Ageing Research Reviews 68 (2021) 101341

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Immunometabolic responses according to physical fitness status and lifelong exercise during aging: New roads for exercise immunology

Camila S. Padilha [a,*], Caique Figueiredo [a], Luciele Guerra Minuzzi [a], Patricia Chimin [b], Rafael Deminice [b], Karsten Krüger [c], José Cesar Rosa-Neto [d,*], Fabio Santos Lira [a]

[a] Exercise and Immunometabolism Research Group, Postgraduation Program in Movement Sciences, Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente, São Paulo, Brazil
[b] Laboratory of Biochemistry Exercise, Department of Physical Education, Faculty of Physical Education and Sport, State University of Londrina, Londrina, Brazil
[c] Institute of Sports Science, Department of Exercise Physiology and Sports Therapy, University of Giessen, Giessen, Germany
[d] Immunometabolism Research Group, Department of Cell Biology and Development, Institute of Biomedical Science, University of São Paulo, São Paulo, Brazil

ARTICLE INFO

Keywords:
Inflammation
Cardiorespiratory fitness
Body adiposity
Immunometabolism
Physical exercise

ABSTRACT

Molecules such as cytokines, energetic substrates, and hormones found in the immune cell environment, especially lymphocytes and monocytes, are crucial for directing energy metabolism. In turn, changes in energy metabolism occur in a synchronized manner with the activation of certain signaling pathways, thereby this crosstalk is responsible for determining the functionality of immune cells. The immunometabolism field has grown over time and that is becoming increasingly promising in several populations; here we discuss the mechanisms involved in sedentary and physically active middle-aged individuals and master athletes. In this context, this review shows that the physical activity status and lifelong exercise seems to be good strategies for the promotion of metabolic and functional adaptations in T lymphocytes and monocytes, counteracting inflammatory environments caused by expanded adipose tissue and sedentary behavior, as well as delaying the immunosenescence caused by aging.

1. Introduction

In the mid-twentieth century, the prominent growth of obesity and physical inactivity democratized globally; more adults and older people are becoming obese and insufficiently active (Dietz et al., 2015; Varela et al., 2018). Population-based studies estimated that in 2014, about 266 million (10.8 %) men and 375 million (14.9 %) women were obese in the world, compared with 34 million (3.2 %) men and 71 million (6.4 %) women in 1975 (NCD-RisC, 2017), with a consequent adverse economic impact estimated to be 2 trillion dollars annually (Dobbs et al., 2014). Most people are aware of the health benefits of being physically active, reducing the population level of physical inactivity by 10 % would prevent around half a million deaths annually and costs 67.5 billion dollars annually in health care expenditures and lost productivity worldwide (Lee et al., 2012).

Sedentarism and physical inactivity are two behavioral factors that increase the probability to develop non-communicable disease (NCD) (Pedersen, 2009; WHO, 2010). Therefore, engagement in exercise training reduces the risk of hypertension (Booth et al., 2017), diabetes *mellitus* type 2 (Lewis et al., 2009), different types of cancers (Ding et al., 2016; Ekelund et al., 2016; Freedland and Aronson, 2004; Hallal et al., 2012) and, the ageing-related low-grade chronic inflammation "inflammaging" (Calçada et al., 2014; Chen and Yung, 2019; Conte et al., 2020; Santoro et al., 2020; WHO, 2018). Moreover, obesity together with physical inactivity lead to early immunosenescence (de Souza Teixeira et al., 2020). Thus, it is the vital importance to advance coordinated public health policy initiatives to combat the obesity and physical inactivity epidemic (Ding et al., 2016).

Physical fitness status has as much potential to shape future human history as the epidemics and pandemics of the past (Ortega, 2016). Managing this threat depends on understanding how to maximize the potential of our sophisticated immune system in the service of human health (Simpson et al., 2015). Innate and adaptive immune systems are recognized mostly as the immunological cellular response, which includes T cells, B cells, dendritic cells (DCs), monocytes, and macrophages (MØ) (Nicholson, 2016; Solana et al., 2012). Among the

* Corresponding authors at: Exercise and Immunometabolism Research Group, Department of Physical Education, Universidade Estadual Paulista (UNESP), Rua Roberto Símonsen 305, Presidente Prudente, São Paulo, 19060-900, Brazil.
E-mail address: cs.padilha@unesp.br (C.S. Padilha).

https://doi.org/10.1016/j.arr.2021.101341
Received 2 December 2020; Received in revised form 29 March 2021; Accepted 2 April 2021
Available online 9 April 2021

immunological cells, here we will discourse about the monocytes and T lymphocytes. Thus, this comprehensive review will contemplate the different responses of T lymphocytes and monocytes according to physical fitness status throughout life.

2. Immunometabolic response according to physical fitness status – a big picture

The immunometabolism field has emerged as one of the most exciting fields of immunological research. Early in this field, the metabolic pathways seemed to be scientifically interesting but unlikely to impinge on research interests into the complexity of the immune response (O'Neill et al., 2016). Overall, immune cells are, at least in part, relatively quiescent in the steady state but share the ability to rapidly respond to infection, inflammation or other perturbations (Pearce and Pearce, 2013). The transition of the immune cell between quiescent and activated state requires nutrients available to support and direct the functional changes (Jung et al., 2019; Pearce and Pearce, 2013). During immune response, the immune cells are sustained by their specific changes in cellular metabolism, in which glucose be used to fuel this response through two different pathways, such as conversing glucose to pyruvate in the cytoplasm and generating nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) via the tricarboxylic acid (TCA) cycle, which donate electrons to the electron transport chain to fuel oxidative phosphorylation (OXPHOS) (Jung et al., 2019; Pearce and Pearce, 2013; Thompson, 2011). The cells also have the flexibility to metabolize other substrates, such as glutamine via glutaminolysis or fatty acids (FA) via β-oxidation. Under hypoxic conditions, cells can produce adenosine triphosphate (ATP) solely by the breakdown of glucose via glycolysis, pyruvate being diverted primarily toward lactate rather than acetyl-CoA (Jung et al., 2019; Pearce and Pearce, 2013; Thompson, 2011). Therefore, as might be expected, cells have several options for producing ATP in different metabolic pathways.

The nutrients availability is regulated by two crucial cellular domain, the mechanistic target of rapamycin complex 1 and 2 (mTORC1−2) and 5′adenosine monophosphate-activated protein kinase (AMPK), which is highly required for supplying energy to support monocytes, macrophages, T cells ($CD4^+$ and $CD8^+$) and natural killer cells (NK) functionality, as well as rapidly dividing T cells (Fukuzumi et al., 1996; Herzig and Shaw, 2018; Newsholme et al., 1986, 1987; Powell et al., 2012). The ability of immune cells to access nutrients will depend on their ability to express appropriate transporters and enzymes within the metabolic pathways that permit the utilization of that nutrient (Pearce and Pearce, 2013; Thompson, 2011). mTORC is a serine-threonine protein kinase member of phosphatidylinositol-4−5-bisphosphate 3-kinase (PI3K) family (Kim et al., 2002) and has a central role in controlling catabolic and anabolic progress by available nutrients and nutrients-induced signal in eukaryotes (Hara et al., 2002); (Kim et al., 2002). mTORC1 is characterized by containing three main components, such as the regulatory-associated protein of mTOR (Raptor) and mammalian lethal with sec13 protein 8 (mLST8) (Hara et al., 2002); (Kim et al., 2002); (Kim et al., 2003)). The Raptor component is responsible for facilitating the recruitment of mTORC1 through binding to the TOR signaling as a central role on several canonical mTORC1 (Nojima et al., 2003) . On the other hand, mLST8 is related to the catalytic domain and may stabilize the cycle of activation of the kinase (Yang and Chi, 2012). Rapamycin displays immunosuppressant activity and down-regulates the cell growth, proliferation, and metabolism through downstream mTORC1 targets, consequently down-regulating the activity of ribosomal protein S6 kinase beta-1 (RPS6KB1) and up-regulating the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), these proteins are characterized by promoting mRNA translation to stimulate cell growth, phagocytosis and control of metabolism (Guarami et al., 2003). The immunosuppressive drug rapamycin (a specific inhibitor of mTOR) is widely used to restrict allograft rejection reactions (Saunders et al., 2001), and most mechanistic studies to date have been focused on understanding the action of rapamycin on $CD4^+$ T lymphocytes responses.

Monocyte is mononuclear cells of the innate immune system developed in the bone marrow from myeloid progenitors and released into the bloodstream in the form of CC-chemokine receptor 2 (CCR2)-dependent (Shi and Pamer, 2011). In the bloodstream, quiescent monocytes present high rate of amino acid glutamine utilization, which provide a satisfactory "patrolling" function within the blood vessels (Auffray et al., 2007; Jakubzick et al., 2013; Newsholme et al., 1985). The monocytes are currently subdivided into monocytes migratory or classical ($CD14^{high}CD16^-$) with high expression of CD14 and release of interleukin-10 (IL-10), patrolling or non-classic monocyte ($CD14^+CD16^{high}$) with a great expression of CD16 and secretion of tumor necrosis factor alpha (TNF-α), IL-1β and IL-6, and intermediate monocyte ($CD14^{high}$ $CD16^+$) with majority expression of CD14 and secretion of IL-10 and TNF-α (Ziegler-Heitbrock et al., 2010). The relative proportion of monocyte subdivisions changes in disease is often associated with an increase in $CD16^+$ monocytes (Kapellos et al., 2019). Although the monocyte subdivisions mentioned above are constantly used, recent studies have found additional phenotypes and providing a better understanding of the functionality of these cells (Aw et al., 2018; Hamers et al., 2019; Wolf et al., 2019).

In an inflammatory scenario, there is an increase in the recruitment and differentiation of monocytes in dendritic cells (DCs) in lymphoid and non-lymphoid tissues, to combat possible microbial pathogens through the release of inducible nitric oxide synthase (iNOS) and TNF-α (Serbina et al., 2003). Another signaling pathway that is extremely discussed in the literature is the influx of monocytes in tissues and subsequent differentiation and polarization for macrophages to reconstitute the tissue homeostasis (Li et al., 2018). The differentiation of monocytes into macrophages is related to a conformational change in their metabolism, size, and protein expression (Curi et al., 2017). The macrophage final state is regulated by the tissue microenvironment, presenting characteristics that widely vary on a large spectrum marked by the pro-inflammatory and repairing extremities, known as classical activation (M1) and alternative activation (M2), respectively (Silveira et al., 2016).

Monocyte-derived macrophage polarization is directly influenced by molecules of the medium, such as lipopolysaccharides (LPS), interferon-gamma (IFN-γ), TNF-α, IL-10, IL-4, IL-13, leptin, and glucocorticoids released by pathogens, T cells, adipose tissue, and others active tissues (Curi et al., 2017). Regarding the release of molecules by the macrophages, the pro-inflammatory state expresses, mainly, a variety of pro-inflammatory cytokines (IL-1β, IL-12, IL-6, IL-23, TNF-α) and iNOS to promote bactericidal, tumoricidal and antigen presentation actions (Lumeng et al., 2007). Additionally, another important feature of monocytes and macrophages in inflammatory processes is the high ability to present antigens and activate the adaptive immune system (Jakubzick et al., 2013). In repairing state, releases predominantly anti-inflammatory cytokines, such as IL-10 and transforming growth factor- beta (TGF-β) combined with increased arginase expression to promote tissue repair and regulate the inflammatory response (Curi et al., 2017). Similar to DCs, after incorporating and processing the antigens, monocytes use their structural machinery to activate the T cell receptor via peptide-MHC, with concomitant interaction of its costimulatory molecules such as CD80 and CD86 releasing protein mediators to stimulate the activation, clonal expansion, and effector activity of T cells (Desch et al., 2014; Larson et al., 2016; León et al., 2007). In summary, monocytes and macrophages establish an important innate immune defense function systemically and tissue homeostasis.

In situations of tissue stress, the inflammatory response stimulates the release of chemokines responsible for attracting monocytes to the site, a mechanism known since the 1950s (Harris, 1953). In locus, monocytes encounter a series of molecules released by tissue cells and pathogen products, which influence their differentiation and polarization to an inflammatory phenotype presenting higher glycolytic demand

and marked by lower OXPHOS demand (Biswas and Mantovani, 2012). After clearance of pathogen, the metabolism of macrophages is reprogramed to repairer and exhibit anti-inflammatory function marked by increased OXPHOS (Biswas and Mantovani, 2012). However, what are the factors responsible for this immunometabolic and functional change in macrophages? The answer may lie in signaling key transcription factors that not only act on the transcription of inflammatory genes but also trigger glycolytic metabolism.

The signaling pathway of Toll-like receptor 4 (TLR-4) plays a major role in the metabolic reprogramming of macrophages for the inflammatory phenotype. One of the mechanisms is the direct overloading of glycolytic enzymes via transcription factors such as hypoxia-inducible factor 1 alpha (HIF-1α) and transcription nuclear factor-κB (NF-κB) (Tannahill et al., 2013). After binding LPS in the TLR-4, the transcription factor HIF-1α and NF-κB are activated and translocate to the nucleus for transcription of glycolytic enzymes and inflammatory cytokines (Tannahill et al., 2013). Key regulatory enzymes such as 6-Phosphofructo-2--Kinase/Fructose-2,6-Biphosphatase 3 (PFKFB3) and fructose-2, 6-bisphosphate and pyruvate kinase isoenzyme M2 (PKM2) are overloaded and enhance glycolytic flow (Luo et al., 2011). The mTORC1 energy sensor also participates in glycolytic modification through hexokinase 1-dependent activation, another enzyme that regulates glycolytic flow (Moon et al., 2015).

Interestingly, in addition to their metabolic action, PKM2 and hexokinase 1 are capable of potentiating the inflammatory response. On the other hand, hexokinase 1 interacts with NLR family pyrin domain containing 3 (NLRP3) and contributes to the activation of caspases and release of IL-1β and IL-18 (Moon et al., 2015). These results were corroborated with suppression of caspase activation and maturation of IL-1β after inhibition of mTORC1 and hexokinase (Moon et al., 2015).

The TLR-4 receptors signaling also positively regulates the glycolytic metabolism indirectly by reducing the rate of the electron transport chain. The TLR-4 signaling pathway stimulates iNOS and consequently increases the NO production, which compete against oxygen in the oxidation of cytochrome C, forming reactive oxygen species (ROS) and reducing the rate of electron transport chain TCA cycle (O'Neill and Hardie, 2013). Other metabolites produced by TCA cycle in inflammatory macrophages are citrate and succinate (Infantino et al., 2011), which are responsible for stabilizing HIF-1α, thereby potentiating the activation of the glycolytic pathway and expression of inflammatory molecules, an event defined as pseudo-hypoxia (Selak et al., 2005).

In contrast to inflammatory phenotype, the regulatory phenotype of macrophages exhibits the Krebs cycle intact next to the electron transport chain and acquires greater use of FA (Wang et al., 2018). It has been shown that the increase in FA oxidation is orchestrated by the signal transducer and activator of transcription 6/ peroxisome proliferator-activated receptor gamma coactivator 1-beta (STAT6 / PGC-1β) signaling pathway, transcription factors that can be activated through cytokines such as IL-4, known for immunoregulatory signaling (Vats et al., 2006). The increase in mitochondrial biogenesis and beta-oxidation via PGC-1β and release of anti-inflammatory cytokines (via STAT6) seem to mediate metabolic reprogramming for a predominance of oxidative phosphorylation found in M2 macrophages (Vats et al., 2006).

