The Microbiota: an Exercise Immunology Perspective

Stéphane Bermon[1,2], Bernardo Petriz[3,4], Alma Kajėnienė[5,6], Jonato Prestes[7], Lindy Castell[8], Octavio L. Franco[3,7,9]

[1] LAMHESS, Nice Sophia Antipolis University, France
[2] Monaco Institute of Sports Medicine and Surgery, Monaco
[3] Centro de Análises Proteômicas e Bioquímicas, Programa de Pós-graduação em Ciências Genômicas e Biotecnologia – Universidade Católica de Brasília, DF, Brasil.
[4] UDF – Centro Universitário, Brasília, DF, Brasil.
[5] Lithuanian University of Health Sciences, Institute of Sport, Kaunas, Lithuania
[6] Kaunas Sports Medicine Centre, Kaunas, Lithuania
[7] Programa de Pós-Graduação em Educação Física, Universidade Católica de Brasília, DF, Brasil.
[8] Green Templeton College, University of Oxford, Oxford, United Kingdom
[9] Pós Graduação em Biotecnologia, Universidade Católica Dom Bosco, Campo Grande, MS, Brasil.

ABSTRACT

The gut microbiota consists of a cluster of microorganisms that produces several signaling molecules of a hormonal nature which are released into the blood stream and act at distal sites. There is a growing body of evidence indicating that microbiota may be modulated by several environmental conditions, including different exercise stimulus, as well some pathologies. Enriched bacterial diversity has also been associated with improved health status and alterations in immune system, making multiple connections between host and microbiota. Experimental evidence has shown that reduced levels and variations in the bacterial community are associated with health impairments, while increased microbiota diversity improves metabolic profile and immunological responses. So far, very few controlled studies have focused on the interactions between acute or chronic exercise and the gut microbiota. However, some preliminary experimental data obtained from animal studies or probiotics studies show some interesting results at the immune level, indicating that the microbiota also acts like an endocrine organ and is sensitive to the homeostatic and physiological changes associated with exercise. Thus, our review intends to shed some light over the interaction a between gut microbiota, exercise and immunomodulation.

Key Words: exercise, gut, immunity, microbiota

Corresponding author:
S. Bermon, MD, PhD Monaco Institute of Sports Medicine and Surgery, 11 avenue d'Ostende, 98000 Monaco.
Email: bermon@unice.fr

1. The microbiota

Human beings have clusters of bacteria (the microbiota) in different parts of the body, such as in the surface or deep layers of skin, the mouth, gut, lungs, vagina, and all surfaces exposed to the external world. With regards to quantitative aspects, it is emerging that we are made of ten times more microbial than mammalian cells. The adult gut microbiota contains up to 100 trillion micro-organisms, including at least 1,000 different species of known bacteria, with more than 3 million genes (150 times more than human genes). Microbiota can, in total, weigh up to 2 kg. One third of our gut microbiota is common to most people, while two thirds are specific to each one of us. In other words, the single individual gut microbiota is like an individual identity card (67). This largely enhances the genetic variation among individuals that is provided by the human genome (48,57,67). The use of new molecular biology techniques using the conserved 16S rRNA gene for phylogenetic analyses that also can detect unculturable bacteria has significantly advanced our understanding of the gut microbiome (the bacteria and their genome) (81).

2. Establishment and changes of the microbiota

While the 'healthy' gut microbiota is seen to be a stable community, there are stages within the life cycle of humans during which there can be alterations in the structure and function of this population. The infant gut microbiota undergoes dynamic changes during development, resulting in an adult-like microbiome at about 3 years of age (90). This process is influenced by genetic, epigenetic and environmental factors such as country of origin, delivery mode, antibiotics and breastfeeding (2). Indeed, the delivery mode at childbirth has an impact on early microbiota composition (22). Vaginally delivered children display a microbiota that shares characteristics with the vaginal microbiota, and includes *Lactobacillus, Prevotella, Atopobium, or Sneathia spp.* On the other hand, babies delivered by caesarean section have more skin-associated microbiota including *Staphylococcus spp.* (22). This suggests that the microbiota derives at least in part from the mother during the delivery. Hence, interpersonal variations are higher

among children than among adults. In adults, individuals coming from different geographic areas also display different microbiota (90).

