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Mechanisms underlying the beneficial effects of physical exercise on multiple sclerosis: focus on immune cells

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Multiple sclerosis (MS) is a prevalent neuroimmunological illness that leads to neurological disability in young adults. Although the etiology of MS is heterogeneous, it is well established that aberrant activity of adaptive and innate immune cells plays a crucial role in its pathogenesis. Several immune cell abnormalities have been described in MS and its animal models, including T lymphocytes, B lymphocytes, dendritic cells, neutrophils, microglia/macrophages, and astrocytes, among others. Physical exercise offers a valuable alternative or adjunctive disease-modifying therapy for MS. A growing body of evidence indicates that exercise may reduce the autoimmune responses triggered by immune cells in MS. This is partially accomplished by restricting the infiltration of peripheral immune cells into the central nervous system (CNS) parenchyma, curbing hyperactivation of immune cells, and facilitating a transition in the balance of immune cells from a pro-inflammatory to an anti-inflammatory state. This review provides a succinct overview of the correlation between physical exercise, immune cells, and MS pathology, and highlights the potential benefits of exercise as a strategy for the prevention and treatment of MS.

KEYWORDS

multiple sclerosis, exercise, immune cell, adaptive immunity, innate immunity

1 Introduction

Multiple sclerosis (MS) is a disease characterized by neuroinflammation, demyelination, and axonal damage, with lesions that involve both the brain and spinal cord. It is estimated that MS affects approximately 2.8 million individuals worldwide, with a higher prevalence in women (1). Symptoms of MS, such as vision loss, numbness, tingling,

motor paralysis, cognitive impairment, and bladder dysfunction, significantly diminish the quality of life for patients (2, 3). In general, the course of MS disease manifests in three main forms: primary progressive MS (PPMS), secondary progressive MS (SPMS), and relapsing-remitting MS (RRMS) (4). Initially, most patients with MS (PwMS) experience the neurological symptoms of RRMS. Within a decade of disease onset, approximately 30–40% of PwMS transition into SPMS, which is characterized by an irreversible and progressive accumulation of neurological disability (3). The disability status of PwMS can be assessed on a scale of zero to ten using the Expanded Disability Status Scale (EDSS), with zero representing a normal neurological examination, and ten representing MS-caused death (5). There is evidence that the disease is associated with genetic, lifestyle and environmental risk factors (6, 7), but the exact cause of MS remains unclear.

The myelin sheath is a protective lipoprotein coating that surrounds axons and is composed mainly of oligodendroglial cell membranes, which help to protect nerves and ensure the normal conduction of nerve impulses. The normal formation of myelin depends on the process of myelination (8). Oligodendrocytes (OLs) are glial cells responsible for myelination, and these cells differentiate from oligodendrocyte progenitor cells (OPCs) (9). However, in MS, dysfunction of OLs and pathology of myelin lead to severe demyelination, impaired remyelination, and axonal degeneration (10). Over the years, the interactions between the immune cell, glial cell, and neuronal cell in the pathology of MS have been extensively studied. In the early stages, pathogenesis is primarily driven by peripheral immune cell responses targeting the CNS (11–13). The peripheral immune cells, such as T cells, B cells, and myeloid cells, infiltrate the CNS and interact with microglia and astrocytes, causing damage to OLs and inhibiting myelin formation (14–19). In the progressive stages, immune responses mediated by CNS-resident microglia and astrocytes predominate (20). In the inflammatory state, microglia generate pro-inflammatory cytokines and chemokines, and increase the expression of costimulatory molecules that facilitate the recruitment and activation of peripheral leukocytes (21, 22). Furthermore, microglia stimulate pro-inflammatory and neurotoxic responses in astrocytes that exacerbate demyelination, neurodegeneration, and atrophy of both grey and white matter (23, 24) (Figure 1). The autoimmune response directed against neuronal axons or synapses interferes with proper neurotransmission, resulting in a variety of motor and non-motor symptoms (25, 26).

Nowadays, pharmacotherapy is considered the primary treatment for MS; however, its efficacy falls short for a significant number of patients. Furthermore, the side effects and exorbitant costs linked with pharmacotherapy may result in reduced patient compliance (27). Non-pharmacological treatments, such as physical exercise, have gained attention as potential disease-modifying therapies for PwMS (28, 29). Physical exercise has been shown to be effective in rehabilitating PwMS, effectively alleviating symptoms, enhancing functionality, improving quality of life, and increasing engagement in daily activities (30–32). Mechanistically, physical exercise provides some protection to the CNS from disease-related atrophy and dysfunction. Structurally, objective research has demonstrated that several months of exercise in

PwMS can preserve cortical thickness (33), pallidum (34) and hippocampal volume (35), as well as the microstructural integrity of the insula (36) and motor-related tracts and nuclei (37). Functionally, research has found that exercise can improve functional connectivity between the caudate and the left inferior parietal, bilateral frontal, and right insula regions (38). In addition, exercise can also increase functional connectivity within the hippocampus and the default-mode network (39). Notably, the utilization of animal models is of great value in investigating cellular and molecular mechanisms. Commonly used models include myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE) and toxin and/or virus-induced demyelination models, such as cuprizone (CPZ) and lysophospholipid, among others (40). In animal studies, there is evidence that regular exercise training can effectively promote the process of remyelination, alleviate demyelination, and enhance neuroplasticity by modulating the activity and function of OLs and neurons (41–45), and exert neuroprotective effects by reducing oxidative stress (46–49), maintaining the integrity and permeability of the blood-brain barrier (BBB) (48, 50), and adjusting the physiological levels of various exercise metabolites (51, 52). Moreover, it is imperative to recognize the anti-inflammatory benefits of physical exercise, as it not only regulates OLs and neurons, but also influences numerous immune cell types. This review will focus on the effect of physical exercise on neuroimmune regulation in MS, specifically regarding T cells, B cells, dendritic cells, neutrophils, macrophages, microglia, and astrocytes.

2 Effect of physical exercise on immune cells in multiple sclerosis

2.1 Adaptive immune cells

2.1.1 T cells and B cells

Lymphocytes, particularly T cells and B cells, are integral components of the adaptive immune system and are required for immune surveillance of the CNS. They can induce significant immunopathological responses in the presence of viral infections and autoimmune disorders (53, 54). T cells are mainly classified into CD4⁺ T cells and CD8⁺ T cells based on distinct cell surface differentiation antigens (55). Aberrant activation of autoreactive CD4⁺ T cells is considered a primary factor in the development of MS (56, 57). Upon activation, naive CD4⁺ T cells differentiate into different T helper (Th) cell subsets, including Th1, Th2, Th17, and T regulatory (Treg) cells. These subsets have distinct cytokine profiles and effector functions (58). Th17 cells can release several pro-inflammatory cytokines, such as interleukin 17A (IL-17A), interferon γ (IFN- γ), and IL-22 (57). In EAE, the number of peripheral Th1/Th17 cells increases significantly, as do the levels of IFN- γ and IL-17. These immune cells and their associated cytokines, infiltrate the CNS to exacerbate autoimmune neuroinflammation (59). In addition to neuroinflammation, excessive inflammatory cytokines (such as members of the IL-17 family) can initiate other malignant events. Within the CNS of the

