MICROBIOME

Working out the bugs: microbial modulation of athletic performance

A multi-faceted translational study provides the first evidence that gut microbial conversion of lactate to propionate may enhance athletic performance during high-intensity endurance exercise.

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Recent insights into the human microbiome have initiated a paradigm shift in our understanding of the human body. The most dense and complex community of microbes resides in the gut and modulates critical functions including digestion, xenobiotic metabolism, immune response, energy homeostasis and even social behavior[1]. The fundamental and interconnected nature of these processes suggests that gut microbes influence virtually all aspects of human physiology. However, investigations of causal links between microbial profiles and human phenotypes have largely focused on risks and treatment outcomes for disease rather than markers of health such as exercise capacity. To date, long-distance running performance, a complex and incompletely understood trait, has not been associated with the composition or function of the gut microbial community.

In a new study published in *Nature Medicine*, Scheiman et al. present intriguing data suggesting that the gut microbiome may modulate lactate homeostasis, a critical determinant of athletic performance, during vigorous physical exercise[2] (Fig. 1). Participants in the 2015 Boston Marathon, studied before and after race completion, demonstrated a variable but compelling increase in *Veillonella*, a microbial genus specializing in lactate fermentation, in the post-race period. A separate cohort of runners and elite rowers also showed post-exercise microbiomes that were enriched in genes encoding enzymes involved in the methylmalonyl-CoA pathway used by *Veillonella* to convert lactate to propionate. Interestingly, probiotic treatment of mice with *Veillonella* or with non-lactate-fermenting *Lactobacillus* improved exhaustive treadmill running times, thus suggesting that *Veillonella* might enhance running performance. Although *Veillonella* could theoretically improve performance by removing lactate from the blood, probiotic treatment with *Veillonella* did not measurably increase blood lactate clearance. In contrast, administration of propionate led to enhanced running times among mice. The authors therefore conclude that propionate production rather than lactate utilization per se underlies the performance-enhancement effects conferred by gut *Veillonella*.

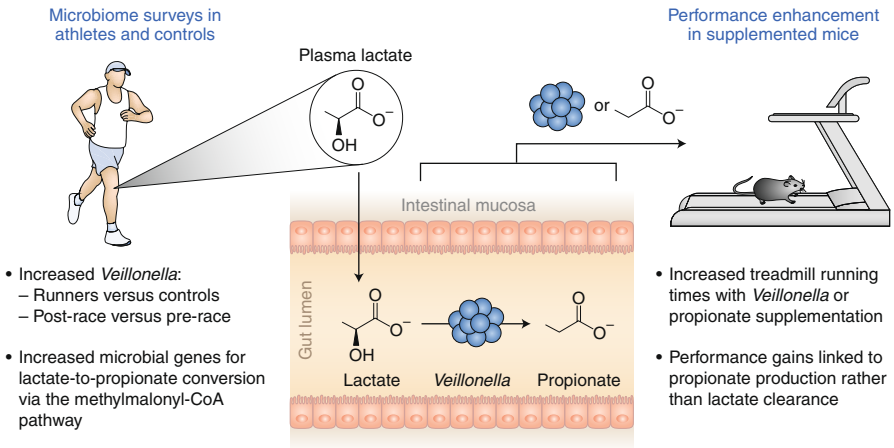

Fig. 1 | Evidence for microbial modulation of athletic performance. Running performance is affected by numerous factors, many of which remain unknown. Scheiman et al.[2] present diverse evidence in humans and mice suggesting that the gut microbiota contributes to running performance. The authors surveyed the gut microbiotas of Boston Marathon participants and found increases in the microbial genus *Veillonella*, a lactate-catabolism specialist, both longitudinally (post-race versus pre-race) and cross-sectionally (as compared with sedentary controls). In a second distinct sample of elite runners and rowers, post-exercise microbiomes were enriched in genes encoding proteins involved in the methylmalonyl-CoA pathway used by *Veillonella* to convert lactate to propionate. Together, these data suggest a model in which gut microbes are affected by exercise and in turn modulate athletic performance via microbial lactate metabolism by serving as a sink for circulating lactate, by producing performance-enhancing metabolites in the lactate-to-propionate conversion, or both. Despite demonstrating that circulating lactate can cross into the lumen, the authors did not observe decreases in circulating lactate with *Veillonella* colonization, results that do not support the lactate-sink model. In contrast, mice colonized with *Veillonella* or administered isolated propionate showed improved performance in exhaustive treadmill running-time experiments, thus suggesting that propionate production was key to the observed performance gains.

