Review

Monocytes, Macrophages, and Exercise Prescription: A New Frontier in Immunomodulation

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Abstract: Exercise is a well-established nonpharmacological intervention with wide-ranging benefits for human health. Among its many physiological effects, exercise has significant immunomodulatory effects, particularly by influencing monocyte and macrophage activity. In this review, we summarize current findings on how acute and chronic exercise of varying modalities affect monocyte/macrophage mobilization, polarization, and function. We also discuss the implications of these changes in the context of exercise-mediated protection against inflammatory, metabolic, oncologic, neurodegenerative, and musculoskeletal diseases. Furthermore, we highlight emerging mechanisms through which exercise modulates monocyte/macrophage biology, including the roles of exerkines, neuroendocrine signaling, and peroxisome proliferator-activated receptors (PPARs). A better understanding of these pathways may offer new insights into the development of exercise-based strategies for immune regulation and disease intervention.

Keywords: exercise; monocyte; macrophage; inflammation; phagocytosis; exerkines; PPARs

1. Introduction

Regular physical exercise has profound benefits on multiple organ systems and is increasingly recognized as a powerful adjunct for the prevention and management of diverse chronic diseases, including metabolic disorders, cancer, and neurodegenerative conditions. In recent decades, the global rise in obesity and its associated metabolic complications—such as type 2 diabetes mellitus (T2DM), hypertension, and nonalcoholic fatty liver disease (NAFLD)—has imposed a substantial burden on health care systems, economies, and society at large. Exercise training improves body composition and enhances cardiovascular and metabolic health in individuals with metabolic syndrome and related disorders [1]. In addition to metabolic regulation, epidemiological and mechanistic studies have demonstrated that regular physical activity reduces the incidence of at least 20 cancer types, augments the efficacy of anticancer therapies, and mitigates treatment-related toxicity. These effects are partially mediated by exercise-induced remodeling of the tumor immune microenvironment (TIME), including enhanced immune surveillance and reduced immunosuppression [2–4]. Similarly, in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease—conditions for which effective therapies remain limited—exercise has been shown to improve cognitive performance, memory, and attentional capacity [5]. Importantly, many chronic diseases share a common feature: a dysregulated immune system characterized by chronic low-grade inflammation and impaired immune surveillance. This immune imbalance predisposes individuals to infections, accelerates disease progression, and worsens therapeutic outcomes. Regular exercise has emerged as a nonpharmacological intervention capable of restoring immune homeostasis and exerting systemic anti-inflammatory effects through multiple mechanisms, including modulating cytokine profiles, reducing visceral adiposity, and enhancing regulatory immune cell populations [6,7]. Consequently, exercise represents a key modifiable lifestyle factor that integrates metabolic and immune regulation to confer broad health benefits.

The immune system is highly responsive to physical activity, and increasing evidence has attributed many of the health-promoting effects of exercise to its ability to beneficially modulate immune function. Chronic moderate-intensity exercise is generally immunoenhancing: it promotes key aspects of innate immunity, including increased antimicrobial activity of tissue-resident macrophages; the mobilization of immunoglobulins and anti-inflammatory cytokines; and the recruitment of neutrophils, natural killer (NK) cells, cytotoxic T lymphocytes, and immature B cells. These adaptive changes contribute to improved immune surveillance and a balanced inflammatory profile. In contrast, excessive training

loads or prolonged high-intensity exercise can transiently impair immune competence, generating a temporary "open window" of immunosuppression characterized by systemic inflammation, oxidative stress, and impaired cellular immunity [6]. Among immune cell subsets, regulatory T cells and B-cell-related immunity have been extensively studied in the context of exercise-induced immune modulation [8–10]. However, despite the growing recognition of monocytes and macrophages as central regulators of inflammation and tissue remodeling, a comprehensive synthesis of how exercise influences their phenotypes and functions is lacking. Given their remarkable plasticity and pivotal roles in orchestrating immune responses, elucidating the mechanisms through which exercise modulates monocyte and macrophage biology could unveil novel therapeutic strategies for managing chronic inflammatory diseases.

In this review, we present a detailed examination of the effects of acute and chronic exercise on monocyte and macrophage populations and explore how different exercise modalities influence their distribution, polarization, and function. We also discuss the implications of these changes for monocyte/macrophage-related diseases and highlight emerging mechanistic insights, including the roles of exercise-induced bioactive factors (exerkines), neuroendocrine pathways, and nuclear receptor signaling, such as PPARs. By integrating advances in immunology, metabolism, and exercise physiology, this synthesis aims to deepen our understanding of the immunometabolic interface shaped by physical activity and to inform future research and clinical applications.

2. Monocytes and Macrophages: Immunological Sentinels at the Interface of Homeostasis and Inflammation

Monocytes and macrophages constitute a central arm of the innate immune system and play indispensable roles in maintaining tissue homeostasis and initiating immune responses to injury and infection. These myeloid cells exhibit remarkable functional heterogeneity and plasticity, contributing to diverse biological processes, including the phagocytosis of pathogens and apoptotic cells, antigen presentation, cytokine and chemokine secretion, tissue remodeling, and metabolic regulation [11].

Circulating human monocytes are traditionally classified into three subsets on the basis of CD14 and CD16 expression: classical ($CD14^{++}CD16^{-}$, Mon1), intermediate ($CD14^{++}CD16^{+}$, Mon2), and nonclassical ($CD14^{+}CD16^{++}$, Mon3). Mon1 cells, the predominant subset (80–90% of circulating monocytes), are highly phagocytic, generate reactive oxygen species (ROS), and secrete proinflammatory cytokines upon Toll-like receptor (TLR) activation. Mon2 monocytes (~5–10%) display potent antigen-presenting capabilities, elevated MHC class II expression, and high intracellular levels of tumor necrosis factor (TNF)-α. Mon3 cells (~5–10%) are patrolling monocytes characterized by reduced phagocytic and ROS activity but a heightened capacity to respond to nucleic acids and lipopolysaccharide (LPS) via cytokine release [11].

Tissue-resident macrophages arise from yolk sac-derived erythro-myeloid progenitors (EMPs) and fetal liver progenitors during embryogenesis and populate organs, where they persist via self-renewal [12]. In contrast, during inflammatory insults, monocytes derived from bone marrow hematopoietic stem cells (HSCs) are recruited to peripheral tissues and differentiate into monocyte-derived macrophages (MDMs). These MDMs often differ from embryonic macrophages in terms of their transcriptomic profiles, effector functions, and lifespan [13]. Macrophages can be polarized along a functional continuum. The M1-like (proinflammatory) phenotype is induced by interferon-γ (IFN-γ) and microbial stimuli, leading to the production of interleukin-12 (IL-12), TNF-α, and nitric oxide (NO), supporting antimicrobial and antitumor responses. M2-like (anti-inflammatory) macrophages are stimulated by IL-4, IL-13, and IL-10, promoting tissue repair, angiogenesis, and immunosuppression via the production of IL-10 and transforming growth factor-β (TGF-β) [11].

Physical exercise has broad effects on immune surveillance, inflammation, and metabolic homeostasis. The magnitude and direction of its effects on monocyte and macrophage populations are influenced by the frequency, intensity, and duration of exercise interventions [14–16]. Exercise intensity is typically defined by oxygen consumption (%maximal oxygen uptake (VO_{2max})) or heart rate reserve (HRR), with moderate intensity classified as 46–63% VO_{2max} or 64–76% HR_max and vigorous intensity as 64–90% VO_2max or ≥90% HR_max [14,15]. In murine studies, treadmill exercise intensity is categorized as low (<15 m/min), moderate (15–20 m/min), or high (>20 m/min) and is often modulated by incline and session duration [16].

2.1. Acute Exercise as an Immune Modulator of Monocytes/Macrophages

As shown in Table 1, moderate-to-high intensity acute exercise frequently increases monocyte counts, whereas acute high-intensity or exhaustive exercise preferentially mobilizes proinflammatory monocytes and increases monocyte infiltration. Low- to moderate-intensity aerobic exercise enhances macrophage phagocytosis in an exercise intensity-dependent manner. Acute moderate-intensity aerobic exercise can also modulate cytokine release by monocytes, whereas high-intensity eccentric exercise further disrupts intracellular cytokine production. Mild to moderate exercise may preserve or even enhance the antioxidant capacity of monocytes.

Table 1. Impact of acute exercise on monocyte/macrophage mobilization, reprogramming, and functions.

Experimental Model	Exercise Protocol	Tissue Sample	Result	Reference
Impact of acute exercise on monocyte/macrophage mobilization and reprogramming				
Male and female participants Marches (n = 20)	Walking, 30 km/day for 4 consecutive days.	Circulating monocytes	Exercise increases monocyte counts, especially in CMV seropositive subjects.	[17]
Female breast cancer patients (n = 20)	Cycling, 10 min without fatigue development.	Circulating monocytes	Exercise increases has no effect on total, Mon1 and Mon3 monocytes, while increases Mon2 monocyte count.	[18]
Moderately trained males (n = 15)	Treadmill training, 70% VO_{2max}, 45 min.	Circulating monocytes	Exercise increases monocytes which drops after exercise.	[19]
Well-trained, non-professional endurance athletes (n = 15)	One ultra-marathon (130 km), One traditional marathon (42.195 km)	Circulating monocytes	The numbers of circulating monocytes increases after both marathon and ultra-marathon with higher levels after ultra-marathon.	[20]
Healthy and physically active individuals (n = 11)	Cycling, 70% VO_{2max}, 30 min.	Circulating monocytes	The absolute numbers of total monocytes, Mon1, Mon2, and Mon3 are all increased during acute exercise and drop after exercise.	[21]
Male marathon runners (n = 27)	A marathon race	Circulating monocytes	Exercise increases the total number total and Mon2 monocytes, but decreases Mon1 and Mon3 monocytes.	[22]
Abdominally obese, physically inactive adults (n = 67)	Cycling, 3 × 2 min at 75% VO_{2max} with 1 min recovery at 30% between the 2 min workouts, 8 min at 40% VO_{2max}, a second set is repeated.	Circulating monocytes	Exercise increases the number of monocytes, T cells and neutrophils in the circulation, these mobilization is unaffected by IL-6.	[23]
Male competitive athletes (n = 12)	Cycling at 70% of the individual anaerobic threshold for 4 h.	Circulating monocyte	Exercise increases monocyte number, while has no effect on monocyte phagocytosis.	[24]
Healthy subjects with normal or high blood pressure (n = 44)	Treadmill training, 65–70 of VO_{2max}, 20 min.	Circulating monocytes	The absolute numbers of all monocyte subsets increase. % of Mon2 and Mon3 increases, but % of Mon1 decreases.	[25]
Healthy endurance-trained males (n = 9)	Cycling, 75% VO_{2max}, 1.5 h.	Circulating monocytes	Total monocyte cell count increases at 0, 1 and 4 h post-exercise.	[26]
Club-level athletes (n = 8)	Cycling, 60 km distance in the fastest possible time	Circulating monocytes	Circulating monocytes increases immediately after exercise and 1 h post-exercise.	[27]
Lean insulin sensitive, obese insulin sensitive, and obese insulin resistance.	Cycling, 20% VO_{2max} for 5 min, followed by a 50% increase in the peak power for 60 min, which are divided into 3 sets of 20 min, separated by 5 min each set,	Circulating monocytes	Exercise increases the absolute monocyte number, while reducing the percentage of $CD16^+$ monocytes in all groups.	[28]
Healthy males (n = 20)	Cycling, 50% of VO_{2max} for 20 min and 65% of VO_{2max} for 40 min.	Circulating monocytes	Exercise increases all monocyte subsets, with Mon3 showing the greatest fold increase; only Mon1 is increased 2 h after exercise.	[29]
Healthy men (n = 12)	Cycling, 82% VO_{2max}, 2 min.	Circulating monocytes	Exercise increases the number of Mon1 and Mon3 monocytes and has no effect on Mon2; Mon3 increases more than Mon1.	[30]
Healthy subjects with normal or elevated blood pressure (n = 77)	Treadmill training, 65–70% of VO_{2max}, 20 min.	Circulating monocytes	% Mon3 monocytes increases, % Mon2 does not change, whereas % Mon1 decreases post-exercise.	[31]
Healthy controls (n = 47), patients with somatization syndromes (n = 26), or major depression (n = 38)	Moderate-intensity exercise, at least 30 min per day, for 1 week.	Circulating monocytes	Exercise increases the number of monocytes in healthy controls, but not in patients with somatization syndromes or major depression.	[32]
Healthy young men (n = 10)	Cycling, 60% VO_{2max}, 30 min/day, 5 consecutive days.	Circulating monocytes	The 5-day moderate-intensity exercise significantly decreases monocyte count.	[33]
Patients with CKD (n = 15)	A single bout of walking, moderate- intensity (RPE 12–14), 30 min.	Circulating monocytes	Exercise induces a systemic anti-inflammatory effect, but has no effect on circulating monocyte count.	[34]
Young males (n = 11)	Treadmill training, 75% VO_{2max}, 45 min.	Salivary monocytes	Exercise does not significantly change salivary, including leukocyte, granulocytes, T cells, and B cells, and monocytes.	[35]
Healthy subjects (n = 40)	Cycling, either 200 W or 400 W for 1 min, or to exhaustion for 3–10 min.	Circulating monocytes	1 min of cycling at 400 W leads to an increase in Mon3 monocytes.	[36]
Healthy volunteers, patients with MetS	Cycling, 100 W for several seconds, and then continuously raises to 400 W in no longer than 5 s and maintains at this level for 60 s or until exhaustion.	Circulating monocytes	Absolute counts of pro-inflammatory monocytes mobilized by a strenuous exercise are similar in healthy and MetS patients.	[37]
Healthy males	Cycling, from 45 s to 2 min at 100, 200, or 400 W.	Circulating monocytes	$CD14^+$ $CD16^+$ monocytes are increased by exercise at 400 W.	[38]