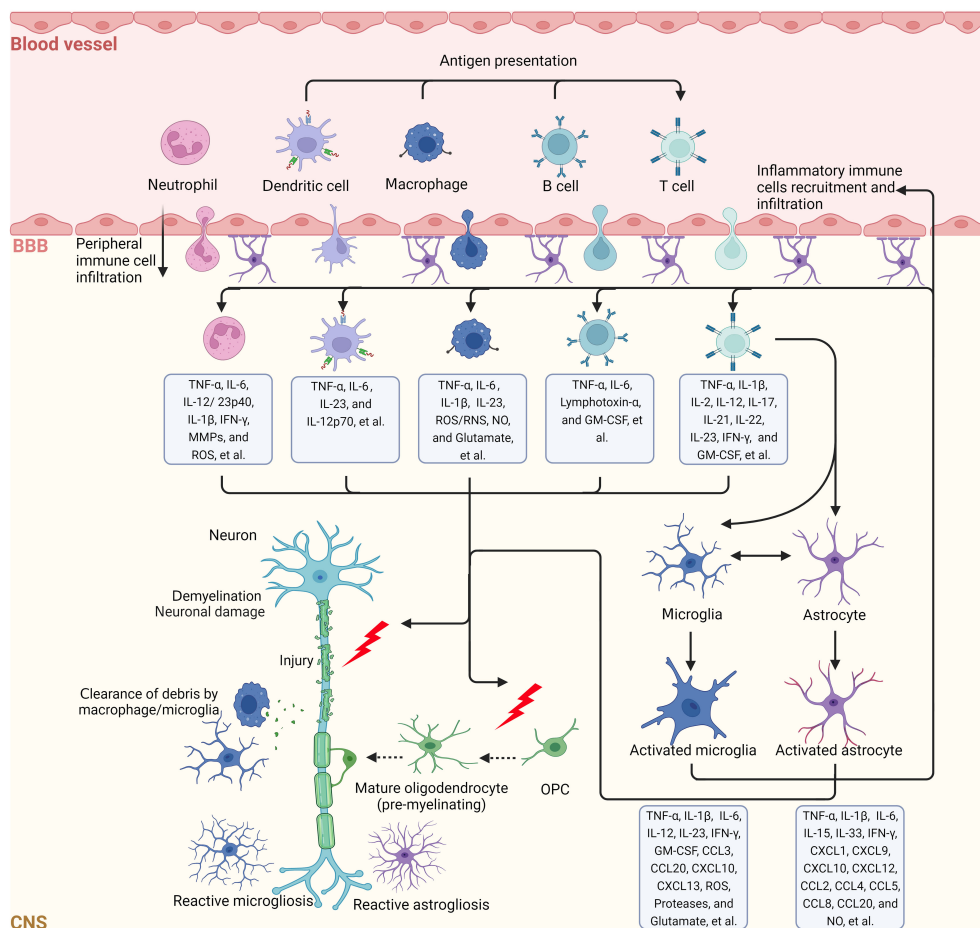


FIGURE 1

Schematic diagram of immune cells-driven multiple sclerosis pathology. In multiple sclerosis, peripheral immune cells, including lymphocytes and monocytes, infiltrate into the central nervous system and secrete pro-inflammatory and neurotoxic substances. These cells, particularly T lymphocytes, possess the ability to interact with CNS-resident microglia and astrocytes, leading to microglial and astrocyte activation and the subsequent release of pro-inflammatory and neurotoxic substances. These substances contribute to the demyelination and neuronal damage, and erode oligodendrocytes, preventing them from forming myelin. Meanwhile, some of the pro-inflammatory substances released by microglia and astrocytes promote the recruitment, infiltration and activation of peripheral immune cells, further enhancing the autoimmune response in the CNS. The figure was created using BioRender. BBB, blood-brain barrier; CCL, chemokine (C-C motif) ligand; CNS, central nervous system; CXCL, chemokine (C-X-C motif) ligand; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN- γ , interferon- γ ; IL, interleukin; MMP, matrix metalloproteinase; NO, nitric oxide; OPC, oligodendrocyte progenitor cell; RNS, reactive nitrogen species; ROS, reactive oxygen species; Th, T helper cells; TNF- α , tumor necrosis factor- α .

EAE model, IL-17 is involved in pain modulation as an upstream regulator of Ca²⁺/calmodulin-dependent protein kinase II α (CaMKII α) (60). During EAE, overexpression of IL-17A results in impaired long-term potentiation (LTP) and synaptic plasticity in the hippocampus. This leads to cognitive decline through activation of the IL-17A receptor and the p38 mitogen-activated protein kinase (MAPK) signaling pathway, as reported by Di Filippo et al. (26). In contrast, Treg cells possess the ability to release anti-inflammatory cytokines such as IL-10, transforming growth factor β (TGF- β), and IL-35 (61). The beneficial effects of natural Treg cells, which express CD4⁺ forkhead box protein 3 (FoxP3), and T regulatory type 1 (Tr1) cells, which produce IL-10, on autoimmune neuroinflammation have been demonstrated in both MS patients (62, 63) and experimental animal models (64, 65). A crucial aspect contributing to tissue inflammation in CNS autoimmunity is the impaired functionality of Th17 and Treg cells. It is noteworthy that

modulation of the Th17/Treg balance, as well as the functional state of the intrasubsets, can attenuate CNS autoimmunity (66, 67). Different substances, compound 21 (68) and ACDT (69), have demonstrated inhibition of the infiltration of pathogenic Th1/Th17 cells into the CNS in the EAE model. Furthermore, the administration of propionic acid to PwMS resulted in a significant and sustained increase in functional Treg and a significant decrease in Th1/Th17 cells (70). Ultimately, the disease severity of EAE is minimized, or the clinical symptoms of PwMS are reduced.

Alongside CD4⁺ T cells, some of the cytotoxic CD8⁺ T cells, such as IL-17-producing CD8⁺ T (Tc17) cells, have been identified as possible drivers of localized autoimmune damage to the CNS in the EAE model (71). Intriguingly, while in most animal models this is not the case, studies examining human patients have revealed that CD8⁺ T cells are the main type of T cells present in the CNS of these

individuals (72–74). Inflammatory active lesions in MS are populated by CD8⁺ tissue-resident memory T cells, exhibiting indications of reactivation and infiltration into the brain parenchyma (73). The CD8⁺ T cells could serve various functions, as they have been assigned both pathogenic and regulatory roles. On one hand, CD8⁺ T cells could act as pathogenic effectors that lead to the breakdown of the BBB (75) and promote pathogenic CD4⁺ T cell activity (71), damage OLS (76) and OPCs (77), and/or direct damage axons (78). On the other hand, CD8⁺ T cells may regulate pathogenic CD4⁺ T cells by directly modulating antigen-presenting cells and/or through releasing immunoregulatory cytokines such as IL-10, IFN- γ , and TGF- β (79, 80). Moreover, the efficacy of several therapeutic interventions that selectively deplete B cells (rituximab, ocrelizumab and ofatumumab) highlights the importance of B cells in the pathogenesis of the disease (81). B cells contribute to the pathology of MS through multiple mechanisms. They present antigens to T cells, driving the auto-proliferation of brain-homing T cells (82). Additionally, B cells secrete pro-inflammatory cytokines, such as TNF- α , IL-6, IL-15, and granulocyte-macrophage colony stimulating factor (GM-CSF) (83), and produce extracellular vesicles and antibodies (84). It should be noted that there are distinct functional differences within subpopulations of CD8⁺ T cells and B cells, emphasising the need for the development and implementation of therapies that target specific pathogenic cell subsets.

Physical exercise has been proven to improve systemic autoimmune inflammation mediated by lymphocytes, in addition to pharmacological treatment, and is generally secure for individuals with autoimmune disorders like systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel diseases and MS, among others (85). Since 2018, numerous studies conducted by Einsteina et al. have investigated the effect of different exercise programs on T cell-mediated autoimmunity from the proteolipid protein (PLP)-induced transfer EAE model in animals. By transferring T cells from lymph nodes (LN-T cells) obtained from mice that underwent six weeks of treadmill running, or from sedentary donor mice, to naive recipients and recipient mice that were either trained prior to EAE induction or sedentary, researchers confirmed that physical exercise limits immune responses to an auto-antigen to weaken EAE, instead of suppressing the immune system in general (86). Further studies have confirmed the superior effect of high-intensity continuous training (HICT) in preventing T cell-induced autoimmunity in EAE through treadmill running, compared to moderate-intensity continuous training (MICT) (87). Remarkly, variations were found in the mechanisms by which continuous and intermittent exercise, performed at the same high intensity, alleviated systemic autoimmunity and T cell encephalitogenicity. Specifically, HICT impeded PLP-induced T cell proliferation without affecting T cell differentiation, while high-intensity intermittent exercise (HIIT) had no noticeable impact on T cell proliferation but hindered T cell polarization into Th1 and Th17 pro-inflammatory phenotypes (88). Taken together, because of the significant variation observed across different disease trajectories, it is essential to implement effective intervention programs that are customized to suit the specific characteristics of each phase of the disease.

