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Database issue

Immunosenescence Inventory—a multi-omics database for immune aging research

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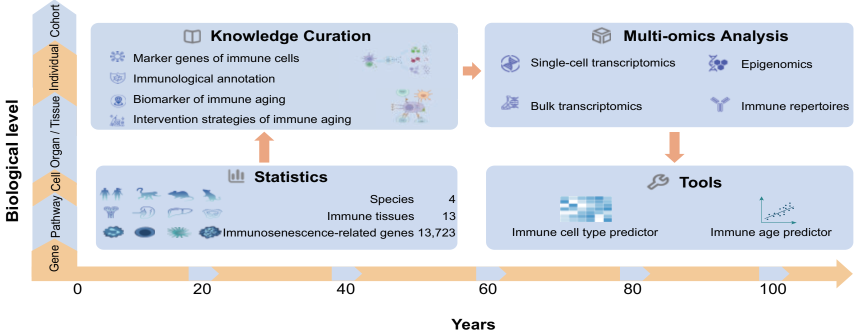
Abstract

The immune system is intricately interconnected with all other bodily systems. As individuals age, the immune system undergoes changes known as immunosenescence, increasing susceptibility to disease, and contributing significantly to the morbidity and mortality observed in older populations. Immunosenescence drives systemic aging and therefore represents a key therapeutic target to extend healthy aging. In recent years, the extensive application of omics technologies has broadened our understanding of aging and immunity, necessitating a comprehensive database to encapsulate these advancements and deepen our insights into immune aging in the era of artificial intelligence. The Immunosenescence Inventory is a pioneering database designed to provide a multidimensional and integrative view of the aging immune system. By leveraging cutting-edge omics technologies and analytical tools, Immunosenescence Inventory offers a comprehensive resource for researchers to explore the intricate relationship between immunosenescence and age-related health outcomes. Furthermore, the database, which aids in the creation of diagnostic tools for immune aging conditions, is now publicly available at https://ngdc.cncb.ac.cn/iaa/home.

Graphical abstract



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Introduction

The immune system is an intricate and vibrant network that experiences significant alterations over the lifespan. With advancing age, its capacity to counter novel challenges and preserve equilibrium diminishes—a process termed immunosenescence (1–3). This decline correlates with heightened susceptibility to infections and an elevated risk of chronic age-related ailments (4–6). Immunosenescence is also characterized by a reduction in the production of new immune cells, alterations in the functionality of existing ones, and a rise in persistent, low-grade inflammation, commonly referred to as 'inflammaging' (7–9). Gaining insights into the molecular and cellular underpinnings of immune aging is essential for devising strategies to foster healthy aging and prolong the human healthspan (10–13).

Currently, immune aging research is characterized by a fragmented landscape of databases that, while valuable, do not offer a cohesive and comprehensive resource for studying the intricate interplay between the immune system and the aging process (14–16). For instance, databases like ImmPort, InnateDB, HiShgAtlas and Gene Ontology fail to fully capture the ongoing and dynamic shifts in the immune system associated with aging (17–20). Furthermore, these databases frequently lack the comprehensive integration of multi-omics data across diverse tissues, species, and age groups, which is crucial for a thorough understanding of immunosenescence. They tend to focus on isolated aspects of the immune system or specific cell types, thereby limiting the scope of research and the ability to draw broad conclusions about the aging immune system (21,22).

For instance, databases like Aging Atlas and Human Aging Genomic Resources do not concentrate on immune aging and provide only a limited and fragmented view of immune aging data, making it difficult to synthesize and analyze knowledge across various studies (23–25). The Human Aging and Longevity Landscape, a comprehensive and multi-modal web resource for the exploration of human physiology and pathology in all stages of the lifespan (26). The ADEIP database compiles RNA-Seq data from the GTEx project to provide a general overview of how gene expression changes with age across various tissues (27–29). However, both database do not delve into the complexities of the aging immune system at the single-cell level, which is critical for understanding the intricate dynamics of immune aging and developing targeted interventions.

In light of these limitations, we propose the Immunosenescence Inventory as a novel solution to bridge this critical gap in the field. The Immunosenescence Inventory is designed to be a specialized, well-organized, and comprehensive compilation of multi-dimensional datasets specifically curated to focus on immune aging. By aggregating diverse and rich datasets from various species across different stages of life, the Immunosenescence Inventory aims to provide a more nuanced and detailed understanding of the aging immune system.

