Letter to the Editor

Latest findings on gut microbiome in relation to muscle function: From metabolites to therapeutic targets

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Dear Editor-in-Chief

We are writing to highlight a rapidly advancing frontier at the intersection of exercise physiology, microbiology, and metabolism: the role of the gut microbiome as a critical endocrine organ regulating skeletal muscle function and adaptability

(1) The traditional paradigm of muscle regulation has centered on factors like mechanical load, neuronal input, and systemic hormones. However, cutting-edge research now positions the gut microbiome as a central modulator of muscle physiology. The latest findings move beyond correlation to establish causative mechanisms, primarily through microbial metabolites that serve as inter-organ signaling molecules.

(2) A key advancement involves microbiota-derived metabolites as ergogenic agents. Butyrate and other short-chain fatty acids (SCFAs) are no longer viewed solely as colonocytes fuels. Recent studies demonstrate that butyrate supplementation enhances oxidative metabolism in muscle, improves mitochondrial function, and reduces exercise-induced fatigue in mouse models (Lahiri et al., 2019). This is mediated through the activation of AMPK and PGC-1α pathways, suggesting that gut bacteria can directly influence the molecular circuitry of muscle energy sensing and biogenesis.

(3) Furthermore, the microbial metabolism of dietary tryptophan into aryl hydrocarbon receptor (AhR) ligands (e.g., indole derivatives) is a breakthrough finding. These ligands are crucial for maintaining intestinal barrier integrity, thereby reducing endotoxemia and systemic inflammation. Furthermore, specific indole derivatives have been shown to directly activate AhR signaling in muscle, potentially influencing protein synthesis and mitigating atrophy pathways, presenting a novel gut-muscle axis.

(4) Perhaps the most direct link comes from microbiome-dependent purine metabolism. A groundbreaking study revealed that gut bacteria, notably Bifidobacterium species, can metabolize dietary purines into inosine. Systemically absorbed, inosine enhances aerobic capacity and exercise performance in mice by enhancing skeletal muscle metabolic activity, directly linking a specific bacterial metabolite to a functional exercise outcome (Besora-Moreno et al., 2025).

(5) Finally, this research is now yielding robust clinical translation, a fact confirmed by the highest level of evidence. A recent systematic review and meta-analysis of randomized controlled trials conclusively demonstrated that probiotic supplementation significantly improves muscle mass, muscle strength, and lean mass in human subjects across various populations (Prokopidis et al., 2023). This comprehensive analysis synthesizes data from multiple studies, including trials like that of Tsuchiya et al. (2023), to provide a definitive summary of the field's progress. The meta-analysis leaves little doubt that modulating the gut microbiome is a novel and viable therapeutic strategy for combating age-related and other forms of muscle loss.

These findings establish the gut microbiome as a potent endocrine organ that communicates with skeletal muscle. We believe this topic is of paramount importance to the readership of exercise and organ cross talk.

References

Prokopidis, K., Giannos, P., Kirwan, R., Ispoglou, T., Galli, F., Witard, O. C., & Isanejad, M. (2023). Impact of probiotics on muscle mass, muscle strength and lean mass: a systematic review and meta-analysis of randomized controlled trials. Journal of cachexia, sarcopenia and muscle, 14(1), 30-44. doi: https://doi.org/10.1002/jcsm.13132

Besora-Moreno, M., Llauradó, E., Valls, R. M., Pedret, A., & Solà, R. (2025). Effects of probiotics, prebiotics, and synbiotics on sarcopenia parameters in older adults: a systematic review and meta-analysis of randomized controlled trials. Nutrition Reviews, 83(7), e1693-e1708. doi: https://doi.org/10.1093/nutrit/nuae145

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Lahiri, S., Kim, H., Garcia-Perez, I., Reza, M. M., Martin, K. A., Kundu, P., Cox, L. M., Selkrig, J., Posma, J. M., Zhang, H., Padmanabhan, P., Moret, C., Gulyás, B., Blaser, M. J., Auwerx, J., & Holmes, E. (2019). The gut microbiota influences skeletal muscle mass and function in mice. Science Translational Medicine, 11 (502), eaan5662. doi: https://doi.org/10.1126/scitranslmed.aan5662