



## Review article

## Nutrients, immune system, and exercise: Where will it take us?

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## ABSTRACT

The immune system plays a key role in controlling infections, repairing injuries, and restoring homeostasis. Immune cells are bioenergetically expensive during activation, which requires a tightly regulated control of the metabolic pathways, which is mostly regulated by two cellular energy sensors: Adenosine monophosphate-activated protein kinase and mammalian target of rapamycin. The activation and inhibition of this pathways can change cell subtype differentiation. Exercise intensity and duration and nutrient availability (especially glucose and glutamine) tightly regulate immune cell differentiation and function through Adenosine monophosphate-activated protein kinase and mammalian target of rapamycin signaling. Herein, we discuss the innate and adaptive immune-cell metabolism and how they can be affected by exercise and nutrients.

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## Introduction

The immune system protects the body against pathogens. It plays a fundamental role in maintaining tissue homeostasis and preventing inflammatory and metabolic diseases [1]. Immune cells are bioenergetically expensive during activation, which requires a tightly regulated control of the metabolic pathways. The metabolic pathway is essential to the fate of differentiation that the immune cell will follow. Thus, these cells are easily affected by nutritional state, exercise volume, and hormonal activities [2].

Innate immune cells are the first line of defense against antigens. They are phagocytes that consume pathogenic bacteria and present antigen fragments to other immune cells inducing an adequate immune response. Innate immune cells are also responsible for maintenance of tissue homeostasis [3]. Mononuclear cells (i.e., monocytes and macrophages), granulocytes (i.e., neutrophils, eosinophils, and basophils), mast cells, and natural killer cells comprise this system. Mononuclear cells are the main innate cell population, modulated by nutritional state and physical activity level.

Macrophages are potent phagocytes that work on pathogen elimination, tissue repair, and antigen presentation. These cells are very heterogeneous in gene expression and can be modulated depending on the stimulus. The two best characterized phenotypes are classic (M1) and alternative (M2) activation [4]. M1

(i.e., proinflammatory macrophages) is activated with lipopolysaccharide and interferon- $\gamma$  (IFN- $\gamma$ ) stimulation and produces proinflammatory cytokines that recruit other immune cells to an inflammation resolution. This phenotype is known to be more glycolytic, and thus presents a high rate of glucose and glutamine uptake and lactate production when activated [5]. However, with prolonged IFN- $\gamma$  stimulation, M1 macrophages also increase mitochondrial gene expression [6]. Mitochondrial respiration enhances reactive oxygen species (ROS) production, which is necessary for an enhanced microbicidal activity of macrophages [7].

M2 (i.e., anti-inflammatory macrophages) polarize under type 2 cytokine stimulation (interleukin [IL]-4 and -13). M2 macrophages prefer fatty acid oxidation to energy metabolism as opposed to a classic activation and thus shows higher rates of mitochondrial mass and respiration. Oxidative phosphorylation (OXPHOS) inhibition dramatically reduces the M2 phenotype and alternative activation markers [8].

Adaptive immune cells respond in a highly specific manner against antigen presentation. Upon stimulation, these cells produce large amounts of cytokines and chemokines and improve the immune response by proliferating. This proliferation requires protein synthesis to support DNA replication, membrane formation, and organelles biogenesis.

Naïve T cells are metabolically active and require adenosine triphosphate (ATP) synthesis for survival and migration. They prime oxidase glucose and fatty acid via mitochondrial B-oxidation and OXPHOS [9] to reach the required levels of ATP. Once activated,

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cluster of differentiation (CD) 4+ T-helper cells switch their metabolic pathways to glycolysis and glutaminolysis to support rapid cell proliferation and increased cytokine production. In a glutamine-deprived medium, naïve CD4+ T cells, when stimulated, fail to differentiate to T helper 1 (Th1) and increased T regulatory (Treg) expression [9].

