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Human multi-tissue transcriptomics identifies galectin-1 and follistatin-like 1 as exerkines with distinct transcript-to-serum coupling after exercise

Jaeseung Song[1], Eun-Suk Cho[2], Yu Rim Kwon[3], Jong Suk Park[4,5], Ji Sun Nam[4,5] and YuSik Kim[6]

[1]*Department of Life Sciences, Dongguk University, Seoul, Republic of Korea*
[2]*Department of Radiology, Gangnam Severance HospitalYonsei University College of Medicine, Seoul, Republic of Korea*
[3]*Department of Physical Education, Yonsei University Graduate School, Seoul, Republic of Korea*
[4]*Division of Endocrinology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea*
[5]*Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Republic of Korea*
[6]*Severance Institute for Vascular and Metabolic Research, Yonsei University College of Medicine, Seoul, Republic of Korea*

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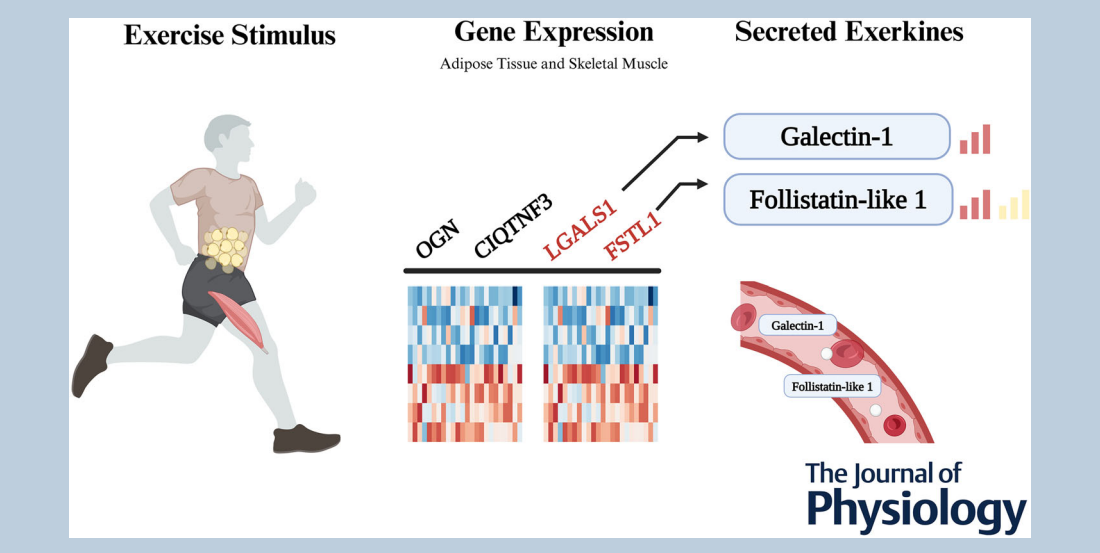

Jaeseung Song received his Ph.D. in Life Science from Dongguk University in 2025. His doctoral research focused on the analysis of multi-omics datasets and the development of scalable computational frameworks to bridge the gap between genetic variants and cell-type-specific biological mechanisms. Currently, as a postdoctoral researcher, he is developing integrative frameworks to quantify the variability and causality linking genetic associations with high-throughput genomic datasets. **Eun-Suk Cho** earned his bachelor's and master's degrees from Yonsei University Wonju College of Medicine and his Ph.D. degree from Yonsei University College of Medicine. He has joined Gangnam Severance Hospital and has served as a Clinical Assistant Professor in the Department of Radiology since 2012. He is a member of the Korean Society of Abdominal Radiology. His clinical and academic work focuses on abdominal and genitourinary radiology, medical physics and radiation dose reduction.

J. Song and E.-S. Cho contributed equally to this work.

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Abstract figure legend Acute aerobic exercise induces *LGALS1*, *FSTL1*, *OGN* and *C1QTNF3* in both skeletal muscle and adipose tissue, with *LGALS1* and *FSTL1* upregulation corresponding to increased circulating galectin-1 and follistain-like 1. Red and yellow brick bars represent the contribution of skeletal muscle and adipose tissue, respectively, integrating tissue size and gene induction. Fstl1 shows tissue-mass-dependent coupling in both depots (red bars: skeletal muscle, yellow bars: adipose tissue), while galectin-1 reflects a muscle-dominant, additive pattern.

Abstract Exercise-induced secreted factors (exerkines) are proposed to coordinate systemic health benefits, yet their human tissue sources and the physiological rules governing transcript-to-serum coupling remain incompletely defined. We integrated multi-tissue transcriptomics with matched serial serum profiling to identify exercise-regulated exerkines and determine whether tissue mass moderates their systemic appearance. Sixteen healthy, sedentary young men performed a single treadmill bout calibrated to expend 300 kcal at 70–75% of maximum heart rate. RNA sequencing was performed on periumbilical subcutaneous adipose tissue, vastus lateralis skeletal muscle and whole blood collected before and immediately after exercise, with serial serum quantification up to 120 min post-exercise. Acute exercise altered adipose and muscle transcriptomes, with a minimal whole-blood response, and upregulated *LGALS1* (galectin-1), *FSTL1* (follistatin-like 1), *OGN* (osteoglycin) and *C1QTNF3* (C1q and tumour necrosis factor-related protein 3) in both tissues. Serum follistatin-like 1 and galectin-1 concentrations increased significantly immediately after exercise and during recovery. Despite robust transcript induction, OGN and C1QTNF3 did not translate into early circulating increases, indicating candidate-specific kinetics and constraints beyond transcript abundance. Moderation models revealed divergent transcript-to-serum coupling: follistatin-like 1 coupling was moderated by tissue mass in both muscle and adipose depots, whereas galectin-1 followed a muscle-dominant additive profile independent of mass scaling. These findings propose galectin-1 and follistatin-like 1 as human exerkines and indicate that body composition regulates systemic exerkine signatures after exercise, providing a mechanistic framework for understanding physiological variability in exercise-induced adaptations.

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Corresponding authors J. S. Nam: Research Centre for Future Medicine, Gangnam Severance Hospital; 211 Eunju-Ro Gangnam-Gu, Seoul, Republic of Korea, 06273. Email: jisunn@yuhs.ac
Y. Kim: Gangnam Severance Hospital Biomedical Research Centre; 237 Dogok-Ro Gangnam-Gu, Seoul, Republic of Korea, 06230. Email: cromoton@yuhs.ac

Key points

- Exercise releases circulating factors that may contribute to health benefits, but the human tissues responsible for their production remain unclear.
- RNA sequencing was performed in human skeletal muscle, subcutaneous adipose tissue and whole blood, with targeted serum protein quantification over 2 h after a single treadmill bout.
- Exercise increased *LGALS1* and *FSTL1* transcripts in skeletal muscle and adipose tissue, with concurrent increases in their circulating protein products immediately post-exercise and during recovery, whereas *OGN* and *C1QTNF3* transcripts increased robustly without an early post-exercise elevation in their circulating protein products.
- Body composition moderated transcript-to-serum coupling: *FSTL1* (follistatin-like 1) showed mass-sensitive coupling, whereas *LGALS1* (galectin-1) displayed a muscle-dominant additive profile.
- Galectin-1 and follistatin-like 1 emerge as exercise-induced exerkines whose circulating responses vary with body composition, supporting their prioritization as candidate mediators of exercise-related health benefits and a framework for interpreting physiological heterogeneity in adaptation.

Introduction

Accumulating evidence consistently demonstrates that physical activity is associated with a reduced risk of premature mortality and broad health benefits across diverse populations and conditions (Posadzki et al., 2020; Warburton & Bredin, 2017; Warburton et al., 2006). While a clear dose–response relationship has been evident (Warburton et al., 2006), even modest increases in activity levels confer significant health benefits, reinforcing the central role of physical activity in chronic disease prevention and the promotion of overall well-being (Posadzki et al., 2020; Warburton & Bredin, 2017). Although numerous hypotheses have been proposed to explain the physiological mechanisms underlying these benefits, the molecular mechanisms remain incompletely understood. Exercise induces complex endocrine adaptations involving a network of organ-to-organ communication, primarily mediated by tissue-derived signalling molecules. Emerging evidence now points to exercise-induced secreted factors from multiple organs, collectively termed *exerkines* (Safdar et al., 2016), as key mediators of systemic adaptations to physical activity, facilitating inter-organ communication and contributing to the pleiotropic effects of exercise (Chow et al., 2022; Walzik et al., 2024). Beyond classical cytokines, exerkines encompass a broad range of bioactive molecules, including *myokines* from skeletal muscle, *cardiokines* from the heart, *hepatokines* from the liver, *adipokines* from adipose tissue, *cytokines* from white blood cells and *neurokines* from neurons, as well as select nucleic acids and metabolites that may exert autocrine, paracrine or endocrine effects (Chow et al., 2022).

Adipokines were among the first exercise-responsive signalling molecules to be characterized in this context, with leptin (Zhang et al., 1994) and adiponectin (Scherer et al., 1995) attracting early attention as key targets in exercise-related endocrine research, followed by the identification of myokines such as interleukin-6 (IL-6) (Steensberg et al., 2000) and irisin (Bostrom et al., 2012), which have become prototypical markers of muscle-derived endocrine activity. The advent and widespread adoption of multi-omics approaches, particularly next-generation sequencing-based transcriptomic profiling and secretome analyses, have facilitated the discovery of novel candidate exerkines from various tissues (Babu & Snyder, 2023). These molecules are now under active investigation for their regulation by physical activity, roles in exercise-induced physiological adaptations, and potential contributions to health maintenance and disease prevention.