Table 1. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	Reference
Healthy male (n = 25)	Treadmill training, VO_{2max} test.	Circulating monocytes	Exercise elicits a pro-inflammatory effect, reduces the percentage of Mon1 monocytes and increases Mon2 and Mon3 monocytes.	[39]
Healthy subjects (n = 15), patients with CHF (n = 20), and CKD (n = 20)	Cycling, starting with either 20 or 40 W and an incremental load of 10 or 20 W per minute until exhaustion.	Circulating monocytes	Exercise increases % Mon2 and Mon3 and decreases % Mon1 in healthy subjects and patients with CKD; this response is attenuated in CHF.	[40]
Healthy volunteers (n = 12)	Treadmill training, VO_{2max} test.	Circulating monocytes	Total monocyte count and numbers of Mon1 increases by 15 min after exercise and drop at 1 h.	[41]
Patients with early-stage prostate cancer (n = 20)	Cycling, a watt-max test, and four high-intensity intervals	Circulating monocytes	Exercise increases monocyte counts while decreasing post-exercise.	[42]
Recreationally trained males (n = 12)	Arm exercise at 60% VO_{2max}; moderate cycling at 60%VO_{2max}; easy cycling at 60% VO_{2max}, 45 min.	Circulating monocytes	Arm exercise and moderate cycling induce larger increases in monocyte numbers and Mon1 in the recovery period than easy cycling, while Mon2 and Mon3 decrease in all groups in the recovery period.	[43]
Wistar rats	Swimming, low-intensity for 5, 10, 15 min, moderate-intensity for 5, 10, 15 min.	Circulating macrophages	Low-intensity groups and moderate- intensity for 5 min exhibit an increase in monocyte levels.	[44]
Sedentary healthy men (n = 25)	Cycling, 40% (mild), 60% (moderate), or 80% (heavy) of VO_{2max} respectively, 40 min.	Circulating monocytes	Heavy exercise increases counts of monocyte subgroups; moderate and mild exercise have no effect.	[45]
Healthy subjects (n = 12)	Continuous exercise: Cycling, 70% VO_{2max}, 45 min; Sprint interval exercise: Cycling, 6 × 20 s.	Circulating monocytes	A single bout of sprint interval exercise increases Tie2-expressing Mon1, Mon2, and Mon3 monocytes and decrease post exercise, but is unchanged by a single bout of continuous exercise.	[46]
Healthy controls (n = 9), T2DM patients (n = 10)	Cycling, HIIT (7 × 1 min @ 85% VO_{2max}, separated by 1-min recovery).	Circulating monocytes	Exercise has overall anti-inflammatory effect; the Mon1 monocyte number increases by acute exercise and drops after exercise in both healthy and T2DM groups.	[47]
17 males (7 resistance-trained, 10 non-resistance-trained)	Resistance exercise circuit, 75% of one-repetition maximum.	Circulating monocytes	Exercise increases the monocytes and reaches the maximum 2 h after exercise.	[48]
Healthy recreationally active subjects (n = 20)	An acute bout of resistance exercise, four whole exercises at 70% of 1 RM.	Circulating monocytes	Exercise increases monocyte counts and returns to basal after exercise, the percent of monocyte subsets is not affected.	[49]
Resistance-trained men (n = 10)	An acute bout of lower-body resistance exercise	Circulating monocytes	Exercise decreases the proportion of $CD14^+$ monocytes and increases Mon1 monocytes	[50]
Healthy, recreationally active physical education students (n = 20)	Level: running, 45 min with 0°; CONC: running, 30 min with 0°, 15 min of uphill with 4.5°; ECC: running, 30 min with 0°, 15 min of downhill with 4.5°.	Circulating monocytes	Monocyte counts increase in all three groups after exercise.	[51]
Healthy male students (n = 11)	300 unilateral, maximal, isokinetic eccentric actions, 30 sets of 10 repetitions, 35 min.	Circulating monocytes	Monocyte counts increase immediately after exercise and peak 6 h after exercise.	[52]
Highly endurance- trained male runners (n = 14)	Concentric exercise: running, 80% VO_{2max}, 60 min. Eccentric exercise: 6 sets of 10 maximal eccentric contractions.	Circulating monocytes	Both exercises decrease monocyte activation 6 h after exercise, with an increase for eccentric exercise 24 h after exercise.	[53]
Young men (n = 10)	300 eccentric contractions of the knee extensors at 30°/s on an isokinetic dynamometer.	Circulating monocytes	Exercise has no effect on monocyte numbers, but increases the proportions of total macrophages, HLA^+ macrophage, and $CD11b^+$ macrophages, and then drop.	[54]
Healthy women (n = 34)	Resistance group: 3 sets of 10 repetitions at 75–80% of 1-RM, 60 min; Spinning group: cycling, 70–85% of HR_{max}, 50 min.	Circulating monocytes	An acute bout of intermittent or anaerobic exercise induces immune suppression, and the proportion of monocytes increases by exercise and then decreases after exercise.	[55]
Male police officers (n = 20)	6 × 35 m maximal sprints interspersed by 10 s passive recovery period.	Circulating monocytes	Short-term anaerobic sprint exercise increases circulating monocytes.	[56]

Table 1. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	Reference
Healthy men (n = 18), men with T2DM (n = 20)	Cycling, 85% HR_{max}, 30 min.	Skeletal muscle macrophages	Exercise triggers an inflammatory response in skeletal muscle of healthy and T2DM men, concomitant with an infiltration of immune cells, including macrophages.	[57]
Health young men (n = 12)	Aerobic cycling (70% VO_{2max}), 60 min.	Skeletal muscle macrophages	Exercise increases M2 monocyte infiltration into human skeletal muscle.	[58]
Diabetic rats	Treadmill training, 0.3 km/h and increases by 0.3 km/h every 3 min, 20 min.	Peritoneal macrophages	The proportion of necrosis macrophages in diabetic rats is increased 24 h after exercise.	[59]
Male C57BL/6 mice	Treadmill training, 15 m/min (73.7 ± 1.8% VO_{2max}) for 0.5 or 1 h.	Skeletal muscle macrophages	Total Macrophage and M2 macrophage, and neutrophils accumulate in the skeletal muscle of mice 24 h after exercise.	[60]
Male C57BL/6 mice	Treadmill training (7% incline), 10 m/min for 15 min, 15 and 20 m/min for 15 min each, 24 m/min until exhaustion.	Skeletal muscle macrophages	Exhaustive exercise increases neutrophil infiltration into the gastrocnemius muscle, thereby inducing monocyte infiltration.	[61]
HFD Wistar rats	Swimming, two 3 h of moderate exercise bouts, separated by one 45-min rest period.	WAT macrophages	Moderate acute exercise induces a phenotypic switch from M1 to M2 macrophages in obese rats.	[62]
HFD male C57BL/6 mice	Treadmill training (5% incline), 15 m/min, 120 min.	Macrophages in the inguinal fat	Exercise improves insulin signaling, upregulates IL-6 and IL-10 signaling, and decreases M1 macrophage.	[63]
Obese mice	Treadmill training, low-intensity: 12 m/min for 75 min; moderate-intensity: 15 m/min for 60 min; high-intensity: 18 m/min for 50 min.	WAT macrophages	The M2/M1 macrophage ratio of WAT is increased immediately after exercise in both normal and obese mice, but differences vary depending on recovery time and exercise intensity.	[64]
Obese adults with regular exercise	Endurance exercise (80 ± 3% HR_{max}), 60 min.	Macrophages in abdominal adipose tissue	Exercise does not change total immune cell, macrophage, or T cell content in adipose tissue.	[65]
Male C57BL/6 mice	Treadmill training (7% incline), 10 m/min for 15 min, 15 m/min for 15 min, 20 m/min for 15 min, 24 m/min until exhaustion.	Kidney macrophages	Exhaustive exercise increases monocyte infiltration into the kidney.	[66]
Physically active young men (n = 9)	Single-leg exercises, such as 45 deg leg press, single-leg squats, knee extensions, and walking lunges, 45 min.	Skeletal muscle macrophages	The number of $CD68^+$ macrophages in muscle is increased after exercise.	[67]
Subjects, age (26–68)	5 sets of 8 repetitions of leg extensions at 80% of 1 RM, with a 6 set performed to exhaustion.	Macrophages in the vastus laterial	M2 macrophages do not increase after acute resistance exercise, but increase in response to chronic resistance training.	[68]
Young exerciser (n = 10), old healthy non-exercisers (n = 10), lifelong exerciser (n = 7)	3 × 10 rep, 70% 1-RM.	Macrophages in the vastus laterial	Exercise has no effect on macrophages in the vastus laterial of all groups.	[69]
Young and elderly males	3 sets of 8 repetitions followed by a 4 sets to voluntary failure for each of the three exercises with resistance of 80% 1-RM, 2 min rest between sets, and 5 min between exercises.	Macrophages in the vastus laterial	Exercise has no effect on total macrophages, but increases the number of $CD163^+$ macrophages in vastus laterial biopsies of young males, but not in the elderly.	[70]
Elderly males (n = 25), young females (n = 12), elderly females (n = 12)	5 sets of 12 concentric repetitions (70% 1 RM) followed by 4 sets of 6 eccentric repetitions (110% 1 RM). 2 min rest between sets and 5-min break between concentric and eccentric exercise.	Macrophages in the vastus laterial	Exercise increases all types of macrophages in the vastus laterial of the elderly, but not in young individuals.	[71]
Patients with COPD	Bilateral lower-limb, high-intensity resistance training, thrice weekly, 8 weeks.	Macrophages in the quadriceps	Acute resistance exercise increases M2 macrophages in quadriceps of patients with COPD, while reversed by regular resistance training.	[72]
SD rats	Treadmill training (16° decline), 16 m/min, 90 min.	Skeletal muscle macrophages	M1 macrophage is infiltrated into muscle necrosis sites 1–3 day after exercise, M2 macrophage is presented in muscle from 0 h to 2 weeks after exercise.	[73]
SD rats	Treadmill training (16° decline), 18 sessions (5 min/session) separated by 2 min of rest at 16 m/min for a total of 90 min.	Skeletal muscle macrophages	Exercise increases M1 and M2 macrophages in the soleus muscle.	[74]
C57BL/6 mice	Treadmill training (16° decline), 18 bouts of running, 5 min/bout with a 2 min rest interval.	Macrophages in triceps brachii	Eccentric exercise recruits $Ly6C^+$ macrophages with important pro-inflammatory cytokine elevation 3 days after exercise.	[75]

Table 1. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	Reference
Male Wistar rats	Treadmill training (17° decline), 16 m/min for 5 min followed by a 2-min rest, 18 sessions, 90 min.	Skeletal muscle macrophages	The CD68 and CD163 mRNA expressions behave distinctly after exercise.	[76]
Impact of acute exercise on monocyte/macrophage phagocytosis				
Adult male Wistar rats	Swimming (5% body weight load), 60 min.	Circulating monocyte	Exercise increases monocyte phagocytosis.	[77,78]
Adult male Wistar rats	Swimming with a load of either 2, 4, 6, or 8% of body weight, 20 min.	Circulating monocytes	Exercise increases monocyte phagocytosis in a workload-dependent way and persists for up to 12 h.	[79]
Male Wistar rats	Swimming until exhaustion.	Peritoneal macrophages	Low- and moderate-intensity aerobic exercise enhances peritoneal macrophage phagocytic capacity.	[80]
Wistar rats	Swimming, low-intensity for 5 (5 L), 10 (10 L), 15 min (15 L), moderate-intensity for 5 (5 M), 10 (10 M), 15 min (15 M).	Peritoneal macrophages	Macrophage phagocytosis increases for the low-intensity groups and 10 M group.	[44]
Male marathon runners (n = 27)	A marathon race	Circulating monocyte	Exercise has no effect on monocyte phagocytosis in marathon runners.	[22]
Male competitive athletes (n = 12)	Cycling at 70% of the individual anaerobic threshold for 4 h.	Circulating monocyte	Exercise increases monocyte number, while has no effect on monocyte phagocytosis.	[24]
Impact of acute exercise on the secretory function of monocyte/macrophage				
Healthy women (n = 8) and women diagnosed with fibromyalgia (n = 8)	Cycling, 55% VO_{2max}, 45 min.	Circulating monocytes	Exercise increases the release of cytokines (IL-1β, TNFα, IL-6, IL-10, and IL-8) by monocytes induced by LPS in healthy women, which are reversed by fibromyalgia.	[81]
Healthy subjects with normal or elevated blood pressure (n = 77)	Treadmill training, 65–70% of VO_{2max}, 20 min.	Circulating monocytes	TNFα production decreases post-exercise in all monocyte subsets.	[31]
Healthy subjects (n = 47)	Treadmill training, 65–70% VO_{2max}, 20 min.	Circulating monocytes	Exercise attenuates LPS-stimulated intracellular TNFα production by monocytes.	[82]
Healthy male (n = 10)	Cycling, 60% VO_{2max}, 60 min.	Circulating monocytes	Exercise decreases TNFα production of monocytes.	[83]
Recreationally active healthy young men (n = 12)	High-intensity eccentric exercise, running, 12 × 5 min, 10% decline, 15 km/h, 60 min.	Circulating monocytes	Exercise intracellular monocyte IL-10 and IL-6 decreases, while serum IL-10 and IL-6 increase.	[84]
Endurance-trained men	Cycling, 70% VO_{2max}, 2 h.	Circulating monocytes	The number of monocytes increases after exercise and 2 h post-exercise, but these cells produce less cytokines post-exercise.	[85]
Obese Zucker rats	Treadmill training, 17 cm/s for 5 min followed by 25–35 min at 35 cm/s.	Peritoneal macrophages	Exercise decreases the spontaneous release of IL-6 and increases TNFα by macrophages of obese rats.	[86]
Obese Zucker rat	Treadmill training, 35 cm/s, 35 min.	Peritoneal macrophages	Exercise increases the release of IL-1β by the LPS-stimulated macrophages from obese rats.	[87]
Adult male Wistar rats	Swimming (5% body weight load), 60 min.	Circulating monocytes	Exercise increases the production of H_2O_2 and NO by monocytes.	[77,78]
Adult male Wistar rats	Swimming with a load of either 2, 4, 6, or 8% of body weight, 20 min.	Circulating monocytes	Exercise increases H_2O_2 production by monocytes in a workload-dependent way; NO production is increased 12 h post exercise.	[79]
Sedentary healthy men (n = 25)	Cycling, 40% (mild), 60% (moderate), or 80% (heavy) of $VO_{2max,}$ respectively, 40 min.	Circulating monocytes	Acute heavy exercise increases monocyte ROS production, possibly by decreasing SOD activity and GSH content in monocytes, while mild and moderate exercise likely protects against suppression of the anti-oxidative capacity of monocytes.	[45]

2.1.1. Acute Exercise: Monocyte Mobilization and Macrophage Reprogramming

Acute bouts of aerobic or resistance exercise induce transient yet significant shifts in monocyte subset distribution and macrophage polarization across multiple tissues (see Table 1). Even a single session of moderate-intensity aerobic exercise can increase circulating monocyte counts in both healthy individuals and those with metabolic comorbidities [19–28]. Some studies have reported post-exercise reductions or no changes, which are likely influenced by exercise type, subject health status, and sampling time points [33–35]. For example, findings on subset-specific mobilization remain inconsistent: some studies report increases across all three monocyte subsets after 30 or 60 min of acute exercise [21,29], whereas others observe preferential mobilization of Mon2 by a marathon race [22] or Mon1 and Mon3 subsets by acute high-intensity interval training (HIIT) [30]. Considering that the exercise protocol and the collection time for postexercise blood samples differed across these studies, these discrepancies may therefore reflect individual variation and the temporal dynamics of monocyte egress and recirculation. Mechanistically, monocyte mobilization during exercise is mediated by catecholamines and glucocorticoids, which facilitate bone marrow egress and demargination from the vascular endothelium. Notably, these responses can be blunted in individuals with chronic stress, depression, or hypertension [31,32]. In contrast, acute high-intensity or exhaustive exercise preferentially mobilizes proinflammatory monocytes and enhances monocyte infiltration into peripheral tissues such as skeletal muscle, adipose tissue, and the kidney [36–41]. For example, acute treadmill exercise in diabetic mice increases peritoneal macrophage inflammation and necrosis [59], whereas in both healthy and diabetic subjects, monocyte infiltration and differentiation of M2 macrophages in skeletal muscle are modulated by oncostatin M signaling [60]. These infiltrating macrophages may mediate beneficial effects, such as improved insulin sensitivity in adipose tissue [62–64], or contribute to tissue injury, as observed in exercise-induced renal inflammation [66].

