New study finds that your genetic sex determines the way your muscle 'talks' to other tissues in your body

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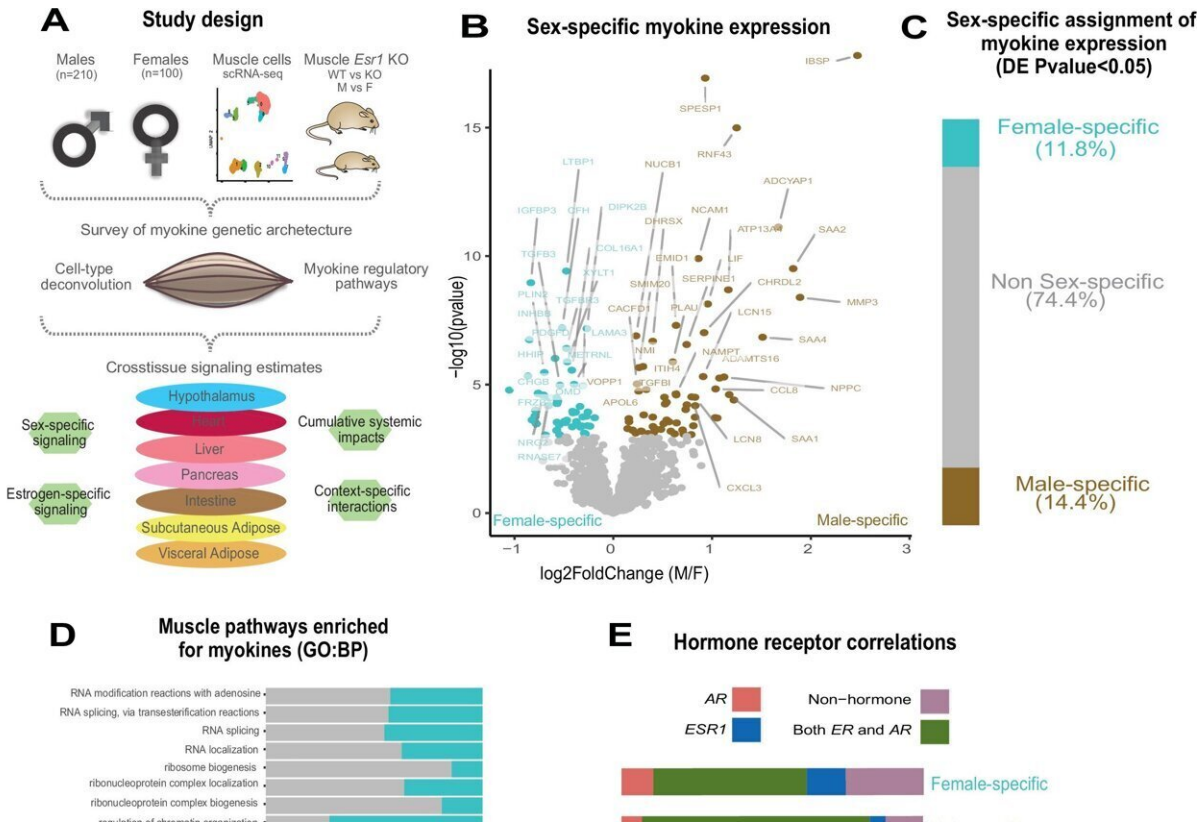

A) Overall study design for integration of gene expression from muscle from 310 humans, single-cell RNA-sequencing (RNA-seq), muscle-specific deletion of Esr1 to infer interorgan coregulatory process across major metabolic tissues. (B–C) Differential expression analysis for sex was performed on all genes corresponding to secreted proteins in skeletal muscle (myokines). The specific genes which showed significant changes in each sex are shown as a volcano plot

(B) and the relative proportions of myokines corresponding to each category at a least-stringent logistic regression p-value less than 0.05 (C). (D) For each differential expression category based on sex shown in C, myokines were correlated with all other muscle genes for pathway enrichment. Then the top 10 enriched pathways in males, females, or non-sex specific (by overall significance) were visualized together where number of genes corresponding to each category shown as a relative proportion. (E) The same analysis as in D, except instead of myokines being correlated with AR, ESR1, both hormone receptors, or neither, as compared to correlating with all genes. (F–G) Myokines were binned into two categories based on significant differential expression (logistic regression adjusted p-value eLife (2022). DOI: 10.7554/eLife.76887

A new University of California, Irvine-led study identifies sex-specific circuits of muscle signaling to other tissues, and that the organs and processes of muscle impacts are markedly different between males and females. This new discovery provides insight into how muscle functions, such as exercise, promote healthy longevity, metabolism and improve cognition.

The study, titled "Genetic variation of putative myokine signaling is dominated by biologic sex and sex hormones," and published in *eLife*, is the first to evaluate how genetic architecture influences muscle signaling to other tissues, highlighting that sex and estrogens are critical determinants of these processes.

"Muscle is critical for maintaining metabolic state and disruption of muscle function is a hallmark of diseases such as obesity, type 2 diabetes and cardiovascular disease," said senior author Marcus M. Seldin, Ph.D., assistant professor of biological chemistry at UCI School of Medicine.

Muscles secrete proteins called myokines, which play roles in a variety of processes by interacting with other tissues. Essentially, myokines

allow skeletal muscles to communicate with organs such as the kidneys, the liver or the brain, which is essential for the body to keep its metabolic balance. Some of the processes in which myokines are involved include inflammation, cancer, the changes brought about by exercise, and even cognition. Despite the clear relevance of myokines to so many physiological outcomes, the way these proteins are regulated and their effects are not well understood.

University of California, Irvine-led study identifies sex-specific circuits of muscle signaling to other tissues, and that the organs and processes muscle impacts are markedly different between males and females. Credit: UCI School of Medicine

For this study, the research team performed a survey of genetic correlations focused on myokine gene regulation, muscle cell composition, cross-tissue signaling and interactions with genetic sex in

humans. While expression levels of a majority of myokines and cell proportions within skeletal muscle showed few relative differences between males and females, nearly all significant cross-tissue enrichments operated in a sex-specific or hormone-dependent fashion; in particular, with estradiol. These sex- and hormone-specific effects were consistent across key metabolic tissues: liver, pancreas, hypothalamus, intestine, heart, visceral and subcutaneous adipose tissue. This study highlighted a few examples, such as muscles signal more to the pancreas in females, compared to males where the liver is dominant.

"We already know that skeletal muscle plays an integral role in coordinating physiologic homeostasis. In this study, we sought to understand how muscle interacts with metabolic tissues and illustrate the importance of considering the effects of genetic sex and sexual hormones when studying metabolism," said Seldin.

Moving forward, the research team plans to generate cell-based systems to evaluate some of the new hormones uncovered as part of this study and investigate why they signal differently between sexes.

More information: Leandro M Velez et al, Genetic variation of putative myokine signaling is dominated by biological sex and sex hormones, *eLife* (2022). DOI: 10.7554/eLife.76887

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