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Review

Unveiling the role of immune response and related cytokines in radiation-induced skin injury: orchestrate inflammation to repair or fibrosis

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ABSTRACT

Radiation-induced skin injury (RISI) poses a significant clinical challenge in radiotherapy, characterized by acute inflammatory responses progressing to chronic fibrosis. Central to its pathogenesis is the dynamic interplay between immune cells and cytokine-mediated cascades following DNA double-strand breaks (DSBs) and oxidative stress induced by. This process triggers localized immune activation, radiation-damaged structural cells release DAMPs, triggering resident Langerhans cells and dermal dendritic cells to initiate antigen presentation and cytokine cascades; subsequently, activated macrophages and DCs recruit neutrophils and monocytes, driving acute inflammation that critically determines tissue fate toward regenerative repair or pathological fibrosis. Meanwhile, ultraviolet (UV) radiation primarily drives immunosuppression and photoaging. This review systematically delineates the dual regulatory roles of diverse immune populations—including T lymphocyte subsets, mast cells, and eosinophils—through comprehensive cytokine profiling. We highlight how temporal shifts in immune phenotypes orchestrate inflammation resolution versus fibrotic transformation. By integrating these insights, we provide a mechanistic framework of immune cells and related cytokines for RISI progression.

1. Introduction

Radiation-induced skin injury (RISI) refers to cutaneous damage resulting from exposure to ionizing radiation (IR). This condition is frequently observed in patients undergoing radiotherapy or individuals exposed to environmental radiation sources.[1–3] Clinically, RISI manifests as erythema, blistering, ulceration, hyperpigmentation, and fibrosis. Acute symptoms typically arise within days to weeks post-exposure and chronic complications—such as fibrosis or carcinogenesis—may develop months to years later.[4] Affecting up to 95% of radiotherapy patients, the incidence and severity of RISI depend on radiation dose, methods of fractionation, and individual susceptibility.[5,6] Notably, except the immediate cellular damage and oxidative stress, the host immune response plays a pivotal and multifaceted role in determining the trajectory of RISI, transitioning from initial injury through inflammation to either resolution/repair or chronic pathology like fibrosis.[7] Immune cells, acting as key sentinels and effectors, are rapidly recruited to the irradiated skin microenvironment.[8] Upon sensing radiation-induced damage associated molecular patterns (DAMPs) released from injured structural cells, resident immune cells like macrophages and dendritic cells (DCs) become activated.[9] This activation triggers a cascade of cytokine and chemokine production, orchestrating the infiltration of various circulating immune cells, including neutrophils, monocytes, and lymphocytes.[10] The dynamic interplay and functional polarization of these infiltrating immune cells critically dictate the outcome.

In this review, we systematically reviewed the mechanisms underlying immune regulatory dynamics—particularly the interplay between pro-inflammatory response and reparative factors, and comprehensive of cytokines across immune cells, highlights their role in inflammation resolution and fibrosis transformation in RISI, providing a detailed mechanistic understanding of clinical interventions as well as developing targeted therapies to mitigate RISI.

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