

Crossing Gene Sets From GTEx, MoTrPAC and RummaGEO Reveals Nicotinamide As a Potential Modulator of Aging and Exercise

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Abstract

Biomedical omics resources are frequently treated as isolated datasets, which fragments insight and hampers discovery of shared mechanisms. By crossing gene sets from multiple Common Fund programs, it becomes possible to identify molecular programs that are reproducible across diverse biological contexts, to assess robustness of findings, and to connect molecular signatures to physiological outcomes. In this report we intersected three complementary gene set libraries: the GTEx Tissue-Specific Aging signatures that capture blood expression changes associated with advancing age, the MoTrPAC Rat Endurance Exercise Training transcriptomics that describe early-life female blood RNA alterations after short-term exercise, and the RummaGEO Drug Perturbation signatures that reflect the response of mouse liver to nicotinamide treatment. The workflow harmonized the libraries, evaluated all possible three-way combinations, and selected the crossing that contained the maximal set of genes shared by all three resources for detailed analysis. The resulting intersecting gene set is enriched for secreted plasma proteins that participate in extracellular matrix organization, complement-mediated immunity, and the regulation of lipid and cholesterol metabolism, including factors such as angiopoietin-like protein 3, apolipoproteins C1 and C2, and coagulation components. Enrichment of hemostatic and lipid-handling pathways, together with transcription factor signatures linked to nuclear receptors, highlights a coherent biological theme. The presence of nicotinamide-responsive genes suggests that nicotinamide or related agents may modulate these pathways, offering a potential therapeutic avenue that aligns with the shared molecular signatures uncovered across the three datasets.

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Introduction

Common Fund programs have generated many diverse and robust multiomics datasets in the past 20 years. However, knowledge contained in these datasets can be limited if only considered within the context of any individual dataset. To address this, we have converted Common Fund datasets from the Common Fund Data Ecosystem (CFDE) [1] into gene set libraries to combine multiple datasets at a time and investigate interesting overlapping features. Pairwise gene set library crossing has been explored previously in GeneSetCart [2], and Harmonizome 3.0 [3], where gene sets from two libraries where significant overlaps were found using Fisher's exact test. These top crossings could then be used to generate LLM hypotheses by augmenting them

with enriched biological terms. Here we extend the strategy by combining more libraries at once. Each combination of three gene sets (one from each library) is analyzed to identify significant pairwise intersections and a robust 3-way intersecting gene set.

For this report, we combined gene sets from the GTEx Tissue-Specific Aging Signatures [4], MoTrPAC Rat Endurance Exercise Training Transcriptomics [5], and RummaGEO Drug Perturbation Signatures [6] datasets. Among the top-ranked crossings, we identified an overlap with rank 2 and a p-value of 1.03886e-26 warranting further investigation.

The GTEx Blood 20-29 vs 70-79 Up signature comprises genes that show increased expression in blood samples

from individuals aged 20-29 compared with those aged 70-79 according to the GTEx TissueSpecific Aging Signatures dataset [4]. The T30BloodRna Female 2W Down signature includes genes whose expression is reduced in blood RNA from female subjects after two weeks, as captured in the MoTrPAC Rat Endurance Exercise Training Transcriptomics collection [5]. The GSE157594 6 V 4 NICOTINAMIDE MOUSE DN signature contains genes that are downregulated in mouse tissue when comparing condition 6 to condition 4 following nicotineamide treatment, derived from the RummaGEO Drug Perturbation Signatures resource [6]. The GlyGen signature corresponds to proteins phosphorylated by the glycan.