Database contents

The Immunosenescence Inventory aims to collect and integrate comprehensive datasets from humans and other animal species encompassing a wide array of immune parameters, molecular signatures and longitudinal immune profiles that change with age. The atlas catalogs multi-omics data on single-cell transcriptomics, bulk transcriptomics, epigenomics, and the analysis of T-cell receptor (TCR) and B-cell receptor (BCR) in the context of aging immune system, contributing to a more nuanced comprehension of the molecular changes associated with immune aging. It also functions as an open-access knowledge graph, featuring meticulously curated information regarding aging-related changes in immune cells and cytokines, biomarkers, and targeted immune aging interventions. The Immunosenescence Inventory database consists of three interconnected and mutually supportive components: Knowledge Curation, Multi-Modal Datasets, and Tools (Figures 1 and 2).

Homepage of immunosenescence inventory

The homepage is designed with a dynamic backdrop of floating immune cells, accentuated by a navigation bar at the top and a central search bar that enables comprehensive queries across various immune regulatory pathways for any gene within the Immunosenescence Inventory domain. The navigation bar indicates that the platform is structured around three core functional modules: Knowledge Curation, Multi-omics Analysis and Tools. The Integrated Immunosenescence Inventory compiles curated knowledge and datasets from an array of databases and scholarly works, serving as an extensive repository for pinpointing immune aging biomarkers and targets.

This section features a knowledge graph that catalogs immune cell types with their molecular markers, annotations of genes pertinent to immunity, shifts in immune cells associated with aging, alterations in cytokines linked to senescence, and markers and interventions for immune aging. The Multi-omics Analysis module presents a spectrum of omics data, including single-cell sequencing, bulk transcriptomics, epigenetic regulation, and TCR/BCR repertoires. The Tools module currently offers two utilities: immune cell identification and immune clock computation. This cohesive resource is instrumental in developing immune aging clocks that assess biological age from diverse health dimensions. These clocks are not only capable of gauging the rate of aging but also of forecasting the propensity for age-related diseases and evaluating the impact of interventions on immune aging, thereby propelling translational research in the realms of human aging and longevity.

Knowledge curation: constructing a digital knowledge atlas of immunosenescence

The Immunosenescence Inventory features a meticulously curated knowledge base that integrates a variety of topics related to immune aging (Figure 3). It provides a detailed taxonomy of immune pathways, cell types, marker genes and cytokines, along with their functionalities. The knowledge graph elucidates the roles these cells undertake in immune responses and demonstrates how these roles are influenced by aging. It highlights genes linked to immune aging within particular cell types, enriched with Gene Ontology (GO) terms, and delves into the relationship between chronic inflammation and aging. This comprehensive approach aids researchers in understanding the intricate dynamics of immune system aging and developing potential interventions to counteract its effects.