Other transcription factors, such as the peroxisome proliferator-activated receptor family (PPAR) and AMPK, present a crucial role in regulating these signaling pathways. AMPK has been considered as a possible master regulator of macrophage polarization (O'Neill and Hardie, 2013), due to its inhibition of mTORC1 and consequent destabilization of HIF-1α (Gwinn et al., 2008) and indirect inhibition of the NF-κB p65 subunit (Yeung et al., 2004). As for PPAR, the γ isoform (PPARγ) participates in the polarization of regulatory macrophages, mainly by the negative regulation of inflammatory signaling pathways of transcription factors such as STAT, NF-κB, and activator-protein 1 (AP-1) and regulation of repressors in the absence of ligands (Pascual et al., 2005; Zhang et al., 2015). The increase in the use of FA and oxidative phosphorylation in regulatory macrophages does not exclude the use of glutamine and glucose as carbon sources.

The α-ketoglutarate produced from glutaminolysis suppresses NF-κB via hydroxylation of IKKβ, impairing pro-inflammatory responses (Liu et al., 2017). The same study showed that α-ketoglutarate stimulates M2 polarization via epigenetic and metabolic reprogramming dependent on histone demethylase JMFD3. N-glycolization is also important for M2 polarization after stimulation with IL-4, mediating the increased expression of murine M2 canonical markers (Liu et al., 2017). Besides, stimulation with IL-4 increased the expression of carbohydrate kinase-like protein (CARKL), a sedoheptulose kinase that catalyzes the formation of sedoheptulose 7-phosphate (S7P) (an intermediate in the pentose phosphate pathway). CARKL is related to the reduction of rate pentose phosphate pathway and the release of pro-inflammatory cytokines after stimulation with LPS (Haschemi et al., 2012). Indeed, the metabolic response of immune cells is not only shaped by infection but also by constant changes in the tissue environment, which allow these cells to alter their metabolism and function as needed, such as macrophage's ability to polarize and repolarize (Tarique et al., 2015).

Regarding adaptive immunity, T cells are a critical cells types recognizing and signaling to antigen-specific responses through its receptor recognition combined with co-stimulation by professional antigen-presenting cells (APCs) (Almeida et al., 2016). In this sense, T lymphocytes co-signaling receptors have been defined as cell surface molecules that can transduce signals into T lymphocytes to co-stimulatory or co-inhibitory receptors (L. Chen and Flies, 2013; Pearce, 2010). The T lymphocytes receptors are very responsive according to metabolic stress conditions, mainly involves increased glycolysis coupled with lactate production, glutaminolysis-driven mitochondrial respiration, serine, and one-carbon metabolism to support the differentiation into T cytotoxic ($CD8^+$) and T helper lymphocytes (Th) (Gerriets et al., 2015; Klysz et al., 2015; Makowski et al., 2020), while to differentiate to regulatory T cells (Tregs) depend mainly on mitochondrial respiration for their survival and immunosuppressive functions (Gerriets et al., 2015; Makowski et al., 2020).

Regarding Th lymphocytes, they are further differentiated based upon the production of cytokines into Th1 which produce IFN-γ, Th2 synthesizing IL-13, IL-4, and IL-5, Th17 producing IL-2, IL-17, and IL-22, and Tregs synthesizing IL-10 and TGF-β (Koch and Radtke, 2011). T cytotoxic lymphocytes present CD8 as a surface marker and produce perforins and some cytokines controlling the progress of immune cells (Oestreich and Weinmann, 2012). Naïve T lymphocytes are quiescent, present low rate glycolytic demands, and use predominantly OXPHOS to generate ATP (Gatza et al., 2011; O'Sullivan and Pearce, 2015). Upon T lymphocyte antigen receptor-mediated recognition by MHC and co-stimulatory signals by type I transmembrane protein CD28 expressed on the surface of the majority of naïve CD4 and CD8 (L. Chen and Flies, 2013), T lymphocytes become activated and adopt the glucose as primary energy supply even when sufficient oxygen is present to utilize OXPHOS, this process is termed as Warburg pathway (Poznanski et al., 2018; Warburg, 1956). Under these circumstances, the nutrients available are used for the generation of building blocks for clonal expansion and for effector functions, such as the secretion of cytokines and cytolytic molecules important for clearing pathogens and no longer used solely for survival and homeostasis (Almeida et al., 2016; Chang and Pearce, 2016).

Signals from the T lymphocytes receptors, co-stimulatory molecules, and growth-factor cytokines lead to the activation of transcriptional genes for important effector functions, mediating the induction of glycolysis to support cell growth, proliferation and function (Linke et al., 2017; Waickman and Powell, 2012). In this sense, these signals also lead to an activation of the mTORC mediating the cell growth, proliferation, and function of T lymphocytes (Linke et al., 2017; Waickman and Powell, 2012). Nevertheless, inhibition of metabolic reprogramming during effector T cell differentiation, as occurs during nutrient deprivation, either leads to insufficient

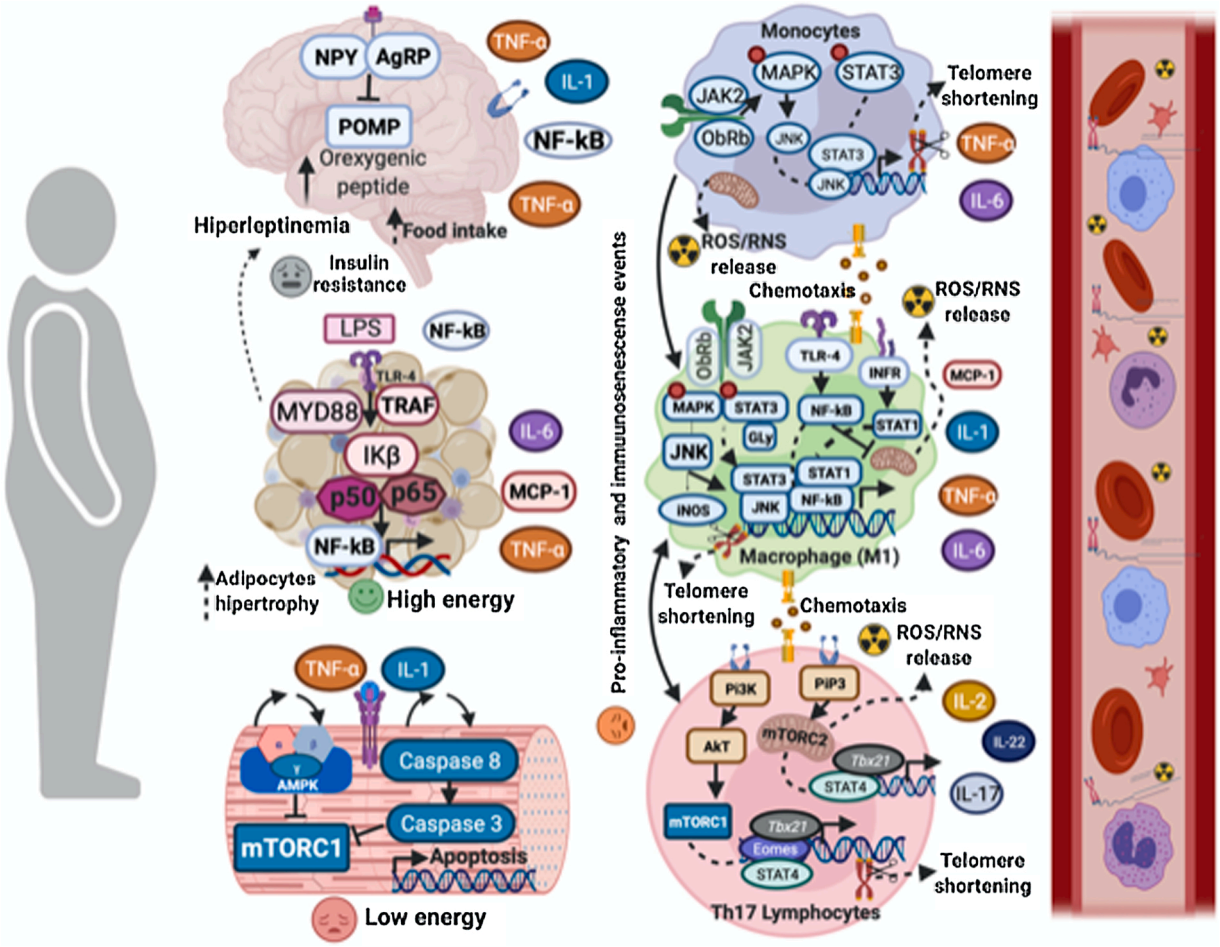

Fig. 1. Mechanisms associated in muscle - visceral fat - brain crosstalk on immunometabolism and immunosenescent response in sedentary middle-age individuals. NPY: neuropeptide y, AgRP: agouti-related protein, POMP: proteasome maturation protein, TNF- α: tumor necrosis factor alpha, IL-1: interleukin 1, NF-kB: nuclear factor kB, LPS: lipopolysaccharide, MyD88: myeloid differentiation protein-88, TRAF: TNF receptor associated factors, IkB: inhibitor of kB, IL-6: interleukin 6, MCP-1: monocyte chemoattractant protein-1, AMPK: AMP-activated protein kinase, mTORC1: mechanistic target of rapamycin complex 1, JAK2: janus kinase 2, ObRb: leptin receptor, MAPK: mitogen-activated protein kinase, STAT3: signal transducer and activator of transcription 3, ROS/RNS: reactive oxygen/nitrogen species, TLR-4: tool-like receptor 4, INFR: interferon receptor, iNOS: induced nitric oxide synthesis, PI3K: phosphoinositide 3-kinases, Pip3: phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P3), AKT: protein kinase B, mTORC2: mechanistic target of rapamycin complex 2, STAT4: signal transducer and activator of transcription 4, Tbx21: T-box transcription factor 21, Eomes: eomesodermin, IL-2: interleukin 2, IL-22: interleukin 22, IL-17: interleukin 17.

activation/differentiation/proliferation or in some cases results in the generation of Tregs.

2.1. No time to lose in sedentary behavior during middle-age

In the last few decades, our society has become known as an "aging society" due to the imminent reduction in birth rates and increased longevity; one in four adults will be aged over 65 years by 2050 (Shaw et al., 2010). Early as middle-age (~ 40 years) men and women naturally experience the decline of cardiorespiratory fitness (CRF) (Astrand et al., 1973; Radak et al., 2019), strength, endurance and functional muscle, and muscle size (Frontera et al., 2000, 1991). On the other hand, middle-aged men and women experience the increase of time spend in sedentary behavior (Diaz et al., 2016) and body adiposity (Santos et al., 2020; Wu et al., 2001). The combination of non-working skeletal muscle, reduced CRF and increased adiposity are associated with the risk of infection and no communicable diseases (Butcher et al., 2001; Shaw et al., 2010). Therefore, our "aging society" does not seems to be "healthier aging".

The processes of adipose tissue expansion lead to the initiation of metabolic stress signals, such as inhibitor of κ kinase (IKK) pathway, c-jun N-terminal kinase (JNK) pathway, and protein kinase R (PKR) pathway, since the storage of capacity of VAT is limited. A further overload lead to fat accumulation in ectopic tissue such as the liver, skeletal muscle, and heart (Oishi and Manabe, 2016). These combined processes are commonly defined as "lipotoxicity", leading to activation of TRAF-MyD88/Ik-β/NF-κB cascade signaling in adipocytes, the expression of monocytes chemoattractant protein-1 (MCP-1) regulating the migration and infiltration of monocytes and macrophages, promoting a local inflammation by an increased invasion of leukocytes and the enhanced production of reactive oxygen and nitrogen species (ROS/RNS), followed by the subsequent release pro-inflammatory cytokines (TNF-α and IL-1β) (Longo et al., 2019; Oishi and Manabe, 2016). The constant adipocytes-induced pro-inflammatory mediators affect the skeletal muscle and immune cells (Macdougall et al., 2018). Pro-inflammatory cytokines circulating trigger the insulin resistance and upregulate the catabolic pathway signaling mediated by AMPK and caspases 8/3 cascade signaling leading to increase of apoptosis, and inhibition of anabolic stimulus of mTORC in skeletal muscle (Hara and Kondo, 2015) promoting the energy declines (Vander Haar et al., 2007), while in brain metabolism signaling, leptin, a hormone secreted by adipose tissue, regulates the appetite and satiety (Warren et al., 2012). Higher endogenous levels of leptin (hyperleptinemia) activate the neuropeptide Y and agouti-related peptide (NPY/AgRP) stimulating

orexigenic peptides which intensify the food intake, and promote insulin resistance (Friedman, 2016).

In summary, the perturbation of metabolism and pro-inflammatory state in adipose tissue results in metabolic reprogramming in skeletal muscle and immune cells. The vicious inflammatory state is mediated by monocytes, T cytotoxic, regulatory and helper lymphocytes (Longo et al., 2019) and repeated inflammatory event results in early exhaustion of immune cells leading to decline in number and function of immune cells and decline on vaccine response; this state induced by ageing have been termed as immunosenescence (Rodriguez et al., 2021). Immunosenescence process can be characterized by changes in age-related robust immunological biomarkers that are associated with negative clinical outcomes such as infection, cancer, cardiovascular disease and autoimmunity (Pawelec, 2017, 2018) **(**Fig. 1**).**

Monocytes from elderly individuals show crucial differences in their number and function, such as increased non-classical monocytes, impaired phagocytosis, reduced HLA-DR and greater basal cytokine release (Hearps et al., 2012). Additionally, monocytes show age-related metabolic impairments such as reduced mitochondrial function and increased glucose uptake (Saare et al., 2020). Corroborating this evidence, the expression of genes related to the coding of ribosomal proteins, oxidative phosphorylation and transport of molecules between the mitochondrial membrane in monocytes is reduced in elderly individuals compared to young people (Saare et al., 2020).

Many age-related functional changes found in monocytes are found in macrophages. There is evidence that shows an increase in the inflammatory phenotype in older individuals (Hsieh et al., 2020). In aging, the largest number of inflammatory monocytes and macrophages is coherent, since it is related to chronic systemic inflammation and these cells (mainly macrophages) use their plasticity capacity to reprogram their metabolism and phenotype according to the environment (Tarique et al., 2015). However, both the ability to fight pathogens and the resolution of inflammation are reduced in macrophages of older individuals. Loss of phagocytic capacity (Linehan et al., 2014), presentation of antigens and wound healing are other dysfunctional features (Fulop et al., 2016). This condition is sustained even with the greatest capacity to release pro-inflammatory cytokines in the absence of stimuli (Fulop et al., 2016). The mechanisms proposed to explain these differences are related to epigenetic changes that macrophages, or even monocytes, have undergone in the environment they were in the past, favoring the gain of a trained memory (Fulop et al., 2016). Another alternative would be the relationship of the concentration of stimuli present in the environment, favoring the immune tolerance framework and, consequently, reducing some functions (Bauer et al., 2018). Research on the relationship between signaling and metabolic pathways that trigger the aforementioned changes is still scarce, however, we can suggest some.

