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Aging Atlas: a multi-omics database for aging biology

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ABSTRACT

Organismal aging is driven by interconnected molecular changes encompassing internal and extracellular factors. Combinational analysis of high-throughput 'multi-omics' datasets (gathering information from genomics, epigenomics, transcriptomics, proteomics, metabolomics and pharmacogenomics), at either populational or single-cell levels, can provide a multi-dimensional, integrated profile of the heterogeneous aging process with unprecedented throughput and detail. These new strategies allow for the exploration of the molecular profile and regulatory status of gene expression during aging, and in turn, facilitate the development of new aging interventions. With a continually growing volume of valuable aging-related data, it is necessary to establish an open and integrated database to support a wide spectrum of aging research. The Aging Atlas database aims to provide a wide range of life science researchers with valuable resources that allow access to a large-scale of gene expression and regulation datasets created by various high-throughput omics technologies. The current implementation includes five modules: transcriptomics (RNA-seq), single-cell transcriptomics (scRNA-seq), epigenomics (ChIP-seq), proteomics (protein–protein interaction), and pharmacogenomics (geroprotective compounds). Aging Atlas provides user-friendly functionalities to explore age-related changes in gene expression, as well as raw data download services. Aging Atlas is freely available at https://bigd.big.ac.cn/aging/index.

INTRODUCTION

As the aging population grows progressively around the globe, the need to research and develop strategies to healthy aging is ever more critical and takes on new urgency. Aging is a complex process, influenced by genetic and epigenetic regulation, post-translational regulation, metabolic regulation, host–microbiome interactions, lifestyle, and many other elements (1–6). Recently, high-throughput omics technologies (including genomics, transcriptomics, epigenomics, metabolomics, proteomics, pharmacogenomics and metagenomics) have been widely applied in aging studies (1,7,8), resulting in large-scale profiling of aging-associated molecular changes and regulatory states (9). In addition, evolving technologies at the single-cell resolution allow us to probe aging with integrated and multi-dimensional data at an unprecedented scale and depth (10,11). As a result, there is a growing volume of valuable aging-related data, calling for an open and integrated database to support new lines of aging research.

Currently, there are several publicly available databases housing aging-specific gene information, including the Human Aging Genomic Resources (HAGR, containing GenAge, AnAge, GenDR, LongevityMap and DrugAge) (12), AgeFactDB (13), the Digital Ageing Atlas (14), and AGEMAP (15). Most of these are knowledgebases that compile aging phenotypes, longevity records, aging/longevity-related genes, and factors with lifespan-extending effects. However, to the best of our knowledge, none of these databases allows one to upload, interactively query, jointly analyze, and visualize aging-related omics or single-cell sequencing data. This is a critical gap, as the construction of an aging database that provides access to large gene expression and regulation datasets created by a variety of high-throughput omics technologies would be a valuable resource for a wide range of life science researchers.

To facilitate integrative, system-level studies of aging and longevity, we developed Aging Atlas, a curated biomedical database comprising a range of aging-related multi-omics datasets (i.e. transcriptomics, single-cell transcriptomics, epigenomics, proteomics, and pharmacogenomics), as well as bioinformatics tools to query and visualize these datasets. This database aims to collect multi-omics data spanning the entire spectrum of aging and longevity biology across model organisms and other species. The database also curates data related to cellular senescence, age-related diseases, lifespan-extension strategies (such as exercise and caloric restriction (CR)) and geroprotective drug development. The datasets are classified according to the nature of the omics data, rather than the type of experiments. Currently, data in Aging Atlas are manually curated from the literature and retrieved from published datasets. Users around the world will be able to upload their data easily according to a specific data category and the raw data will be deposited in public databases such as the National Genomics Data Center (NGDC), which hosts Aging Atlas (16). This database is searchable either by gene name or DOI of any literature reference. Moreover, search results can be presented as ta-

†Members of Aging Atlas Consortium (arranged by modules) are listed in Appendix section.

bles or interactive charts, and the corresponding raw data can also be downloaded. In this way, Aging Atlas provides users with interactive, user-friendly functionalities to facilitate query and analysis of gene expression and regulation with age, and helps identify regulatory networks related to such gene expression changes during aging. Aging Atlas is freely available at https://bigd.big.ac.cn/aging/index.