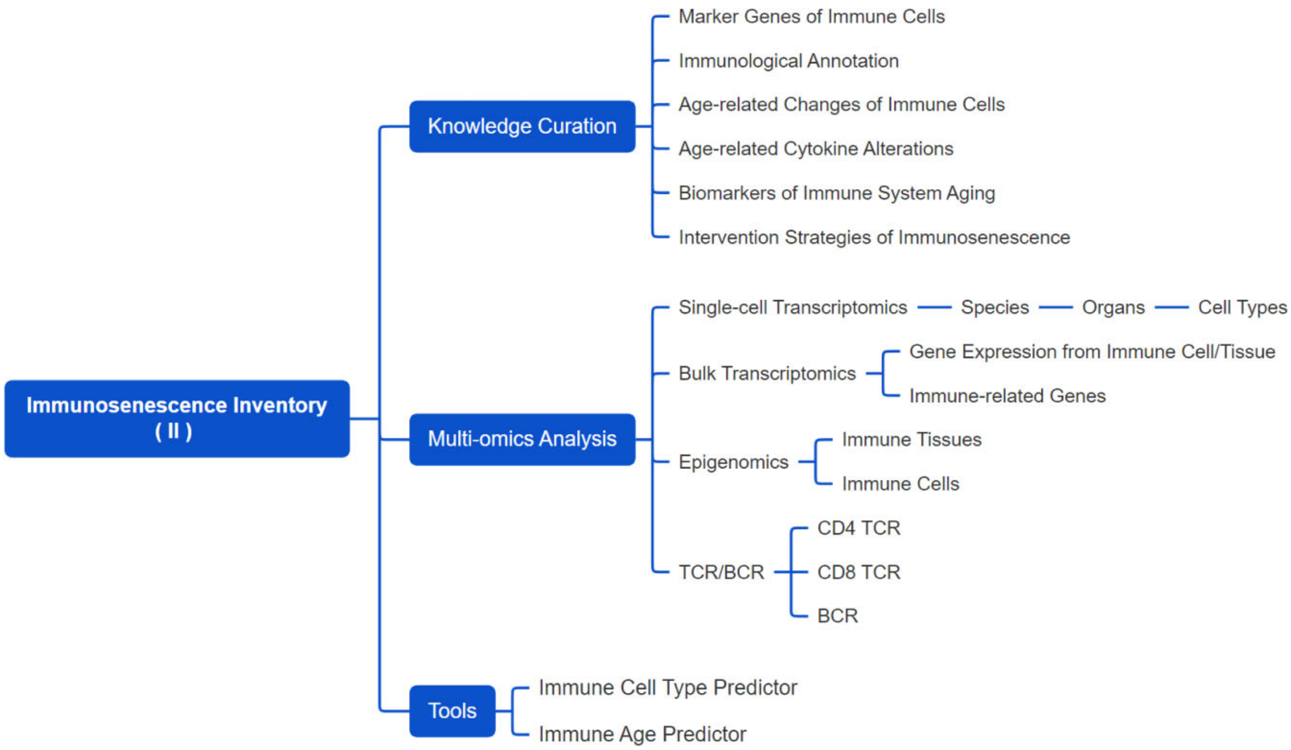


Figure 1. The Immunosenescence Inventory site map delineates the platform's hierarchical architecture. It serves as a guide, facilitating user navigation through the various tiers of the Immunosenescence Inventory interface.

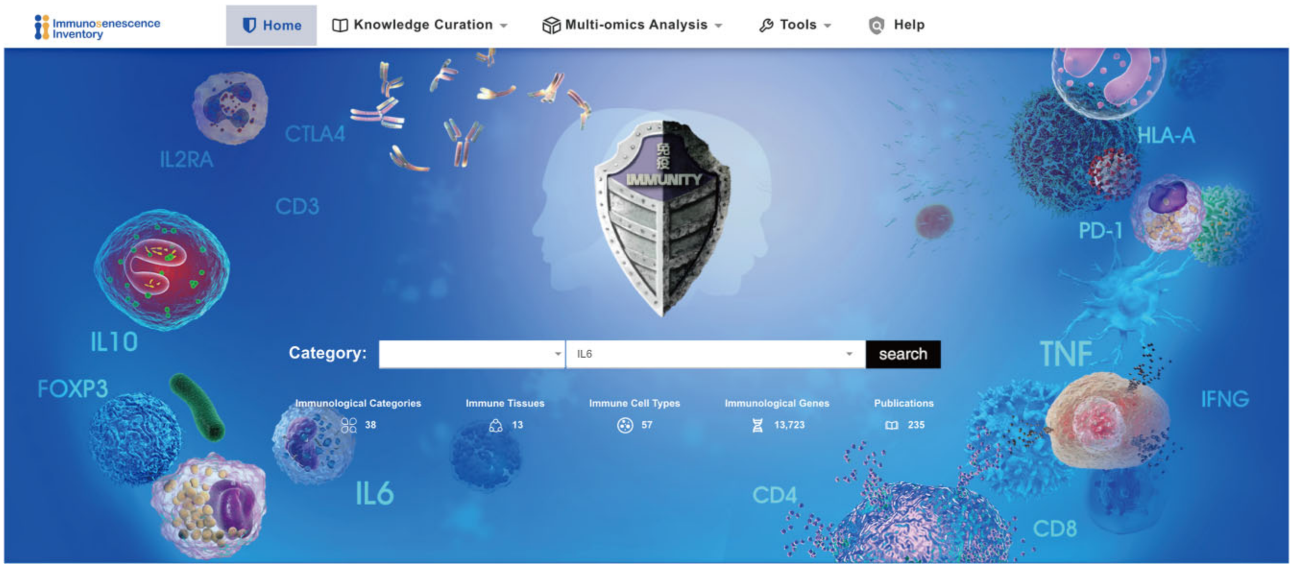


Figure 2. Homepage of Immunosenescence Inventory. The Immunosenescence Inventory database consists of three interconnected and mutually supportive components: Knowledge Curation, Multi-Modal Datasets and Tools.

