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Letter to the Editor

Exerkines as precision mediators: Decoding the tissue-specific vesicular packaging and metabolic reprogramming of remote organs

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Dear Editor-in-Chief

While the systemic benefits of exercise are undeniable, the precise language of inter-organ communication remains a "black box." Recent advances suggest we are poised to decode this language, transitioning from a model of diffuse hormonal signaling to one of targeted vesicular trafficking and epigenetic reprogramming. This letter posits that the next frontier for the Journal of Exercise & Organ Cross Talk lies in elucidating the rules of cargo loading, addressing, and delivery within exercise-induced extracellular vesicles-a process likely fundamental to the remarkable specificity of organ crosstalk.

This topic moves beyond cataloguing exerkines to interrogate the mechanisms of their targeted delivery and organ-specific effects. The most compelling frontier is understanding how exercise governs the packaging, release, and uptake of extracellular vesicles, including exosomes, which function as discrete signaling packets between organs. This intersects powerfully with metabolomics and epigenetics, bearing profound implications for metabolic disease, cancer, and neurodegeneration.

First, the paradigm is shifting from humoral to vesicular signaling. The field is moving beyond viewing exerkines as freely circulating factors to recognizing their active encapsulation into extracellular vehicles (EVs). These vesicles protect their cargo, enable tissue tropism (e.g., liver-derived EVs homing to adipose tissue or brain), and deliver diverse cargo-proteins, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and metabolites. This mechanism explains specificity in organ crosstalk previously attributed to stochastic distribution (Vechetti Jr et al., 2021).

Second, regarding the "exercise metabolome" and organ reprogramming, focus has turned to exercise-induced metabolites (e.g lactate, succinate) which serve as potent signaling molecules. A cutting-edge perspective is how these metabolites act as histone modifiers (e.g., via lactylation) in remote organs, directly altering gene expression in the liver, brain, and immune system to mediate long-term adaptive crosstalk (Xiao et al., 2025).

Third, the gut-muscle-brain axis represents a critical microbiome-mediated highway. Exercise modulates gut microbiota composition, which subsequently produces metabolites (e.g., short-chain fatty acids (SCFAs), bile acids) that signal to both muscles, enhancing anabolic processes, and brain, modulating neurogenesis and brain-derived neurotrophic factor (BDNF) expression. This tripartite axis is a major, yet underexplored, vector in systemic communication (Frampton et al., 2020; Liu et al., 2025).

Looking forward, the concept of personalized exerkine signatures presents a translational goal. Given individual variability in exerkine response, can we define an individual's "exerkine signature" to predict their metabolic or neuroprotective gains from exercise? This links the mechanistic basis of crosstalk directly to precision medicine.

We therefore urge the research community to prioritize the following key questions:

1. What are the exercise-intensity- and modality-dependent "sorting signals" that dictate cargo loading into EVs from distinct tissues?

2. How do tissue-specific EV uptake mechanisms confer selectivity to the remote effects of exercise?

3. To what extent do chronic exercise patterns establish organ-specific epigenetic "memories" via persistent metabolite signaling?

By leveraging single-vesicle analyses, spatially resolved metabolomics, and cell-type-specific models, we can advance from observing crosstalk to understanding its precise syntax. decoding

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Decoding this language will not only illuminate fundamental physiology but also pave the way for rationally designed, organ-specific "exercise mimetic" therapies.

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