In humans, regular physical activity or exercise training has been shown to positively modulate the secretion of several known exerkines, including adipokines, myokines and more recently classified factors from other tissues, thereby contributing to systemic physiological adaptations and health benefits (Chow et al., 2022; Jin et al., 2024). However, precise identification of exerkines in humans remains technically challenging due to methodological limitations. Comprehensive profiling requires access to human tissue biopsies for transcriptomic or proteomic analyses, alongside matched serum samples to quantify secreted protein levels before and after exercise (Chow et al., 2022). These logistical and ethical constraints have led to a predominant reliance on animal models, which, although informative, often lack direct translational relevance to human physiology. Most studies examining transcriptomic or proteomic profiles have been conducted in genetically homogeneous animal models and/or small human cohorts, thereby limiting generalizability (Chow et al., 2022). Furthermore, widespread expression of many exercise-responsive proteins across multiple tissues complicates assignment of tissue origin, obscuring their classification as bona fide myokines, adipokines or other tissue-specific exerkines (Chow et al., 2022; Walzik et al., 2024). For instance, fibroblast growth factor 21 (FGF-21) is expressed in skeletal muscle (Hojman et al., 2009), contributing to its classification as a potential myokine; this has been further supported by clinical evidence demonstrating increased circulating FGF-21 levels after exercise in humans (Khalafi et al., 2021). However, its gene expression is predominantly hepatic, with substantially lower levels in adipose tissue and skeletal muscle (Keipert et al., 2014). Consistent with this, animal and human data indicate that exercise-induced elevation of circulating FGF-21 is primarily liver-derived (Catoire et al., 2014; Kim et al., 2013). Nevertheless, definitive evidence confirming the hepatic origin of exercise-induced FGF-21 in humans remains limited, due to practical and ethical constraints of liver biopsy sampling. These challenges highlight the pressing need for integrative, human-based approaches that combine multi-tissue sampling with high-resolution omics technologies to advance the mechanistic understanding of exerkine biology.

While tissue-specific classifications such as myokines, adipokines and hepatokines have provided valuable context for understanding the inter-organ communication mediated by individual organs, strict categorization based solely on tissue of origin may be overly reductive. Many exercise-responsive molecules are expressed and secreted by multiple tissues, making it difficult to definitively assign a single source. The term *exerkine* has therefore emerged as a unifying concept, encompassing all bioactive factors, regardless of origin, that are induced by exercise and exert autocrine, paracrine or endocrine effects (Chow et al., 2022; Safdar et al., 2016; Walzik et al., 2024). Nevertheless, identifying the tissue of origin remains biologically important, as it can inform the

signalling modality, functional specificity and potential relevance to disease states. Accordingly, integrative approaches that combine multi-tissue profiling are essential to elucidate the mechanistic roles and clinical implications of exerkines.

Despite growing interest, human studies that integrate transcriptomic profiling across multiple tissues with matched circulating protein profiles remain limited, largely due to the logistical and ethical challenges of acquiring repeated tissue biopsies. To date, only one human study has combined serum proteomics with transcriptomic profiling of multiple tissues following exercise training (Lee-Ødegård et al., 2024), reflecting the rarity of such integrative approaches. Consequently, identification of candidate exerkines and their tissue-specific transcriptional responses to exercise in humans remains poorly characterized. Aiming to expand current understanding, we conducted a human study involving young adult males, in which skeletal muscle, adipose tissue and blood samples were collected before and after a single bout of acute aerobic exercise. Using mRNA profiling and targeted serum protein analysis, we aimed to identify exercise-responsive genes with secretory potential across multiple tissues and evaluate their correspondence with circulating protein changes. We hypothesized that acute aerobic exercise would induce coordinated transcriptional responses across skeletal muscle, adipose tissue and whole blood, with corresponding increases in selected circulating exerkines.

Methods

Ethical approval

Our study was conducted in accordance with the standards set by the latest version of the *Declaration of Helsinki* and was approved by the Institutional Review Board of Gangnam Severance Hospital (3-2024-0268). All subjects provided written informed consent prior to participating in any study procedures.

Study participants

Sixteen sedentary male participants were recruited based on the following inclusion criteria: (1) weight-stable ($\leq$5% change over the preceding three months); (2) no participation in exercise training programmes within 6 months; (3) physical inactivity ($\leq$600 metabolic equivalent of task (MET)-minutes/week, as assessed by the Korean Version of Global Physical Activity Questionnaire; Lee et al., 2020); and (4) absence of diagnosed metabolic disorders and no current use of chronic medications. Participant characteristics are provided in Table 1. To minimize the influence of recent behavioural and environmental factors on the primary outcomes and to ensure that observed responses reflected the effect of the study protocol, participants were instructed to refrain from any structured exercise and to limit additional voluntary physical activity, and to avoid sauna bathing for at least 48 h before the assessment and exercise protocol, while otherwise maintaining their usual daily activities and habitual lifestyle.

Table 1. Clinical characteristics of participants

Clinical variables	Data (mean ± SD)
Age (years)	28.6 ± 2.38
BM (kg)	76.42 ± 12.98
BMI (kg/m^2)	25.56 ± 3.35
WC (cm)	85.64 ± 8.49
VFA (cm^2)	73.14 ± 28.01
FM (kg)	18.14 ± 7.23
FMP (%)	23.11 ± 5.69
SMM (kg)	32.96 ± 4.35
SMMP (%)	43.44 ± 3.1
SBP (mmHg)	121.71 ± 14.63
DBP (mmHg)	81.41 ± 10.54
RHR (bpm)	80.71 ± 8.01
GPAQ (MET-min/week)	426.47 ± 142.92

Abbreviations: BM, body mass; BMI, body mass index; DBP, diastolic blood pressure; FM, fat mass; FMP, fat mass proportion; GPAQ, Global Physical Activity Questionnaire; MET, metabolic equivalent of task; RHR, resting heart rate, SBP, systolic blood pressure; SMM, skeletal muscle mass; SMMP, skeletal muscle mass proportion; VFA, visceral fat area; WC, waist circumference;

Study protocol and biological sample collections

To minimize confounding by nutritional status on exercise-induced gene expression, all participants were provided a standardized meal (590 kcal; sandwich 510 kcal plus orange juice 80 kcal) following an overnight fast of at least 8 h. Two hours following the meal, participants performed moderate-intensity aerobic exercise on a treadmill (Medtrack ST65, Quinton, Bothell, WA, USA), designed to expend 300 kcal. The 2 h interval was selected to standardize the pre-exercise nutritional condition while avoiding excessive food or fluid intake proximal to exercise. This approach is consistent with pre-exercise nutrition principles emphasizing a balance between substrate availability and gastrointestinal tolerance within the final 4 h before endurance-type exercise (Kerksick et al., 2017). Exercise intensity was individually calibrated to maintain a heart rate (HR) between 70% and 75% of the age-predicted maximum (220 − age). HR was continuously monitored during the exercise protocol using an HR monitor (H10, Polar Electro,

Kempele, Finland), and the running speed was adjusted to maintain the target HR range for each individual. Energy cost estimation used the heart rate index (HRI; target HR/resting HR), with METs calculated as (HRI × 6) − 5 and energy expenditure per minute as METs × 3.5 × body mass (kg)/200; total session duration equalled 300 divided by kcal/min (Wicks et al., 2011). All participants completed the treadmill bout at the prescribed intensity, and the mean exercise duration required to achieve the target energy expenditure was 35.21 ± 7.78 min.

Venous blood samples were collected at six time points: prior to exercise (baseline), immediately post-exercise (P_0), and at 30, 60, 90 and 120 min following exercise (P_{30}, P_{60}, P_{90} and P_{120}, respectively). Samples were obtained via an indwelling catheter placed in the antecubital vein. Serum was separated by centrifugation at approximately 1,510 *g* for 15 min at 4°C and stored at −80°C. All exercise sessions were conducted between 11.30 and 12.30 h to minimize circadian variation.

For transcriptomic analyses, tissue biopsies of vastus lateralis skeletal muscle and periumbilical subcutaneous adipose tissue, and whole blood were collected at two time points: 7 days prior to the exercise protocol and immediately after the protocol. To standardize prandial status, participants consumed the standardized meal after an overnight fast, administered 2 h before each sampling. This fixed timing was applied on both the baseline sampling visit and the exercise test day to maintain a consistent pre-sampling nutritional milieu across time points. Biopsies were performed under local anaesthesia using 1% lidocaine (Hospira Inc., Lake Forest, IL, USA). An 18-gauge core needle attached to a semi-automatic biopsy gun (MAB1810, Meditech, Ahmedabad, India) was used under ultrasound guidance (HSP70A, Samsung, Seoul, Korea). Muscle and adipose samples were obtained within a 10-min window by an experienced radiologist. Immediately after collection, tissue biopsies were placed in RNA stabilization solution (AM7022, Thermo Fisher Scientific, Waltham, MA, USA) and whole blood in PAXgene® Blood RNA tubes (761165, BD Biosciences, San Jose, CA, USA). All samples were promptly processed for RNA sequencing (RNA-Seq) to prevent potential degradation or freeze–thaw artifacts. A schematic of the study workflow is shown in Fig. 1.