CD8+ cytotoxic T cells also assume a glycolytic metabolism after stimulation to sustain the effector functions. Inhibiting glycolysis [10] and activity of the mammalian target of rapamycin (mTOR) protein complex 1 (C1) [11] impaired effector cells formation and induced a memory cell phenotype. mTORC1 is responsive to amino acids, growth factors, and insulin, and regulates cellular anabolism (discussed below). mTORC1 is necessary for the initial differentiation of effector cells and the effector response activated by memory T cells. However, the hyperactivation of mTORC1 prejudices cells that transition into a memory state [12]. A memory CD8+ T cell induced-phenotype (by mTORC1 and glycolysis inhibition) enhances the antitumor function [10,12].

B-lymphocytes have many similarities with T cells (e.g., oxidative metabolism in quiescent state and glycolysis and mTOR activation when stimulated). Upon activation, these cells increase the consumption and production of the by-products alanine and glutamate [13], which is followed by an increase in glycolytic and amino acid that metabolizes enzymes up to 3 d after stimulation [14].

These results suggest that both T and B cells present a metabolic flexibility to adapt into different states of activation. Glucose is the main substrate required during cell stimulation; however, emerging ideas indicate that amino acids also play an important role in cell function.

## Immunonutrition

### Glucose

Glucose is the first substrate that cells metabolize to generate ATP rapidly. Moreover, glycolysis provides fast energy and produces nicotinamide adenine dinucleotide (NAD)<sup>+</sup>, which is converted to NAD-H and used by many enzymes and cofactors that support biosynthetic growth pathways [15]. To maintain the glycolysis flux, immune cells increase the expression of glucose transporter 1 to increase glucose uptake and reduce pyruvate to lactate despite oxygen (i.e., Warburg effect) [16] and maintain NAD<sup>+</sup> levels. Similarly, a large amount of glutamine is required to support the tricarboxylic acid (TCA) cycle.

T cells that are activated in a low-glucose medium reduce cytosolic Ca<sup>2+</sup> signaling, which leads to a defective activation [17]. Macrophages also require glycolysis for efficient phagocytosis and cytokine production. Furthermore, glyceraldehyde 3-phosphate dehydrogenase (GAPDH; glycolytic enzyme) is sensitive to glycolysis in T cell and can act by binding to RNA and inhibiting the transcription of some cytokines such as IL-2 and IFN- $\gamma$ . High rates of glycolysis impair GAPDH binding to IL-2 and IFN- $\gamma$  messenger RNA, which increases the transduction of these cytokines. On the other hand, low levels of glucose allow GAPDH to inhibit these proinflammatory cytokines [18] and decrease T effector function.

### Glutamine

Glutamine is the most abundant amino acid in the body, and it is essential for protein synthesis in all cell types. However, glutamine has a fundamental role in the metabolism of immune cells. During activation, immune cells quickly switch from oxidative to glycolytic metabolism and redirect glucose to glycolysis. At this point, glutamine is converted to  $\alpha$ -ketoglutarate in a process called glutaminolysis and enters directly into the TCA cycle to maintain

this pathway. Furthermore, glutamine is a nitrogen donor and is essential for purine and pyrimidine nucleotide synthesis. Glutamine also supplies glutathione, which facilitates the transport of amino acids [19].

A great deal of research has been undertaken to investigate the role of glutamine in immune cells. Culturing T lymphocytes in a glutamine-free medium completely abolished cell proliferation, activation, and IL-2 production [20], which replaced the medium with glutamate (glutamine-driven metabolite) or other amino acids, and did not restore T-cell functions [20]. These results demonstrated that T-cell proliferation is dependent on the presence of glutamine. Furthermore, activating T cells in a low glutamine-concentration medium induced FOXP3<sup>hi</sup> CD4 T (Treg marker) expression [21]. These FOXP3<sup>hi</sup> cells increased endogenous glutamine production to sustain cell functions, and blocking glutamine synthetase (GS; enzyme responsible for glutamine synthesis) abolished Treg cell resilience and proliferation [21].