In other previous animal studies, mice that underwent regular swimming exercise before EAE induction showed suppressed infiltration of CD4⁺ T cells, CD8⁺ T cells, and B cells into the spinal cord. Meanwhile, the proliferation of antigen-specific T cells was halted and the proliferation of Treg cells was promoted, while restricting the secretion of IFN- γ and IL-17 and enhancing the secretion of IL-10 and TGF- β . Furthermore, regular swimming exercise also alleviated damage to myelin and axons and reduced clinical scores (89, 90). Notably, research suggests that high-intensity swimming (4% body weight) may prove more effective than moderate-intensity swimming (0% body weight) (90). It seems that swimming exercise represents a noteworthy non-pharmacological intervention for improving chronic inflammation or autoimmunity; however, the success of this intervention could be modified by the intensity of the exercise. In addition, it is probable that the efficacy of exercise interventions is also reliant on the type of exercise employed. Over a four-week period, it was observed that both strength and endurance training programs impeded the development and progression of disease, improved genomic antioxidant defense-nuclear factor erythroid 2-related factor (Nrf2)/antioxidant response elements (ARE) pathway, lowered the production of IFN- γ , IL-17, and IL-1 β , reduced the expression of adhesion molecules, such as platelet and endothelial cell adhesion molecule 1 (PECAM-1), and reinstated the expression of tight junction proteins such as occludin and claudin-4 in the spinal cord after EAE induction. However, only strength training significantly increased the expression of Treg cell markers, specifically CD25 and IL-10, obtained from spleen cells, and inhibited the production of IL-6, monocyte chemoattractant protein 1 (MCP-1), and TNF- α (48). Further analyses revealed that while endurance exercise was superior in delaying disease progression and lowering clinical scores as well as antioxidants, strength training was more effective in improving immune system function. Voluntary wheel running, as a rehabilitation approach, has been demonstrated as an effective intervention for promoting motor recovery. Regular voluntary wheel running had a significant positive effect on demyelination and axonal damage in EAE mice, in comparison to their sedentary counterparts. However, the impact of lymphocyte infiltration was insignificant (47, 91). Additionally, gender of the subjects must be taken into consideration as it may have an influence on the exercise intervention's efficacy (47, 92). Further, a study has investigated the potential of combined interventions and has discovered a substantial positive interaction between exercise and galantamine medication. The outcome of this interaction led to a notable rise in the quantity of Foxp3⁺ T cells in the brainstem of rats affected by EAE (93). The animal studies' collective findings suggest that physical exercise could potentially suppress lymphocyte infiltration, including CD4⁺ T cells, CD8⁺ T cells, and B cells. Additionally, it could modulate the Th cell phenotype and regulate related cytokine levels, eventually leading to a reduction in autoimmune responses in the CNS, an improvement in MS pathology, and a decrease in disease severity (Table 1). Nonetheless, the effects of exercise may be impacted by different aspects of the exercise intervention, such as the type and intensity of the exercise, as well as the heterogeneity of the subjects.

TABLE 1 Effect of exercise on adaptive immune cells in animal models and human patients of MS.

Subjects		Exercise intervention program			Region	Mode of action	References
Model	Characteristics	Type	Intensity	Duration			
MOG ₃₅₋₅₅ -induced EAE model	C57BL/6 mice; female; 8 weeks old	Voluntary wheel running	ND	60 min/session for 40 consecutive days	Brain and spinal cord	CD4 ⁺ T cells, and CD8 ⁺ T cells infiltration →; Synaptic plasticity ↑; Clinical scores ↓	(91)
	C57BL/6 mice; female; 7 weeks old	Prior swimming	7% BW	30 min/session, 5 sessions/week for 6 weeks	Spinal cord	B cells, CD4 ⁺ T cells, and CD8 ⁺ T cells infiltration ↓; Myelin and axonal damage ↓	(89)
	C57BL/6 mice; female; 6~12 weeks old	Strength training (ST): Climbing the ladder Endurance training (ET): Treadmill running	(i) ST: 25%, 50%, and 75% BW (ii) ET: 13~17 m/min	30 min/session, 5 sessions/week for 4 weeks	Spinal cord	(i) ST: Treg cell markers: CD25 and IL-10 ↑; IFN-γ, IL-17, and IL-1β ↓; Clinical scores ↓; Protein oxidation and NO levels ↓; GPx activity ↑; TjPs ↑; CAMs ↓ (ii) ET: IFN-γ, IL-17, and IL-1β ↓; Clinical scores and weight loss ↓; Lipid peroxidation, protein oxidation and NO levels ↓; GPx activity, GSH content and Nrf-2 expression ↑; TjPs ↑; CAMs ↓	(48)
	C57BL/6 mice; male and female; 6~8 weeks old	Voluntary wheel running	ND	60 min/session for 30 consecutive days	Spinal cord	(i) Male: CD4 ⁺ T cells infiltration →; Demyelination and axonal loss ↓; Oxidative stress ↓; Clinical scores → (ii) Female: No effect	(47)
	C57BL/6 mice; female; 6~8 weeks old	Prior swimming	(i) HE: 4% BW (ii) ME: 0% BW	50 min/session, 5 sessions/week for 6 weeks	Spinal cord	(i) HE: Treg proliferation ↑; Antigen-specific T cell proliferation ↓; Th1 and Th17 populations ↓; IFN-γ and IL-17 ↓; IL-10 and TGF-β ↑; BDNF ↑; Demyelination ↓; Clinical scores ↓ (ii) ME: No effect	(90)
	C57BL/6 mice; male and female; 6~8 weeks old	Voluntary wheel running	ND	60 min/session, 6 sessions/week for 1 week	Spleen	(i) Male: T cell proliferation ↑; IFN-γ, TNF-α, IL-17A ↑; Dorsal root ganglia excitability and calcium responses →; Nociceptive behaviour →; (ii) Female: T cell proliferation ↑; IFN-γ, TNF-α, IL-17A ↓; Dorsal root ganglia excitability and calcium responses ↓; Nociceptive behaviour ↓	(92)
	C57BL/6 mice; female; 3~4 weeks old	Stair climbing	ND	20, 40, and 60 min/session, 6 sessions/week for 4 weeks	Intestine lymphoid tissues and spinal cord	Th17 responses ↓; Treg responses ↑; IL-17A and IFN-γ ↓; Firmicutes/Bacteroidetes ratio and intestinal mucosal permeability ↓; Microbial abundance and diversity ↑; Demyelination and axonal damage ↓	(94)
	SD rats; male; 2~3 months old	Walking on a rotating metallic rod with galantamine	ND	30 min/session for 30 consecutive days	Brain stem and cerebrospinal fluid	Foxp3 ⁺ T cells ↑; TNF-α and IL-6 ↓; Demyelination ↓; BDNF and Bcl-2/Bax ratios ↑; Motor performance ↑	(93)
CPMS and RRMS patients	12 female/10 male; (46.0 ± 2.0) years old; EDSS score < 6	Endurance training (walking and bicycling) combined with strength training (resistance exercise)	(i) ET: 65% HRR (ii) ST: 70% 1RM	A single bout	Blood	(i) Immediate post-exercise: Lymphocytes number ↑; CD25 ^{hi} Foxp3 ⁺ Treg and antigen-induced IL-10-producing Tr1 number ↑; Th3 cells number → (ii) 2 hours post-exercise: Lymphocytes number ↑; CD25 ^{hi} Foxp3 ⁺ Treg and antigen-induced IL-10-producing Tr1 number ↑; Th3 cells number →	(95)
	16 female/13 male; (46.0 ± 2.0) years old; EDSS score (3 ± 0.2)	Endurance training (cycling and treadmill walking or running) combined with strength	ND	5 sessions/2 weeks for 12 weeks	Blood	Treg cells number and proportion →; CD25 ^{hi} Foxp3 ⁺ , Tr1, and Th3 cells →	(96)