Anthropometric measurements

Anthropometric assessments were performed on the day of the exercise protocol. Body mass (BM), height and body mass index (BMI) were measured with an electronic stadiometer (BSM370, BioSpace, Seoul, Korea). Waist circumference (WC) was measured using a non-elastic circumference measuring tape (SECA201, SECA, Hamburg, Germany) at the midpoint between the lowest rib and iliac crest. Body composition, including

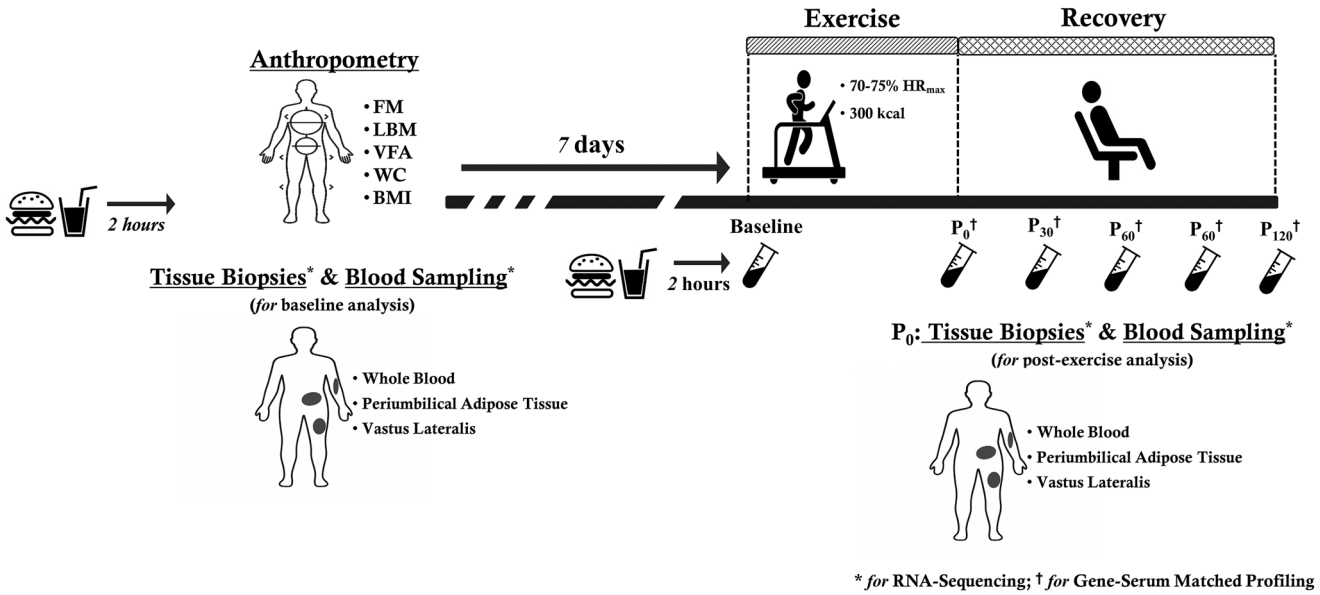

Figure 1. Study schema
Overview of the study protocol and sampling timeline. Baseline biopsies (periumbilical subcutaneous adipose; skeletal muscle) and whole blood were collected 7 days before the exercise session. On the test day, participants completed a single bout of moderate-intensity treadmill exercise calibrated to expend 300 kcal with continuous heart-rate monitoring. Venous blood was obtained at baseline, P_0, P_{30}, P_{60}, P_{90} and P_{120}; adipose tissue and skeletal muscle biopsies and whole blood sampling were repeated at P_0. Both baseline and exercise-day sampling occurred 2 h after a standardized meal following an overnight fast. P_0, immediately post-exercise; P_{30}/P_{60}/P_{90}/P_{120}, minutes post-exercise.

skeletal muscle mass (SMM) and percentage (SMM%), total fat mass (FM) and percentage (FM%), and visceral fat area (VFA), was assessed using a bioelectrical impedance analyser (InBody770, BioSpace). All anthropometric data were obtained by averaging two assessments conducted at a consistent time of day for all participants, under controlled environmental conditions (20–22°C; 45–50% humidity) with routine device maintenance. Preceding physical activity and nutritional status were also standardized as part of the study protocol.

Library preparation, sequencing and RNA-Seq data processing

Total RNA was isolated from skeletal muscle, subcutaneous adipose tissue and whole blood using standard protocols. RNA extracted from whole blood reflects the composite transcriptome of circulating leukocytes, encompassing both mononuclear and polymorphonuclear cell populations. RNA integrity was assessed using the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA), and the samples with RNA integrity number (RIN) $\geq$ 7.0 proceeded to library preparation. mRNA libraries were constructed with the TruSeq Stranded mRNA Library Preparation Kit (Illumina, San Diego, CA, USA), following the manufacturer's protocol. Poly(A)-selected, strand-specific mRNA libraries (TruSeq Stranded mRNA; Illumina) were quality-checked, quantified and sequenced on the NovaSeq X Plus to generate paired-end 150 bp reads (~50 million/sample). Raw RNA-seq reads (*.FASTQ) were processed using BBduk (v. 39.01) to remove sequencing adapters and low-quality bases (Bushnell et al., 2017), aligned to the human reference genome (*GRCh38*, Gencode v. 39) using STAR (v. 2.7.10a) (Dobin et al., 2013). The resulting SAM files were converted to BAM format using SAMtools (v. 1.10) (Li et al., 2009), and gene-level quantification was performed using HTSeq-count (v. 2.0.2) in union mode with reverse-stranded settings (Anders et al., 2015).

Differential expression analysis and exerkine annotation

Differential expression for tissue biopsies was assessed with the DESeq^2 R package (v. 1.36.0) (Love et al., 2014). Gene counts were normalized and tested using the likelihood ratio test; differentially expressed genes (DEGs) were defined by $|\log_2$ fold change (FC)$| > 1$ with Benjamini–Hochberg adjusted $P < 0.05$. To identify potential exerkines, DEGs were annotated for predicted subcellular localization using data from the Human Protein Atlas (Uhlen et al., 2015), and genes classified as 'predicted to be secreted' were selected for further analysis. To evaluate their tissue-agnostic regulatory behaviour, Pearson's correlation coefficients were calculated between $|\log_2$FC$|$ values. Based on these analyses, four candidate exerkines – osteoglycin (MBS2516031; RRID: AB_3720228), galectin-1 (MBS2511728; RRID: AB_3720229), follistatin-like 1 (Fstl1) (MBS2088287; RRID: AB_3720230), and C1q and TNF-related protein 3 (C1qTNF3) (MBS2515681; RRID: AB_3720231) – were quantified in serum using commercially available enzyme-linked immunosorbent assay kits (MyBioSource, San Diego, CA, USA). For each protein, the incremental area under the concentration–time curve (iAUC) above baseline was calculated using the linear trapezoidal rule across fixed post-exercise time points (P_0, P_{30}, P_{60}, P_{90}, P_{120}), with the baseline concentration as the reference.

Integration of genetic regulation and functional networks of candidate exerkines

To evaluate genetic regulation of candidate exerkines in relation to physical activity, we performed transcriptome-wide association study (TWAS) using the functional summary-based imputation (FUSION) (Gusev et al., 2016). Expression quantitative trait loci (eQTL) reference panels were obtained from the Genotype-Tissue Expression (GTEx) Project (v. 8) (Consortium et al., 2017). To match the tissue sources with RNA-seq, two eQTL panels were used for analysis: subcutaneous adipose (n = 479; no. of eGene = 23,292) and skeletal muscle (n = 588; no. of eGene = 19,893). Genome-wide association study (GWAS) summary statistics for moderate physical activity (UK Biobank, Atlas ID: 3206; n = 367,908) were retrieved from the GWAS Atlas (Bycroft et al., 2018). Statistical significance was determined by Bonferroni correction (TWAS.$P < 0.05/15{,}441$). To assess potential functional interactions between TWAS-significant genes and the previously identified candidate exerkines, we queried HumanBase tissue-specific gene–gene networks for adipose, skeletal muscle and blood (Greene et al., 2015). Only high-confidence gene–gene edges were included in the analysis to explore biologically credible, tissue-specific regulatory networks.

Statistical analysis

Serum protein concentrations across the sampling time points are presented as mean $\pm$ standard deviation. Time-course differences across six repeated measures were evaluated using a one-way repeated-measures ANOVA. Pairwise comparisons of interest were adjusted using the Bonferroni method, with a two-sided α level of 0.05 defining statistical significance. To assess moderation by tissue mass of the relationship between

tissue-specific gene induction and circulating protein responses, linear regression models were constructed for Fstl1 and galectin-1. Each model included three predictors: mean-centred gene fold change, mean-centred tissue mass (FM and SMM), and their interaction term. The iAUCs for Fstl1 and galectin-1 served as the dependent variables. Regression results are presented as unstandardized coefficients, standard errors, and corresponding two-sided *P*-values. All analyses were conducted using SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA).