In skeletal muscle, macrophage recruitment after acute eccentric or resistance exercise reflects both damage-related inflammation and reparative responses [73–76]. Increased post-exercise M2 macrophage content has been documented in young adults [70], older individuals [71], and patients with chronic obstructive pulmonary disease (COPD) [72]. However, the magnitude and nature of these responses remain heterogeneous across studies, likely because of differences in training history, age, sex, and systemic inflammatory status [67–69].

2.1.2. Impact of Acute Exercise on Monocyte/Macrophage Functions

Acute physical exercise modulates monocyte and macrophage function in an intensity-dependent and context-specific manner. In both rodent and human studies, a single bout of swimming has been shown to increase monocyte phagocytic activity [77,78]. Furthermore, low- to moderate-intensity aerobic exercise increases macrophage phagocytosis in an exercise intensity-dependent manner [44,79,80]. In contrast, participation in a marathon race does not appear to alter monocyte phagocytic capacity in trained runners [22,24], suggesting that extreme endurance exercise may not further stimulate innate immune functions in well-adapted individuals.

Acute moderate-intensity aerobic exercise can also modulate cytokine release by monocytes. In healthy women, exercise transiently increases monocyte-derived cytokines, although this response is blunted in individuals with fibromyalgia [81]. Paradoxically, several studies have shown that TNF-α production decreases across all monocyte subsets following moderate-intensity aerobic exercise [31,82,83], indicating a shift toward an anti-inflammatory monocyte phenotype. In obesity models, acute aerobic exercise elicits divergent macrophage responses. Macrophages isolated from obese rats display reduced spontaneous IL-6 release and increased TNF-α secretion following exercise [86]. Moreover, LPS-stimulated macrophages from obese animals exhibit elevated IL-1β production after acute exercise [87], highlighting a potentially exacerbated inflammatory tone in metabolically compromised settings.

High-intensity eccentric exercise further disrupts intracellular cytokine production, inhibiting IL-10 and IL-6 synthesis in monocytes, despite concurrent increases in circulating IL-10 and IL-6 levels [84]. This dissociation suggests that monocytes may not be the primary source of the increase in systemic IL-10 and IL-6 observed post-exercise. In support of this, exercise-induced expansion of circulating monocytes is often accompanied by reduced cytokine output from these cells [85].

Oxidative function is another critical parameter influenced by acute exercise. Both hydrogen peroxide (H_2O_2) and NO production by monocytes increase in a workload-dependent manner during aerobic exercise [77–79]. While heavy exercise is associated with increased ROS production in monocytes—likely because of reduced superoxide dismutase (SOD) activity and diminished glutathione (GSH) content—mild to moderate exercise may preserve or even enhance the antioxidant capacity of monocytes [45].

Together, these findings indicate that acute exercise initiates rapid, multifaceted changes in monocyte and macrophage function shaped by exercise intensity, metabolic status, and underlying health conditions. Importantly,

while moderate-intensity activity may support innate immune competence and anti-inflammatory signaling, excessive or strenuous exercise can disrupt cytokine balance and promote oxidative stress, particularly in individuals with metabolic dysfunction.

2.2. Chronic Exercise as an Immune Modulator of Monocytes/Macrophages

As shown in Table 2, moderate-intensity chronic exercise training and HIIT typically reduce monocyte counts and downregulate proinflammatory cytokine expression. Similarly, chronic exercise reduces monocyte infiltration and promotes M2 polarization in various tissues. The phagocytic function of macrophages is improved by chronic moderate-intensity training and HIIT, while prolonged or strenuous aerobic exercise has been shown to reduce the phagocytic function of macrophages and monocytes. Exercise intensity and host metabolic status also influence macrophage cytokine responses, and excessive exercise can be immunosuppressive.

Table 2. Impact of chronic exercise on monocyte/macrophage mobilization, reprogramming, and functions.

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
Impact of chronic exercise on monocyte/macrophage mobilization and reprogramming				
People with Axial SpA (n = 20)	Walking, 30 min/day, 5 days/week, 12 weeks.	Circulating monocytes	Exercise significantly decreases the proportion of pro-inflammatory Mon3 monocytes.	[88]
Adults with hypertension (n = 31)	Cycling, 30–40 min/time, 40–65% of HR_{max}, 3 months.	Circulating monocytes	Exercise has no effect on all monocyte counts.	[89]
Adolescents with obesity (n = 62)	Low-intensity: 20% VT1 and lasts longer than 50 min. High-intensity: VT1, 24 weeks.	Circulating monocytes	Both low and high intensity exercise for 24 weeks improves the inflammatory profile, high-intensity exercise reduces monocytes but not for low-intensity.	[90]
Healthy, sedentary females (n = 19)	Moderate-intensity walking, 3 times/day, 8 weeks.	Circulating monocytes	Exercise suppresses M1 markers while increases M2 markers expression on monocytes, potentially via PPARγ signaling to improve insulin sensitivity.	[91]
Overweight women (n = 42)	Cycling, the lactate threshold intensity, 30–60 min/day, 1–6 times/week, 6 weeks.	Circulating monocytes	Aerobic exercise may be anti-inflammatory; monocyte counts significantly decrease after exercise.	[92]
Patients with CKD (n = 15)	Walking, speed at RPE 12–14, 30 min/day, 5 days/week, 6 months.	Circulating monocytes	Regular exercise exerts anti-inflammatory effects and has no effect on total circulating monocyte counts.	[34]
Diet-induced obese mice	Voluntary wheeling running: 5 days/week, 8 weeks; treadmill training: 22 m/min, 60 min/day, 8 weeks.	Circulating monocytes	Voluntary wheeling running group has higher monocytes than the control and treadmill training group.	[93]
Patients with CABG (n = 49)	Cycling, low-intensity or vigorous-intensity, 30 min/session, 2 sessions/day, 5 days/week, 20–21 sessions.	Circulating monocytes	Vigorous-intensity decreases blood Mon1 and Mon2 monocyte counts but not the low-intensity, Mon3 count remains unaffected.	[94]
Female Wistar rats (n = 64)	Treadmill training, 5 days/week (including two exhausting tests), 5 weeks.	Circulating monocytes	Exercise impairs innate and acquired immunity while having no effect on the proportion of circulating monocytes.	[95]
Physically inactive overweight/obese adults (n = 40), physically active lean/overweight adults (n = 9)	70% 1 RM, 15 repetitions, the intensity increases gradually, 3 days/week on alternate days, 12 weeks.	Circulating monocytes	Resistance exercise decreases circulating $CD14^+CD16^+$ monocytes.	[96]
Sedentary overweight men (n = 30)	80%1-RM, 4 sets of 8 repetitions, and a 2 min rest between sets, 17–20 min/day, 8 weeks.	Circulating monocytes	Resistance exercise increases the percentage of $CD14^+CD16^-$ monocytes and reduces the percentage of $CD14^-CD16^+$ monocytes.	[97]
Patients with multiple myeloma (n = 8)	30 min of interval cycling, followed by 60 min of total body resistance training, 2 days/week, 5 months.	Circulating monocytes	Exercise increases the percentage of blood monocytes.	[98]
Physically active (n = 15) and physically inactive subjects (n = 15)	Endurance training: 20 min at 70–80% HR_{max}, resistance training: 8 exercises, 2 sets at 70–80% 1 RM. 3 days/week, 12 weeks.	Circulating monocytes	Exercise reduces the $CD14^+CD16^+$ monocyte percentage in the physically inactive group.	[99]
Peripubertal children with overweight or obesity (n = 109)	20-week combined aerobic and resistance exercise training, 80% HR_{max}.	Circulating monocytes	Exercise has no effect on circulating monocytes.	[100]
Healthy, sedentary, elderly subjects (n = 24)	Endurance exercise: cycling, 10 min; resistance exercise: 20–40% 1 RM, 1–2 sets of 15 repetitions. 2 days/week, 12 weeks.	Circulating monocytes	Exercise has no effect on the total number of circulating monocytes, but increases CD80-expressing monocytes in elderly subjects.	[101]
Children with high-risk cancer (n = 20)	Aerobic and resistance exercise, 3 weeks.	Circulating monocytes	Exercise has no significant effect on circulating monocytes in children with high-risk cancer.	[102]
Lean or obese subjects (n = 27)	Cycling, 24 sessions, each session consists of 8–12 cycling exercise bouts of 60 s, at 80–110% VO_{2max}, Followed by active recovery of 60 s at 30 W. 3 days/week, 8 weeks.	Circulating monocytes	HIIT reduces the percentage of Mon3 monocytes in individuals with obesity, restore the balance among the $CD16^+$ monocytes.	[103]

Table 2. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
Older adults with RA (n = 12)	3 × 30-min sessions/week of 10 ≥ 60 s intervals of high intensity (80–90% VO_{2max}) separated by similar bouts of lower-intensity intervals (50–60% VO_{2max}), 10 weeks	Circulating monocytes	HIIT reduces circulating Mon2 and Mon3 monocytes in older adults with RA.	[104]
Obese mice	Treadmill training, 15–20 m/min, 60 min/day, 5 days/week, 16 weeks.	Hepatic macrophages	Exercise decreases the $F4/80^+$ macrophages in the liver of diet-induced obese mice.	[105,106]
Male db/db mice	Treadmill training, 10 m/min, 5 days/week, 12 weeks.	Hepatic macrophages	Exercise mitigates the diabetes-induced increase in hepatic macrophages.	[107]
C57BL/6 mice with HFD	Treadmill training, 12–20 m/min, 30–60 min/day, 5 days/week, 12 weeks.	Hepatic macrophages	Exercise reduces total macrophages and increases M2 macrophages in the liver of HFD mice.	[108]
NAFLD mice	Voluntary wheel running, 12 weeks.	Hepatic macrophages	Exercise inhibits NF-κB activation as well as reduces hepatic macrophage recruitment in NAFLD mice.	[109]
Male C57BL/6 mice with acute liver injury	Voluntary wheel running, 45 days	Hepatic macrophages	Exercise decreases total macrophages, and the mRNA expression of inflammatory cytokines IL-6, IL-1β, TGF-β, and CCL2 in the liver of mice with acute liver injury.	[110]
Male C57BL/6 mice with liver ischemia-reperfusion injury	Treadmill training, 12.5 m/min, 5 days/week, 1 h/day, 4 weeks.	Hepatic macrophages	Exercise preconditioning polarizes macrophages to an anti-inflammatory state after liver ischemia-reperfusion injury.	[111]
C57BL/6 mice with NASH	Treadmill training, 13–20 m/min, 37.5–41.5 min/day, 14 weeks.	Hepatic macrophages	HIIT is superior to moderate-intensity training for reducing the accumulation of pro-inflammatory, monocyte-derived macrophages in the NASH liver and reducing myeloid progenitor populations in the bone marrow.	[112]
Male C57BL/6 mice, B6.129X1 mice, B6(Cg) mice	Treadmill training, 12.5 m/min, 60 min/day, 5 days/week, 16 weeks.	KCs	Exercise drove KCs to be an anti-inflammatory phenotype with trained immunity via metabolic reprogramming.	[113]
Obese OLETF rats	Treadmill training (15% incline), 40 m/min, 6 × 2.5 min bouts/d, 5 d/week, 12 weeks	Hepatic macrophages	Eccentric exercise has no significant effect on total hepatic macrophage population, but inhibits M1 macrophage polarization and increases M2 macrophages.	[114]
T2DM mice	Treadmill training (15% incline), 5 days/week, 8 weeks. 4 min/time and rest for 2 min/time for 10 consecutive groups/day, 16–26 m/min.	Hepatic macrophages	Eccentric exercise reduces total hepatic macrophages and M1 macrophages, and increases M2 macrophages.	[115]
Male mice	Treadmill training (10% inclination), 12 m/min, 1 h/day, 6 days/week, 6 weeks.	Macrophages in scWAT and BAT	Exercise upregulates M2 macrophage marker genes expression while downregulates M1 macrophage marker genes expression in scWAT and BAT.	[116]
Caucasian overweight men (n = 60)	Endurance training (jogging, cycling, rowing, cross training), 7 days/week, 65–85% HRmax, 12 weeks.	adipose tissue macrophages	Exercise increases the number of anti-inflammatory $CD163^+$ macrophages in subcutaneous abdominal adipose tissue of overweight men.	[117]
Adults with overweight or obesity	The exercise group has almost tenfold greater MET versus sedentary, and VO_{2max} is nearly 25% higher in the exercise group.	Macrophages in subcutaneous adipose tissue	Exercise decreases macrophages in the subcutaneous adipose tissue of adults with overweight or obesity.	[118]
Male C57BL/6 mice with HFD	Treadmill training, 60 min/day, 5 days/week, 15–20 m/min, 16 weeks.	adipose tissue macrophages	Exercise inhibits monocyte infiltration and reduces $CD11c^+$ inflammatory macrophages in adipose tissue of HFD mice.	[119]
Male C57BL/6 mice with HFD	Treadmill training (8% incline), 12 m/min, 40 min/day, 5 days/week, for 4, 8, 12 weeks	Adipose tissue macrophages	Exercise inhibits monocyte infiltration, increases M2, and suppresses M1 macrophages in HFD mice	[120]
C57BL/6 mice with HFD	Treadmill training. Low intensity: 12 m/min for 75 min; mid-intensity: 15 m/min for 60 min; high-intensity: 18 m/min for 50 min.	Adipose tissue macrophages	Exercise increases M2 macrophage polarization in the adipose tissue of HFD mice, and the M2 macrophage polarization is most pronounced in high-intensity exercise group.	[121]
HFD rats	Swimming exercise, 1 h/day, 5 times/week, 6 weeks.	Macrophages in visceral adipose tissues	Exercise increases M2 macrophages while reducing M1 macrophages in visceral adipose tissues of HFD rats.	[122]
Wistar rats with HFD	Treadmill training, 5 days/week, 10 weeks. 50–60% of VO_{2max}, 30 min/day.	Adipose tissue macrophages	Exercise inhibits M1 macrophages and increases M2 macrophages in the adipose tissue of HFD rats.	[123]
HFD-induced obese mice	Treadmill training, 12–20 m/min, 60 min/day, 16 weeks.	Adipose tissue macrophages	Exercise inhibits M1 monocyte infiltration, induces the phenotype switching from M1 to M2 macrophage in adipose tissue of obese mice.	[124]
HFD-induced obese mice	Treadmill training, 14 m/min, 60 min/day, 5 days/week, 8 weeks.	Renal sinus adipose tissue macrophages	Exercise reduces CCL2 and CD68 expression, improves the conversion from M1 to M2 macrophages in renal sinus adipose tissue macrophages of obese mice.	[125]