(Continued)

TABLE 1 Continued

Subjects		Exercise intervention program			Region	Mode of action	References
Model	Characteristics	Type	Intensity	Duration			
		training (resistance exercise)					
RRMS patients	7 female/1 male; (41.1 ± 12.9) years old; EDSS score < 2	Strength training combined with bicycling	ST: <35%, 35%~65%, >65% 1RM; AT: 60% AC _{max}	60 min/ session, 12 weeks	Blood	TNF-α and IL-6 ↓; IL-22 ↓; IFN-γ and IL-17 →; IL-10 ↑; Fatigue ↓	(97)
	7 female/12 male; 20~60 years old; EDSS score < 4.5	Normoxic (N) or hypoxic (H) treadmill training	65% HR _{max}	60 min/ session, 3 sessions/ week for 4 weeks	Blood	(i) N: CD39 ⁺ Treg cells ↑; CD31 ⁺ Treg cells ↓; IL-17A-producing CD4 ⁺ T cells ↓; Fitness and mood ↑ (ii) H: CD39 ⁺ Treg cells, CD31 ⁺ Treg cells, and IL-17A-producing CD4 ⁺ T cells →; Fitness and mood ↑	(98)
PwMS treated with either ATZ, FTY, or NAT	17 female/13 male	Climbing stairs at normal speed (CN) or fast (CF) or cycling (C)	C: 1, 2 Watt per kilogram BW	CN: ND CF: ND C: 20 min	Blood	(i) CN: Absolute lymphocyte number ↑ (ii) CF: Absolute lymphocyte number ↑; CD19 ⁺ B cell, and CD3 ⁺ T cell number ↑ (iii) C: Absolute lymphocyte number ↑	(99)

1RM, repetition maximum; AC_{max}, maximal aerobic capacity; ATZ, alemtuzumab; Bax, BCL2-associated X; Bcl2, B-cell lymphoma-2; BDNF, brain-derived neurotrophic factor; BW, body weight; CAMs, cell adhesion molecules; CPMS, chronically progressive MS; EAE, experimental autoimmune encephalomyelitis; EDSS, Expanded Disability Status Scale; Fcγ3, forkhead box protein 3; FTY, Fingolimod; GPx, glutathione peroxidase; GSH, glutathione; HE, high-intensity exercise; HR_{max}, maximal heart rate; HRR, heart rate reserve; IFN-γ, interferon-γ; IL-10, interleukin-10; ME, moderate-intensity exercise; MOG, myelin oligodendrocyte glycoprotein; NAT, natalizumab; ND, not determined; NO, nitric oxide; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PwMS, patients with MS; TGF-β, transforming growth factor-β; Th, T helper cells; TJPs, tight junction proteins; TNF-α, tumor necrosis factor-α; RRMS, relapsing-remitting MS. ↑, significantly increased or improved; ↓, significantly decreased or reduced; →, no significant change.

In human studies, lymphocyte proliferation has been observed to be suppressed after acute exercise in healthy individuals. This effect is more pronounced during exercise sessions exceeding an hour in duration, regardless of exercise intensity (100). However, some studies have reported inconsistent findings. For example, individuals who are healthy controls and those with PwMS receiving alemtuzumab, fingolimod, or natalizumab displayed an increase in the absolute number of lymphocytes and specific subsets following exercise. The degree of response was impacted by the intensity of the exercise program (99). In Deckx's study, naturally occurring CD25^{hi}Foxp3⁺ Treg cells and antigen-induced IL-10-producing Tr1 cells increased in the peripheral blood of patients with chronically progressive MS and RRMS following a single session of moderate-to-high-intensity endurance with resistance exercise. The number of Tr1 cells remained elevated for up to two hours after exercise (95). This increase in Treg cells may serve as a negative feedback mechanism to the immune system's capacity to elicit tissue damage and inflammation when responding to exercise. Moreover, the findings of regular exercise intervention studies require careful observation. A four-week experiment of treadmill running in normoxic conditions (rather than hypoxic conditions) caused modifications in circulating Treg subpopulations among patients with RRMS. These alterations comprised of an increase in CD39⁺ Treg cells and a decrease in CD31⁺ Treg cells, as well as a reduction in IL-17A-producing CD4⁺ T cells. These results imply that treadmill running has a vital function in adjusting the adaptive immune response in MS through impacting distinct T cell subsets (98). Remarkably, conflicting results have also emerged. As early as 2012, a cross-sectional study revealed that there were no discernible

differences in the proportions of circulating CD4⁺ T cells (including Foxp3⁺ Treg cells), CD8⁺ T cells, and B cells in the peripheral blood between physically active and inactive PwMS, and no correlation with physical performance parameters (101). These findings suggest that prolonged physical activity may not have a significant impact on the adaptive immune cells in PwMS. In accordance with this, Deckx et al. (96) discovered that 12 weeks of endurance and strength training had no effect on the circulating Treg subsets, including CD25^{hi}Foxp3⁺, Tr1, and Th3 cells in PwMS. These inconsistent findings in human patients have significant implications for experimental and clinical research, particularly regarding the development of interventions to address autoimmune factors in MS.

The BBB is a dynamic interface linking the blood with the brain parenchyma. It comprises capillary endothelial cells (ECs) from the brain and spinal cord, and perivascular cells including smooth muscle cells, microglia, pericytes, and astrocytes. Of note, the ECs have adherens junctions and tight junctions between cells and lack fenestration (102). It has been suggested that the destruction of BBB integrity and permeability may be the initial pathological features of MS. This results in the infiltration of immune cells from the periphery into the brain parenchyma (103). This is indicated by changes in biomarker levels, such as enzymes gelatinase A/MMP-2 (104), gelatinase B/MMP-9 (105), S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) (106), among others. Although it is unclear whether the destruction of the BBB is the cause or the result of MS, several studies have confirmed that MS-related neuroinflammation has an impact on the structure and function of the BBB (107). Physical exercise has been shown to

regulate BBB permeability through various pathways, including systemic inflammation, the brain renin-angiotensin and noradrenergic systems, central autonomic function, and the kynurenine pathway (108). In human studies, Mokhtarzade et al. (106) found that acute cycling causes a significant increase in circulating S100B, but has no effect on NSE in RRMS patients. Proschinger et al. (109) showed that a 12-month combination of functional resistance and endurance training programs reduce serum MMP-2 concentration in RRMS patients. Furthermore, Zimmer et al. (104) discovered that patients with RRMS or SPMS who participated in HIIT or MICT programs for three weeks reported a significant decrease in serum MMP-2 levels, while the level of MMP-9 remained stable. Therefore, exercise can partially ameliorate the disruption of the BBB in PwMS, as evidenced by circulating biomarkers. Tight junction proteins, consisting mainly of transmembrane and cytoplasmic proteins, are essential components of the BBB. The transmembrane structure of tight junctions is comprised primarily of three classical proteins: claudins, occludins, and junction adherence molecules. Furthermore, the support structure of tight junctions is established by cytoplasmic attachment proteins such as zonula occludens (ZO) and cingulin, among others (110). During the development of neuroinflammation, certain chemokines and cytokines may induce the expression of EC adhesion molecules, specifically intercellular cell adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and PECAM-1, among others. As a result, peripheral immune cells could cross the BBB (111). Abnormal expression of tight junction proteins has been observed in animal models of MS and in human studies. For instance, the permeability of the BBB to Evans blue in the brain homogenate of mice with EAE significantly increased, accompanied by a reduction in claudin-5, occludin and ZO-1, while ICAM-1 and VCAM-1 expression increased (112). Similar findings were attained by other researchers in their evaluation of the degree of loss or redistribution of tight junction proteins, and the expression of ICAM-1 and VCAM-1 in the brains of EAE models (113). Another animal research demonstrated that after four weeks of strength or endurance training programs, the expression levels of tight junction proteins, including occludin and claudin-4, were restored in the CNS, and the expression of PECAM-1 was significantly suppressed, thus preserving the BBB from injury in EAE (48). A recent study conducted by Hamdi et al. (114) has implemented a PLP-induced transfer EAE model. The results show that HICT has an impact on T cell migration and invasion and is linked to a decrease in interactions between very late antigen 4 (VLA-4)/VCAM-1 and lymphocyte function antigen 1 (LFA-1)/ICAM-1. Thus, physical exercise could indirectly regulate lymphocyte infiltration by modifying BBB integrity and permeability.