Macrophages also require sufficient amounts of glutamine for proper activation. The M1 phenotype upregulates glucose and glutamine uptake to supply glycolysis and proinflammatory cytokine production, but M2 macrophages maintain an intact TCA cycle, which favors fatty-acid oxidation. However,  $\alpha$ -ketoglutarate from glutaminolysis is essential to support an anti-inflammatory macrophage phenotype. Glutamine deprivation has been shown to impair M2 markers' gene expression in mice macrophages. The phenotype was restored with the addition of a cell-permeable analog of  $\alpha$ -ketoglutarate [22]. Furthermore, glutaminolysis is also required during M1 activation to precipitate lipopolysaccharide-induced endotoxin tolerance.

However, M2-like macrophages increased the expression of GS compared with M1-induced phenotype, and when GS was inhibited in M2 macrophages, the cells started to express M1 markers and assumed M1 metabolism [23]. In addition, the authors observed that monocytes cultured in a low-glutamine medium increased GS activity in a feedback mechanism and consequently enhanced M2 markers. These data suggest that glutamine availability can control macrophage-induced phenotypes, and keeping the balance between M1 and M2 activation is essential to maintain a proper resolution of infections.

### Amino acids

Branched chain amino acids (BCAAs) are composed of leucine, isoleucine, and valine that are classified as essential amino acids. Essential amino acids are not synthesized by cells, but must be supplied in the diet. However, BCAAs are necessary to regulate muscle synthesis protein via mTOR and inflammatory responses [24].

Leucine transport inside the cell is dependent on glutamine efflux through the complex Slc7a5 (LAT1) and Slc3a2. Whereas LAT1 transports leucine across the membrane intracellularly in lymphocytes, Slc3a2 is responsible for the extracellular exit of glutamine [25]. Inside the cell, leucine is required for mTORC1 activation and T-lymphocyte proliferation [26]. A leucine antagonist promotes similar effects to mTORC1 inhibition, such as reducing cytokine production and cell cycle arrest [26].

In macrophages, leucine can improve mitochondrial respiration and ATP production [27]. Leucine modulates the energetic status of the cell, which is used for protein synthesis or degradation, and the amino group can be transferred to  $\alpha$ -ketoglutarate, which leads to energy production [28]. Papanthanasius et al [29] blocked branched chain-amino transferases (enzymes responsible for catabolism of BCAA) in human macrophages, which resulted in low oxygen consumption and glycolysis.

## AMPK and mTOR pathways regulating immune fate

Adenosine monophosphate–activated protein kinase (AMPK) and mTOR are two important metabolic regulators that work in opposing ways to orchestrate cellular response. The balance between these enzymes is a key controller of cellular homeostasis (Fig. 1).

AMPK is a complex kinase that it is activated under catabolic conditions when the AMP:ATP ratio is increased. At this point, AMPK increases the catabolic processes that generate ATP (i.e. OXPHOS) and decreases the anabolic processes that consume ATP (i.e., amino acid synthesis). Activated immune cells require high amounts of substrates to keep ATP at an appropriate level for proliferation and cytokine production. Glucose and glutamine deprivation have been observed to result in AMPK activation in stimulated T cells [30].