Marker genes of immune cells

A detailed annotation of immune cell marker genes

This module is dedicated to the meticulous assembly of a knowledge base on immune cell marker genes, pivotal for the identification and differentiation of diverse immune cells. Our repository encompasses nine pivotal immune cell types along with their 29 distinct subtypes. This compilation integrates both established and novel cell markers, identified through significant expression patterns in RNA sequencing and single-cell RNA sequencing datasets. By amalgamating these markers, we offer a lucid and exhaustive perspective on the cellular constituents of the immune system, crucial for discourse on aging and for devising potential therapeutic interventions.

Immunological annotation

This section offers an extensive compendium of gene sets crucial for immune functionality

Our gene collection is meticulously curated from a suite of esteemed public databases, such as ADEIP, ImmPort, InnateDB, HisgAtlas, and Gene Ontology. These authoritative sources

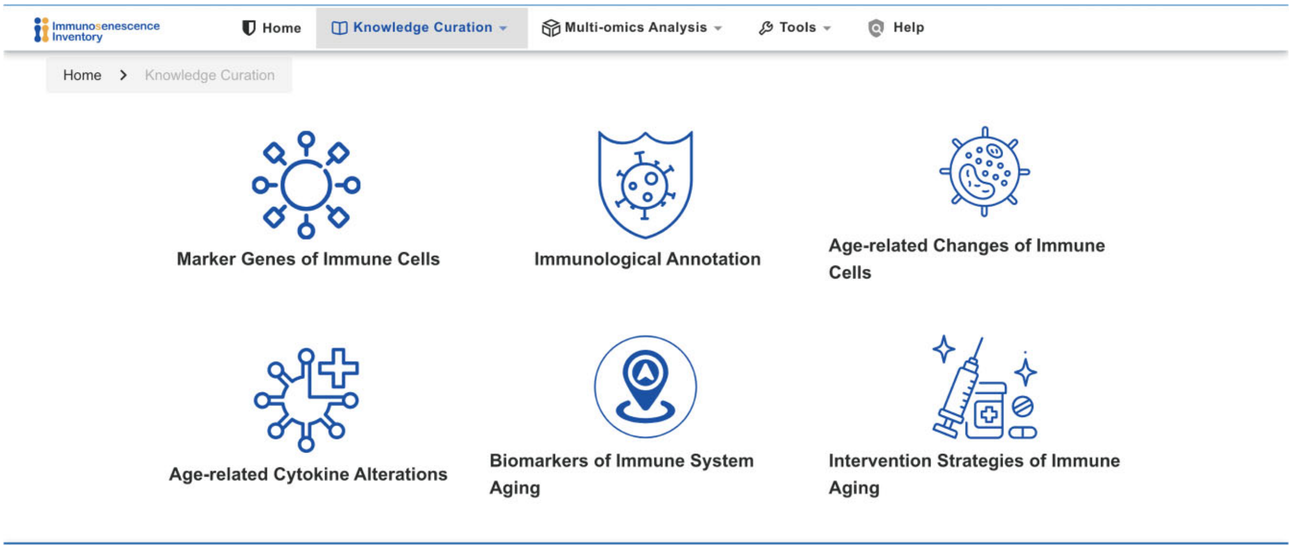


Figure 3. Knowledge curation. This part operates as an open-access knowledge base that provides carefully curated information on marker genes of immune cells, immunological annotation, age-related changes of immune cells, age-related cytokine alterations, biomarkers of immune system aging and knowledge pertaining to immune aging interventions.

furnish an abundance of gene annotations, establishing an intricate framework that empowers researchers to delve into the intricacies of the immune system's aging dynamics.

Age-related changes in immune cells

A compendium of the dynamics of immune cell changes associated with aging

Immunosenescence—the reconfiguration of the immune system by the passage of time—results in a reduced ability to respond to antigens and maintain immune surveillance. This section meticulously chronicles the aging process's impact on a spectrum of immune cell types, such as T cells, B cells, NK cells, macrophages and dendritic cells. It spans both human and murine models, utilizing diverse analytical methods to capture the nuances of these cellular transformations.