In light of emerging evidence on the disruption of gut microbiota in PwMS, the mechanism by which gut microbiota disorder exacerbates the condition is progressively becoming more apparent (115–118). Studies have shown that the intestinal microbiome can promote the development of CNS-reactive pathogenic T cells in both

EAE (119, 120) and MS (121). Aberrant alterations in colony patterns were noted in PwMS. These changes were accompanied by an increase in *Desulfovibrionaceae*, *Akkermansia muciniphila*, and *Acinetobacter calcoaceticus* levels, among others, as well as a decrease in *Faecalibacterium prausnitzii*, *Parabacteroides*, *Prevotella*, and *Bacteroides fragilis* (122). There is an increasing body of evidence that suggests physical exercise could positively influence the composition and function of the gut microbiota (123–125). The implementation of a four-week strength training program, performed six times per week, led to significant outcomes in EAE. Specifically, this intervention resulted in increased abundance and diversity of gut microbiota, a decrease in the *Firmicutes* to *Bacteroidetes* ratio, and improvement in intestinal mucosal permeability. Various bacteria including *Akkermansia*, *Clostridium*, *Parabacteroides*, *Christensenella*, *Dorea*, *Roseburia*, and *Paraprevotella* can produce short-chain fatty acids (SCFAs). The training program efficiently decreased Th17 responses and increased Treg responses in lymphoid tissues of the small intestine. It is noteworthy that after completing four weeks of strength training, with each session lasting up to 60 minutes, there was a significant improvement in disease severity and neuropathology in EAE. Moreover, the microbiome fecal transplantation of trained mice into microbiota-depleted mice alleviated disease severity and neuropathology scores in microbiota-depleted mice relative to controls. However, shorter training durations, either 20 or 40 minutes per session, do not appear to affect T cell-mediated autoimmunity in EAE (94). These observational data indicate that the modulation of gut microbiota through exercise represents a mechanism that can improve T cell-mediated autoimmunity in MS. The beneficial effects of exercise on the pathology of EAE mice may be affected by the duration of training sessions, except for exercise type and intensity. For human patients, a brief high-impact multidimensional rehabilitation program that incorporates physical activity in a leisurely setting has demonstrated a decrease in proportions of pathobionts, such as *Collinsella* and *Ruminococcus*, while increasing amounts of SCFA producers, such as *Coprococcus*, *Bacteroides*, and *Oscillospira*. The alterations in the colony were associated with a reduction in the quantity of pro-inflammatory T lymphocyte subpopulations, especially CD4⁺/IFN- γ ⁺ Th1 cells and CD4⁺/ROR- γ ⁺ and CD4⁺/IL-17⁺ Th17 cells, as well as a decrease in circulating lipopolysaccharide (LPS). Simultaneously, the rehabilitation program also improved physical performance and relieved fatigue (126). In a separate study, a six-month home-based exercise training program held with a frequency of five sessions per week exhibited a significant increase in *Prevotella* populations and a reduction in *Akkermansia muciniphila* populations among PwMS. Furthermore, this intervention had a positive effect on adverse psychological states such as anxiety and depression. However, no substantial influence was observed on fatigue, *Faecalibacterium prausnitzii* and *Bacteroides* counts, or the presence of anti-inflammatory cytokines in the serum. Nonetheless, changes in *Akkermansia muciniphila*, *Prevotella*, and *Bacteroides* counts in response to the intervention were correlated with changes in IL-10 (127). The above results strongly indicate that exercise can elicit neuroimmunomodulatory effects by regulating the gut microbiome.

2.2 Innate immune cells

2.2.1 Dendritic cells

Dendritic cells (DCs) are specialized antigen-presenting cells and are vital regulators of innate and adaptive immune responses (128). They have the ability to express many molecules associated with antigen presentation that interact with T cells, including major histocompatibility complex-I (MHC-I), MHC-II, and CD1, as well as co-stimulatory molecules, including CD80, CD86, and CD40 (129). Moreover, upon activation, DCs also produce multiple cytokines, such as GM-CSF, IL-23 (130, 131), and IL-27 (132), which direct the differentiation of naive T cells. A human study compared the phenotypes and cytokine secretion of DCs among PwMS, individuals with other neurological disorders, and healthy controls. The research discovered that the number, morphology, and phenotype of DCs were comparable in PwMS and healthy controls. The phenotypic features included immature myeloid lineages such as CD1a⁺ and CD11c⁺. However, PwMS showed a higher proportion of CD1a⁺ DCs and a lower proportion of CD86⁺ DCs compared to controls (133). It is evident that alterations in the surface molecules of DCs, which have functional significance, are related to MS. In the EAE model, dysfunctional or deficient DC genes result in abnormal responses from effector T cells. For instance, researchers have identified that mammalian sterile 20-like kinase 1 (MST1) to be an essential regulator of EAE, promoting Th17 differentiation depending on DCs. The absence of MST1 in DCs causes CD4⁺ T cells to produce higher quantities of IL-17, whereas the amplification of MST1 in DCs restrains IL-17 production. Mechanically, activation of p38 MAPK signaling occurs in DCs lacking MST1, resulting in increased IL-6 secretion in Th17 differentiation induction and the activation of IL-6 receptor α/β and signal transducer and activator of transcription 3 (STAT3) in CD4⁺ T cells (134). Additional *in vivo* research with rodents revealed worsened autoimmune neuroinflammation with increased Th17 cell polarization during EAE induction in REG γ -deficient mice. Moreover, *ex vivo* experiments have confirmed that a REG γ deficit enhances integrin $\alpha\beta$ 8 expression in DCs, which stimulates TGF- β 1 maturation and promotes Th17 cell development. The process is supported by REG γ proteasome-dependent degradation of IRF8 (135). DCs play an important role in immune regulation initiation and maintenance of inflammatory events. It is essential to conduct further research on DC genes that affect T cell-mediated pathology in MS. This will improve our basic understanding of MS pathogenesis and support the creation of more effective treatments for this disease. Bilirubin nanomedicine (136), urolithin A (137), and optineurin (138) have already been demonstrated to be effective in impacting disease progression by regulating the activity and function of DCs.

