

Original Article

Integrating AI and Causal Genetics to Prioritize Therapeutic Targets for Aging and Age-Related Diseases

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ABSTRACT: Aging is increasingly viewed as a pathological process and a principal driver of diverse age-related diseases (ARDs). Framing aging as a disease offers an opportunity to identify therapeutic targets capable of modifying multiple chronic disorders simultaneously. Here, we developed an artificial intelligence (AI)-driven target discovery framework that integrates large-scale multi-omic datasets to prioritize therapeutic targets shared between aging and 12 ARDs spanning four major disease areas: neurological, inflammatory, metabolic, and fibrotic disorders. We identified 29 high-confidence and 16 previously unrecognized aging-associated targets implicated across the selected disease areas, together with convergent pathway perturbations characterized by robust upregulation of interferon and inflammatory signaling, alongside coordinated downregulation of MYC-driven proliferative programs, consistent with heightened inflammatory activation and reduced anabolic activity during aging. Age-dependent transcriptomic alterations across tissues were observed for all identified target genes. Hallmarks of aging assessment revealed chronic inflammation as the most enriched hallmark across aging and ARDs. Mendelian randomization analyses provided genetic causal support for *IL6*, *IL6R*, *NLRP3*, *NOS2*, *TLR4*, and *GLP1R* in aging-related traits and multiple ARDs, highlighting potential opportunities for drug repurposing. Co-localization analyses suggested that the same genetic variants influencing *IL6R* expression are also associated with parental survival, a proxy for human lifespan, supporting a role for IL-6 signaling in longevity, and indicated a shared genetic signal at the *NOS2* locus associated with rheumatoid arthritis risk. Together, our findings outline a scalable AI-guided multi-omic framework for identifying causal and repurposable therapeutic targets for aging and ARDs.

Keywords: machine learning, therapeutic targets, drug repurposing, inflammaging, multi-omics, causal inference

INTRODUCTION

Aging is the dominant risk factor for most chronic diseases, including cardiovascular disorders, cancer, neurodegenerative conditions, and metabolic syndromes. Traditionally regarded as an inevitable biological process, aging is now increasingly recognized as a quantifiable and potentially modifiable driver of pathology. This paradigm

shift is particularly important in the context of rapidly aging global populations. The escalating prevalence of multimorbidity and the associated demand for long-term care place unprecedented strain on healthcare systems and socioeconomic infrastructures, underscoring the need for interventions that prolong healthspan [1, 2]. Consequently, contemporary drug discovery efforts are increasingly pivoting toward targeting the fundamental

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mechanisms of aging to simultaneously ameliorate multiple diseases, though identifying robust, clinically translatable targets remains a formidable challenge [3]. Advances in geroscience have demonstrated that core molecular mechanisms underlying aging, such as loss of homeostasis, impaired stress responses, and cellular senescence, are amenable to therapeutic intervention. Viewing aging as a disease, or at least as a treatable pathological process, raises the possibility of simultaneously delaying or preventing multiple age-related diseases (ARDs), thereby extending healthspan and reducing the long-term burden on healthcare systems. Reflecting this conceptual shift, aging has been formally incorporated into major biomedical classification frameworks, including the World Health Organization's ICD-11 (codes MG2A and XT9T) [4, 5] and the Experimental Factor Ontology (EFO_0022597) [6], underscoring its growing clinical and research relevance.

Recent advances in high-throughput molecular profiling have enabled comprehensive interrogation of aging biology across multiple omic layers, including genomic variation, transcriptomic reprogramming, and epigenetic modifications. These molecular alterations interact through complex and often non-linear networks to drive both physiological decline and increased susceptibility to ARDs. However, the scale, heterogeneity, and dimensionality of such datasets present substantial challenges for conventional analytical approaches, thereby limiting their translational utility.

Artificial intelligence (AI), particularly deep learning-based methods, offers a powerful solution to address these limitations by enabling the integration of heterogeneous data types, identifying latent patterns across biological systems, and prioritizing therapeutic targets at scale [7-12]. For example, recent applications of AI have successfully facilitated the identification of novel therapeutic targets and the discovery of active compounds for complex neurodegenerative conditions, including Alzheimer's disease and amyotrophic lateral sclerosis [13-15]. By systematically combining multi-omic data with disease knowledge, AI-driven methods can uncover shared molecular mechanisms linking aging with diverse pathological outcomes [16].

In our previous work, we compared transcriptomic signatures of ARDs and non-ARDs as a proxy for aging biology, identifying therapeutic targets enriched across age-related pathologies [17]. In the present study, we extend this framework by conceptualizing aging as a modifiable disease process. By integrating state-of-the-art AI-driven target prioritization methods and causal genetics analyses, we identify circulating therapeutic targets and pathways that mechanistically link aging with multiple ARDs (Fig. 1). Our findings highlight both established and previously unrecognized aging-related targets with geroprotective potential and demonstrate the utility of AI-driven multi-omic integration as a scalable framework for systematic target discovery and drug repurposing aimed at extending human healthspan.

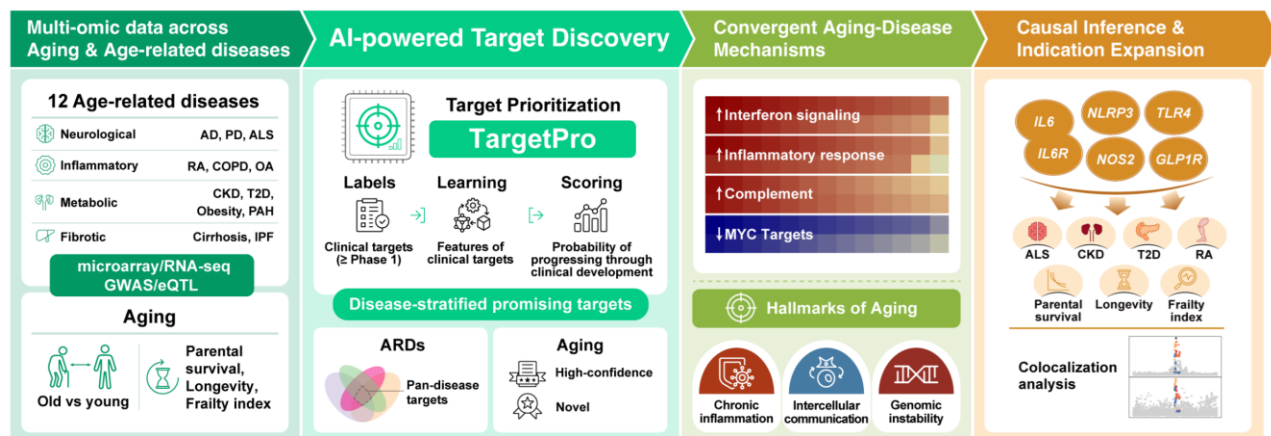


Figure 1. Overview of study design. Multi-omic datasets, including transcriptomic and genetic data, were assembled for aging and 12 age-related diseases (ARDs). AI-based target prioritization was performed using the TargetPro platform, where clinically investigated targets (≥ Phase I) served as training labels to learn molecular features associated with successful drug targets. Candidate genes were subsequently scored based on similarity to these clinical targets, enabling prioritization of disease-specific and shared targets across aging and ARDs. Pathway enrichment analysis and hallmarks of aging assessment were then used to define convergent molecular signatures. Finally, genetic analyses, including Mendelian randomization and co-localization, were performed to assess causal relationships and identify potential indication expansion opportunities.

MATERIALS AND METHODS

Data collection and processing

Publicly available datasets were retrieved from the Gene Expression Omnibus (GEO) and ArrayExpress repositories. Only human-derived studies were considered. To ensure sufficient statistical power and analytical robustness, datasets were required to include at least three case samples and three control samples. Analyses were restricted to circulating biospecimens. Raw microarray expression data were normalized by quantile normalization, and RNA-sequencing (RNA-seq) data were normalized by upper-quartile normalization. Genes were filtered to retain protein-coding genes only, as annotated using the biomaRt R package (v2.54.1) [18]. Features with zero coverage in $\geq 25\%$ of samples were excluded to reduce sparsity and improve downstream statistical stability. In total, 51 datasets spanning aging and 12 age-related diseases were included, comprising 2,839 case samples and 1,886 control samples (Supplementary Table 1). To evaluate age-associated expression patterns of prioritized targets, RNA-seq data were obtained from the Genotype-Tissue Expression (GTEx) consortium (available at <https://gtexportal.org/home/>). The GTEx resource includes post-mortem samples from a total of 946 non-diseased adult donors across 54 tissue types. Gene-level expression values reported as transcripts per million (TPM) were downloaded and log-transformed using $\log_2(\text{TPM} + 1)$ prior to analyses.

For Mendelian randomization and colocalization analyses, full GWAS summary statistics for each ARD and two aging-related traits, longevity and frailty index, were obtained from the GWAS Catalog [19] (Supplementary Table 2). In the longevity GWAS, cases were defined as individuals surviving to or beyond the 90th percentile of age within the cohort, while controls were defined as individuals who died before the 60th percentile of age [20]. Frailty index was defined as the number of health deficits during an individual's life-course such as immobility, disability, and hospitalization [21]. In addition, parental survival was included as a proxy for lifespan, under the assumption of shared genetic effect sizes between maternal and paternal survival [22]. To minimize genetic differences across ancestries, only GWAS conducted in European-ancestry cohorts were included. For traits with multiple eligible GWAS, the study with the largest sample size and most comprehensive variant coverage was retained. Expression quantitative trait loci (eQTL) data were obtained from the eQTLGen Phase I dataset [23]. To ensure consistency across genetic analyses, all GWAS and eQTL genomic coordinates were harmonized to the GRCh37 reference

genome using the UCSC's LiftOver tool where necessary [24].