3. The microbiota acts like an endocrine organ

The microbiota produces numerous compounds of a hormonal nature which are released into the blood stream and act at distal sites. Among the targets for these substances are many other organs including the brain. The microbiota releases its hormonal products into interstitial tissue, to be picked up by blood and lymph capillaries. These secretions are usually effective in low concentrations on target organs or tissues remote from the enteric milieu. Thus, considering the ability to influence the function of distal organs and systems, in many respects the gut microbiota resembles an endocrine organ. It is more biochemically heterogeneous than any other endocrine organ because it has the potential to produce hundreds of chemicals with hormonal properties. For example GABA, the most important inhibitory transmitter in the brain is produced by several strains of *lactobacilli* (7), while monoamines such as noradrenaline, dopamine and serotonin are also produced by many other strains of bacteria (17). The gut microbiome has been reported to regulate psychiatric health and influence etiopathology of autism. For example, Bravo et al. (10) reported that chronic administration of *Lactobacillus rhamnosus* induced anxiolytic and antidepressant effects by modulating the expression of GABA receptors in the brain, and Lyte et al. (50) observed that infection with *Citrobacter rodentiumin* induced anxiety-like behaviours through vagal sensory regulation.

Short chain fatty acids (SCFAs) are the major products of the bacterial fermentation of carbohydrates and proteins in the gut. Bacteria that produce SCFA include, but are not limited to, *Bacteroides, Bifidobacterium, Propionibacterium, Eubacterium, Lactobacillus, Clostridium, Roseburia* and *Prevotella* (52). SCFA are produced in high amounts when poorly digestible polysaccharides from plant origin are used as a carbohydrate source. Acetate, butyrate and propionate are then secreted into the gut lumen, transported across the epithelial barrier and transported to the effector organs. SCFAs actively