Methods

The GTEx Tissue-Specific Aging dataset was constructed using gene expression count data from the Genotype Tissue Expression (GTEx) Portal [4]. Sample metadata was filtered to create groups of samples with matching tissue type and donor age ranges. Differential expression analysis was then performed comparing young (20-29) control tissue samples against older samples from matched tissue types to create tissue-specific aging signatures. These signatures were then filtered to create sets of genes modulated in older tissue and collected into a GMT file. The MoTrPAC Rat Endurance Exercise Training dataset was processed from transcriptomic data from the Molecular Transducers of Physical Activity Consortium (MoTrPAC) Data Hub [5]. Differential expression data from MoTrPAC was filtered to keep associations where gene expression changed over the course of 8 weeks of endurance exercise. Exercise tissue samples were differentiated by sex and tissue type in addition to exercise time-point. The downloaded data also included training data of genes with modulated expression over the training window in addition to the timewise data. The differential expression data was filtered to create gene sets and a GMT. RummaGEO is a webserver developed to enable expression signature search against human and mouse RNA-seq studies deposited to GEO [6]. To enable this search, offline processing automatically identified groups of samples were based on shared conditions and differential expression analysis was performed. The RummaGEO Drug Perturbation Signatures dataset was processed by querying the RummaGEO metadata search API to identify a subset of signatures where one condition included a control term and the other included a drug. Gene sets for each signature in the subset were combined to construct a GMT file. The workflow starts with selecting the GTEx Tissue-Specific Aging Signatures, MoTrPAC Rat Endurance Exercise Training Transcriptomics, and

RummaGEO Drug Perturbation Signatures datasets. Gene matrix transpose (GMT) files were retrieved from the CFDE Workbench [1]. GMTs were crossed to analyze all possible combinations of one gene set from each library. For each combination, the p-value was computed by computing the hypergeometric test of each gene set against the intersection of the remaining sets, using the most conservative p-value as the value for the crossing. The top 5,000 combinations were kept, ranked by ascending (most conservative) p-value and descending Jaccard index. The crossing with rank 2 was selected for further investigation, and the intersecting gene set was extracted. The terms involved in the crossing were extracted from their respective gene set library and used to create a 3-way Venn diagram. The intersecting gene set was submitted to Enrichr [7]. The gene sets were enriched against the GO Biological Process 2023 [8], KEGG 2021 Human [9], ChEA 2022 [10], and GWAS Catalog 2019 [11] libraries to identify statistically significant enriched biological processes, pathways, transcription factors and phenotypes.

Results

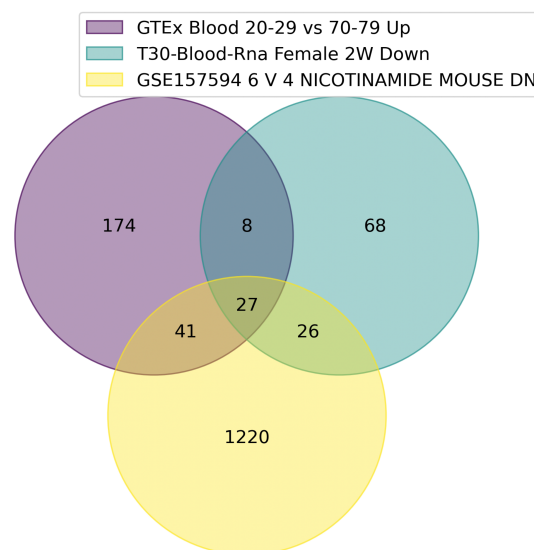


Figure 1. Crossed gene sets Venn diagram. A venn diagram of the crossed gene sets. Sizes of each set and 2- and 3-way intersection are labelled.

The crossing had a rank of 2, p-value of 1.038864e-26, and Jaccard index of 0.017263. The intersecting gene set identified 27 genes appearing in all involved sets (Figure 1). The intersecting gne set consists of AGXT AGXT2 AMBP ANGPTL3 APCS APOC1 APOC2 APOC4 APOH C8A CYP8B1 FGA FGB FGG FGL1 HABP2 HAMP HAO1 HMGCS2 HRG PAH RBP4 SERPINA6 SLC2A2 TDO2