Quality control

Quality control (QC) was applied to each dataset prior to downstream analyses. Initial assessment included visualization of sample distributions using boxplots and principal component analysis to identify batch or plate effects and detect potential outlier samples arising from technical artefacts. Datasets exhibiting suspected technical outliers or non-biological clustering patterns were examined further prior to inclusion. For ARD datasets, additional steps were taken to account for potential confounding by chronological age, as age-associated molecular changes in gene expression could bias disease-control comparisons. The contribution of age to feature-level variability was quantified using the variancePartition R package (v1.28.9) [25], which estimates the proportion of variance explained by each covariate. Age was included as a covariate in linear models if it explained more than 5% of the variance in over 25% of features within a dataset, and adjusted residuals were derived from linear regression models using the `lm()` function in R. The resulting age-adjusted feature matrix was used for all subsequent analyses. The same QC framework was applied to other available covariates across all datasets, including both aging and ARD cohorts. Potential confounders such as sex, geographic region, and ethnicity were evaluated for their contribution to feature-level variance. Where these covariates exceeded the predefined (5%) variance thresholds, their effects were similarly regressed out prior to downstream analyses. All QC-filtered and covariate-adjusted matrices were subsequently uploaded to PandaOmics for AI-driven target discovery by TargetPro.

Case-control comparisons and target prioritization

Case-control comparison was performed separately for each dataset in each condition using *limma* implemented in PandaOmics. For aging datasets, cases were defined as individuals aged ≥ 60 and controls as those aged ≤ 50 . For 1 aging dataset (GSE16717), long-lived individuals (mean age = 93.4 years) were treated as cases where non-long-lived individuals (mean age = 61.9 years) from the same families were included as controls. For each condition, results from all eligible datasets were subsequently combined by meta-analysis to derive consensus disease-associated effect estimates across studies. P values were adjusted for multiple testing using the Benjamini-Hochberg (BH) procedure, and genes with BH-adjusted P values (P_{BH}) < 0.05 (i.e., leading to an FDR < 0.05) were considered significantly dysregulated.

Target prioritization was performed using the AI-driven target identification tool TargetPro available on PandaOmics [26, 27]. Briefly, TargetPro integrates evidence from 22 independent models, which are subsequently combined using an XGBoost ensemble to rank genes according to their likelihood of causal involvement in a given disease and the probability of success in advancing through clinical stages. These models leverage multiple evidence types, including clinical annotations and prior knowledge of target-disease associations, such as whether a gene has been investigated in clinical trials or approved therapies for the disease of interest. Since aging has only recently been classified as a disease and lacks standardized clinical trial endpoints, direct clinical evidence for aging-targeted interventions remains sparse. To address this limitation, we incorporated a curated list of aging-associated genes from the GenAge database (302 genes) [28] as a surrogate source of prior biological evidence for high-confidence aging-related targets. This gene set was used to inform and calibrate target prioritization for aging within the TargetPro framework, enabling systematic ranking of candidate targets despite the limited availability of clinical aging-specific data. In contrast, novel aging-related targets were defined as those not annotated in the GenAge database.

Pathway enrichment analysis

Gene Set Enrichment Analysis (GSEA) was performed on aging and each ARD using ranked gene lists derived from the meta-analyzed effect estimates (β), representing overall transcriptomic changes between cases and controls. Fifty human hallmark gene sets were obtained from the Molecular Signatures Database (MSigDB) via the msigdb R package (v25.1.1) [29]. GSEA was conducted using the fgsea R package (v1.24.0) [30]. Gene sets with positive normalized enrichment scores ($NES > 0$) were interpreted as transcriptionally activated, whereas those with negative scores ($NES < 0$) were considered inhibited. In addition to GSEA, over-representation pathway enrichment analysis was performed to identify biological pathways enriched among gene sets commonly implicated across disease areas, as well as among high-confidence and novel aging-specific target genes. Reactome-annotated pathways were analyzed using the R package ReactomePA (v1.42.0) [31]. For both hallmark gene sets and Reactome pathways, multiple testing correction was applied using the BH procedure, and pathways with $P_{BH} < 0.05$ were considered significantly enriched.

Robust rank aggregation

Robust rank aggregation (RRA) was applied to identify hallmark gene sets and target genes that were consistently prioritized higher than expected across multiple ARDs [22]. RRA was performed using the Robust RankAggregation R package (v1.2.1) [32]. Briefly, ranked lists of hallmark gene sets (50 gene sets) or target genes (19,291 genes) were generated for each ARD. RRA was conducted in a two-stage manner. First, ranked lists were combined within each disease area to identify gene sets and targets that were consistently enriched or prioritized across area-specific ARDs. Subsequently, ranked lists from all ARDs were aggregated to identify pan-ARD hallmark gene sets and target genes shared across disease areas. RRA assigns a score to each gene set or target gene that reflects the probability of observing its aggregated rank under a null model of random ordering, with lower scores indicating stronger and more consistent prioritization. For visualization and interpretability, RRA scores were $-\log_{10}$ -transformed, such that higher aggregated scores correspond to stronger evidence of consistent enrichment or prioritization across ARDs.

Hallmarks of aging assessment

Assessment on the associated hallmark(s) of aging was performed for each target gene based on their annotated gene ontology (GO) terms retrieved from biomaRt and literature by mapping the keywords as previously described [33]. A gene was defined as associated with a particular hallmark if it had ≥ 1 GO term matched to the keyword(s) of that corresponding hallmark.

Mendelian randomization and colocalization analyses

Cis-acting eQTLs (cis-eQTLs) were used as instrumental variables in Mendelian randomization (MR) analyses to minimize horizontal pleiotropy and enhance biological interpretability. It is important to note that MR provides genetically informed, probabilistic estimates of directional effects predicated on specific instrumental variable assumptions, rather than definitive proof of biological causality. Cis-eQTL variants were first filtered using a genome-wide significance threshold ($P < 5 \times 10^{-8}$). Linkage disequilibrium (LD) clumping was then performed to retain approximately independent variants using PLINK (v1.9) [34] with the European reference panel from the 1000 Genomes Project (phase 3). Variants were clumped using an LD threshold of $r^2 < 0.1$ within a ± 100 kb window. The resulting LD-pruned cis-eQTL variants were used as instruments in two-sample MR analyses using the R package TwoSampleMR (v0.5.7) [35] to test for putative causal effects of gene expression on the risk of each ARD and aging-related trait. Summary statistics were obtained from independent eQTL and

MR evidence, using the approximate Bayes factor method implemented in the coloc R package (v5.2.3) [36]. Posterior probabilities were computed to assess whether the eQTL and disease association signals were consistent with a shared causal variant. Strong colocalization was defined as $PP.H4 > 0.8$, and moderate colocalization as $PP.H4 > 0.6$. Prior probabilities were set to $p_1 = 1 \times 10^{-4}$, $p_2 = 1 \times 10^{-4}$, and $p_{12} = 1 \times 10^{-5}$.

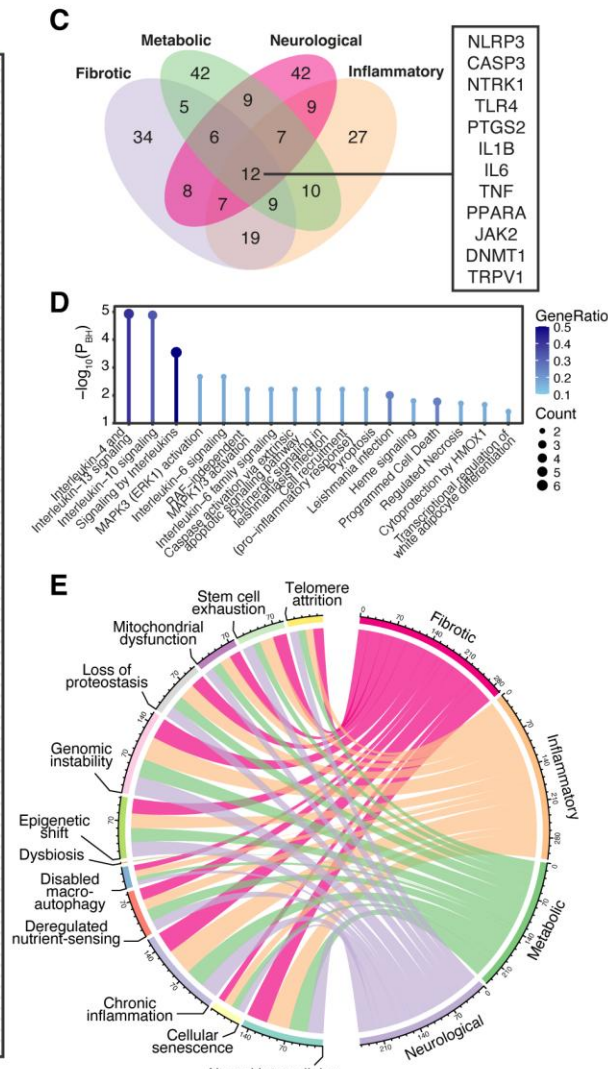


Figure 2. Transcriptional changes and targets implicated in age-related diseases. (A) The 10 most significantly perturbed hallmark gene sets ranked by robust rank aggregation (RRA) across ARDs. Red, NES > 0; Blue, NES < 0. (B) Ninety-three target genes highly ranked across ARDs by RRA. The heatmap displays aggregated scores for each disease area, and the dotplot summarizes overall scores together with the number of contributing disease areas. (C) Overlap of prioritized genes between disease areas, highlighting twelve highly-ranked shared targets. (D) Pathway enrichment of the 12 shared targets identified in C. (E) Associations between hallmarks of aging and disease areas based on prioritized targets. NES, Normalized enrichment score; P_{BH}, Benjamini-Hochberg-corrected P value.