Results

Transcriptome analysis to identify tissue-agnostic exerkine signatures

To characterize transcriptional responses to acute endurance exercise, we performed RNA-Seq on subcutaneous adipose tissue, skeletal muscle and whole blood collected before and immediately after the bout. Using $|\log_2 FC| > 1$ and false discovery rate (FDR) < 0.05, we identified a substantial number of DEGs in adipose tissue (1515 upregulated; 246 downregulated) (Figs. 2*A* and 3*A*) and skeletal muscle (478 upregulated; 60 downregulated) (Figs. 2*B* and 3*B*), whereas whole blood exhibited a minimal response (five upregulated DEGs) (Fig. 3*C*). Intersecting DEGs across the sample tissues revealed 208 genes commonly upregulated and 15 commonly downregulated between adipose tissue and skeletal muscle, with no robust overlap in blood (Fig. 2*C*). Subcellular annotation (Human Protein Atlas) nominated four shared, secreted candidates: *OGN* (osteoglycin), *LGALS1* (galectin-1), *FSTL1* (Fstl1) and *C1QTNF3* (C1qTNF3); all four were upregulated in both adipose tissue and skeletal muscle (Fig. 2*D*). These data indicate that acute endurance exercise elicits a coordinated, tissue-level secretory programme in adipose tissue and skeletal muscle, with negligible transcriptional change in whole blood. Among these candidates, *LGALS1* and *FSTL1* exhibited relatively higher basal expression in adipose tissue (*LGALS1*, 51.642; *FSTL1*, 94.857) than skeletal muscle (*LGALS1*, 17.142; *FSTL1*, 24.017). Both were significantly increased post-exercise in adipose tissue [*LGALS1*, 121.071 (+134.4%); *FSTL1*, 315.286 (+232.4%)] and skeletal muscle [*LGALS1*, 54.000 (+215.0%); *FSTL1*, 157.142 (+554.3%); normalized units]. By contrast, *OGN* and *C1QTNF3* exhibited very low baseline expression in both adipose tissue (*OGN*: 4.142; *C1QTNF3*: 2.00) and skeletal muscle (*OGN*: 0.786; *C1QTNF3*: 0.428) with marked post-exercise increases in both adipose tissue [*OGN*: 26.071 (+529.4%); *C1QTNF3*: 10.357 (+417.8%); normalized units] and skeletal muscle [*OGN*: 7.428 (+845%); *C1QTNF3*: 6.214 (+1,351.8%); normalized units], indicating strong inducibility from low basal states.

Serum protein dynamics of candidate exerkines

One-way repeated-measures ANOVA demonstrated a significant main effect of exercise for both Fstl1 and galectin-1 (both Mauchly's test and Greenhouse–Geisser-corrected tests with $P < 0.001$). Using within-subject contrasts against baseline, Fstl1 (all $P < 0.01$) and galectin-1 (all $P < 0.001$) were significantly elevated at all post-exercise time points, peaking at P_{30} for Fstl1 (4.874 *vs.* 9.764 ng/mL) and at P_{60} for galectin-1 (11.442 *vs.* 27.831 ng/mL) (Fig. 4*A* and *C*). Peak values did not differ significantly from other post-exercise time points. By contrast, for osteoglycin and C1qTNF3, Mauchly's test indicated sphericity violations ($P = 0.00101$; P_{120}, $P = 0.000977$, respectively). After Greenhouse–Geisser correction, the one-way repeated-measures ANOVA showed no main effect of time (osteoglycin: $P = 0.267$; C1qTNF3: $P = 0.462$). Consistently, baseline-anchored pairwise contrasts were non-significant at all post-exercise time points (Fig. 4*B* and *D*). Aligning with their comparatively higher basal tissue expression and further induction by exercise, Fstl1 and galectin-1 manifested as exercise-responsive circulating proteins, whereas *OGN* and *C1QTNF3* showed tissue-level inducibility without concomitant short-term changes in circulation, suggesting limited acute release from muscle/adipose and that circulating pools are not predominantly derived from these tissues.

Genetic regulation and network context of candidate exerkines

Using FUSION TWAS with GTEx v8 expression weights for subcutaneous adipose tissue, visceral adipose tissue and skeletal muscle, paired with UK Biobank GWAS for habitual moderate physical activity, we identified 12 unique genes meeting Bonferroni significance across three tissue panels (Fig. 5*A*; Zenodo dataset; Kim, 2025). Specifically, five genes (*PDCD11*, *KANSL1*, *DGCR8*, *ANKDD1B* and *PRPS1P2*) from subcutaneous adipose panel, six (*CH17-472G23.2*, *RBBP5*, *CSPG4P10*, *KANSL1*, *TYW5* and *RP4-555D20.2*) from visceral adipose panel and three (*NARS2*, *KANSL1* and *NTN5*) in skeletal muscle panel showed significant associations. Notably, *KANSL1* was negatively associated with moderate physical activity in all panels. None of the four pre-specified candidates (*OGN*, *LGALS1*, *FSTL1*, *C1QTNF3*) reached TWAS significance. To place these signals in a tissue-specific regulatory context, we queried HumanBase networks; in adipose tissue, three of four candidates (*OGN*, *LGALS1*, *FSTL1)* were first-neighbour connected to six adipose

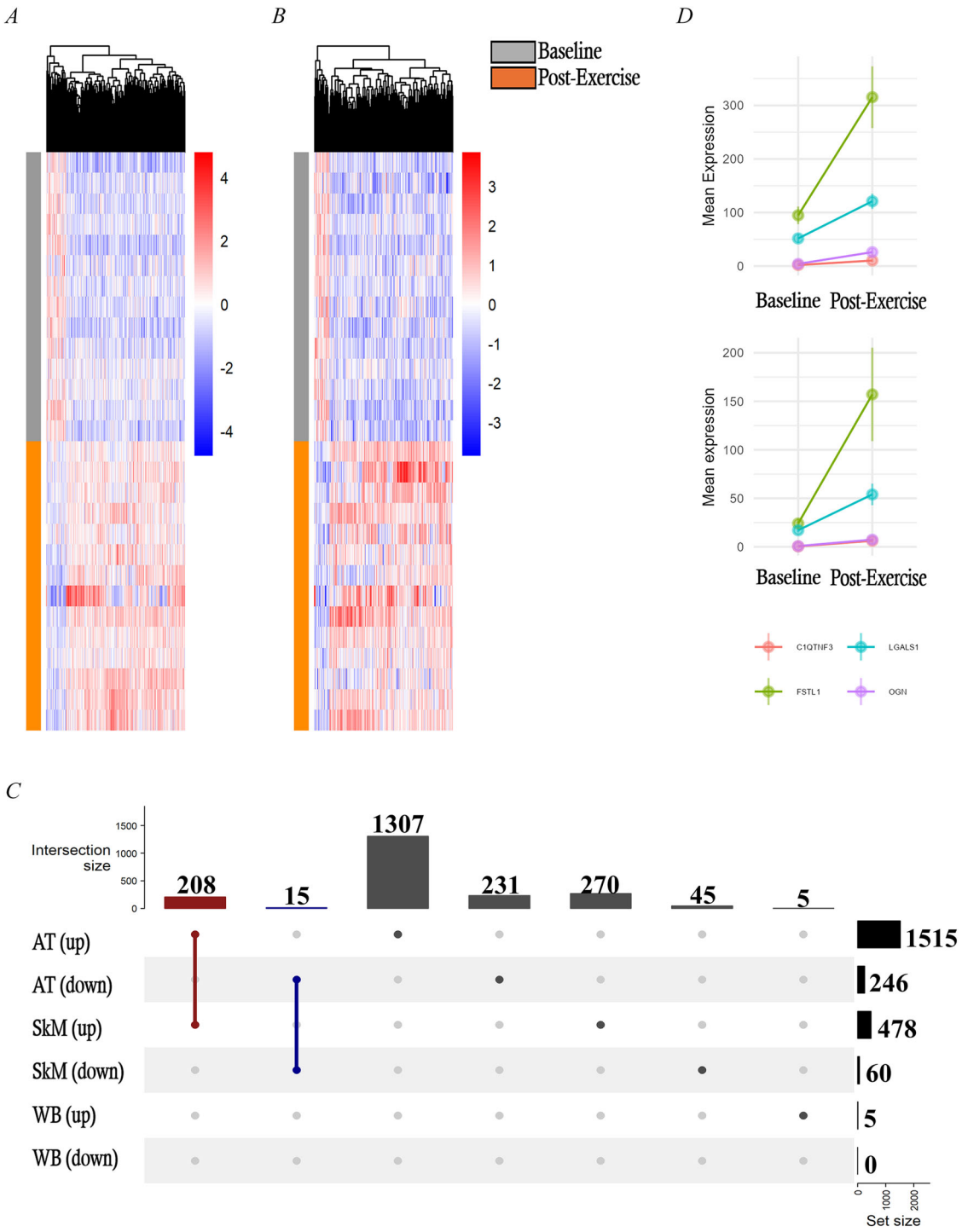

Figure 2. Multi-tissue transcriptomic responses to acute aerobic exercise and nomination of shared secretory candidates
A and *B*, heatmaps of differentially expressed genes (DEGs) in adipose tissue (*A*) and skeletal muscle (*B*) at baseline and immediately post-exercise. Rows are DEGs ($|\log_2 FC| > 1$, FDR < 0.05); columns are participants. Values are variance-stabilized, *z*-scored counts; hierarchical clustering shown. *C*, UpSet plot showing intersections of significant DEGs across adipose tissue and skeletal muscle. Adipose tissue and skeletal muscle share a set of regulated genes (208 up and 15 down), whereas whole blood shows a minimal response and no robust overlap. *D*, changes in expression of exerkine candidates at baseline and immediately post-exercise in adipose tissue (top) and skeletal muscle (bottom); points and lines denote mean expression changes of the exerkine candidates.

