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ORIGINAL ARTICLE

Single-Cell eQTL MR Identifies Immune Aging Genes Linking Inflammaging to Ovarian Cancer Risk

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ABSTRACT

Background: **Aging exerts profound, long-term impacts on human health, notably by driving immunosenescence and chronic inflammation, which contribute to heightened risks of malignancies such as ovarian cancer (OC). Despite growing understanding, few immune-modulating anti-aging interventions have translated into effective clinical therapies.**
Methods: **We conducted a Mendelian randomization (MR) analysis using 867 single-cell expression quantitative trait loci (sc-eQTL) to proxy the effects of gene expression across 14 peripheral blood immune cell types, evaluating their causal impact on ovarian cancer risk and aging-related phenotypes. To explore translational potential, we mapped MR-identified genes to clinical trial data and drug-gene interaction databases to uncover candidates for drug repurposing. Finally, we established a tiered prioritization framework to identify immune-cell-specific therapeutic targets with dual relevance to ovarian cancer and aging.**
Results: **We identified 66 aging-associated genes causally linked to OC, many with strong cell-type specificity (e.g., SIRT2 in NK cells). Enriched pathways included DNA damage response, chromatin remodeling, apoptosis, hypoxia signaling, and immunometabolic reprogramming. Of 44 MR-prioritized genes, 18 were druggable and 5 (ATM, CTNNB1, RAD51C, RB1, SAMHD1) achieved the highest translational priority. A prognostic gene signature derived from these targets was predictive of overall survival across independent cohorts, suggesting dual utility in risk stratification and therapeutic targeting.**
Conclusions: **Our findings reveal a gene-resolved, immune-cell–specific framework linking inflammaging to OC susceptibility and outcome. This study highlights potential targets for age-adapted intervention and establishes a path toward immune-informed prevention and precision oncology in aging populations.**
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Supplementary Data

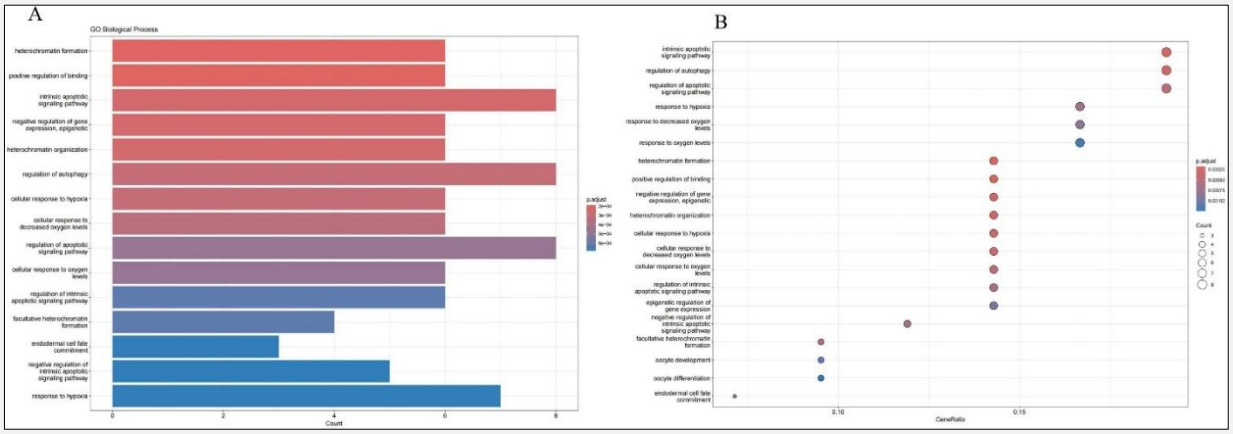


Figure S1. Enrichment analysis and functional module characterization.

A: Bar plot showing the top 10 significantly enriched GGO Biological Process terms for the prognostic gene set, ranked by gene count and color-coded by adjusted p-value. B: Bubble plot illustrating the top 10 significantly enriched KEGG terms for the prognostic gene set, ranked by gene count and color-coded by adjusted p-value.

