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Follistatin-like 1 and galectin-1 as potential exerkinases: a cross-study evaluation of tissue attribution and implications for metabolic disease

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INTRODUCTION

Physical activity is a powerful non-pharmacological intervention for obesity, type 2 diabetes, and broader cardiometabolic risk. Its benefits include improvements in insulin sensitivity, adipose tissue inflammation, hepatic lipid handling, vascular function, and muscle metabolic flexibility. However, the molecular signals that translate exercise into these benefits remain incompletely understood. Exercise-induced secreted factors, termed “exerkinases”, offer a framework for understanding these mechanisms and for identifying molecular pathways that might be leveraged therapeutically for metabolic disease^[1]. These molecules include proteins, metabolites, lipids, nucleic acids, and extracellular vesicle (EV)-associated cargo released from multiple tissues in response to acute or chronic exercise, acting in autocrine, paracrine, and endocrine fashions. Major examples of exerkinases include brain-derived neurotrophic factor for neuronal survival and plasticity, interleukin-6 for metabolic and immune regulation, and irisin for energy expenditure and browning of adipose tissue^[1]. Yet the tissue origin of many exerkinases remains unclear because numerous candidates are genetically expressed in and released from multiple tissues, making it difficult to identify their primary source or infer tissue-specific contributions from changes in circulating levels alone^[1]. We define exerkinases as signaling molecules released from cells or tissues in response to exercise that mediate local or systemic physiological effects.

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Song *et al.* attempted to address this challenge by integrating skeletal muscle and adipose tissue transcriptomics with serial serum protein measurement using enzyme-linked immunosorbent assays (ELISA) following acute aerobic exercise in 16 healthy sedentary young men [mean age $\pm$ standard deviation (SD): 28.6 ± 2.4 years]^[2]. Participants completed a treadmill bout calibrated to expend 300 kcal at 70%-75% of age-predicted maximal heart rate (mean duration $\pm$ SD: 35.2 ± 7.8 min). RNA sequencing was performed in vastus lateralis skeletal muscle, periumbilical subcutaneous adipose tissue, and whole blood collected before and immediately after exercise. In addition, serum proteins were measured at baseline, immediately post-exercise, and 30-, 60-, 90-, and 120-min time points during recovery. Follistatin-like 1 (*FSTL1*) and galectin-1 (*LGALS1*) were transcriptionally upregulated in both skeletal muscle and adipose tissue following exercise, and their corresponding protein products, FSTL1 and LGALS1, increased in circulation at all post-exercise recovery time points (30 to 120 min). To investigate the relationship between tissue gene expression and circulating protein levels, the authors used moderation analyses incorporating tissue-specific transcript changes and tissue mass estimates. These analyses suggest distinct transcript-to-serum coupling patterns, with FSTL1 exhibiting tissue-mass-dependent coupling involving both muscle and adipose tissue, whereas LGALS1 followed a muscle-dominant additive profile in which skeletal muscle expression and muscle mass independently contributed to circulating protein levels. Notably, osteoglycin (OGN) and C1q/TNF-related protein 3 (C1QTNF3) were also transcriptionally induced in skeletal muscle and adipose tissue but did not increase in serum. Thus, OGN and C1QTNF3 serve as potential negative comparators, as they may show that exercise-induced transcripts do not necessarily behave as circulating exerkines and may instead reflect tissue-level responses.