Correlation between gene expression levels and age

Spearman's rank-based correlation analyses were performed to test for associations between gene expression levels of prioritized target genes and age in the GTEx samples, stratified by tissue type. Expression levels were adjusted for sex before correlation analyses. Multiple testing was corrected by the BH method. Genes with P_{BH} < 0.05 were considered significantly correlated with age in the tissue.

RESULTS

Targets and pathways implicated in age-related diseases

A total of 12 ARDs spanning 4 disease areas were included in this study: (i) neurological diseases [Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD)]; (ii) inflammatory diseases [chronic obstructive pulmonary disease (COPD), Osteoarthritis (OA), Rheumatoid arthritis (RA)]; (iii) metabolic diseases [Chronic kidney disease (CKD), Obesity, Pulmonary arterial hypertension (PAH), Type II diabetes (T2D)]; and (iv) fibrotic diseases [Cirrhosis of liver (Cirrhosis), Idiopathic pulmonary fibrosis (IPF)] (Supplementary Table 1). Samples obtained from non-diseased individuals in each dataset were used as controls for case-control comparisons. Gene Set Enrichment Analysis (GSEA) was performed on each ARD using meta-analyzed effect estimates obtained from differential expression analysis to identify perturbed gene sets. Among the 50 hallmark gene sets tested, IPF exhibited the most extensive dysregulation, with 25 gene sets (50%) significantly altered (FDR < 0.05), followed by PAH (20 gene sets, 40%) and obesity (18 gene sets, 36%) (Supplementary Fig. 1). Robust rank aggregation (RRA) was then applied to identify hallmark gene sets consistently perturbed across diseases within each disease area (Fig. 2A). This analysis revealed a core set of recurrently activated pathways, including interferon gamma response, inflammatory response, complement, and apoptosis. In contrast, MYC targets v1 pathway was broadly downregulated across most ARDs, suggesting suppression of proliferative and biosynthetic programs in chronic disease states (Fig. 2A).

Target prioritization was performed for each disease to identify the most promising therapeutic gene candidates using 22 machine learning models (see Materials and Methods). Ranked gene lists were aggregated using RRA within each disease area (top 100 genes per area; union = 246 genes) and across all ARDs, yielding 93 target genes that were prioritized more frequently than expected (Fig. 2B). The top genes, ranked by the overall aggregated score across all diseases, were *NLRP3*, *TLR4*, and *NOS2*. Twelve target genes were shared by all disease areas, including *NLRP3*, *CASP3*, *NTRK1*, *TLR4*, *PTGS2*, *IL1B*, *IL6*, *TNF*, *PPARA*, *JAK2*, *DNMT1*, and *TRPV1* (Fig. 2C). Pathway enrichment analysis of these 12 pan-disease genes identified 17 significantly enriched pathways (FDR < 0.05). Interleukin-4 and Interleukin-13 signaling was the most significantly enriched (P_{BH} = 1.2x10⁻⁵), followed by Interleukin-10 pathway (P_{BH} = 1.3x10⁻⁵). Additional enriched axes included MAPK signaling, programmed cell death, immune regulation, and adipocyte differentiation, highlighting shared inflammatory and metabolic mechanisms underlying ARDs (Fig. 2D).

We next examined the relationship between prioritized targets and aging by mapping these genes to established hallmarks of aging (see Materials and Methods). Of the 93 genes tested, 91 (98%) were associated with at least one hallmark. As expected, inflammatory diseases showed the strongest enrichment for the hallmark of chronic inflammation, with 52 of 63 inflammatory-associated targets mapping to this process (P = 1.5x10⁻³, hypergeometric test). Considering all disease areas, chronic inflammation was the most frequently implicated hallmark (67 genes, 72%), followed by altered intercellular communication (65 genes, 70%) and genomic instability (64 genes, 69%) (Fig. 2E). Together, these findings demonstrate substantial involvement of aging-related biological processes across ARDs, with inflammation emerging as a central shared axis.

Targets and pathways implicated in aging

To characterize aging-associated transcriptomic changes, four independent datasets comparing older (n=125) and younger (n=264) individuals were analyzed (see Materials and Methods; Supplementary Table 1). Meta-analysis revealed 878 genes significantly altered in older adults, including 312 upregulated and 566 downregulated (FDR

< 0.05 , Fig. 3A). The most significantly upregulated genes included *FLVCR2*, *SORT1*, *ANXA2*, *LGALS1*, and *FCGR1A*, whereas *LRRN3*, *CD248*, *CR2*, *NOG*, and *SLC4A10* were among the most significantly downregulated. GSEA identified 33 enriched hallmark gene sets. Interferon gamma response ($P_{BH} = 3.9 \times 10^{-32}$) and interferon alpha response ($P_{BH} = 8.4 \times 10^{-25}$) showed

the strongest enrichment (Fig. 3B), consistent with pronounced activation of immune and inflammatory signaling in aging. Notably, these pathways overlapped with those consistently perturbed in ARDs (Fig. 2A), indicating shared transcriptional programs linking aging and disease.

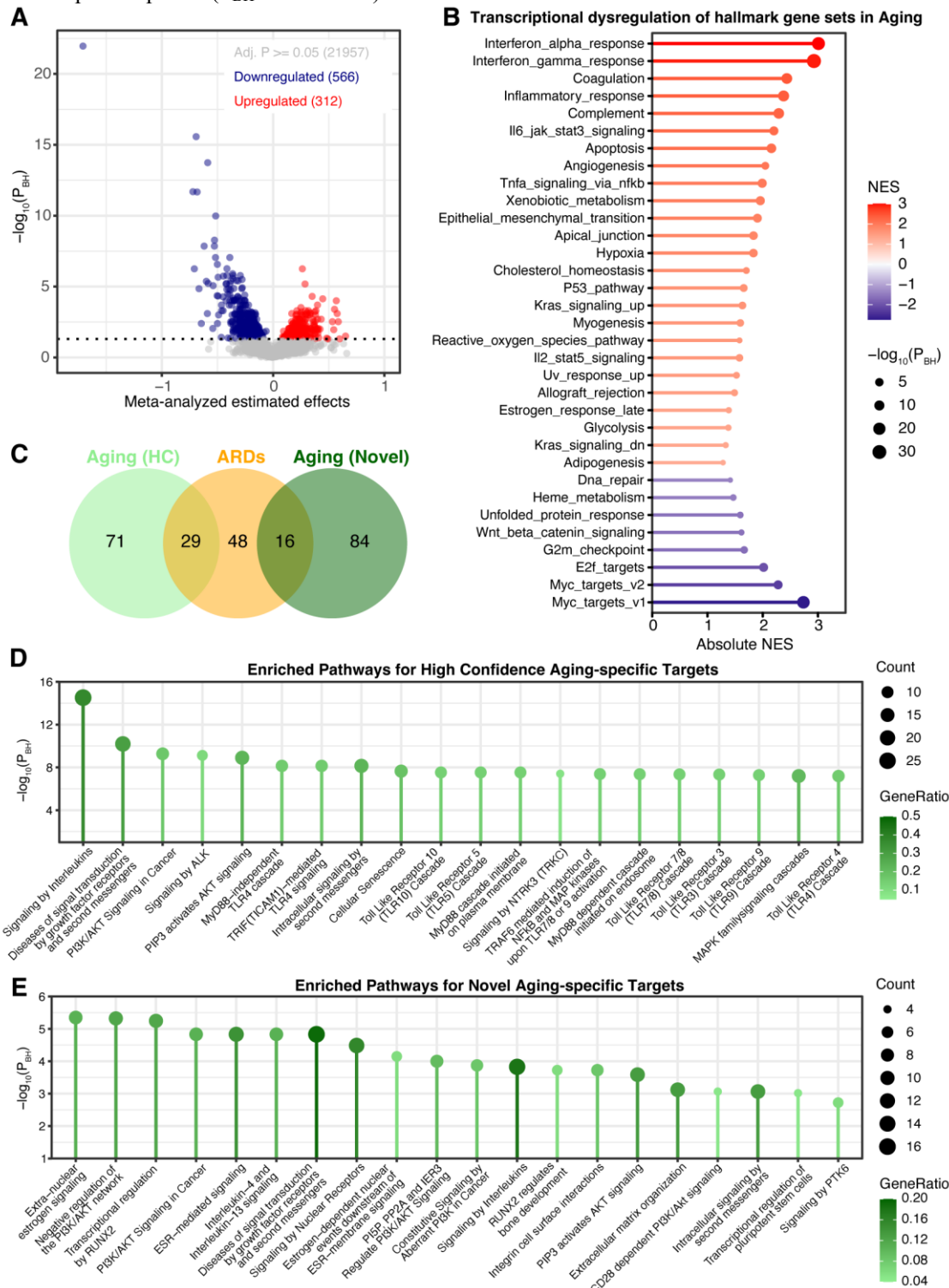


Figure 3. Transcriptional changes and targets implicated in aging. (A) Volcano plot of meta-analyzed estimated effects ($\log_2$ fold change) across the 4 transcriptomic datasets of aging. Each point represents one gene. Red, significantly upregulated; Blue, significantly downregulated; Grey; not significantly dysregulated at $P_{BH} > 0.05$. (B) Dysregulation patterns of 33 significantly perturbed hallmark gene sets in aging. (C) Venn diagram showing the number of overlapped targets between aging and age-related diseases, and aging-specific target genes. (D) Pathways enrichment analysis of high-confidence aging-specific targets. (E) Pathways enrichment analysis of novel aging-specific targets. HC, High confidence; NES, Normalized enrichment score; P_{BH} , Benjamini-Hochberg-corrected P value.

Target prioritization identified a set of genes previously implicated in aging that are cataloged in the GenAge database. These comprised *CDKN2A*, *PTPN11*, *JAK2*, *SOD1*, and *VEGFA* (Supplementary Table 3), which we define as high-confidence aging targets. To expand discovery, we further prioritized genes absent from GenAge, yielding a set of putative novel aging targets. Highly ranked candidates encompassed *CXCL8*, *CD19*, *IL3*, *CASP3*, and *TLR4* (Supplementary Table 4). Aging-specific targets were defined as those prioritized in aging but not present in the pan-ARD target list (Fig. 2B), resulting in 71 high-confidence and 84 novel aging-specific targets (Fig. 3C).