Age-related changes of cytokines

This section delves into the shifts in cytokine levels that accompany the aging process of the immune system

Cytokines, a group of small protein molecules pivotal to immune function, regulate immune responses by modulating cell interactions and signal transduction. This diverse family encompasses lymphokines, monokines, chemokines and interleukins, which can be autocrine or paracrine and exert either pro-inflammatory or anti-inflammatory effects. Consequently, we have meticulously curated data on cytokine alterations associated with aging, including notable increases in interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP). Such elevations are indicative of a condition termed 'inflammaging', which correlates with an elevated risk for health complications in the elderly. Gaining insights into the interplay between cytokines and aging is instrumental in devising interventions aimed at alleviating immunosenescence and fostering healthy aging practices.

Biomarkers of immune system aging

This section showcases a meticulously curated compendium of biomarkers reflective of the aging dynamics within the immune system

These biomarkers span various levels, manifest in distinct cell types, and are detected through diverse methodologies, collectively painting a multifaceted picture of the state of immunosenescence. Therefore, there is an imperative for the systematic development of additional immunosenescence biomarkers to construct more precise immunological clocks.

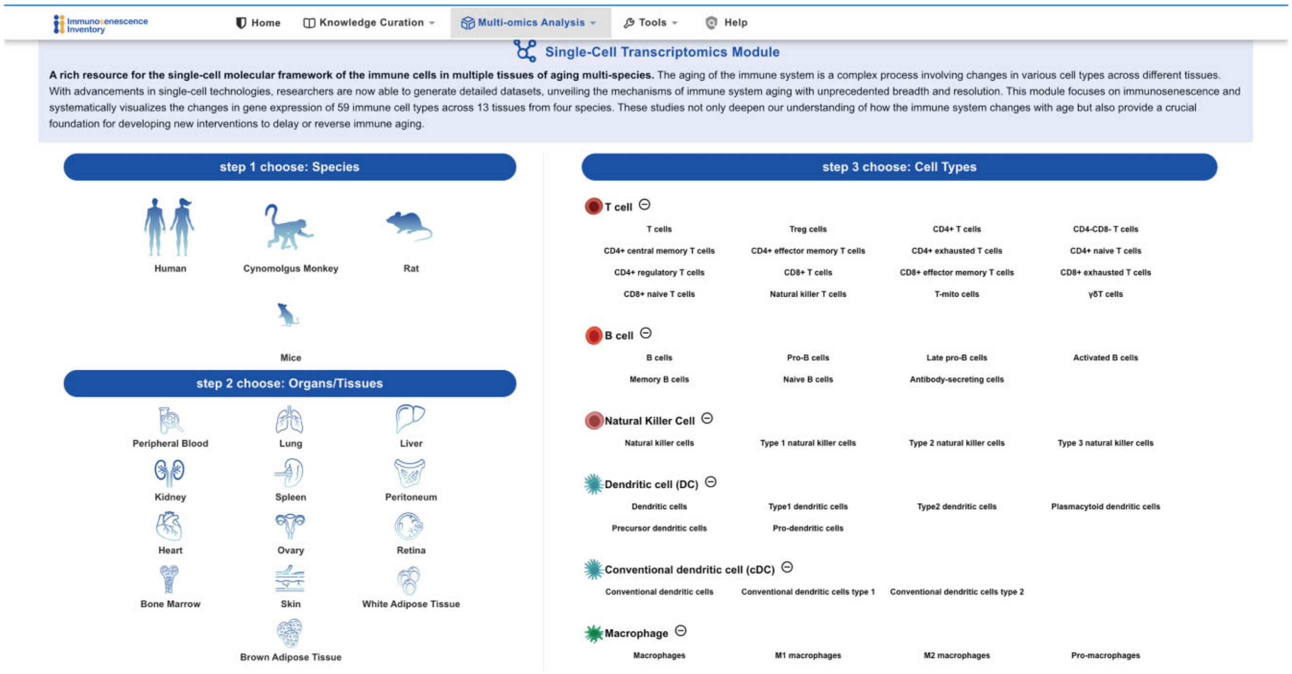
Intervention strategy of immune aging

This section introduces a strategic toolkit designed to combat immune aging and its associated diseases

It encompasses a diverse array of interventions, ranging from small molecule therapies and senolytics to stem cell therapies and vaccinations. Additionally, lifestyle modifications, including dietary adjustments, physical exercise, and the regulation of circadian rhythms, are also integrated into the database. Highlighting the role of biologics therapy and microbiota transplantation, this segment emphasizes the journey of these promising treatments from research to clinical application.