Table 2. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
Wistar rats with HFD	Treadmill training, 5 days/week, 10 weeks. Aerobic-interval training: 3-min bouts at 40 m/min, interspersed by 3-min active recovery at 20 m/min with 15% incline, repeated 6 times per session, increasing to 36 min/session. Continuous training: 15% incline, 40 m/min (≥85% VO_{2max}).	Macrophages in mesenteric adipose tissue	Compared to continuous training, aerobic-interval training is more effective in increasing the number of M2 macrophages and decreasing the crown-like structure in mesenteric adipose tissue of HFD rats.	[126]
Mice with HFD	Treadmill training, 15 m/min, 40 min/day, 5 days/week, 8 weeks.	Macrophages in visceral adipose tissue	Exercise decreases total macrophages in visceral adipose tissue of mice fed with a chow diet or high fat diet.	[127]
Db/db mice	Treadmill training, 10 m/min, 60 min/day, 5 days/week, 8 weeks.	Macrophages in perivascular adipose tissue	Exercise promotes M1 to M2 macrophage polarization, associating with an increase of adiponectin and IL-10 levels and decreases IFNγ, IL6, TNFα levels in the perivascular adipose tissue of db/db mice.	[128]
T2DM mice	Treadmill training (15% incline), 5 days/week, 8 weeks. 4 min/time and rest for 2 min/time for 10 consecutive groups/day, 16–26 m/min.	Adipose tissue macrophages	HIIT increases pan-monocyte infiltration, decreases M1 macrophages, and increases M2 macrophages.	[129]
Wistar rats with HFD	Treadmill training, 5 repeated intervals of 2-min sprints at 80–90% VO_{2max} with 1 minute's 30–35% VO_{2max} interval for each rat.	Adipose tissue macrophages	HIIT is more effective in inhibiting M1 macrophage polarization and increasing M2 macrophage markers in the adipose tissue of HFD rats.	[123]
HFD-induced obese mice	climbing a ladder for 7 days and 15 days with an overload corresponding to 70% of the maximum voluntary carrying capacity.	Macrophages in epididymal and subcutaneous adipose tissue	Strength training for 7 days reduces total monocyte infiltration and M2 macrophages without effect on M1 macrophages. Strength training for 15 days increases total macrophages, M1 macrophages, and the M1/M2 ratio.	[130]
HFD mice	Treadmill training (-5°incline), moderate intensity (45% of peak running speed, 1 h/day, 6 days/week, 8 weeks.	Macrophages in epididymal adipose tissue	Eccentric exercise significantly decreases M1 macrophages and increases M2 macrophages in epididymal adipose tissue of HFD mice.	[131,132]
Young (n = 7) and old (n = 7) trained men	Biking 7 to 9 h/day at 63% and 65% HR_{max}, 15 consecutive days.	Adipose tissue macrophages	Exercise increases $CD163^+$ macrophages in both gluteal and abdominal adipose tissue of young and old subjects.	[133]
Young and old mice	Lifelong spontaneous voluntary wheel running	Adipose tissue macrophages	Exercise increases M2 macrophages in both young and old mice.	[134]
Older men (n = 6)	Chronic excessive training, Cycling, 10h/day, 31 ± 37 min, 53 ± 1% of VO_{2max}, 14 days, 2706 km in total.	Adipose tissue macrophages	Exercise has no effect on plasma TNFα, IL-18, hsCRP, and CD163 macrophage content, but IL-6 increases, in adipose tissue	[135]
SD rats with endometriosis	Voluntary wheel running, 2 weeks.	Macrophages in mesenteric fat	Exercise decreases monocyte infiltration in the mesenteric fat tissue of rats with endometriosis.	[136]
SD rats	Treadmill training, 8 weeks.	Macrophages in the infrapatellar fat pad	Running at low-intensity, medium-intensity, and high-intensity have no effect on macrophage polarization in the infrapatellar fat pad of rats.	[137]
LDL receptor knockout mice	Treadmill training, 15 m/min, 60 min/day, 5 days/week, 90 days.	Macrophages in periepididymal adipose tissue	Aerobic exercise has no significant effect on the macrophage profile in periepididymal adipose tissue of the LDL receptor knockout mice with a low-sodium diet.	[138]
Subjects, age (26–68)	Cycling ergometer, 3 days/week, 45 min/bout, 65% of VO_{2max}, 12 weeks	Macrophages in vastus laterial biopsies	Exercise increases M2 macrophages and M2c macrophages, which are correlated with fiber hypertrophy. Exercise decreases IL-6, C/EBPβ, and MuRF, and increases IL-4, TNFα, and FN14.	[68]
Healthy women and men aged 65 and more	14 weeks of supervised, variable intensity, bilateral, upper, and lower body resistance training.	Skeletal muscle macrophages	Resistance training increases total macrophages and M2 macrophages in skeletal muscle.	[139,140]
Male C57BL/6 mice with HFD	Treadmill training (5% grade), 40 min/day, 12 m/min, 5 days/week, 12 weeks.	Skeletal muscle macrophages	Exercise attenuates the increase of F4/80 and IL-6 in skeletal muscle of HFD mice.	[141]
HFD mice	Treadmill training, 15–20 m/min (55–65% VO_{2max}), 60 min/day, 5 days/week, 8 weeks.	Skeletal muscle macrophages	Exercise inhibits monocyte infiltration in the skeletal muscle of HFD mice.	[142]
HFD-induced obese mice	Treadmill training, running for 2 min followed by 2 min of active rest for 60 min, 3 days/week.	Skeletal muscle macrophages	Exercise downregulates muscle inflammation and macrophage content independently of changes in adiposity in the muscle of obese mice	[143]
Obese subjects with T2DM	9 months of aerobic and resistance training	Macrophages in the vastus laterals	Muscle macrophage content in obese type 2 diabetics is unchanged after a 9-month exercise program.	[144]
$ApoE^{-/-}$ male mice	Voluntary wheel running, 5 weeks.	Macrophages in the gastrocnemius	Preventive exercise prevents ischemia- induced increased gene expression of M1 macrophage markers and cytokines in the ischemic muscle, while no changes are observed for M2 macrophage marker.	[145]
Male Swiss mice	Swimming exercise, 50 min/day, 15 days.	Muscle tissue macrophages	Exercise modulates the macrophage phenotypes during the acute and chronic persistent muscle hyperalgesia in muscle tissue via PPARγ receptors.	[146]

Table 2. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
Patients with moderate to severe COPD (n = 30), healthy sedentary controls (n = 8)	Ergometer cycling or treadmill walking at moderate intensity, individually adjusted to level 14–15 on the Borg scale of perceived exertion, 35 min/time, 3 times/week, 8 weeks.	Macrophages in Vastus lateralis	Exercise has no effect on the number of muscle-infiltrating macrophages or systemic levels of other pro-inflammatory cytokines or leukocytes in patients with COPD.	[147]
Patients with moderate to severe COPD (n = 30), healthy sedentary controls (n = 8)	4 strength exercises of the major upper and lower body muscle groups, each exercise includes 4 sets with a duration of 30 s with a 20-s break between sets and a 60-s break between exercises, 8 weeks.	Macrophages in the vastus lateralis muscle	Exercise has no effect on the number of muscle-infiltrating macrophages or systemic levels of other pro-inflammatory cytokines or leukocytes in patients with COPD.	[147]
Patients with COPD	Bilateral lower-limb, high-intensity resistance training, thrice weekly, 8 weeks	Macrophages in the quadriceps	$CD163^+$ macrophages are increased significantly by acute resistance training, but drop to baseline after chronic resistance training.	[147]
Cerebral ischemic mice	Treadmill training, every day for 3 consecutive weeks.	Skeletal muscle macrophages	Exercise has no significant effect on skeletal muscle macrophages of cerebral ischemic mice.	[148]
Cerebral ischemic mice	Treadmill training, 5 times/week, 3 weeks.	Skeletal muscle macrophages	HIIT decreases M1 macrophages and increases M2 macrophages via inhibiting the TLR4/MyD88/NFκB signaling pathway in skeletal muscle of cerebral ischemic mice.	[148]
SD rats with work-related musculoskeletal disorders	Treadmill training, 1 h/day, 5 days/week, speed ramps to 23 m/min, 6 weeks.	Macrophages in the median nerves and the flexor digitorum muscle	Exercise decreases $CD68^+$ macrophages in the flexor digitorum muscle of rats with work-related musculoskeletal disorders.	[149]
Female BALB/c mice with a tumor	Swimming training, 5 days/week, 8 weeks.	Peritoneal macrophages	Exercise inhibits tumor development and promotes immune system polarization towards an anti-tumor M1 macrophage profile.	[150]
Mice with PPARγ deficiency in macrophages	Treadmill training, 5 days/week, 8 weeks.	Peritoneal macrophages, subcutaneous macrophages	M2 peritoneal macrophages' ability is impaired by PPARγ deletion, while subcutaneous macrophages are not affected by PPARγ deletion.	[151]
Mice with PPARγ deficiency in macrophages	Treadmill training, 60% of maximum speed, 50–60 min/day, 5 days/week, 12 weeks.	Peritoneal macrophages, adipose tissue macrophages	Despite the attenuation of M2 macrophages by PPARγ deletion, the exercise-mediated anti-inflammatory effect is not affected by PPARγ deletion.	[152]
Male C57BL/6 mice exposed to cigarette smoke	Swimming, 5 days/week, 8 weeks, two 30 min sessions separated by a 5 min break.	alveolar macrophages	Exercise reduces alveolar macrophage number in mice exposed to cigarette smoke.	[153]
Male C57BL/6 mice exposed to cigarette smoke	Treadmill training, 50% of maximal speed, 30 min/day, twice a day, 5 days/week, for 4,8, 12 weeks	bronchoalveolar lavage macrophages	Exercise reduces the number of total inflammatory cells, macrophages, neutrophils, and lymphocytes in mice exposed to cigarette smoke.	[154]
Male C57BL/6 mice with PM 2.5- and PM 10 exposure	Treadmill training, 50% of maximal exercise capacity, 5 x/week, 60 min/time, 5 weeks.	bronchoalveolar lavage macrophages	Exercise inhibits PM 2.5- and PM 10-induced accumulation of total leukocytes, neutrophils, and macrophages in brochoalveolar lavage of mice	[155]
Male BALB/c mice with infection	Treadmill training, 50% of maximum speed, 60 min/day, 5 days/week, 4 weeks.	Lung macrophages	Exercise reduces macrophages in bronchoalveolar lavage fluid and in the pulmonary parenchyma of mice with infection.	[156]
Male C57BL/6 mice with acute lung injury	Treadmill training, 60% of average maximum speed, 60 min/day, 5 days/week, 5 weeks.	Alveolar macrophages	Exercise reduces neutrophil infiltration, NET release, and the pro-inflammatory polarization of alveolar macrophages in mice with acute lung injury.	[157]
Male Wistar rats with myocardial infarction	Treadmill training, 5 days/week, durations and velocity gradually increase to 60 min and 40% of the maximum exercise test, 8 weeks.	Lung macrophages	Exercise prevents myocardial infarction-induced monocyte infiltration in the lung.	[158]
Ovalbumin-sensitized mice	Treadmill training, 50% of maximum speed, 1 h/day, 5 days/week, 5 weeks.	Macrophages in the lung and lymphoid tissue	Exercise increases the recruitment of M2 macrophages in the lungs, as well as the influx and activation of Treg and $CD4^+$ and $CD8^+$ T cells in ovalbumen-sensitized mice.	[159]
Aged male C57BL/6 mice	Voluntary wheel running, 2 months	Alveolar macrophages	Exercise increases alveolar macrophages in aged mice and they are more responsive to an anti-inflammatory stimulus.	[160]
C57BL/6 male mice	Treadmill training, 5 days/week, 5 weeks. In the first week, 6 m/min for 5 min, 9 m/min for 5 min, 12 m/min for 5 min, and 15 m/min for 5 min. For the next 4 weeks, 6 m/min for 5 min and 12 m/min for 35 min.	Cardiac resident macrophages	Low-intensity exercise training does not change the number of cMacs in the heart, while remodeling the subsets of cMacs and increasing $MHC\text{-}II^{low}$ cardiac resident macrophages.	[161]
Male $APOE^{-/-}$ mice	Swimming, 50 min/day, 5 days/week for 24 weeks.	Cardiac resident macrophages	Exercise reduces macrophages in the heart of $APOE^{-/-}$ mice.	[162]
Male SD rats with DXO-induced myocardial injury	Treadmill training, 13 m/min, 60 min/day, 5 days/week, 6 weeks.	Macrophages in myocardial tissue	Exercise modulates the miR-30d-5p/GALNT7 axis to inhibit the expression of TSHR, thereby regulating the polarization of macrophages to the M2 phenotype and ultimately alleviating doxycycline-induced myocardial injury.	[163]
Male db/db mice	Treadmill training, 5.2 m/min, 5 days/week, 3 weeks.	Cardiac macrophages	Exercise inhibits monocyte infiltration and reduces circulating chemokines and cytokines in db/db mice.	[164]

