तीव्र विकिरण सिंड्रोम के प्रभावों का न्यूनीकरण

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तीव्र विकिरण सिंड्रोम में रेडियोसुरक्षा और ऊतक पुनर्जनन के लिए व्हार्टन की जेली से प्राप्त स्टेम कोशिकाओं की क्षमता का उपयोग

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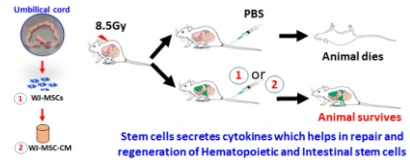

WJ-MSCs (1)और उनके वातानुकूलित माध्यम (2) द्वारा चिकित्सीय रेडियो सुरक्षा

सारांश

अप्रत्याशित परिस्थितियों में यदि कोई व्यक्ति आयनकारी विकिरण के उच्च डोज़ के संपर्क में आता है, तो इससे शरीर के भीतर महत्वपूर्ण रेडियोसंवेदनशील ऊतकों को नुकसान हो सकता है, जिसमें हेमटोपोइएटिक प्रणाली और जठरांत्र संबंधी मार्ग शामिल हैं। अप्रत्याशित विकिरण जोखिम की घटनाओं के बाद इन ऊतकों को पुनर्जीवित करने के लिए तत्काल प्रभावी उपचार की आवश्यकता है। वर्तमान में, मुख्य रूप से रक्त विकारों जैसे न्यूट्रोपेनिया, एनीमिया और थ्रोम्बोसाइटोपीनिया के लिए केवल चार वृद्धि कारक/साइटोकिन्स; न्यूपोजेन, न्यूलास्टा, ल्यूकिन और एनप्लेट को रेडियोमिटिगेटर के रूप में पुन: उपयोग किया जाता है। रेडियोथेरेपी से संबंधित क्षति के लिए एफ. डी. ए.-अनुमोदित औषधियाँ एमिफोस्टिन और पैलिफर्मिन तक सीमित हैं। तीव्र विकिरण सिंड्रोम प्रभावों को कम करने में स्टेम सेल थेरेपी, विशेष रूप से व्हार्टन की जेली मेसेनकाइमल स्टेम सेल्स (डब्ल्यूजे-एमएससी) आशाजनक परिणाम दर्शाता है। वर्तमान अध्ययन में, हमने किरणित माइस (चूहों) में डब्ल्यूजे-एमएससी के रेडियोसुरक्षा प्रभावों की जांच और संभावित चिकित्सीय लाभों का अन्वेषण किया है।

Mitigation of Acute Radiation Syndrome

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Harnessing the Potential of Wharton's Jelly-derived Stem Cells for Radioprotection & Tissue Regeneration in Acute Radiation Syndrome

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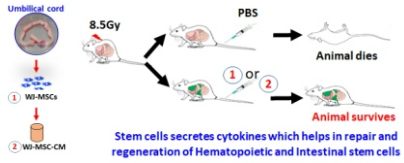

Therapeutic radioprotection by WJ-MSCs (1) and their conditioned medium (2)

ABSTRACT

Unforeseen situations in which individuals are exposed to high doses of ionizing radiation can result in damage to critical radiosensitive tissues within the body, including the hematopoietic system and the gastrointestinal tract. Urgently needed are effective treatments to regenerate these tissues after unexpected radiation exposure incidents. Currently, only four growth factors/cytokines; Neupogen, Neulasta, Leukine, and Nplate are repurposed as radiomitigators, mainly for blood disorders, such as neutropenia, anemia, and thrombocytopenia. FDA-approved drugs for radiotherapy-related damage are limited to Amifostine and Palifermin. Stem cell therapy, particularly Wharton's Jelly Mesenchymal Stem Cells (WJ-MSCs), shows promise in mitigating Acute Radiation Syndrome effects. In the current study, we have investigated the radioprotective effects of WJ-MSCs in irradiated mice, exploring their potential therapeutic benefits.

KEYWORDS: *Ionizing radiation, Radioprotector, Stem cells, Wharton's jelly mesenchymal stem cells*