DATABASE CONTENT

The current implementation of Aging Atlas includes five modules: transcriptomics, single-cell transcriptomics, epigenomics, proteomics, and pharmacogenomics (Figure 1). In addition, the Aging Atlas Consortium has manually curated a collection of aging-related human and mouse genes, hereafter referred to as Genes Archived in Aging Atlas (GAAA). The GAAA section now contains hundreds of human and mouse aging-related genes, divided into 10 'Gene Sets' and corresponding KEGG pathways. The Gene Sets are featured by well-established aging hallmarks (17), including genomic instability, telomere attrition, epigenetic alteration, loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, altered intercellular communications, cellular senescence, and stem cell exhaustion. Each gene in GAAA has been attributed to these Gene Sets by gerontological experts of Aging Atlas Consortium. Therefore, GAAA provides a benchmark section of Aging Atlas to help our user better interpret the biological implications of these aging-related genes.

Transcriptomics (RNA-Seq) Module

The RNA-seq module catalogs genome-wide transcriptomic changes related to aging. The datasets collected in the RNA-seq module are derived from published articles related to aging research. This module collects changes in transcriptomes observed upon specific gene interventions (overexpression, knockout, etc.), such as alterations seen upon the manipulation of *FOXO3* (18,19), *CLOCK* (20) and other key aging regulators. This module also collects changes in gene expression profiles during physiological and pathological aging in specific tissues and organs. This includes data such as genome-wide gene expression changes across multiple tissues in the monkey model of the Hutchinson–Gilford progeria syndrome (HGPS) (21). The RNA-seq module currently contains >18 000 differentially expressed genes (DEGs) that may be related to aging. In the RNA-seq module , DEGs can be easily searched by gene name and each DEG entry contains underlying experimental conditions and the fold change of gene expression along with its published source. All search results and the corresponding DEG database in each article can be downloaded. To provide more information about the gene of interest, the RNA-seq module also includes reference information from other databases, including basic gene descriptions from RefSeq (22) and GenAge (12), and gene ontology obtained from AmiGO (23). Our database has been updated continually, and users are encouraged to upload their data to the database as well. As such, in this module, we have been integrating a large amount of RNA sequencing data from aging research articles to promote the sharing and analysis of information and knowledge among researchers.

Single-cell transcriptomics (scRNA-Seq) Module

The scRNA-seq module systematically organizes tissue- and cell type-specific heterogeneous changes in gene expression with age. This module provides high-resolution, comprehensive reference maps of different cell types or subtypes, as well as information on their temporal and spatial distribution, along with gene expression patterns of each cell type or subtype under different aging-related or disease conditions. An increasing number of studies have probed the single-cell transcriptome of a range of aged organs in different species, including fly, rodent, monkey and human (10,24). Recently, the *Tabula Muris* Consortium and our group reported single-cell transcriptomic atlases that span multiple aging tissues in rats and mice (24–26), representing existing large-scale single-cell transcriptome resources. This progress, along with the growing application of single-cell sequencing to questions related to aging, calls for an integrated database that stores and analyzes such cell type-specific gene expression information. Accordingly, here we provide a scRNA-seq module, which currently includes single-cell RNA sequencing datasets from 14 types of aged tissues from rats, monkeys, and humans. These data include cell type annotations and cell type-specific DEGs extracted from multiple mammalian tissues in the single-cell transcriptomic atlas for aging and under caloric restriction (CR) (24). This module also contains single-cell transcriptomic data covering ovary, islet, aorta, retina, and cardiopulmonary aging in the non-human primate (,19,27–30), as well as the single-cell transcriptomic landscape of human circulating immune cells in elderly COVID-19 patients (31).

In this module, users can easily access information about specific cell types, visualize and download it with a interactive interface. Information includes the number of cells, known and novel marker genes, and DEGs during the aging process or aging interventions. These functions will help users extract the molecular characteristics of different cell types at the single-cell resolution, and even reutilize these datasets to uncover new information about cellular regulation during aging. In addition, we keep compiling new datasets from more species and tissues in this module, allowing the construction of a systematic multi-species aging map to strengthen our understanding of aging and aging interventions at the single-cell resolution. Altogether, this module collects datasets from multi-organ single-cell transcriptomes, and clarifies the commonality and specificity of aging in different organs across species, providing a valuable resource for the aging biology community.