Table 2. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
T2DM rats	Treadmill training, 18 m/min at 5° inclination, 1 h/day, 5 days/week, 18 weeks.	Macrophages in left ventricular tissues	Aerobic exercise elevates total, M1, and M2 macrophages, and pro-inflammatory cytokines in the left ventricular tissues of T2DM rats.	[165]
T2DM rats	Treadmill training (30° incline), 10 bouts of 2 min of high-intensity running (18 m/min) alternated with 1 min of low-intensity running (12 m/min). 5 days/week, 18 weeks.	Macrophages in left ventricular tissues.	HIIT increases total, M1 macrophages, and pro-inflammatory cytokines in the left ventricular tissues of T2DM rats.	[165]
Male BALB/c mice with a tumor	Treadmill training, 17 m/min for 10 days, 15, 30, 60, 90,120 min/day.	Spleen macrophages	Exercise augments the tumoricidal activity of macrophages, increases the production of IL-1, TNF, and NO by macrophages in mice with tumors.	[166]
BALB/c mice with a tumor	Treadmill training, 30, 60 min, 17 m/min, 10 days.	TAMs	Exercise increases TAM-mediated tumor cytotoxicity.	[167]
Male Swiss mice with tumor	Swimming with a load from 2% body weight until exhaustion, 1 h/day, 5 days/week for 6 weeks.	TAMs	Exercise suppresses tumor growth and inhibits macrophage infiltration in the tumor tissue.	[168]
BALB/C mice with a breast tumor	Treadmill training before and after tumor cell injection. Low intensity: 10 m/min; moderate intensity: 15 m/min on a slope of 2.5°. 8 weeks.	TAMs	Low-intensity exercise before and after the development of cancer may delay cancer growth by inhibiting M2 monocyte infiltration into the tumor tissue.	[169]
C57BL/6 mice with lung cancer	Voluntary wheel running is performed 1 day after implantation, 3 weeks.	TAMs	Exercise inhibits tumor growth and $CD8^+$ T cells, increases M1 macrophages, and decreases M2 macrophages in tumors.	[170]
Mice with YUMMER tumors	Treadmill training, 12 m/min, 45 min/day, 12–14 consecutive days	TAMs	Exercise increases $F4/80^+$ TAMs while decreases M2-like TAMs in tumor of mice.	[171]
C57BL/6 mice with a B16F10 tumor were fed with chow or a high-fat diet.	Voluntary wheel running, 2/4/6 weeks.	TAMs	Exercise reduces tumor growth. Moreover, the exercise- suppressed tumor growth is dose-dependent with greater suppression of tumor growth after 4 and 6 weeks of exercise than with 2 weeks.	[172]
6–8-week-old male mice with HR-NB	5-week combined aerobic (treadmill training) and resistance training (forelimb grip test), 4 days/week.	TAMs	Exercise increases the proportion of M2-like TAMs in the tumor tissue.	[173]
BALB/c mice with lung cancer	Treadmill training, 15 m/min (80% VO2max) for 45 min, 5 times/week, 12 weeks.	TAMs	Exercise reduces the proportions of M1 TAMs in lung cancer tissue.	[174]
BALB/c female mice with lung cancer	Swimming exercise with load, swimming for 20 s, and then passively recovered for 10 s, repeated 10 times, 4 times/week, the weight load is 10% of body weight in the first 6 weeks and increases to 12% of body weight in the last 6 weeks.	TAMs	HIIT has no significant effect on M1 and M2 macrophages in lung cancer tissue.	[174]
Female C57BL/6 mice	Treadmill training, 20 m/min, 1 h/day, 5 days/week, with a 10% increase in speed every week up to a maximum of 30 m/min, 8 weeks.	BMDM	Exercise inhibits the LPS-induced NF-κB activation and proinflammatory gene expression but increases M2 macrophages in BMDMs.	[175]
Wistar SD rats with CKD	Vertical climbing ladder, 3 days/week, 8 weeks.	Kidney macrophages	Exercise decreases interstitial macrophages in kidney of rats with CKD.	[176]
Adults with asthma (n = 46)	Moderate-intensity exercise: 55–70% HR_{max}, 45 min/time, 3 times/week, 12 weeks. Vigorous intensity exercise: 70–90% HR_{max}, 30 min/time, 3 times/week, 12 weeks.	Sputum macrophage	Moderate-intensity exercise reduces sputum macrophage and lymphocyte counts relative to control in adults with asthma.	[177]
Obese Swiss mice	Treadmill training, 60% of peak workload for 1 h, 5 days/week, 8 weeks.	Macrophages in the hypothalamus	Exercise inhibits monocyte infiltration, reduces inflammatory cytokines and increases IL-10 in hypothalamus of obese mice.	[178]
Mice with obese-related lymphatic dysfunction	Treadmill training, 30 min/day, 5 days/week, 6 weeks	perilymphatic macrophages	Exercise has a significant anti-inflammatory effect, decreasing perilymphatic macrophage accumulation in obese mice.	[179]
Aged B6D2F1 mice	Voluntary wheel running, 8 weeks	Aorta macrophages	Age-related increases in T cell and monocyte infiltration in the aorta are abolished by exercise.	[180]
Aged C57BL/6J mice	Swimming training, 60 min/day, 5 days/week, 6 weeks.	Retina Macrophages	Exercise abrogates injury-induced astrocytic gliosis and macrophage activation in the aged retina.	[181]
Male aged SAMP1 mice	Climbing ladder with load from 50% to 100% body weight, 6–8 sets each time, 1 min rest between sets, 3 times/week, 12 weeks.	Macrophages in the heart, liver, small intestine, brain, aorta, adipose, and skeletal muscle	Exercise reverses the increase in F4/80 mRNA expression, the ratio of CD11c/CD163 mRNA expression, and MCP-1 mRNA expression in the heart, liver, small intestine, brain, aorta, adipose, and skeletal muscle of aged SAMP1 mice	[182]
Mice with EAE	Treadmill training, 70–75% of maximal speed. 10, 20, and 30 min at 23 cm/min for the first, second, and third week. 23 min at 30 cm/min in the last 2 weeks.	microglia	High-intensity continuous training reduces the number of resident microglia without affecting their profile in healthy mice.	[183]

Table 2. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
Young mice and aged mice	Voluntary wheel running, 6 months.	Microglia/monocytes in the cortex	Aerobic exercise from midlife to old age prevents age-related neurovascular decline, reduces microglia/monocytes in the cortex through elevating APOE.	[184]
Male C57BL/6 mice with PD	Treadmill training, 12 m/min, 1 h/day, 5 days/week, 6 weeks.	Microglia	Exercise effectively alleviates neuronal damage via inhibition of NLRP3 inflammasome and microglial activation in the PD mouse model.	[185]
Female SD rats with spinal cord injury	Forced wheel walking, 4 weeks	Microglia and macrophages in DRG	Early exercise inhibits the spinal cord injury-induced microglial activation, decreases the macrophages in DRG.	[186]
Male SD rats with neuropathic pain	Voluntary wheel running, 6 weeks	DRGs and sciatic nerve	Prior exercise attenuates monocyte infiltration into the injured lumbar DRGs and sciatic nerve of mice with neuropathic pain.	[187]
Mice with neuropathic pain	Treadmill training, 10 m/min, 30 min/day, 5 days/week, 2 weeks	Macrophages in the sciatic nerve	Exercise increases the percentage of M2 macrophages and decreases M1 macrophages, suppresses glial cells activation in the sciatic nerve of mice with neuropathic pain.	[188]
Mice with Charcot-Marie-Tooth disease 1X (CMT1X)	Voluntary wheel running, 18 h/day, 3 times/week, 3 weeks for short-term exercise, 6 months for long-term exercise.	Macrophages in peripheral nerves and femoral quadriceps nerves	Short-term and long-term exercise reduces the number of macrophages and alters their activation in the femoral quadriceps nerves of mice with CMT1X.	[189]
SD rats with spinal cord injury	Treadmill training, 30 min/day, 5 days/week, 12 weeks.	Macrophages in spinal cord tissue	Exercise decreases the overall macrophages, but does not affect macrophage polarization in the injured spinal cord tissue after injury.	[190]
SD rats with work-related musculoskeletal disorders	Treadmill training, 1 h/day, 5 days/week, speed ramps to 23 m/min, 6 weeks.	Macrophages in the median nerves and the flexor digitorum muscle	Exercise increases $CD68^+$ macrophages in the median nerves of rats with work-related musculoskeletal disorders.	[149]
BALB/c mice with MSU treatment	Treadmill training (5% incline), 8 m/min, 11 m/min, 15 m/min for 45 min. 2 weeks.	Macrophages in synovium	Low and moderate-intensity exercise mitigates MSU-induced NF-κB activation and synovial infiltration of macrophages and neutrophils, while high-intensity exercise shows no significant difference in inflammation.	[191]
SD rats with osteoarthritis	Treadmill training, 5° inclination, 19.3 m/min, 60 min/day,5 days/week, 4 weeks.	Macrophages in synovium	Exercise exerts protective effects on articular cartilage and facilitates M2 polarization of synovial macrophages of rats with osteoarthritis.	[192]
Male ICR mice with knee osteoarthritis	Treadmill training, 10, 15, or 20 m/min (mild, moderate, and high intensity) for 30 min/day, 3 days/week, for 4 weeks.	Macrophages in synovium	Mild exercise delays the cartilage degeneration, with a decrease in the M1 and increases in M2 macrophage ratio in synovium of mice with knee osteoarthritis. High-intensity exercise exerts the opposite effect.	[193]
$ApoE^{-/-}$ mice	Treadmill training, 60 min/day, 5 days/week, 8 weeks.	aortic root plaque macrophages	Exercise induces M2 macrophage polarization in isolated aortic root plaque macrophages of $ApoE^{-/-}$ mice.	[194]
$APOE^{-/-}$ mice	Voluntary wheel running, 4 weeks	Pericollateral macrophages	Macrophages are increased in pericollateral macrophages of $APOE^{-/-}$ mice after exercise.	[195]
Male $APC^{Min/+}$ mice	Treadmill training (5% grade), 18 m/min, 60 min/day, 6 days/week, 9 weeks	Macrophages in intestinal polyps	Exercise decrease total macrophage in intestinal polyps.	[196]
Male $APC^{Min/+}$ mice	Treadmill training (5% incline), 15 m/min, 1 h/day, 6 days/week, 12 weeks	Macrophages in intestinal mucosal tissue	Exercise reduces mRNA expression of overall macrophages, as well as markers associated with both M1 and M2 subtypes.	[197]
Male C57BL/6 mice with a dorsal excisional wound	Treadmill training, 9 m/min (70% $VO2_{max}$), 60 min/day, 10 days.	Macrophages in skin wound sites	Exercise significantly inhibits M1 monocyte infiltration and increases M2 macrophages in skin wound sites of mice.	[198]
Young and old mice with dermal wounds	Treadmill training (5% grade), 30 min/day, 18 m/min (70%$VO2_{max}$) for young mice, 12 m/min for old mice.	Macrophages in dorsum wound	Exercise decreases wound size, reduces TNFα and MCP-1 in the wound of aged mice, whereas has no significance on macrophage content.	[199]
Impact of chronic exercise on monocyte/macrophage phagocytosis				
Male Wistar rats and mice	Treadmill training, 70% VO_{2max}, 5 days/week, 60 min/day, 8 weeks.	Bronchoalveolar macrophages	Exercise increases the phagocytosis of macrophages in acute stress	[200]
Wistar rats	Swimming, moderate trained group (MOD): 1 h/day, 5 days /week for 6 weeks. Exhaustively trained group (EXT): similar to MOD for 5 weeks, in the 6th week, trained with 5.5% body weight load in three 1 h sessions per day with 150 min of rest between sessions	Peritoneal macrophages	Moderate exercise increases macrophage phagocytosis, H_2O_2 production is increased in the MOD and EXT group, glutamine consumption and metabolism are improved by exercise intervention.	[201]
Male C57BL/6 mice	Treadmill training, 10–18 m/min, 50 min/day, 5 days/week, 3 months.	KCs	Exercise increases phagocytic capacity and the clearance of exogenously-injected endotoxin.	[202]
Adult and old male Wistar rats	Swimming training with overload gradually increases to 2% of body weight, 1 h/day, 5 days/week, 6 weeks.	Peritoneal macrophages	Exercise promotes macrophage phagocytosis in old mice, and increases H_2O_2 production by macrophage.	[203]
Male SD rats with HFD	Treadmill training, 20 m/min, 60 min/day, 5 days/week, 8 weeks	Peritoneal macrophages	Exercise improves peritoneal macrophage phagocytosis and reduces the apoptotic peritoneal macrophages in HFD mice.	[204]
NAFLD mice	Treadmill training, 10, 12, 14, 16 m/min for 5 min each and at 18 m/min for 30 min (50 min total), 5 days/week, 4 weeks.	KCs	Exercise restores the impaired phagocytic capacity of KCs in NAFLD mice.	[205]

