Immunometabolism-fit: How exercise and training can modify T cell and macrophage metabolism in health and disease

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ABSTRACT

Background: The term immunometabolism describes cellular and molecular metabolic processes that control the immune system and the associated immune responses. Acute exercise and regular physical activity have a substantial influence on the metabolism and the immune system, so that both processes are closely associated and influence each other bidirectionally.

Scope of review: We limit the review here to focus on metabolic phenotypes and metabolic plasticity of T cells and macrophages to describe the complex role of acute exercise stress and regular physical activity on these cell types. The metabolic and immunological consequences of the social problem of inactivity and how, conversely, an active lifestyle can break this vicious circle, are then described. Finally, these aspects are evaluated against the background of an aging society.

Major conclusions: T cells and macrophages show high sensitivity to changes in their metabolic environment, which indirectly or directly affects their central functions. Physical activity and sedentary behaviour have an important influence on metabolic status, thereby modifying immune cell phenotypes and influencing immunological plasticity. A detailed understanding of the interactions between acute and chronic physical activity, sedentary behaviour, and the metabolic status of immune cells, can help to target the dysregulated immune system of people who live in a much too inactive society.

Keywords: Immune System; Inflammation; Metabolism; Exercise; Sedentary behavior

Abbreviations: AMPK: 5' AMP-activated kinase; mTORC1: mTOR complex 1; HIF-1α: hypoxia inducible factor-1α; PPAR-γ: peroxisome proliferator-activated receptor gamma; ATP: adenosine triphosphate; PI3K: phosphoinositide 3-kinase; IFN-γ: interferon gamma; mTOR: mammalian target of rapamycin; IL: interleukin; CD: cluster differentiation; LPS: lipopolysaccharide; TLR-4: toll like receptor 4; TCR: T cell receptor; BCAA: branched-chain amino acids; PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; NF-kB: nuclear factor kappa B; AP-1: activator protein 1; STAT: signal transducer and activator of transcription; PBMC: peripheral blood mononuclear cells; WBC: white blood cells; TGF-β: transforming growth factor beta; FFA: free fatty acids; UPR: unfolded protein response; OXPHOS: oxidative phosphorylation; TNF-α: tumor necrosis factor alpha; CRP: C-reactive protein; BMI: body mass index; TAK: transforming growth factor-B-activated-kinase; TAB: TAK1-binding protein-1; IKK: IkB kinase; JNK: c-Jun N-terminal kinase; IRS: insulin receptor substrates; NLRP3: pyrin domain-containing protein 3; LDL: low density lipoprotein; ER: endoplasmic reticulum stress; HSP: heat shock proteins; MAPK: mitogen-activated protein kinases.

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INTRODUCTION

The term "immunometabolism" was coined in 2011, describing an emerging research topic focused on understanding the metabolic pathways used by immune cells in response to challenges (e.g., pathogen exposure, inflammation), and their ability to crosstalk with metabolic tissues [1]. Immune cells show high metabolic flexibility with different subsets of lymphocytes, monocytes/macrophages, and neutrophils exhibiting deep metabolic alterations when moving from the resting to the activated state. Both the aging process and numerous infectious diseases, as well as diseases accompanied by chronic inflammation, are associated with changes in the metabolic function of leukocytes [2,3]. For example, HIV and COVID-19, cancer, cardiovascular and neurodegenerative diseases, obesity, and type 2 diabetes are morbidities associated with dysregulation in the metabolic response of immune cells. This, in turn, causes metabolic derangements in immune cells leading to a 'vicious cycle' of inflammation and disease progression [4–6]. Various lifestyle-associated diseases with an excess or lack of nutrients are associated with a modified immune response. Chronic hyperglycemia associated with excess release of amino acids and fatty acids into the circulation causes a chronic activated immune system [7,8]. In many conditions including SARS-COV-2 infection, an excess of nutrients (especially fats and glucose) reduces the ability to immune cells to resolve inflammatory conditions potentially increasing the likelihood of immunological overreaction, which might favor massive and unregulated cytokine secretion (a "cytokine storm") [9]. On the other hand, undernourishment can also be associated with a poor immune response given the importance of nutrients for basic functions of immune cells including proliferation [10]. Consequently, an adequate supply of substrates and nutrients is important for the balanced control of immunometabolism [11,12].

Prolonged physical inactivity is associated with a reduction in life expectancy and quality of life [13,14]. Physical inactivity favors development of visceral adiposity, and causes imbalances in the production of adipokines, myokines, hepatokines and other mediators of inflammation [15]. Sedentarism is considered a catalyst for development of low-grade inflammation associated with various lifestyle diseases. In contrast, a physically active lifestyle can positively stimulate various aspects of immune function on a clinical, cellular, and molecular level to reduce low-grade inflammation [16]. Acute exercise (especially aerobic exercise) induces the release of multiple signaling molecules (e.g., cytokines, hormones) and alters substrate and nutrient concentration in the immune cell environment [17]. Particular importance is attached to the secretome of skeletal muscles. For this purpose, the term "exerkines" was introduced as a collective term, covering any biomolecules such as peptides, metabolites and RNAs, secreted into circulation by tissues in response to exercise [18].

Regular exercise contributes to a balanced immunological state that can serve as an effective countermeasure against the development of chronic low-grade inflammation, particularly in older adults and those living with obesity and/or metabolic disease [19]. Understanding how exercise affects immunometabolism is a recent scientific endeavor, and there is a critical need to ascertain the metabolic processes and pathways by which the immune system responds to acute exercise and adapts to exercise training. The immunometabolic rearrangement of lymphocytes and macrophages in well-trained humans may have the potential to regulate immune response in chronic inflammatory diseases, such as obesity, cancer, cardiovascular and neurodegenerative diseases, and to delay immunosenescence.

In this review, we examine the complex interplay between immunometabolism and exercise with a focus on T cells and macrophages, and present new challenges and opportunities for this field. Our focus here ranges from the acute effects of single bouts of exercise, to the chronic effects of regular physical activity, and exercise training for fitness and sports. We review the immunometabolic regulators in immune cells (AMPK, mTORC1, HIF-1α and PPAR-γ) and examine the role and potential impact that exercise can have on the metabolism and function of lymphocytes and macrophages, and their interplay with skeletal muscle. Finally, we discuss the impact of sedentarism on immunometabolism, and how these effects can potentially be counteracted with exercise to reduce cardiometabolic risk factors and immunological aging. We examine the effect of both acute exercise (in the hours after a single bout of exercise), and the long-term effects of exercise training and regular physical activity on immunometabolism. Concepts in immunometabolism are inherently interdisciplinary and can be viewed from the perspective of how alterations in: a) molecular metabolic pathways and sensors within immune cells; and/or b) the global metabolic environment and impact immune cell function. In this review we have attempted to balance and integrate these perspectives, highlighting key molecular signaling pathways and how they may relate to, or be influenced by, whole-body metabolic changes initiated by changes in exercise, sedentary time, chronic disease, and aging.

IMMUNOMETABOLIC SENSORS

Molecular regulation of immunometabolism is associated with sensors that control the metabolic routes, inflammatory mediators, and differentiation and function of immune cells. Thus, the immunometabolic sensors are an important bridge that link metabolism and immunology particularly in lymphocytes and macrophages. Nutrient sensors are largely modulated by different intra- and extra-cellular concentrations of glucose, amino acids and fatty acids (and their intermediary metabolites). The levels of nutrients that immune cells are exposed to influence different intracellular energetic sensors, principally AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), hypoxia inducible factor-1α (HIF-1α) and peroxisome proliferator-activated receptors (PPAR) [8].