Epigenomics (ChIP-Seq) Module

The ChIP-seq module currently contains large Chromatin Immunoprecipitation Sequencing (ChIP-seq) data, reflecting how specific aging-related loci are regulated by histone modifications and transcription factors. These data help elucidate how regulatory factors impact gene expression during aging at a genome-wide scale. In the future, this module will be expanded to include a wider range of epigenetic data, including DNA methylation, ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing), DamID-seq (DNA adenine methyltransferase identification (DamID)), R-loop landscape, and mapping of the

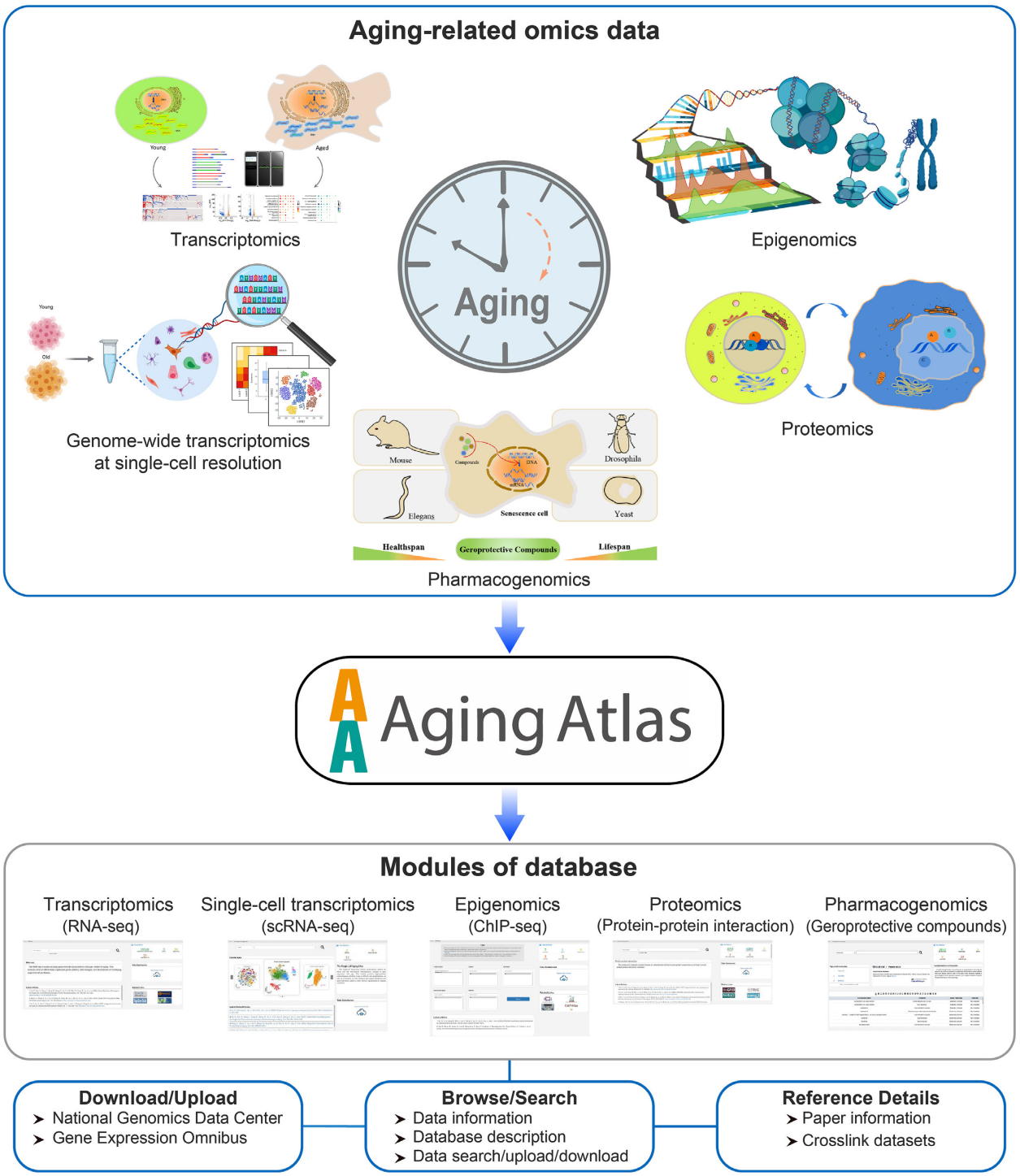

Figure 1. Overview of the Aging Atlas database. Aging Atlas provides a platform for joint analysis of aging-related omics data, as well as online tools to visualize and compare these data. The current implementation of Aging Atlas includes five modules: transcriptomics (RNA-seq), single-cell transcriptomics (scRNA-seq), epigenomics (ChIP-seq), proteomics (protein–protein interaction), and pharmacogenomics (geroprotective compounds), which will be expanded according to the needs of aging research and the availability of data.

higher-order chromatin structure (such as Hi-C). ChIP-seq data were curated from published aging-related articles and raw data were processed using the same analytical methods to maintain consistency. The results can be visualized in the WashU Epigenome Browser (32), which intuitively displays changes in the enrichment of different transcription factors or histone modifications at specific genomic loci during aging. Therefore, this module aims to provide a systematic database of epigenomic regulation for researchers.