One of the proposed mechanisms responsible for immunosenescence is mitochondrial dysfunction (Bratic and Larsson, 2013), a feature previously highlighted in macrophages and monocytes. Autophagy is a recognized anti-inflammatory mechanism (Deretic et al., 2013) and its mitochondrial fission and fusion processes (mitophagy) are essential for maintaining stable and functional mitochondria (Yarbro et al., 2020). In aging, macrophage inhibits mitophagy and mitochondrial fission, increasing the release of protons and the formation of ROS and intermediates in the Krebs cycle (Yarbro et al., 2020). Upstream proteins that regulate cellular autophagy may be directly related to the process of age-related metabolic changes. In addition to being modulators of energy metabolism and macrophage function, AMPK and mTOR are potent modulators of cellular autophagy pathways, with AMPK stimulating autophagy and mTOR inhibiting (Glick et al., 2010). In macrophages stimulated with LPS, activation of the AKT / mTOR signaling pathway was responsible for inhibiting autophagy and increasing the secretion of IL-6 (Zhang et al., 2020). Activation of AMPK via AICAR or *Astragalus membranaceus* (plant used in traditional Chinese medicine) increased autophagy and reduced the release of IL-6 after stimulation with LPS, thereby this effect was mediated by inhibitory regulation in mTOR conducted by AMPK (Zhang et al., 2020). In addition, the results were confirmed by a reduction in autophagy and anti-inflammatory response after selective AMPK block and an increase in autophagy and anti-inflammatory response after selective mTOR block.

Studies have demonstrated that rapamycin-induced mTOR inhibition promotes the differentiation of $CD4^+$ T lymphocytes into positive forkhead box transcription factor ($FoxP3^+$) regulatory T lymphocytes (Kang et al., 2008; Zheng et al., 2007). Besides, rapamycin has implicated the requirement of mTOR kinase signaling in regulating effector *versus* regulatory of T lymphocytes $CD4^+$, demonstrating its ability to regulate T-bet and eomesodermin expression (Delgoffe and Powell, 2009). mTORC1 is activated not only by nutrients available but also by signaling pathways that coordinate cell growth through activation of insulin pathway and mitogenic signals (Hall, 2016; Schmelzle and Hall, 2000). PI3K and signal transducer and activator of transcription 4 (STAT4) signaling pathways increase mTORC1 activity, or determine the functional and memory results of T lymphocytes, regulating the expression of two crucial members of the T-box gene family of transcription factors expressed in immune cells (*Tbx-21* and eomesodermin), as named T-bet (Pearce et al., 2003; Szabo et al., 2000). The balance between transcriptional factors T-bet and eomesodermin has been shown to determine effector and memory cell T lymphocytes fate (Intlekofer et al., 2005).

Unlike mTORC1, mTORC2 controls proliferation and survival primarily (Jacinto et al., 2004). The RICTOR containing mTORC2 or its down-stream target and glucocorticoid-regulated kinase (SGK1) have been shown to promote the differentiation of Th2 lymphocytes (Delgoffe et al., 2011). However, mTORC2-deficient T lymphocytes promote memory T lymphocyte generation via nuclear accumulation of forkhead box protein O1 (Foxo1), which in turn decreases the expression of T-bet and eomesodermin (Zhang et al., 2016). The findings from Zang and co-authors (2016) raise the possibility that inhibition of mTORC2 may represent an effective strategy for generating robust memory responses. Therefore, it has been postulated that mTORC1, but not mTORC2, is critically required for the functional competency of Tregs (Chapman and Chi, 2014; De Rosa et al., 2015; Delgoffe et al., 2011; Zeng et al., 2013). Moreover, the deregulated nutrient sensing mTORC1/2, pro-inflammatory condition, exacerbate ROS/RNS and mitochondrial disfunction are tightly linked to altered intercellular communication leading to premature immunosenescence (Jenny, 2012).

When $CD4^+$ T cells react to a foreign antigen from a pathogen, they usually produce various lymphokines, causing an immune response that increase the activation and antibody production in response to T-cell receptor (TCR) stimulation. Senescent $CD4^+$ T cells do not proliferate in response to TCR stimulation and produce abundant osteopontin, as well as inflammatory cytokines. These functional differences are mainly caused by the upregulation of CCAAT/enhancer binding protein α (C/EBP) in T cells. C/EBPα is a master differentiation gene that functions in leukocytes or macrophages, but not expressed in regular T cells. Senescent T cells are indicated to be converted from this memory T-cell type by unique genetic programming that resembles the partial transdifferentiating of T cells. T cells usually react to a specific pathogen and maintain immunity (memory) for a long time as memory T cells; however, aged T cells do not contribute to maintaining the immune system. During aging, the number of naïve T cells is decreased, whereas the number of memory T cells is increased (Pawelec et al., 2001). Programmed death -1 (PD-1) in T cells, the number of which is increased in aging, are mainly part of the population of $CD44^{high}$ and CD62 L low T cells (Pawelec et al., 2001). $CD4^+$ T cells gradually increase in number with age and become predominant at the senescent stage, and their predominance is associated with a decrease in the specific $CD4^+$ T-cell response. In this sense, the big picture of body adiposity and spent time in sedentary behavior during middle-age reveals several concerns regarding an “aging society”. Under a pro-inflammatory state, perturbation of metabolism induced by adipose tissue expansion and sedentary

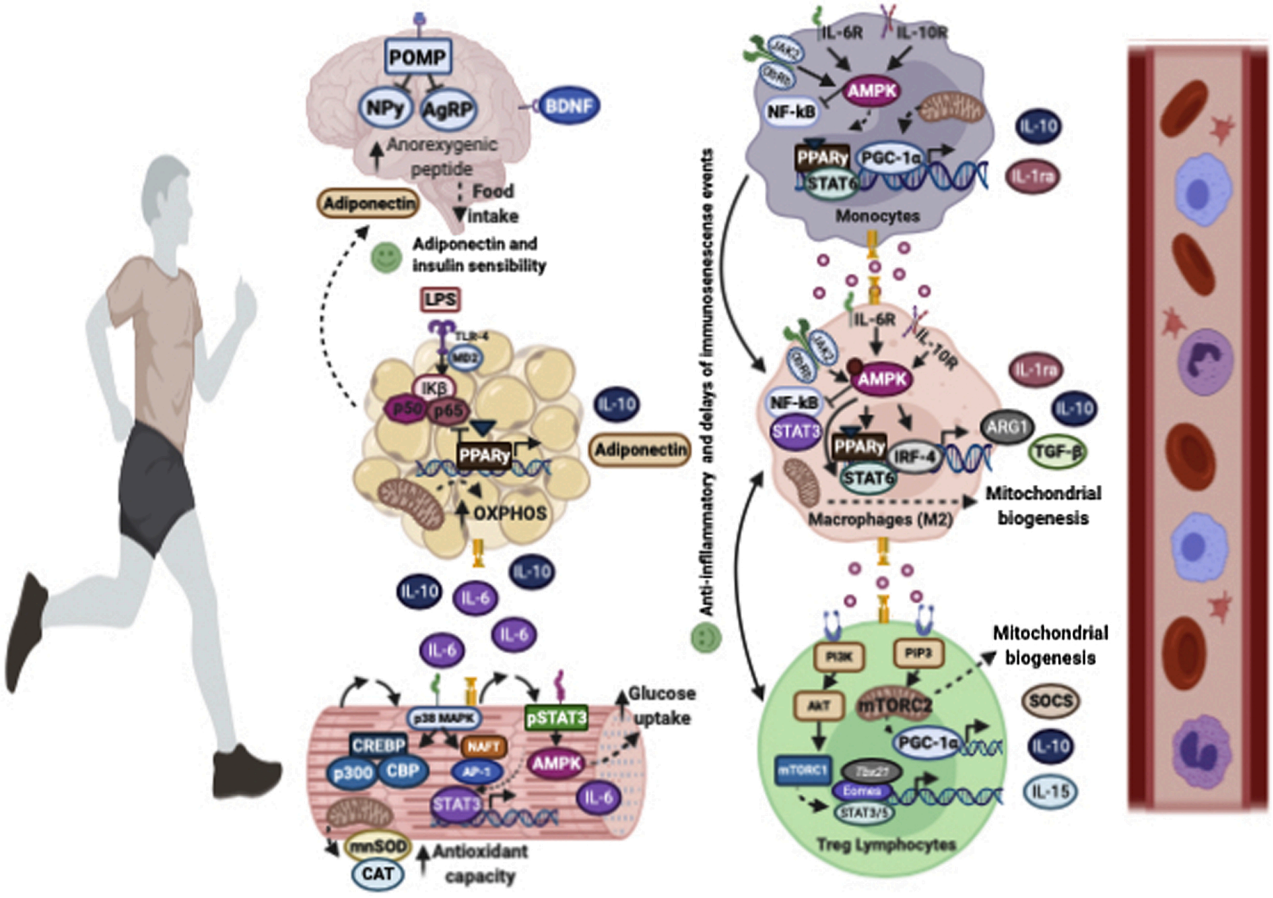

Fig. 2. Mechanisms associated in muscle - visceral fat - brain crosstalk on immunometabolism and immunosenescent response in physically active middle-age individuals. NPY: neuropeptide y, AgRP: agouti-related protein, POMP: proteasome maturation protein, BDNF: brain-derived neurotrophic factor, LPS: lipopolysaccharide, MD2: myeloid differentiation factor 2, IkB: inhibitor of kB, PPAR-gamma: peroxisome proliferator-activated receptor gamma, IL-10: interleukin 10, OXPHOS: oxidative phosphorylation, CREBP: cAMP (cyclic adenosine monophosphate)-responsive element binding protein, NAFT: nuclear factor of activated T-cells, AP-1: activator protein 1, mnSOD: manganese superoxide dismutase, CAT: catalase, AMPK: AMP-activated protein kinase, NF-kB: nuclear factor kB, JAK2: janus kinase 2, ObRb: leptin receptor, MAPK: mitogen-activated protein kinase, STAT3/5: signal transducer and activator of transcription 3 and 5, IL-6: interleukin 6, IL-6R: interleukin 6 receptor, IL-10R: interleukin 10 receptor, PGC1- α : peroxisome proliferator-activated receptor gamma coactivator 1-alpha, IRF-4: interferon regulatory factor 4, IL-1ra: interleukin 1 receptor antagonist, ARG-1: arginase 1, TGF-β: transforming growth factor beta, SOCS: suppressor of cytokine signaling proteins, mTORC1: mechanistic target of rapamycin complex 1, PI3K: phosphoinositide 3-kinases, Pip3: phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P3), AKT: protein kinase B, mTORC2: mechanistic target of rapamycin complex 2, Tbx21: T-box transcription factor 21, Eomes: eomesodermin, IL-15: interleukin 15.

behavior interferes with macrophages polarization and T lymphocyte differentiation and the effector function in a vicious circle, leading to premature immunosenescence.

2.2. Physically active during middle-age

Regular physical activity or exercise during middle-age may either downregulate and upregulate the immune function and susceptibility to minor illnesses (Krüger and Mooren, 2007). The clinical benefit of the physical exercise session is an effective method of immuno-neuroendocrine stabilization that, in the long-term (training), is responsible for the immune function of the organism (Ortega, 2016).

It is endorsed that during muscle contraction, the influx of calcium released by the sarcoplasmic reticulum stimulates an increased AMP/ATP ratio signaling pathways of cytosolic proteins such as calcineurin, AMPK, and P38 mitogen-activated protein kinases (p38 MAPK), which culminate in the translocation of transcription factors (CREBP and NFAT/AP1) to the nucleus and subsequent expressing IL-6 (Pedersen, 2017). The increase of IL-6 levels is preceded by a decrease of muscular glycogen stores during an exercise bout, and immediately after exercise bout it is possible to detect high endogenous levels of IL-6 systemically (Petersen and Pedersen, 2005) and sequentially increase of IL-1ra and IL-10. Indeed, the cumulative effect of exercise practice increases the antioxidant capacity by improving electron transport chain, OXPHOS and enhancing the activity of superoxide dismutase, catalase and glutathione peroxidase in skeletal muscle (Azizbeigi et al., 2015; Febbraio and Pedersen, 2005).

The paracrine, autocrine, and endocrine action of IL-6 is mediated by the gp130Rβ/IL-6Rα homodimer found in several cell types, including immune cells (Wolf et al., 2014). In adipose tissue, the exercise-induced IL-6 lead to activation of TLR-4 cascade signaling and translocation of PPAR-γ to promote the transcription of anti-inflammatory markers (IL-10, IL-1ra and adiponectin) in resident M2 macrophages (Ruffino et al., 2016). The production and release of anti-inflammatory markers induced by exercise restore the metabolism of adipose tissue via insulin and adiponectin sensitivity, and becoming a tissue less inflamed (Lurier et al., 2017). Nevertheless, the endocrine action of exercise practice leads to increase of adiponectin availability “hyperadiponectinemia” systemically stimulating the activation of anorexigenic neuropeptides and inhibiting the neuropeptides NPY and AgRP, which aids regulation of appetite and satiety, decreasing the food intake by improved satiety (Sotak, 2020) (Fig. 2). Therefore, regular physical exercise improves the metabolic efficiency and establishes an anti-inflammatory and antioxidant environment in tissues such as skeletal muscle, adipose tissue, and

brain (Suzuki, 2019).

In the last decades, the central discussion of exercise immunology research field has incontrovertibly persisted that severe intensity in exercise session or cumulative periods of intensified training induce the impairment of immunity, exposing the host to an 'open window' of infection risk (Simpson et al., 2020). The rapid increase in peripheral blood T lymphocytes during exercise is one of the most replicated findings in exercise immunology (Gleeson, 2007). The transient lymphocytosis is largely comprised of $CD8^+$ T lymphocytes and NK cells due to, at least in part, by the increases of cardiac output and hemodynamic shear forces induced by β2-adrenergic receptors, which are highly expressed in these cells (Krüger et al., 2008). Furthermore, studies have demonstrated that the exercise-induced lymphocytosis may be inhibited by administering β2-adrenergic antagonists (Fragala et al., 2011; Landmann, 1992; Mills et al., 1999; Murray et al., 1992). In short, it has been documented that acute exhaustive exercise session can lead to a depressive effect on immune function (Gleeson, 2007).