AMPK

AMPK is an enzyme that acts as the energetic sensor of eukaryotic cells. A low ATP:AMP ratio increases AMPK activity [20], and subsequently fatty acid oxidation and ATP generation by the electron transport chain [21]. Moreover, AMPK inhibits the PI3K/AKT/mTOR pathway, essential for aerobic glycolysis. Immune cells in resting form (naïve T Lymphocytes and memory T or B lymphocytes) show strong activation of AMPK [22].

It is well established that AMPK is activated in different tissues, such as skeletal muscle, liver and adipose tissue after acute exercise and regular exercise training. While there are limited data for AMPK regulation after acute exercise or in regular exercise training in leukocytes, various regulatory effects of AMPK in immune cells have been shown. During T cell receptor (TCR) and CD28 co-stimulation in T lymphocytes, the activity of AMPK is upregulated. This increase in AMPK activation after TCR stimulation is fast, and then blunted during the effector phase [23]. Activation of AMPK reduces the release of IFN-γ by T effector lymphocytes. Moreover, AMPK is important for the fate of T cells. The reduction of AMPK and increase in mTOR induces the differentiation of the effector subset of CD8 lymphocytes, while an increase in AMPK and reduction in mTOR lead to long-lived memory CD8 T cells. Regarding CD4 cells, activation of AMPK induces the production of regulatory T cells (Tregs) and inhibits the differentiation of Th17 lymphocytes. Moreover, IL-10 induces AMPK activation particularly after acute bouts of exercise [24,25]. In this framework, well-trained subjects can have a lower Th1:Th2 ratio, which represents an aspect of the anti-inflammatory T cell profile specifically promoted by regular endurance training [26].

In terms of B cells, AMPK signaling is essential to mitochondrial homeostasis. For this cell type, a loss of AMPK can reduce antibody production. Accordingly, AMPK signaling appears to be of particular importance, especially for long-lived memory B cells [27]. A physically active lifestyle can enhance antibody production after vaccination in older adults [28]. The discovery of mechanisms associated with this improvement is important for new adjuvant therapies to increase the immunization response in the elderly [28,29].

In macrophages, activation of AMPK is an important mechanism to induce a shift to acquire the alternative and anti-inflammatory phenotypes (formely named M2), that are characterized by the production of anti-inflammatory mediators (IL-10, and IL-1ra) and growth factors (TGF-beta) [30]. Several anti-inflammatory drugs, such as salicylates, metformin, and corticosterone, blunt an inflammatory response and induce the acquisition of an anti-inflammatory/restorative phenotype by activation of the AMPK pathway [31–33]. Particularly, activation of dopaminergic signaling (more specifically by the D1 receptor) induces AMPK activation, leading to a shift in macrophage inflammatory phenotype [34].

mTORc1

mTOR is a highly conserved protein complex that can phosphorylate different targets [35], which exists in two sub-complexes called mTORC1 and mTORC2. mTORC1 is an energetic sensor that acts in opposition to AMPK [36], and is positively regulated by amino acids (e.g., leucine) and growth factors via the PI3K/AKT pathway [35]. Moreover, mTORC1 is a complex protein that induces the anabolic pathways and participates in the regulation of lipids, protein, and glycogen synthesis.

Aerobic glycolysis is critical for sustaining the effector functions of lymphocytes, which is in turn dependent on mTORC1/HIF-1α (Nieman and Pence 2020). mTORC1 deletion in CD4 lymphocytes reduces their proliferation and impairs their effector functions [22]. Moreover, mTORC1 inhibition increases Foxp3 activity and Treg numbers [37]. mTORC1 is essential for the differentiation of naïve T lymphocytes into CD4 and CD8 T effector lymphocytes, as well as antibody production by B lymphocytes [38].

The knowledge of the role of mTORC1 is inconclusive regarding the polarization to classic or alternative phenotype. Glycolysis stimulated by the mTORC-1/HIF-1α pathway is essential for mounting a pro-inflammatory response and production of reactive oxygen species [39]. Moreover, LPS-TLR4 canonical signaling, nutrient excess by inflammasome, and pro-inflammatory cytokines, all induce mTORC-1 [39,40]. While mTORC-1 is considered an essential player for classically activated macrophages (M1), that produce pro-inflammatory cytokines (IL-1β, TNF-α) and lipid mediators (PGE2), specific deletion of raptor can block mTORC1 pathway. Macrophages treated with rapamycin exhibit a more inflammatory phenotype, and show impaired acquisition of the alternative phenotype [41,42]. High intensity exercise decreases the circulating levels of branched chain amino acids (BCAAs) in endurance athletes [43]. It is well established that BCAAs can activate the mTORC. Therefore, reduced BCAA availability could also facilitate reduced immune cell activity [40]. Glutamine activates mTORC1 through a Rag GTPase-independent mechanism [44]. Serum glutamine is reduced after exhaustive exercise, and supplementation of endurance athletes with BCAA mitigates the reduction in glutamine. Furthermore, BCAA administration can divert cytokine production towards Th1 type response after exercise [45].

In summary, the maintenance and fine-tuning of mTORC-1 signaling is necessary, whereas chronic activation or deletion/inhibition of mTORC1 induces a pro-inflammatory response, and in combination with other players, this sensor is an important determinant of immune cell fate. mTORC-1 and HIF-1α are essential for activation of aerobic glycolysis and thus induces and supports inflammation. mTORC-1 and PPAR-γ/PGC1α are important for reprogramming the metabolism mediated by mitochondrial biogenesis and anti-inflammatory responses [46]. The type, intensity and duration of exercise are likely important in regulating mTORC activation in immune cells by modifying substrate availability.

HIF-1α

HIF-1 is a family composed by three isoforms of α and β subunits of a heterodimeric transcription factor that senses cellular oxygen [47]. HIF-1 is expressed in most immune cell types and essential for immunometabolic flexibility and the inflammatory response [48]. mTORC-1/HIF-1α pathway is essential to trigger glycolysis during TCR activation in CD4 lymphocytes, and cytotoxic activity of CD8 lymphocytes [49,50]. Furthermore, HIF-1α is necessary to induce the Th17 differentiation, while inhibition of this transcription factor is observed in Tregs [47].

HIF-1α is essential in development of B cells. Given that the germinal centers of B cells are hypoxic, HIF-1α plays a role in the induction of B cell development [51]. Moreover, HIF-1α is necessary for IL-10 production and CD-11b expression in B cells, and lack of HIF-1α reduces the anti-inflammatory signaling between B cells and dendritic cells, otherwise promoting inflammation [47,52].

HIF-1α deletion reduces ATP levels and bactericidal function in macrophages stimulated by LPS [53]. Macrophages can function in a hypoxic environment, but this ability is depen-

dent on HIF-1α expression. In normoxic conditions, LPS stimulation promotes HIF-1α nuclear activity with upregulation of the glycolytic and pentose phosphate pathways (PPP). Moreover, overexpression of HIF-1α induces the M1 phenotype [54]. While succinate, an intermediary of the Krebs cycle, induces HIF-1α stabilization and M1 activation of macrophages [55], itaconate, generated by catabolism of cis-aconitate in mitochondria, inhibits the HIF-1α pathway and activates the alternative phenotype of macrophages [56,57].

Most data regarding the regulation of HIF-1α during exercise has come from studies of skeletal muscle. Within this tissue, acute bouts of exercise stabilize HIF-1α, and HIF-1α response is blunted during long-term exercise training, as part of a local physiological response to exercise [58]. The effect of acute or chronic exercise on HIF-1α expression in leukocytes remains uncertain. Elevated serum IL-10 after high volume training [25] increases CD11b expression by monocytes [59], contributing to the notion that physical fitness could modulate the effects of HIF-1α on monocytes. However, another study did not find differences in monocytes between low and high VO2max subjects, pre or post-acute exercise session, with and without LPS stimulation [60].

