even though the vast majority of human exposure to radiation is at low doses

and low dose rates.

The natural background radiation provides several millisieverts in a year and other exposures are associated with medical imaging- especially computed tomography, occupational exposures, environmental exposures and aviation or spaceflight [1], [2]. Therefore, the biological response in this dose range is critical to effective estimation of risks, optimization of medical practice, and evidence based radiation protection policy.

The peculiarity of radiobiology is that the regulatory frameworks have historically come before the knowledge of the mechanisms in biomedicine. The linear no-threshold (LNT) model, which was adopted in the middle of the 20th century, uses a linear version of the epidemiological data on cancer risk at moderate and high doses to extrapolate to zero dose [3], [4]. Although this method represents the precautionary principle and has obvious regulatory value, it was developed before the current understanding of the DNA repair fidelity, cellular signaling, non-targeted effects, and epigenetic control. More and more, experimental evidence suggests that low-dose biological responses are regulated and adapted by mechanisms which are not well explained by straight-line extrapolation one is that regulatory mechanisms govern low-dose biological responses; the other that such responses are adaptive. It would be scientifically as well as policy-relevant to reexamine low-dose radiobiology. [5] -[9].

Historical Perspective on Low-Dose Radiobiology

Fears over radiation exposure were compounded in the middle of the 20 th century with the development of nuclear arms and non weaponry civilian nuclear technology. Critical evidence to support the association between radiation exposure and cancer risk was obtained by epidemiological studies of survivors of atomic-bombs, although the evidence was statistically significant at moderate and high doses. Regulatory authorities on the lack of conclusive low-dose data assumed the LNT model was a default on the negative side [1], [3].

DNA repair pathways, cell-cycle regulation, and genomic maintenance findings revolutionized the radiation responses in higher doses as the field of molecular radiobiology developed. But these findings were slow in being applied to low-dose exposures. Consequently, policy is still affected by regulatory assumptions that were formulated many decades ago despite the accumulating evidence of non-linearity, dose-rate dependence, and biological context dominance at low doses [9] -[12].

2. Methodology

The methodology of this article is based on a comprehensive qualitative and critical review of contemporary low-dose radiobiology literature, integrating historical perspectives, experimental evidence, and modern mechanistic insights. Peer-reviewed scientific publications indexed in major academic databases were systematically examined, with particular attention to studies addressing biological effects of ionizing radiation at doses below 100 mGy and low dose rates. The analysis focused on molecular, cellular, and systems-level responses, including DNA damage and repair dynamics, adaptive responses, non-targeted effects, epigenetic regulation, and dose–rate dependence. Conceptual comparison was employed to evaluate the biological assumptions of the linear no-threshold (LNT) model against alternative non-linear dose–response frameworks such as threshold, hormetic, and adaptive models. Rather than conducting new experimental measurements, this study synthesizes existing empirical findings to identify consistencies, contradictions, and emerging patterns across different biological systems and exposure contexts. Special emphasis was placed on mechanistic studies utilizing advances in molecular biology, epigenomics, microdosimetry, and systems biology, as these approaches provide explanatory power beyond traditional epidemiological extrapolation. The selected literature was critically appraised for methodological rigor, biological relevance, and

translational significance for radiation risk assessment. Through integrative interpretation, the methodology aims to bridge the gap between regulatory risk models and current biological understanding, allowing for a more nuanced assessment of low-dose radiation effects. This approach supports the development of biologically informed yet pragmatically applicable frameworks for radiation protection and clinical decision-making, while maintaining a precautionary perspective grounded in empirical evidence.

3. Results and Discussion

Biological Mechanisms at Low Doses

1. DNA Damage and Repair at Low Doses

The ionizing radiations cause a range of DNA damage, such as base damage, single-strand break, and double-strand break (DSB). At low doses, radiation-induced DSBs in a cell are very low and are typically comparable in amount to the endogenous DNA damage produced by natural metabolic activities [4], [13-16]. Notably, DNA repair systems are active on a continuous basis and are seldom saturated at low dose.

Experimental results have shown that fidelity of DSB repair can be increased at low doses and low dose rates, which disputes the theory that radiation damage increases at a linear rate with dose [17-20]. Such results contradict a fundamental biological assumption of the LNT model, i.e. that every increase in dose causes irreparable harm with proportionate risk.