The intensity of exercise is an important variable for modulating the immunological response. Thus, choosing the intensity of the session applied to a given level of physical-metabolic fitness could be a strategy for enhancing long-term immune functionality by establishing appropriate immunization stimuli (Ortega, 2016; Spielmann et al., 2011). The application of high-intensity aerobic training (intermittent (HIIT) or continuous) and moderate-intensity continuous training (MICT) has been frequently used to ascertain the acute and chronic influence of intensity on the cellular immune response (Ezema et al., 2014; Robinson et al., 2015; Tsai et al., 2016). These two modalities seem to have similar systemic anti-inflammatory effects in normal-weight and obese people (Cabral-Santos et al., 2019, 2015; Gerosa-Neto et al., 2020) and the nutritional offering has a great influence on the immune response (Von Ah Morano et al., 2020). Regarding the balance of immune cells, changes in the inflammatory or anti-inflammatory pattern, senescent or naive, have been observed in people with different CRF (Antunes et al., 2019; Dorneles et al., 2019a; 2019b). Most recent study in collaboration with our research group demonstrated that individuals with high levels of CRF presents lower percentage of T lymphocytes compared with individuals with moderate levels of CRF, which presents higher percentage of T lymphocytes. In addition, no difference was observed on production of IL-10 and IFN- γ in individuals with high and moderate levels of CRF (Dorneles et al., 2021). In addition, Dorneles et al. (2019a) investigated the peripheral frequency of monocytes, $CD4^+$ T cell subsets and the systemic levels of cytokines in lean and obese men with different levels of CRF (lean: low – 37.8 mL/kg/min^{-1}, moderate – 44.6 mL/kg/min^{-1}, or high – 54.4 mL/kg/min^{-1} VO_{2Peak}, obese: low – 33.6 mL/kg/min^{-1}, moderate – 42.4 mL/kg/min^{-1}, or high – 49.9 mL/kg/min^{-1} VO_{2Peak}). High CRF reflected a frequency increased of Tregs and mTregs and intermediate non-classical monocytes, both in lean and obese volunteers. The same occurred for cytokines concentrations, with systemic lower levels of pro-inflammatory (IL-6 and TNF-α) and higher concentrations of IL-10 and IL-33 cytokines were observed in subjects with moderate and high CRF. More studies have shown that individuals with higher CRF exhibit either higher frequency and function of cells with anti-inflammatory pattern, compared to those individuals with low CRF (Dorneles et al., 2019a; Elsner et al., 2019; Handzlik et al., 2013).

Peripheral blood mononuclear cells (PBMCs) from physically active individuals have higher brain-derived neurotrophic factor (BDNF) production and lower thiobarbituric acid reactive species (TBARS) compared to sedentary individuals at rest (Elsner et al., 2019; Inoue et al., 2020). These results indicate a high anti-inflammatory profile, since the decrease of ROS may stimulate inflammatory pathways (Powers et al., 2010) and BDNF is a potential activator of OXPHOS metabolism (via AMPK) (Zhang et al., 2017). Furthermore, sprint-trained athletes and endurance-trained athletes showed higher production of IL-10 from antigen-stimulated whole blood culture compared to sedentary and recreationally active individuals (Handzlik et al., 2013). The same study identified a higher percentage of Tregs in the group of athletes compared to the sedentary group.

The mechanisms for the reduction of senescent cells after physical exercise sessions involve an increased mobilization to the circulation followed by an extravasation into lymphoid tissues or apoptosis. These processes seem to be part of the immunoregulatory effects of exercise mediated by hormones such as catecholamines and cortisol (Krüger et al., 2009). In this sense, Krüger et al. (2016) compared the effects of an isocaloric session of MICT versus HIIT on progenitor cell and lymphocyte subtypes counts associated with apoptotic markers (annexin V) and hormonal concentrations. Both protocols increased the concentrations of catecholamines and cortisol. However, interestingly, MICT induced greater apoptosis of low differentiation T cells ($CD3^+CD28^+CD57^-$) and Tregs while HIIT showed a higher apoptotic frequency of highly differentiated T cells ($CD3^+CD28^-CD57^+$) and mobilization of Tregs. Thus, the MICT session mainly affected cells that act in defense against new infective agents. However, contradictory results are found in MICT protocols that provided greater mobilization of $CD4^+$ and $CD8^+$ T cells, total lymphocytes and $CD4^+/CD8^+$ ratio in a patient living with HIV/AIDS with low CRF and physically inactive (Ezema et al., 2014; Rigsby et al., 1992), or increased the T angiogenic (TANG) total, $CD4^+$/TANG and $CD8^+$/TANG cells in physically active men of different ages (Ross et al., 2018), as well as induced greater mobilization of lymphocytes, $CD14^+$ monocytes and $CD3^+$ T post-exercise session on trained cyclists (Bishop et al., 2014) (Fig. 2).

2.3. *Lifelong benefits of exercise: master athletes a model of successful aging?*

Master athletes, men and women over 35 years who participate in athletics competitions, are a rapidly growing population. Although the vigorous and regular training regimens are typically performed by master athletes, they represent an interesting sub-demographic group because many of them express a unique physiological phenotype (Kusy and Zielinski, 2015; Tanaka and Seals, 2008). The healthy and active lifestyle and a balanced diet of master athletes, even in old age, confer numerous health benefits. There is some evidence suggesting that master athletes have a more efficacious immune defense, including stronger and longstanding antibody responses to the influenza vaccine, better immune-metabolic and redox balance, besides attenuated biological age (Aguiar et al., 2019; de Araújo et al., 2015; Minuzzi et al., 2018; Simoes et al., 2017; Walsh, 2018).

Most recently, lifelong exercises have been indicated as crucial regulator of clock gene expression and improves effector-memory of $CD4^+$ response in master athletes (Teixeira et al., 2021. *Data in press*). In collaboration with our research group, Teixeira et al. (2021 *data in press*) demonstrated that effector-memory T-cells from master athletes presents different peripheral and cellular inflammatory responses after single-bout of exercise when compared to untrained healthy individuals. There was observed increases on level of cytokines (IL-8, IL-10, IL-12p70 and IL-17A) after single-bout of exercise and increased on gene expression in effector-memory CD4 + T-cells for Cry1, REV-ERBα and Tbx21 in master athletes. In other study, lifelong exercise promoted higher basal levels of IL-10, TGF-β, and the expression of EP4 (an anti-inflammatory PGE2 receptor) compared to old healthy non-exercisers (Lavin et al., 2020). Given its anti-inflammatory roles, these factors likely contribute to the suppression of the transcription and signaling activity of pro-inflammatory factors. Interestingly, lifelong training intensity appears to have a minimal effect on this pattern (Lavin et al., 2020).

Likewise, when men that consistently exercised for more than 50 years were challenged to an unaccustomed acute resistance exercise, they modified the expression patterns of TLRs receptors (i.e., TLR3), associated adaptors and downstream signaling components (i.e., Myd88) (Perkins et al., 2020). Hence, the immune system could be modified by exercise training in older individuals, but, for immune

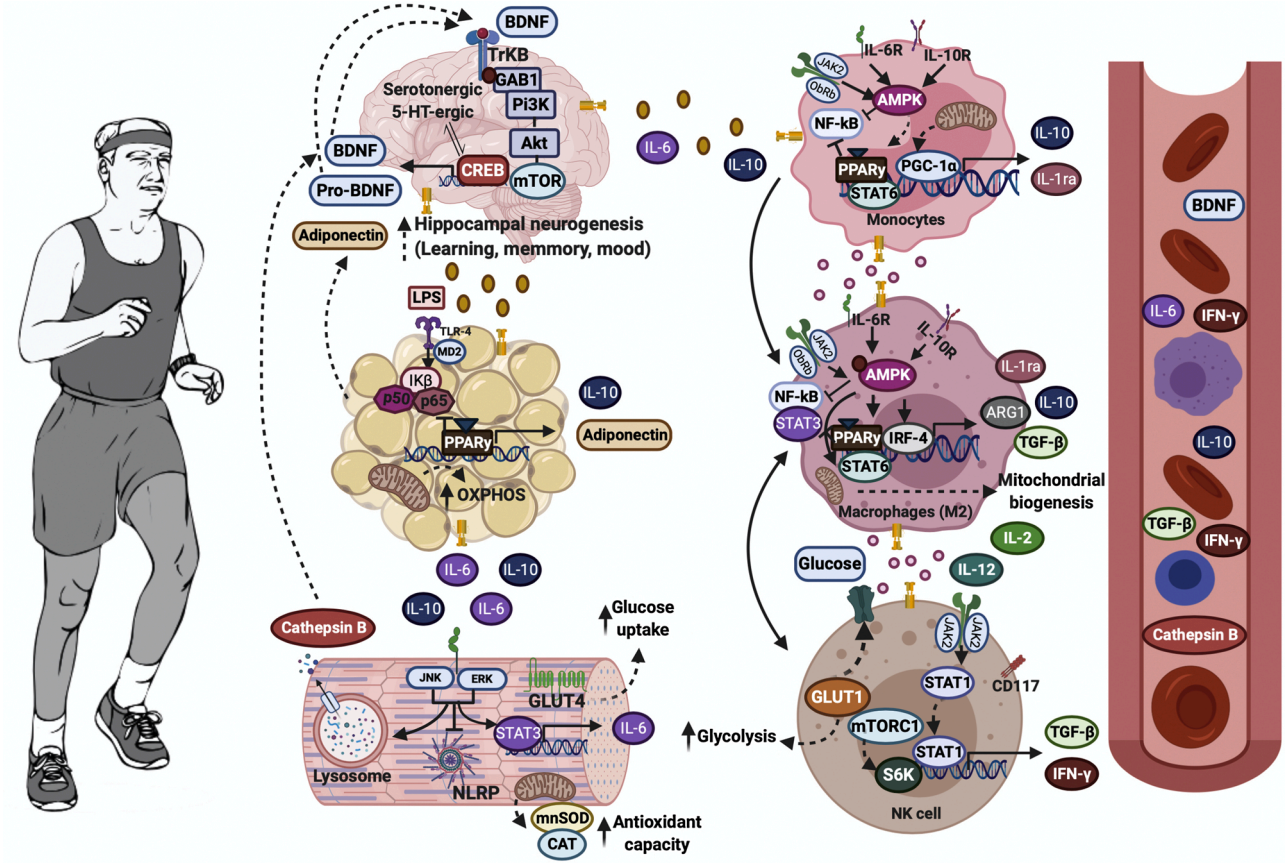

Fig. 3. Mechanisms associated in muscle – visceral fat - brain crosstalk on immunometabolism and immunosenescent response during lifelong exercise. BDNF: brain-derived neurotrophic factor, TrKB: tropomyosin receptor kinase B, GAB1: GRB2-associated-binding protein 1, PI3K: phosphoinositide 3-kinases, AKT: protein kinase B, mTORC1: mechanistic target of rapamycin complex 1, CREBP: cAMP (cyclic adenosine monophosphate)-responsive element binding protein, LPS: lipopolysaccharide, MD2: myeloid differentiation factor 2, IkB: inhibitor of kB, PPAR-gamma: peroxisome proliferator-activated receptor gamma, IL-10: interleukin 10, OXPHOS: oxidative phosphorylation, JNK: janus kinase, ERK: extracellular signal-regulated kinases, GLUT4: glucose transporter 4, STAT3: signal transducer and activator of transcription 3, NLRP: nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing proteins, mnSOD: manganese superoxide dismutase, CAT: catalase, AMPK: AMP-activated protein kinase, NF-kB: nuclear factor kB, JAK2: janus kinase 2, ObRb: leptin receptor, MAPK: mitogen-activated protein kinase, and 5, IL-6: interleukin 6, IL-6R: interleukin 6 receptor, IL-10R: interleukin 10 receptor, PGC1- α : peroxisome proliferator-activated receptor gamma coactivator 1-alpha, IRF-4: interferon regulatory factor 4, IL-1ra: interleukin 1 receptor antagonist, ARG-1: arginase 1, TGF-β: transforming growth factor beta, SOCS: suppressor of cytokine signaling proteins, STA1: signal transducer and activator of transcription 1, mTORC2: mechanistic target of rapamycin complex 2, S6K: ribosomal S6 kinase, IFN-y: interferon gamma.

adaptations, the duration of exercise training likely needs to extend years or even the course of lifespan (Perkins et al., 2020). This provides support of our hypothesis that master athletes are likely better prepared for a stress that challenges the immune system, including the age-related increase in infection susceptibility.

Previous studies from our research group showed that the most relevant adaptations to exercise found in master athletes at middle-age (~55 years old and have not less than 20 years of training experience) were the maintenance of their aerobic capacity and an anti-inflammatory state similar to that observed in healthy young adults. While aging had the most pronounced effects on levels of IL-10 and the TNF-α/IL-10 ratio, master athletes have elevated levels of the immunoregulatory cytokine IL-10, at rest and in response to a maximal effort test, close to those found in young adults (~30 years old) (Minuzzi et al., 2019).

Tregs cells produce IL-10 and TGF-β as additional mechanisms to suppress the activity of target cells, being crucial in maintaining immune tolerance and control the pro-inflammatory immune response. Minuzzi's study was the first to show that master athletes maintain the number and function of Tregs similar to the age-matched healthy control group. Suggestions that Tregs are more activated in the master athletes were found, including higher Tregs markers of activation (i.e., increased percentage of subjects expressing FoxP3 and TGF-β) compared to the control group (Minuzzi et al., 2017).

Maintaining the ability to redeploy immune cells in response to a single exercise bout is fundamental to immune-surveillance (Turner, 2016). Immune-surveillance declines with age but exercising regularly might also preserve this fundamental aspect of immune cell trafficking. Furthermore, regular exercise might prevent accumulation of terminally differentiated/exhausted T-cells with age possibly by preventing cytomegalovirus reactivation (Simpson and Bosch, 2014). In addition, exercise could reverse the immunosenescent phenotype by causing selective apoptosis (Simpson, 2011; Turner, 2016; Simpson et al., 2016). Indeed, a previous study of our group showed that VO2max was positively related to $CD4^{+}$naive T cells proportions, suggesting that individuals with better physical fitness condition better preserve their $CD4^{+}$ naïve T cells population able of recognizing and responding to new pathogens (Minuzzi et al., 2018). Thus, the big picture of maintaining high levels of aerobic fitness during the natural course of aging may help decrease the risk of infection and increase healthy longevity. Indeed, a previous study of our group showed that VO_{2max} was positively related to $CD4^{+}$ naïve T cells proportions, suggesting that individuals with better physical fitness condition better preserve their $CD4^{+}$ naïve T cells population able of recognizing and responding to new pathogens (Minuzzi et al., 2018). Thus, the big picture of maintaining high levels of aerobic fitness during the natural course of aging may help decrease the