PPAR-γ

PPARs are a family (PPAR-α, PPAR-β and PPAR-γ) of transcription factors responsible for regulating lipid metabolism (lipogeneses, lipid mediators, synthesis, and fatty acid oxidation) [61]. The three different isoforms of PPARs exert various regulatory roles in immune cells. However, the most studied isoform is PPAR-γ and its effects on metabolism of immune cells. Expression of PPAR-γ is increased in both lymphocytes (Th2) and macrophages (M2) [62,63]. Although the fatty acid synthase and de novo lipogenesis is essential in early effector response of lymphocytes after TCR stimulation, this step is regulated by mTORC1/SREBP axis and not affected by PPAR-γ deletion in T cells [64]. On the other hand, the activation of PPAR-γ impairs the clonal expansion of effector T cells [65].

The maintenance of fatty acid metabolism necessary to promote the effector function of Th2 cells is dependent of PPAR-γ [62]. AP-1, STAT5, GATA-3, IL-5 and IL-13 are all target genes of PPAR-γ in Th2 cells [66]. PPAR-γ is necessary to increase the fatty acid uptake, lipolysis and glycolysis in Th2 cells. Activation of PPAR-γ activates downstream mTORC1 in this lymphocyte subset [64]. For Tregs, PPAR-γ is not essential for differentiation of all its subsets. However, the expression of FOXP-3 and Treg differentiation is dependent of PPAR-γ expression in Tregs residents on adipose tissue and deletion of this subset by specific KO of PPAR-γ on Foxp3 flox, and induces a range of metabolic disturbances [67]. Moreover, agonist or inhibitor effects of PPAR-γ reduce the expression of Foxp3, indicating that PPAR-γ expression should be within the specific range for Foxp3 activation and lymphocyte differentiation into Tregs [68]. PPAR-γ induces the expression of genes that increase mitochondria biogenesis and oxidative metabolism, and reduces the transcription of pro-inflammatory genes by the repression of NF-kB, AP-1 and STAT family [69].

Concerning exercise, moderate aerobic trained mice with PPAR-γ deletion in myeloid cells show a reduced subset of macrophages expressing CD206 in subcutaneous adipose tissue macrophages as compared with trained wild type mice [70]. In obese mice, despite the absence the PPAR-γ expression in myeloid cells, aerobic training increases the concentration of anti-inflammatory cytokines, but the expression of surface markers (e.g. CD206) remained low as observed in non-obese mice [61]. Finally, PPAR-γ expression in monocytes appears to be dependent of physical fitness level, given that monocytes from high VO_2 max subjects show increased PPAR-γ mRNA after LPS stimulation [60]. An anti-inflammatory profile of macrophages is observed in endurance athletes and may be induced by PPAR-γ, although further confirmation is required. In the same study, rosiglitazone (PPAR-γ agonist) increases mRNA expression of AMPK in monocytes, providing evidence that these two energetic sensors may act synergistically [60].

THE COMPLEX ROLE OF EXERCISE ON THE METABOLIC FUNCTION OF IMMUNE CELLS

A recent multi-omics approach indicates intensive crosstalk between immunity and metabolism during exercise [71]. Various molecules are affected by acute exercise and T cells are highly sensitive to changes in their microenvironment [72]. There is emerging evidence that exercise-induced alterations directly and indirectly affect T cell immunometabolism.

Effects of exercise on T cell metabolism

Exercise training improves TCR activation signal and increases the expression of Zap70 in peripheral blood mononuclear cells (PBMC)s [73]. Correspondingly, intracellular calcium stores and proliferative capacity of CD3+ cells are increased by chronic voluntary exercise in mice [74]. A potential mechanism is that exercise itself induces a mild T cell activation, as increased expression of CD25, a typical activation marker of T cells, has been reported in humans after acute moderate intensity endurance and resistance exercise combined, and resistance exercise alone [75]. Another explanation is that an acute bout of exercise activates the TCR and the TCR signal quality associated with increased body temperature [76]. Overall, an effect of exercise on TCR activation and function is likely but remains to be shown conclusively.

Depending on the exercise type, intensity, and duration, cytokine signatures and substrate availability can be affected [25,77]. TGF-β1 [78], IL-6 [79], IL-1β, and IL-23, which are released in response to muscle damage, play an essential role in T cell metabolism and differentiation [80]. Lactate accumulation, which increases after acute bouts of high-intensity exercise, increases STAT3 activity followed by increased Th17 polarization of lymphocytes [81]. Similarly, endurance exercise alters the Th17/Treg balance towards Th17 [82].

During exercising in a fasted state or for a long duration without adequate carbohydrate supplementation, a very large neuroendocrine response is observed to ensure that the blood glucose level is maintained. Thus, we observed the impact on immune-neuroendocrine response by elevation in cortisol levels that induces an immunosuppressive response [83]. Moreover, the levels of glucose, as one of the main substrates of T cells, facilitates T-cell activation. While blood glucose levels can remain relatively constant, however, it is possible that the

glucose and amino acids levels are reduced in lymphoid organs, whereas the blood flow is reduced to central organs to provide the increase of blood flow in skeletal muscle, although this hypothesis has yet been evaluated fully. Therefore, during low glucose conditions, activated naïve T cells and central memory T cells reduce their function, including lowering of IFN-γ expression. During conditions of glucose deprivation, these cells increase OXPHOS and fatty acid metabolism by upregulating the expression of the FFA transporter CD36, increasing autophagy, and utilizing glutamine for biosynthesis [84]. However, athletes may be at higher risk for immunosuppression at the onset of overtraining, when plasma glutamine concentrations decrease, such as after 8 weeks of high-intensity interval exercise [77]. Glutamine, next to glucose, is essential for the hexosamine biosynthesis of T cells and for their proliferation [85]. Exercising in a well-nourished state should not put athletes at a higher risk of immune dysregulation by maintaining the availability of substrates for T cell activation.

Besides macrophages and neutrophils, the anti-tumoral effect of acute and chronic exercise is largely dependent on the CD8 cytotoxic T cells [86]. Moreover, acute exercise modifies metabolites in the circulation in both humans and mice. Addition of malate, succinate and fumarate reduces the expression of the surface marker CD62L on cytotoxic CD8. Low expression of CD62L occurs after TCR activation of the CD8 cytotoxic T cells [86]. Moreover, lactate induces the migratory capability and increases granzyme B production in a dose-dependent manner in CD8 cytotoxic cells. Finally, in a murine model of cytotoxicity induced in an ovalbumin vaccination model, 20 min of aerobic exercise increases pyruvate and alpha ketoglutaric acid derived from glucose metabolism and consequently improvement the cytotoxic CD8 cells response after vaccination [86]. Remodeling of metabolism in lymphocytes may be important in the anti-tumoral response induced by acute exercise. A proposed model of mechanisms supporting future research in exercise immunology is presented in Figure 1.