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Introduction

In today's world, the looming threat of radiological and nuclear incidents, whether accidental or deliberate, has propelled a renewed focus on developing effective radiation countermeasures and pharmacotherapeutics. These measures are not only essential for individual safety but also critical for national security. Thus, there is a growing emphasis on the development of treatments to mitigate the effects of radiation exposure. Syndromes associated with radiation exposure can be classified based on the timing of their manifestation: acute, delayed, late, and chronic syndromes. Acute Radiation Syndrome (ARS), distinguished into hematopoietic, gastrointestinal, and neurovascular subsyndromes, based on the absorbed radiation dose and its distribution in tissues [1]. Despite bone marrow transplantation's success in ARS-associated mortality prevention, effective treatments for gastrointestinal injury induced by ionizing radiation remain elusive. Hence, urgent development of novel therapeutics targeting tissues susceptible to acute damage, such as bone marrow and the gastrointestinal system, is imperative. Current research focuses on pharmacotherapeutics including radioprotectors, radiomitigators, and radiation therapeutics, administered pre- or post-exposure to prevent damage or stimulate recovery. Consequently, there's an urgent need to develop novel therapeutics capable of regenerating acutely responding tissues, such as bone marrow, spleen, blood, and the gastrointestinal system, which contain cells with high mitotic potential, emphasizing the high demand for additional FDA-approved agents to address delayed, late, and chronic radiation effects [2].

Stem cells are a distinctive group of cells found throughout life stages, characterized by their capacity for self-renewal and differentiation into various cell types [3]. Adult stem cells like mesenchymal stem cells (MSCs), including those from the umbilical cord, and are favoured due to their versatility and safety. Research has shown promising results regarding Wharton-Jelly mesenchymal stem cells (WJ-MSCs) regenerative capabilities without adverse effects [4]. Previously our lab and others have explored the regenerative potential of WJ-MSCs isolated from the umbilical cord [5-7]. This study aims to investigate the impact of WJ-MSCs infusion on spleen health and morphology of radiosensitive tissues, potentially elucidating therapeutic radioprotective effects. Understanding how WJ-MSCs affect tissue health post-radiation could enhance their clinical application in regenerative medicine and radiation therapy.

Materials and Methods

Ethical approval was secured from the Institutional Ethical Review Board at Bhabha Atomic Research Centre Hospital, Mumbai, India, for umbilical cord collection with written consent. Stem cells were isolated from the cord following established protocols and characterized for stemness. The therapeutic radioprotective potential of these cells was investigated in irradiated mice, assessing spleen colonies and spleen index. Mice were exposed to sub-lethal (6Gy) and lethal (8Gy) radiation doses and infused with WJ-MSCs via tail vein. Histological evaluation of organs like spleen, bone marrow, and jejunum was conducted after 30 days.

Results and Discussion

Radiation-induced septicemia and death are primarily due to damage of the gastrointestinal and hematopoietic system. Due to hematopoietic damage susceptibility to infections increases in parallel to progressive radiation-induced damage of the intestine epithelium lining which allowing for an influx of pathogens into the blood stream. A number of substances have been shown to protect animals from irradiation and include thiol compounds, interleukin 1 (IL-1), tumor necrosis factor-α, granulocyte colony-stimulating factor (G-CSF), and granulocyte/macrophage colony stimulating factor (GM-CSF). Transplantation of normal bone marrow cells into lethally irradiated animals and humans results in long-term survival and provides proof that the hematopoietic system is crucial for defense against the lethal complications induced by radiation. Our study also showed that systemic infusion of WJ-MSCs, 24h after 6Gy radiation exposure increases the formation of endogenous spleen colonies in the 6Gy radiation + WJ-MSCs infused group compared to 6Gy radiation alone (Fig. 1A).