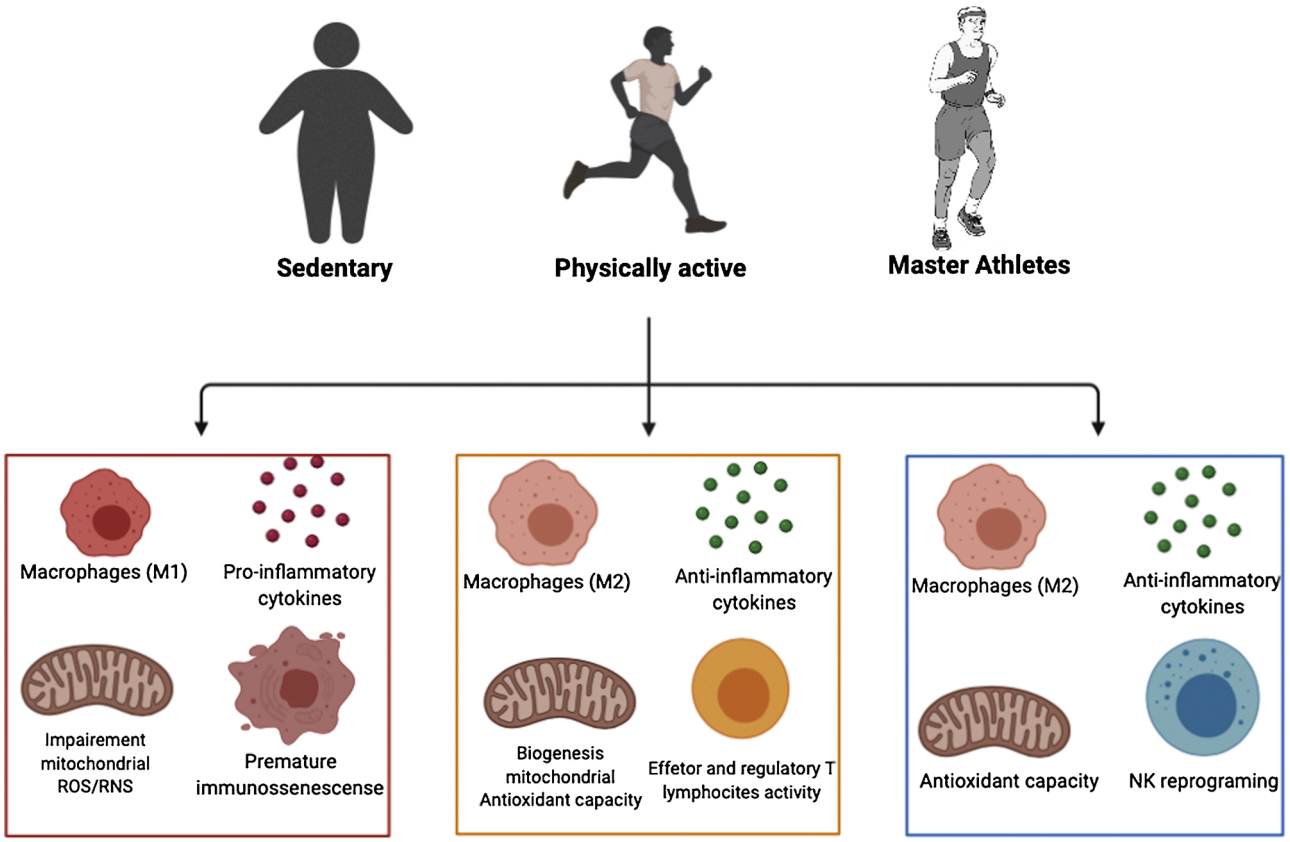

Fig. 4. Summary of cellular and systemic events according to physical fitness status during aging, and the life's mirror.

risk of infection and increase healthy longevity.

Therefore, if aging has a profound impact on the immune system, affecting its capacity to mount robust immune responses with T cell responses being the most affected, the athlete's training routine (repeated periods of energy overload and physiological stress) also adapt the immune cells. Besides, it is possible that lifelong training remodels the metabolism of different cells, creating a metabolic landscape, that improves immunosurveillance and viral response (Minuzzi, Teixeira, Santos, Rosa-Neto, & Lira, 2020).

The frequent sessions of physical exercise, like performed by master athletes, reduce the frequency of KLRG1 + T cells (senescent) over time and may help preserve the proportion of $CD4^+$ naïve T cells, hallmarks of a successful, and not maladaptive T cell aging (Minuzzi et al., 2019). Inhibitory cell signaling and energy-sensing pathways converge to inhibit the function of highly differentiated T as well as NK cells. One such inhibitory receptor, expressing killer cell lectin-like receptor G1 (KLRG1) increases on NK cells in individuals aged >70 years and KLRG1 orchestrate AMPK-dependent metabolic pathways to inhibit NK cell function. KLRG1-expressing NK cells stimulated AMPK activity and signaling through this pathway inhibited NK cell cytotoxicity, IFN-γ production, proliferation and telomerase (Müller-Durovic et al., 2016).

AMPK is spontaneously active in highly differentiated / senescent T cells (Lanna et al., 2014). KLRG1 is also increased in $CD8^+$ T cells of older individuals (Voehringer et al., 2002), raising the possibility that a similar process may be involved in these cells. More importantly, this inhibitor pathway can be targeted at different points to enhance functional responses that may be exploited to improve immunity during aging. Since our previous results from master athletes showed that lifelong training decreased the percentage of the T-cells expressing KLRG1 (Minuzzi et al., 2018) is reasonable that master athletes showing lower $KLRG1^+$ T-cells and under conditions of glucose limitation, like the high-volume and intensity of exercise training sessions, reflects the plasticity of the immune cells metabolic pathways (Mah et al., 2017) (Fig. 3). Considering that NK cells are the most responsive immune cells, and mobilized NK cells are affected by muscle-derived myokines, and exercise-dependent hyperthermia, it is reasonable that lifelong physical exercise remodels the energy metabolism of different cells, including NK cells, creating a favorable metabolic environment that improves immune-surveillance and protect to viral infections and maybe also cancer (Pedersen et al., 2016; Minuzzi et al., 2021) (Fig. 4).

The mechanisms underlying the anti-inflammatory and anti-immunosenescence effects of lifelong training are complex and have not yet been fully elucidated.

3. Future perspectives – what we know and what we don't know

- This final section summarizes the established concepts that connect immunometabolism and physical fitness status;
- Previous studies have corroborated with increased autophagy and anti-inflammatory response after inhibitory regulation of mTOR conducted by AMPK (Shao et al., 2019);
- The dysregulation between antagonistic AMPK / mTOR signaling pathways may favor the immunometabolic and functional changes found in monocytes and macrophages with advancing age. This theory is promising since the two energy sensors command the recycling of proteins and organelles, metabolic routes and inflammatory signaling pathways;
- Although studies indicate the potential effect of physical fitness on immunometabolic modulation at different levels of physical fitness, the ability of physical fitness to directly modify the metabolism of immune cells is unproven. The studies reflecting potential immunometabolic alterations induced by physical fitness are based on associative measures or indirectly measures, for example, metabolites and expression of determined genes and proteins;

- In hope of stimulating future discussion and research, we summarize the unresolved questions linked to physical fitness and the immune system.

3.1. What we know

- This comprehensive review points out the substantial importance of increasing the status of physical fitness, represented by the practice of physical exercise, as a new way to regulate the function of immune cells and to reduce the impacts of immunosenescence.
- Lifelong exercise is proposed to be a model of successful aging due to the improvement of immunometabolic responses.

3.2. What we don't know

- Although the practice of chronic physical exercise is able to counteract the damage in immune function related to age or accumulation of body fat, molecular research is necessary to detect the main signaling pathways that mediate these changes, especially in monocytes and lymphocytes;
- In addition, should be mention that empirical studies using metabolomics, metabolic flux analysis and/or seahorse assays, for example, are necessary to establish the ability of exercise to directly alter the metabolism in immune cells;
- Due to the ability of each exercise session to modulate the immune cell environment, whether due to the availability of substrates, cytokines or hormones, future studies on the crosstalk between signaling pathways and metabolic changes will certainly open the door to new strategies to combat or prevent diseases;
- It is clear that the increase in physical fitness is a protective factor against diseases in both young or elderly individuals, however, it is unclear if the type of exercise, intensity and volume may be decisive to potentiate the immunometabolic alterations of immune cells. Similar to the dose of a drug, the optimal dose of exercise for a given population to achieve more benefits on different subsets of cells of the immune system is still controversial;
- Exercising throughout life, regardless of intensity, seems to be a crucial factor. These and other questions have not yet been fully answered, but they are certainly of the extreme importance in achieving successful aging.

Acknowledgment

This study was supported by São Paulo Research Foundation (FAPESP), São Paulo-Brazil and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) #001. CSP is granted with Post Doctorate scholarship from the FAPESP (Process 2018/23402-0), CF is granted with Doctorate scholarship from the FAPESP (Process 2019/26378-6), LGM is granted with Post Doctorate scholarship from the FAPESP (Process 2019/25626-6), FSL is granted with research grants from the FAPESP (Process 2018/19678-0).

References

Aguiar, S.S., Rosa, T.S., Sousa, C.V., Santos, P.A., Barbosa, L.P., Deus, L.A., et al., 2019. Influence of body fat on oxidative stress and telomere length of master athletes. J. Strength Cond. Res. https://doi.org/10.1519/jsc.0000000000002932.

Almeida, L., Lochner, M., Berod, L., Sparwasser, T., 2016. Metabolic pathways in T cell activation and lineage differentiation. Semin. Immunol. 28 (5), 514–524. https://doi.org/10.1016/j.smim.2016.10.009.

Antunes, B.M., Campos, E.Z., Dos Santos, R.V.T., Rosa-Neto, J.C., Franchini, E., Bishop, N.C., Lira, F.S., 2019. Anti-inflammatory response to acute exercise is related with intensity and physical fitness. J. Cell. Biochem. 120 (4), 5333–5342. https://doi.org/10.1002/jcb.27810.

Astrand, I., Astrand, P.O., Hallbäck, I., Kilbom, A., 1973. Reduction in maximal oxygen uptake with age. J. Appl. Physiol. 35 (5), 649–654. https://doi.org/10.1152/jappl.1973.35.5.649.

Auffray, C., Fogg, D., Garfa, M., Elain, G., Join-Lambert, O., Kayal, S., et al., 2007. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. Science 317 (5838), 666–670. https://doi.org/10.1126/science.1142883.

Aw, N.H., Canetti, E., Suzuki, K., Goh, J., 2018. Monocyte subsets in atherosclerosis and modification with exercise in humans. Antioxidants 7 (12), 196. https://doi.org/10.3390/antiox7120196.

Azizbeigi, K., Azarbayjani, M.A., Atashak, S., Stannard, S.R., 2015. Effect of moderate and high resistance training intensity on indices of inflammatory and oxidative stress. Res. Sports Med. 23 (1), 73–87. https://doi.org/10.1080/15438627.2014.975807.

Bauer, M., Weis, S., Netea, M.G., Wetzker, R., 2018. Remembering pathogen dose: long-term adaptation in innate immunity. Trends Immunol. 39 (6), 438–445. https://doi.org/10.1016/j.it.2018.04.001.

Bishop, N.C., Hayashida, H., Clark, M., Coombs, C., Miller, S., Stensel, D.J., 2014. Effect of acute and regular exercise on growth hormone secretagogue receptor-1a expression in human lymphocytes, T cell subpopulation and monocytes. Brain Behav. Immun. 39, 172–179. https://doi.org/10.1016/j.bbi.2013.09.017.

Biswas, S.K., Mantovani, A., 2012. Orchestration of metabolism by macrophages. Cell Metab. 15 (4), 432–437. https://doi.org/10.1016/j.cmet.2011.11.013.

Booth, F.W., Roberts, C.K., Thyfault, J.P., Ruegsegger, G.N., Toedebusch, R.G., 2017. Role of inactivity in chronic diseases: evolutionary insight and pathophysiological mechanisms. Physiol. Rev. 97 (4), 1351–1402. https://doi.org/10.1152/physrev.00019.2016.

Bratic, A., Larsson, N.G., 2013. The role of mitochondria in aging. J. Clin. Invest. 123 (3), 951–957. https://doi.org/10.1172/jci64125.

Butcher, S.K., Chahal, H., Nayak, L., Sinclair, A., Henriquez, N.V., Sapey, E., et al., 2001. Senescence in innate immune responses: reduced neutrophil phagocytic capacity and CD16 expression in elderly humans. J. Leukoc. Biol. 70 (6), 881–886.

Cabral-Santos, C., Gerosa-Neto, J., Inoue, D.S., Panissa, V.L., Gobbo, L.A., Zagatto, A.M., et al., 2015. Similar anti-inflammatory acute responses from moderate-intensity continuous and high-intensity intermittent exercise. J. Sports Sci. Med. 14 (4), 849–856.

Cabral-Santos, C., de Lima Junior, E.A., Fernandes, I.M.D.C., Pinto, R.Z., Rosa-Neto, J.C., Bishop, N.C., Lira, F.S., 2019. Interleukin-10 responses from acute exercise in healthy subjects: a systematic review. J. Cell. Physiol. 234 (7), 9956–9965. https://doi.org/10.1002/jcp.27920.

Calçada, D., Vianello, D., Giampieri, E., Sala, C., Castellani, G., de Graaf, A., et al., 2014. The role of low-grade inflammation and metabolic flexibility in aging and nutritional modulation thereof: a systems biology approach. Mech. Ageing Dev. 136-137, 138–147. https://doi.org/10.1016/j.mad.2014.01.004.

Chang, C.H., Pearce, E.L., 2016. Emerging concepts of T cell metabolism as a target of immunotherapy. Nat. Immunol. 17 (4), 364–368. https://doi.org/10.1038/ni.3415.

Chapman, N.M., Chi, H., 2014. mTOR links environmental signals to t cell fate decisions. Front. Immunol. 5, 686. https://doi.org/10.3389/fimmu.2014.00686.

Chen, L., Flies, D.B., 2013. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat. Rev. Immunol. 13 (4), 227–242. https://doi.org/10.1038/nri3405.

Chen, G., Yung, R., 2019. Meta-inflammaging at the crossroad of geroscience. Aging Med. (Milton) 2 (3), 157–161. https://doi.org/10.1002/agm2.12078.

Conte, M., Martucci, M., Chiariello, A., Franceschi, C., Salvioli, S., 2020. Mitochondria, immunosenescence and inflammaging: a role for mitokines? Semin. Immunopathol. https://doi.org/10.1007/s00281-020-00813-0.

Curi, R., de Siqueira Mendes, R., de Campos Crispin, L.A., Norata, G.D., Sampaio, S.C., Newsholme, P., 2017. A past and present overview of macrophage metabolism and functional outcomes. Clin. Sci. 131 (12), 1329–1342. https://doi.org/10.1042/cs20170220.

de Araújo, A.L., Silva, L.C., Fernandes, J.R., Matias, Me.S., Boas, L.S., Machado, C.M., et al., 2015. Elderly men with moderate and intense training lifestyle present sustained higher antibody responses to influenza vaccine. Age Dordr. 37 (6), 105. https://doi.org/10.1007/s11357-015-9843-4.

De Rosa, V., Galgani, M., Porcellini, A., Colamatteo, A., Santopaolo, M., Zuchegna, C., et al., 2015. Glycolysis controls the induction of human regulatory T cells by modulating the expression of FOXP3 exon 2 splicing variants. Nat. Immunol. 16 (11), 1174–1184. https://doi.org/10.1038/ni.3269.

de Souza Teixeira, A.A., Lira, F.S., Rosa-Neto, J.C., 2020. Aging with rhythmicity. Is it possible? Physical exercise as a pacemaker. Life Sci. 261, 118453 https://doi.org/10.1016/j.lfs.2020.118453.

Delgoffe, G.M., Powell, J.D., 2009. mTOR: taking cues from the immune microenvironment. Immunology 127 (4), 459–465. https://doi.org/10.1111/j.1365-2567.2009.03125.x.