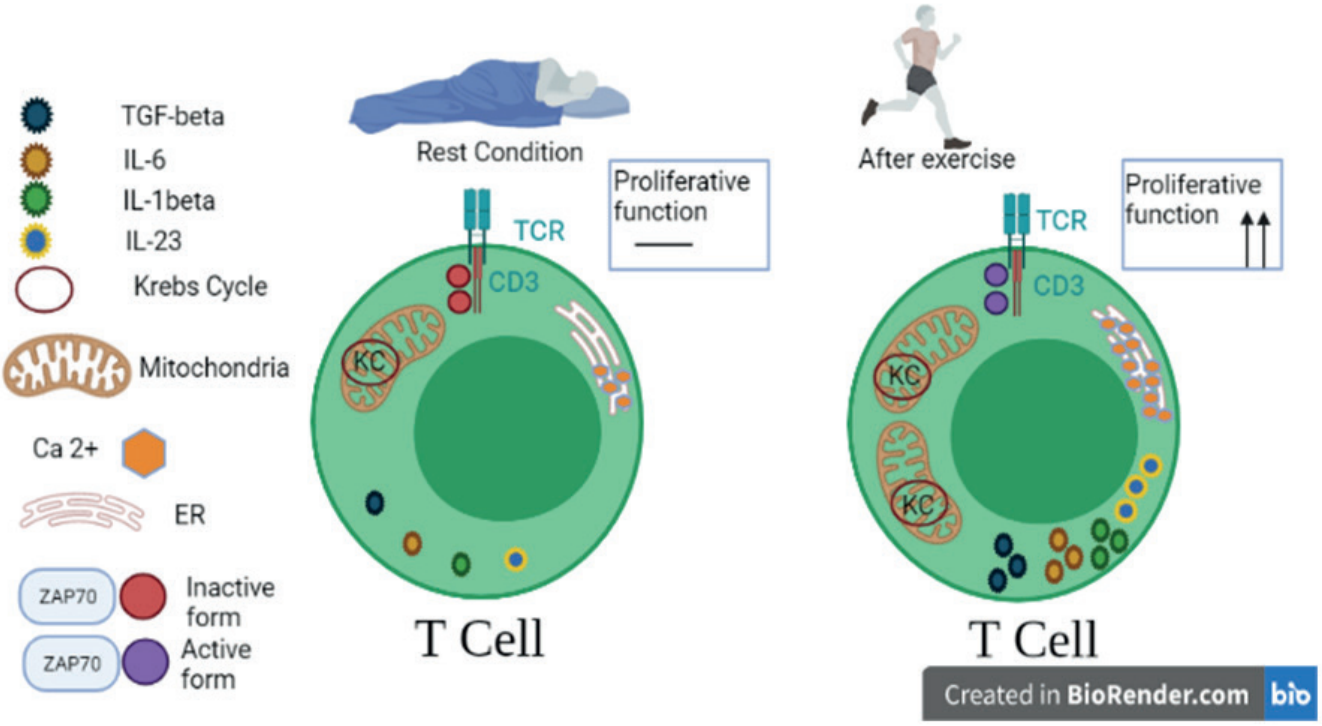

Figure 1. Molecular mechanisms that influence T cell metabolism during acute stress.

Effects of exercise on macrophages

The role of metabolic plasticity in the fate of macrophage phenotype is well characterized. While classical macrophage activation is induced by aerobic glycolysis, the alternative phenotype is induced by a proportional increase in oxidative metabolism [87]. Moreover, different macromolecules and metabolites, which are affected by acute exercise, are potent regulators of macrophage function [8,88,89]. Lactate-treated macrophages show a reduction in glycolysis and an increased fatty acid oxidation. Moreover, they show increased phagocytic function against Mycobacterium Tuberculosis and reduced TNF-α and IL-1ß production after LPS stimulation [90]. Besides lactate, glutaminolysis is essential for efficient clearance of apoptotic cells [91]. Studies also show that amino acids and several fatty acids are immunomodulating agents for macrophages [92,93]. Mode, intensity, duration of exercise, and fitness levels can differentially modify cytokine secretion and availability of various metabolites. Understanding the detailed metabolic effects these changes have on macrophages will further characterize mechanistic links between exercise and immune function [71].

The anti-inflammatory effects of aerobic exercise training and its role in the treatment and prevention of metabolic and chronic inflammatory diseases is influenced by macrophage function. The first step for macrophage activation is chemotaxis of monocytes. Data show that improvement in physical fitness mitigates the migration of pro-inflammatory monocytes in patients with central obesity [94]. Aerobic exercise training promotes alternative phenotypes and decreases classical macrophages in the obese adipose tissue [95]. A 16-week program of treadmill exercise, in high fat diet (HFD) treated mice, de-

creases CD11c gene expression (pro-inflammatory marker) and increases CD163 (anti-inflammatory marker) in adipose tissue macrophages [95]. Both continuous and interval aerobic training induce pro- to anti-inflammatory transition and increase the total number of anti-inflammatory macrophages in adipose tissue of high fat diet (HFD)-treated rats. However, in the same study, interval training was more effective than continuous training [96].

tion of mitochondrial biogenesis and increased mitochondrial activity in immune cells via β-AR stimulation [97]. Mice that receive daily catecholamine injections, increase the anti-inflammatory phenotype in peritoneal macrophages, and enhance IL-10 production [98]. Interestingly, obese animals show a reduction in β-ARs in comparison with lean exercised mice [99] (Figure 2).

In summary, acute and chronic aerobic exercise may ex-

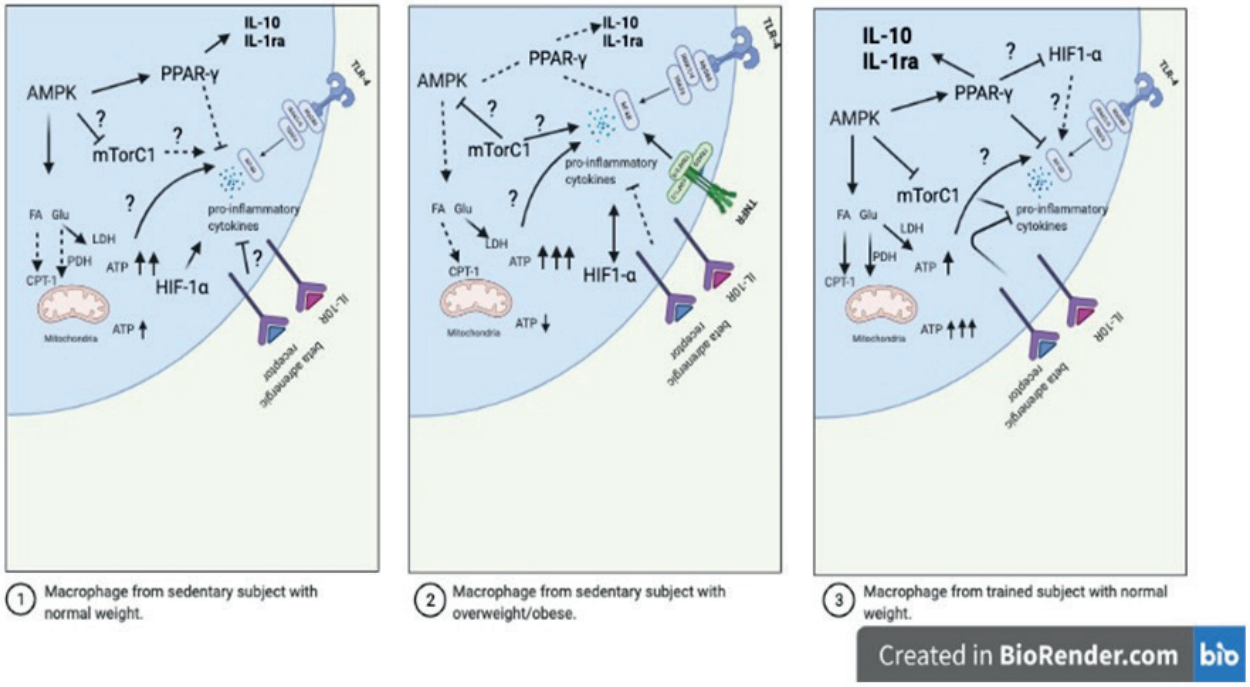

Figure 2. Metabolic profile of macrophages and its adaptations in dependence on physical fitness and body composition. FA = fatty acid; Glu = glucose; PDH = pyruvate dehydrogenase; LDH = lactate dehydrogenase; ATP = adenosine triphosphate; CPT-1 = carnitine palmitoyltransferase 1; mTORC1 = mammalian target of rapamycin complex 1; AMPK = AMP-activated protein kinase; PPAR-γ = peroxisome proliferator-activated receptor γ; TLR-4 = Toll like receptor 4; TNFR = Tumor Necrosis factor receptor; IL-10 = interleukin 10; IL-1ra = interleukin 1 receptor antagonist; HIF-1 alpha = hypoxia-inducible factor 1-alpha; MYD88 = Myeloid differentiation primary response protein; IRAK1/4 = interleukin-1 receptor-associated kinase 4; TRAF6 = TNF Receptor Associated Factor 6; NF-kB = factor nuclear kappa B; TRADD = Tumor necrosis factor receptor type 1-associated DEATH domain protein; cIAP1/2 = encoding a copper-transporting ATPase; TRAF2/5 = TNF receptor-associated factor 2.