Multi-modal datasets: omics database for immune aging

The Immunosenescence Inventory serves as an extensive resource, delivering a comprehensive overview of age-related alterations in the immune system across various biological levels. It includes cellular resolution gene expression profiles of 59 immune cell types across 13 tissues from four species through Single-Cell RNA Sequencing (scRNA-Seq). The database also demonstrates age-associated disparities in immune-related gene expression levels and cell ratios based on Bulk RNA Sequencing (RNA-Seq), it is also features data on how epigenetic modifications in immune cells change with age. The epigenetic module offers a user-friendly platform for



A rich resource for the single-cell molecular framework of the immune cells in multiple tissues of aging multi-species. The aging of the immune system is a complex process involving changes in various cell types across different tissues. With advancements in single-cell technologies, researchers are now able to generate detailed datasets, unveiling the mechanisms of immune system aging with unprecedented breadth and resolution. This module focuses on immunosenescence and systematically visualizes the changes in gene expression of 59 immune cell types across 13 tissues from four species. These studies not only deepen our understanding of how the immune system changes with age but also provide a crucial foundation for developing new interventions to delay or reverse immune aging.

Figure 4. Single-cell transcriptomics module. This module examines gene expression in 59 immune cell types across 13 tissues and four species, offering insights into the immune system's aging process and paving the way for potential interventions to combat immune aging.

researchers to explore aging-related methylation patterns, enabling the discovery of epigenetic signatures of aging. Additionally, the TCR/BCR Module provides comprehensive single-cell sequencing data on T and B cell receptors across various tissues, revealing the impact of aging on immune diversity and functionality. The database also contains comprehensive data on cytokine and antibody levels and information on how receptor–ligand interactions within the immune system are affected by aging.

The single-cell transcriptomics module: rich resource for elucidating the single-cell molecular framework underlying immunosenescence across tissues

The aging of the immune system is a complex process involving changes in various cell types across different tissues. With advancements in single-cell technologies, researchers are now able to generate detailed datasets, unveiling the mechanisms of immune system aging with unprecedented breadth and resolution. This module focuses on immunosenescence and systematically visualizes the changes in gene expression of 59 immune cell types across 13 tissues from four species (Figure 4).

The transcriptomics module: the bulk transcriptomics module offers a comprehensive dataset that meticulously documents the molecular changes occurring within the immune system as it ages

This valuable resource provides an extensive array of transcriptomic profiles across a spectrum of immune cells and tissues, delivering an intricate perspective on the immune system's aging trajectory. The module is furnished with two principal search methodologies for efficient data navigation. The initial approach enables researchers to scrutinize age-related gene expression variations in immune tissues, including peripheral blood, bone marrow, thymus and lymph nodes, which are significantly impacted by aging. The second method concentrates on pathways pertinent to immune function, elucidating the age-dependent evolution of immune-related genes at the tissue level (Figure 5).

Epigenomics module: an essential tool for DNA methylation analysis in human immune aging