Recent studies have demonstrated that AMPK is a key metabolic regulator of T cells, allowing for metabolic plasticity to adapt to an energy stress that is found in an inflammatory microenvironment [31]. In CD8 T cells, AMPK knockout causes several defects in the generation of memory [30]. Memory CD8+ T cells play a key role in mounting a quick and efficient response to infections and as a tumor suppressor [32]. Furthermore, T lymphocytes from AMPK $\alpha$ 1-KO mice presented higher sensitivity to metabolic stress, but exhibited normal cytokine production when stimulated [33]. These results clarified the notion that AMPK is essential for ATP homeostasis, but not required for cell-effector function, and can occur because activated AMPK switches off almost all anabolic pathways, including mTOR, which is indispensable to cell activation and proliferation. mTORC1 is primordial to immune-cell activation and proliferation. In T cells, mTOR signaling is essential for effector cell differentiation (Th1 and Th17) [34]. Suppressed mTORC1 activation in a mouse model led to low macrophage numbers in bone marrow, impaired monocyte-to-macrophage differentiation, and inhibited the macrophage phagocytosis ability [35]. However, constant activation of mTOR can be detrimental because of increased reactive oxygen species and further induction of cell senescence. Furthermore, studies have shown that the pharmacologic inhibition of mTOR (by rapamycin treatment) increased IL-12 production by mouse dendritic cells and human T cells [36,37]. IL-12 is a key immunomodulatory cytokine that induces Th1 differentiation and IFN- $\gamma$  production. mTOR is activated mainly by growth factors and insulin signaling; however, mTOR activity also depends on the availability of certain amino acids (e.g., leucine). In the absence of amino acids, mTORC1 signaling is decreased even in the presence

of growth factors [38]. Amino acids act through sensors to promote mTOR activation, especially through leucine and arginine cytosolic sensors. In lymphocytes, mTORC1 activity is sensitive to leucine concentration. T cells that lack leucine transaminase present higher intracellular leucine concentrations, followed by increased mTORC1 activation and higher glycolysis rates [39]. Furthermore, a CD8+ T-cell-cultivated medium without an amino-acid medium gave rise to impaired mTOR phosphorylation, and the addition of leucine (0.4 mM) completely restored mTOR activity [40].

Therefore, an appropriate amino acid concentration appears necessary for efficient mTOR function, especially at the initial stages of immune-cell activation. However, keeping mTOR activity for a prolonged period of time can increase oxidative stress and drive cells to an immunosenescent phenotype, resulting in impaired antigen recognition, phagocytosis, and cytokine production. Moreover, mTOR inhibits AMPK phosphorylation and, consequently, decreases regulatory and memory-cell formation (Fig. 2).

## Exercise and the immune system

### Exercise as an immunomodulatory agent

Exercise has immunomodulatory actions. Acute exercise increases the total numbers of leucocytes in the blood, and neutrophils are mainly responsible for this situation. From zero to 3 h after a single bout of aerobic exercise, the total leucocyte numbers enhanced two- to threefold and returned to baseline levels within 24 h after exercise sensation [41].

Not only are the total circulating numbers increased during recovery after prolonged exercise, but cell function is also decreased. CD4+ and 8+ T cells fail to migrate after a 2 h treadmill run [42]. T-cell proliferation is also reported to decrease during and after exercise, as does the lymphocyte response to an antigen challenge. Furthermore, monocyte phagocytosis is impaired after exhaustive prolonged exercise [43], and 2 h of cycling at 80% VO $_{2max}$  decreased the neutrophil oxidative burst [44]. Moderate exercise volume, however, has an immunostimulatory effect. Neutrophil and monocyte phagocytosis was enhanced immediately after a submaximal prolonged exercise [45].

These results indicate that, in relation to exercise, the immune response depends on exercise intensity and duration, and therefore it is not surprising that endurance athletes are more vulnerable to illness up to 72 h after completing a race. This is known as the Open window hypothesis, proposed by Pedersen and Bruunsgaard, and