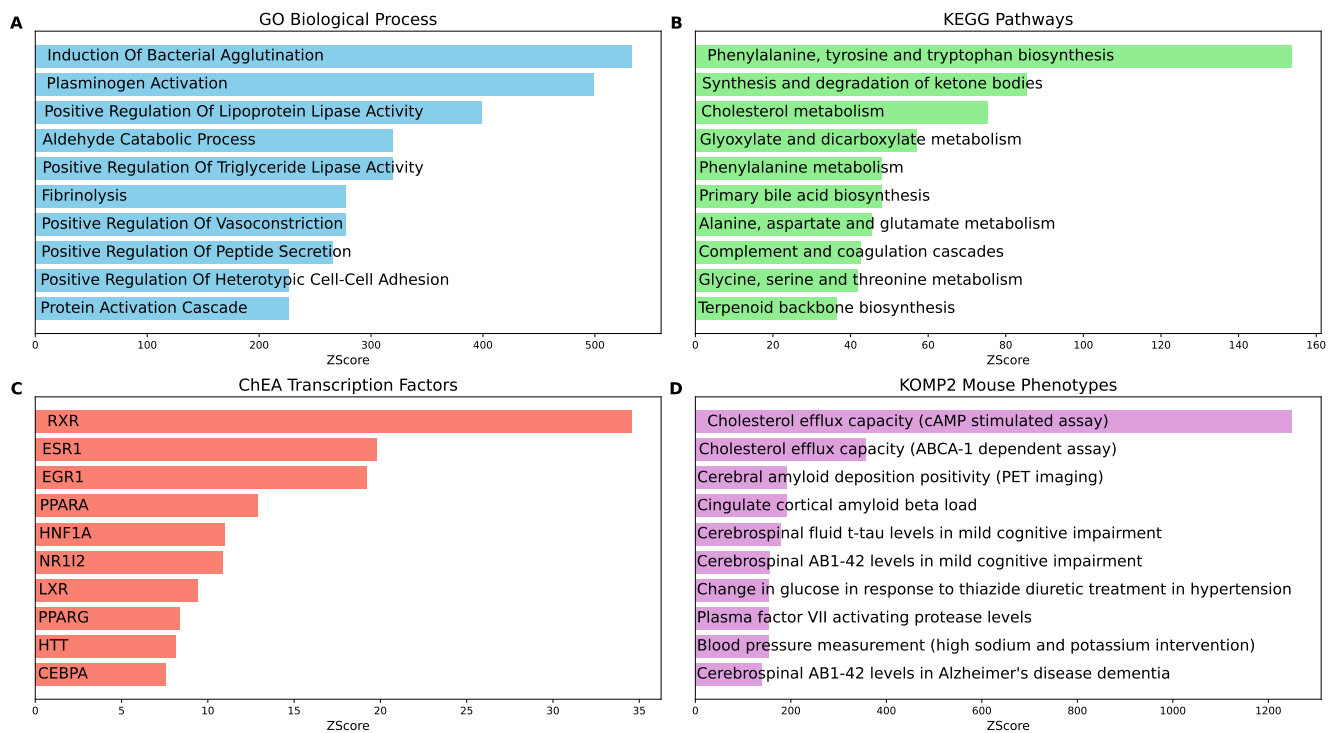


Figure 2. Enriched Terms for Intersecting Gene Set. Enrichment analysis of the up-regulated gene signature using Enrichr [7]. Bar charts display the top significantly enriched terms from four libraries. A. GO Biological Process 2023 [8], B. KEGG 2021 Human [9], C. ChEA 2022 [10], and D. GWAS Catalog 2019 [11]. Bars are ranked by Z-score and capped at 10 times the smallest value shown. Color indicates the source library. The full enrichment results are available to view at [Enrichr](#).

THRSP, and TTR. Functional enrichment analysis of the gene set identified associations with Induction Of Bacterial Agglutination and Plasminogen Activation from enrichr, Phenylalanine, tyrosine and tryptophan biosynthesis and Synthesis and degradation of ketone bodies from enrichr, RXR and ESR1 from enrichr, and Cholesterol efflux capacity and Cerebral amyloid deposition positivity from enrichr (Figure 2).