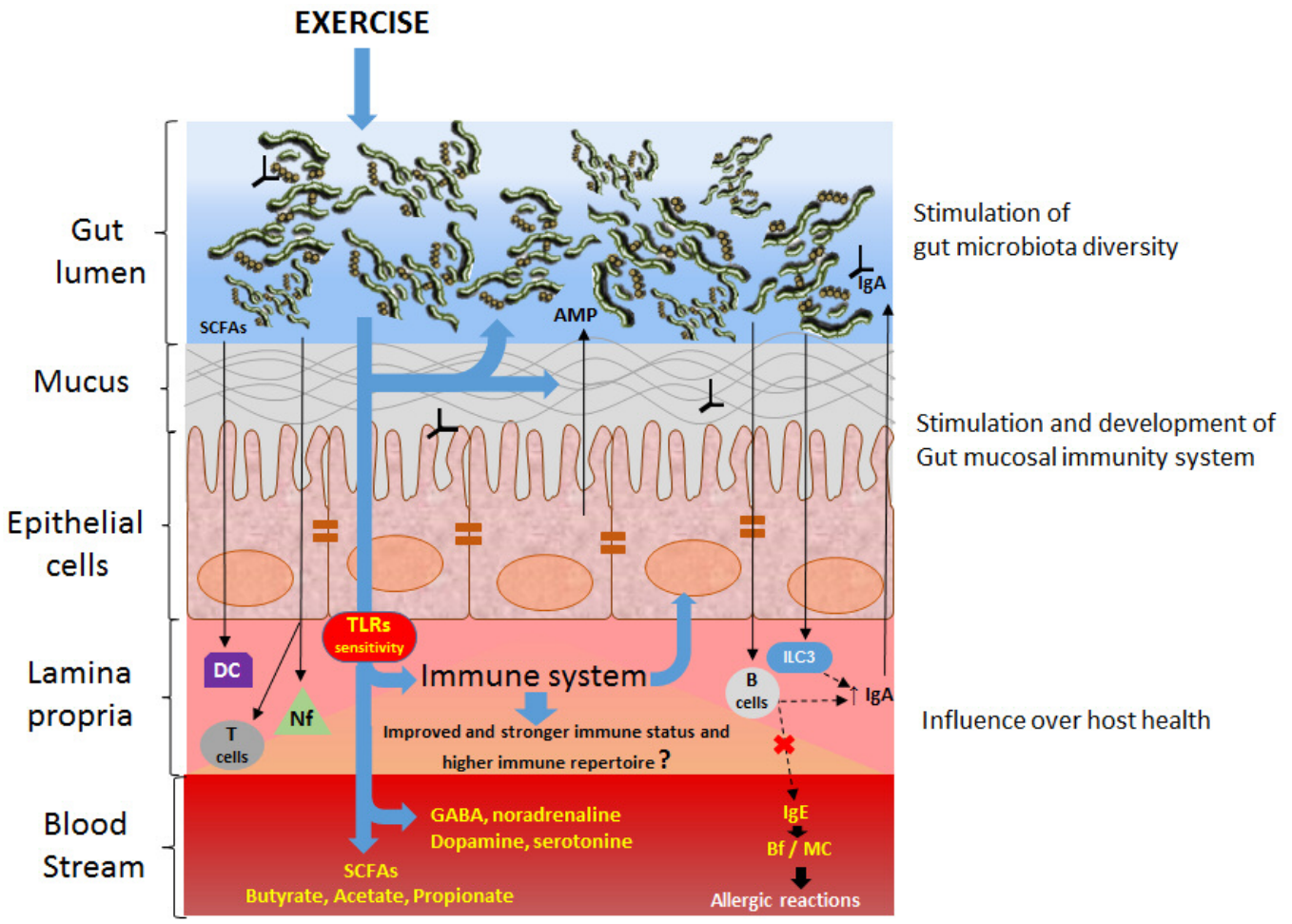

Figure 1: Exercise and the "cross-talk" between the gut microbiota and immune system.
Exercise may enhance sensitivity of toll like receptors (TLRs). Short chain fatty acids (SCAFs) then stimulate dendritic cells (DC) which are associated with inflammation protection. Microbiota also stimulates T cells and neutrophils (Nf), inducing a pathogen spreading control and B cells, where IgA production enhanced to produce IgE. IgE production and its release in serum, activates basophils (Bf) and mast cells (MC) leading to allergic reactions. Stimulation of ILC3 cells also enhances IL-22 production and IgA, and protects epithelial cells and antimicrobial peptide (AMP) synthesis and its release in gut lumen. The microbiota also produces hormonal-neurotransmitter agents (GABA, noradrenaline, dopamine and serotonin) and metabolic products (SCFAs: butyrate, acetate and propionate) which are related to neurotransmitters synthesis and food satiety control.

participate in the gut-brain axis, for instance by modulating entero-endocrine 5 hydroxy tryptophan secretion (25) and neuropeptide YY release (36). Butyrate and propionate, when in the blood stream, can be carried by monocarboxylate transporters which are abundantly expressed at the blood-brain-barrier and enter the central nervous system. They are a major energy source for neurons, but can potentially influence neurotransmitter synthesis through regulation of tyrosine hydroxylase gene expression (21).

4. The microbiota interacts with our immune system

The microbiota consists of symbiotic innocuous bacteria and potential pathogens also called pathobionts (16). The first role identified for the microbiota was the degradation of complex food macromolecules. However, there is growing evidence showing that the microbiota plays important roles in the maturation of the immune system and protection against some infectious agents (37,44,69,78). This is particularly true in the early phases of life when the microbiota 'teaches' our immune system how to deal with both innocuous and harmful bacteria, which in turn keep the microbiota under control. As far as the gut is concerned, this early programming is of utmost importance because it leads to the concept of a 'healthy' gut. When dysregulation (or dysbiosis) among these bacterial communities occurs, it can lead to inflammatory disorders, including inflammatory bowel disease, obesity, diabetes and autism (see below).