Pathway enrichment analysis of high-confidence aging-specific targets identified signaling by interleukins as the dominant enriched pathway ($P_{BH} = 3.0 \times 10^{-15}$), accompanied by enrichment of PI3K/AKT signaling, cellular senescence, NTRK signaling, growth factor signaling, and multiple Toll-like receptor pathways (Fig. 3D, Supplementary Table 5). In contrast, analysis of novel aging-specific targets highlighted extra-nuclear estrogen signaling ($P_{BH} = 4.5 \times 10^{-6}$), along with enrichment of PI3K/AKT, interleukin signaling, RUNX2 transcriptional programs, extracellular matrix organization, pluripotency-related transcription, and PTK6 signaling (Fig. 3E, Supplementary Table 6). Together, these findings delineate aging-specific regulatory programs that extend beyond canonical inflammatory pathways to include hormonal, developmental, and stem cell associated signaling networks.

Commonly perturbed pathways and targets implicated in aging and age-related diseases

To directly compare aging and ARDs at the pathway level, we examined enrichment patterns of the 33 aging-associated hallmark gene sets in ARDs. Most gene sets exhibited consistent dysregulation across diseases, including activation of complement, TNF- α signaling, inflammatory response, and interferon pathways (Fig. 4A). Notably, this was accompanied by concurrent alterations in metabolic and proliferative programs, including downregulation of MYC and E2F targets and perturbation of glycolysis and cholesterol homeostasis. In parallel, pathways related to cellular stress and damage responses, such as apoptosis, hypoxia, and reactive oxygen species signaling, were also enriched. The

simultaneous dysregulation of inflammatory, metabolic, and stress-response pathways across diverse diseases underscores the multifactorial nature of aging biology, suggesting that the coordinated therapeutic modulation of these intersecting processes may yield superior clinical benefits compared to isolated interventions. Correlation analysis of normalized enrichment scores demonstrated strong concordance between aging and neurological diseases (PD: $\rho = 0.93$; AD: $\rho = 0.86$; ALS: $\rho = 0.73$), indicating shared transcriptional architectures (Fig. 4B). Moderate-to-strong correlations were also observed in several other diseases, whereas cirrhosis ($\rho = 0.15$) and OA ($\rho = -0.03$) showed minimal concordance with aging, likely reflecting limited statistical power, tissue heterogeneity, or disease-specific biology.

Forty-five targets (29 high-confidence and 16 novel aging-related candidates) were prioritized in aging and ARDs (Fig. 3C). Among these, *NOS2*, *IL6*, *NLRP3*, and *TLR4* were each implicated in 10 ARDs (Fig. 4C). All targets were associated with at least one hallmark of aging (Fig. 4D). Within the high-confidence set, *AKT1*, *MTOR*, and *SIRT1* were linked to 11 hallmarks, whereas among the novel targets, *SRC* and *GLPIR* were associated with 10 and 9 hallmarks, respectively. Chronic inflammation remained the most enriched hallmark, involving 38 genes (84%), underscoring its central role in both aging and disease. We further assessed correlations between expression of these 45 targets and age across 54 tissues in the GTEx cohort (see Materials and Methods). Each gene showed a significant association with age in at least one tissue (FDR < 0.05; Supplementary Fig. 2). *MTOR* exhibited significant correlations in the largest number of tissues (30), followed by *GSK3B* and *CXCR4* (26 tissues each).

Mendelian randomization identifies genes causally linked to aging-related traits

To evaluate potential causal relationships between prioritized targets and aging, we performed Mendelian randomization (MR) analyses using cis-eQTL instruments (see Materials and Methods). Aging-related traits included parental survival [22], longevity [20], and frailty index [21] (see Materials and Methods). We selected one high-confidence (*IL6*) and 3 novel aging genes (*NOS2*, *NLRP3* and *TLR4*) since they showed the most associations with ARDs (each prioritized in 10

ARDs). *GLP1R* was additionally included based on its strong association with nine hallmarks of aging and prioritization in 7 ARDs. Given that IL-6 signals through its receptor IL6R, which is more abundant in circulation

and represents a pharmacological target of approved IL-6 pathway inhibitors, *IL6R* was also evaluated as a mechanistically linked candidate.

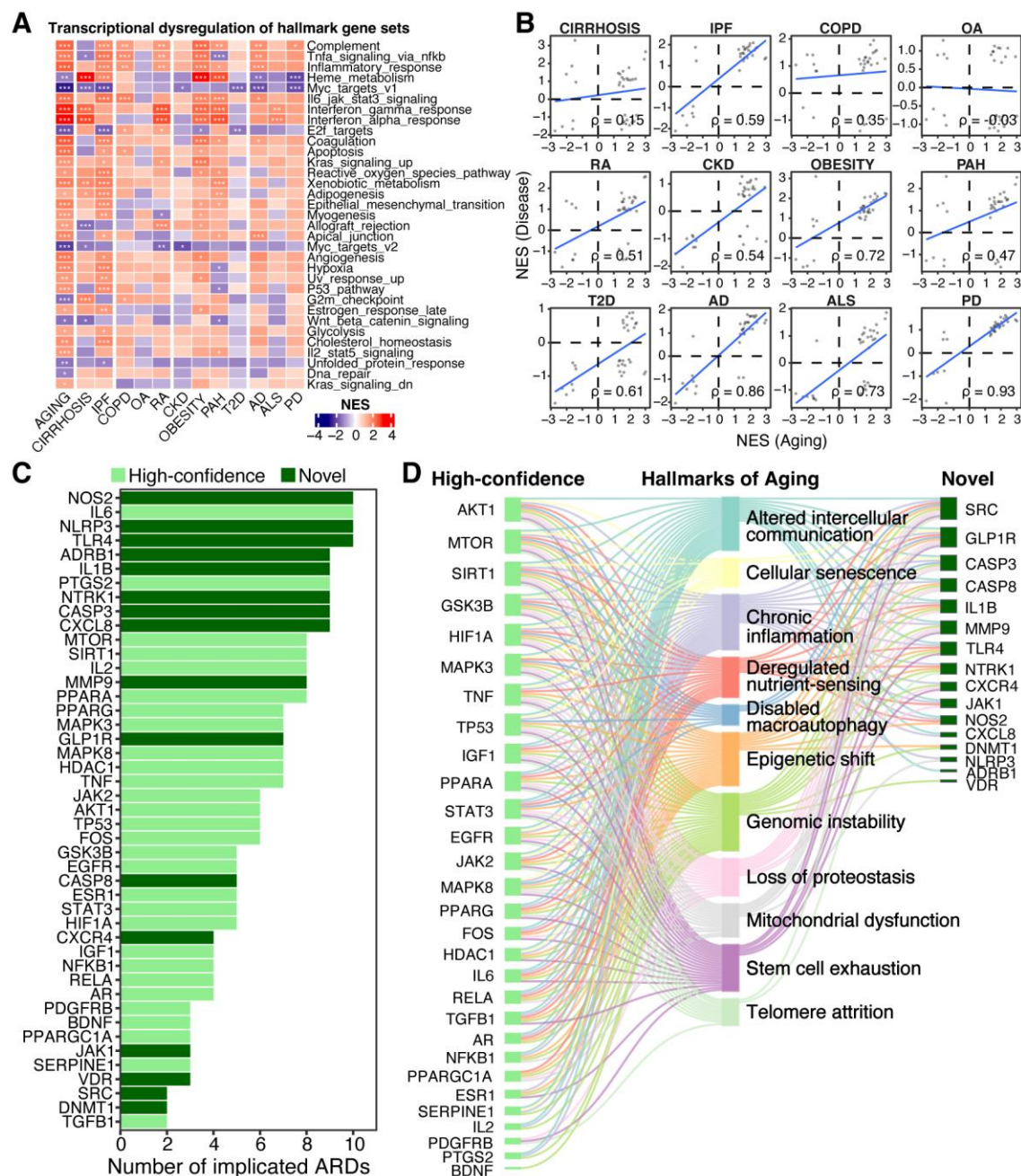


Figure 4. Shared pathways and targets between aging and age-related diseases. (A) Transcriptional dysregulation patterns of 33 hallmark gene sets in aging and ARDs that were significantly perturbed in aging. * $P_{BH} < 0.05$, ** $P_{BH} < 0.01$, *** $P_{BH} < 0.001$. (B) Correlation of normalized enrichment scores for all hallmark gene sets between aging and ARDs. Each point represents one gene set. Blue line indicates the best-fit line obtained from linear regression. (C) Forty-five target genes commonly implicated in aging and ARDs. (D) Sankey plot illustrating associations between the 45 targets (29 high-confidence and 16 novel aging targets) and hallmarks of aging. NES, Normalized enrichment score; P_{BH} , Benjamini-Hochberg-corrected P value.