Table 2. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
Sedentary obese men with NAFLD (n = 61)	Resistance training, HIIT, moderate-intensity continuous aerobic training (MICT), 12 weeks.	KCs	Resistance training, HIIT and MICT are equally effective in reducing hepatic fat content, but only HIIT is effective in improving hepatic stiffness and restore KCs phagocytic function.	[206]
Older adults with RA (n = 12)	3 × 30-min sessions/week of 10 ≥ 60 s intervals of high intensity (80–90% VO_{2max}) separated by similar bouts of lower-intensity intervals (50–60% VO_{2max}), 10 weeks.	Circulating monocytes	HIIT increases monocyte phagocytosis in older adults with RA.	[104]
Female Wistar rats (n = 64)	Treadmill training, 5 days/week (including two exhausting tests), 5 weeks.	Circulating monocytes	Intensive training for 5 weeks impairs innate and acquired immunity, including inhibiting monocyte phagocytosis.	[95,207]
Male Wistar rats	Treadmill training,6–36 m/min, 10–60 min, 5 days/week, 4 weeks.	Peritoneal macrophage	Long-term intensive exercise impairs phagocytosis, ROS production, and MHC II mRNA of peritoneal macrophages.	[208]
Male Wistar rats	Treadmill training, 6 consecutive days of training sessions followed by 1 day of recovery, 11 weeks.	Peritoneal macrophage	Overload training inhibits the chemotaxis capacity, the phagocytosis capacity, and the cytokine response capability.	[209,210]
Kunming mice	Swimming with load of 5% body weight, 20–45 min/day, 6 days/week, 4 weeks.	Peritoneal macrophage	Heavy-load exercise reduces the peripheral white blood cells, absolute neutrophil count, and macrophage phagocytic index in mice.	[211]
Balb/c mice with bacterial pulmonary infection	Voluntary wheel running prior to pulmonary infection with bacteria, 28 days.	Macrophages in spleen and lung	Exercise enhances bacterial infection susceptibility with no effect on the phagocytic capacity of monocytes from spleen and lungs.	[212]
Impact of chronic exercise on the secretory function of monocyte/macrophage				
HFD-induced obese mice and the control lean group	Treadmill training, from 10 m/min for 10 min to 18 m/min for 45 min, 3 days/week, 8 weeks.	Circulating monocytes	Exercise induces anti-inflammatory cytokines in monocytes from obese individuals and pro-inflammatory cytokines in monocytes from lean individuals.	[213]
C57BL/6 mice	Voluntary wheel running, 8 weeks.	Peritoneal macrophages	Exercise increases IL-1β, IL-18 and caspase-1 protein in peritoneal macrophages in the presence and absence of LPS.	[214]
Male BALB/c mice	Treadmill training, 18 m/min, 30 min/day, 5 days/week, 3 weeks.	Peritoneal macrophages	Exercise increases LPS-stimulated NO and pro-inflammatory cytokine production in macrophages.	[215]
BALB/c mice	Swimming with load from 2% body weight to 6% body weight, 30 min/day, 12 weeks.	Peritoneal macrophages	Macrophages isolated from exercised mice produce more TNFα, NO and IL-12 following LPS stimulation, and higher IL-12 with pathogens.	[216]
Obese Zucker rats	Treadmill training, 25 cm/s for 10 min to 35 cm/s for 35 min, 5 days/week, 14 weeks.	Peritoneal macrophages	Habitual exercise increases IL-1β, TNFα, and IFNγ production, and decreases IL-6 by peritoneal macrophages from obese rats.	[86,87,217]
Male BALB/c mice with a tumor	Treadmill training, 17 m/min for 10 days, 15, 30, 60, 90,120 min/day.	Spleen macrophages	Exercise increases the production of IL-1, TNF, and NO by macrophages in mice with tumor.	[166]
Overweight-to-mildly obese adults (n = 20)	Moderate to vigorous intensity aerobic/cardiovascular exercise, 30–60 min/section, ≥4 days/week.	Adipose tissue macrophages	Regular exercise elevates IL-6 mRNA in adipose tissue macrophages.	[218]
Male C57BL/6 mice with HFD	Voluntary wheel running, 6 weeks	Adipose tissue, peritoneal macrophage	Exercise reduces the expression of TNFα, MCP-1, and F4/80 in adipose tissue of HFD mice, inhibits the expression of TNFα and increases the expression of ghrelin in peritoneal macrophage of HFD mice.	[219]
Post-MI CHF rats	Treadmill training, 13–20 m/min, 60 min/day, 5 days/week, 8–10 weeks.	Peritoneal macrophages	Exercise reverses the increases in peritoneal macrophage number, chemotaxis, and the production of TNFα stimulated by LPS in post-MI CHF rats.	[220]
HFD-induced obese mice	Treadmill training, 12–20 m/min, 50 min/day, 5 days/week, 8 weeks.	BMDM	Exercise inhibits NLRP3 inflammasome activation and the secretion of IL-1β and IL-18 in BMDMs of HFD-induced obese mice.	[221]
Female Wistar rats (n = 64)	Treadmill training, 5 days/week (including two exhausting tests), 5 weeks.	Peritoneal macrophages	Intensive training for 5 weeks impairs innate and acquired immunity, including increasing the production of IFNγ by peritoneal macrophages stimulated by LPS.	[95]
Healthy untrained Standardbred horses (n = 8)	8 weeks of moderate training followed by 8 weeks of intensive training	pulmonary alveolar macrophages	Exercise inhibits the production of TNF and IFN in nonstimulated and stimulated pulmonary alveolar macrophages.	[222]
Physically inactive obese/overweight adults (n = 40), and physically active lean/overweight adults (n = 9)	70% 1 RM, 15 repetitions, the intensity increases gradually, 3 days/week on alternate days, 12 weeks.	Circulating monocytes	Resistance exercise inhibits the production of LPS-stimulated TNFα and IL-6.	[96]
Sedentary overweight men (n = 30)	Strength training, 80%1-RM, 4 sets of 8 repetitions, and a 2 min rest between sets, 17–20 min/day, 8 weeks.	Circulating monocytes	Strength training inhibits the production of TNFα by LPS-stimulated cells.	[97]
Physically active (n = 15) and physically inactive subjects (n = 15)	Endurance training: 20 min at 70–80% HR_{max}, resistance training: 8 exercises, 2 sets at 70–80% 1 RM. 3 days/week, 12 weeks.	Circulating monocytes	Exercise inhibits LPS-stimulated TNFα production and serum CRP in the physically inactive group.	[99]

Table 2. *Cont.*

Experimental Model	Exercise Protocol	Tissue Sample	Result	References
Women with fibromyalgia (n = 9), age-matched controls (n = 9)	Pool-aquatic exercise with resistance and aerobic training, 2 days/week, 60 min/day, 8 months.	Circulating monocytes	Exercise for 4 months decreases TNFα and increases IL-6 production, exercise for 8 months decreases TNFα and increases IL-10 production, and inhibits LPS-induced production of IL-1β, TNFα, IL-6, and IL-10.	[223]
Women with breast cancer (n = 11)	Aerobic exercise: 10–30 min/day, Resistance exercise: 30 min/day. Low to high intensity, 3 days/week, 16 weeks.	Circulating monocytes	Exercise training reduces monocyte intracellular pro-inflammatory cytokine production, especially IL-1β.	[224]
Mice with EAE	Treadmill training, 70–75% of maximal speed. 10, 20, and 30 min at 23 cm/min for the first, second, and third week. 23 min at 30 cm/min in the last 2 weeks.	microglia	Exercise reduces the ROS formation and the released IL-6 and MCP-1 by microglia of mice with EAE.	[183]
Diabetic rats	Treadmill training, 60% VO_{2max}, 30 min/day, 6 days/week, 3 weeks.	Peritoneal macrophages	Exercise diminishes the ROS release by macrophages, but does not change the proportion of macrophages in necrosis.	[225]
Male Wistar rats	Treadmill training,6–36 m/min, 10–60 min, 5 days/week, 4 weeks.	Peritoneal macrophage	Long-term intensive exercise impairs the ROS production of peritoneal macrophages.	[208]
Male Wistar rats	Treadmill training, 6 consecutive days of training sessions followed by 1 day of recovery, 11 weeks.	Peritoneal macrophage	Overload training inhibits the ROS generation of macrophages.	[209,210]

2.2.1. Chronic Exercise: Monocyte Mobilization and Macrophage Reprogramming

Chronic exercise exerts systemic immunomodulatory effects, with consistent evidence supporting its role in mitigating inflammation through the modulation of monocyte and macrophage function. Across various disease models—including obesity, T2DM, NAFLD, cardiovascular disease, aging, and cancer—exercise interventions such as aerobic, resistance, concurrent, eccentric, and high-intensity interval training (HIIT) have been shown to impact monocyte/macrophage responses in peripheral blood, adipose tissue, liver, skeletal muscle, and other organs (Table 2).

In circulation, moderate-intensity chronic aerobic training typically reduces monocyte counts and downregulates proinflammatory cytokine expression. A common observation is the phenotypic shift of macrophages from M1 (proinflammatory) to M2 (anti-inflammatory) polarization [91]. For example, chronic low- and moderate-intensity aerobic training significantly reduced the number of proinflammatory monocytes in patients with axial spondyloarthritis and overweight [88,92]. However, similar interventions yield inconsistent results in populations with obesity, hypertension, and chronic kidney disease (CKD) [34,89,90,93], indicating that monocytes/macrophages may differ among diverse pathological models. In some contexts, PPARγ signaling appears to mediate exercise-induced M2 polarization and is associated with improved insulin sensitivity. Resistance and combined aerobic resistance training also modulate monocyte phenotypes, reducing the number of $CD14^{+}CD16^{+}$ proinflammatory subsets and increasing the number of $CD14^{++}CD16^{-}$ classical monocytes in overweight adults [96–99]. HIIT consistently reduces the number of the Mon2 and Mon3 subsets in obese and elderly individuals [103,104] and, in some cases, is more effective than moderate-intensity training in downregulating inflammatory monocyte profiles [112].

In tissue compartments, chronic aerobic exercise reduces monocyte infiltration and promotes M2 polarization in the liver [105–111], adipose tissue [116–128,133,134], and skeletal muscle [68,141–143]. In high-fat diet (HFD)-induced and diabetic mouse models, long-term aerobic training suppresses hepatic macrophage accumulation and skews macrophage polarization toward the M2 phenotype [105–109]. These effects are mediated through mechanisms such as nuclear factor erythroid-2-related factor 2 (NRF2) activation, inhibition of the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) and nuclear factor-κB (NF-κB) signaling pathways, and modulation of macrophage metabolism [107,109,113]. Similarly, in adipose tissue, chronic exercise suppresses M1-associated genes and increases M2 gene expression, with HIIT showing superior efficacy in inhibiting NF-κB and NOTCH signaling to attenuate M1 polarization and promote M2 phenotypes [123]. The macrophages in skeletal muscle are also responsive to training modality and intensity. Both endurance training and resistance training promote M2 polarization in muscle tissue, which is associated with muscle fiber hypertrophy and satellite cell expansion, partly through the downregulation of tumor necrosis factor-like weak inducers of apoptosis [68,139–143]. However, disease-specific differences exist: in T2D and COPD, muscle macrophage numbers remain unchanged following training [144,147], whereas in peripheral artery disease (PAD), exercise reduces M1 polarization, enhancing tissue perfusion [145]. These discrepancies across studies may be attributed to the differences in research models and exercise protocols. Mechanistically, PPARγ and the TLR4/myeloid differentiation primary response 88 (MyD88)/NF-κB axis have been implicated in exercise-induced regulation of muscle macrophage function.

In addition to affecting metabolic tissues, chronic exercise modulates macrophage polarization and functions in various organs. Exercise promotes anti-inflammatory polarization in peritoneal [150,151], pulmonary [153–159], cardiac [161–164], renal[181], and central nervous system-resident macrophages [149,183–190], often conferring protection against tissue injury or chronic inflammation. In cancer models, aerobic training inhibits tumor growth and metastasis by increasing M1 macrophage infiltration and reducing M2-like tumor-associated macrophages (TAMs) [166–172]. However, notable exceptions exist. In a high-risk neuroblastoma mouse model, concurrent training increased M2 TAM infiltration[173], aerobic training reduced M1 TAMs, and HIIT had no effect on TAMs in lung cancer [174], highlighting potential context-dependent effects. In the lung [153–159], heart [161–164], and brain [178], exercise generally suppresses proinflammatory macrophage responses and enhances tissue repair and resilience, although in certain settings (e.g., cardiac and tumor tissues), exercise may alter macrophage polarization without affecting total cell numbers [161].

Exercise also enhances wound healing in both young and aged mice by promoting M2 polarization in dermal macrophages [198,199]. In chronic inflammatory models such as atherosclerosis and arthritis, exercise reduces M1 monocyte infiltration, dampens synovial inflammation, and slows disease progression [180,191–195]. However, excessive or prolonged high-intensity training may negate these benefits, potentially exacerbating tissue damage and impairing joint and cartilage integrity [191,193].

Collectively, these findings suggest that regular exercise elicits anti-inflammatory effects partially through reducing monocyte counts; inhibiting monocyte infiltration; promoting the phenotypic shift of macrophages from M1 (proinflammatory) to M2 (anti-inflammatory) polarization; and downregulating proinflammatory cytokine expression, thus conferring protection against obesity, diabetes, muscular atrophy, tissue injury, cancer, and wounds. These findings underscore the highly plastic and tissue-specific nature of macrophage responses to chronic exercise and support its application as a potent nonpharmacological strategy for modulating innate immune function and controlling chronic inflammation across a range of disease contexts.

2.2.2. Effects of Chronic Exercise on Monocyte/Macrophage Functions

Chronic aerobic exercise modulates macrophage and monocyte function across multiple tissues, enhancing immune surveillance and influencing inflammatory balance in a context-dependent manner. Moderate-intensity aerobic training improves the phagocytic function of macrophages in the bronchoalveolar space [200], peritoneal cavity [201], and liver [202]. Notably, exercise also reverses impaired phagocytosis in Kupffer cells (KCs) and peritoneal macrophages under pathological conditions such as aging [203], HFD exposure [204], and NAFLD [205], suggesting that improved innate immune clearance may contribute to exercise-mediated protection against metabolic and age-associated disorders. However, moderate-intensity aerobic exercise in healthy mice may paradoxically suppress macrophage phagocytosis and increase susceptibility to bacterial infection following pulmonary challenge, despite having no measurable effect on monocyte phagocytic capacity in the spleen and lungs [212].

Among exercise modalities, HIIT appears particularly effective: in obese mice with NAFLD, HIIT improves hepatic stiffness and restores KC phagocytic capacity [206], and monocyte phagocytosis is also enhanced by HIIT in older adults with rheumatoid arthritis [104]. In contrast, prolonged or strenuous aerobic exercise has been shown to reduce phagocytic function in macrophages and monocytes [95,207–210]. Mechanistically, macrophage-derived mechanogrowth factor may contribute to this dysfunction [208,210]. Interestingly, glutamine supplementation—but not branched-chain amino acid supplementation—restores the impairment of peritoneal macrophage phagocytosis induced by overload training [208,209].

Exercise intensity and host metabolic status also influence macrophage cytokine responses. Moderate aerobic training induces anti-inflammatory cytokine profiles in monocytes from obese individuals but promotes proinflammatory responses in those from lean individuals. In murine models, chronic aerobic exercise increases IL-1β, IL-18, IL-12, TNFα, NO, and pro-caspase-1 protein expression in peritoneal macrophages [214–216]. However, in obese rodents, the production of IL-1β, TNFα, and IFNγ by peritoneal macrophages is suppressed, while that of IL-6 is upregulated—a cytokine profile that is reversed by habitual exercise [86,87,217]. These findings suggest that exercise-induced correction of systemic inflammation in metabolic disease may depend on restoring the balance of key pro- and anti-inflammatory mediators, including TNFα, IL-6, IL-1β, and IFNγ. Additionally, moderate-intensity resistance exercise inhibits LPS-stimulated TNFα and IL-6 production in elderly individuals with overweight or obesity [96,97], and combined aerobic resistance training exerts anti-inflammatory effects by reducing TNFα while increasing IL-6 and IL-10 production in sedentary individuals [99], patients with fibromyalgia [223], and women with breast cancer [224]. In overweight and obese adults, moderate to vigorous aerobic training increases IL-6 expression in adipose tissue [218], whereas in murine models of HFD-induced obesity

or postmyocardial infarction (MI) heart failure, aerobic training reduces monocyte infiltration and downregulates TNFα and monocyte chemoattractant protein-1 (MCP-1) in adipose tissue and the peritoneal cavity [219,220]. In bone marrow-derived macrophages (BMDMs), exercise suppresses the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and limits the secretion of IL-1β and IL-18 [221]. Exercise also enhances macrophage-mediated antitumor responses; in tumor-bearing mice, aerobic training increases macrophage cytotoxicity and the production of IL-1, TNFα, and NO [166]. However, excessive exercise can be immunosuppressive. Intensive training impairs both innate and adaptive immunity, increasing IFNγ production by LPS-stimulated peritoneal macrophages[95] and suppressing TNFα and IFNγ production in both stimulated and unstimulated pulmonary alveolar macrophages [222]. ROS production is also modulated by exercise. In experimental autoimmune encephalomyelitis (EAE), moderate exercise reduces ROS generation by microglial macrophages [183]. Similarly, reduced ROS release by macrophages is observed in necrotic tissue from diabetic rats following moderate exercise [225], whereas long-term aerobic exercise diminishes peritoneal macrophage ROS production [208–210].