All the immune system components are directly or indirectly regulated by the microbiota. For instance, the microbiota and their metabolic by-products influence dendritic cells and macrophages either directly or through the intervention of epithelial cells. This cellular activity can be regulated by microbiota-driven epigenetic mechanisms. Similarly, T regulatory cells can be induced by metabolic products of the microbiota. The gut microbiota can induce B cell maturation as well as switching their immunoglobulin isotype. A preference for IgE rather than IgA can drive the activation of basophils and mast cells, which in turn results in a modified microbiota. The cross-talk between the gut flora and the immune system stimulates the development of the gut mucosal immune system, which is one of the mechanisms to prevent exogen pathogen intrusion (14). The pattern recognition receptors, among them, the toll-like receptors (TLRs) and the nucleotide-binding oligomerization domain receptors are known mechanisms by which the innate immune system recognizes molecules with opposing characteristics. In turn, this leads to the recognition of, and distinction between, pathogens and non-harming elements (40). Considering that the expression of TLRs is modulated by the microbiota through the microbe-associated molecular pattern (MAMP), a complex molecular cascade is triggered, which includes the activation of the nuclear factor-kappa B pathway, followed by cytokine production and activation of T cells (40). The major components in the interaction of the microbiota with the host immune system are summarized in a review article (70) and presented in Figure 1.

SCFAs produced by the anaerobic bacterial fermentation at the gut level also act as signaling molecules. Indeed, propionate and acetate are ligands for two G protein coupled receptors, Gpr41 and Gpr43, which are broadly expressed in the distal small intestine, colon and adipocytes (11,89). SCFA linkage with Gpr43 decreases inflammatory responses, as it was shown that Gpr43 is largely expressed in neutrophils and eosinophils. This suggests that SCFA-Gpr43 signaling is one of the molecular pathways whereby commensal bacteria regulate immune and inflammatory responses (54). Moreover, SCFAs can modulate intracellular calcium levels in neutrophils suggesting another way of cell signaling (58-60). SCFAs present multiple effects in different cells involved in the inflammatory and immune responses. These fatty acids not only affect the production of inflammatory mediators, and ability of leukocytes to migrate. They can also induce apoptosis in lymphocytes, macrophages and neutrophils (82). In general, SCFAs, such as propionate and butyrate, inhibit stimuli-induced expression of adhesion molecules, chemokine production and consequently suppress monocyte/macrophage and neutrophil recruitment, suggesting an anti-inflammatory action of the microbiota byproducts.

5. Dysbiosis and immune-mediated diseases

The epidemic rise in allergic disease over the last decades has coincided with progressive Westernization (increased hygiene, smaller family sizes, dietary change and excessive antibiotic use). To explain this rise, Strachan (75) introduced the hygiene hypothesis suggesting that microbial exposures in childhood are critical for normal immune development. This hypothesis was later revised by the 'gut microbial deprivation hypothesis', which proposed that the observed changes in early intestinal colonisation patterns over the last decades in Western countries have resulted in failure to induce and maintain tolerance (12). There is emerging evidence that early gut microbiota establishment during critical periods of development has the potential to influence the risk of developing environmentally influenced disease, including allergic disease. Studies have reported that infants born by caesarean section are at greater risk for developing asthma and atopy (45,53,79), mainly because they show gut microbiota patterns with lower abundance of *Bacteroidetes* and lower diversity within the Bacteroidetes phylum (38,39,63,80). More generally, lower overall microbiota diversity and diversity within *Bacteroidetes* in early infancy have also been observed to precede development of allergic manifestations (1,9,22,86).

In recent years, considerable evidence has accumulated supporting the notion that the gut microbiota induces mucosal regulatory T cells which then play a vital role in maintaining gut homeostasis under normal conditions or in controlling inflammatory responses that would lead to disease. A breakdown in mucosal unresponsiveness to gut commensal organisms as well as a gut dysbiosis are now known to be associated with inflammatory bowel diseases such as Crohn's disease (CD) and ulcerative colitis (76). The gut microbiota may cause or aggravate CD by defective induction of regulatory T cells, or by infection of the mucosa and the induction of inflammatory cytokines. Indeed, studies of mice and humans with gastrointestinal inflammation have led to the identification of at least two kinds of bacteria that may cause or aggravate the inflammation of CD: *Faecalibacterium prausnitzii (Firmicutes),* and adherent–invasive *Escherichia coli.*

Assuming that obesity is at least partly an immune-mediated disease, it has been shown that the gut microbiota plays an important role in weight control, in addition to diet, lifestyle, genetics, and the environment. Obese mice and humans show higher proportion of *Firmicutes* and lower proportion of *Bacteroidetes* than their lean counterparts. One postulated explanation for this finding is that *Firmicutes* produce more complete metabolism of a given energy source than do *Bacteroidetes*, thus promoting more efficient absorption of calories and subsequent weight gain. Ridaura et al. (71) confirmed these findings in their pivotal study on colonization of the intestine of germ-free mice with the microbiome obtained from either obese or lean individuals. Other possible mechanisms by which the intestinal microbiome affects host obesity include induction of low-grade inflammation with lipopolysaccharide, regulation of host genes responsible for energy expenditure and storage, and hormonal communication between the intestinal microbiome and the host (42).