Delgoffe, G.M., Pollizzi, K.N., Waickman, A.T., Heikamp, E., Meyers, D.J., Horton, M.R., et al., 2011. The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. Nat. Immunol. 12 (4), 295–303. https://doi.org/10.1038/ni.2005.

Deretic, V., Saitoh, T., Akira, S., 2013. Autophagy in infection, inflammation and immunity. Nat. Rev. Immunol. 13 (10), 722–737. https://doi.org/10.1038/nri3532.

Desch, A.N., Gibbings, S.L., Clambey, E.T., Janssen, W.J., Slansky, J.E., Kedl, R.M., et al., 2014. Dendritic cell subsets require cis-activation for cytotoxic CD8 T-cell induction. Nat. Commun. 5, 4674. https://doi.org/10.1038/ncomms5674.

Diaz, K.M., Howard, V.J., Hutto, B., Colabianchi, N., Vena, J.E., Blair, S.N., Hooker, S.P., 2016. Patterns of sedentary behavior in US middle-age and older adults: the REGARDS study. Med. Sci. Sports Exerc. 48 (3), 430–438. https://doi.org/10.1249/MSS.0000000000000792.

Dietz, W.H., Baur, L.A., Hall, K., Puhl, R.M., Taveras, E.M., Uauy, R., Kopelman, P., 2015. Management of obesity: improvement of health-care training and systems for prevention and care. Lancet 385 (9986), 2521–2533. https://doi.org/10.1016/S0140-6736(14)61748-7.

Ding, D., Lawson, K.D., Kolbe-Alexander, T.L., Finkelstein, E.A., Katzmarzyk, P.T., van Mechelen, W., et al., 2016. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. Lancet 388 (10051), 1311–1324. https://doi.org/10.1016/S0140-6736(16)30383-X.

Dobbs, R., Sawers, C., Thompson, F., Manyika, J., Woetzel, J., Child, P., et al., 2014. Overcoming Obesity: an Initial Economic Analysis. McKinsey Global Institute.

Dorneles, G.P., da Silva, I., Boeira, M.C., Valentini, D., Fonseca, S.G., Dal Lago, P., et al., 2019a. Cardiorespiratory fitness modulates the proportions of monocytes and T helper subsets in lean and obese men. Scand. J. Med. Sci. Sports 29 (11), 1755–1765. https://doi.org/10.1111/sms.13506.

Dorneles, G.P., da Silva, I.M., Peres, A., Romao, P.R.T., 2019b. Physical fitness modulates the expression of CD39 and CD73 on CD4(+) CD25(-) and CD4(+) CD25(+) T cells following high intensity interval exercise. J. Cell. Biochem. 120 (6), 10726–10736. https://doi.org/10.1002/jcb.28364.

Dorneles, G.P., Lira, F.S., Romão, P.R., Krüger, K., Rosa Neto, J.C., et al., 2021. Levels of cardiorespiratory fitness in men exerts strong impact on lymphocyte function after mitogen stimulation. J. Appl. Physiol. (1985). https://doi.org/10.1152/japplphysiol.01051.2020.

Ekelund, U., Steene-Johannessen, J., Brown, W.J., Fagerland, M.W., Owen, N., Powell, K. E., et al., 2016. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet 388 (10051), 1302–1310. https://doi.org/10.1016/s0140-6736(16)30370-1.

Elsner, V.R., Dorneles, G., Santos, M.A., da Silva, I.M., Romão, P., Peres, A., 2019. Exercise-induced BDNF production by mononuclear cells of sedentary and physically active obese men. J. Sports Med. Phys. Fitness. https://doi.org/10.23736/S0022-4707.19.10113-2.

Ezema, C.I., Onwunali, A.A., Lamina, S., Ezugwu, U.A., Amaeze, A.A., Nwankwo, M.J., 2014. Effect of aerobic exercise training on cardiovascular parameters and CD4 cell count of people living with human immunodeficiency virus/acquired immune deficiency syndrome: a randomized controlled trial. Niger. J. Clin. Pract. 17 (5), 543–548. https://doi.org/10.4103/1119-3077.141414.

Febbraio, M.A., Pedersen, B.K., 2005. Contraction-induced myokine production and release: is skeletal muscle an endocrine organ? Exerc. Sport Sci. Rev. 33, 114–119. United States.

Fragala, M.S., Kraemer, W.J., Mastro, A.M., Denegar, C.R., Volek, J.S., Hakkinen, K., et al., 2011. Leukocyte beta2-adrenergic receptor expression in response to resistance exercise. Med. Sci. Sports Exerc. 43 (8), 1422–1432. https://doi.org/10.1249/MSS.0b013e31820b88bc.

Freedland, S.J., Aronson, W.J., 2004. Examining the relationship between obesity and prostate cancer. Rev. Urol. 6 (2), 73–81.

Friedman, J., 2016. The long road to leptin. J. Clin. Invest. 126 (12), 4727–4734. https://doi.org/10.1172/jci91578.

Frontera, W.R., Hughes, V.A., Lutz, K.J., Evans, W.J., 1991. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. J. Appl. Physiol. (1985) 71 (2), 644–650. https://doi.org/10.1152/jappl.1991.71.2.644.

Frontera, W.R., Hughes, V.A., Fielding, R.A., Fiatarone, M.A., Evans, W.J., Roubenoff, R., 2000. Aging of skeletal muscle: a 12-yr longitudinal study. J. Appl. Physiol. (1985) 88 (4), 1321–1326. https://doi.org/10.1152/jappl.2000.88.4.1321.

Fukuzumi, M., Shinomiya, H., Shimizu, Y., Ohishi, K., Utsumi, S., 1996. Endotoxin-induced enhancement of glucose influx into murine peritoneal macrophages via GLUT1. Infect. Immun. 64 (1), 108–112. https://doi.org/10.1128/IAI.64.1.108-112.1996.

Fulop, T., Dupuis, G., Baehl, S., Le Page, A., Bourgade, K., Frost, E., et al., 2016. From inflamm-aging to immune-paralysis: a slippery slope during aging for immune-adaptation. Biogerontology 17 (1), 147–157. https://doi.org/10.1007/s10522-015-9615-7.

Gatza, E., Wahl, D.R., Opipari, A.W., Sundberg, T.B., Reddy, P., Liu, C., et al., 2011. Manipulating the bioenergetics of alloreactive T cells causes their selective apoptosis and arrests graft-versus-host disease. Sci. Transl. Med. 3 (67), 67ra68.

Gerosa-Neto, J., Monteiro, P.A., Inoue, D.S., Antunes, B.M., Batatinha, H., Dorneles, G.P., et al., 2020. High- and moderate-intensity training modify LPS-induced ex-vivo interleukin-10 production in obese men in response to an acute exercise bout. Cytokine 136, 155249. https://doi.org/10.1016/j.cyto.2020.155249.

Gerriets, V.A., Kishton, R.J., Nichols, A.G., Macintyre, A.N., Inoue, M., Ilkayeva, O., et al., 2015. Metabolic programming and PDHK1 control CD4+ T cell subsets and inflammation. J. Clin. Invest. 125 (1), 194–207. https://doi.org/10.1172/JCI76012.

Gleeson, M., 2007. Immune function in sport and exercise. J. Appl. Physiol. (1985) 103 (2), 693–699. https://doi.org/10.1152/japplphysiol.00008.2007.

Glick, D., Barth, S., Macleod, K.F., 2010. Autophagy: cellular and molecular mechanisms. J. Pathol. 221 (1), 3–12. https://doi.org/10.1002/path.2697.

Guarami, A., Zwartkruis J. T, F., Nobukuni, T., Joaquin, M., Roccio, M., Stocker, H., Kozma C, S., Hafen, E., Bos L, J., Thomas, G., 2003. Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. Mol Cell. 11 (6), 1457–1466. https://doi.org/10.1016/s1097-2765(03)00220-x.

Gwinn, D.M., Shackelford, D.B., Egan, D.F., Mihaylova, M.M., Mery, A., Vasquez, D.S., et al., 2008. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol. Cell 30 (2), 214–226. https://doi.org/10.1016/j.molcel.2008.03.003.

Hall, M.N., 2016. TOR and paradigm change: cell growth is controlled. Mol. Biol. Cell 27 (18), 2804–2806. https://doi.org/10.1091/mbc.E15-05-0311.

Hallal, P.C., Andersen, L.B., Bull, F.C., Guthold, R., Haskell, W., Ekelund, U., Group, L. P. A. S. W, 2012. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 380 (9838), 247–257. https://doi.org/10.1016/S0140-6736(12)60646-1.

Hamers, A.A.J., Dinh, H.Q., Thomas, G.D., Marcovecchio, P., Blatchley, A., Nakao, C.S., et al., 2019. Human monocyte heterogeneity as revealed by high-dimensional mass cytometry. Arterioscler. Thromb. Vasc. Biol. 39 (1), 25–36. https://doi.org/10.1161/ATVBAHA.118.311022.

Handzlik, M.K., Shaw, A.J., Dungey, M., Bishop, N.C., Gleeson, M., 2013. The influence of exercise training status on antigen-stimulated IL-10 production in whole blood culture and numbers of circulating regulatory T cells. Eur. J. Appl. Physiol. 113 (7), 1839–1848. https://doi.org/10.1007/s00421-013-2614-y.

Hara, K.Y., Kondo, A., 2015. ATP regulation in bioproduction. Microb. Cell Fact. 14, 198. https://doi.org/10.1186/s12934-015-0390-6.

Hara, K., Maruki, Y., Long, X., Yoshino, K., Oshiro, N., Hidayat, S., Tokunaga, C., Avruch, J., Yonezawa, K., 2002. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. Cell 110 (2), 177–189. https://doi.org/10.1016/s0092-8674(02)00833-4.

Harris, H., 1953. Chemotaxis of monocytes. Br. J. Exp. Pathol. 34 (3), 276–279.

Haschemi, A., Kosma, P., Gille, L., Evans, C.R., Burant, C.F., Starkl, P., et al., 2012. The sedoheptulose kinase CARKL directs macrophage polarization through control of glucose metabolism. Cell Metab. 15 (6), 813–826. https://doi.org/10.1016/j.cmet.2012.04.023.

Hearps, A.C., Martin, G.E., Angelovich, T.A., Cheng, W.J., Maisa, A., Landay, A.L., et al., 2012. Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. Aging Cell 11 (5), 867–875. https://doi.org/10.1111/j.1474-9726.2012.00851.x.

Herzig, S., Shaw, R.J., 2018. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat. Rev. Mol. Cell Biol. 19 (2), 121–135. https://doi.org/10.1038/nrm.2017.95.

Hsieh, S.W., Huang, L.C., Chang, Y.P., Hung, C.H., Yang, Y.H., 2020. M2b macrophage subset decrement as an indicator of cognitive function in Alzheimer's disease. Psychiatry Clin. Neurosci. 74 (7), 383–391. https://doi.org/10.1111/pcn.13000.

Infantino, V., Convertini, P., Cucci, L., Panaro, M.A., Di Noia, M.A., Calvello, R., et al., 2011. The mitochondrial citrate carrier: a new player in inflammation. Biochem. J. 438 (3), 433–436. https://doi.org/10.1042/BJ20111275.

Inoue, D.S., Monteiro, P.A., Gerosa-Neto, J., Santana, P.R., Peres, F.P., Edwards, K.M., Lira, F.S., 2020. Acute increases in brain-derived neurotrophic factor following high or moderate-intensity exercise is accompanied with better cognition performance in obese adults. Sci. Rep. 10 (1), 13493 https://doi.org/10.1038/s41598-020-70326-1.

Intlekofer, A.M., Takemoto, N., Wherry, E.J., Longworth, S.A., Northrup, J.T., Palanivel, V.R., et al., 2005. Effector and memory CD8+ T cell fate coupled by T-bet and eomesodermin. Nat. Immunol. 6 (12), 1236–1244. https://doi.org/10.1038/ni1268.

Jacinto, E., Loewith, R., Schmidt, A., Lin, S., Rüegg, M.A., Hall, A., Hall, M.N., 2004. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nat. Cell Biol. 6 (11), 1122–1128. https://doi.org/10.1038/ncb1183.

Jakubzick, C., Gautier, E.L., Gibbings, S.L., Sojka, D.K., Schlitzer, A., Johnson, T.E., et al., 2013. Minimal differentiation of classical monocytes as they survey steady-state tissues and transport antigen to lymph nodes. Immunity 39 (3), 599–610. https://doi.org/10.1016/j.immuni.2013.08.007.

Jenny, N.S., 2012. Inflammation in aging: cause, effect, or both? Discov. Med. 13 (73), 451–460.

Jung, J., Zeng, H., Horng, T., 2019. Metabolism as a guiding force for immunity. Nat. Cell Biol. 21 (1), 85–93. https://doi.org/10.1038/s41556-018-0217-x.

Kang, J., Huddleston, S.J., Fraser, J.M., Khoruts, A., 2008. De novo induction of antigen-specific CD4+CD25+Foxp3+ regulatory T cells in vivo following systemic antigen administration accompanied by blockade of mTOR. J. Leukoc. Biol. 83 (5), 1230–1239. https://doi.org/10.1189/jlb.1207851.

Kapellos, T.S., Bonaguro, L., Gemünd, I., Reusch, N., Saglam, A., Hinkley, E.R., Schultze, J.L., 2019. Human monocyte subsets and phenotypes in major chronic inflammatory diseases. Front. Immunol. 10, 2035. https://doi.org/10.3389/fimmu.2019.02035.

Kim H, D., Sarbassov D, D., Ali M, S., King E, J., Latek R, R., Erdjument-Bromage, H., Tempst, P., Sabatini M, D., 2002. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 110 (2), 163–175.

Kim H, D., Sarbassov D, D., Ali M, S., Latek R, R., Guntur V. P, K., Erdjument-Bromage, H., Tempst, P., Sabatini M, D., 2003. GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. Molecular Cell 11 (4), 895–904.

Klysz, D., Tai, X., Robert, P.A., Craveiro, M., Cretenet, G., Oburoglu, L., et al., 2015. Glutamine-dependent α-ketoglutarate production regulates the balance between T helper 1 cell and regulatory T cell generation. In: In Science Signaling, Vol. 8. American Association for the Advancement of Science, United States, p. ra97. © 2015.

Koch, U., Radtke, F., 2011. Mechanisms of T cell development and transformation. Annu. Rev. Cell Dev. Biol. 27, 539–562. https://doi.org/10.1146/annurev-cellbio-092910-154008.

Krüger, K., Mooren, F.C., 2007. T cell homing and exercise. Exerc. Immunol. Rev. 13, 37–54.

Krüger, K., Lechtermann, A., Fobker, M., Völker, K., Mooren, F.C., 2008. Exercise-induced redistribution of T lymphocytes is regulated by adrenergic mechanisms. Brain Behav. Immun. 22 (3), 324–338. https://doi.org/10.1016/j.bbi.2007.08.008.

Krüger, K., Frost, S., Most, E., Völker, K., Pallauf, J., Mooren, F.C., 2009. Exercise affects tissue lymphocyte apoptosis via redox-sensitive and Fas-dependent signaling pathways. Am. J. Physiol. Regul. Integr. Comp. Physiol. 296 (5), R1518–1527. https://doi.org/10.1152/ajpregu.90994.2008.