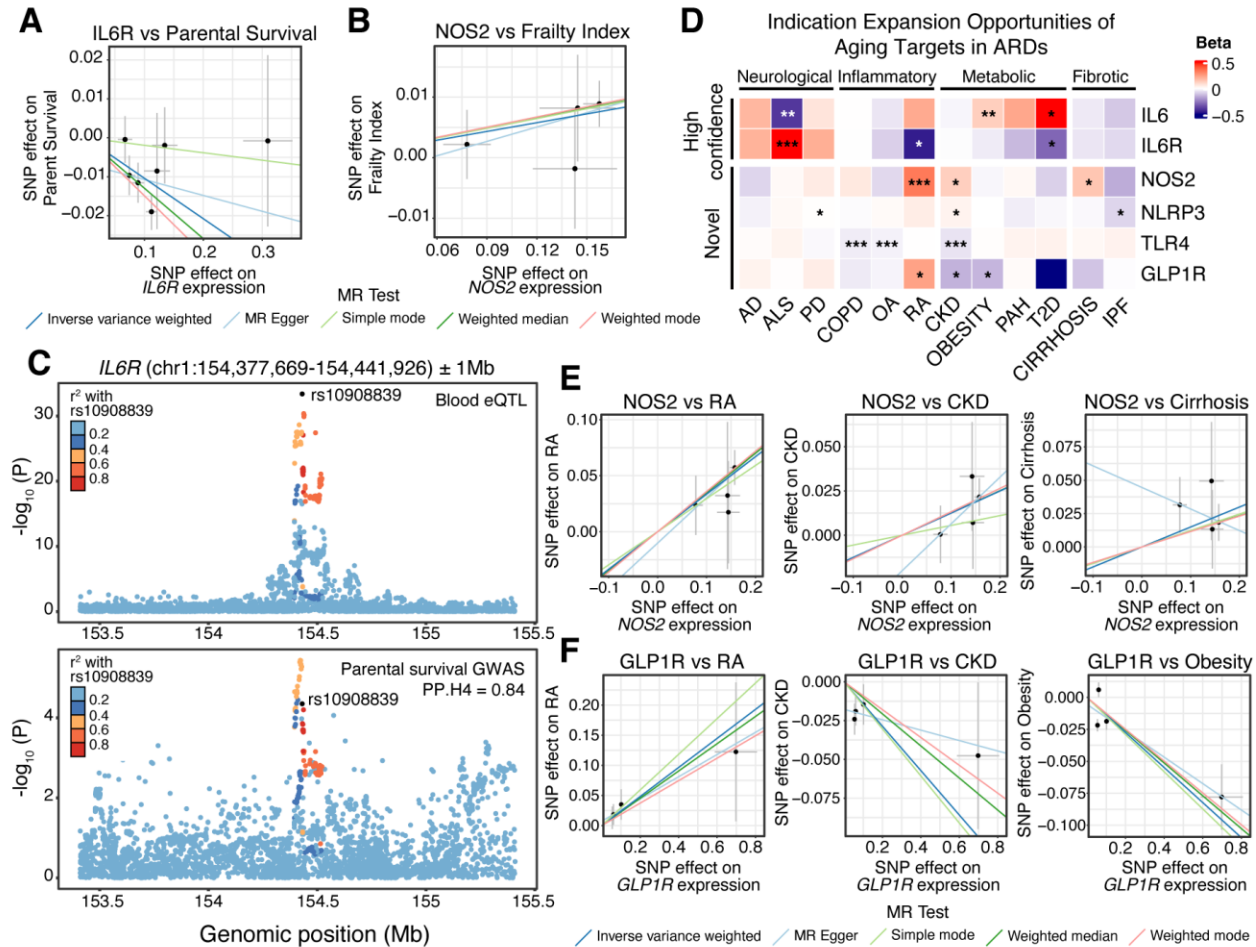


Figure 5. Genetic associations of prioritized dual-purpose targets in age-related diseases. (A) MR indicates a significant causal association between *IL6R* variants and parental survival. (B) MR evidence linking *NOS2* expression and frailty index. (C) Co-localization analysis showing shared genetic signals between blood eQTL (top) and parental survival (bottom) at the *IL6R* locus. Each point represents a genetic variant, colored by linkage disequilibrium (r^2) with the lead SNP (rs10908839) in blood eQTL. (D) Indication expansion opportunities of prioritized aging targets across ARDs; * $P_{BH} < 0.05$, ** $P_{BH} < 0.01$, *** $P_{BH} < 0.001$. (E) MR supported associations of *NOS2* with RA, CKD, and liver cirrhosis. (F) Significant causal relationships between *GLP1R* and RA, CKD, and Obesity.

IL6R, *NOS2*, *NLRP3* and *TLR4* showed significant MR associations with at least one aging-related trait. Increased *IL6R* expression was associated with reduced parental survival ($\beta = -0.10$, $P = 1.6 \times 10^{-4}$, Fig. 5A), consistent with prior evidence linking IL-6 signaling to inflammaging [37-39]. *NOS2* expression was positively associated with frailty index ($\beta = 0.048$, $P = 0.018$, Fig. 5B). *NLRP3* showed a positive association with longevity ($\beta = 0.077$, $P = 0.014$) and an inverse correlation with frailty index ($\beta = -0.018$, $P = 6.6 \times 10^{-3}$). *TLR4* was modestly associated with parental survival ($\beta = 0.008$, $P = 0.048$) and more strongly with reduced longevity ($\beta = -0.066$, $P = 1.1 \times 10^{-4}$). *GLP1R* showed no significant associations with any of the analyzed aging-related traits. Co-localization analysis revealed strong evidence for a shared causal variant between *IL6R* expression and parental survival (PP.H4 = 0.84; Fig. 5C), driven by

rs10908839 (SNP.PP.H4 = 0.99), supporting a shared genetic architecture linking IL-6 signaling and survival. The other five genes showed no evidence of co-localized genetic signals with any of the aging-related traits.

Indication expansion opportunities across ARDs

We next evaluated indication expansion opportunities by testing causal associations between shortlisted targets and ARDs. All nominated targets showed significant MR associations with at least one ARD (Fig. 5D). Specifically, *IL6* ($\beta = -0.39$, $P = 9.9 \times 10^{-3}$) and *IL6R* ($\beta = 0.55$, $P = 3.6 \times 10^{-4}$) were linked to ALS risk, whereas *NOS2* was associated with RA, CKD, and cirrhosis (Fig. 5E), supporting its candidacy for therapeutic inhibition. *NLRP3* showed suggestive associations with CKD and IPF, while *TLR4* displayed strong causal links to CKD,

COPD, and OA. Finally, *GLP1R* was associated with RA, obesity, and CKD (Fig. 5F), consistent with established metabolic effects of GLP-1R agonists, while indicating disease-specific complexity. Notably, all four novel targets converged on CKD, pointing to shared inflammatory and metabolic mechanisms in renal aging and disease. Co-localization analysis further identified a moderately shared signal at the *NOS2* locus with RA risk (PP.H4 = 62.1%, Supplementary Fig. 3), supporting shared genetic mechanisms underlying *NOS2* regulation and RA susceptibility.

To evaluate the translational potential of prioritized targets, we annotated their clinical development status alongside representative compounds and reported safety profiles (Table 1). Notably, IL6R antagonists (e.g., tocilizumab, sarilumab, satralizumab) and GLP1R agonists (e.g., semaglutide, liraglutide, dulaglutide, exenatide) are approved for inflammatory and metabolic indications, respectively. In contrast, NLRP3 inhibitors (e.g., dapansutride) and NOS2 inhibitors (e.g., L-NMMA) remain in early- to mid-stage clinical development. TLR4

represents a more complex case: while TLR4 agonism is clinically established through the use of monophosphoryl lipid A as a vaccine adjuvant, therapeutic inhibition of TLR4 (e.g., eritoran, resatorvid) has reached late-stage evaluation but has not demonstrated clinical efficacy in disease settings. Across targets, reported adverse effects were broadly consistent with their underlying biology. Modulation of immune pathways (IL6R, NLRP3 and TLR4 inhibition) was associated with increased infection risk, whereas targeting metabolic regulators such as GLP1R was primarily associated with gastrointestinal and metabolic effects. Inhibition of NOS2, which regulates nitric oxide signaling, was associated with cardiovascular liabilities, including hypertension and impaired perfusion. Collectively, these findings indicate that while multiple prioritized targets are clinically actionable, their therapeutic deployment is inherently constrained by mechanism-related safety considerations, which must be carefully evaluated to expand their indications across ARDs.

Table 1. Summary of prioritized targets identified in this study with existing or emerging therapeutic modulation.

Target	Drug action	Max. clinical stage	Drug/Compound	Approved indication(s)	Potential adverse effects
IL6R	Antagonist	Approved	Tocilizumab, Sarilumab, Satralizumab	Rheumatoid arthritis, giant cell arteritis, cytokine release syndrome	Infection risk, neutropenia, gastrointestinal perforation, anaphylaxis
NLRP3	Inhibitor	Phase 2	Dapansutride (OLT1177)	-	Gastrointestinal events; infection risk
NOS2	Inhibitor	Phase 1/2	L-NMMA (non-selective NOS inhibitor)	-	Hypertension, cardiovascular risk
TLR4	Agonist	Approved	Monophosphoryl lipid A	Vaccine adjuvant (e.g., HPV vaccine)	Mild inflammatory response
	Antagonist	Phase 3	Eritoran, Resatorvid	-	Infection risk
GLP1R	Agonist	Approved	Semaglutide, Liraglutide, Dulaglutide, Exenatide	Type 2 diabetes, obesity/weight management	Gastrointestinal effects, pancreatitis, gallbladder disease

Maximum clinical development stage was defined as the most advanced stage of any drug or compound modulating the target. Approved indications (where applicable), and key potential adverse effects were retrieved from clinical trial data and regulatory reports.

Lastly, we examined whether these targets exhibit age-dependent expression patterns in human blood in the GTEx cohort (n=755; aged 20-70). All six shortlisted genes were significantly associated with age (FDR < 0.05; Supplementary Fig. 4). *IL6R* showed the strongest negative correlation ($\rho = -0.35$, $P_{BH} = 1.5 \times 10^{-22}$), followed by *TLR4* ($\rho = -0.31$, $P_{BH} = 2.1 \times 10^{-17}$) and *NLRP3* ($\rho = 0.24$, $P_{BH} = 6.8 \times 10^{-11}$). In contrast, *IL6* ($\rho = 0.16$, $P_{BH} = 1.4 \times 10^{-5}$), *GLP1R* ($\rho = 0.09$, $P_{BH} = 1.8 \times 10^{-2}$) and *NOS2* ($\rho = -0.08$, $P_{BH} = 2.1 \times 10^{-2}$) demonstrated smaller effect sizes despite statistical significance, likely reflecting low expression levels in blood. Collectively, these findings suggest that the identified targets not only exhibit genetically supported disease associations but also

display age-related transcriptional dynamics consistent with roles in aging biology.