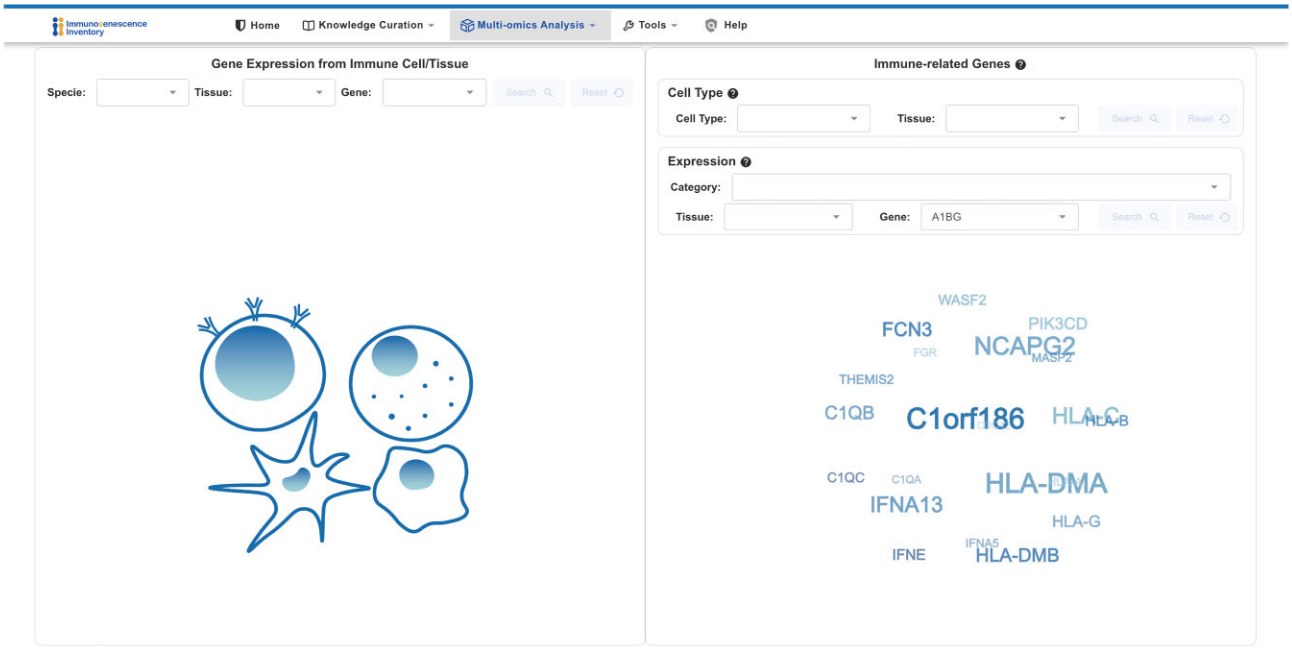
This section compiles a comprehensive collection of DNA methylation changes in immune organs and cells as they undergo the aging process. Users can select specific tissues or cell types to access and download the complete DNA methylation profiles. Furthermore, the module enables targeted searches for methylation alterations of specific genes and probes within the context of immune aging (Figure 6).

The TCR/BCR module: the TCR/BCR module is a vital resource that compiles data on CD4 T-cell receptor, CD8 T-cell receptor and B-cell receptor in various tissues, offering insights into the aging process's impact on the immune system

As the body ages, there are notable alterations in the diversity and functionality of these receptors, which are crucial for the immune response. This module presents single-cell TCR-sequencing data for both CD4 and CD8 T cells, as well as TCR and BCR-sequencing data, derived from both young and aged mice. The data spans across different tissues, including the liver, lung, spleen, and peritoneal cells. By analyzing these receptor characteristics within multiple tissue environments, users can gain a comprehensive understanding of the immune variations associated with aging.

