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Letter to the Editor

Advancing Immunosenescence Research: Mechanistic Depth, Predictive Models, and Digital Translation for Global Equity

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To the Editor,

The recent paper [1], "*Multi-modal analysis reveals tissue-specific features of human immune cells altered with age*," marks a significant advance in comprehending immunosenescence across human tissues. Its comprehensive multi-modal approach (RNA-seq and surface protein profiling) across a broad age range offers an invaluable foundational map for understanding immune system dynamics in aging. While the study effectively delineates age-related shifts and tissue-specific immune cell characteristics, I propose three avenues for deeper exploration that, by further leveraging this rich dataset, could significantly expand our current understanding and redefine future research paradigms in immunology and aging.

Firstly, to fully elucidate the profound implications of "tissue-specific features" in immune aging, the discourse warrants an explicit focus on the epigenetic and metabolic underpinnings of organ-specific immune-senescence. The paper commendably identifies age-related changes in cell function, signaling, and metabolism. However, a critical dimension remains unexplored: how distinct tissue microenvironments—with their unique metabolic profiles and cellular milieus—actively shape and dictate the epigenetic landscapes and metabolic reprogramming of resident immune cells, thereby orchestrating their specific aging trajectories [2]. Elucidating this "tissue-epigenetic-metabolic coupling" promises a transformative framework to explain the differential manifestation of immunosenescence across various anatomical sites. Computational inference of metabolic fluxes or epigenetic states from the existing transcriptomic data could pinpoint novel regulatory nodes, elevating the analysis from observed phenomena to mechanistic insights into how aging is differentially programmed within the immune system, thereby illuminating avenues for precise, localized interventions.

Secondly, the study's extensive age-related data from diverse tissues presents an unparalleled opportunity to develop and validate "tissue-specific immune aging clocks" [3] with predictive functional utility, extending beyond chronological age prediction. While the paper broadly outlines age-related transformations, the true innovation lies in constructing predictive models capable of precisely gauging the "biological age" and functional decline of immune systems within specific organs. Such organ-specific immune clocks, built upon multi-modal data and potentially incorporating advanced machine learning, could transcend simple age estimation to forecast vulnerability to particular age-related diseases or responsiveness to specific immune challenges. This approach portends a significant paradigm shift in geriatric medicine and immunology, enabling organ-targeted immune monitoring and precision aging interventions, fundamentally reshaping the assessment and management of age-related immune health.

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Finally, while the study meticulously details changes within major immune cell types, a deeper computational exploration of rare cell populations and dynamic "intermediate states" within these broad categories holds critical importance. Complex biological processes, particularly those involved in aging and disease, are frequently governed by subtle shifts in small, highly specialized cell subsets or continuous transitions through functional states. Immunosenescence may stem not merely from the overall decline of dominant populations, but also from the accumulation of dysfunctional rare cells or impaired cellular transitions [4]. The multi-modal data in this study possess the requisite resolution to identify such elusive, yet potentially pivotal, cellular entities. Advanced single-cell trajectory inference methods could unveil novel, age-associated "intermediate" cell states or rare, dysfunctional clones.

Moreover, the practical translation of these sophisticated immunological insights into widespread clinical utility [5]—particularly for early diagnosis, screening, and prevention in geographically remote or underserved regions—will be critically empowered by digital health technologies. For instance, the core pathogenesis of inflammatory bowel disease (IBD) is the persistent inflammation resulted from immune system dysregulation. Depending on the disease severity, there is wide variation in therapeutic option. Amino salicylic acids (ASAs) are suitable for mild patients, while immunomodulators are applicable to severe cases. Obviously, the judgment of the disease severity based on endoscopic findings is critical for IBD personalized treatment, which greatly depends on the technological levels of practitioner. This poses a great challenge to the accuracy clinical assessment of IBD especially for the region with underdeveloped healthcare conditions. In this context, Peyrin-Biroulet L et al. have developed a novel AI algorithm to accurately measure the histological disease activity of IBD using state-of-the-art image processing and machine learning algorithms [6], thereby reducing the reliance on the subjectivity of gastroenterologist and medical resource. Clearly, digital health technologies have potential to bridge the gap between immune flux data and clinical practice.

Predictably, leveraging digital platforms facilitates remote data collection and AI-driven analysis of multi-modal immunological data. This integration enables the application of tissue-specific immune clocks and rare cell discoveries to improve health outcomes where access to specialized medical resources is constrained. However, there are also some ethical challenges to applying immune big data and medical digital translation. First, equity and accessibility. These cutting-edge immune analytical technologies may exacerbate global health inequalities [7]. Affluent areas are more likely to benefit them, while resource-poor regions hardly to share these advancements due to the lack of digital infrastructure and medical resources, leading the ‘digital divide’ to evolve into the ‘health divide’. Second, data privacy and ownership. Remote collection and transmission of individual health data may introduce substantial risks of privacy breaches [8]. These health data may be implemented only by the commercial or research institutions, whereas data providers have difficulty in benefiting from them.

These suggestions aim not to diminish the paper's significant contributions but rather to highlight its immense potential to catalyze foundational advancements.

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Competing interests

The authors declare that they have no competing interests.

References

[1] Wells SB, Rainbow DB, Mark M, Szabo PA, Ergen C, Caron DP, et al. (2025). Multimodal profiling reveals tissue-directed signatures of human immune cells altered with age. Nat Immunol, 26:1612-1625.

[2] Saggese P, Sellitto A, Martinez CA, Giurato G, Nassa G, Rizzo F, et al. (2020). Metabolic Regulation of Epigenetic Modifications and Cell Differentiation in Cancer. Cancers (Basel), 12.

[3] Sayed N, Huang Y, Nguyen K, Krejciova-Rajaniemi Z, Grawe AP, Gao T, et al. (2021). An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. Nat Aging, 1:598-615.

[4] Mittelbrunn M, Kroemer G (2021). Hallmarks of T cell aging. Nat Immunol, 22:687-698.

[5] Lareyre F, Chaptoukaev H, Kiang SC, Chaudhuri A, Behrendt CA, Zuluaga MA, et al. (2022). Telemedicine and Digital Health Applications in Vascular Surgery. J Clin Med, 11.

[6] Peyrin-Biroulet L, Adsul S, Stancati A, Dehmeshki J, Kubassova O (2024). An artificial intelligence-driven scoring system to measure histological disease activity in ulcerative colitis. United European Gastroenterol J, 12:1028-1033.

[7] Xu F, Fu H, Ma J (2024). Multifaceted efforts of governments, medical institutions, and financial organizations contribute to reducing the health inequality caused by economic differences. Cancer Biol Med,

21:1100-1103.

[8] Williams PA, Hossack E (2013). It will never happen to us: the likelihood and impact of privacy breaches on health data in Australia. Stud Health Technol Inform, 188:155-161.