DISCUSSION

Aging is a major risk factor for a broad spectrum of chronic conditions, yet the extent to which shared molecular processes underlie both intrinsic ageing biology and clinically defined age-related diseases (ARDs) remains incompletely understood. By integrating transcriptomic meta-analysis, AI-driven target prioritization, and genetic causal inference, we establish a systematic framework to identify shared and aging-specific mechanisms with translational relevance.

Across 12 ARDs, we observed consistent activation of interferon signaling, complement, inflammatory response, and apoptosis pathways. Importantly, these signatures were not confined to classically immune-mediated conditions (e.g., RA) but were also evident in neurodegenerative, metabolic, and fibrotic diseases, indicating a shared systemic immune perturbation among clinically distinct phenotypes. This pattern is consistent with the geroscience concept of “inflammaging”, which describes chronic, low-grade inflammatory activation as a defining feature of aging that contributes to multimorbidity and mortality risk [40]. In parallel, coordinated downregulation of MYC targets suggests suppression of proliferative and metabolic programs, potentially reflecting chronic stress adaptation or altered immune cell composition. Together, these findings position immune activation and metabolic reprogramming as core, shared features underlying ARDs.

AI-based target prioritization combined with robust rank aggregation identified a focused set of 93 pan-ARD targets enriched for innate immune sensors and inflammatory mediators, including *NLRP3* and *TLR4*, alongside canonical cytokines (*IL1B*, *IL6*, *TNF*). Their recurrence across disease areas suggests that upstream inflammatory sensing and downstream cytokine signaling extend beyond disease specific correlates and instead reflect shared, potentially targetable processes across multiple ARDs. This is consistent with accumulating evidence implicating NLRP3 inflammasome activation and innate immune signaling in aging-associated chronic inflammation and degenerative pathology [41]. Beyond classical inflammatory mediators, enrichment of metabolic and regulatory targets such as *PPARA*, *DNMT1*, and *JAK2* supports a model of ARDs as manifestations of integrated immune-metabolic dysfunction, where inflammatory activation, epigenetic regulation, and cellular stress responses converge. Pathway analysis of the 12 consensus targets further emphasized interleukin signaling (including IL-4/IL-13 and IL-10 pathways), MAPK activation, apoptosis, and adipocyte differentiation, pointing to a cytokine-centered framework linking immune regulation with tissue remodeling and metabolic dysregulation. Alignment with the hallmarks of aging showed that most pan-ARD targets map to chronic inflammation, altered intercellular communication, and genomic instability, supporting the view that many ARDs reflect accelerated or dysregulated manifestations of aging biology rather than independent disease entities.

Our aging meta-analysis revealed widespread transcriptional changes, with interferon- γ and interferon- α responses emerging as the most significantly enriched hallmark pathways. The prominence of interferon

programs is consistent with evidence that aging is accompanied by immune remodeling, characterized by heightened interferon-driven transcriptional activity in human blood and immune cells across multiple inflammatory contexts [42-44]. Notably, these interferon signatures mirrored the most conserved pathways identified in ARDs, supporting the hypothesis that immune activation is not solely a consequence of disease but reflects an aging-associated baseline state that predisposes tissues to maladaptive responses. Beyond inflammatory responses, consistent perturbation of metabolic and stress-response programs was observed across aging and ARDs. The convergence of these distinct biological axes suggests that simultaneous targeting of complementary pathways, such as combined immuno-metabolic modulation, may offer greater therapeutic efficacy than single-pathway interventions. Strong concordance of effect sizes obtained from GSEA was observed between aging and neurological diseases (particularly PD and AD), supporting that neurodegenerative disorders may represent an intensified or context-specific deployment of aging-associated immune and stress programs. This is consistent with the steep age-dependence of neurodegenerative conditions and the expanding literature linking neuroinflammation and innate immunity to neurodegeneration [45]. In contrast, OA and cirrhosis exhibited weak concordance with aging signatures in our dataset. This divergence may reflect limited statistical power (particularly for OA, where only one dataset was available), heterogeneity between circulating signatures and tissue-specific pathology, or dominant contributions from non-aging drivers (e.g., biomechanical loading in OA; toxin-, metabolic-, or infection-driven injury in cirrhosis) [46-48]. Future studies incorporating larger cohorts, tissue-resolved profiling, and longitudinal sampling will be essential to distinguish true biological divergence from these constraints.

We identified 45 commonly prioritized target genes shared between aging and across ARDs, highlighting the potential for developing dual-purpose therapeutic strategies that target both aging and ARDs. In addition to identifying established aging regulators (e.g., *CDKN2A*, *JAK2*, *VEGFA*), stratification into high-confidence and novel aging targets suggested that aging-associated remodeling encompasses both canonical senescence-linked pathways and underexplored immune signaling programs.

Integration of human genetics into our framework strengthened causal inference. Using cis-eQTL instruments, MR and co-localization analyses provided orthogonal support for several prioritized targets and helped distinguish causal regulators from reactive transcriptional changes. *IL6R*, the receptor for our top hit

IL6, showed a significant association with parental survival alongside strong co-localization, consistent with prior genetic evidence linking IL-6 signaling to cardiovascular and immune-related outcomes as well as longevity-related phenotypes [49-51]. These findings support the relevance of IL-6 pathway modulation not only for inflammatory disease endpoints but also for aging-related functional decline. However, parental survival represents an indirect proxy for lifespan and may be influenced by shared environmental, socioeconomic, and behavioral factors, which could partially confound genetic interpretation. Consistent with our findings, Rosa et al. reported that genetically proxied higher soluble IL6R, interpreted as reduced IL-6 signaling, was associated with improved parental survival [52]. In contrast, experimental inhibition of IL6R has not consistently extended lifespan despite reducing inflammation [53], suggesting that IL-6 signaling may have a greater impact on disease susceptibility and functional decline than on organismal lifespan, or that compensatory inflammatory pathways attenuate survival benefits. Together, these observations support a context-dependent role for IL6R in aging, whereby modulation of IL-6 signaling may improve healthspan and disease outcomes without necessarily extending lifespan. Notably, this is supported by clinical translation, as IL6R blockade (e.g., tocilizumab) is established for multiple inflammatory diseases, including RA and giant cell arteritis [54, 55], providing proof of concept for targeting chronic inflammatory signaling in humans.

MR evidence further supported associations of *NOS2*, *NLRP3*, *TLR4*, and *GLP1R* with aging-related traits and/or ARDs, although heterogeneity in effect directionality and trait specificity underscores the context-dependent roles of innate immune signaling and necessitates careful translational interpretation. Convergence of causal signals in CKD across multiple targets highlights indication expansion opportunities and positions the kidney as a nexus where inflammatory, metabolic, and vascular aging processes intersect. For *NOS2*, moderate co-localization and significant MR result with RA risk support shared regulatory mechanisms linking nitric oxide signaling to inflammatory disease susceptibility. Prior pharmacological efforts underscore the challenges of clinical translation, as selective iNOS inhibition (e.g., GW-274150) showed limited efficacy in migraine and asthma [56, 57]. Other *NOS2* inhibitors remain in early-phase development and are constrained by safety concerns related to systemic nitric oxide inhibition [58-60]. Nonetheless, broader targeting of nitric oxide pathways has been implicated in cardiovascular disease [61], cancer [62], erectile dysfunction [63], and neurodegeneration [64], supporting continued interest in *NOS2*-related mechanisms across ARDs and potentially

aging. In addition, the identification of *NLRP3* is particularly notable given its central role in inflammasome activation and the perpetuation of chronic inflammation. The *NLRP3*-caspase-1-IL-1 β axis has been widely implicated in age-related inflammatory processes and is increasingly recognized as a key driver of neuroinflammation in Alzheimer's disease [65, 66]. Our genetic findings support a model in which *NLRP3* contributes to inflammaging that drives multiple aging-related traits (e.g., frailty) and specific pathologies (e.g., PD, CKD and IPF), reinforcing *NLRP3* as a high-priority therapeutic target in aging and ARDs. Importantly, this is aligned with ongoing clinical development, as *NLRP3* inhibitors (e.g., dapansutride) have progressed to phase 2 trials for gout flares [67] and Parkinson's disease (NCT07157735). Our prioritization of *TLR4* further supports a role for dysregulated innate immune sensing in aging and ARDs. As an upstream mediator of inflammatory signaling and a known activator of *NLRP3* inflammasome priming through NF- κ B activation [68], *TLR4* links tissue stress and inflammatory cues to chronic inflammation implicated in aging biology. *TLR4* antagonists such as eritoran have reached late-stage clinical evaluation; however, phase III studies in severe sepsis demonstrated limited efficacy despite strong preclinical rationale [69], highlighting the challenges of targeting innate immune pathways in heterogeneous diseases. Nevertheless, the involvement of *TLR4* in inflammatory and aging-related processes suggests that context-specific modulation may still hold therapeutic potential. Alternatively, *GLP1R* represents a complementary, clinically validated axis that couples metabolic regulation to ARD biology. *GLP1R* agonists (e.g., semaglutide) are approved for T2D and obesity, with well-established cardiometabolic benefits [70-72]. Although our analyses did not detect a direct genetic association between *GLP1R* and intrinsic aging traits, given emerging evidence of broader anti-inflammatory and cardiometabolic effects, *GLP1R* modulation could indirectly mitigate multimorbidity, supporting its potential for broader therapeutic repurposing across ARDs [73, 74].