FSTL1 AND LGALS1 IN INTEGRATED TRANSCRIPTOMIC-PROTEOMIC STUDIES AND META-ANALYTICAL RESOURCES

While Song *et al.* identified FSTL1 and LGALS1 as potential exercise-responsive candidates, the central question of whether FSTL1 and LGALS1 are sufficiently validated as exerkines in cellular origin and systemic function, or whether they reflect broader non-specific responses remains unaddressed^[2]. Consequently, the metabolic interpretation of FSTL1 and LGALS1 depends on how consistently these signals appear across compartments, populations, and exercise timescales. The Molecular Transducers of Physical Activity Consortium (MoTrPAC)^[3,4] provides a head-to-head acute-exercise comparison to Song *et al.*^[2] in a substantially larger cohort that includes both men and women. MoTrPAC collected blood, skeletal muscle, and adipose tissue samples during endurance, resistance, and control conditions at multiple time points, including during exercise, early recovery, 3.5-4 h post-exercise, and approximately 24 h post-exercise. For FSTL1, skeletal muscle [Supplementary Figure 1A and B] and adipose tissue [Supplementary Figure 1C and D] transcriptomics and proteomics showed no significant alterations. In contrast, blood transcriptomics showed a significant early *FSTL1* response following both endurance and resistance exercise in the early 15/30-45 min recovery period [Supplementary Figure 1E]. FSTL1 was not available in MoTrPAC's proteomic dataset, making it unclear whether these transcriptional changes translated into altered circulating protein levels. For LGALS1, skeletal muscle [Supplementary Figure 2A and B] and adipose tissue [Supplementary Figure 2C and D] transcriptomics and proteomics showed no significant alterations. In contrast, blood transcriptomics demonstrated a significant *LGALS1* response during 20 min of endurance exercise [Supplementary Figure 2E]. However, this did not translate into significant alterations in circulating LGALS1 protein levels [Supplementary Figure 2F]. In contrast to Song *et al.*, MoTrPAC localized the strongest exercise-induced signals for *FSTL1* and *LGALS1* to circulating blood transcriptomics, with minimal evidence of regulation in skeletal muscle, adipose tissue, or circulating protein levels^[2]. This pattern suggests that leukocyte, vascular, or other circulating-cell responses may contribute substantially to the early exercise-induced signal. This distinction matters from a metabolic disease perspective, as obesity, diabetes, and related metabolic dysfunction can alter all these potential sources of exercise-responsive signals, including muscle, adipose tissue, vascular cells, and immune cells. However, potential cellular sources within blood (e.g.,

leukocytes, endothelial cells) remain speculative without single-cell sequencing or cellular deconvolution and should be evaluated in future studies. These findings should also be interpreted in the context of important population differences between studies, as Song *et al.* examined a small cohort of healthy young Asian men, whereas MoTrPAC included a substantially larger and more diverse population spanning both sexes and multiple racial and ethnic groups^[2]. Such demographic variations may alter exerkine secretion and kinetics, as population-level differences in body composition, muscle fiber type distribution, vascular density, and exercise-induced immune responses can shift both the cellular source and magnitude of circulating signals.

The ExTraMeta (<https://www.extrameta.org/>) transcriptomic resource provides a complementary systems-level analogy by integrating transcriptomic datasets across multiple exercise studies and applying meta-analytic and machine-learning approaches to identify reproducible exercise-responsive genes^[5]. Analyses were available for FSTL1 in both acute blood and acute skeletal muscle and for LGALS1 in acute skeletal muscle. FSTL1 increased significantly in acute skeletal muscle but not in acute blood, whereas LGALS1 did not change significantly in acute skeletal muscle. Given that FSTL1 is widely regarded as a candidate skeletal muscle-derived exerkine, these findings are not unexpected. However, the lack of a corresponding blood signal and the absence of significant LGALS1 responses further challenge Song *et al.*'s assumption that coordinated tissue transcript and circulating protein changes reflect tissue origin^[2]. This uncertainty is particularly relevant when extending findings from healthy participants to metabolic disease populations, where adipose tissue inflammation, skeletal muscle insulin resistance, mitochondrial dysfunction, and metabolically activated immune cells may reshape both the source and magnitude of exercise-responsive signals.

Additionally, Lee-Ødegård *et al.* applied a similar integrated proteomic-transcriptomic approach by profiling 3,072 serum proteins alongside skeletal muscle and subcutaneous adipose tissue transcriptomes before and after 12 weeks of combined endurance and resistance training in 26 previously sedentary men^[6]. CD300LG, rather than FSTL1 or LGALS1, showed concordant increases in circulating protein levels and tissue gene expression. In contrast to the acute exercise findings reported by Song *et al.*, neither FSTL1 nor LGALS1 emerged as prominent markers of chronic exercise adaptation^[2]. This discrepancy may reflect differences in the timing and duration of the exercise stimulus assessed. Song *et al.* captured serum and tissue responses over 2 h following a single treadmill bout^[2], whereas Lee-Ødegård *et al.* examined adaptations following 12 weeks of exercise training measured at least 3 days after the final exercise session^[6]. Together, these findings suggest that FSTL1 and LGALS1 may reflect transient responses to an acute exercise stimulus while other exerkines may better capture sustained improvements in metabolic health. However, acute-only responses of FSTL1 or LGALS1 do not diminish their therapeutic potential in metabolic disorders such as type 2 diabetes, as these factors may act as brief signals whose repeated surges drive adaptations like improved insulin sensitivity and reduced adipose inflammation. Translationally, this suggests that therapeutic strategies should employ exercise-mimicking intermittent dosing rather than continuous dosing to avoid cellular resistance while delivering metabolic benefits.