The greatest strength of this study is its novel focus on the gut microbiome as a potential modulator of athletic performance. However, the work from Scheiman et al. also represents an impressive multi-faceted translational effort, combining longitudinal experiments in humans and mice with multi-omics analyses probing changes in microbial community structure, microbial gene content and host metabolic phenotypes. This robust study design leads to some interesting and informative findings en route to the key conclusions. For instance, via intraperitoneal injection of isotopically labeled lactate, the authors report the first evidence that circulating lactate crosses into the gut lumen. Although the authors appropriately contextualize this

finding as suggestive evidence that the gut microbiome could theoretically serve as a sink for exercise-generated lactate, evidence of systemic-to-luminal lactate translocation raises other intriguing hypotheses that await testing, including whether bidirectional lactate exchange occurs. This finding is particularly interesting given recent evidence in mice that circulating lactate is a predominant fuel for tricarboxylic acid metabolism in all tissues except the brain[3].

The idea that the gut microbial community can affect athletic performance is alluring, and we anticipate that people who read the headlines will look forward to setting personal marathon records with *Veillonella* or propionate supplements. However, such inferences are premature for several reasons. First, the available data do not support the conclusion that probiotic treatment with *Veillonella* enhances performance; instead, this treatment has only been shown to enhance performance relative to probiotic treatment with *Lactobacillus*. *Lactobacillus bulgaricus* was selected as a control because it cannot catabolize lactate. However, *L. bulgaricus* readily synthesizes lactate, including under anaerobic conditions[4]. Excess lactate in the gut, particularly if it translocates into the systemic circulation, could be detrimental to performance, just as lactate clearance may be beneficial. Consequently, the observed differences in performance might have been driven by negative effects of *Lactobacillus* colonization rather than, or in addition to, performance-enhancing effects of *Veillonella*. Although a *Veillonella*–*Lactobacillus* trade-off clearly supports a larger picture in which gut microbial composition matters in athletic performance, in the future the authors could discriminate between these possibilities by including baseline data and/or a no-probiotic control group. Second, because all tests evaluating the effects of *Veillonella* colonization or propionate supplementation were performed on mice after a 7-hour fast, a period sufficient to induce acute energy constraint and associated changes in metabolism[5], whether these effects would be reproducible under the less constrained conditions typical of most athletes remains unclear. This caveat is especially notable in the case of propionate, which is absorbed in the colon and serves as a substrate for hepatic gluconeogenesis. Propionate supplementation in this study could thus have enhanced performance simply because it provided energy to otherwise energy-starved mice.

This pioneering paper by Scheiman et al. encourages future efforts to clarify the ecological and mechanistic bases of microbial contributions to athletic performance and raises several key questions. First, do *Veillonella* and other lactate metabolizers respond to exercise itself or to some environmental or lifestyle factor associated with exercise? Whereas runners had higher *Veillonella* abundance overall, runners and sedentary controls exhibited similar pre-marathon to post-marathon fold changes in *Veillonella*, thus suggesting a sensitivity to effects beyond exercise. Second, because marathon running typically is a moderate-intensity effort performed below the lactate threshold, would variable microbial lactate metabolism be an even stronger determinant of performance in shorter-duration and higher-intensity sports, such as middle-distance running, in which lactate kinetics is more relevant? Finally, given the apparent importance of propionate in exercise performance, could more profound performance enhancement be achieved through lifestyle factors, such as dietary fiber consumption, which is known to generate most of the propionate found in the gut[6]?

Each of these areas of uncertainty will best be addressed by longitudinal diet-controlled training studies[7] designed with careful attention to the volume, intensity and frequency of the prescribed exercise dose. Prospective and concomitant assessment of gut microbial profiles and athletic performance among previously sedentary humans and/or mice will be required to determine whether exercise truly modulates the gut microbiome in a manner that has implications for athletic performance. If so, relationships would be expected among exercise dose, quantity of *Veillonella* and other lactate-metabolizing microbes, blood lactate concentrations during exercise and propionate levels in the intestinal lumen. Such training experiments would ideally be coupled with fecal transplants into germ-free mice showing that the improvements in performance with training can be at least partially recapitulated in untrained mice.

As evidence documenting the plasticity and physiologic relevance of the gut microbiome continues to mount[8], the notion that the gut microbiome serves as a key determinant of athletic performance seems increasingly plausible. We commend Scheiman et al. for their exciting start and await further studies that elucidate how the human–microbiome interaction contributes to human health and probe the evolutionary roots of this extraordinary partnership. ❐

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Competing interests

The authors declare no competing interests.