Furthermore, it should be noted that DCs may also exhibit heterogeneity in the pathogenesis of MS. DCs are generally classified into two main subsets, referred to as myeloid/conventional DCs (cDCs) and plasmacytoid DCs (pDCs). Interestingly, cDCs and pDCs obtained from PwMS manifested significant tolerogenic (139) or regulatory effects (140) in comparison with control groups. The cDCs are further categorized into cDC1 and cDC2 cells, which exhibit distinct

ontogenies, surface markers, localizations, and immunological functions (141). In a stable condition, the cDCs commonly reside in the meninges, brain, and spinal cord of the CNS. They are capable of stimulating the activation and secretion of pro-inflammatory cytokines directly *ex vivo* from naive, effector, myelin-specific T cells. The population of cDCs increases in the meninges and CNS parenchyma during the development of EAE. Upon selective depletion of cDCs, the quantity of myelin-primed donor T cells in the CNS decreased, resulting in a 50% reduction in the incidence of clinical presentation (142). The pDCs can be subdivided into pDC1 and pDC2. The former displays increased levels of CD123 expression, while demonstrating decreased expression of CD86 and Toll-like receptor 2 (TLR2). It also facilitates the secretion of IFN- α and IL-10. Conversely, the latter subtype, pDC2, exhibits reduced expression of CD123 but higher expression of CD86 and TLR2. It promotes the secretion of TNF- α and IL-6 (143). Thewissen et al. (144) reported that circulating DCs in PwMS demonstrate a pro-inflammatory state and possess a migratory phenotype. DCs derived from MS patients exhibited increased production of IL-12p70 following TLR ligation. Additionally, these DCs had heightened expression levels of the migratory molecules C-C chemokine receptor 5 (CCR5) and CCR7, as well as improved *in vitro* chemotaxis when compared to healthy controls. Another study showed a significant alteration in the pDC1/pDC2 ratio, with a ratio of approximately 4.4:1 observed in healthy controls and 0.69:1 observed in PwMS. This shift towards pDC2 may contribute to the preferential activation of IL-17-secreting cells in MS, over IL-10-secreting CD4⁺ T cells (145). The concurrent occurrence of various DC subpopulations suggests their dual function in MS pathology.

In 2007, research conducted on DCs in Sprague-Dawley rats showed that progressive endurance exercise for five weeks modified the development of DCs and directed them towards a more mature state (146). However, in studies of animal disease models, Mackenzie et al. (147) found that four weeks of treadmill running led to a reduction in DC activation. This was shown by a decrease in production of the inflammatory markers IL-6, chemokine (C-X-C motif) ligand 1 (CXCL1)/KC, IL-12p70, and TNF- α , as well as a decrease in MHC-II expression, indicating a decrease in DC maturation (147). It also appears that the effects of exercise on different DC subtypes may vary considerably. In a study of an asthma model, a four-week treadmill exercise program led to a reduction of co-stimulatory molecules, CD80, CD86, and inducible T-cell costimulator ligand (ICOSL), in cDCs located in the lymph nodes that drained from the affected areas, and an increase in ICOSL expression in pDCs (148). Human studies have demonstrated that acute exercise causes a transient increase in DCs in the blood and a greater mobilization of pDCs than cDCs (149). In patients suffering from chronically progressive MS or RRMS, an increase in the numbers of cDC and pDC, along with the expression of the cell adhesion molecule CD62 ligand (CD62L) and CCR5, were noticed after a session of endurance and resistance training, and most of the markers did not return to their resting state within two hours of exercising. This increase may be mediated by FMS-like tyrosine kinase 3 ligand (FLT3L)- and MMP-9-dependent DCs mobilization. Acute exercise can potentially

reduce the responsiveness of circulating DCs to TLR, thus establishing a negative feedback regulatory mechanism to counteract the heightened inflammatory state resulting from acute exercise (95). In the chronic exercise intervention program, a 12-week training program that combining endurance with resistance exercise significantly increased the absolute number of pDCs in patients with chronically progressive or RRMS. This increase was observed specifically in those pDCs expressing CD80 and CD62L, whereas there were no significant changes in cDCs. Further analysis demonstrated a positive correlation between the quantity of CD80⁺ pDCs and IL-10-producing Tr1 cells. These findings suggest that regular exercise may enhance the immunomodulatory function of circulating pDCs. Moreover, the exercise program suppressed the production of TNF- α and MMP-9 by DCs in response to TLR activation, indicating that the program could reduce inflammation in individuals (96). Although acute exercise resulted in an elevation of cDCs and pDCs, that is not indicative of an exercise-induced response of DCs contributing to the advancement of an inflammatory state. Additionally, a regular exercise program in PwMS can result in an increase in activated pDCs, and is associated with the occurrence of Tr1 cells. However, only two human investigations have studied the influence of exercise on DCs in MS; further research is necessary on this issue.

2.2.2 Neutrophils

Neutrophils, which originate from the bone marrow, are the most prevalent leukocyte in peripheral blood and are crucial for non-specific host defense. They are responsible for phagocytosis of microbial, bacterial, and viral pathogens, while also producing and releasing cytokines that regulate T cell and B cell activities (150). Several studies have shown that neutrophils in PwMS exhibit a higher quantity and activated phenotype compared to healthy controls. This phenotype is distinguished by an elevated surface expression of TLR-2, N-Formyl-methionyl-leucyl-phenylalanine (fMLP) receptor, IL-8 receptor, and CD43, an increased granule release and oxidative burst, and also higher serum levels of neutrophil extracellular traps (NETs) (151–153). Multiple mechanisms exist through which neutrophils promote MS, including the secretion of inflammatory mediators and enzymes such as IL-1 β (154, 155), myeloperoxidase (156), and various proteinases (157, 158), the production of reactive oxygen species (ROS) (159, 160), and antigen presentation to T cells (161). In EAE, a lineage tracing study has demonstrated a significant increase in myelopoiesis in the bone marrow resulting in the enhanced production and subsequent invasion of neutrophils in the CNS (162). The regulation of neutrophil-associated factors, specifically granulocyte colony-stimulating factor (G-CSF) and CXCL1, plays a crucial role in this process (163). Deficiency of the G-CSF receptor and obstruction of CXCL1 lessened myeloid cell accumulation in the bloodstream and ameliorated the clinical outcomes of mice that received injections of myelin-reactive Th17 cells (163). Additionally, the presence of CXCL1, CXCL2, and CXCL6 was essential for the recruitment of neutrophils in the CNS. These chemokines exert their effects via activation of the G protein-coupled receptor CXCR2, which is predominantly expressed on

mature neutrophils (164). The existence of neutrophils positive for CXCR2 has been shown to contribute to the process of inflammatory demyelination in demyelination models, such as EAE and CPZ intoxication. In contrast, CXCR2-deficient mice exhibit greater resistance to CPZ-induced demyelination (165). It can be inferred that CXCR2 may be a pivotal molecular target for MS therapy. Additionally, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) are frequently observed in clinical practice as dependable indicators of inflammation related to various pathologies (166, 167). In PwMS, the NLR has been proposed as a marker of disease activity, with elevated levels displaying a positive association with the severity of MS symptoms (168, 169). Therefore, it may be crucial to monitor neutrophil activity and function to gain understanding of the progression of MS.

The evidence clearly shows that acute exercise affects neutrophil response. At the gene expression level, a study discovered that a brief bout of intense exercise modifies neutrophil gene expression, including the janus kinase (Jak)/STAT pathway involved in apoptosis, and genes linked to inflammation, such as IL-32, TNF receptor superfamily member 8 (TNFSF8), CCR5 and Annexin A1 (ANXA1), in addition to genes related to growth and repair, such as Amphiregulin (AREG) and fibroblast growth factor receptor 2 (FGFR2) genes (170, 171). In terms of activity and function, physical exercise typically induces an initial activation of neutrophils. This is demonstrated through the release of enzymes (172, 173) and subsequent changes in crucial effector functions, including phagocytosis and respiratory burst activity (174, 175). Acute exercise has been shown to attenuate neutrophil apoptosis, possibly by its action on the inducible nitric oxide synthase (iNOS)-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)-myeloid cell leukemia 1 (Mcl-1) pathway (176), as well as calcium and redox signaling (177). Furthermore, although acute aerobic exercise was able to increase the number of total circulating neutrophils, the number of neutrophils expressing CXCR2 decreased during the recovery period (178). Previous research indicates that regular, chronic exercise can have a positive impact on neutrophil-mediated immune function in both physiological and pathological conditions. A cross-sectional study involving older adults found that increasing habitual physical activity can potentially enhance neutrophil-mediated immunity (179). Moreover, several months of exercise training not only reduce individual neutrophil chemotaxis and lower IL-8 and noradrenaline concentrations (180), but also enhance deoxyribonuclease (DNase) activity, increasing the ability to degrade NETs (181). In the case of EAE and MS, one study conducted with animals suggested that EAE mice that underwent six weeks of voluntary wheel running prior to the disease had a lower rate of neutrophil infiltration in the spinal cord and lesser severity of EAE in the chronic period (49). Furthermore, three weeks of HIIT programs during inpatient rehabilitation of patients with RRMS or SPMS resulted in a greater decrease of NLR compared to MICT. This could be attributed to the repetitive inflammatory status and compensatory anti-inflammatory balance after each high-intensity exercise, as suggested by Joisten et al. (182). The research shows that regular exercise has the potential to

ameliorate the clinical symptoms of MS by modulating the activity of neutrophils.