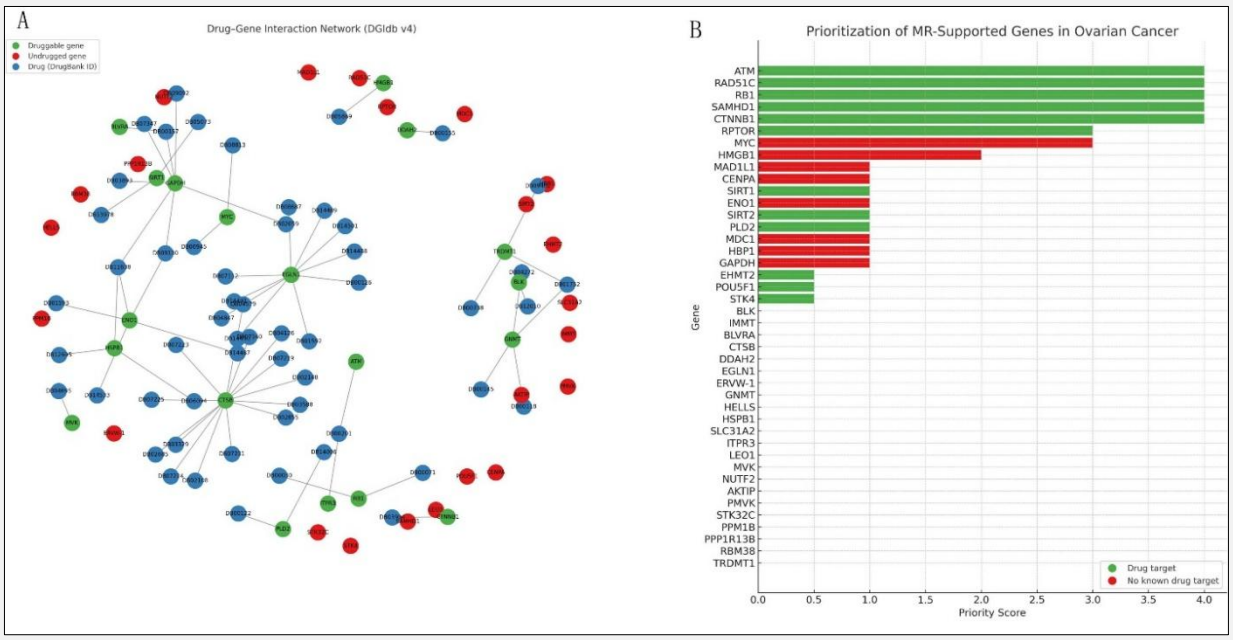


Figure S2. Drug-gene interaction and druggability assessment.

A: Drug-gene interaction network constructed using DGIdb v4. Red nodes indicate known druggable genes, green nodes indicate potentially druggable genes, and blue nodes represent associated drugs. B: Bar chart of druggability scores for the prognostic genes, with scores labeled above each bar. ATM, RAD51C, CTNNB1, RB1, and SAMHD1 achieved the highest score (4.0), suggesting strong potential for clinical translation.

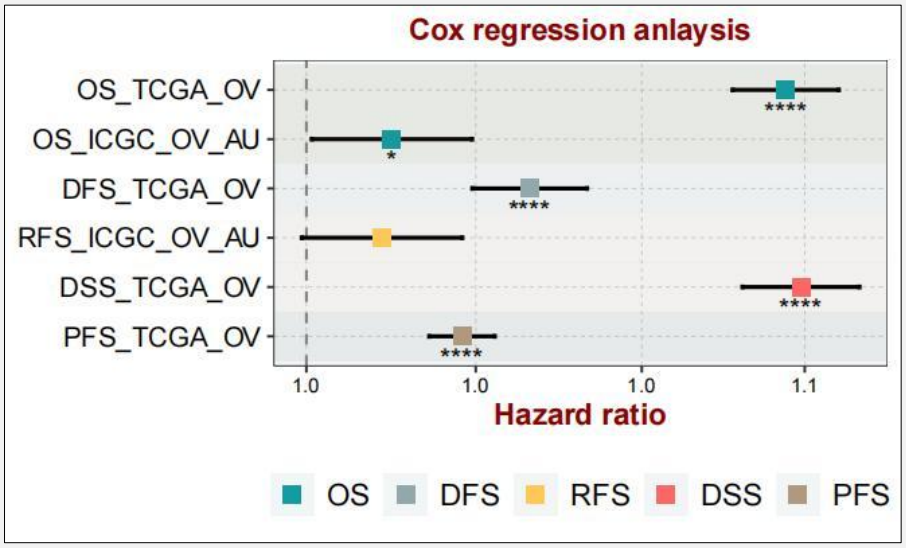


Figure S3. Multivariate Cox regression forest plot for overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), disease-specific survival (DSS), and progression-free survival (PFS) in the TCGA and ICGC cohorts.