TWAS genes (Fig. 5*B*), and in skeletal muscle, all four candidates were directly connected to the three muscle TWAS genes (Fig. 5*C*).

Network-level proximities between TWAS hits and the candidate exerkines suggest that genetic influence on habitual physical activity acts upstream within regulatory pathways rather than by directly regulating these candidates via *cis* effects. Consistent with this, the TWAS-negative yet network-positive pattern indicates that activity-associated genetic variation converges on pathways encompassing these exerkines through indirect (*trans*) regulatory mechanisms. Within this framework, the observed directions of several TWAS signals, including the inverse association of KANSL1, are compatible with upstream programmes that could attenuate or enhance the magnitude of acute, putatively beneficial exercise responses.

Associations between anthropometry, tissue expression changes and serum dynamics

Correlation analyses relating anthropometric indices to exercise-induced changes in gene expression identified *OGN* in adipose tissue as the only candidate exhibiting statistically significant associations. Increases in adipose *OGN* expression appeared to be positively correlated with BMI ($r = 0.654$, $P = 0.027$), FM ($r = 0.702$, P = 0.009), FM% ($r = 0.706$, P = 0.007) and VFA ($r = 0.744$, P = 0.002), WC ($r = 0.734$, P = 0.003), and inversely with SMM% ($r = 0.698$, P = 0.005). No significant associations were observed for *LGALS1*, *FSTL1*, or *C1QTNF3* in adipose tissue (Fig. 6*A*), and none of the four genes showed associations in skeletal muscle (Fig. 6*B*).

We tested tissue-mass moderation using linear interaction models for each circulating protein and tissue (fold change, tissue mass and their interaction), and in parallel fitted main-effects regressions entering gene fold change (FC) and tissue mass independently (no interaction) to assess their individual associations with iAUC. For Fstl1, the adipose model showed a significant interaction between FC and FM [$B = 13.706$ (5.351), P = 0.031], with no main effect [FC: $B = 8.671$ (16.742), P = 0.517; fat mass: $B = 12.495$ (8.304), P = 0.167]. In the skeletal muscle model, FC, SMM, and the interaction were significant [FC: $B = 9.016$ (1.404), $P < 0.001$; SMM: $B = 39.505$ (9.453), P = 0.002; interaction: $B = 3.361$ (1.413), P = 0.041] (Table 2). These findings indicate mass-dependent modulation of circulating Fstl1, whereby FC yields greater serum output with increasing skeletal muscle mass, while adipose effects appear only at higher fat mass. For galectin-1, the adipose model was null [FC: $B = -12.855$ (62.356), P = 0.841; fat mass: $B = -0.101$ (24.019), P = 0.997; interaction: $B = 8.339$, P = 0.628], whereas the skeletal-muscle model showed significant main effects of FC and SMM without interaction [FC: $B = 118.892$ (22.733), $P < 0.001$; SMM: $B = 70.247$ (20.985), P = 0.007; interaction: $B = 4.991$ (7.809), P = 0.537] (Table 2). These results suggest that the galectin-1 response is muscle-derived, reflecting additive effects of FC and SMM without detectable mass-dependent amplification, and with no evident adipose contribution

Discussion

Exercise induces transient elevations in circulating proteins, collectively termed exerkines, which contribute

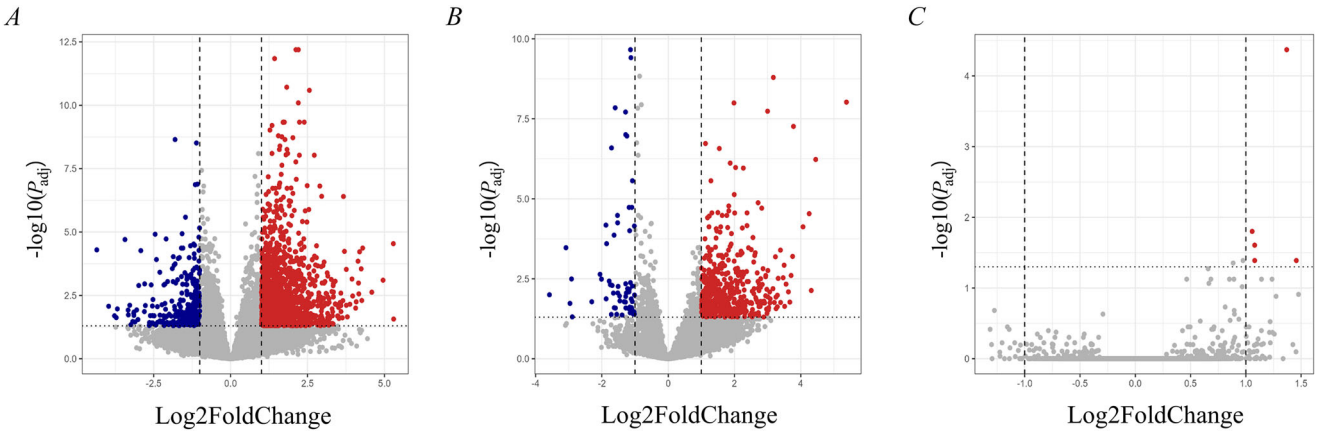

Figure 3. Volcano plots of differential gene expression after acute exercise in
A, adipose tissue; *B*, skeletal muscle; and *C*, whole blood. The *x*-axis shows $\log_2$ fold change (post *vs*. baseline) and the *y*-axis shows $-\log_{10}$(FDR). Points meeting $|\log_2 FC| > 1$ with FDR < 0.05 are coloured as upregulated (red) or downregulated (blue); non-significant genes are grey. Dashed lines mark the significance and fold-change thresholds. Adipose exhibited extensive regulation (up 1515; down 246), skeletal muscle showed a moderate response (up 478; down 60), and whole blood showed a minimal response (up 5; none down).

Table 2. Tissue mass-moderated linear regression of exercise-induced circulating Fstl1 and galectin-1

	Fstl1		LGALS1	
	B (SE)	*P*	*B* (SE)	*P*
$_c\Delta Gene^{AT}$	8.671 (16.742)	0.517	−12.855 (62.356)	0.841
$_c$FM	12.495 (8.304)	0.167	−0.101 (24.019)	0.997
Interaction ($_c\Delta Gene^{AT} \times {}_c$FM)	13.706 (5.351)	0.031	8.339 (10.127)	0.628
$_c\Delta Gene^{SM}$	9.016 (1.404)	8.139×10^{-4}	118.892 (22.733)	9.171×10^{-4}
$_c$SMM	39.505 (9.453)	0.002	70.247 (20.985)	0.007
Interaction ($_c\Delta Gene^{SM} \times {}_c$SMM)	3.361 (1.413)	0.041	4.991 (7.809)	0.537

B, unstandardized regression coefficient; SE, standard error; *P*, two-sided *P*-value. Abbreviations: AT, adipose tissue; FM, fat mass; iAUC, incremental area under the concentration–time curve; LGALS1, galectin-1; SM, skeletal muscle; SMM, skeletal muscle mass; ΔGene, gene-expression fold change; c-prefix, mean-centred predictor.

to metabolic adaptation and inter-organ communication. However, the transcriptional origins and tissue contributions to acute exerkine release in humans remain incompletely defined. We integrated multi-tissue transcriptomics with matched serial serum profiling to identify exerkines induced by an acute aerobic bout and to test whether tissue mass modulates the translation of transcriptional activation into circulating protein. Acute exercise elicited a coordinated secretory programme in adipose tissue and skeletal muscle, whereas whole