2.2.3 Microglia/macrophages

Microglia and macrophages are integral components of the mononuclear phagocytic system. They accumulate at the sites of active demyelination and neurodegeneration in the CNS of MS and are believed to be central to the disease process. Evidence suggests an increase in macrophage infiltration into the CNS and exaggerated activation of resident microglia and pathological microgliosis (183, 184). Microglia and macrophages can be classified into two subtypes: the classically activated M1 phenotype, which is associated with inflammatory and degenerative processes, and the alternatively activated M2 phenotype, which has protective properties. In addition to these two subtypes, there may exist intermediate polarization phenotypes (185). Classical activation can be induced by various stimuli such as IFN- γ and LPS. This activation results in the increased expression of antigen presentation related molecules, specifically CD80, CD86, and CD40, which demonstrate a significant ability to present antigens. Furthermore, M1 microglia/macrophages can produce pro-inflammatory cytokines like TNF- α and IL-6, and chemokines such as CCL2 and CCL3, as well as neurotoxic NO. In contrast, M2 microglia/macrophages lack cytotoxicity and can be stimulated by IL-4 and IL-13. They could exhibit raised levels of CD14 and CD163, among other markers, and release anti-inflammatory cytokines such as IL-10 and TGF- β (21, 186). It should be noted that microglia and macrophages play a dual role in the pathology of MS. In the early stages of demyelination and neurodegeneration present in active lesions, microglia with a pro-inflammatory phenotype were observed. They expressed molecules involved in phagocytosis, oxidative injury, antigen presentation, and T cell co-stimulation. In later stages, the microglia and macrophages in active lesions shifted to a phenotype that was intermediate between pro- and anti-inflammatory activation (187). Activated microglia have the ability to directly drive demyelination and are necessary for it (188). Conversely, microglia and monocyte-derived macrophages play a significant role in facilitating efficient remyelination by secreting growth factors and eliminating inhibitory myelin debris (189). Genetic fate mapping and multiphoton live imaging demonstrate that administering niacin at therapeutically relevant doses to demyelinated aged mice assists in clearing myelin debris in lesions through the action of both peripherally-derived macrophages and microglia (190). Moreover, M2 microglia and macrophages were found to drive OLS differentiation during CNS remyelination (191). Notably, the triggering receptor expressed on myeloid cells 2 (TREM2) is believed to play a significant part in the remyelination process. Research indicates that TREM2 is highly expressed on myelin-laden phagocytes in active demyelinating lesions in the CNS of PwMS. Gene expression research indicates that macrophages in individuals with genetic deficiency in TREM2 lack phagocytic pathways (192). Additionally, when TREM2 is deficient, the capability of microglia to phagocytose myelin debris is significantly diminished. These microglia also display impaired

mobility and are unable to metabolize cholesterol, leading to deficient remyelination in TREM2-deficient mice (193). However, TREM2 activation in microglia led to increased OPC density in demyelinated regions, contributed to the development of mature OL, which subsequently improved remyelination and axonal integrity (192). Furthermore, regulation of neuroinflammation can be attained by adjusting the dynamic alterations in two phenotypes of microglia/macrophages. It has been recommended that to alleviate clinical symptoms in EAE mice, M1 microglia/macrophage polarization should be suppressed and shifted towards the protective M2 phenotype (194–196). As a result, the regulation of the activation and polarization of microglia/macrophages may be an effective approach to MS pathology.

Accumulated evidence over the past decades suggests that exercise have a considerable impact on macrophage chemotaxis, antigen presentation, phagocytosis, inflammatory cytokine release, antiviral capability, and antitumor activity (197–202). These effects could be attributed to exercise's regulation of immunometabolism and macrophage polarization. Murugathasan et al. (203) conducted a study which revealed bone marrow-derived macrophages (BMDMs) obtained from mice that underwent eight weeks of moderate-intensity treadmill running exhibited reduced LPS-induced NF- κ B activation, decreased expression of pro-inflammatory genes (such as *Il-1 β* and *Tnf α*), and increased M2-like-associated genes (such as *Arg1* and *Hmox-1*) in contrast to BMDMs from sedentary mice. This was linked to improved mitochondrial quality and higher dependence on oxidative phosphorylation, accompanied by reduced mitochondrial ROS production. Similarly, physical exercise has a wide range of effects on microglia activity and function by modulating the expression of cytokines and their receptors (204) and attenuating oxidative stress (205). Recently, mounting evidence has confirmed the influence of exercise on microglia in the physiology of the CNS and various conditions, such as AD (206–208), PD (209), and cerebral ischemia (210). In MS, the effects of physical exercise on microglia/macrophages can be summarized in three key ways: (i) inhibiting macrophage infiltration into the CNS, (ii) constraining atypical microglia activation and microgliosis at lesion sites, and (iii) inhibiting M1 polarization and promoting M2 polarization. Specifically, the results of a pre-training program, involving either a three-week voluntary wheel running or six-week treadmill running, demonstrated the capacity to restrain the infiltration of macrophages into the spinal cord, which was induced by EAE (49, 211). Regarding CNS-resident microglia, Rizzo et al. (212) showed that engaging in voluntary wheel running for three weeks alleviated microgliosis and reduced the expression of TNF- α and IL-1 β in the hippocampal CA1 area of EAE mice. In CPZ-induced mice, six weeks of voluntary wheel running alleviated microgliosis in the striatum and corpus callosum (42). Additionally, regular exercise may lower the number of neurotoxic M1-like phenotype cells while increasing the number of M2-like phenotype cells. Before the induction of EAE by injecting PLP-reactive T-cells, the mice underwent six weeks of HICT, which reduced the number of neurotoxic microglia expressing the ionized calcium binding adapter molecule 1 (Iba1⁺) and the M1-like marker inducible nitric oxide synthase (iNOS⁺). The content of pro-inflammatory

cytokines IL-6 and MCP-1 secreted by microglia in response to PLP and LPS stimulations also decreased (213). Meanwhile, a daily one-hour voluntary exercise on a wheel reduces the number of Iba1⁺ microglia/macrophages expressing iNOS in the spinal cord of EAE mice (46). In mice with lysolecithin-induced demyelination, voluntary wheel running for a duration of time augments the M2-like phenotype in the myelin lesions and enhances the phagocytic function of myelin fragments. This reduction in inhibitory lipid debris likely facilitates the prolonged proliferation of OPCs with exercise to produce increased numbers of OLs, ultimately promoting the remyelination process (214). However, other studies have reported negative and contradictory results regarding macrophage infiltration and microgliosis (47, 51, 91) (Table 2). Although there is no data available for humans, research on animals confirms that exercise elicits a response in MS-afflicted microglia/macrophages. In addition, it is noteworthy that several studies have demonstrated the impact of exercise on microglia activation, microglial glucose metabolism, and morphological plasticity by modifying the TREM2 pathway (207, 218). Xu et al. (219) propose that physical exercise can assist in the regeneration of OLs to protect against white matter damage after a stroke. This is primarily achieved by increasing TREM2 and microglia-generated factors. Due to TREM2's regulatory function in microglia, and its impact on myelin regeneration and neuroinflammation, it is imperative to investigate whether TREM2 can assist physical exercise in mitigating MS pathology in an animal model of MS.