The mechanisms behind exercise-induced changes in macrophage polarization and metabolism remain elusive. The ability of aerobic exercise training to promote an anti-inflammatory phenotype in obese adipose tissue macrophages is lost when mice have selective deletion of PPAR-γ in the myeloid lineage [61]. Thus, it seems PPAR-γ plays an important role in switching macrophage metabolic and phenotype induced by aerobic exercise training. The same group showed that lean sedentary mice, lacking PPAR-γ in the myeloid cells, have an exacerbated pro-inflammatory profile. An 8-week intervention of treadmill, moderate aerobic training (continuous exercise 70% Vo2 max) promotes the anti-inflammatory phenotype of adipose tissue macrophages but not peritoneal macrophages [70]. It appears that aerobic exercise training plays distinct roles in macrophage phenotype and metabolism, depending on the basal level of inflammation.

One possible mechanism by which aerobic exercise training alters macrophage polarization is catecholamine release. Both monocytes and macrophages express adrenergic receptors (ARs) and respond to catecholamine stimulation. During the exercise session there is release of adrenaline and promovert immunomodulatory effects, improving pro-inflammatory macrophage response in healthy individuals, and inducing an anti-inflammatory phenotype in individuals with higher basal levels of inflammation. However, the molecular mechanisms behind this immunomodulatory effect remain unclear.

IMMUNOMETABOLIC DYSREGULATION IN SEDENTARY BEHAVIOR AND INCREASED RISK OF CARDIOMETABOLIC DISEASE: THE PROTECTIVE ROLE OF EXERCISE.

We can define sedentary behavior as an energy expenditure of ≤1.5 metabolic equivalents of task (METs). Physical activity as any body movement generated by the contraction of skeletal muscles that raises energy expenditure above resting metabolic rate, and physical inactivity represents the non-achievement of physical activity guidelines [100].

Engaging in physical activity elicits many health benefits, including a reduced risk of cardiometabolic disease (e.g.,

type 2 diabetes, atherosclerosis, hypertension). A key underlying mechanism appears to be exercise-mediated reduction in chronic low-grade inflammation, which is a key contributor to development of insulin resistance and vascular endothelial dysfunction [19]. Conversely, sedentary behavior is associated with various adverse metabolic and health-related outcomes, independently of physical activity levels [101,102]. Given the widespread prevalence of sedentary lifestyles and inadequate physical activity levels [103], it is important to understand how sedentary behavior impacts the interaction between inflammatory and metabolic pathways, as well as the potential of exercise to rescue immunometabolic defects arising from increased sedentary behavior. We propose that a perpetual cycle of immunometabolic dysregulation links sedentary behavior to increased cardiometabolic diseases, on the other hand, we suggest evaluating the potential of exercise to enable preventive or therapeutic effects.

Evidence supporting a link between sedentary behavior and immunometabolic dysregulation

Numerous epidemiological studies support a detrimental association between sedentary behavior, impaired metabolic outcomes (e.g. fasting/postprandial glucose, insulin sensitivity and FFAs) [104,105], and elevated serum/plasma concentrations of inflammatory markers (e.g. IL-6, IL-1β, CRP, TNF-α) [106–108]. Moreover, white blood cell (WBC) count – a potential biomarker of cardiometabolic disease risk [109] – increases linearly with sedentary time [110]. Allocating as little as 30 min of daily sedentary time to moderate-to-vigorous physical activity lowers circulating IL-6 and WBC [111]. The association between sedentary time and markers of chronic inflammation is attenuated when adjusting for body mass index (BMI) and/or waist circumference in some [105, 107, 112] but not all [104] studies. This outcome highlights the potential of sedentary behavior to impact inflammatory markers independent of adiposity. Despite these conflicting findings, it is generally accepted that adipose tissue dysfunction initiates immunometabolic derangements that lead to chronic inflammation [113,114]. A large proportion of the detrimental effects of sedentarism may be attributable to increases in visceral fat mass.

Intervention studies examining the impact of reducing sedentary time on markers of inflammation are currently limited. Reducing sedentary behavior by increasing walking time reduces levels of circulating IL-6 and monocytes, and also lowers LPS-stimulated cytokine production [115]. Overweight/obese individuals who replaced prolonged sitting with light intensity activity show a gene expression shift towards an anti-inflammatory profile in both adipose tissue [116] and skeletal muscle [117]. Despite the paucity of research examining the impact of reducing sedentary behaviors on inflammatory markers, studies consistently demonstrate clinically meaningful improvements in various metabolic parameters including glycemia, insulin sensitivity and blood lipids [118–120]. Combining evidence from cross-sectional analyses and experimental studies supports the hypothesis that the detrimental effects of sedentary behavior on inflammatory outcomes are driven by metabolic derangements.

Mechanisms by which sedentary behavior fuels the vicious cycle of metabolic dysfunction and inflammation

Long-term physical inactivity favors the development of visceral adipose tissue characterized by a shift towards a pro-inflammatory adipocyte profile related to accumulation of pro-inflammatory macrophages, neutrophils, B lymphocytes and CD8+ T lymphocytes [121]. Local release of pro-inflammatory cytokines, such as TNF-α, directly stimulates adipose tissue lipolysis while reducing the inhibitory effect of insulin on lipolytic enzymes The ensuing spillover of FFAs and pro-inflammatory cytokines into systemic circulation induces ectopic lipid accumulation and insulin resistance in vital organs/tissue (e.g., liver, skeletal muscle), exacerbating fasting and post-prandial hyperglycemia and hyperlipidemia [113,114]. Importantly, elevated blood glucose and FFA levels directly impair immune cell function causing the release of inflammatory mediators that further propagate systemic low-grade inflammation. On the other hand, the systemic depletion of CD4 cells improves glucose tolerance while leaving insulin sensitivity, adipose tissue morphology, adipose tissue macrophage activation, and adipose tissue macrophage proliferation as signs of adipose tissue dysfunction unaffected [122].

Toll-like receptors (TLRs) have emerged as key integrators of the relationship between metabolic dysfunction and chronic inflammation-induced insulin resistance. TLR2 and TLR4 are involved in both innate and adaptive immune responses. These receptors are typically activated by bacterial cell wall lipids, but also respond to host lipids and other damage-associated molecular patterns, playing an important role in non-infectious (sterile) inflammatory responses [123]. Activation of TLR2/4 promotes the association of transforming growth factor-B-activated-kinase 1 (TAK1) with TAK1-binding protein-1 (TAB1) activating IkB kinase (IKK) and the c-Jun N-terminal kinase (JNK). IKK and JNK activation induces pro-inflammatory cytokine expression via nuclear-factor kappa B (NF-kB) and impairs insulin action via serine phosphorylation of the insulin receptor substrates (IRS1/2) [114]. TLR4 activation is also a key event in priming the NLRP3 inflammasome, thereby contributing to NLRP3 inflammasome formation and the caspase-1-dependent release of the pro-inflammatory cytokines IL-1β and IL-18 [124].