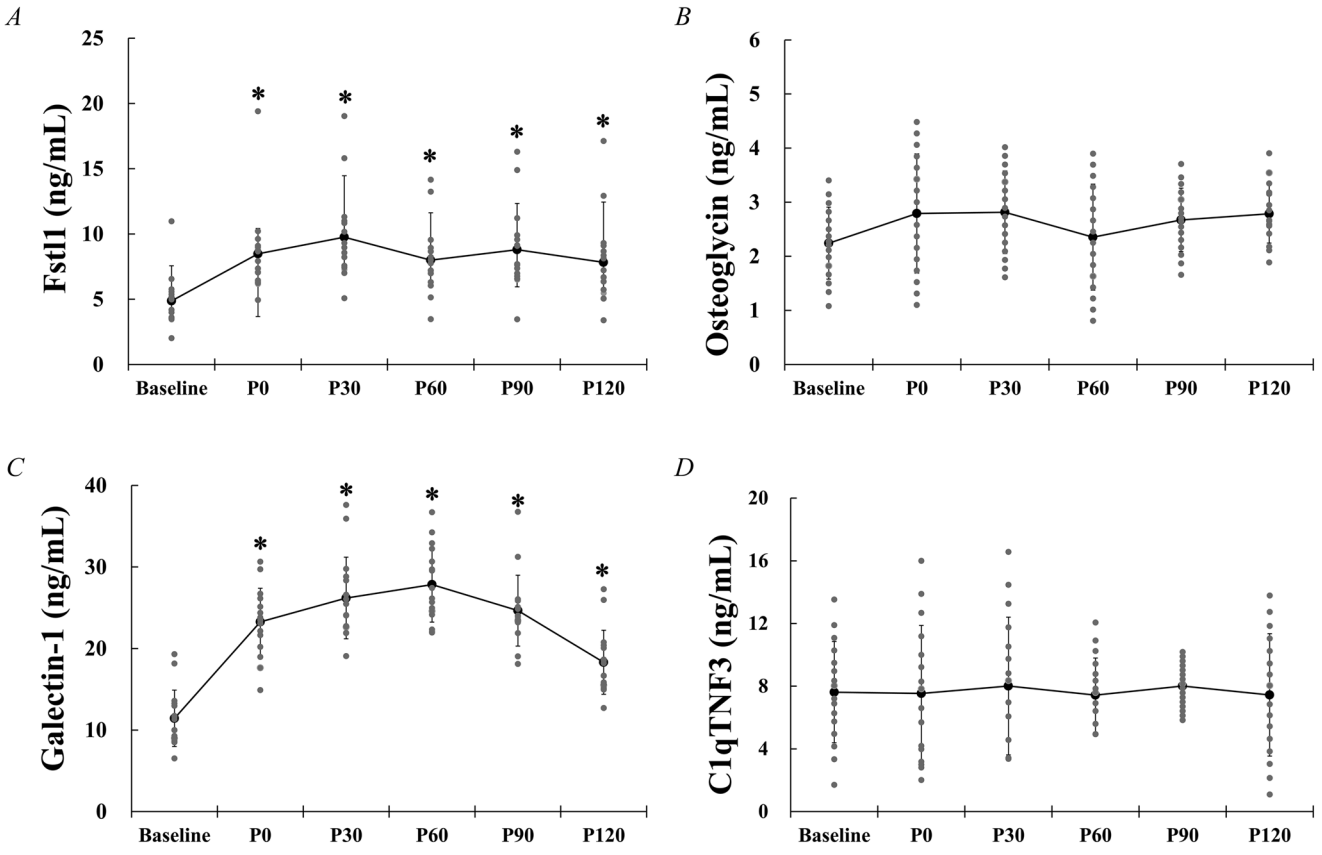

Figure 4. Serum dynamics of candidate exerkines following acute aerobic exercise
A–D, concentration–time profiles for Fstl1 (*A*), osteoglycin (*B*), galectin-1 (*C*) and C1qTNF3 (*D*) at baseline and post-exercise (P_0, P_{30}, P_{60}, P_{90}, and P_{120}). Grey circles indicate individual participant values, and black circles and lines indicate the mean (n = 16); error bars denote ±SD. Fstl1 and galectin-1 increased relative to baseline across the sampling window (*$P < 0.001$ *vs.* baseline), whereas osteoglycin and C1qTNF3 showed no significant change. Fstl1, follistatin like 1; C1qTNF3, C1q and tumor necrosis factor–related protein 3; P_0, immediately post-exercise; P_{30}/P_{60}/P_{90}/P_{120}, minutes post-exercise.

blood (predominantly leukocytes) showed minimal change and no overlap with adipose–muscle responses. Four candidates, *LGALS1*, *FSTL1*, *OGN* and *C1QTNF3*, were upregulated in both tissues; galectin-1 and Fstl1 also increased in circulation, whereas osteoglycin and C1qTNF3 were strongly inducible from low basal expression without acute serum changes. Moderation analyses indicated tissue-mass dependence for Fstl1 in both depots, whereas galectin-1 reflected additive muscle effects (independent associations of muscle FC and SMM without interaction), consistent with skeletal muscle as the predominant near-term source. Collectively, these findings establish galectin-1 and Fstl1 as human exerkines and indicate that tissue mass is a determinant of transcription-to-circulation coupling.

Fstl1 is a secreted matricellular glycoprotein of the secreted protein acidic and rich in cysteine (SPARC) family with clinical relevance across cardiovascular, inflammatory, fibrotic and malignant diseases, with the strongest evidence in cardiovascular pathology. Circulating Fstl1 concentrations are elevated in several cardiovascular conditions and have been examined as a prognostic marker of treatment response and recovery, as well as a therapeutic target (Mattiotti et al., 2018). *FSTL1* is transcriptionally active in both skeletal muscle and adipose tissue and is dynamically regulated at the mRNA and circulating protein levels in response to both

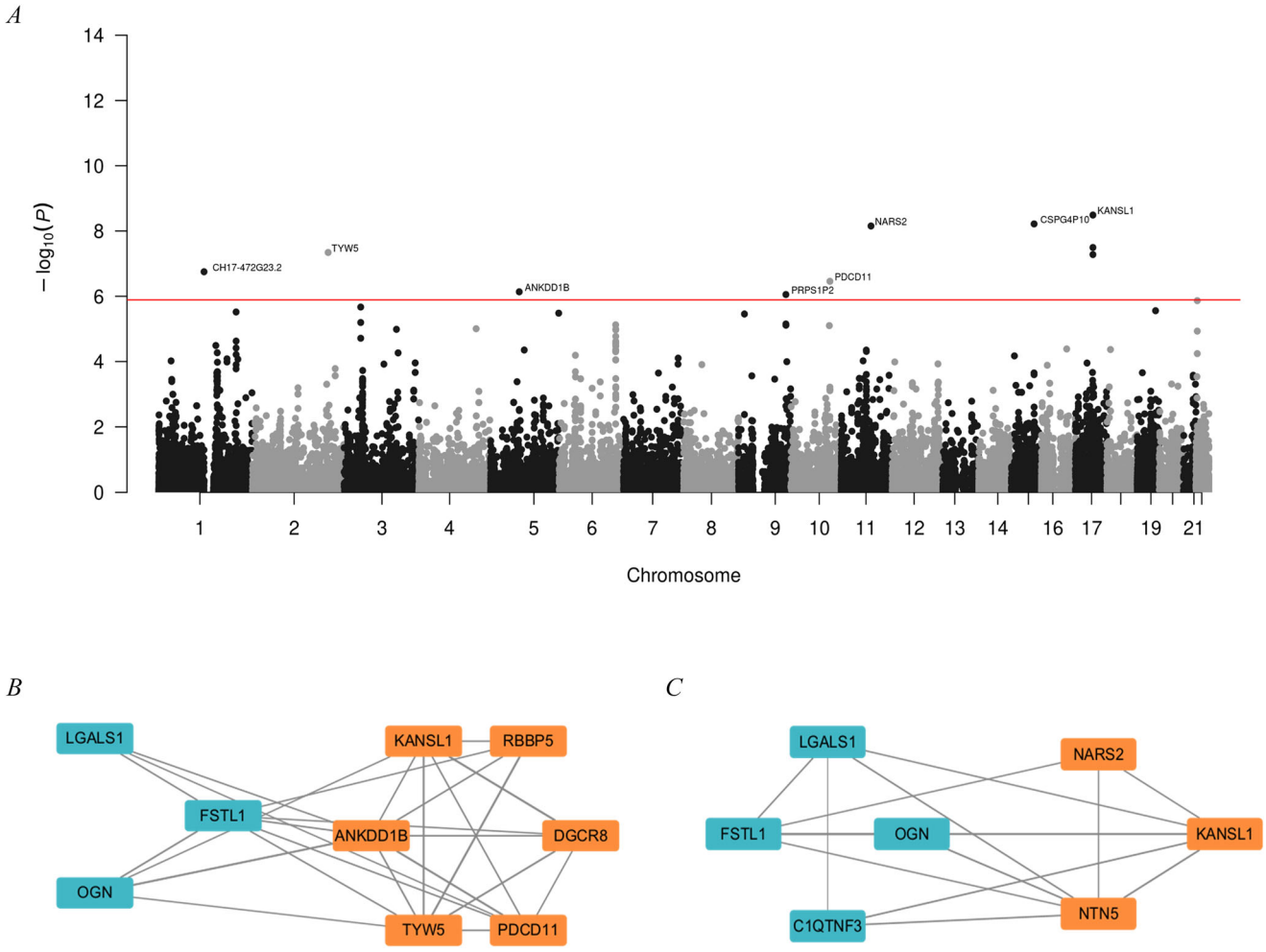

Figure 5. Genetic context of candidate exerkines in physical-activity GWAS and tissue networks
A, TWAS Manhattan plot for habitual moderate physical activity (UK Biobank) using FUSION with GTEx v8 subcutaneous adipose tissue and skeletal-muscle weights. Each point represents a gene; the red line marks the Bonferroni threshold (TWAS $P < 0.05/15{,}441$). *B* and *C*, tissue-specific gene–gene interaction networks (HumanBase) for adipose tissue (*B*) and skeletal muscle (*C*). Blue nodes: exerkine candidates (LGALS1, Fstl1, OGN, C1qTNF3); orange nodes: TWAS-significant genes from the corresponding tissue panel. Edges denote high-confidence interactions. Candidates cluster as first neighbours of TWAS genes despite no *cis*-TWAS hits, indicating pathway-level convergence. GWAS, genome-wide association study; TWAS, transcriptome-wide association study; FUSION, functional summary-based imputation; GTEx, genotype-tissue expression.

acute and chronic exercise. In humans, transcriptomic analyses of skeletal muscle biopsies following endurance (Neubauer et al., 2014) and strength exercise training (Norheim et al., 2011) have consistently identified *FSTL1* as an exercise-inducible gene, with parallel increases in serum concentrations observed during or shortly after aerobic exercise (Gorgens et al., 2013; Nam et al., 2024; Xu et al., 2020), supporting its classification as a myokine. *In vitro* studies further demonstrate that differentiated primary human myotubes express and secrete Fstl1 (Gorgens et al., 2013), further supporting skeletal muscle as a source tissue. Preclinical studies have also identified Fstl1 as an exercise-responsive myokine, demonstrating positive associations between circulating levels and both muscle expression (Inoue et al., 2022; Xi et al., 2016) and muscle mass (Inoue et al., 2022). In parallel, Fstl1 also has been proposed as an adipomyokine, given substantial expression, greater exercise-induced upregulation in adipose tissue relative to skeletal muscle, and correlations with fat mass (Xu et al., 2020). However, evidence for coordinated Fstl1 transcriptional responses across multiple tissues in humans has been lacking, as prior studies have not concurrently profiled skeletal muscle and adipose tissue with matched serum measures to delineate depot-specific contributions.