FUTURE DIRECTIONS AND REMAINING QUESTIONS

Although Song *et al.* observed biological plausibility between matched tissue messenger RNA (mRNA) and serum protein increases in FSTL1 and LGALS1, these findings do not establish tissue origin^[2]. A time-matched, non-exercise control visit, combined with correction for exercise-induced plasma volume shifts, could help distinguish protein secretion from confounds related to circadian rhythm or plasma concentration/dilution effects. The temporal relationship between transcription and translation raises an important limitation, as changes in gene expression immediately after exercise may not translate into detectable protein synthesis and systemic secretion within the same short recovery period. This biological time lag is seen in the MoTrPAC data, where early spikes in blood mRNA failed to increase circulating

LGALS1 protein. Furthermore, the study did not perform proteomic analyses of skeletal muscle or adipose tissue, precluding direct assessment of whether tissue protein abundance paralleled transcriptomic changes and correlated with circulating protein levels. Targeted tissue protein measurement is paramount because mRNA and protein abundance correlate only moderately across human tissues. This discordance reflects multiple layers of post-transcriptional regulation, as translation, secretion, degradation, and post-translational modification can all disrupt transcript-to-protein inference^[7]. Future studies should therefore validate these findings using targeted [e.g., ELISA for protein and quantitative PCR (qPCR) for RNA] tissue measurements to determine whether exercise-induced transcriptional changes translate into corresponding protein-level responses. Furthermore, linking these molecular responses to glucose disposal, insulin sensitivity, adipose inflammatory markers, hepatic fat, and cardiorespiratory fitness would help determine whether FSTL1 and LGALS1 are merely candidate biomarkers of exercise exposure or plausible mediators of metabolic benefit. Prioritizing this mechanistic confirmation of metabolic health before pursuing precise tissue origin may help avoid premature attribution and can better align discovery efforts with translational needs.

This distinction is particularly important because establishing true tissue sources remains inherently complex. It remains unclear whether the exercise-induced transcriptomic changes observed in skeletal muscle and adipose tissue directly contribute to the corresponding increases in circulating protein levels. Skeletal muscle and adipose tissue are well-known contributors of exerkinins in circulation, but they are not necessarily the only or dominant sources of exercise-responsive factors. Recent cell type-specific secretome mapping studies demonstrated that exercise-responsive circulating proteins can originate from diverse cellular sources, including Pdgfra+ mesenchymal progenitor cells, and that skeletal muscle ranked only 12th of 21 cell types in overall exercise responsiveness. These findings suggest that tissues beyond skeletal muscle may contribute substantially to exercise-induced changes in the circulating proteome^[8]. This source uncertainty is especially relevant for metabolic diseases, where obesity, diabetes, and metabolic dysfunction-associated conditions can remodel adipose tissue, skeletal muscle, vascular cells, and immune-cell populations that may generate or modify exercise-responsive signals. Arteriovenous sampling across exercising limbs, *ex vivo* secretion assays, cell-specific proteomics, and simultaneous tissue protein measurements would potentially help identify the tissue origin and secretion of candidate exerkinins more directly. Applying analogous approaches in humans could directly identify the cellular origins and tissue contributions of exercise-induced exerkinins and potentially determine whether acute FSTL1 and LGALS1 responses are preserved, blunted, exaggerated, or shifted in source across healthy, insulin-resistant, and metabolically unhealthy states. Furthermore, establishing true tissue sources is complicated by widespread methodological heterogeneity across current studies, including small cohort sizes, varying exercise modalities, and non-standardized sampling timelines. Addressing these limitations will require standardized multicenter studies employing synchronized multi-omics platforms and controlled sampling intervals across diverse populations. Beyond human multi-omics profiling, pre-clinical animal models could be valuable for resolving these mechanistic ambiguities^[9]. Tissue-specific lineage tracing and conditional knockouts can definitively establish cellular origin, while comparing high and low exercise models offers a framework to distinguish between functional exerkinins and non-specific stress responses.