Our study has several limitations. First, transcriptomic analyses were restricted to circulating biospecimens to maximize cross-study comparability, which may underrepresent tissue-local mechanisms critical in certain ARDs (e.g., synovium in OA/RA, liver in cirrhosis, lung parenchyma in IPF). Consistent with this, although *IL6R*, *TLR4*, and *NLRP3* exhibited robust age-associated expression changes in whole blood (GTEx), *IL6*, *NOS2*, and *GLP1R* showed weaker associations, likely reflecting low baseline expression in blood rather than absence of biological relevance in disease-specific tissues. Notably, *IL6* and *NOS2* are

inducible, cell state-dependent genes with tightly regulated expression that becomes prominent primarily under inflammatory activation or within tissue-resident immune populations. Similarly, *GLP1R* expression is enriched in metabolic and endocrine tissues rather than circulating leukocytes. Consequently, whole-blood transcriptomic profiles may underestimate age-related regulation occurring in tissue-resident cells and disease-relevant microenvironments. Incorporating single-cell and tissue-specific transcriptomic data will be important to refine these associations. Second, heterogeneity across public datasets (platform differences, batch effects, clinical covariates, and case definitions) is unavoidable. Although QC procedures and meta-analysis were implemented to mitigate these issues, residual heterogeneity may still influence disease-specific signals. Third, AI-driven target prioritization relies on pre-existing knowledge (e.g., clinical annotations), which can bias rankings toward well-studied targets. Stratification into high-confidence and novel aging targets partially mitigates this limitation but does not eliminate ascertainment bias. Fourth, MR and co-localization analyses involve important assumptions and constraints. *cis*-eQTL instruments reflect localized gene regulation in specific tissues and contexts (blood in this study) and may not capture disease-relevant cell states. These analyses remain susceptible to LD structure or pleiotropy. In addition, restriction of predominantly European-ancestry GWAS limits generalizability.

While our findings illuminate multiple therapeutically actionable targets, modulating these pathways requires careful safety considerations. For example, inhibition of IL-6/IL-6R signaling (e.g., via tocilizumab) is associated with increased susceptibility to infections and altered lipid profiles, reflecting its central role in host defense and metabolic regulation [75]. Similarly, GLP-1 receptor agonists (e.g., semaglutide) are widely used and generally well tolerated but can induce gastrointestinal adverse effects and, in some cases, systemic metabolic perturbations [76, 77]. More broadly, therapeutically targeting foundational aging pathways entails inevitable biological trade-offs. Processes such as inflammation, cellular senescence, and nutrient sensing exert context-dependent, protective functions in tissue repair, immune surveillance, and metabolic homeostasis. Consequently, modulating these systems may yield clinical benefit in certain pathological states while simultaneously inducing unintended consequences in others. These dynamics underscore the importance of careful patient selection and risk stratification, especially when repurposing agents across a broad spectrum of ARDs. Ultimately, the efficacy and safety of aging-targeted interventions are contingent upon pharmacological dosing, administration timing, and the

clinical context, specifically, whether the interventions are deployed in preventive or established disease settings.

Several next steps could strengthen mechanistic and translational impact. First, integration of tissue- and cell type-resolved data (single-cell transcriptomics, spatial profiling, and cell-state eQTLs) will clarify whether shared inflammatory signatures reflect pathway activation within disease-relevant cells or shifts in circulating immune composition. Second, incorporation of orthogonal molecular layers such as proteomics (including *cis*-pQTL MR), methylation, and chromatin accessibility, may prioritize targets with consistent multi-omic support and strengthen causal inference. Third, expansion to diverse ancestries and harmonized phenotypes will improve robustness and generalizability. Fourth, experimental validation using perturbation models (CRISPR perturb-seq, organoids, and *in vivo* aging models) should determine whether modulation of candidate targets (e.g., IL6/IL6R, TLR4, NLRP3, NOS2, and GLP1R) recapitulates predicted pathway changes and improves aging-relevant functional endpoints. Fifth, clinical translation will require standardized aging endpoints and biomarker strategies, including genetically informed patient stratification and target engagement metrics, to bridge genetic causality, molecular signatures, and therapeutic efficacy. Finally, future studies integrating longitudinal clinical data and biomarker-driven stratification will be critical to define optimal therapeutic windows and to balance efficacy with safety in the context of aging-targeted interventions.

In summary, our integrative framework delineates conserved inflammatory and immune mechanisms that connect aging with diverse ARDs, prioritizes shared and aging-specific targets with coherent pathway level support, and provides genetic evidence for a subset of candidates with potential for indication expansion. These findings support both aging-related and pan-disease therapeutic strategies and motivate future efforts to refine target selection through tissue-resolved multi-omics, genetics-guided stratification, and experimental validation.

Declaration of Interest

All authors except I.A.E and E.I are affiliated with Insilico Medicine. Insilico Medicine is a global clinical-stage commercial generative artificial intelligence company with several hundred patents, pending patent applications, and commercially available software.

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Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2026.0356.

References

- [1] Fang EF, Fang Y, Chen G, Wang HL, Zhang J, Wu C, et al. (2025). Adapting health, economic and social policies to address population aging in China. *Nat Aging*, 5:2176-2187.
- [2] Fang EF, Xie C, Schenkel JA, Wu C, Long Q, Cui H, et al. (2020). A research agenda for ageing in China in the 21st century (2nd edition): Focusing on basic and translational research, long-term care, policy and social networks. *Ageing Res Rev*, 64:101174.
- [3] Partridge L, Fuentealba M, Kennedy BK (2020). The quest to slow ageing through drug discovery. *Nat Rev Drug Discov*, 19:513-532.
- [4] Bischof E, Maier AB, Lee KF, Zhavoronkov A, Sinclair D (2022). Advanced pathological ageing should be represented in the ICD. *Lancet Healthy Longev*, 3:e12.
- [5] Organization WH. 2025. ICD-11 for Mortality and Morbidity Statistics.
- [6] McLaughlin J, Lagrimas J, Iqbal H, Parkinson H, Harmse H (2025). OLS4: a new Ontology Lookup Service for a growing interdisciplinary knowledge ecosystem. *Bioinformatics*, 41.
- [7] Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. (2019). Applications of machine learning in drug discovery and development. *Nat Rev Drug Discov*, 18:463-477.
- [8] Eraslan G, Avsec Z, Gagneur J, Theis FJ (2019). Deep learning: new computational modelling techniques for genomics. *Nat Rev Genet*, 20:389-403.
- [9] Zhavoronkov A, Ivanenkov YA, Aliper A, Veselov MS, Aladinskiy VA, Aladinskaya AV, et al. (2019). Deep learning enables rapid identification of potent DDR1 kinase inhibitors. *Nat Biotechnol*, 37:1038-1040.
- [10] Leung GHD, Pun FW, Naumov V, Gennert D, Kamya P, Aliper A, et al. 2026. Artificial Intelligence for Drug Target and Pathway Identification, Assessment, Validation, and Indication Expansion. In Lavecchia, A. (eds) *Applied Artificial Intelligence for Drug Discovery*: Springer, Cham. 73-104.
- [11] Pun FW, Podolskiy D, Izumchenko E, Mortlock A, Oprea TI, Scheibye-Knudsen M, et al. (2026). Target identification and assessment in the era of AI. *Nat Rev Drug Discov*.
- [12] Leung H, Duan C, Gou W, Chen J, Xin Y, Zheng Z, et al. (2026). Advancing target discovery through disease-specific integration of multi-modal target identification models and comprehensive benchmarking system. *Sci Rep*.
- [13] Xie C, Zhuang XX, Niu Z, Ai R, Lautrup S, Zheng S, et al. (2022). Amelioration of Alzheimer's disease pathology by mitophagy inducers identified via machine learning and a cross-species workflow. *Nat Biomed Eng*, 6:76-93.
- [14] Ai R, Xiao X, Deng S, Yang N, Xing X, Watne LO, et al. (2025). Artificial intelligence in drug development for delirium and Alzheimer's disease. *Acta Pharm Sin B*, 15:4386-4410.
- [15] Li A, Xiao X, Liu G, Li K, Ling Y, Deng S, et al. (2026). Isoginkgetin protects against degeneration of ALS motor neurons via regulating the GSK-3 β -TFEB signaling axis. *Pharmacol Res*, 227:108172.
- [16] Chen J, Leung GHD, Leung H, Ustiugova A, Shneyderman A, Korzinkin M, et al. (2025). From clock to clock: Therapeutic target discovery for aging and age-related diseases. *Ageing Res Rev*, 112:102871.
- [17] Pun FW, Leung GHD, Leung HW, Liu BHM, Long X, Ozerov IV, et al. (2022). Hallmarks of aging-based dual-purpose disease and age-associated targets predicted using PandaOmics AI-powered discovery engine. *Aging (Albany NY)*, 14:2475-2506.
- [18] Durinck S, Spellman PT, Birney E, Huber W (2009). Mapping identifiers for the integration of genomic datasets with the R/Bioconductor package biomaRt. *Nat Protoc*, 4:1184-1191.
- [19] Cerezo M, Sollis E, Ji Y, Lewis E, Abid A, Bircan KO, et al. (2025). The NHGRI-EBI GWAS Catalog: standards for reusability, sustainability and diversity. *Nucleic Acids Res*, 53:D998-D1005.
- [20] Deelen J, Evans DS, Arking DE, Tesi N, Nygaard M, Liu X, et al. (2019). A meta-analysis of genome-wide association studies identifies multiple longevity genes. *Nat Commun*, 10:3669.
- [21] Atkins JL, Jylhava J, Pedersen NL, Magnusson PK, Lu Y, Wang Y, et al. (2021). A genome-wide association study of the frailty index highlights brain pathways in ageing. *Aging Cell*, 20:e13459.
- [22] Timmers PR, Mounier N, Lall K, Fischer K, Ning Z, Feng X, et al. (2019). Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. *Elife*, 8.
- [23] Vosa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. (2021). Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat Genet*, 53:1300-1310.
- [24] Perez G, Barber GP, Benet-Pages A, Casper J, Clawson H, Diekhans M, et al. (2025). The UCSC Genome Browser database: 2025 update. *Nucleic Acids Res*, 53:D1243-D1249.
- [25] Hoffman GE, Schadt EE (2016). variancePartition: interpreting drivers of variation in complex gene expression studies. *BMC Bioinformatics*, 17:483.
- [26] Leung H, Duan C, Gou W, Chen J, Xin Y, Zheng Z, et al. (2025). Advancing Target Discovery Through Disease-Specific Integration of Multi-Modal Target Identification Models and Comprehensive Target Benchmarking System. *bioRxiv*.
- [27] Kamya P, Ozerov IV, Pun FW, Tretina K, Fokina T, Chen S, et al. (2024). PandaOmics: An AI-Driven Platform for Therapeutic Target and Biomarker Discovery. *J Chem Inf Model*, 64:3961-3969.
- [28] de Magalhaes JP, Toussaint O (2004). GenAge: a genomic and proteomic network map of human ageing.