In addition to innate immune responses, TLRs can also activate adaptive immune response to upregulate the expression of major histocompatibility complex II, a co-stimulatory molecule on antigen presenting cells, and promote the release of IL-12 from dendritic cells [125]. Although saturated FFAs have been traditionally implicated as the main TLR4 ligand through which metabolic overload drives inflammation and insulin resistance [126,127], recent evidence indicates that saturated FFAs do not directly activate TLR4. TLR4 can prime macrophages for FFA-dependent activation of pro-inflammatory pathways via alterations in cellular lipid metabolism and accumulation of lipid species [128]. Despite the controversial role of FFAs in TLR4 activation, circulating levels of other TLR4 ligands (e.g., LPS, oxidized LDL) and TLR4 expression are also elevated in individuals with overweight/obesity and type 2 diabetes [129,130]. Collectively these effects provide additional mechanisms by which metabolic defects arising from sedentary behavior may drive inflammation.

Another proposed mechanism of inflammation in seden-

tarism and adiposity is endoplasmic reticulum (ER) stress. This stress occurs when the cellular protein folding capacity and calcium homeostasis of the ER are perturbed, and the unfolded protein response (UPR) activated to re-establish ER homeostasis [131]. The UPR has three effects: to inhibit protein translation that decreases the workload of the ER, to induce the expression of genes encoding chaperone proteins that increase the protein folding capacity of the ER, and to activate ER-associated degradation machinery to clear misfolded proteins [131]. Integral to the sensing of the ER stress and induction of the UPR are inositol-requiring protein-1 (IRE1), activating transcription factor-6 (ATF6), and RNA-dependent protein kinase (PKR) – like ER kinase (PERK) [131]. Importantly for inflammation-induced insulin resistance, activation of the UPR leads to nuclear translocation of NF-kB thereby priming the NLRP3 inflammasome and inducing expression of pro-inflammatory cytokines that impair insulin signaling [132,133]. Moreover, IRE1 and PERK can induce serine phosphorylation of IRS1/2 via JNK and IKKB [132–134], providing an additional mechanism by which ER stress induces insulin resistance [132]. Taken together, metabolic overload due to higher FFAs and glucose increases ER stress in several tissues provides an additional mechanism by which sedentarism drives immunometabolic dysfunction. There is also evidence that interventions that decrease body fat can reduce ER stress and improve insulin signaling [133].

Interleukin-6 (IL-6) is the prototypical myokine released from contracting skeletal muscle in proportion to exercise volume and intensity, thus the long-endurance exercise with high intensity, as marathon and triathlon induce the huge increase of IL-6 into circulation. IL-6 binds to its monocyte membrane-bound receptor to upregulate anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1Ra) [134]. IL-6 infusion in humans increases circulating levels of IL-10 and IL-1Ra [135]. IL-10 is also produced by contracting skeletal muscle in response to acute endurance exercise and released into the vasculature independent of IL-6 [136]. Contracting skeletal muscle also releases heat shock proteins (HSP) to maintain cellular homeostasis during acute exercise [137,138] and chronic increase of circulating HSP 60 and 70 levels are associated with a decrease in monocyte TLR4 expression, subsequently downregulating the secretion of pro-inflammatory cytokines TNF-α and IL-1β [139]. Given that sedentary behavior is associated with prolonged periods of inactivity, the absence of skeletal muscle contraction (and thus the lack of release of the anti-inflammatory molecules) could partly explain how sedentary behavior drives immunometabolic dysfunction.

The chronic energy surplus that accompanies sedentary lifestyles may also reduce anti-inflammatory cytokine action. The ability of IL-10 to inhibit TNF-α production is reduced in cells from individuals with type 2 diabetes (T2D), and in macrophages grown in high-glucose media [140]. This defect in IL-10 action likely involves diminished STAT3 phosphorylation, and is restored when cells are treated with a small molecule activator of the inositol phosphatase SHIP1 [140]. Thus, loss of anti-inflammatory cytokine action due to nutrient surplus represents another mechanism by which a sedentary lifestyle may exacerbate inflammation-induced insulin resistance. The concept of immune cell dysfunction under metabolic overload is consistent with experiments demonstrating that hyperglycemia and hyperlipidemia induce TLR-dependent inflammation in human monocytes, thereby propagating a state of systemic inflammation [141,142].

Mechanisms by which aerobic training exercise interrupts the vicious cycle of metabolic dysfunction and inflammation

Given that sedentary behavior is associated with increased fat mass, and adipose tissue hypertrophy is a primary contributor to the initiation of chronic inflammation and insulin resistance, a reduction in visceral fat mass is a major mechanism by which exercise counteracts immunometabolic dysfunction. However, rodent studies demonstrate that aerobic exercise training may also prevent macrophage infiltration into adipose tissue, and induces a phenotypic shift in adipose tissue macrophage profile to an anti-inflammatory phenotype [95,143]. Although the ability of aerobic exercise training to reduce adipose tissue inflammation independent of fat loss remains to be established in humans [144], a decrease in adipocyte inflammation is presumably reflected by systemic elevations in adiponectin. Reductions in TNF-α, CRP, IL-6, and/or IL-8 are also apparent after an exercise training intervention in overweight/obese individuals. Importantly, the reduction in adipocyte size/inflammation, and subsequent decrease in circulating FFAs and pro-inflammatory mediators, should prevent development of inflammation and insulin resistance in circulating immune cells and metabolic tissues (e.g., muscle, liver). The improvement in systemic inflammation is presumably aided an exercise-mediated reduction in hepatic lipid content [145], and improved capacity of skeletal muscle to oxidize fatty acids [146,147]. These changes would prevent accumulation of macrophages and/or desensitization of insulin signaling cascades in these tissues [124].

A reduction in TLR4 expression and/or activation of immune cells provides an additional mechanism by which aerobic exercise counteracts the cycle of inflammation and insulin resistance arising from sedentarism. In support of this mechanism, both acute exercise and chronic training [148] can reduce TLR4 expression on monocytes in healthy human participants. Importantly, the exercise-mediated reduction on monocyte TLR2/4 expression is maintained in individuals at high risk for cardiometabolic disease, and individuals diagnosed with T2D [149]. These data indicate the ability of aerobic exercise to reduce TLR expression persists even in the presence of metabolic dysfunction. The precise mechanisms for reduced TLR expression with exercise remain unclear, but likely involve downregulation of TLR expression, TLR shedding and/or TLR internalization from the cell surface [19]. Exercise training also reduces various TLR ligands including FFAs [147] and oxidized LDL [150]. Circulating levels of fetuin – a hepatokine that promotes the effects of circulating lipids on TLR-mediated inflammation [151], and inversely correlates with improved glucose tolerance following training, are also reduced following training in humans [152]. These decreases in TLR expression and ligation likely mitigate activation of various downstream targets mediating pro-inflammatory cytokine production and insulin resistance [133].