Together, these pieces of evidence indicate that the composition of the gut microbiota during early life, as well as a possible dysregulation, influence the way in which energy from dietary compounds is extracted, stored and expended in the host. This in turn influences the development of obesity and metabolic disorders. Diet has also been shown to rapidly alter the composition of gut microbiota independently of the obesity phenotype (26,35). In fact, it is suggested that the microbiota of lean and obese subjects responds in a different manner to alterations in caloric content of diet (41). In this sense, diet and an obese host-environment may also contribute to the modification of the gut microbiota consortia. However, the order in which these events occur is still unknown, and it is likely that both events progress in parallel. In a similar idea, up to now, it has not been established if exercise shifts the gut microbiota by promoting weight loss or if the weight loss promoted by exercise influences the regulation of the microbiota itself. Although weight loss has been shown to modulate the ratio of *Firmicutes* to *Bacteroidetes*, a role of exercise *per se* independently of a weight loss is still to be confirmed.

In this field, nutritional supplementation therapy (e.g. glutamine, prebiotics and probiotics) together with fecal microbiota transplantation have been used to manipulate and re-establish gut microbiota status (31,62,74). Glutamine is well known to be important in gut function and is avidly used by rapidly dividing cells such as enterocytes, colonocytes and gut lymphocytes. Moreover, glutamine alone or in combination with other gut-trophic nutrients improves the intestinal barrier function in children (49).

6. Exercise and the gut microbiota

As discussed above, the contribution of gut microbiota to the pathogenesis of obesity occurs through the alteration of host energy homeostasis. The ability of gut microbiota to process indigestible polysaccharides increases the viability of short chain fatty acids including butyrate, acetate and propionate (4). It has been demonstrated that butyrate is used as an energy source for colonic epithelial cells, whereas acetate and propionate are used by the liver for the lipogenesis process (73). Moreover, it is proposed that pro-inflammatory dietary compounds, such as saturated fat, together with genetic predisposition may shape the gut microbiota and increase caloric load. The inability to restore healthy gut microbiota status may lead to inflammation and bacterial metabolites leaking out to the mesenteric fat. This process is associated with the activation of pro-inflammatory gene expression, cytokine production, and macrophage infiltration. It has been proposed by Lam et al. (46) that the enhancement of adipose-derived cytokines and fatty acids promotes inflammation, steatosis and insulin resistance in the liver, which may lead to a metabolic systemic dysfunction. As exercise is known to exert a beneficial role in energy homeostasis and regulation, it might also modulate and help to restore the gut microbiota when altered by a high fat diet.

6.1. General effects of exercise on gut physiology.

There are several well-known effects of exercise on gut physiology. Exercise volume and intensity have been shown to exert an influence on gastrointestinal health status (64). For example, exercise reduces the transient stool time in the gastrointestinal tract, reducing the prolonged contact of pathogens with the gastrointestinal mucus layer and circulatory system. Moreover, moderate exercise is associated with reduced levels of cecum cancer, while exhaustive endurance exercise has been associated with a disturbance in the gastrointestinal tract due to toxicity effects induced by reduced local blood flow and bacterial translocation to blood stream (64).