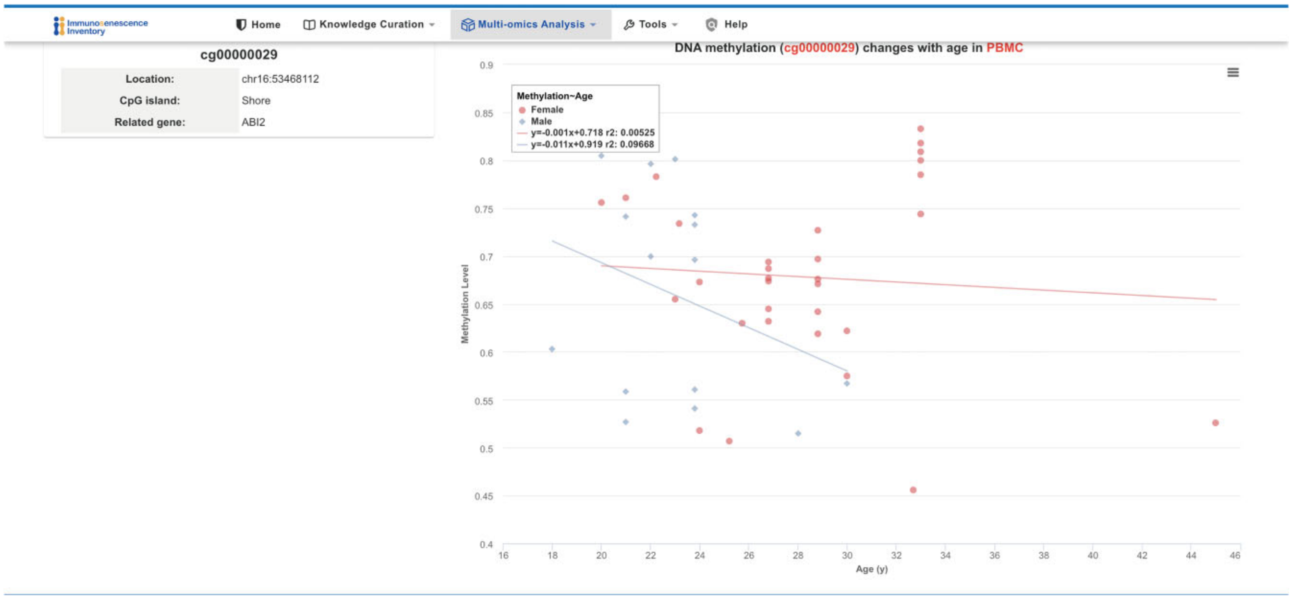
Tools

We aspire to provide users with a diverse suite of online tools to aid in the study of immunosenescence. Currently, we offer two fundamental functionalities: immune cell identification and immune age calculation. Given the high complexity and dynamism of immune cells, the classification based on simple cell markers warrants refinement. Leveraging the unique gene expression profiles of various immune cells within our



Gene: A1BG

Figure 5. Transcriptomics module. The bulk transcriptomics module details molecular aging in the immune system, with search tools to explore gene expression and immune function evolution.



cg00000029

Location:	chr16:53468112
CpG island:	Shore
Related gene:	ABI2

Figure 6. Epigenomics module. The epigenetic module examines DNA methylation in aging immune cells, identifying potential intervention points for immune health.

database, we present an online tool for immune cell identification using transcriptome matching methods. Additionally, we have developed an immune age clock that requires users to input data in a single format, offering insights into how their body's functions relate to their chronological age. It is crucial to emphasize that, due to the complexities of individual health conditions, this tool is intended solely as an advisory resource for assessing one's biological age. Furthermore, acknowledging the current limitations in immune clock research, our calculation methods are subject to ongoing optimization and improvement.

CellTypist is an automated cell type annotation tool for scRNA-seq datasets on the basis of logistic regression classifiers optimised by the stochastic gradient descent algorithm (30,31).

Immune age predictor: A model for age estimation that seamlessly integrates a spectrum of immune-related omics data, employing the ElasticNet algorithm for robust prediction accuracy (32).The algorithm is utilized to construct a regression model based on multi-omics data, including transcriptomics, proteomics, and metabolomics, to predict biological age related to immune function.

Data upload and feedback

For users who wish to submit data to this database, we added a data upload feature. Users can submit data by providing their email and properly formatted omics data. User feedback is essential for interactively improving the database. We also included a feedback function in Immunosenescence Inventory to receive suggestions from the users. We will promptly review and make necessary improvements in response to the feedback to continuously enhance the user experience and data quality.

Concluding remarks

The establishment of the Immunosenescence Inventory database represents a milestone in the scientific community's efforts to comprehend and combat the complex processes of immune aging. This integrated platform demonstrates the power of multi-omics data integration in elucidating the intricate biological mechanisms underlying immunosenescence. The Inventory serves not only as a dynamic repository of current knowledge but also as a catalyst for future discoveries, fostering a deeper understanding of the molecular and cellular changes associated with aging.

While the Inventory has integrated extensive multi-omics data, we recognize the importance of incorporating broader demographic representation in future data to ensure universality and applicability across diverse ethnicities and geographies. We are actively expanding the database to encompass a more diverse population, revealing subtle differences in the aging process of the immune system among various individuals and communities. Furthermore, valuing interdisciplinary collaboration, we are actively seeking partnerships with experts in computer science, bioinformatics, and statistics. These collaborations will enhance the database's analytical capabilities and ensure the Inventory remains a cutting-edge resource for researchers. Additionally, the database places a premium on data privacy. All data within the Inventory is managed with strict adherence to ethical standards and privacy laws. We have implemented state-of-the-art security measures to safeguard sensitive information and established a transparent data access policy that prioritizes user privacy.

In summary, the Immunosenescence Inventory is a dynamic and growing resource that will continue to evolve alongside the scientific community's expanding knowledge of immune aging. Our commitment to regular updates, interdisciplinary collaboration, and data privacy underscores our dedication to providing a comprehensive and reliable tool for researchers worldwide.

Data availability

Immunosenescence Inventory is freely available at https://ngdc.cncb.ac.cn/iaa/home.

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Conflict of interest statement

None declared.

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