Discussion

The intersecting gene set is enriched for secreted proteins that participate in extracellular matrix organization and complement-mediated immunity, processes that depend on glycosylation. Bikunin forms intertrypsin inhibitor complexes that are covalently linked to hyaluronan, thereby stabilizing the matrix and modulating inflammation and tissue remodeling. [12–14] The C8a subunit of the membrane attack complex exhibits microheterogeneity, including multiple glycosylation events that influence MAC assembly and stability. [15–17] Histidinerich glycoprotein binds heparan sulfate in a Z-independent manner and acts as an opsonin that bridges apoptotic and necrotic cells to phagocytic receptors, contributing to clearance and hemostatic balance. [18–33].

Another prominent theme is the regulation of lipid metabolism by circulating glycoproteins that affect lipoprotein processing. Angiopoietinlike protein3 is a liver-derived secreted glycoprotein that inhibits lipoprotein lipase and endothelial lipase, modulating the clearance of triglyceride-rich lipoproteins and influencing plasma triglyceride, LDLC and HDLC levels. [34–43] ApolipoproteinC1 participates in lipoprotein clearance and cholesterol homeostasis, with variation linked to plasma lipid levels and metabolic syndrome features. [44–55] ApolipoproteinC2 serves as the essential activator of lipoprotein lipase, promoting efficient plasma triglyceride clearance, and loss-of-function mutations cause severe hypertriglyceridemia. [56–61].

The enrichment patterns reveal convergence on several biological themes across the different libraries. Both the GO biological process results and the KEGG pathway analysis highlight coagulation-related processes, with fibrinolysis and protein activation cascades appearing in GO and complement and coagulation cascades emerging from KEGG, indicating a consistent focus on hemostatic mechanisms [8], [9]. Cholesterol-related terms are also shared, as cholesterol metabolism is prominent in KEGG while cholesterol efflux capacity features strongly in the GWAS-derived results, suggesting that the gene sets intersect lipid handling pathways

and clinical measures of cholesterol transport [9], [11]. Vascular regulation is another point of overlap: positive regulation of vasoconstriction is enriched in GO, and bloodpressure measurement traits are highlighted in GWAS, linking the molecular signals to bloodpressure phenotypes [8], [11]. In contrast, the transcription-factor enrichment from ChEA is dominated by nuclear receptors and related factors such as RXR, ESR1, PPARA and HNF1A, which are not directly represented in the GO, KEGG or GWAS lists, indicating a distinct regulatory layer [10]. Together, these patterns suggest that the upregulated and downregulated gene sets jointly engage metabolic, coagulation and lipidprocessing pathways while also connecting to diseaserelevant traits captured in GWAS, with transcriptionfactor binding providing a complementary signature.

The reanalysis revealed a highly significant overlap between the agerelated blood expression changes in GTEx, the earlylife female blood RNA changes, and the nicotinamidetreated mouse liver response, with 27 shared genes that include numerous secreted plasma proteins such as ANGPTL3, APOC1, APOC2, AMBP, C8A, HRG and several coagulation factors. Enrichment of these intersecting genes consistently pointed to hemostatic and lipidhandling pathways [8, 9]; cholesterol metabolism and efflux [9, 11]; as well as vascular regulation through vasoconstriction and bloodpressurerelevant traits [8, 11]. Deepdive literature summaries reinforced this picture by describing the roles of the overlapping proteins in extracellular matrix organization, complementmediated immunity, and the regulation of triglyceride and cholesterol homeostasis through glycosylated secreted factors. A distinct regulatory signature emerged from transcriptionfactor analysis, which identified nuclearreceptor family members such as RXR, ESR1, PPARA and HNF1A, a layer not captured by the primary GO or KEGG terms and therefore somewhat unexpected [10]. Together, these findings link the coordinated up and downregulation observed across the three datasets to integrated metabolic, coagulation and vascular processes, supporting the central research question that the intersecting gene sets reflect shared biological themes underlying agerelated blood expression changes, early developmental blood signatures, and nicotinamideresponsive metabolic pathways.

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