Another promising avenue involves EVs, nanosized membrane-bound particles released by virtually all cell types that carry proteins, RNAs, lipids, and metabolites reflective of the physiological state of their parent cells. Importantly, EVs retain many surface proteins and receptors from their cells of origin, enabling enrichment of tissue-specific EV populations using immunoprecipitation approaches. For example, antibody-conjugated beads directed against skeletal muscle- or adipose tissue-associated surface markers could isolate tissue-enriched EVs from circulation. Simultaneous collection of skeletal muscle and adipose tissue biopsies would then permit direct comparison of tissue protein abundance with EV cargo and

circulating protein levels. Such approaches could help determine which tissues contribute to the exercise-induced elevation of FSTL1, LGALS1 and related molecules and whether EVs participate in their transport and inter-organ signaling. This approach has been widely applied in neuroscience^[10]. Compared with crude biofluids, tissue-enriched EV populations may provide improved specificity by reducing background contamination from unrelated cellular sources while remaining readily accessible through minimally invasive blood sampling. This source-resolved approach may be particularly useful in metabolic disease because EV cargo could reflect adipose inflammation, muscle insulin resistance, or hepatic metabolic stress while remaining measurable in blood. Furthermore, EVs can be isolated, characterized, and experimentally administered, providing a platform to directly test the biological activity of candidate exerkines. Such studies could help determine whether FSTL1, LGALS1, or other exercise-responsive molecules exert the autocrine, paracrine, or endocrine functions required to be considered true exerkines rather than simply biomarkers of exercise exposure.

CONCLUSION

Determining whether FSTL1 and LGALS1 are sufficiently validated as exerkines in both origin and function remains a central challenge. While Song *et al.* provided an innovative RNA and protein framework for identifying candidate exercise-responsive molecules, their findings represent an exploratory start^[2]. The integrated design of their study, combining pre- and post-exercise skeletal muscle and adipose tissue transcriptomics with serial serum protein measurements, represents an important methodological contribution to the study of exerkines and provides a foundation for identifying candidate molecules and generating targets for subsequent tissue-specific and functional analysis. However, current evidence does not support classifying FSTL1 or LGALS1 as canonical muscle- or fat-derived exerkines. Rather, given comparative evidence from MoTrPAC, ExTraMeta, and chronic training studies, they more likely represent systemic, transient stress signals. Although the concordant increases in skeletal muscle and adipose tissue transcripts alongside elevated circulating protein levels represent an important step toward linking tissue-specific molecular responses with systemic exercise signaling, comparative evidence from MoTrPAC, ExTraMeta, and chronic training studies suggests that the tissue origins and broader biological significance of these molecules remain unclear. Moving forward, tissue proteomics, cell type-specific secretome mapping, EV profiling, and mechanistic evaluation are needed to clarify the tissue origins, biological activity, and potential roles of these molecules as autocrine, paracrine, or endocrine mediators. Establishing whether these molecules contribute to improved insulin sensitivity, adipose remodeling, glucose homeostasis, or other metabolic outcomes will determine whether they are mechanistic mediators, clinically useful biomarkers, or short-term correlates of acute exercise.

DECLARATIONS

Authors' contributions

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Availability of data and materials

All data analyzed in this manuscript are publicly available through published datasets. Multi-omic exercise datasets are available through the MoTrPAC data repository (<https://motrpac-data.org/data-download/file-browser/human-precovid>) and can be interactively explored using the MoTrPAC data visualization portal (<https://data-viz.motrpac-data.org/precawg/>). Transcriptomic datasets for ExTraMeta are available as

supplementary files attached to the primary publication (<https://www.nature.com/articles/s41467-021-23579-x#data-availability>) and can be visualized using the ExTraMeta web application (<https://www.extrameta.org/>).

AI and AI-assisted tools statement

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Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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