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Commentary

Cross-species radioprotection: insights from tardigrade multi-omics

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ABSTRACT

Although the search for appropriate radiation countermeasures has been ongoing for decades, there remains a lack of safe and effective radioprotective pharmaceuticals for preventing, mitigating, or treating acute radiation syndrome (ARS) and other severe radiation injuries, and only a handful of drugs have been approved for clinical use with various side-effects. It has been increasingly recognized that valuable radiation countermeasures can be derived from Earth-based species exhibiting resistance to extremely high levels of ionizing radiation. In the pursuit of the mechanisms that govern radiosensitivity, a groundbreaking study in *Science* has delved into the radiation tolerance mechanisms of the tardigrade *Hypsibius henanensis sp. nov.*, revealing cross-species radiation defense strategies by integrating genomics, transcriptomics, and proteomic. Three key findings emerged: The horizontal transfer of the 4,5-DOPA dioxygenase gene from bacteria enhanced antioxidant production. The tardigrade-specific protein TRID1 was crucial for DNA double-strand break repair through liquid-liquid separation. The up-regulation of mitochondrial function-related genes accelerated NAD^+ regeneration for DNA damage repair. This multi-omics approach not only sheds light on the extraordinary survival strategies of radiotolerant species, but also opens a promising avenue for harnessing cross-species radiation tolerance to develop innovative radioprotective compounds.

1. Introduction

Radiation-induced tissue damage remains a critical challenge in both clinical radiotherapy and nuclear emergency scenarios. Despite decades of research, the development of effective radioprotective agents with minimal side effects has been slow and limited. Recent advances in comparative biology and multi-omics technologies have opened new frontiers in the search for radiation countermeasures by turning to nature's most resilient organisms. This research highlight explores a groundbreaking study by Li et al.,[1] which deciphers the molecular basis of extreme radio-tolerance in a newly identified tardigrade species. In this context, we further explore the broader implications of leveraging cross-species radiotolerance mechanisms, particularly from extremotolerant organisms, as a strategic reservoir for discovering new bioactive molecules and therapeutic targets. We discuss the translational potential and existing challenges in adapting these evolutionarily refined defenses into clinically viable radiation countermeasures, emphasizing the need for rigorous validation of safety, efficacy, and delivery systems. Ultimately, this research highlight underscores the transformative potential of cross-species research in reshaping the future of radiation medicine, offering new hope for mitigating radiotherapy-induced normal tissue injury and managing accidental radiation exposures.

2. Normal tissue injury challenges in radiotherapy

Radiotherapy is one of the primary modalities for treating malignant tumors and certain non-neoplastic diseases.[2] The fundamental principle of radiotherapy lies in utilizing high-energy ionizing radiation to inflict damage upon critical biomacromolecules such as DNA, thereby inducing cell death, suppressing cellular proliferation, or inhibiting specific cellular functions (such as hyperactive secretion). Furthermore, ionizing radiation induces complex immunomodulation (concurrent immunosuppression and pro-inflammatory activation), remodels the tumor

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