

Letter to the Editor

Intelligent substrate utilization: Remodeling the endocrine matrix through chronic exercise

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Dear Editor-in-Chief

As our field continues to map the intricate networks of exercise-induced organ crosstalk, the concept of "intelligent substrate utilization" remains a compelling yet incompletely understood frontier. While much focus has been placed on the acute actions of individual myokines and exerkines, a more integrated, systems-level perspective is emerging—one that positions chronic exercise adaptation as the remodeling of an endocrine matrix. This matrix, I propose, governs a form of metabolic intelligence characterized by the dynamic, context-dependent allocation and utilization of energetic substrates across organs. Recent breakthroughs are beginning to decode the spatiotemporal logic of this system, moving beyond simple linear pathways to reveal complex networks that enable the body to adapt fuel metabolism with remarkable precision. Three key advances, in particular, illuminate new variables and pathways that underpin this intelligent substrate utilization.

First, the "Myokine-mediated Multi-organ Metabolic Network" theory provides a comprehensive framework for understanding how myokines act not in isolation but as a coordinated signaling hub. This work meticulously maps interactions from skeletal muscle to over a dozen organs, orchestrating programs across six biological axes, including energy substrate flux. Crucially, the framework highlights how myokines function as pleiotropic modulators within an integrated system, a property that fundamentally reshapes our view of substrate allocation. It suggests that the "intelligence" of the system lies not in any single molecule but in the emergent properties of this multi-target network (Chen et al., 2025). Second, a landmark systems genetics study, leveraging multi-tissue data from the MoTrPAC consortium, reveals that endurance training fundamentally remodels the entire

inter-organ endocrine network. This work demonstrates that the strength and specificity of endocrine signals between tissues are significantly altered with training. Notably, subcutaneous white adipose tissue (scWAT) emerged as a major endocrine hub, and extracellular matrix factors, along with secretory WNT signaling molecules, were identified as central mediators of training adaptations. These discoveries offer a crucial new variable—the network-wide remodeling of endocrine crosstalk—demonstrating that "intelligent" substrate use is a learned property of the whole system, not a pre-programmed one. The bidirectional and training-dependent plasticity of tissue-pair signaling adds a new layer of complexity to how we model metabolic control during exercise (Ahn et al., 2025).

Finally, the identification of novel metabolic signaling molecules, termed "metabokines" and "lipokines," expands the classic myokine paradigm to include bioactive metabolites and lipids as direct mediators of inter-organ signaling. These molecules are not mere energy sources but are sophisticated signals that coordinate systemic adaptations. This reframes substrate utilization itself as a mode of communication: the very act of metabolizing a substrate can generate a signal that informs and directs systemic metabolic priorities (Gad et al., 2024). These three insights—the multi-organ myokine network, the training-induced remodeling of the endocrine matrix, and the signaling roles of metabolites—converge to describe a system with genuine adaptive intelligence. Chronic exercise, through this lens, is not simply a stressor but an educational process for the body's metabolic network, teaching it to anticipate demands and allocate resources with greater efficiency and precision.

I write this letter to the *Journal of Exercise and Organ Crosstalk* because it stands at the ideal intersection to champion such a systems-level, integrative approach. Pursuing these ideas will require not only advanced multi-omics but also sophisticated computational modeling to predict network-level adaptive strategies. This is the central challenge for our field: to decode the syntax of exercise-induced communication.

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