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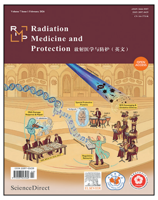

Original article

Deep DIA proteomic analysis of mouse serum in early-stage acute irradiation

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ABSTRACT

Objective: To investigate the early serum proteomic response in acute radiation syndrome (ARS) and identify potential biomarkers for early diagnosis and injury stratification using deep data-independent acquisition (DIA) proteomic.

Methods: 24 male C57BL/6 J mice (8 weeks old) were randomly assigned to four groups for γ-ray whole-body irradiation at doses of 0, 2, 6.5 and 10 Gy, respectively. Serum samples were collected 6 h post-irradiation for deep DIA proteomic analysis combined with nanoparticle-based enrichment. Bioinformatics methods were employed for screening differentially expressed proteins (DEPs), functional enrichment and core protein set identification. Western blot was used to validate the dose and time effects of candidate biomarkers.

Results: Leveraging deep DIA proteomics, we established an early-stage radiation injury proteomic profile in mice, quantifying over 4500 serum proteins. Analysis revealed a distinct dose-dependent response pattern: at a dose of 2 Gy, DNA damage repair pathways were activated concurrently with significant downregulation of cardiovascular function-related proteins; when the irradiation dose reached 6.5 Gy, the response shifted to immune hyperactivation coupled with widespread impairment of fundamental cellular functions; at a cumulative radiation dose of 10 Gy, complete collapse of basic biological processes including protein synthesis was observed. Notably, neutrophil granule protein (NGP) demonstrated stable, dose-dependent elevation within 24 h post-irradiation. At 6 h post-exposure, NGP levels increased approximately 2-fold, 7.2-fold, and 7.5-fold at doses of 2 Gy (t=3.47, $P<0.05$), 6.5 Gy (t=4.51, $P<0.05$), and 10 Gy (t=15.91, $P<0.001$), respectively, indicating its strong potential as an early biomarker for radiation injury.

Conclusion: This study elucidates a dose-dependent serum proteomic response pattern in early ARS, revealing that molecular alterations associated with long-term cardiovascular effects of radiation occur as early as the initial post-irradiation phase. The stable early response of NGP within 24 h post-exposure provides a potential molecular target and theoretical foundation for early warning and clinical intervention in ARS.

1. Introduction

The clinical manifestations of acute radiation syndrome (ARS) primarily include bone marrow suppression, gastrointestinal injury and infection-related hemorrhage.[1,2] Pre-symptomatic diagnosis and assessment of radiation injury through molecular-level detection would significantly improve the clinical management of ARS. Currently, ARS diagnosis relies mainly on lymphocyte count analysis[3,4] and cytogenetic methods (chromosomal aberrations).[5,6] However, lymphocyte counting is only applicable within 12–48 h post-irradiation, cytogenetic assays require 48–72 h of cell culture, and the detection of γH2AX foci in peripheral blood lymphocytes is technically complex.[7,8] Serum proteins, which hold significant promise as disease biomarkers by providing a direct reflection of pathophysiological status in real time,[9] are ideal for uncovering early molecular events in ARS.[10] In recent years, the advanced deep data-independent acquisition (DIA) technology,

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