2. Adaptive Responses and Non-Targeted Effects

Adaptive responses can be induced by low doses of radiation where priming a small dose strengthens cellular responses to further exposures by increasing DNA repair, antioxidant systems, and checkpoint control systems [5], [18], [21]. These reactions are strongly dose-rate dependent and radiation-quality dependent and will most regularly occur at low-LET radiation that is concerning environmental and medical exposures.

Simultaneously, non-targeted effects, such as bystander signaling and genomic instability, prove that radiation effects are not localized to irradiated cells only [6], [7], [10], [22]. These effects complicate dose response relations in space and in time, adding more to the assumption of linear extrapolation.

3. Epigenetic Regulation as a Central Mechanism

The mechanisms of epigenetics have been found to be a common denominator of low dose radiation effects. Very low doses are capable of modulating the pattern of DNA methylation, histone modifications, as well as non-coding RNA expression without any DNA strand-breaks being produced [8], [23]–[25]. The effects of this may be long-lasting and effectively reprogramme gene expression and cellular phenotype.

These observations are major challenges of risk models based on damages. This may not be the only way that radiation can alter regulatory networks that are upstream of DNA damage; low-dose radiation can disrupt radiation responses with non-linearity, reversibility, and biological memory, introducing non-linearity, reversibility, and biological memory into radiation reactions.

Dose–Response Models and Paradigm Shifts

1. Limitations of the Linear No-Threshold Model

The LNT model presupposes that the risk of cancer rises with the dose, independent of the magnitude and speed of dose [1], [9]. On the one hand, this assumption makes regulation simple and safe on the other hand, it overlooks biological processes including repair saturation thresholds, adaptive signaling and epigenetic modulation. There is growing evidence that LNT remains mainly because of the convenience of its regulation, but not biological realism [14], [16], [17].

2. Threshold, Hormesis, and Adaptive Models

According to threshold models, there is a dose level that causes no harm, and according to hormesis, low levels of dose can cause protective biological effects [5], [11], [21]. Though these models are supported in certain experimental systems, these models are challenged with difficulties in generalization and translating them to populations in general.

3. Toward Mechanistically Informed Frameworks

New paradigms include adaptive reactions, non-targeted actions, genomic instability as well as epigenetic control in systems-biology frameworks [17], [18], [26]. These methods focus on radiation quality, dose rate, and biological situation, which give a more comprehensive and biologically-based alternative to linear extrapolation.

Methodological Advances and Translational Relevance

The revolution in microdosimetry, high-throughput omics, and integrative systems biology has changed the low-dose research [27], [28]. Notably, such technologies allow quantitatively connecting molecular responses and phenotypic outcomes and generate the opportunity to inform the risk modeling, and not indicate the effects.

Clinical and Public Health Implications

Contemporary diagnostic imaging and image-guided intervention is based on low-dose radiation. Although dose optimization is fundamental, overestimation of risks at diagnostic dose levels can be made by the sole use of LNT-based risk estimate [29], [30]. Risk communication may also be enhanced through precautionary protection and incorporation of biological modifiers in risk communication to enhance clinical decision and patient understanding.

Future Directions

The next step is to incorporate epigenetic and systems-level data into the quantitative risk models which should be backed with properly developed epidemiological studies. A realistic and scientifically viable way forward is hybrid regulatory frameworks which maintain precaution whilst recognizing biological complexity.

4. Conclusion

In conclusion, this study demonstrates that the biological effects of low-dose ionizing radiation cannot be adequately explained by a simple linear extrapolation of high-dose data, as assumed by the linear no-threshold (LNT) model. The reviewed evidence highlights that low-dose radiation responses are governed by complex and regulated biological mechanisms, including enhanced DNA repair fidelity, adaptive cellular signaling, non-targeted effects, and persistent epigenetic modifications, which together introduce non-linearity, dose-rate dependence, and biological context into radiation responses. These findings indicate that low-dose exposures may induce qualitative biological changes rather than proportionally increasing damage, thereby challenging the mechanistic validity of LNT as a universal risk model. The implications of this work are significant for radiation protection policy, clinical imaging, and public health risk communication, suggesting that overly conservative risk estimates based solely on LNT may lead to unnecessary fear, suboptimal medical decision-making, and inefficient regulatory practices. At the same time, the continued use of LNT as a precautionary regulatory tool remains pragmatic in the absence of universally accepted alternatives. Future research should focus on integrating epigenetic and systems-biology data with epidemiological studies to develop hybrid, biologically informed risk assessment frameworks, as well as on identifying biomarkers that can reliably link low-dose molecular responses to long-term health outcomes, thereby advancing evidence-based and balanced radiation protection strategies.

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