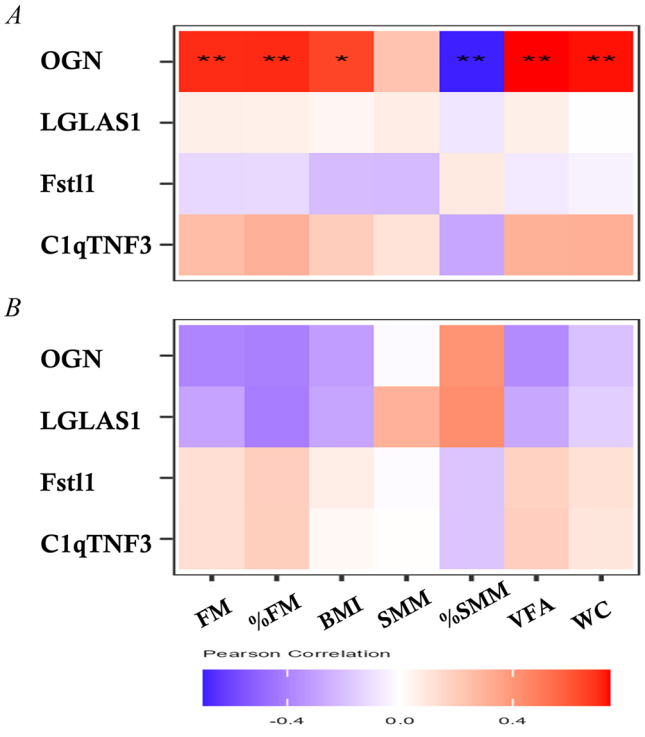

Figure 6. Associations between anthropometry and exercise-induced gene-expression changes
A, adipose tissue: heatmap of Pearson correlations between $\log_2$ fold change (baseline *vs*. post) for OGN, LGALS1, Fstl1 and C1qTNF3 and FM, %FM, BMI, SMM, %SMM, VFA and WC. OGN shows positive associations with FM, %FM, BMI, VFA and WC, and an inverse association with %SMM; no other adipose gene is significant. *B*, skeletal muscle: no significant correlations between gene $\log_2$ fold change and anthropometric measures. Cells display *r*-values with two-sided *P*; *P < 0.05, **P < 0.01. BMI, body mass index; FM, fat mass; %FM, body fat percentage; SMM, skeletal muscle mass; %SMM, skeletal muscle mass percentage; VFA, visceral fat area; WC, waist circumference; OGN, osteoglycin; LGALS1, galectin-1; Fstl1, follistatin-like 1; C1QTNF3, C1q and tumour necrosis factor–related protein 3; $\log_2$FC, $\log_2$ fold change.

Accordingly, our study was designed to identify exercise-responsive secreted factors by integrating multi-tissue transcriptomic profiling with serial serum proteomics through acute aerobic exercise in humans. We demonstrated that Fstl1 is significantly upregulated at the mRNA level in both skeletal muscle and adipose tissue following an aerobic exercise bout, while whole blood exhibited no such response. Moderation analyses indicated that gene-to-serum translation is contingent on tissue mass, with the circulating response scaling with muscle gene induction and SMM and, in adipose tissue, emerging conditionally at higher FM in the absence of main effects. Our findings align with prior human studies reporting Fstl1 upregulation in skeletal muscle (Neubauer et al., 2014; Norheim et al., 2011) and concurrent increases in circulating levels following exercise (Gorgens et al., 2013; Nam et al., 2024; Neubauer et al., 2014), reinforcing its classification as a myokine. Moreover, we extend previous animal data suggesting adipose-derived regulation (Xu et al., 2020) by providing the first human evidence of exercise-induced Fstl1 transcription in adipose tissue and its mass-dependent contribution to circulating levels. Together with the larger exercise-induced transcriptional upregulation observed in skeletal muscle than adipose tissue, these data indicate that, in humans, acute aerobic exercise more strongly engages skeletal muscle *FSTL1*, while adipose contributions are mass dependent. Preclinical data further support this framework, showing that aerobic training increases Fstl1 secretion in proportion to muscle mass, particularly in slow-twitch muscle, with circulating levels correlating with muscle expression (Inoue et al., 2022). This positions Fstl1 as an exercise-regulated exerkine whose circulating abundance reflects both the magnitude of tissue-specific gene activation and the scale of the contributing depot. In addition, these findings provide the first human evidence linking depot-specific transcriptional responsiveness to acute exercise with systemic Fstl1 secretion.

Galectin-1 is a ubiquitously expressed β-galactoside-binding lectin with context-dependent roles in immune regulation, angiogenesis, neurogenesis and tissue remodelling. Elevated tissue and circulating galectin-1 are observed across cancer, fibrotic, cardiovascular- and metabolic–inflammatory conditions, including acute myocardial infarction, heart failure, obesity and type 2 diabetes mellitus, supporting its utility

as a biomarker and therapeutic target (Novak et al., 2025). *LGALS1* is induced by hypoxia, inflammatory signalling and differentiation cues during active remodelling (Novak et al., 2025) and is exported via non-classical pathways (Popa et al., 2018). Thus, disease-associated elevations likely reflect stress- and remodelling-driven induction and release. These features suggest that transient physiological stressors, such as exercise, can also acutely modulate galectin-1. Direct evidence linking exercise to *LGALS1* transcription or circulating galectin-1 is currently limited; only one cross-sectional clinical study has been identified. That study reported an inverse association between cardiorespiratory fitness (CRF) and fasting serum galectin-1 that was largely attenuated after BMI adjustment, whereas adiposity remained positively associated, indicating that basal galectin-1 level is predominantly driven by FM with only a modest adiposity-independent component (Arvidsson et al., 2024). This pattern accords with higher galectin-1 in obesity and related metabolic–inflammatory states (Fryk et al., 2024; Fryk et al., 2019), where chronic low-grade inflammation likely upregulates *LGALS1* transcription, increasing basal circulating levels. However, because CRF is an integrative phenotype influenced by multiple factors, and the design was cross-sectional, a causal exercise–*LGALS1* or exercise–galectin-1 relationship cannot be inferred.

This study provides direct evidence that acute aerobic exercise induces *LGALS1* transcription in both adipose tissue and skeletal muscle, accompanied by concordant increases in circulating galectin-1. Tissue-serum modelling implicates skeletal muscle as the predominant near-term source, and muscle *LGALS1* induction and SMM each contributed independently to the circulating response, whereas adipose *LGALS1* induction and FM did not. This positions galectin-1 as an exercise-regulated exerkine whose immediate appearance in blood reflects the extent of transcriptional activation within skeletal muscle and the size of the muscular reservoir. These findings link tissue engagement to systemic signalling during and shortly after the exercise window and nominate galectin-1 as a marker of muscle-derived endocrine output. Relative to the mass-contingent pattern observed for *FSTL1*, *LGALS1* exhibited a muscle-dominant, additive profile with non-significant adipose predictors. This divergence is likely attributable to differences in secretory pathways, with Fstl1 using classical endoplasmic reticulum–Golgi export that enables mass-sensitive gene-to-serum coupling (Gorgens et al., 2013), whereas galectin-1 is secreted via non-classical, leaderless routes (Popa et al., 2018), which may explain the absence of adipose associations and the lack of interaction between gene induction and SMM scaling observed within the sampling window.

