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Commentary

Network biology approach unveils transcriptomic alterations triggered by particle radiation

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Space particle radiation emerges as a pivotal environmental challenge in spaceflight, notorious for its capability to inflict physiological harm and potentially instigate carcinogenesis through mechanisms that remain largely elusive. In the present issue of *Molecular Therapy Nucleic Acids*, Yan et al. conducted a comprehensive study, utilizing a network-based systems biology approach, to systematically dissect the transcriptomic consequences triggered by particle radiation.

Spaceflight imposes unique environmental stresses to organisms, radiation exposure being a prominent one, which holds the potential to exert detrimental impacts on biological systems. Fundamentally, radiation targets DNA, inflicting foundational damage in the form of single- and double-strand breaks, chromosomal aberrations, micronucleus formation, and genomic instability. Moreover, it can manifest as physical damage at the phenotypic level. Beyond this, space radiation exposure may disrupt mitochondrial function, predisposing individuals to pathological conditions, including osteoporosis and accelerated aging. The paramount concern is its potential to elevate the risk of tumorigenesis and cancer, particularly with chronic low-dose radiation exposure, which is a recognized factor contributing to cancer risk.[1] While the association between radiation exposure and increased cancer risk is well established, the intricacies of the molecular mechanisms underlying its carcinogenic potential remain partially understood, especially in the context of chronic low-dose radiation exposure experienced by astronauts during extended deep space missions.

To unravel these intricate molecular mechanisms, Yan et al.[2] embraced a network biology approach, as depicted in Figure 1, leveraging large-scale omics technologies to probe the far-reaching consequence of spaceflight on living organisms. Within the intricate landscape of biological systems, genes do not operate in isolation but instead intertwine into complex protein-protein interaction networks (PPINs), governed by universal principles.[3] Delving into the perturbations within these networks provides profound functional insights into biological processes. Differential network analysis, an influential technique, transcends mere analysis of individual molecular alternations, capturing the nuanced shifts and rewiring of molecular interactions across diverse conditions. It finds widespread application in elucidating the molecular basis of tissue differentiation, disease-specific genes, and crucial signaling pathways disrupted during tumorigenesis and disease progression.[4] Given the complex nature of space biology, which encompasses a myriad of environmental stressors such as particle radiation exposure and microgravity, systems biology methodologies and network modeling are imperative for a comprehensive portrayal of these components. In response to these research queries and contexts, Yan et al. pioneered a systematic investigation of the transcriptome impacts elicited by particle radiation, employing differential exposure strategies.

Space particle radiation encompasses a wide-ranging spectrum, extending from high to low doses. In the research undertaken by Yan et al. (shown in Figure 1), BEAS-2B cells were subjected to both individual high-dose and cumulative low-dose exposures of α-particle radiation, with subsequent transcriptome profiling conducted utilizing RNA sequencing technology. Leveraging weighted PPINs, the core networks of SENetCore and MENetCore were constructed, enabling the analysis of differential gene expression patterns across the diverse radiation conditions. This comprehensive approach identified pivotal functional modules within BEAS-2B cells under these specific conditions, which were then subjected to functional enrichment analyses and topological assessments for deeper insights.

The analysis illuminated profound alterations in gene expression patterns, particularly in pathways linked to cell adhesion, extracellular matrix (ECM) interactions, and immune responses. Yan et al.'s study focused on the ECM receptor interaction pathway, where genes consistently exhibited upregulation across varying radiation doses, hinting at a possible role in fostering early-stage cancer initiation. Notably, COL1A1, a core gene within this module, emerged as a crucial factor in the multiple-low-dose radiation cohort, as supported by network parameter analysis and expression studies conducted on lung cancer samples.

Both rigorous *in vitro* experimental scrutiny and *in vivo* immunohistochemical staining concurred that the upregulation of the COL1A1 gene promoted the emergence of malignant transformation traits in BEAS-2B cells. The differential network analysis approach highlights the intricate interplay existing between the ECM receptor interaction pathway and other cellular machineries, encompassing signaling cascades and cytoskeletal dynamics. Given the ECM's pivotal role in providing structural and biochemical scaffolds for adjacent cells,[5] its dysregulation can trigger unchecked cell proliferation and migration—key hallmarks of cancer progression. The research findings of Yan et al. indicate that α-particle radiation disrupts the normal ECM interactions, thereby fostering a microenvironment favorable