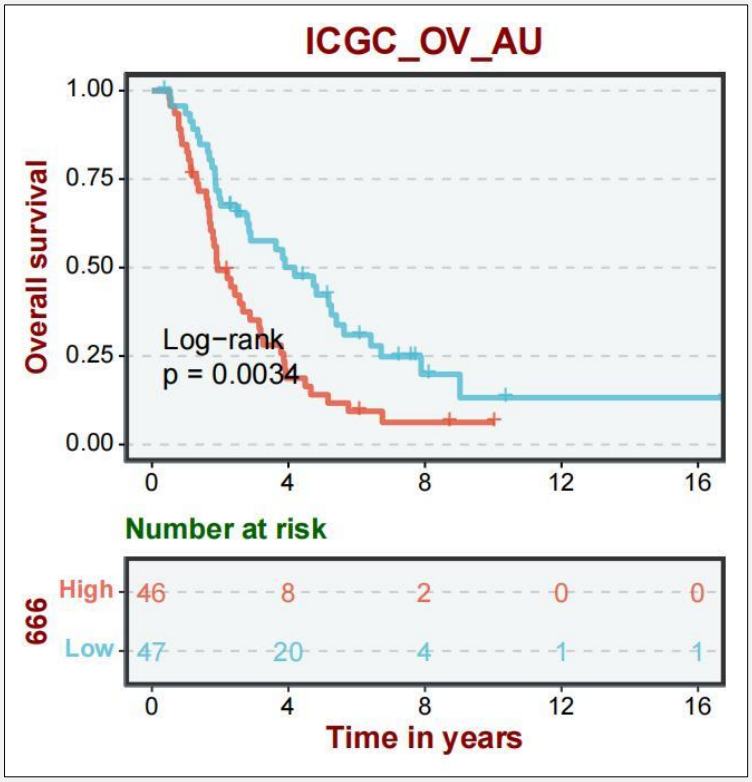


Figure S4. Kaplan-Meier survival curves for the ICGC_OV_AU cohort, with significantly shorter overall survival in the high-risk group (p = 0.0034).