6.2. The effects of voluntary exercise on the gut microbiota

To date, very few studies have investigated the role of exercise on the gut microbiota. However, exercise is a potential external agent with the capacity to change gut microbiota diversity in quantitative and qualitative ways. This was initially observed by Matsumoto et al. (55), who reported an alteration in the microbiota content and an increase of n-butyrate concentrations in rats submitted to voluntary running exercise. These authors also reported an increase in the cecum diameter in the trained rats. In addition, exercise alters the gut microbiota in mice on both a low and high fat diet, and normalizes major phylum-level changes for mice on the high fat diet. Furthermore, the total distance run by these animals inversely correlates with the *Bacteroidetes-Firmicutes* ratio (24). However, exercise, when associated with food restrictions (mimicking anorexia in a rat model), seems to have a potential negative impact on the quantity of health-promoting bacteria. In addition, it can enhance the growth of bacteria which may be related to the disruption of the gut mucosal barrier and the optimal exploitation of the very low caloric diet (68). These authors also reported that serum leptin was positively correlated with the quantity of *Bifidobacterium* and *Lactobacillus*, and negatively correlated with the quantity of Clostridium, *Bacteroides* and *Prevotella*. Conversely, serum ghrelin levels were negatively correlated with the quantity of *Bifidobacterium, Lactobacillus* and *B. coccoides–Eubacterium rectale* group, and were positively correlated with the number of *Bacteroides* and *Prevotella.* These findings highlight the associations between gut microbiota and appetite-regulating hormones. Moreover, voluntary exercise also appeared to attenuate the microbiome changes induced by polychlorinated biophenyls (PCB) (15). In this study, mice exposed to two days of PCB mixture, presented an alteration

in the abundance of 1,223 bacterial taxa, with an overall abundance reduction (2.2%) whereas the biodiversity of the gut microbiota was not altered. Interestingly, predicted analysis for micro arrays identified seven phila *(Firmicutes)* with significantly higher abundance when comparing exercising to sedentary mice.

6.3. Controlled training and gut microbiota modification in animals

Again, very few studies have investigated the alteration of gut microbiota following controlled exercise. As observed in voluntary exercise regimens, recent studies have shown that controlled training also exerted some beneficial effect on the gut microbiome of obese and hypertensive rats (65) and in obese mice with a phenotype induced by high fat diet (HFD) (43). Moderate treadmill training (around the maximal lactate steady state, 12.5 $m.min^{-1}$ for obese $Zucker^{fa/fa}$ rats and 20 $m.min^{-1}$ for non-obese and hypertensive rats (SHR), 30 min/day, 5 days/weeks, during 4 weeks) altered the composition and the diversity of the gut bacterial at genus level in non-obese, obese animals, and SHR. Exercise promoted *Allobaculum* in SHR and *Pseudomonas* and *Lactobacillus* genus in the obese rats. Moreover, the abundance of operation taxonomic units from two bacteria families (*Clostridiaceae* and *Bacteroidaceae*) and genera (*Oscillospira* and *Ruminocossus*) was significantly correlated with blood lactate concentration. These findings indicate that training status may be linked to these bacterial proliferations (65). The effect of 16 weeks of training (running wheels, 1 h, 7 m/min, 5 days/week) on rats submitted to HFD was also used to study anxiety and cognitive dysfunction which are associated with the development of obesity (65). HFD and exercise alone caused massive but opposite changes in the gut microbiome. However, exercise failed to reverse the changes induced by the HFD at the microbiome level.

6.4 Effect of training on the human gut microbiota

A study involving elite rugby players also reported that exercise increases gut microbiota richness and diversity (18). Moreover, this pioneering work in humans showed that the indices of the gut microbiota diversity positively correlated with protein intake and creatine kinase concentration, suggesting that diet and exercise are drivers of biodiversity in the gut. This work highlighted that exercise is another important factor in the complex relationship among the host, host immunity and the microbiota in elite athletes.

6.5 Gut Permeability and Ischemia –Reperfusion

One of the essential functions of the intestine is to maintain a barrier which prevents the entry of potentially harmful microorganisms to adjacent and distant sterile organs. This mechanical barrier can be disrupted through splanchnic hypoxia and subsequent reperfusion. This often results in bacterial translocation, with most of the translocating bacteria originating from the colon. Strenuous and prolonged exercise such as endurance competitions and training are associated with various levels of splanchnic hypoperfusion and ischemia and subsequent reperfusion (64). In a murine model, Gutekunst et al. (32) recently reported increased apoptosis and altered permeability following exhaustive and acute endurance exercise. Although relevant to the topic of this article, this pathophysiological phenomenon and its potential consequences on the gut microbiota have not been addressed in exercising humans. Using an ischemia-reperfusion model in rats, Wang et al. (85) reported that the damage-repair of the epithelium preceded dysbiosis and subsequent tendency to recovery of the colonic microbiota. While the epithelial barrier started repairing after 3 hours and gained full recovery at 24 hours of reperfusion, a normal microbiome was not fully recovered after 72 hours of reperfusion. Colonic flora started to change as early as 1 hour into reperfusion. At 6 hours, *Escherichia coli* (a pro-inflammatory strain of bacteria with high translocation potential) reached a construction peak. Speeding-up the gut microbiota recovery process by consuming a probiotic containing *Lactobacilli* strains prior to a lasting endurance event is a hypothesis which deserves further investigation.