The exercise-induced induction of the UPR is emerging as an important mediator of the adaptive response to aerobic exercise training [153,154]. Unresolved ER stress leading to

chronic activation of the UPR is associated with inflammation-induced insulin resistance in multiple tissues [131]. The ability of aerobic exercise to moderate ER stress via UPR activation represents an additional mechanism by which aerobic exercise interrupts immunometabolic dysregulation. Since weight loss-induced improvements in insulin sensitivity following gastric bypass surgery are associated with reduced markers of ER stress and JNK phosphorylation in adipose tissue, exercise-induced reduction in fat mass may mitigate ER stress [133]. However, reductions in p-IRE1, p-eIF2α (a surrogate marker of PERK activation), and p-ATF6 are observed following 3 months of training without corresponding changes in BMI or waist circumference in individuals with obesity [155], implying that exercise-mediated resolution of ER stress may be independent of fat loss. Evidence supporting the contribution of reduced ER stress to exercise-induced improvements in inflammation and insulin resistance is limited (Figure 3).

activation of the JAK1-STAT3 pathway [156]. Importantly, IL-10 counteracts insulin resistance in rodents [157,158] and correlates positively with insulin sensitivity in humans [159]. IL-1ra is a competitive inhibitor of signaling through the IL-1 receptor and blocks the effects of the classical pro-inflammatory cytokine IL-1β [124], which is a key contributor to obesity-induced insulin resistance [160]. The ability of IL-6 to stimulate IL-10 and IL-1ra production from immune cells likely explains why LPS-induced TNFα production is attenuated in exercising healthy males compared to resting controls [161]. In addition to IL-6, other myokines such as IL-7 and IL-15 are also implicated in control of immune cell function [162], and can mediate the anti-inflammatory effects of chronic and acute exercises (Figure 4)

Given that anti-inflammatory actions of IL-10 are impaired in cells from individuals with T2D and monocytes exposed to high glucose [140], and that hyperglycemia/hyperlipidemia induce immune cell inflammation/overactiva-

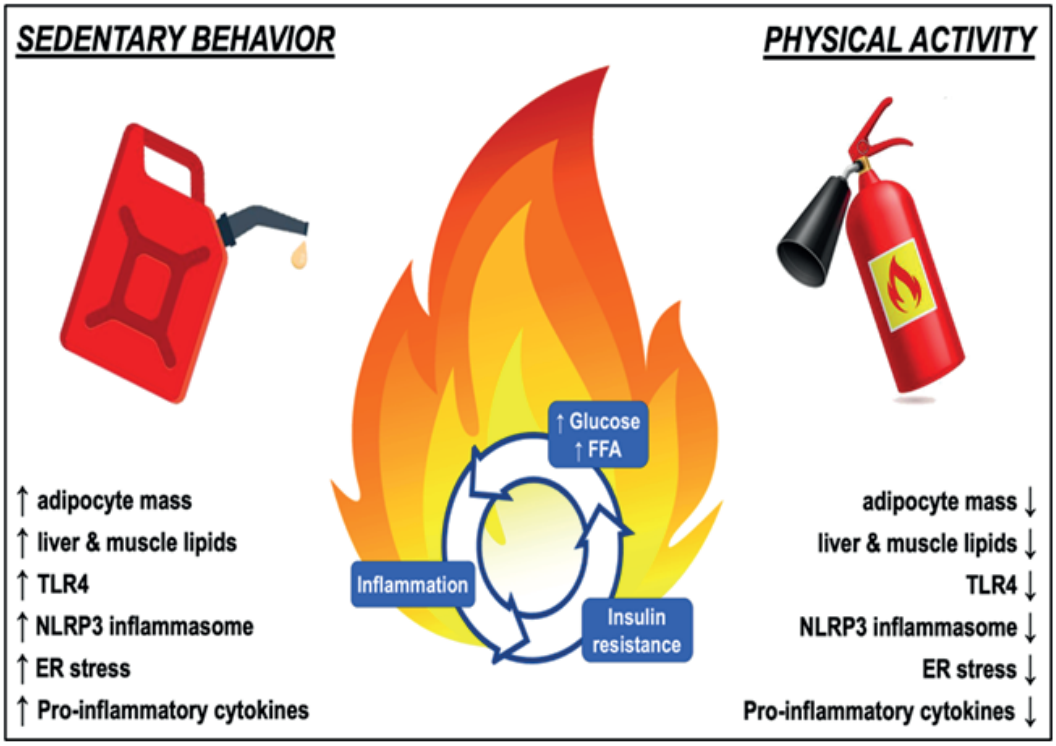

Figure 3. Vicious cycle of immunometabolic dysfunction that fuels cardiometabolic disease. Sedentary behavior feeds, and physical activity counteracts, the vicious cycle through multiple potential mechanisms.

Another mechanism of acute and chronic aerobic exercises that mitigates the vicious cycle in sedentary individuals is myokine production. The production and release of IL-6 from contracting skeletal muscle is widely implicated as a key mechanism underlying the anti-inflammatory effects of aerobic exercise [134]. Other mechanisms are likely involved as some patients cannot exercise at an intensity that leads to significant myokine release, yet experience significant anti-inflammatory benefits. Based on studies involving IL-6 infusion in healthy humans, the exercise-mediated increase in muscle-derived IL-6 purportedly mediates effects in IL10 and IL-1Ra [135] – molecules that exert potent anti-inflammatory effects. IL-10 is a prototypical anti-inflammatory cytokine released from various types of immune cells that inhibits production of pro-inflammatory mediators via

tion [141,142], exercise may counteract immunometabolism dysregulation via reduced post-meal blood glucose/lipid excursions. Several studies support the ability of short bouts of exercise centered around main meals (i.e., shortly before or after) to reduce hyperglycemia [163–165] in individuals at high risk for, or diagnosed with, T2D. Structuring exercise around meals may also be an efficacious strategy for breaking up prolonged bouts of inactivity. The impact of pre/post-meal exercise interventions aimed at lowering post-prandial glucose/lipid spikes on anti-inflammatory cytokine action remains unclear.