Krüger, K., Mooren, F.C., Pilat, C., 2016. The immunomodulatory effects of physical activity. Curr. Pharm. Des. 22 (24), 3730–3748. https://doi.org/10.2174/1381612822666160322145107.

Kusy, K., Zielinski, J., 2015. Sprinters versus long-distance runners: how to grow old healthy. Exerc. Sport Sci. Rev. 43 (1), 57–64. https://doi.org/10.1249/jes.0000000000000033.
Landmann, R., 1992. Beta-adrenergic receptors in human leukocyte subpopulations. Eur. J. Clin. Invest. 22 (Suppl 1), 30–36.
Lanna, A., Henson, S.M., Escors, D., Akbar, A.N., 2014. The kinase p38 activated by the metabolic regulator AMPK and scaffold TAB1 drives the senescence of human T cells. Nat. Immunol. 15 (10), 965–972. https://doi.org/10.1038/ni.2981.
Larson, S.R., Atif, S.M., Gibbings, S.L., Thomas, S.M., Prabagar, M.G., Danhorn, T., et al., 2016. Ly6C(+) monocyte efferocytosis and cross-presentation of cell-associated antigens. Cell Death Differ. 23 (6), 997–1003. https://doi.org/10.1038/cdd.2016.24.
Lavin, K.M., Perkins, R.K., Jemiolo, B., Raue, U., Trappe, S.W., Trappe, T.A., 2020. Effects of aging and lifelong aerobic exercise on basal and exercise-induced inflammation. J. Appl. Physiol. (1985) 128 (1), 87–99. https://doi.org/10.1152/japplphysiol.00495.2019.
Lee, I.M., Shiroma, E.J., Lobelo, F., Puska, P., Blair, S.N., Katzmarzyk, P.T., Group, L. P. A. S. W, 2012. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 380 (9838), 219–229. https://doi.org/10.1016/S0140-6736(12)61031-9.
León, B., López-Bravo, M., Ardavín, C., 2007. Monocyte-derived dendritic cells formed at the infection site control the induction of protective T helper 1 responses against Leishmania. Immunity 26 (4), 519–531. https://doi.org/10.1016/j.immuni.2007.01.017.
Lewis, C.E., McTigue, K.M., Burke, L.E., Poirier, P., Eckel, R.H., Howard, B.V., et al., 2009. Mortality, health outcomes, and body mass index in the overweight range: a science advisory from the American Heart Association. Circulation 119 (25), 3263–3271. https://doi.org/10.1161/CIRCULATIONAHA.109.192574.
Li, C., Xu, M.M., Wang, K., Adler, A.J., Vella, A.T., Zhou, B., 2018. Macrophage polarization and meta-inflammation. Transl. Res. 191, 29–44. https://doi.org/10.1016/j.trsl.2017.10.004.
Linehan, E., Dombrowski, Y., Snoddy, R., Fallon, P.G., Kissenpfennig, A., Fitzgerald, D.C., 2014. Aging impairs peritoneal but not bone marrow-derived macrophage phagocytosis. Aging Cell 13 (4), 699–708. https://doi.org/10.1111/acel.12223.
Linke, M., Fritsch, S.D., Sukhbaatar, N., Hengstschläger, M., Weichhart, T., 2017. mTORC1 and mTORC2 as regulators of cell metabolism in immunity. FEBS Lett. 591 (19), 3089–3103. https://doi.org/10.1002/1873-3468.12711.
Liu, P.S., Wang, H., Li, X., Chao, T., Teav, T., Christen, S., et al., 2017. α-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming. Nat. Immunol. 18 (9), 985–994. https://doi.org/10.1038/ni.3796.
Longo, M., Zatterale, F., Naderi, J., Parrillo, L., Formisano, P., Raciti, G.A., et al., 2019. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int. J. Mol. Sci. 20 (9) https://doi.org/10.3390/ijms20092358.
Lumeng, C.N., Deyoung, S.M., Bodzin, J.L., Saltiel, A.R., 2007. Increased inflammatory properties of adipose tissue macrophages recruited during diet-induced obesity. Diabetes 56 (1), 16–23. https://doi.org/10.2337/db06-1076.
Luo, W., Hu, H., Chang, R., Zhong, J., Knabel, M., O'Meally, R., et al., 2011. Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1. Cell 145 (5), 732–744. https://doi.org/10.1016/j.cell.2011.03.054.
Lurier, E.B., Dalton, D., Dampier, W., Raman, P., Nassiri, S., Ferraro, N.M., et al., 2017. Transcriptome analysis of IL-10-stimulated (M2c) macrophages by next-generation sequencing. Immunobiology 222 (7), 847–856. https://doi.org/10.1016/j.imbio.2017.02.006.
Macdougall, C.E., Wood, E.G., Loschko, J., Scagliotti, V., Cassidy, F.C., Robinson, M.E., et al., 2018. Visceral adipose tissue immune homeostasis is regulated by the crosstalk between adipocytes and dendritic cell subsets. Cell Metab. 27 (3), 588–601. https://doi.org/10.1016/j.cmet.2018.02.007 e584.
Mah, A.Y., Rashidi, A., Keppel, M.P., Saucier, N., Moore, E.K., Alinger, J.B., et al., 2017. Glycolytic requirement for NK cell cytotoxicity and cytomegalovirus control. JCI Insight 2 (23). https://doi.org/10.1172/jci.insight.95128.
Makowski, L., Chaib, M., Rathmell, J.C., 2020. Immunometabolism: from basic mechanisms to translation. Immunol. Rev. 295 (1), 5–14. https://doi.org/10.1111/imr.12858.
Mills, P.J., Rehman, J., Ziegler, M.G., Carter, S.M., Dimsdale, J.E., Maisel, A.S., 1999. Nonselective beta blockade attenuates the recruitment of CD62L(-)T lymphocytes following exercise. Eur. J. Appl. Physiol. Occup. Physiol. 79 (6), 531–534. https://doi.org/10.1007/s004210050548.
Minuzzi, L.G., Rama, L., Bishop, N.C., Rosado, F., Martinho, A., Paiva, A., Teixeira, A.M., 2017. Lifelong training improves anti-inflammatory environment and maintains the number of regulatory T cells in masters athletes. Eur. J. Appl. Physiol. 117 (6), 1131–1140. https://doi.org/10.1007/s00421-017-3600-6.
Minuzzi, L.G., Rama, L., Chupel, M.U., Rosado, F., Dos Santos, J.V., Simpson, R., et al., 2018. Effects of lifelong training on senescence and mobilization of T lymphocytes in response to acute exercise. Exerc. Immunol. Rev. 24, 72–84.
Minuzzi, L.G., Chupel, M.U., Rama, L., Rosado, F., Munoz, V.R., Gaspar, R.C., et al., 2019. Lifelong exercise practice and immunosenescence: master athletes cytokine response to acute exercise. Cytokine 115, 1–7. https://doi.org/10.1016/j.cyto.2018.12.006.
Minuzzi, L.G., Teixeira, A.M., Thomatieli-Santos, R.V., Rosa-Neto, J.C., Lira, F.S., 2021. Immunometabolism and covid-19: could lifelong exercise training have a protective effect? Immunometabolism 3 (1), e210001. https://doi.org/10.20900/immunometab20210001.
Moon, J.S., Hisata, S., Park, M.A., DeNicola, G.M., Ryter, S.W., Nakahira, K., Choi, A.M. K., 2015. mTORC1-induced HK1-Dependent glycolysis regulates NLRP3 inflammasome activation. Cell Rep. 12 (1), 102–115. https://doi.org/10.1016/j.celrep.2015.05.046.
Müller-Durovic, B., Lanna, A., Covre, L.P., Mills, R.S., Henson, S.M., Akbar, A.N., 2016. Killer cell lectin-like receptor G1 inhibits NK cell function through activation of adenosine 5'-monophosphate-activated protein kinase. J. Immunol. 197 (7), 2891–2899. https://doi.org/10.4049/jimmunol.1600590.
Murray, D.R., Irwin, M., Rearden, C.A., Ziegler, M., Motulsky, H., Maisel, A.S., 1992. Sympathetic and immune interactions during dynamic exercise. Mediation via a beta 2-adrenergic-dependent mechanism. Circulation 86 (1), 203–213. https://doi.org/10.1161/01.cir.86.1.203.
NCD-RisC, 2017. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 390 (10113), 2627–2642. https://doi.org/10.1016/S0140-6736(17)32129-3.
Newsholme, E.A., Crabtree, B., Ardawi, M.S., 1985. The role of high rates of glycolysis and glutamine utilization in rapidly dividing cells. Biosci. Rep. 5 (5), 393–400. https://doi.org/10.1007/BF01116556.
Newsholme, P., Curi, R., Gordon, S., Newsholme, E.A., 1986. Metabolism of glucose, glutamine, long-chain fatty acids and ketone bodies by murine macrophages. Biochem. J. 239 (1), 121–125. https://doi.org/10.1042/bj2390121.
Newsholme, P., Gordon, S., Newsholme, E.A., 1987. Rates of utilization and fates of glucose, glutamine, pyruvate, fatty acids and ketone bodies by mouse macrophages. Biochem. J. 242 (3), 631–636. https://doi.org/10.1042/bj2420631.
Nicholson, L.B., 2016. The immune system. Essays Biochem. 60 (3), 275–301. https://doi.org/10.1042/ebc20160017.
O'Neill, L.A., Hardie, D.G., 2013. Metabolism of inflammation limited by AMPK and pseudo-starvation. Nature 493 (7432), 346–355. https://doi.org/10.1038/nature11862.
O'Neill, L.A., Kishton, R.J., Rathmell, J., 2016. A guide to immunometabolism for immunologists. Nat. Rev. Immunol. 16 (9), 553–565. https://doi.org/10.1038/nri.2016.70.
O'Sullivan, D., Pearce, E.L., 2015. Targeting T cell metabolism for therapy. Trends Immunol. 36 (2), 71–80.
Nojima, H., Tokunaga, C., Eguchi, S., Oshiro, N., Hidayat, S., Yoshino, K., Hara, K., Tanaka, N., Avruch, J., Yonezawa, K., 2003. The mammalian target of rapamycin (mTOR) partner, raptor, binds the mTOR substrates p70 S6 kinase and 4E-BP1 through their TOR signaling (TOS) motif. Journal of Biology Chemistry 278 (18), 15461–15464.
Oestreich, K.J., Weinmann, A.S., 2012. Master regulators or lineage-specifying? Changing views on CD4+ T cell transcription factors. Nat. Rev. Immunol. 12 (11), 799–804.
Oishi, Y., Manabe, I., 2016. Integrated regulation of the cellular metabolism and function of immune cells in adipose tissue. Clin. Exp. Pharmacol. Physiol. 43 (3), 294–303. https://doi.org/10.1111/1440-1681.12539.
Ortega, E., 2016. The "bioregulatory effect of exercise" on the innate/inflammatory responses. J. Physiol. Biochem. 72 (2), 361–369. https://doi.org/10.1007/s13105-016-0478-4.
Pascual, G., Fong, A.L., Ogawa, S., Gamliel, A., Li, A.C., Perissi, V., et al., 2005. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. Nature 437 (7059), 759–763. https://doi.org/10.1038/nature03988.
Pawelec, G., 2017. Does the human immune system ever really become "senescent"? F1000Res 4 (6), 1323. https://doi.org/10.12688/f1000research.11297.1.
Pawelec, G., 2018. Age and immunity: what is "immunosenescence"? Exp. Gerontol. 105, 4–9. https://doi.org/10.1016/j.exger.2017.10.024.
Pawelec, G., Hirokawa, K., Fülöp, T., 2001. Altered T cell signalling in ageing. Mech. Ageing Dev. 122 (14), 1613–1637. https://doi.org/10.1016/s0047-6374(01)00290-1.
Pearce, E.L., 2010. Metabolism in T cell activation and differentiation. Curr. Opin. Immunol. 22 (3), 314–320.
Pearce, E.L., Pearce, E.J., 2013. Metabolic pathways in immune cell activation and quiescence. Immunity 38 (4), 633–643. https://doi.org/10.1016/j.immuni.2013.04.005.
Pearce, E.L., Mullen, A.C., Martins, G.A., Krawczyk, C.M., Hutchins, A.S., Zediak, V.P., et al., 2003. Control of effector CD8+ T cell function by the transcription factor Eomesodermin. Science 302 (5647), 1041–1043. https://doi.org/10.1126/science.1090148.
Pedersen, B.K., 2009. The diseasome of physical inactivity–and the role of myokines in muscle–fat cross talk. J. Physiol. 587 (Pt 23), 5559–5568.
Pedersen, B.K., 2017. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. Eur. J. Clin. Invest. 47 (8), 600–611. https://doi.org/10.1111/eci.12781.
Pedersen, L., Idorn, M., Olofsson, G.H., Lauenborg, B., Nookaew, I., Hansen, R.H., Hojman, P., 2016. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. Cell Metab. 23 (3), 554–562. https://doi.org/10.1016/j.cmet.2016.01.011.
Perkins, R.K., Lavin, K.M., Raue, U., Jemiolo, B., Trappe, S.W., Trappe, T.A., 2020. Effects of aging and lifelong aerobic exercise on expression of innate immune components in human skeletal muscle. J. Appl. Physiol. (1985). https://doi.org/10.1152/japplphysiol.00615.2020.
Petersen, A.M., Pedersen, B.K., 2005. The anti-inflammatory effect of exercise. J. Appl. Physiol. (1985) 98 (4), 1154–1162. https://doi.org/10.1152/japplphysiol.00164.2004.
Powell, J.D., Pollizzi, K.N., Heikamp, E.B., Horton, M.R., 2012. Regulation of immune responses by mTOR. Annu. Rev. Immunol. 30, 39–68. https://doi.org/10.1146/annurev-immunol-020711-075024.

Powers, S.K., Duarte, J., Kavazis, A.N., Talbert, E.E., 2010. Reactive oxygen species are signalling molecules for skeletal muscle adaptation. Exp. Physiol. 95 (1), 1–9. https://doi.org/10.1113/expphysiol.2009.050526.

Poznanski, S.M., Barra, N.G., Ashkar, A.A., Schertzer, J.D., 2018. Immunometabolism of T cells and NK cells: metabolic control of effector and regulatory function. Inflamm. Res. 67 (10), 813–828. https://doi.org/10.1007/s00011-018-1174-3.

Radak, Z., Torma, F., Berkes, I., Goto, S., Mimura, T., Posa, A., et al., 2019. Exercise effects on physiological function during aging. Free Radic. Biol. Med. 132, 33–41. https://doi.org/10.1016/j.freeradbiomed.2018.10.444.

Rigsby, L.W., Dishman, R.K., Jackson, A.W., Maclean, G.S., Raven, P.B., 1992. Effects of exercise training on men seropositive for the human immunodeficiency virus-1. Med. Sci. Sports Exerc. 24 (1), 6–12.