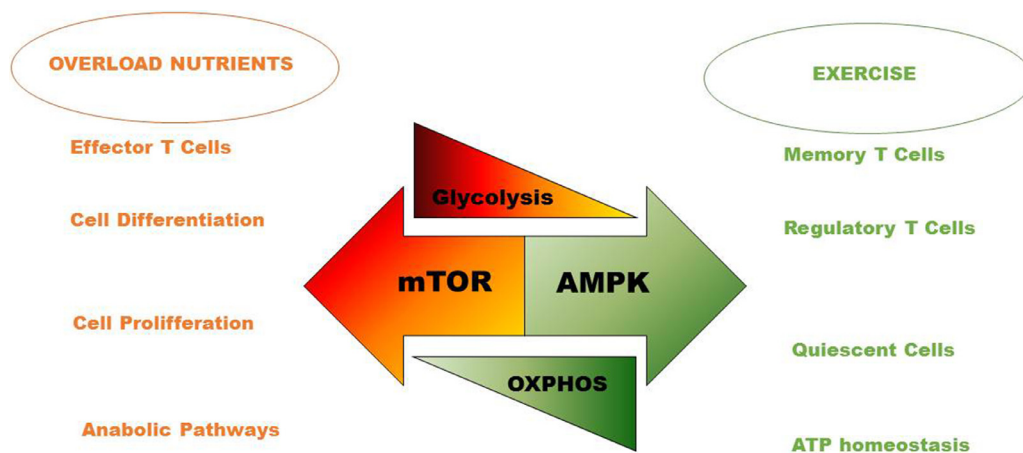
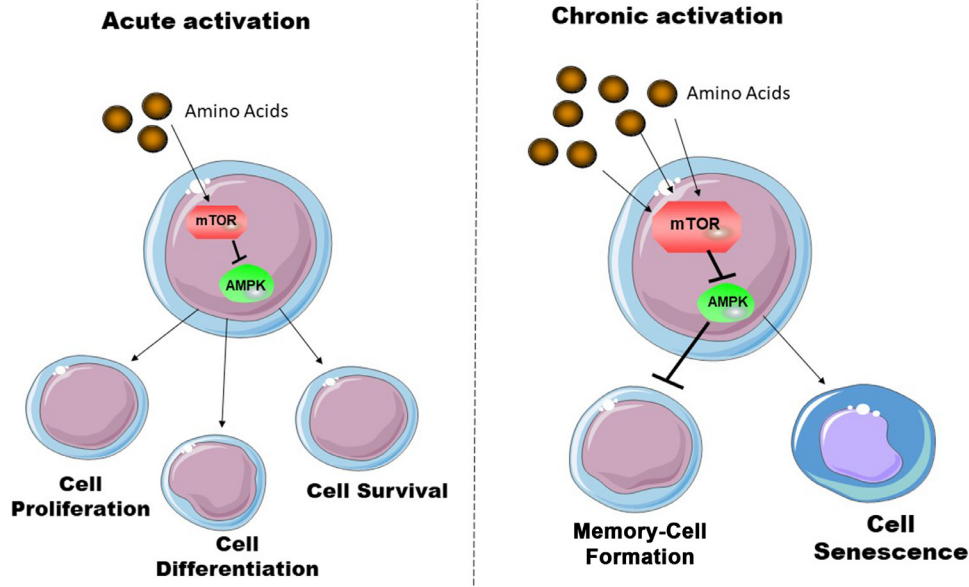


Fig. 1. Immune cells can easily change metabolic pathways depending on substrate viability and stimulations.



**Fig. 2.** During initial cellular activation, mammalian target of rapamycin signaling is required to provide cell proliferation, differentiation, and cell survival, for which amino acids are essential. However, super activation of mammalian target of rapamycin during prolonged periods can lead to a deep adenosine monophosphate-activated protein kinase inhibition, which impairs memory-cell formation and induces early cell senescence.

coincides with the period when numbers and function of immune cells are impaired [46]. Furthermore, repeated single bouts of strenuous exercise without proper recovery can prolong this open window, and culminate in chronic immunodepression [46].

Nevertheless, exercise intensity and duration is not only important for the immune response, but also for nutritional status. As discussed earlier, immune cells are tightly regulated by substrate availability, and exercise-induced decreases in glucose and amino acid concentrations can contribute to immune system impairment.

#### *Exercise, nutrient availability, and immune function*

During exercise, there is a huge glucose utilization to maintain the heart rate and muscle contraction, which leads to a decrease of this substrate in the bloodstream. Glutamine concentration is also affected. Glutamine is mainly synthesized, stored, and released by the skeletal muscle, and repeated muscle contraction can increase the TCA cycle intermittent flux, which leads to glutamine synthesis and release. Therefore, moderate intensity training has been associated with increased glutamine availability [47].