Proteomics (Protein–protein Interaction) Module

Impaired protein homeostasis is typical during aging, and protein interactions undergo significant changes with age (33). Here, the protein–protein interaction module (referred to as PPI) is designed to allow the query of protein of interest and its interacting partners associated with aging. Raw PPI data were manually collected from published articles in the aging field. The primary function of PPI is to search for interacting partners of the protein of interest by its UniProt entry name or accession number. The results are presented in two ways: an interactive table and a network diagram. The former presents more detailed information, including the number of interactive proteins, cell/tissue types, and publications supporting the interaction; the latter allows for the visualization of protein interaction networks and provides options to perform gene ontology or KEGG pathway analyses on selected data with online tools. Meanwhile, the download button allows users to scan the list of interacting proteins and related publications locally. To incorporate more aging-related PPI data, we have designed the data deposition port to facilitate PPI data uploaded by the users into the database. Furthermore, we plan to expand this module to include quantitative proteomics and post-translational modification analyses. Thus, PPI will be a useful module for the analysis of crucial protein interactions during cellular senescence, allowing a better understanding of human aging at the protein level.

Pharmacogenomics (Geroprotective Compounds) Module

This geroprotective compounds module focuses on geroprotectors and allows users to query compounds related to aging, providing summary data of related compounds as applied in model organisms, according to aging phenotypes, targets, pathways, and age-related diseases. The module currently contains a list of hundreds of compounds and omics datasets from drug therapy analyses (both *in vivo* and *in vitro*), revealing changes in gene expression caused by specific lifespan/healthspan-extending drugs. The data are primarily curated from the published literature and other aging-associated databases (12). On the homepage of this module, users can browse through the 'Top small molecules' function, which lists most searched compounds by weekly updates; 'Clinical Trials' presents clinical trial data of geroprotectors; 'Feature articles' displays the latest research in the aging field. Importantly, users can easily search by the name of the drug, target gene, or DOI of the source paper, to access detailed information about the geroprotective compounds. If a corresponding RNA-seq dataset is available, a link will be provided in the gene expression tables (34,35). Compared with existing databases such as DrugAge (12), this module not only presents a list of lifespan-extending and healthspan-extending compounds, but also provides information on the changes in gene regulation and expression caused by the drugs.

CONCLUDING REMARKS

Aging is a multifactorial and gradual process that causes cell type-specific and tissue-specific changes. This complex process affects most regulatory mechanisms at different hierarchical levels in living systems progressively (36). The development of novel multi-omics techniques has resulted in the rapid accumulation of a massive number of aging-related datasets, including genomic, epigenetic, transcriptomic, proteomic, metabolic and physiological data, providing a potential treasure trove of integrated information on the aging process (8,11). In order to explore these aging-related multi-omics data more efficiently, we constructed Aging Atlas– a multi-omics database for aging biology. (i) To the best of our knowledge, Aging Atlas is the first database to curate single-cell transcriptomes data in the field of aging research. (ii) As we have embedded a quick search box on the Aging Atlas homepage, users can easily obtain aging-related data on their factor of interest across data sets and technologies. (iii) Aging Atlas provides user-friendly functionalities to explore age-related gene expression changes and help identify critical regulatory networks in the aging process. (iv) In addition, users are encouraged to share data through the 'upload' functionality. With the combined efforts of our users and our team, the database has been updated continually to add high-quality omics data from aging research, which is freely available to the public. Furthermore, we will integrate more data and additional data-analysis tools, including deep learning tools for aging and longevity research (37). Along with other databases focusing on different perspectives in aging study, such as HAGR, Encyclopaedia of introductive aging knowledge (12), and Digital Aging Atlas that aims to collect data covering different biological levels (14), Aging Atlas focuses on big data generated by omics technologies and provides a valuable resource for the aging research community and other life scientists more broadly.

DATA AVAILABILITY

All data in Aging Atlas is available to the users without registration or login (https://bigd.big.ac.cn/aging/index). Users can directly download the searched data in the corresponding module.

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APPENDIX

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