Together, these findings underscore the dual effects of exercise on macrophage function, with beneficial outcomes largely dependent on exercise intensity, duration, and host immunometabolic status. Moderate, chronic training generally promotes phagocytic capacity and anti-inflammatory cytokine profiles, whereas excessive or strenuous exercise may compromise innate immune competency (Figure 1).

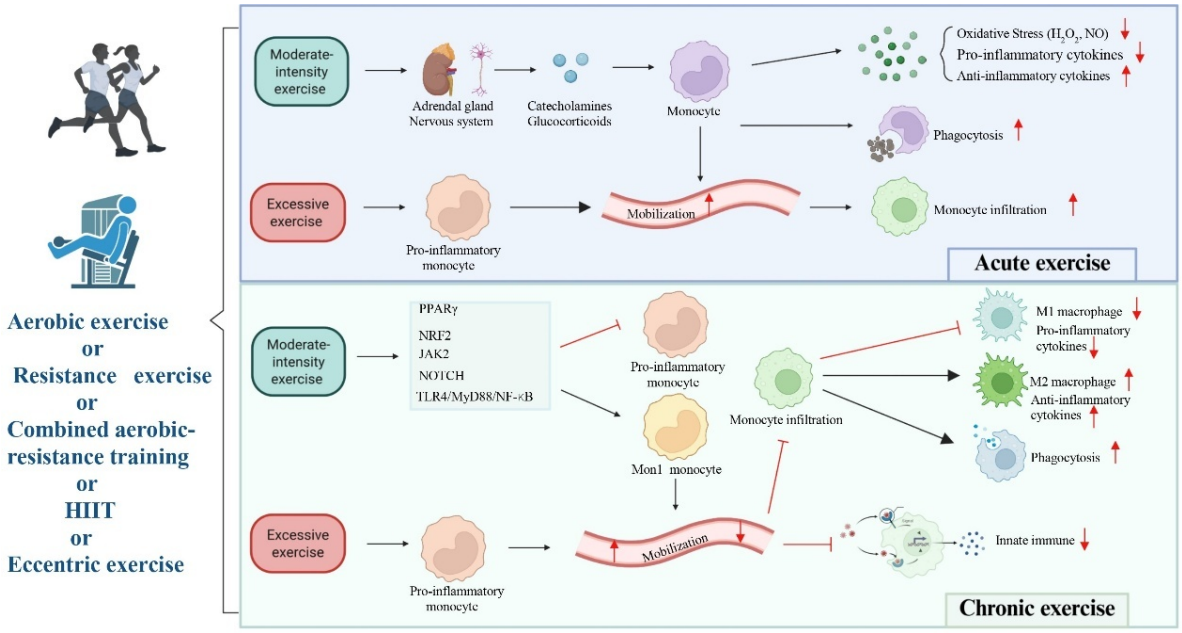

Figure 1. Acute and chronic exercise affect monocyte/macrophage mobilization, reprogramming, and functions. In general, moderate-intensity exercise promotes an anti-inflammatory milieu characterized by reduced circulating and tissue-infiltrating monocytes, enhanced phagocytic capacity, polarization of macrophages toward an M2 anti-inflammatory phenotype, and suppressed pro-inflammatory cytokine production. By contrast, excessive exercise may exhibit the opposite effect. HIIT: high-intensity interval training; PPARγ: peroxisome proliferator-activated receptor γ; NRF2: nuclear factor erythroid-2-related factor 2; JAK2: Janus kinase 2; TLR4: Toll-like receptor 4; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor-κB.

3. Effects of Exercise on Monocyte and Macrophage-Related Diseases

As discussed above, monocytes and macrophages perform diverse biological functions, including pathogen clearance, antigen presentation, tissue remodeling, and immune regulation. Dysregulation of macrophage activity has been implicated in the pathogenesis of a broad range of diseases, including metabolic disorders, cancer, neurodegenerative conditions, and musculoskeletal injury. Through its systemic and local immunomodulatory effects, exercise can influence monocyte and macrophage function in these contexts, contributing to disease prevention, attenuation, or resolution (Figure 2).

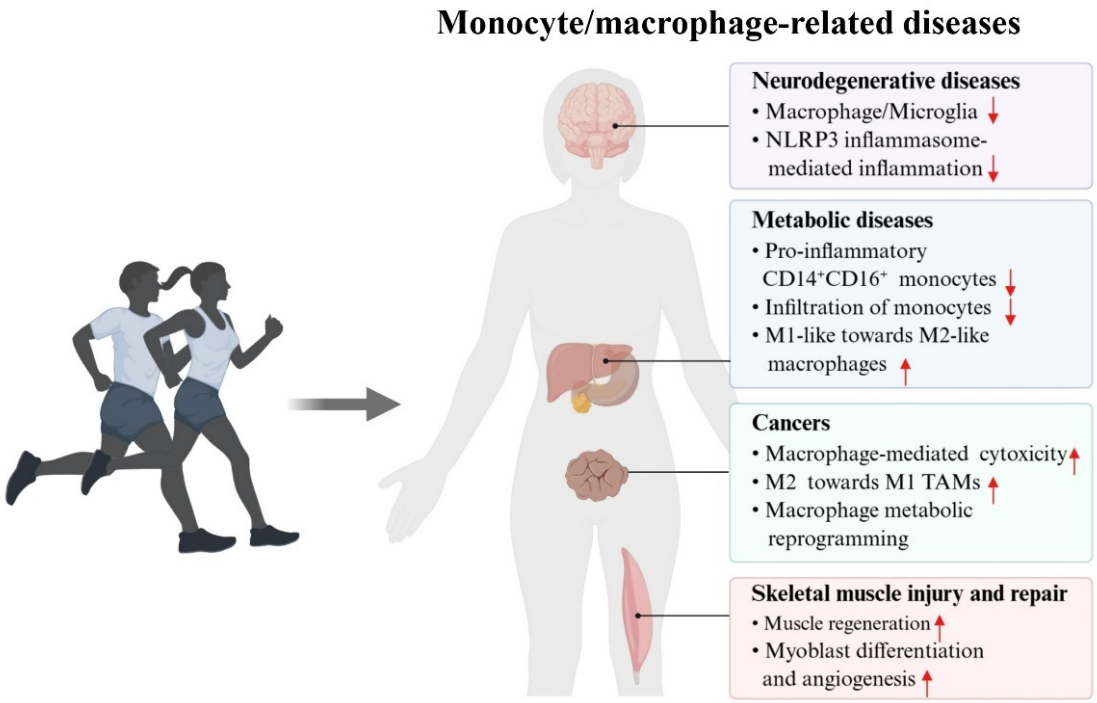

Figure 2. The Effect of Exercise on Monocyte and Macrophage–Related Diseases. Monocytes/macrophages are implicated in the protective effects of exercise against a wide spectrum of diseases, including metabolic disorders, cancer, neurodegenerative conditions, and muscle injury. NLRP3: NOD-like receptor protein 3; TAMs: tumor-associated macrophages.

3.1. Effects of Exercise on Monocyte and Macrophage-Related Metabolic Diseases

Growing evidence supports the notion that metabolism and immunity are tightly interconnected, leading to the emerging field of immunometabolism. The global rise in metabolic diseases is primarily attributed to an imbalance between energy intake and expenditure, although the underlying mechanisms remain incompletely understood. Notably, metabolic dysfunction is known to impair immune homeostasis and is associated with a range of immunological abnormalities.

Individuals with obesity, insulin resistance, or physical inactivity exhibit an increased proportion of circulating proinflammatory $CD14^+CD16^+$ monocytes [28,96,103], with the $CD16^+$ monocyte frequency positively correlated with both body mass index (BMI) and fasting plasma insulin levels. In contrast, moderate-intensity aerobic or resistance exercise and HIIT reduce the number of circulating $CD14^+CD16^+$ monocytes [28,96,103]. Long-term aerobic training is associated with a reduction in the total number of circulating monocytes, which is correlated with decreased fasting triglyceride levels and BMI, along with improvements in insulin sensitivity and VO_{2max} [92].

Metabolic disorders are often accompanied by subclinical inflammation, driven in part by increased monocyte infiltration into peripheral tissues [226]. This infiltration, particularly the polarization of macrophages toward a proinflammatory M1 phenotype, contributes to insulin resistance [227,228]. In contrast, chronic aerobic exercise promotes polarization toward the anti-inflammatory M2 phenotype, which is associated with enhanced insulin sensitivity in skeletal muscle. Mechanistically, compared with those from healthy controls, monocytes from individuals with obesity exhibit diminished insulin-binding capacity; this defect is partially reversed by both acute and chronic exercise, which improves insulin binding and thus contributes to enhanced glucose tolerance [229–232].

Collectively, these findings highlight the potential of exercise as a nonpharmacologic strategy to modulate the monocyte/macrophage phenotype and function in metabolic disease, offering new avenues for therapeutic intervention (Figure 2).

3.2. Effects of Exercise on Monocyte- and Macrophage-Related Cancers

Tumor progression is profoundly influenced by the tumor microenvironment (TME), within which TAMs represent a major hematopoietic component, accounting for up to 50% of infiltrating immune cells [233]. TAMs originate from either yolk sac-derived tissue-resident macrophages or hematopoietic stem cell-derived monocytes, which differentiate into TAMs upon recruitment to the tumor milieu. During tumor development, these

macrophages adopt a TAM phenotype, often skewed toward an M2-like state, which supports both antitumor and protumor functions [11]. TAMs promote tumor progression through several mechanisms: enhancing tumor cell proliferation and invasion, increasing cancer stem cell activity, driving angiogenesis, and suppressing cytotoxic T-cell and NK cell function [234]. However, under certain conditions, TAMs may exert antitumor effects by phagocytosing malignant cells and secreting proinflammatory cytokines that activate adaptive immunity [235]. The extent of TAM infiltration is correlated with poor prognosis and reduced overall survival in patients with various malignancies. Consequently, therapeutic strategies aimed at reprogramming TAMs from an M2-like phenotype to an M1-like phenotype are under investigation as a novel avenue for cancer immunotherapy [236].

Exercise is associated with a reduced incidence of at least 20 cancer types and may enhance the efficacy of anticancer therapies, alleviate treatment-related side effects, and modulate the TME via multiple mechanisms [2,3]. Regular physical activity has been shown to remodel the TME, including normalization of the tumor vasculature, a reduction in hypoxia, and increased infiltration of cytotoxic immune cells [171]. In tumor-bearing mice, moderate exercise enhances macrophage-mediated tumor cytotoxicity and increases the production of tumoricidal molecules such as IL-1, TNFα, and NO [166] (Figure 2). Chronic exercise may further suppress tumor progression by reducing the polarization of macrophages toward the protumor M2 phenotype and downregulating the expression of proangiogenic factors through the inhibition of extracellular-regulated protein kinase 5 s496 phosphorylation in TAMs [171], thus inhibiting angiogenesis [237].

The functional state of macrophages in the TME is closely linked to their metabolic programming. In general, classically activated M1 macrophages rely predominantly on aerobic glycolysis, whereas alternatively activated M2 macrophages favor oxidative phosphorylation (OXPHOS). Although TAMs are generally M2-like and promote tumor growth by inducing immune suppression, their metabolism is not as simple as previously thought and does not completely follow the M1 and M2 subtypes [238]. Moreover, the exact metabolic pathways of macrophages in tumors remain incompletely understood. Exercise may influence this metabolic reprogramming (Figure 2). Physical activity downregulates glycolysis-related gene expression in tumor-infiltrating myeloid cells while upregulating the expression of OXPHOS-associated transcripts [171]. Mechanistically, aerobic exercise has been shown to enhance mitochondrial metabolism in macrophages via AMP-activated protein kinase (AMPK) signaling, which may underlie the anti-inflammatory and cardiovascular protective effects of exercise [239].

Despite these insights, the precise contribution of macrophages to the anticancer effects of exercise remains incompletely understood. Further mechanistic studies are needed to elucidate how exercise-mediated modulation of macrophage phenotype and metabolism influences tumor progression and therapeutic responsiveness within the TME.

3.3. Effects of Exercise on Monocyte- and Macrophage-Related Neurodegenerative Diseases

Accumulating evidence highlights the central role of brain-associated macrophages and microglia in the pathogenesis of neurodegenerative diseases [240], particularly Alzheimer's disease (AD) and Parkinson's disease (PD)—the two most prevalent forms. In both disorders, neuroinflammation is intricately linked to neuronal injury, with microglia and macrophages serving as key mediators of disease onset and progression.

In AD, the accumulation of amyloid-β (Aβ) plaques and hyperphosphorylated tau (p-tau) is considered a hallmark of disease pathology. Inflammation, which is increasingly recognized as a direct contributor to AD pathogenesis, can exacerbate Aβ and p-tau aggregation [240]. Notably, activation of the NLRP3 inflammasome in M1-like microglia and macrophages has been shown to drive neuroinflammatory cascades and accelerate disease progression [241]. Similarly, in PD, the progressive degeneration of dopaminergic neurons in the substantia nigra is associated with the accumulation of intraneuronal protein aggregates (e.g., α-synuclein), with microglia-mediated inflammation playing a critical role in both neuronal loss and disease progression [242,243].

While there is currently no curative therapy for these neurodegenerative diseases, regular physical exercise has long been associated with broad neuroprotective effects, including improvements in cognitive performance, memory, learning, and attention [5]. These benefits are thought to be mediated in part through the modulation of macrophage/microglial function. As discussed above, long-term aerobic exercise, resistance training, and high-intensity continuous training attenuate age-related neurovascular decline and reduce the number or activation status of microglia and monocytes in animal models. Furthermore, integrative multiomics analyses have shown that exercise reprograms the transcriptional regulatory networks of peripheral monocytes in patients with AD [244], suggesting the presence of systemic immunomodulation. Importantly, exercise has been shown to attenuate the activation of the NLRP3 inflammasome, a key driver of neuroinflammation in AD and PD. In AD, regular physical activity dampens NLRP3 signaling in brain-resident immune cells, potentially reducing the neuroinflammatory load and slowing disease progression [241]. Similarly, in PD models, aerobic training suppresses NLRP3 inflammasome activation and microglial reactivity, leading to a reduction in neuronal damage [185].