6.6. The Hypothalamic-Pituitary-Adrenal (HPA) axis and the Microbiota

Cross-talk between the gut microbiota and the HPA axis has recently been described. It is now clearly established that the gut microbiota is involved in the development of the HPA axis in rodents (20,77). Animals raised in the absence of microorganisms show exaggerated release of corticosterone and ACTH after mild stress exposure, when compared with specific pathogen free controls. These results demonstrate that the early life microbial colonization of the gut is critical to the development of an appropriate stress response later in life. It has also been proven that stress and the HPA can influence the composition of the gut microbiome. The functional consequences of such changes are probably relevant to the field of exercise immunology. In animal experiments, maternal separation, an early life stressor, or exposure to social stressors (6,61) result in long-term HPA changes, and also has long term effects on the microbiome (5). These stressed animals showed decreased relative abundance of the *Bacteroidetes* genus and increased relative abundance of the *Clostridium* genus in their cecum, as well as increased circulating levels of IL-6 and MCP-1 (6). In a recent randomized controlled study, healthy humans supplemented with *Lactobacillus helveticus* R0052 and *Bacteroidetes longum* R0175 for 30 days showed reduced urinary free cortisol output (56).

An elevation in the plasma concentration of noradrenaline, associated with physical exercise or mental stress, stimulates the growth of non-pathogenic commensal *E.Coli* (27), as well as other gram-negative bacteria (50). These preliminary findings in humans attest to hormonally-driven changes in the composition and distribution of the intestinal microbiota, which in turn might modify host behavior. This topic is of particular interest in the field of exercise immunology, and deserves future studies in exercising humans or elite athletes.

7. Prebiotics and Probiotics in Exercise Immunology

Probiotics may improve health, either by the immunomodulation of local immunity by maintaining gut wall integrity or by acting on systemic immunity; enhancing non-specific and specific arms of the immune system (33). As far as the innate immune function is concerned, probiotics have been shown to enhance phagocytic capacity of peripheral blood polymor-

phonuclear cells and monocytes as well as NK cells cytotoxic activity. Acquired immunity also seems to be improved following supplementation with probiotics, with significantly higher specific IgG, IgA and IgM immunoglobulins. Local immunity is modified with an enhanced gut barrier function and an improved local immune response. One of the main clinical outcomes from these *in vitro* results is a reduced rate of upper respiratory tract illness (URTI) in children and adults when given specific strains of probiotics (33). Although there is a scarcity of supplementation studies with athletes, it seems that this particular population may also benefit from a regular probiotics use (66). This is of particular interest since athletes engaging in prolonged intense exercise may be more susceptible to URTI (84). This benefit is believed to be strain specific: the most common strains used to promote immune function are lactic acid bacteria; *Lactobacillus* and *Bifidobacterium* species. Cox et al. (19) reported that oral administration of *Lactobacillus fermentum* was associated with a substantial reduction in the number of days and severity of URTI in twenty highly trained distance runners. These beneficial effects occurred without any significant changes in salivary IgA or interleukin-4 or -12 levels. The same type of results, after using probiotics, were reported for lower respiratory illness use of cold and flu medication, and severity of gastrointestinal symptoms at higher training loads, in male (but not female) competitive cyclists (88). The authors observed a reduction in exercise-induced immune perturbations, interestingly in both anti-and pro-inflammatory cytokines, which could have mediated these effects. Two other studies performed on physically active subjects and elite rugby union players confirmed a positive effect of a probiotic supplementation on the incidence, but not severity or duration of URTI (28,34). The study using physically active subjects also observed a positive effect on salivary IgA.