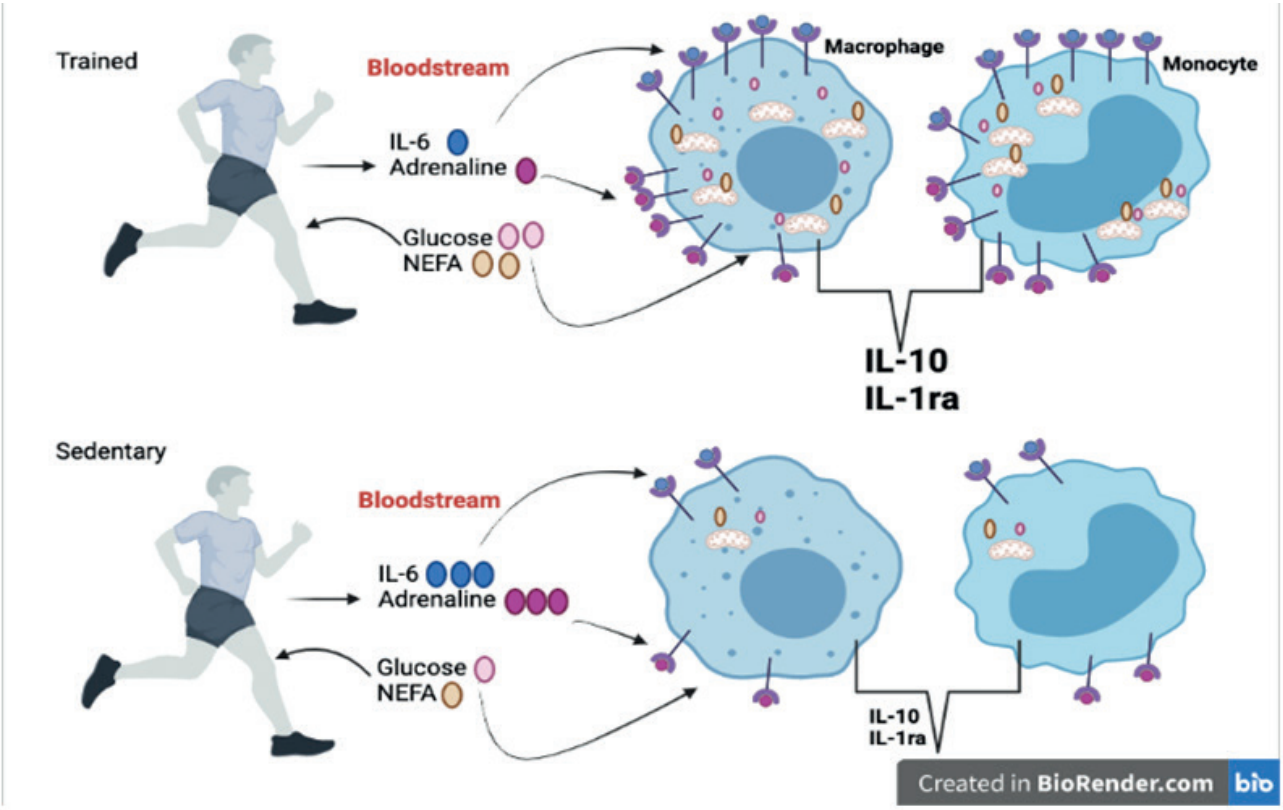

Figure 4. Effects of an acute bout of exercise session on monocytes/macrophages from sedentary and trained subjects. IL-6 = interleukin 6; NEFA = Non-Esterified Fat Acids; IL-10 = interleukin 10; IL-1ra = interleukin 1 receptor antagonist.

METABOLIC PERTURBATION OF IMMUNE CELLS DURING AGING, AND THE PROMINENT ROLE OF LIFELONG EXERCISE

Aging has profound impact on the immune system, affecting its capacity to mount robust immune responses, particularly T cell responses. Healthy aging depends on a complex gene-environment interaction culminating in a lower pro-inflammatory status, and a preserved humoral immune response [166]. Thymic involution is one of the main features of aging, and naïve T cells then have to rely on homoeostatic proliferation to maintain the peripheral T-cell pool. Characteristics of T-cell immunosenescence include an inverted CD4:CD8 ratio, low numbers and proportions of naive T-cells (that would impair the capacity of the immune system to deal with new pathogens), and larger numbers of effector memory T-cells in late stage of differentiation [167]. Other T cell changes with aging include diminished T cell receptor (TCR) clonal diversity, a more tolerogenic phenotype retained selectively [168], and declining ability of naïve and memory T cells to proliferate in response to TCR stimulation. T cell responses are impaired, which leads to poor vaccination efficacy and increased susceptibility to infections, cancer, and auto-immune diseases. Persistent infections, such as cytomegalovirus, further reduce the naïve T-lymphocyte repertoire and drive effector T-cells into senescence [169]. These senescent T-cells are apoptosis resistant, incapable of dividing, and thought to be the major cause of the chronic low-grade inflammation seen with age [170]. Older persons with a pronounced chronic low-grade inflammatory profile are more prone to frailty and mortality [171]. Age-related loss of Treg function would contribute to a greater risk of autoimmune disease, while an increase in Treg numbers could compromise immune responses, increasing the risk of malignancies and infection.

In aged T cells, signaling pathways linked to metabolism are dysregulated, for example, increased basal activation of the PI3K/Akt/mTOR and MAPK signaling pathways [172]. Inflammaging can lead to chronic PI3K/Akt/mTOR pathway activation, increased basal Glut1 expression, and glycolytic activity [173]. Aged senescent memory T cells can hyperactivate the MAPK pathway [174]. Increased activation of PI3K/Akt/mTOR and MAPK signaling pathways seem to be characteristic of T cell aging which increases the rate of glycolysis and mitochondrial mass [175].

Aging will also affect the metabolic machinery of the cells resulting in accumulation of dysfunctional mitochondria with damage to mtDNA [175], increased ROS production [176], decreased levels of NAD+ in the cell, and lower efficiency in metabolic pathways [177]. The role of mitochondrial dysfunction in aging-related progressive immune system alterations has been recognized [178], and exercise is considered an effective non-pharmacological strategy to counteract mitochondrial aging and dysfunction [179]. The crosstalk between exercise and the immune system is well known [180]. For example, hexokinase I activates the NLRP3 inflammasome leading to caspase 1 activation and processing of pro-IL-1b, while glyceraldehyde-3-phosphate dehydrogenase binds to mRNA encoding IFN-γ repressing its translation [181]. Cytokine-induced differentiation into Th1, Th2 and Th17 appears to depend on activation of the mTOR signaling pathway [37].

Regular bouts of exercise can offset T-cell immunosenescence by inducing apoptosis of senescent and functionally exhausted late stage differentiated T-cells [182,183]. A few studies have investigated the impact of lifelong exercise on inflammation

and immunosenescence, using a "master athletes' model". Master athletes, who maintain a healthy lifestyle, even in advanced age, represent an interesting cohort given many express a unique physiological phenotype that could be termed 'exceptionally successful aging' [184]. Master athletes show great motor skills and excellent body composition, and are predisposed to have a more efficacious immune defense, including stronger and longstanding antibody responses to the influenza vaccine, better immune-metabolic regulation, and redox balance, and attenuated biological age [185–187].

Master athletes usually have higher aerobic capacity values than age-matched non-athlete controls, and exhibit higher numbers of CD4+ naive T cells [185]. Individuals with a better physical fitness condition have fewer CD4+ and CD8+ T cells with a senescent/differentiated phenotype and lifelong exercise has been purported to limit accumulation of senescent T cells with age [183]. Lifelong training can also maintain the balance between pro- (e.g., TNF-α) and anti-inflammatory (e.g., IL-10) cytokines, and plasma IL-10 levels are similar to those of younger individuals [29]. Tregs numbers and activation (e.g., increased percentage of subjects expressing forkhead box P3 (FoxP3) and transforming growth factor beta (TGF-β) were also maintained as adaptive responses to lifelong training [188]. Lifelong athletes can show modifications in clock genes in CD4 effector memory cells implicating physical exercise as a pacemaker in lymphocytes [189,190]. While some studies have examined exercise and signaling pathways in muscle [180].

CONCLUSIONS

Like all leukocytes, T cells and macrophages are sensitive to changes in energy supply. The quantity and proportional composition of the substrate supply has both indirect and direct effects on central functions of these cells, including differentiation, activation, cell death, and proliferation. Many intracellular pathways are interrelated between energetic metabolism control and immune cell response. Understanding the regulation and factors influencing the metabolism of immune cells in health and disease can help optimize lifestyle measures for prevention and treatment of inflammatory diseases, and provide insights into healthy aging. Exercise and physical activity clearly has a significant impact on the metabolic status of T cells and macrophages.. It appears that many of the effects that exercise immunology has described over the past 20 years in terms of the effects of physical activity on macrophages and T cells are mediated via a change in the metabolic status of immune cells. It is important now to identify further mechanisms and factors that regulate specific optimization of immune metabolism in health and disease. On this basis it would be possible to optimize exercise, training and physical activity programs based on immunometabolic-regulation, and further develop preventive and sports therapy processes in a forward-looking way.

Author contributions:

JCRN, FSL, JPL and KK conceived the review and drafted the first version of the manuscript. JCRN, FSL and JPL made the figures, reviewed and edited the manuscript. GL, HI, BC, DBP JP and RJS reviewed and edited the manuscript. AMT, HB, BMA, LGM, JCRN, FSL, JPL and KK conceived the review, reviewed and edited the manuscript. All authors approved the final version of the manuscript

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Conflict of interest:

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