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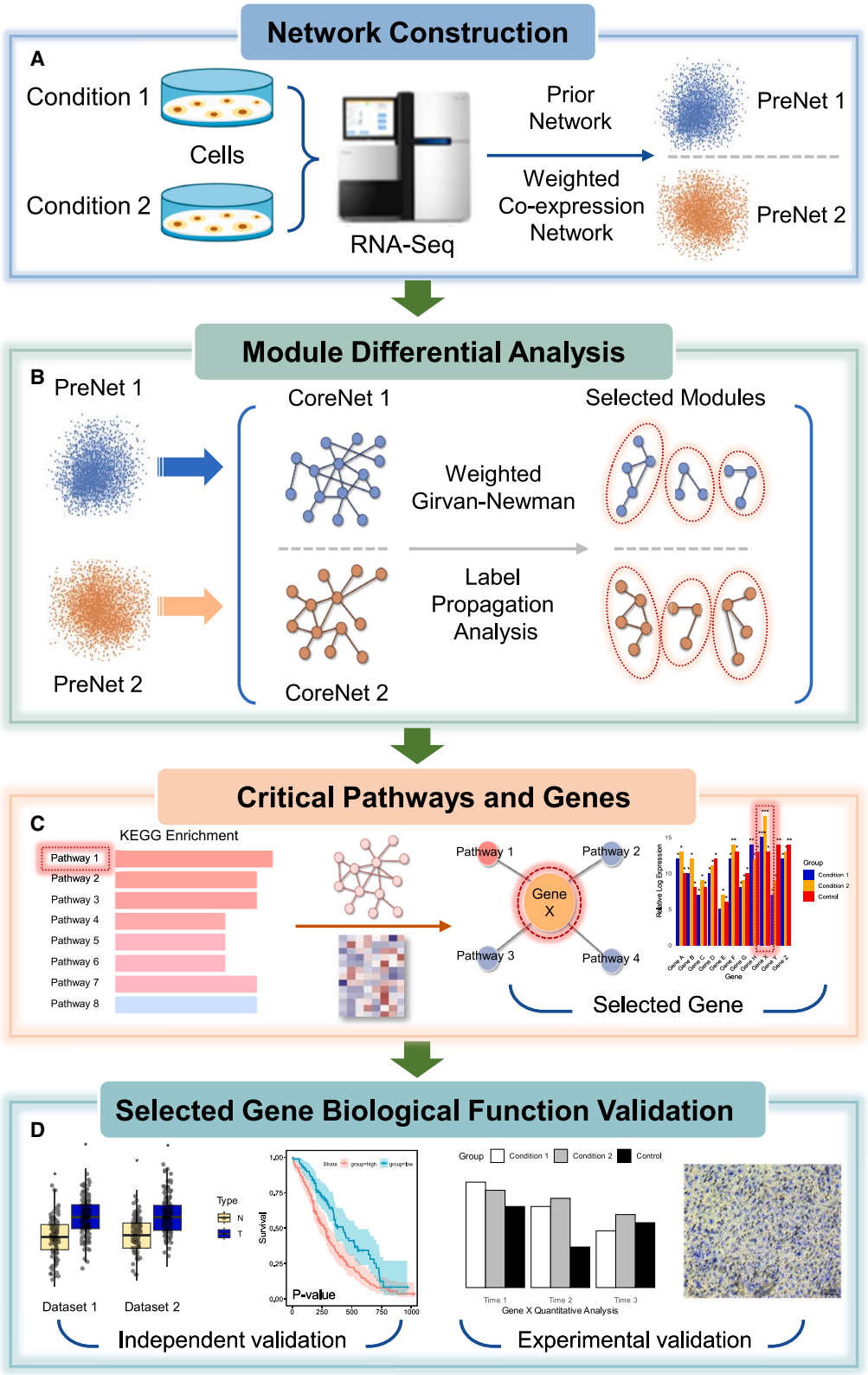

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for malignancy, particularly in scenarios involving multiple exposures to low-dose radiation.

In summary, the differential network analysis conducted by Yan et al. serves as a robust framework for elucidating complex biological interactions within stressful environments. By intertwining transcriptome analysis with differential network analysis, this resource sheds light on the molecular consequences of space radiation, emphasizing the critical role of ECM receptor interaction pathways in α-particle-induced malignancy. This work not only forges a potential avenue for pharmacological interventions and space biology research but also deepens our comprehensive understanding of space radiation's impact on human health, underlining the urgency for continued investigation to safeguard astronauts' wellbeing.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Afshinnekoo, E., Scott, R.T., MacKay, M.J., Pariset, E., Cekanaviciute, E., Barker, R., Gilroy, S., Hassane, D., Smith, S.M., Zwart, S.R., et al. (2020). Fundamental biological features of spaceflight: advancing the field to enable deep-space exploration. Cell *183*, 1162–1184.

2. Yan, W., Hu, W., Song, Y., Liu, X., Zhou, Z., Li, W., Cao, Z., Pei, W., Zhou, G., and Hu, G. (2024). Differential network analysis reveals the key role of the ECM-receptor pathway in A-Particle-induced malignant transformation. Mol. Ther. Nucleic Acids *35*, 102260.

3. Ideker, T., and Krogan, N.J. (2012). Differential network biology. Mol. Syst. Biol. *8*, 565.

4. Liu, Z.P. (2016). Identifying network-based biomarkers of complex diseases from high-throughput data. Biomark. Med. *10*, 633–650.

5. Walker, C., Mojares, E., and del Río Hernández, A. (2018). Role of extracellular matrix in development and cancer progression. Int. J. Mol. Sci. *19*, 3028.

Figure 1. Overview of the proposed framework for differential network analysis by Yan et al.

(A) BEAS-2B cells were subjected to sequencing under two distinct conditions, each featuring varying doses of radiation exposure. Following this, condition-specific networks were constructed, leveraging prior PPINs and gene co-expression networks. (B) Core components within these networks were identified through the application of a weight threshold. Subsequently, robust differential modules within the core networks were selected for further analysis using the weighted Girvan-Newman algorithm and label propagation analysis. (C) Pathway enrichment analysis and topological importance assessments were conducted to pinpoint critical pathways and genes. (D) Validation of the hub gene COL1A1 across independent datasets aimed to confirm consistent patterns of differential gene expression and survival prediction capabilities. Both *in vitro* and *in vivo* experiments concurred with the initial data-driven findings, reinforcing their validity.