Robinson, E., Durrer, C., Simtchouk, S., Jung, M.E., Bourne, J.E., Voth, E., Little, J.P., 2015. Short-term high-intensity interval and moderate-intensity continuous training reduce leukocyte TLR4 in inactive adults at elevated risk of type 2 diabetes. J. Appl. Physiol. (1985) 119 (5), 508–516. https://doi.org/10.1152/japplphysiol.00334.2015.

Rodriguez, I.J., Lalinde Ruiz, N., Llano León, M., Martínez Enríquez, L., Montilla Velásquez, M.D.P., Ortiz Aguirre, J.P., Parra López, C.A., 2021. Immunosenescence study of t cells: a systematic review. Front. Immunol. 15 (11), 604591. https://doi.org/10.3389/fimmu.2020.604591.

Ross, M.D., Malone, E.M., Simpson, R., Cranston, I., Ingram, L., Wright, G.P., et al., 2018. Lower resting and exercise-induced circulating angiogenic progenitors and angiogenic T cells in older men. Am. J. Physiol. Heart Circ. Physiol. 314 (3), H392–H402. https://doi.org/10.1152/ajpheart.00592.2017.

Ruffino, J.S., Davies, N.A., Morris, K., Ludgate, M., Zhang, L., Webb, R., Thomas, A.W., 2016. Moderate-intensity exercise alters markers of alternative activation in circulating monocytes in females: a putative role for PPARgamma. Eur. J. Appl. Physiol. 116 (9), 1671–1682. https://doi.org/10.1007/s00421-016-3414-y.

Saare, M., Tserel, L., Haljasmägi, L., Taalberg, E., Peet, N., Eimre, M., et al., 2020. Monocytes present age-related changes in phospholipid concentration and decreased energy metabolism. Aging Cell 19 (4), e13127. https://doi.org/10.1111/acel.13127.

Santoro, A., Martucci, M., Conte, M., Capri, M., Franceschi, C., Salvioli, S., 2020. Inflammaging, hormesis and the rationale for anti-aging strategies. Ageing Res. Rev., 101142 https://doi.org/10.1016/j.arr.2020.101142.

Santos, M.D., Buti, M., López-Cano, C., Sánchez, E., Vidal, A., Hernández, M., et al., 2020. Dynamics of anthropometric indices in a large paired cohort with 10 years of follow-up: paving the way to sarcopenic obesity. Front. Endocrinol. (Lausanne) 11, 209. https://doi.org/10.3389/fendo.2020.00209.

Saunders N, R., Metcalfe S, M., Nicholson L, M., 2001. Rapamycin in transplantation: a review of the evidence. Kidney Int . 59 (1), 3–16. https://doi.org/10.1046/j.1523-1755.2001.00460.x.

Schmelzle, T., Hall, M.N., 2000. TOR, a central controller of cell growth. Cell 103 (2), 253–262.

Selak, M.A., Armour, S.M., MacKenzie, E.D., Boulahbel, H., Watson, D.G., Mansfield, K. D., et al., 2005. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. Cancer Cell 7 (1), 77–85. https://doi.org/10.1016/j.ccr.2004.11.022.

Serbina, N.V., Salazar-Mather, T.P., Biron, C.A., Kuziel, W.A., Pamer, E.G., 2003. TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. Immunity 19 (1), 59–70.

Shao, B.Z., Wang, S.L., Fang, J., Li, Z.S., Bai, Y., Wu, K., 2019. Alpha7 nicotinic acetylcholine receptor alleviates inflammatory bowel disease through induction of AMPK-mTOR-p70S6K-Mediated autophagy. Inflammation 42 (5), 1666–1679. https://doi.org/10.1007/s10753-019-01027-9.

Shaw, A.C., Joshi, S., Greenwood, H., Panda, A., Lord, J.M., 2010. Aging of the innate immune system. Curr. Opin. Immunol. 22 (4), 507–513. https://doi.org/10.1016/j.coi.2010.05.003.

Shi, C., Pamer, E.G., 2011. Monocyte recruitment during infection and inflammation. Nat. Rev. Immunol. 11 (11), 762–774. https://doi.org/10.1038/nri3070.

Silveira, L.S., Antunes Bde, M., Minari, A.L., Dos Santos, R.V., Neto, J.C., Lira, F.S., 2016. Macrophage polarization: implications on metabolic diseases and the role of exercise. Crit. Rev. Eukaryot. Gene Expr. 26 (2), 115–132. https://doi.org/10.1615/CritRevEukaryotGeneExpr.2016015920.

Simoes, H.G., Sousa, C.V., Dos Santos Rosa, T., da Silva Aguiar, S., Deus, L.A., Rosa, E.C. C.C., et al., 2017. Longer telomere length in elite master sprinters: relationship to performance and body composition. Int. J. Sports Med. 38 (14), 1111–1116. https://doi.org/10.1055/s-0043-120345.

Simpson, R.J., 2011. Aging, persistent viral infections, and immunosenescence: can exercise "make space"? Exerc. Sport Sci. Rev. 39 (1), 23–33. https://doi.org/10.1097/JES.0b013e318201f39d.

Simpson, R.J., Bosch, J.A., 2014. Special issue on exercise immunology: current perspectives on aging, health and extreme performance. Brain Behav. Immun. 39, 1–7. https://doi.org/10.1016/j.bbi.2014.03.006.

Simpson, R.J., Kunz, H., Agha, N., Graff, R., 2015. Exercise and the regulation of immune functions. Prog. Mol. Biol. Transl. Sci. 135, 355–380. https://doi.org/10.1016/bs.pmbts.2015.08.001.

Simpson, R.J., Bigley, A.B., Spielmann, G., LaVoy, E.C., Kunz, H., Bollard, C.M., 2016. Human cytomegalovirus infection and the immune response to exercise. Exerc Immunol Ver 22, 8–27.

Simpson, R.J., Campbell, J.P., Gleeson, M., Kruger, K., Nieman, D.C., Pyne, D.B., et al., 2020. Can exercise affect immune function to increase susceptibility to infection? Exerc. Immunol. Rev. 26, 8–22.

Solana, R., Tarazona, R., Gayoso, I., Lesur, O., Dupuis, G., Fulop, T., 2012. Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. Semin. Immunol. 24 (5), 331–341. https://doi.org/10.1016/j.smim.2012.04.008.

Sotak, Š., 2020. Adipocytokines and thyreopathies. Vnitr. Lek. 66 (2), 47–52.

Spielmann, G., McFarlin, B.K., O'Connor, D.P., Smith, P.J., Pircher, H., Simpson, R.J., 2011. Aerobic fitness is associated with lower proportions of senescent blood T-cells in man. Brain Behav. Immun. 25 (8), 1521–1529. https://doi.org/10.1016/j.bbi.2011.07.226.

Suzuki, K., 2019. Chronic inflammation as an immunological abnormality and effectiveness of exercise. Biomolecules 9 (6), 223. https://doi.org/10.3390/biom9060223.

Szabo, S.J., Kim, S.T., Costa, G.L., Zhang, X., Fathman, C.G., Glimcher, L.H., 2000. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell 100 (6), 655–669. https://doi.org/10.1016/s0092-8674(00)80702-3.

Tanaka, H., Seals, D.R., 2008. Endurance exercise performance in masters athletes: age-associated changes and underlying physiological mechanisms. J. Physiol. 586 (1), 55–63. https://doi.org/10.1113/jphysiol.2007.141879.

Tannahill, G.M., Curtis, A.M., Adamik, J., Palsson-McDermott, E.M., McGettrick, A.F., Goel, G., et al., 2013. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature 496 (7444), 238–242. https://doi.org/10.1038/nature11986.

Tarique, A.A., Logan, J., Thomas, E., Holt, P.G., Sly, P.D., Fantino, E., 2015. Phenotypic, functional, and plasticity features of classical and alternatively activated human macrophages. Am. J. Respir. Cell Mol. Biol. 53 (5), 676–688. https://doi.org/10.1165/rcmb.2015-0012OC.

Teixeira, A.A., Minuzzi, L.G., Lira, F.S., Gonçalves, A.S.V., Martinho, A., et al., 2021. Lifelong exercise improvement in effector-1 memory CD4+ response and anti-inflammatory profile are related to clock gene expression in master athletes. Exerc. Immunol. Rev. v. Publish ahead of print.

Thompson, C.B., 2011. Rethinking the regulation of cellular metabolism. Cold Spring Harb. Symp. Quant. Biol. 76, 23–29. https://doi.org/10.1101/sqb.2012.76.010496.

Tsai, H.H., Chang, S.C., Chou, C.H., Weng, T.P., Hsu, C.C., Wang, J.S., 2016. Exercise training alleviates hypoxia-induced mitochondrial dysfunction in the lymphocytes of sedentary males. Sci. Rep. 6, 35170 https://doi.org/10.1038/srep35170.

Turner, J.E., 2016. Is immunosenescence influenced by our lifetime "dose" of exercise? Biogerontology 17 (3), 581–602. https://doi.org/10.1007/s10522-016-9642-z.

Vander Haar, E., Lee, S.I., Bandhakavi, S., Griffin, T.J., Kim, D.H., 2007. Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40. Nat. Cell Biol. 9 (3), 316–323. https://doi.org/10.1038/ncb1547.

Varela, A.R., Pratt, M., Harris, J., Lecy, J., Salvo, D., Brownson, R.C., Hallal, P.C., 2018. Mapping the historical development of physical activity and health research: a structured literature review and citation network analysis. Prev. Med. 111, 466–472. https://doi.org/10.1016/j.ypmed.2017.10.020.

Vats, D., Mukundan, L., Odegaard, J.I., Zhang, L., Smith, K.L., Morel, C.R., et al., 2006. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. Cell Metab. 4 (1), 13–24. https://doi.org/10.1016/j.cmet.2006.05.011.

Voehringer, D., Koschella, M., Pircher, H., 2002. Lack of proliferative capacity of human effector and memory T cells expressing killer cell lectinlike receptor G1 (KLRG1). Blood 100 (10), 3698–3702. https://doi.org/10.1182/blood-2002-02-0657.

Von Ah Morano, A.E., Dorneles, G.P., Peres, A., Lira, F.S., 2020. The role of glucose homeostasis on immune function in response to exercise: the impact of low or higher energetic conditions. J. Cell. Physiol. 235 (4), 3169–3188. https://doi.org/10.1002/jcp.29228.

Waickman, A.T., Powell, J.D., 2012. mTOR, metabolism, and the regulation of T-cell differentiation and function. Immunol. Rev. 249 (1), 43–58. https://doi.org/10.1111/j.1600-065X.2012.01152.x.

Walsh, N.P., 2018. Recommendations to maintain immune health in athletes. Eur. J. Sport Sci. 18 (6), 820–831. https://doi.org/10.1080/17461391.2018.1449895.

Wang, F., Zhang, S., Vuckovic, I., Jeon, R., Lerman, A., Folmes, C.D., et al., 2018. Glycolytic stimulation is not a requirement for M2 macrophage differentiation. Cell Metab. 28 (3), 463–475. https://doi.org/10.1016/j.cmet.2018.08.012 e464.

Warburg, O., 1956. On the origin of cancer cells. Science 123 (3191), 309–314.

Warren, M.W., Hynan, L.S., Weiner, M.F., 2012. Leptin and cognition. Dement. Geriatr. Cogn. Disord. 33 (6), 410–415. https://doi.org/10.1159/000339956.

WHO, 2010. Global Recommendations on Physical Activity for Health. World Health Organization, Geneva.

WHO, 2018. Ageing and Health. World Health Organization.

Wolf, J., Rose-John, S., Garbers, C., 2014. Interleukin-6 and its receptors: a highly regulated and dynamic system. Cytokine 70 (1), 11–20. https://doi.org/10.1016/j.cyto.2014.05.024.

Wolf, A.A., Yáñez, A., Barman, P.K., Goodridge, H.S., 2019. The ontogeny of monocyte subsets. Front. Immunol. 10, 1642. https://doi.org/10.3389/fimmu.2019.01642.

Wu, C.H., Yao, W.J., Lu, F.H., Yang, Y.C., Wu, J.S., Chang, C.J., 2001. Sex differences of body fat distribution and cardiovascular dysmetabolic factors in old age. Age Ageing 30 (4), 331–336. https://doi.org/10.1093/ageing/30.4.331.

Yang, K., Chi, H., 2012. mTOR and metabolic pathways in T cell quiescence and functional activation. Semin Immunol. 24 (6), 421–428. https://doi.org/10.1016/j.smim.2012.12.004.

Yarbro, J.R., Emmons, R.S., Pence, B.D., 2020. Macrophage immunometabolism and inflammaging: roles of mitochondrial dysfunction, cellular senescence, CD38, and NAD. Immunometabolism 2 (3), e200026. https://doi.org/10.20900/immunometab20200026.

Yeung, F., Hoberg, J.E., Ramsey, C.S., Keller, M.D., Jones, D.R., Frye, R.A., Mayo, M.W., 2004. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 23 (12), 2369–2380. https://doi.org/10.1038/sj.emboj.7600244.

Zeng, H., Yang, K., Cloer, C., Neale, G., Vogel, P., Chi, H., 2013. mTORC1 couples immune signals and metabolic programming to establish T(reg)-cell function. Nature 499 (7459), 485–490. https://doi.org/10.1038/nature12297.

Zhang, Y., Zhan, R.X., Chen, J.Q., Gao, Y., Chen, L., Kong, Y., et al., 2015. Pharmacological activation of PPAR gamma ameliorates vascular endothelial insulin resistance via a non-canonical PPAR gamma-dependent nuclear factor-kappa B trans-repression pathway. Eur. J. Pharmacol. 754, 41–51. https://doi.org/10.1016/j.ejphar.2015.02.004.

Zhang, L., Tschumi, B.O., Lopez-Mejia, I.C., Oberle, S.G., Meyer, M., Samson, G., et al., 2016. Mammalian target of rapamycin complex 2 controls CD8 t cell memory differentiation in a Foxo1-dependent manner. Cell Rep. 14 (5), 1206–1217. https://doi.org/10.1016/j.celrep.2015.12.095.

Zhang, Y., Reichel, J.M., Han, C., Zuniga-Hertz, J.P., Cai, D., 2017. Astrocytic process plasticity and IKKbeta/NF-kappaB in central control of blood glucose, blood pressure, and body weight. Cell Metab. 25 (5), 1091–1102 e1094.

Zhang, X., Liang, T., Yang, W., Zhang, L., Wu, S., Yan, C., Li, Q., 2020. Injection suppresses production of Interleukin-6 by activating autophagy through the AMPK-mTOR pathway in lipopolysaccharide-stimulated macrophages. Oxid. Med. Cell. Longev. 2020, 1364147 https://doi.org/10.1155/2020/1364147.

Zheng, Y., Collins, S.L., Lutz, M.A., Allen, A.N., Kole, T.P., Zarek, P.E., Powell, J.D., 2007. A role for mammalian target of rapamycin in regulating T cell activation versus anergy. J. Immunol. 178 (4), 2163–2170.

Ziegler-Heitbrock, L., Ancuta, P., Crowe, S., Dalod, M., Grau, V., Hart, D.N., et al., 2010. Nomenclature of monocytes and dendritic cells in blood. Blood 116 (16), e74–80. https://doi.org/10.1182/blood-2010-02-258558.