However, high intensity and prolonged exercise play opposing roles. An acute bout of high intensity interval exercise decreases serum glutamine concentration compared with basal levels [48], and prolonged, exhaustive exercise has a profound negative effect on glutamine concentration compared with exercise of a shorter duration [49]. Furthermore, glutamine concentration in the muscle of rats was markedly reduced 24 h after exhaustive exercise [50]. These results were followed by a decrease in GS, which suggests an impairment in muscle glutamine synthesis after exhaustive exercise. Blomstrand and Essen-Gustavsson [51] provided further evidence by showing that glutamine levels were reduced in both types I and II muscle fibers in humans, 2 h after submaximal resistance exercise. In addition, overtrained athletes have shown a marked decrease in glutamine levels, even at rest, compared with adequately trained athletes. The plasma concentration of glutamine appears to be a marker for impaired immune cell function [52].

A decline in substrate availability has a direct impact on the function of immune cells. Performing a single bout of exercise in low-glycogen conditions or after a few days on a low carbohydrate diet decreased T cell, natural killer cell, and neutrophil function compared with exercise performed during a diet of normal cholesterol [53]. Both the plasma concentration of glutamine and immune-cell function decrease after prolonged, exhaustive exercise. However, several studies have found no relation between glutamine and aspects of exercise-induced immunodepression [54]. Recently, sufficient glutamine availability has been suggested to combat postexercise decreases in immune function after endurance events [54,55].

As discussed earlier, a fall in the concentration of nutrients has been suggested as one of the mechanisms for the open-window condition, which increases the risk of upper respiratory tract infection (URTI). In this context, supplementing individuals with carbohydrate or amino acids has emerged as a strategy to avoid exercise-induced immunodepression.

In the early 1990s, oral L-glutamine ingestion attenuated the exercise-induced decrease in plasma glutamine concentration [56]. Researchers speculated that glutamine supplementation could restore immune function and decrease the incidence of susceptibility to URTIs [56]. Many studies have shown that, in individuals who take glutamine versus placebo, glutamine supplementation was able to maintain the plasma glutamine concentration after an exhaustive exercise intervention, but there was no link with improving immune cell function or trafficking [57–59].

However, recent studies on rats have found that glutamine supplementation reduces oxidative stress [60] and muscle damage and inflammation [61] after prolonged exercise. Furthermore, despite plasma concentration increase not being directly related to improvements in immune function, athletes who supplemented with glutamine reported a lower incidence of URTIs than those who received placebo [56]. Interestingly, 10 wk of BCAA supplementation (precursor for glutamine) had a positive effect on neutrophils in trained cyclists [62].

Glucose supplementation during and after prolonged exercise seasons have positive effects on immune cell function. The intake of 30 or 60 g/h of carbohydrate during 2.5 h of cycling restored the CD4+ and 8+ T-lymphocytes production of IFN- $\gamma$  [63]. Moreover, the ingestion of carbohydrates before, during, and after exhaustive exercising, performed during 2 consecutive days, enhanced lymphocytes proliferation in response to an antigen-stimulation and increased T-cell proliferation on the second day [64].

All these findings suggest that a suitable dietary intake of amino acids and carbohydrates is required to keep immune functions in response to exhaustive exercise. Carbohydrates appear to have a positive acute answer because its intake before, during, and after exercising can avoid immune depression. Glutamine has a direct impact on the improvement of muscle regeneration, immune function, and the intestinal barrier.

## Conclusions

Prolonged and strenuous aerobic exercise induces a marked decrease in plasma concentration of glucose and amino acids, which can lead to immunodepression. In this case, the maintenance of nutrient availability during and after vigorous exercise is essential for proper immune system control, which is coordinated by nutrient sensors (i.e., AMPK and mTOR) and metabolic pathways (i.e., glycolytic or oxidative phosphorylation) in immune cells.

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