- FEBS Lett, 571:243-247.
- [29] Dolgalev I (2025). msigdb: MSigDB Gene Sets for Multiple Organisms in a Tidy Data Format.
- [30] Korotkevich G, Sukhov V, Budin N, Shpak B, Artyomov MN, Sergushichev A (2021). Fast gene set enrichment analysis. *bioRxiv*.
- [31] Yu G, He QY (2016). ReactomePA: an R/Bioconductor package for reactome pathway analysis and visualization. *Mol Biosyst*, 12:477-479.
- [32] Kolde R, Laur S, Adler P, Vilo J (2012). Robust rank aggregation for gene list integration and meta-analysis. *Bioinformatics*, 28:573-580.
- [33] Pun FW, Leung GHD, Leung HW, Rice J, Schmauck-Medina T, Lautrup S, et al. (2023). A comprehensive AI-driven analysis of large-scale omic datasets reveals novel dual-purpose targets for the treatment of cancer and aging. *Aging Cell*, 22:e14017.
- [34] Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*, 4:7.
- [35] Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. (2018). The MR-Base platform supports systematic causal inference across the human phenome. *Elife*, 7.
- [36] Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, Plagnol V (2014). Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet*, 10:e1004383.
- [37] Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, et al. (1999). Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc*, 47:639-646.
- [38] Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*, 908:244-254.
- [39] Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH, Jr., et al. (1999). Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med*, 106:506-512.
- [40] Ferrucci L, Fabbri E (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*, 15:505-522.
- [41] Liang R, Qi X, Cai Q, Niu L, Huang X, Zhang D, et al. (2024). The role of NLRP3 inflammasome in aging and age-related diseases. *Immun Ageing*, 21:14.
- [42] Li X, Li C, Zhang W, Wang Y, Qian P, Huang H (2023). Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduct Target Ther*, 8:239.
- [43] Yamamoto R, Chung R, Vazquez JM, Sheng H, Steinberg PL, Ioannidis NM, Sudmant PH (2022). Tissue-specific impacts of aging and genetics on gene expression patterns in humans. *Nat Commun*, 13:5803.
- [44] Cao W (2022). IFN-Aging: Coupling Aging With Interferon Response. *Front Aging*, 3:870489.
- [45] Calabrese V, Santoro A, Monti D, Crupi R, Di Paola R, Latteri S, et al. (2018). Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. *Free Radic Biol Med*, 115:80-91.
- [46] Loeser RF (2013). Aging processes and the development of osteoarthritis. *Curr Opin Rheumatol*, 25:108-113.
- [47] Stegeman R, Weake VM (2017). Transcriptional Signatures of Aging. *J Mol Biol*, 429:2427-2437.
- [48] Gan C, Yuan Y, Shen H, Gao J, Kong X, Che Z, et al. (2025). Liver diseases: epidemiology, causes, trends and predictions. *Signal Transduct Target Ther*, 10:33.
- [49] Interleukin-6 Receptor Mendelian Randomisation Analysis C, Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, et al. (2012). The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet*, 379:1214-1224.
- [50] Ferreira RC, Freitag DF, Cutler AJ, Howson JM, Rainbow DB, Smyth DJ, et al. (2013). Functional IL6R 358Ala allele impairs classical IL-6 receptor signaling and influences risk of diverse inflammatory diseases. *PLoS Genet*, 9:e1003444.
- [51] Bonafe M, Olivieri F, Cavallone L, Giovagnetti S, Mayegiani F, Cardelli M, et al. (2001). A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. *Eur J Immunol*, 31:2357-2361.
- [52] Rosa M, Chignon A, Li Z, Boulanger MC, Arsenault BJ, Bosse Y, et al. (2019). A Mendelian randomization study of IL6 signaling in cardiovascular diseases, immune-related disorders and longevity. *NPJ Genom Med*, 4:23.
- [53] Wissel S, Hovey KM, Andrews CA, Miller CR, Shadyab AH, Wallace RB, et al. (2025). Genetic interleukin-6 receptor blockade, Chronic Disease Risk and Longevity. Results from the Women's Health Initiative. *Eur J Prev Cardiol*.
- [54] Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. (2013). Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet*, 381:1541-1550.
- [55] Stone JH, Tuckwell K, Dimonaco S, Kleerman M, Aringer M, Blockmans D, et al. (2017). Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med*, 377:317-328.
- [56] Singh D, Richards D, Knowles RG, Schwartz S, Woodcock A, Langley S, O'Connor BJ (2007). Selective inducible nitric oxide synthase inhibition has no effect on allergen challenge in asthma. *Am J Respir Crit Care Med*, 176:988-993.
- [57] Hoivik HO, Laurijssens BE, Harnisch LO, Twomey CK, Dixon RM, Kirkham AJ, et al. (2010). Lack of efficacy of the selective iNOS inhibitor GW274150 in prophylaxis of migraine headache. *Cephalalgia*, 30:1458-1467.
- [58] Grover R, Zaccardelli D, Colice G, Guntupalli K, Watson D, Vincent JL (1999). An open-label dose escalation study of the nitric oxide synthase inhibitor, N(G)-methyl-L-arginine hydrochloride (546C88), in patients with septic shock. Glaxo Wellcome International Septic Shock Study Group. *Crit Care Med*, 27:913-922.

- [59] Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, et al. (2004). Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med*, 32:21-30.
- [60] Chung AW, Anand K, Anselme AC, Chan AA, Gupta N, Venta LA, et al. (2021). A phase 1/2 clinical trial of the nitric oxide synthase inhibitor L-NMMA and taxane for treating chemoresistant triple-negative breast cancer. *Sci Transl Med*, 13:eabj5070.
- [61] Papapetropoulos A, Hobbs AJ, Topouzis S (2015). Extending the translational potential of targeting NO/cGMP-regulated pathways in the CVS. *Br J Pharmacol*, 172:1397-1414.
- [62] Li CY, Anuraga G, Chang CP, Weng TY, Hsu HP, Ta HDK, et al. (2023). Repurposing nitric oxide donating drugs in cancer therapy through immune modulation. *J Exp Clin Cancer Res*, 42:22.
- [63] Burnett AL (2006). The role of nitric oxide in erectile dysfunction: implications for medical therapy. *J Clin Hypertens (Greenwich)*, 8:53-62.
- [64] Tewari D, Sah AN, Bawari S, Nabavi SF, Dehpour AR, Shirooie S, et al. (2021). Role of Nitric Oxide in Neurodegeneration: Function, Regulation, and Inhibition. *Curr Neuropharmacol*, 19:114-126.
- [65] Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, et al. (2019). Mitophagy inhibits amyloid-beta and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci*, 22:401-412.
- [66] Cabral JE, Wu A, Zhou H, Pham MA, Lin S, McNulty R (2025). Targeting the NLRP3 inflammasome for inflammatory disease therapy. *Trends Pharmacol Sci*, 46:503-519.
- [67] Kluck V, Jansen T, Janssen M, Comarniceanu A, Efde M, Tengesdal IW, et al. (2020). Dapansutrile, an oral selective NLRP3 inflammasome inhibitor, for treatment of gout flares: an open-label, dose-adaptive, proof-of-concept, phase 2a trial. *Lancet Rheumatol*, 2:e270-e280.
- [68] Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK (2021). An update on the regulatory mechanisms of NLRP3 inflammasome activation. *Cell Mol Immunol*, 18:1141-1160.
- [69] Opal SM, Laterre PF, Francois B, LaRosa SP, Angus DC, Mira JP, et al. (2013). Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. *JAMA*, 309:1154-1162.
- [70] Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*, 384:989-1002.
- [71] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*, 375:1834-1844.
- [72] Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. (2019). Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*, 394:121-130.
- [73] Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. (2021). A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*, 384:1113-1124.
- [74] Alicic RZ, Neumiller JJ, Tuttle KR (2026). GLP-1 receptor agonists and next-generation metabolic hormone therapies in chronic kidney disease. *Nat Rev Nephrol*, 22:265-282.
- [75] Aletaha D, Kerschbaumer A, Kastrati K, Dejaco C, Dougados M, McInnes IB, et al. (2023). Consensus statement on blocking interleukin-6 receptor and interleukin-6 in inflammatory conditions: an update. *Ann Rheum Dis*, 82:773-787.
- [76] Filippatos TD, Panagiotopoulou TV, Elisaf MS (2014). Adverse Effects of GLP-1 Receptor Agonists. *Rev Diabet Stud*, 11:202-230.
- [77] Ghusn W, Hurtado MD (2024). Glucagon-like Receptor-1 agonists for obesity: Weight loss outcomes, tolerability, side effects, and risks. *Obes Pillars*, 12:100127.