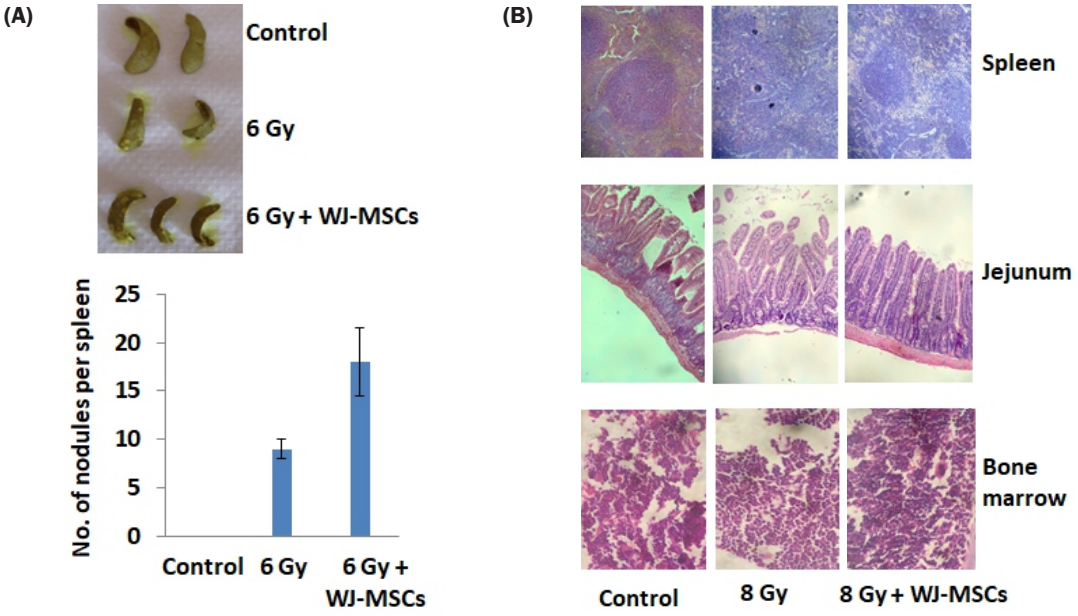

Fig.1: Therapeutic radioprotective effect of WJ-MSCs. (A) Systemic infusion of WJ-MSCs (0.25 million cells/ mice), 24h after 6Gy radiation exposure increases the formation of endogenous spleen colonies in the 6Gy radiation. (B) Systemic infusion of WJ-MSCs (0.25 million cells/mice), 24h after 8Gy radiation exposure restore the tissue morphology in radiosensitive tissues such as Spleen, Jejunum and Bone marrow by day 30.

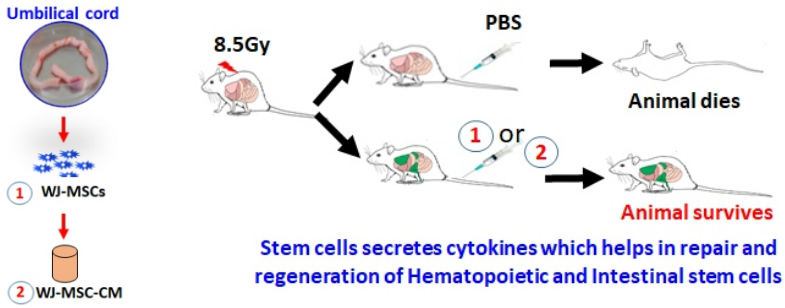

Fig.2: Therapeutic radioprotection by WJ-MSCs (1) and their conditioned medium (2).

The study assessed spleen, jejunum, and bone marrow histology to evaluate the effects of radiation and WJ-MSCs infusion (Fig. 1B). The cellular composition of the spleen's white pulp and red pulp serves as a crucial indicator of spleen function. In the study, histological examination of spleen sections from a control group displayed normal cellular characteristics, while those from a group exposed to 8Gy radiation showed disorganized cellularity in both red and white pulp. However, the group treated with 8Gy radiation and WJ-MSCs exhibited a more organized cellularity, suggesting a better recovery. Physical examination of spleens further supported this, showing less radiation-induced damage and improved morphology in the 8Gy radiation + WJ-MSCs group compared to the radiation-alone group.

The study also observed the effects of radiation on the jejunum and bone marrow. Jejunum morphology in both radiation groups resembled controls after 30 days, with better crypt morphology in the WJ-MSCs infused group. Bone marrow showed morphological recovery in all groups by day 30. These findings suggest that WJ-MSCs infusion aids in mitigating radiation-induced damage, particularly in spleen and jejunum, likely by promoting tissue regeneration. Additionally, bone marrow recovery highlights the importance of replenishing functional hematopoietic stem cells and progenitors for long-term hematopoietic system restoration post-radiation exposure.

Previous studies demonstrate that administering human WJ-MSCs or their conditioned media (WJ-MSC-CM) to mice significantly enhances survival post-lethal radiation exposure [5,6] (Fig. 2). WJ-MSCs migrate to radiosensitive tissues, such as the spleen, bone marrow, and small intestine, promoting tissue repair and modulating the microenvironment by releasing cytokines and growth factors. These cells protect hematopoietic and intestinal stem cells from radiation damage, facilitating regeneration of the hematopoietic system and gastrointestinal tract lining, thus preventing acute radiation syndrome-related fatalities. Xenogeneic WJ-MSCs transplantation stimulates human and mouse cytokine production, with human-derived IL-6 and G-CSF identified as crucial for radioprotection [5]. Additionally, WJ-MSC-CM treatment post-radiation exposure significantly reduces mortality, with anti-G-CSF antibody neutralization abolishing its radioprotective effects. While WJ-MSC-CM provides around 40% protection, indicating potential additional mechanisms, it underscores the significant role of WJ-MSCs and their secretory factors in conferring radioprotection [6].

Conclusion

In conclusion, stem cell-based radioprotection offers promising prospects for enhancing survival post-radiation exposure. WJ-MSCs demonstrate potential in aiding recovery from radiation-induced hematopoietic and gastrointestinal injuries through their secretion of anti-inflammatory and tissue-protective molecules. This presents a viable option for developing radiation countermeasures and as an alternative to bone marrow transplantation.

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