Taken together, these findings suggest that physical exercise exerts neuroprotective effects, in part by modulating the inflammatory phenotype of microglia and brain-associated macrophages (Figure 2). Targeting microglia/macrophage-mediated neuroinflammation through structured exercise regimens may represent a promising adjunct strategy for mitigating the onset and progression of neurodegenerative diseases.

3.4. Effects of Exercise on Monocyte- and Macrophage-Mediated Muscle Injury and Repair

Bidirectional communication between skeletal muscle fibers and immune cells is fundamental to the orchestration of muscle repair following injury, including that induced by exercise. Monocytes and macrophages are central players in this regenerative process, facilitating both inflammation resolution and tissue remodeling.

Following acute muscle injury, circulating proinflammatory monocytes are rapidly recruited to damaged tissue, where they contribute to debris clearance and the initiation of regeneration. These monocytes subsequently differentiate into macrophages and undergo phenotypic switching from a proinflammatory (M1-like) state to an anti-inflammatory (M2-like) state, thus promoting myoblast differentiation, angiogenesis, and tissue regeneration [245]. Disruption of this transition impairs tissue repair; indeed, genetic or pharmacologic depletion of monocytes and macrophages markedly compromises muscle regeneration in vivo [245,246] (Figure 2). At the molecular level, skeletal muscle fibers actively participate in immune cell recruitment by upregulating the expression of chemokines in response to injury. Notably, myoblasts express the macrophage chemotactic factors CX3C chemokine ligand 1 (CX3CL1) and C-X-C motif ligand 12 (CXCL12), whose expression is significantly increased following a single bout of exercise [57,247]. These signals increase monocyte/macrophage infiltration and support tissue regeneration.

The inflammatory response to eccentric exercise-induced muscle damage is modulated in a dose-dependent manner by bioactive compounds such as dammarane steroids. The administration of low to moderate doses of these compounds mitigates muscle fiber necrosis and reduces M1 monocyte infiltration, suggesting anti-inflammatory and tissue-protective effects. In contrast, high doses exacerbate muscle damage, underscoring the complexity of immune regulation in muscle repair [248].

These findings challenge the conventional view that exercise-induced adaptations are uniformly beneficial. Instead, they highlight the importance of exercise intensity, modality, and individual physiological context—including susceptibility to psychological stress—in shaping immune responses and tissue outcomes. Optimizing these parameters is essential when designing exercise interventions aimed at enhancing recovery and minimizing muscle injury.

4. Mechanisms Underlying Exercise-Regulated Monocyte and Macrophage Function

4.1. Exerkines

A growing body of evidence suggests that the systemic immunomodulatory effects of exercise are largely mediated by "exerkines", a diverse group of bioactive molecules secreted by contracting skeletal muscles and other tissues in response to physical activity [249]. Muscle has emerged as a potent secretory organ, and several exerkines have been implicated in regulating macrophage polarization and function (Figure 3). For instance, the expression of meteorin-like (Metrnl) is induced in skeletal muscle following exercise and in adipose tissue upon cold exposure. Exercise-induced Metrnl stimulates an eosinophil-dependent increase in IL-4 and IL-13 expression, promoting M2 macrophage polarization and enhancing beige adipocyte thermogenesis [250]. Conversely, parvalbumin, a skeletal muscle-derived factor repressed by exercise, can antagonize colony-stimulating factor-1 receptor (CSF1R) signaling via extracellular vesicles (EVs), thus suppressing M2 polarization and ameliorating obesity [116].

Exercise also modulates cancer immunity through macrophage regulation. Chronic low-intensity aerobic exercise induces the expression of myostatin, a myokine that inhibits M2 polarization via JAK1/STAT6 signaling, reducing breast tumor volume and delaying tumor progression [169]. Similarly, exercise promotes the release of miR-29a-3p in muscle-derived EVs, which facilitates $CD8^+$ T-cell and M1-like monocyte infiltration while decreasing M2-like macrophage accumulation in tumors [170]. MiR-124-3p expression is also induced by aerobic exercise, which inhibits the M1 macrophage phenotype to ameliorate lung inflammation [251]. Additionally, exercise-induced muscle-derived IL-6 is involved in NK redistribution to suppress tumor growth, but the effect of IL-6 on macrophages has not been detected [252]. Oncostatin M (OSM), a member of the IL-6 family, is upregulated in muscle following a single bout of aerobic exercise and promotes M2 macrophage accumulation via chemokine regulation [60].

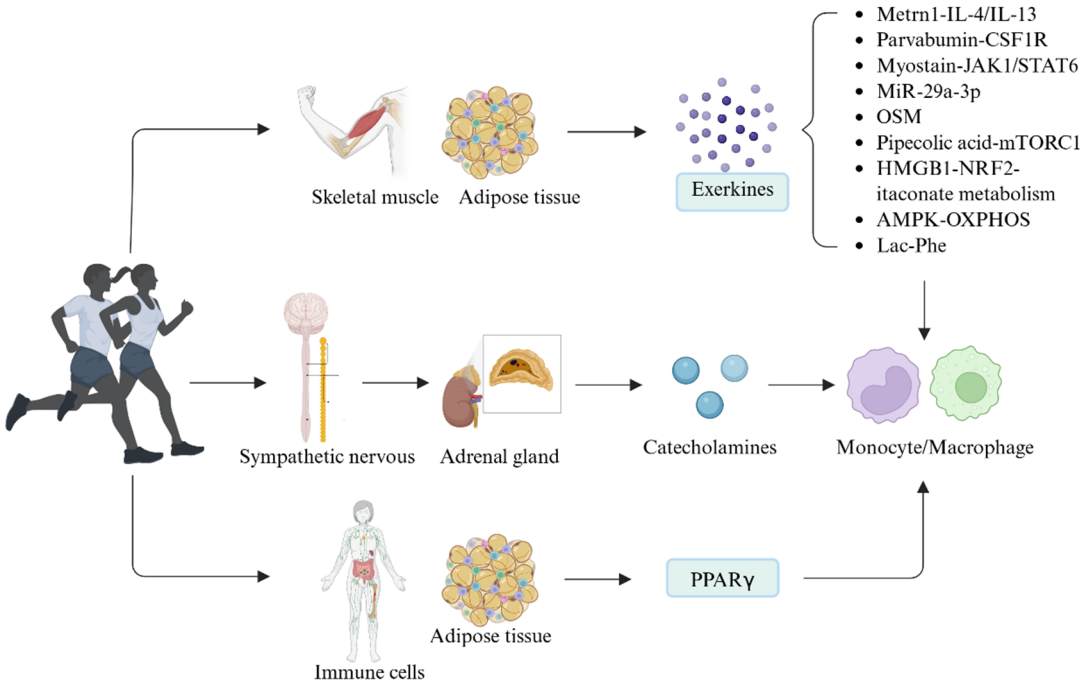

Figure 3. Mechanisms Underlying Exercise-Regulated Monocyte and Macrophage Function. Exercise-induced exerkines, neuroendocrine activation via the sympathetic-adrenal axis, and PPARγ signaling may serve as pivotal regulators of exercise-mediated monocyte/macrophage reprogramming. Metrn1: Metrn-like; IL-4/IL-13: interleukin-1/13; CSF1R: colony-stimulating factor-1 receptor; JAK1: Janus kinase 1; STAT6: signal transducer and activator of transcription 6; OSM: oncostatin M; mTORC1: mammalian target of rapamycin complex 1; HMGB1: High mobility group box-1 protein; NRF2: nuclear factor erythroid-2-related factor 2; AMPK: AMP-activated protein kinase; OXPHOS: oxidative phosphorylation. PPARγ: peroxisome proliferator-activated receptor γ.

Recent metabolomics studies suggest that exercise-modified metabolic intermediates also modulate macrophage function. For example, early-life exercise increases pipecolic acid levels, which inhibit mammalian target of rapamycin complex 1 (mTORC1) signaling in macrophages, reducing proinflammatory cytokine production and protecting against LPS-induced sepsis [253]. Similarly, high-mobility group box-1 protein (HMGB1) expression induced by aerobic exercise enhances itaconate metabolism in KCs via NRF2-dependent pathways, promoting an anti-inflammatory phenotype [113]. Aerobic exercise upregulates AMPK-driven mitochondrial metabolism in macrophages, contributing to systemic anti-inflammatory effects and reduced cardiovascular risk [239]. Aerobic exercise inhibits LPS-induced NF-κB activation and proinflammatory gene expression but increases the number of M2 macrophages among BMDMs by affecting the chromatin accessibility of genes associated with inflammatory and metabolic pathways [175]. Notably, exercise-induced Lac-Phe, produced from lactate in $CNDP2^{+}$ cells, including macrophages and mesenchymal stem cells, suppresses feeding and obesity [254] and mitigates colitis by inhibiting M1 macrophage polarization via suppression of the NF-κB signaling pathway [255]. However, lactate produced by tumor cells promotes M2-like TAM polarization [256], and these conflicting results suggest that the effects of lactate on tumors are complex. Given that exercise increases lactate levels, optimizing the exercise prescription to minimize lactate acid production may elicit better inhibitory effects on tumors.

In addition to these well-characterized mediators, numerous other exercise-responsive metabolites—such as citrate, itaconate, succinate, and α-ketoglutarate—have been shown to influence macrophage polarization [257–259]. For instance, succinate promotes IL-1β production via HIF-1α stabilization during inflammation [260], whereas cold-induced hormones such as adiponectin, fibroblast growth factor 21, and CXCL14 activate M2 macrophages and enhance glucose/lipid metabolism [261–263]. Irisin (FNDC5), another myokine upregulated by exercise, promotes M2 differentiation through the JAK2–STAT6–PPARγ axis and NRF2-associated antioxidant pathways [264]. Its homolog FNDC4 reduces M1/M2 macrophage levels and protects against colitis [265], although its direct regulation by exercise remains to be confirmed.

4.2. Neuroendocrine Axis

The neuroendocrine axis, particularly the sympathetic nervous system**,** is another important regulator of exercise-induced immunomodulation. Physical activity activates the SNS and increases systemic levels of catecholamines—epinephrine and norepinephrine—which signal via α- and β-adrenergic receptors (ARs) on immune cells, neurons, and tumor cells (Figure 3).

While α-ARs generally promote inflammation, β2-AR signaling has well-documented immunosuppressive effects and governs the mobilization of monocytes, NK cells, and $CD8^+$ T cells during exercise [38,252,266]. Epinephrine also suppresses TNFα production by monocytes during acute exercise via β2-AR [82]. In the tumor microenvironment, it promotes M2-like TAM polarization via the tripartite-motif-containing protein 2–NF-κB axis [267].

Despite limited studies, emerging evidence links sympathetic activation to macrophage reprogramming in metabolic disease. For instance, HIIT induces adipose tissue browning and improves glucose metabolism in T2DM mice by enhancing M2 macrophage polarization and increasing sympathetic innervation [129]. Additionally, chronic exercise increases the level of cortisol, which increases CCR2 expression in monocytes, enhancing their migratory potential [268]. Notably, acute exercise alone does not affect CCR2 levels, suggesting that prolonged hormonal changes are necessary for monocyte programming.

4.3. PPARγ Signaling

PPARs, particularly PPARγ, have emerged as key regulators of macrophage metabolism, differentiation, and immune function [269,270]. PPARγ suppresses glycolysis and promotes M2 macrophage polarization. Loss of PPARγ in macrophages impairs M2 activation and predisposes animals to obesity and insulin resistance [269,271] (Figure 3). Interestingly, PPARγ plays a dual role in cancer. Its deletion in macrophages exacerbates tumor growth and diminishes the efficacy of PPARγ agonists such as rosiglitazone [272], whereas in some contexts, PPARγ deficiency delays tumor progression and enhances prognosis [273,274]. These contradictory findings may reflect tissue-specific roles of PPARγ in macrophages versus tumor cells.

Exercise consistently upregulates PPARγ expression and activity in monocytes and tissue macrophages. Chronic low-intensity aerobic training enhances PPARγ-dependent gene expression associated with reverse cholesterol transport and anti-inflammatory responses in circulating monocytes. Aerobic exercise also modulates macrophage polarization in muscle tissue, promoting M2 phenotypes, an effect mediated through PPARγ [146,275–277]. Deletion of PPARγ reduces M2 peritoneal macrophages after exercise [151], although exercise-induced anti-inflammatory benefits can still occur in the absence of macrophage PPARγ, suggesting the involvement of alternative or compensatory pathways [152].

Given the interdependence among PPAR isoforms, future studies should explore how PPARα, β/δ, and γ cooperatively regulate monocyte/macrophage responses during exercise to better understand their collective impact on inflammation and tissue homeostasis.

Taken together, these findings suggest that exerkines, the neuroendocrine activation axis, and nuclear receptor signaling may serve as pivotal regulators of exercise-mediated alterations in monocyte/macrophage function. However, the underlying mechanisms through which exercise influences these organs or tissues are unclear. Given that Ca^{2+} flux and high demand for ATP are the most significant changes induced by exercise [278], it is speculated that exercise may modulate monocyte/macrophage reprogramming by affecting ion flux and the generation of ATP.

5. Conclusions

Monocytes and macrophages play indispensable roles in innate immunity, orchestrating inflammatory responses, tissue homeostasis, and immune surveillance. In this review, we comprehensively summarize the effects of both acute and chronic exercise training on monocyte/macrophage mobilization, phenotype, and function. Evidence indicates that chronic moderate-intensity exercise promotes an anti-inflammatory milieu characterized by reduced numbers of circulating and tissue-infiltrating monocytes, increased phagocytic capacity, increased polarization of macrophages toward an M2 anti-inflammatory phenotype, and suppressed proinflammatory cytokine production. These adaptations underpin the protective effects of exercise against a wide spectrum of diseases, including metabolic disorders, cancer, neurodegenerative conditions, and muscle injury. Despite accumulating evidence supporting the immunomodulatory effects of exercise, the underlying mechanisms regulating monocyte/macrophage plasticity remain incompletely understood. Emerging data suggest that exercise-induced secreted factors (exerkines), neuroendocrine activation via the sympathetic–adrenal axis, and nuclear receptor signaling—particularly through PPARγ—may serve as pivotal regulators of exercise-mediated

monocyte/macrophage reprogramming. Regrettably, although exercise benefits various diseases through regulating monocytes/macrophages, as mentioned above, evidence is lacking to translate exercise-induced macrophage modulation into therapeutic strategies. Given that the immune system can be influenced by age, physical condition, the amount of physical activity, and so forth, different populations might respond differently to exercise-induced immunomodulation. Additionally, exercise is not always beneficial for some vulnerable populations and may lead to immunosuppression. Future studies dissecting these mechanistic pathways in specific pathological contexts will be critical for harnessing the full therapeutic potential of exercise as a modulator of innate immunity.

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