Prebiotics are non-digestible polysaccharides and other substances that selectively stimulate the growth or activities of one or more species of bacteria in the gut microbiota: this confers a health benefit on the host (72). For instance, high amylose maize starch supplementation showed some beneficial effects on markers of bowel health in healthy physically active adults (87). In general, prebiotics favor the growth of *Bifidobacteria* and *Lactobacilli* over potentially harmful proteolytic and putrefactive bacteria. Prebiotics have been classified mainly into two groups, the inulin type fructans (ITF) and the galacto oligosaccharides (GOS), based on their chemical structures. So far, no studies focusing on the purported beneficial effects of prebiotics on athletic performance have been conducted. However, a study examining the effects of various GOS supplementation protocols in a large cohort of 427 students showed that supplementation with GOS was associated with lower GI illness symptom scores. Moreover, supplementation with 2.5 g of GOS was associated with reduced cold and flu severity scores (38). Another study of GOS supplementation providing a dose of 5.5 g/day, showed a significant reduction of in the incidence and duration of diarrhoea in healthy volunteers undertaking international travel (23).

Regular consumption of 16 g per day of FOS has been found to influence host metabolism favorably, increasing plasma gut peptide concentration and reducing appetite (13). Reduced levels of C-reactive protein have also been reported with FOS supplementation (82). Whether these findings could be relevant and useful to elite athletes as prophylaxis and recovery means should be further investigated.

8. Perspectives in Exercise Immunology

There are interesting questions to be discussed, such as the effect of exercise on the gut, its microbiota and the brain-gut interactions. For example, does exercise enhance the sensitivity of TLRs and the recognition of the MAMPs, leading to a stronger innate immune system? If so, does this occur through modification of the communication between the immune system and the flora? It is known that TLRs have been associated with a sedentary lifestyle and inflammation status, and that exercise reduces the expression of these receptors in the monocyte cell-surface, contributing to a post-exercise immunodepression status (29). However, the link between gut microbiota, mucosal immunity and exercise stimulation has not yet been explored, leading to several possibilities in the exercise-immunology research field.

Advances in sequencing technologies have made it possible to identify the presence of bacterial strains in the airways. The most prevalent phyla identified in the airways are *Proteobacteria, Firmicutes,* and *Bacteroidetes*. Although there is no direct evidence that the airway microbiota has, like the gut, a function in developing and maintaining the steady-state immune phenotype of the lung, several recent studies showed an association between the airway microbiota and a variety of chronic lung diseases such as asthma, chronic obstructive pulmonary diseases, and cystic fibrosis (30). It is, however, difficult to understand whether the observed differences between the compositions of the airway microbiota between healthy and diseased subjects is driven by changes at the gut level. It is also difficult to estimate the causative roles of treatments such as glucocorticosteroïds or antibiotics. As some athletes are prone to respiratory illnesses from inflammatory or viral origins (8), characterization and comparison of the airway microbiota in this population would certainly be of clinical interest.

10. Conclusion

Experimental evidence has shown that alterations in the bacterial community are associated with health impairments, while increased microbiota diversity improves metabolic profile and immunological responses, and may provide a possible biomarker for health improvement. Therefore, it is of vital importance to have a better understanding of the effects of exercise on the interaction of the microbiota and innate immune system, as well as further outcomes in relation to host health. In obesity and diabetes, the immunological system plays a key role in the development of the pathological conditions influenced by microbiota alterations. Although exercise may induce positive restorative effects on the microbiota, it is definitely too soon to define exercise as a therapeutic element for the treatment of diseases associated with a disturbance of the gut microbiota. Moreover, few groups have embraced this particular field in terms of linking exercise physiology and the possible outcomes of disturbed gut microbiota treatment. In contrast to other new treatments, such as microbiota trans-

plantation or nutritional supplements, exercise is still an effective and non-pharmacological treatment for a number of pathologies. Exercise may hopefully contribute to positive manipulations within gut microbiota and its close relationship with the immunological system. It is hypothesized that the key to this process is linked to the effects of exercise on the cross talk between the immune system and the microbiota. These effects remain largely unknown and should be a research focus in the near future.

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