While Fstl1 exhibits context-dependent roles in cancer (Du et al., 2024) and autoimmune conditions (Li et al., 2021), its exercise-responsive regulation and cardiometabolic profile support a more direct physiological relevance to acute exercise adaptation. In the present study, we provide the first human evidence linking depot-specific transcriptional responsiveness to acute exercise with systemic Fstl1 secretion, with a particularly strong mass-sensitive contribution from skeletal muscle. Beyond its value as an exercise-responsive biomarker, Fstl1 has been implicated in vascular and endothelial protection, anti-fibrotic remodelling (Horak et al., 2022), cardiometabolic regulation, tissue repair (Mattiotti et al., 2018) and energy-substrate mobilization (Nam et al., 2024; Seki et al., 2018), suggesting that its post-exercise increase may contribute to early vascular and metabolic adaptation following an acute exercise bout. Given the mass-dependent contribution of skeletal muscle to the circulating Fstl1 response, our findings support a potential protective role for exercise-induced Fstl1 in processes relevant to cardiometabolic disease progression (Lee et al., 2019) and suggest that increasing skeletal muscle mass through resistance exercise, alongside aerobic exercise, may further enhance these cardiometabolic benefits. In parallel, although galectin-1 is elevated in several pathological contexts, including cancers, metabolic diseases (Novak et al., 2025) and neuropsychiatric disorders (Tanir et al., 2023; Wang et al., 2022), current evidence suggests that it may function not merely as a stress- or inflammation-associated biomarker but as an active regulator of tissue remodelling and metabolic control. Beyond source attribution, the acute increase in circulating galectin-1 observed in our study also has functional relevance to the early adaptive response to exercise. Galectin-1 has been implicated in myogenic differentiation and skeletal muscle regeneration (Van Ry et al., 2015; Wuebbles et al., 2019), glycaemic regulation (Sundblad et al., 2021), and neuroplasticity (Kajitani et al., 2014; Sakaguchi et al., 2011), suggesting that the muscle-dominant galectin-1 response observed here may reflect an early remodelling-related signal during exercise and post-exercise recovery. In humans, circulating galectin-1 has been inversely associated with fasting glucose in obese children (Acar et al., 2017), whereas mechanistic studies indicate that galectin-1 may facilitate glycolytic flux and downstream tricarboxylic acid cycle activity under conditions of cellular stress (Guda et al., 2022; Nguyen et al., 2025). However, it has also been positively associated with obesogenic states; circulating galectin-1 is elevated in paediatric obesity (Acar et al., 2017), and experimental deletion of *LGALS1* attenuated high-fat diet-induced weight gain, adiposity and fasting hyperglycaemia in mice (Baek et al., 2021). These observations suggest that the metabolic actions of galectin-1 are context dependent. Taken together, these

observations support galectin-1 as an exercise-responsive candidate exerkine that may participate in early recovery, tissue remodelling and metabolic adaptation following an acute aerobic bout, while also highlighting the need for further studies to define its metabolic significance in obesity-related conditions.

Osteoglycin (*OGN*) is a leucine-rich proteoglycan secreted by bone, cartilage and skeletal muscle with roles in cardiovascular function, glucose metabolism and bone remodelling. Human intervention studies consistently show limited exercise responsiveness of circulating osteoglycin, remaining unaffected by acute aerobic exercise (Bauer et al., 2022; Parker et al., 2022) or concurrent training (Martin-Olmedo et al., 2025). In our study, *OGN* transcripts were markedly inducible from very low baselines in adipose tissue and skeletal muscle, yet circulating osteoglycin did not change in circulation within the sampling window, suggesting minimal acute release from these depots and/or dominance of non-muscle/adipose sources. C1qTNF3, an adiponectin-paralogue implicated in metabolic and vascular regulation, shows heterogeneous exercise responses across contexts; its circulating level increased with aerobic training in association with reduced arterial stiffness (Hasegawa et al., 2018) and decreased following concurrent training in obesity (Choi et al., 2013), and its mRNA level in skeletal muscle was downregulated with chronic exercise in peripheral artery disease models (Nagase et al., 2017). Here, *C1QTNF3* transcription markedly increased from its low basal expression in adipose tissue and skeletal muscle, whereas circulating C1qTNF3 was unchanged, indicating limited acute release and/or slower kinetics beyond the sampling window. Overall, both *OGN* and *C1QTNF3* are exercise-responsive at the transcript level but do not manifest acute circulating exerkine behaviour under this protocol; longer sampling horizons and training exposures may be required to investigate their systemic regulation.

Although none of the four candidates (*LGALS1*, *FSTL1*, *OGN*, *C1QTNF3*) reached TWAS significance with GTEx (*cis*-eQTL panel) weights and UK Biobank physical-activity GWAS (Bycroft et al., 2018; Consortium et al., 2017; Gusev et al., 2016), this does not exclude genetic regulation. By design, TWAS chiefly interrogates *cis*-heritable components of steady-state expression within the assayed tissue and has limited power for context-dependent *trans* mechanisms, cross-tissue influences or post-transcriptional control (Consortium et al., 2017; Gusev et al., 2016). Consistent with such an indirect architecture, tissue-resolved functional networks placed the candidates as first-neighbours of TWAS-significant genes in subcutaneous adipose and muscle, suggesting that activity-associated variants converge on pathways that encompass these exerkines rather than acting through direct *cis* effect on the candidate loci (Greene et al., 2015). This 'TWAS-negative, network-positive' pattern supports a gene–environment framework in which inherited propensity for habitual activity and acute exercise stimulus act on shared tissue programmes; definitive causal inference will require formal localization with *cis*-eQTL signals, stimulus conditional (exercise-state) eQTL and pQTL maps, mediation analyses, and Mendelian randomization using appropriately powered datasets. Considering the inherent limitations of our data, specifically the need for further causality assessments and more sophisticated gene-regulatory network modelling, our findings nonetheless motivate a working model of *trans*-network regulation, which could include repressive effects in certain contexts. In this regards, the functional roles of two TWAS-significant genes provide biological plausibility for upstream control; *KANSL1*, a component of the NSL histone acetyltransferase complex implicated in epigenetic regulation (Dias et al., 2014), and *DGCR8*, a core microprocessor essential for miRNA biogenesis (Han et al., 2004), could modulate chromatin accessibility and post-transcriptional silencing, respectively, thereby shaping the transcriptional and proteostatic milieu through which exercise-induced changes in candidate exerkine expression are realized. Thus, while our data do not establish direct *cis* genetic effects on *LGALS1*, *FSTL1*, *OGN* or *C1QTNF3*, the observed network topology is compatible with a *trans*-regulatory pathway model that reconciles genetic predisposition for physical activity with the acute molecular responses to exercise intervention.

Although this study was explicitly designed to identify human exerkines by integrating multi-tissue transcriptomics with matched serial serum profiling, several limitations warrant consideration. First, we interrogated a single aerobic bout without a non-exercise control condition, constraining inference to acute responsiveness rather than training adaptations or causality. Second, transcriptomic sampling was restricted to baseline and immediately post-exercise (P_0) for tissue biopsies and whole blood, precluding time-course resolution and risking misalignment with 0–120-min serum-protein kinetics; late-peaking leukocyte programmes that often emerge during recovery (Perandini et al., 2016) may have been missed, contributing to the minimal whole-blood response and its lack of overlap with tissue signatures. Third, our acute-bout candidates did not overlap with those reported in the prior training study that combined adipose and muscle biopsies with serum proteomics (Lee-Odegard et al., 2024), highlighting exposure (acute *vs.* training), matrix (RNA *vs.* protein) and platform dependencies and motivating harmonized, multi-omic designs across acute and training paradigms. Fourth, nutritional state can modulate exercise-induced

myokine/exerkine responses (Hennigar et al., 2017). Although we standardized pre-exercise nutrition following established feeding principles (Kerksick et al., 2017), gastrointestinal absorption kinetics were not measured; therefore, potential differences between fed and post-absorptive exercise cannot be resolved in the present design. This should be addressed in future studies incorporating controlled feeding-state comparisons. Finally, the inclusion of only male participants limits the generalizability of the findings. This design was chosen to reduce biological heterogeneity related to sex-specific endocrine status (Oosthuyse et al., 2023; Pataky et al., 2023), as well as sex-related differences in skeletal muscle molecular profiles and exercise-induced transcriptomic responses (Nie et al., 2022; Pataky et al., 2023), in this initial study using an invasive multi-tissue design. Further studies with larger and more diverse cohorts are warranted. Taken together, these limitations and the current evidence base motivate more controlled, time-resolved studies across acute and training paradigms, incorporating more diverse populations and closer integration with clinical variables, to validate tissue origins and tissue-to-serum kinetics and to refine the identification of human exerkines.

In conclusion, integrating multi-tissue transcriptomics with matched serial serum profiling identifies galectin-1 and Fstl1 as exercise-induced exerkines in humans. Their coordinated tissue activation with concomitant circulating increases following an acute aerobic exercise bout supports their candidacy as mediators of systemic adaptation to exercise and as translational biomarkers for future longitudinal and cardiometabolic studies. Limitations include the modest sample size, male-only cohort, restricted 0–120 min window and absence of a non-exercise control. While at least one study has evaluated training effects, future work should test training adaptations within this framework and include women under defined hormonal states and disease-enriched cohorts to assess relationships between exerkine dynamics and pathogenesis.

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Additional information

Data availability statement

RNA-seq count matrices and DESeq2 differential-expression objects are publicly available at Zenodo (https://doi.org/10.5281/zenodo.17106883). Raw sequencing reads (FASTQ) are available from the corresponding author upon reasonable request and institutional approval.

Competing interests

The authors declare they have no competing interests.

Author contributions

All experiments were performed at Gangnam Severance Hospital and the Biomedical Research Center of Gangnam Severance Hospital. Data analysis was performed in part at the Department of Life Sciences, Dongguk University. J.S., E.S.C., Y.R.K., J.S.N. and Y.S.K. contributed to the conception and design of the work. J.S., E.S.C., Y.R.K., J.S.P., J.S.N. and Y.S.K. contributed to the acquisition, analysis, or interpretation of data for the work. J.S., E.S.C., J.S.P., J.S.N. and Y.S.K. drafted the manuscript. Y.S.K. revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Keywords

C1q and tumour necrosis factor-related protein 3, exercise, exerkine, follistatin-like 1, galectin-1, osteoglycin

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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