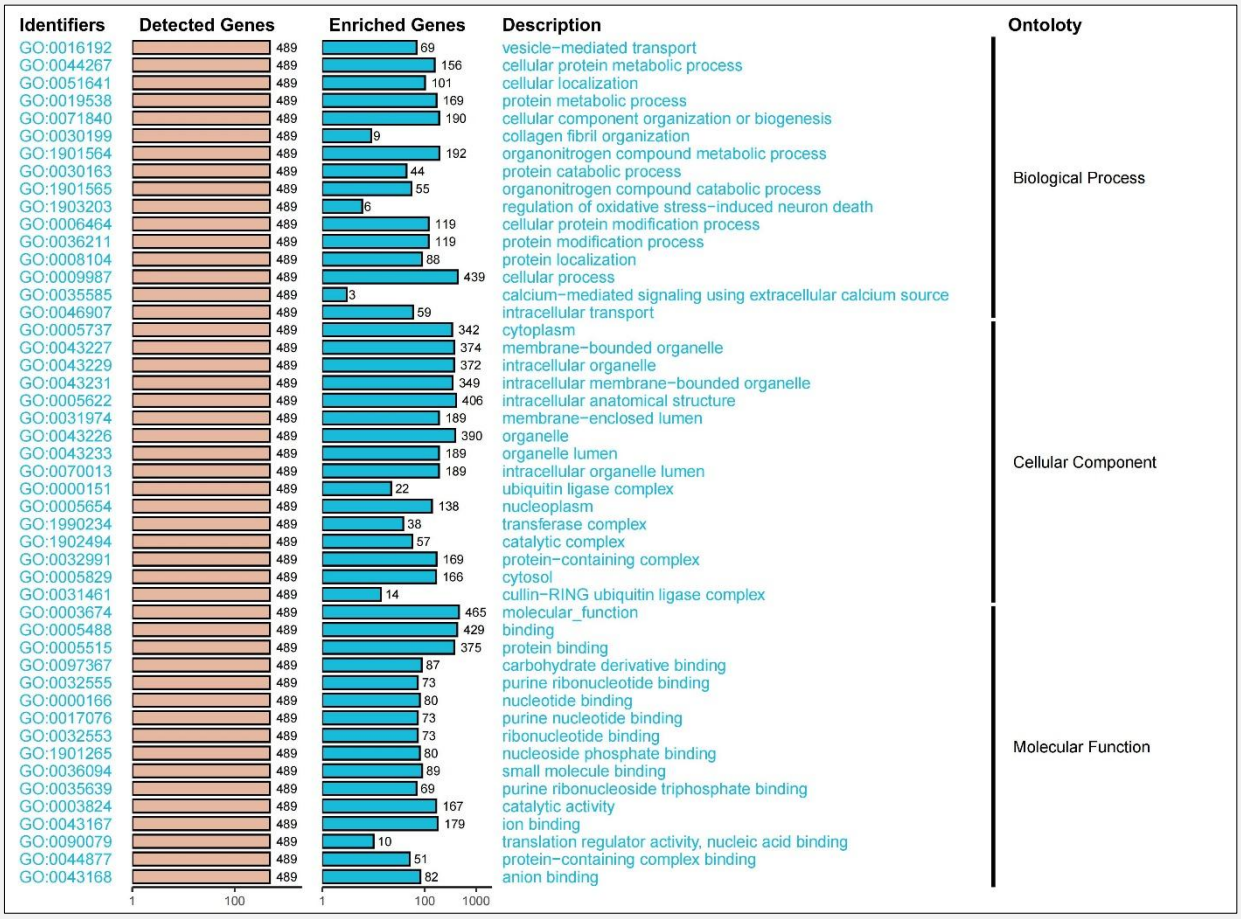


Figure S5. Gene Ontology (GO) enrichment analysis of candidate genes in this study.

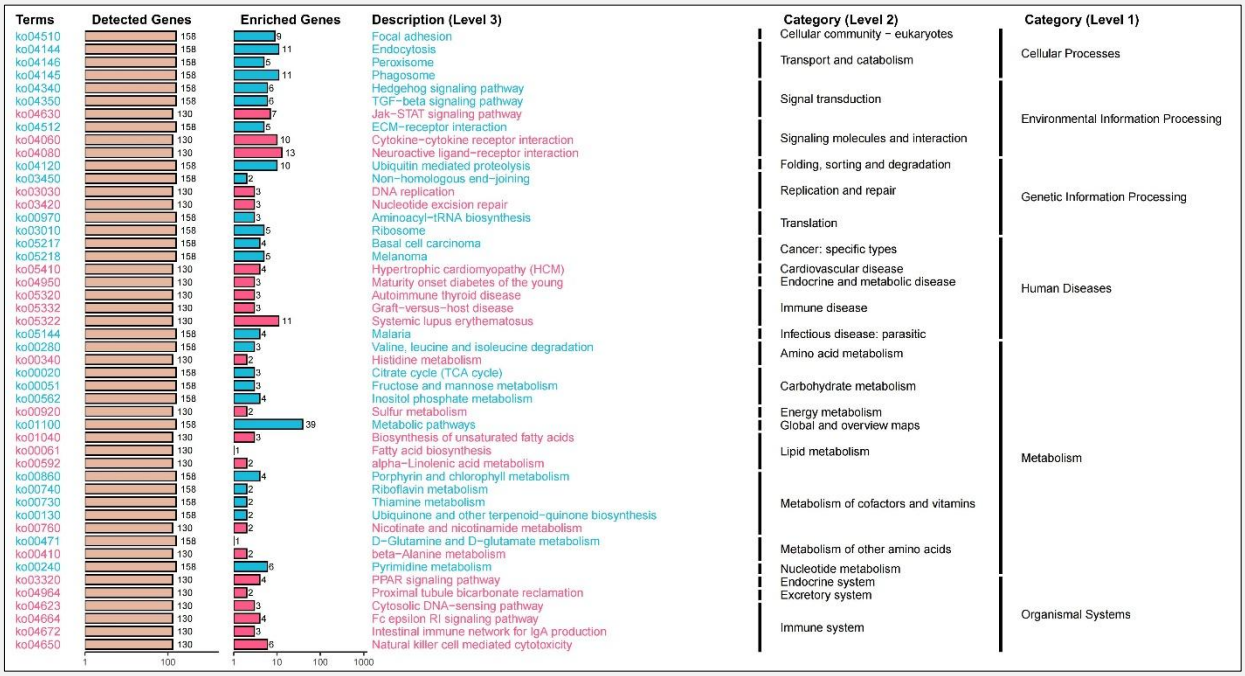


Figure S6. Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of candidate genes in this study.