2.2.4 Astrocytes

Astrocytes represent the most prevalent type of glial cells in the mammalian brain and perform various physiological functions, including regulating ion homeostasis, neurotransmitter clearance, synapse formation and removal, and neurovascular coupling, among others (220–222). It is noteworthy that astrocyte dysfunction can lead to the development of MS, including neuroinflammation and demyelination. In MS/EAE, the excess activation of astrocytes may foster innate inflammation and neurodegeneration via the production of cytokines such as IL-6, IL-15, and TNF- α , chemokines such as CXCL1, CXCL10, CCL2, and CCL20, and neurotoxic metabolites such as NO (19). Despite being neither immune progenitors nor strictly classified as innate immune cells, astrocytes can perceive inflammatory signals and regulate neuroinflammation. Some studies have suggested a possible connection between abnormal gene expression in astrocytes or metabolic abnormalities and increased neuroinflammation (223–225). Wheeler et al. (226) utilized single-cell RNA sequencing combined with cell-specific Ribotag RNA profiling, assay for transposase-accessible chromatin with sequencing, chromatin immunoprecipitation with sequencing, genome-wide analysis of DNA methylation and *in vivo* CRISPR-Cas9-based genetic perturbations to examine astrocytes in MS and EAE. The results showed that astrocytes in both EAE and MS exhibit reduced expression of Nrf2 and an upregulation of V-maf musculoaponeurotic fibrosarcoma oncogene homolog G (MAFG). MAFG collaborates with methionine adenosyltransferase II alpha

(MAT2 α) to propagate DNA methylation and impede antioxidant and anti-inflammatory transcriptional programs. GM-CSF signaling in astrocytes induces the expression of MAFG and MAT2 α , as well as pro-inflammatory transcriptional modules, which potentially lead to CNS pathology in both EAE and MS. In general, astrocytes experience persistent and extensive activation in response to pathological stimuli, resulting in a reactive state that encompasses two subtypes: A1, characterized by a pro-inflammatory function, and A2, which exerts a protective effect (227). Additionally, numerous studies have identified the beneficial and detrimental roles performed by astrocytes in the process of remyelination. Molina-Gonzalez et al. (228) employed unbiased RNA sequencing, functional manipulation, and rodent models *in vivo/ex vivo/in vitro*, as well as human brain lesion analyses, to investigate the interaction between astrocytes and OLs during remyelination. The investigation has revealed that astrocytes can promote the survival of regenerating OLs by suppressing the Nrf2 pathway and stimulating the cholesterol biosynthesis pathway. This finding highlights the importance of astrocyte-OL interaction in myelin repair. In contrast, demyelinating lesions exhibit an augmented degree of reactive astrogliosis. Such reactive astrocytes present a hypertrophic phenotype and generate astroglial scars that can create an inhibitory milieu, ultimately obstructing tissue repair (229). Moreover, it has been discovered that irregular copper transportation in astrocytes may lead to demyelination in MS (230). The regulation of reactive astrocytes could hold significant therapeutic potential in the context of inflammation and myelin damage associated with MS.

Similar to microglia and OLs, the effect of physical exercise on the activity and function of astrocytes in the CNS has been widely researched. Appropriate exercise can alter astrocyte activation (231), phenotype (232, 233), remodeling (234, 235), tropic factor release (236), and energy metabolism (237), among others. Furthermore, it can regulate astrocyte-mediated neuroinflammatory responses (234) and intercellular interactions of astrocytes with other cells (238). In mouse models of MS, Bernardes et al. (211) found that a pre-exercise program involving six weeks of treadmill running contributed to a further reduction in astrocyte responses in the dorsal horn of the spinal cord, induced by GA drug therapy in EAE mice after the first relapse. This reduction was demonstrated using glial fibrillary acidic protein (GFAP) immunofluorescence. In addition, simultaneous voluntary wheel running during CPZ-induced demyelination alleviated astrogliosis in the striatum and corpus callosum, while decreasing CXCL10 expression and ameliorating axonal pathology in CPZ-treated mice (42). These findings imply that physical exercise has the potential to mitigate the pathophysiological features of MS through the reduction of the astrocytic response. However, it is important to acknowledge that the human studies have yet to provide concrete evidence for the consistency of these findings. GFAP is released into the cerebrospinal fluid and blood in disorders associated with astrocyte activation and astrogliosis following inflammation and neurodegeneration and therefore is highly expressed in MS lesions (239). In 2021, Ercan et al. (216) conducted a study observing a decrease in serum levels of GFAP and neurofilament light (NFL) after eight weeks of cycling in

TABLE 2 Effect of exercise on innate immune cells in animal models and human patients of MS.

Subjects		Intervention program			Region	Mode of action	References
Model	Characteristics	Type	Intensity	Duration			
MOG ₃₅₋₅₅ -induced EAE model	C57BL/6 mice; female; 8 weeks old	Voluntary wheel running	ND	60 min/session for 40 consecutive days	Brain and spinal cord	Macrophages infiltration →; Synaptic plasticity ↑; Clinical scores ↓	(91)
	C57BL/6 mice; male and female; 6~8 weeks old	Voluntary wheel running	ND	60 min/session for 30 consecutive days	Spinal cord	Microgliosis →	(47)
	C57BL/6 mice; male and female; 4~6 weeks old	Prior treadmill running	11 m/min	30 min/session, 5 sessions/week for 6 weeks	Spinal cord	Microglial reactivity and macrophages infiltration ↓; Astrocyte reactivity ↓; Synaptic plasticity ↑; Demyelination ↓	(211)
	C57BL/6 mice; female; 9~10 weeks old	Prior voluntary wheel running	ND	60 min/session, 5 sessions/week for 6 weeks	Spinal cord	Neutrophils and macrophages infiltration ↓; Nrf-2 and IL-10 ↑; IL-17 ↓; Clinical scores ↓	(49)
	C57BL/6 mice; female; 9 weeks old	Voluntary wheel running	ND	3 weeks	Hippocampus	Microgliosis ↓; Microglial TNF-α ↓; IL-1β ↓; Cognition ↑; Synaptic plasticity ↑; Clinical scores ↓	(212)
CPZ-induced toxic-demyelinating model	C57BL/6 mice; male; 4 weeks old	(i) Interval treadmill running (IT) (ii) Continuous treadmill running (CT)	(i) IT: 50%, 90% EC _{max} (ii) CT: 70% EC _{max}	5 sessions/week for 4 weeks	Hippocampus	(i) IT: Microglial number ↑; Oligodendrocytes number ↑; BDNF, GDNF, and NGF ↑ (ii) CT: Microglial number →; Oligodendrocytes number ↑; BDNF, GDNF, and NGF ↑	(51)
	C57BL/6N mice; female; 8 weeks old	Voluntary wheel running	ND	6 weeks	Corpus callosum and striatum	Microgliosis ↓; Astroglial ↓; CXCL10 ↓; TNF-α, IL-1β, TGF-β, and CXCL12 →; Demyelination ↓; Remyelination ↑; Axonal damage ↓; Weight loss ↓; Motor and neuromuscular function ↑	(42)
Lysocithin-demyelinating model	C57BL/6 mice; female; 8~12 weeks old	Voluntary wheel running	ND	14 consecutive days	Spinal cord	CD206 anti-inflammatory phenotype macrophage and microglia ↑; CD16/32 pro-inflammatory phenotype macrophage and microglia ↓; Phagocytic Clearance of Lipid Debris ↑; Remyelination ↑; Axonal degeneration ↓	(214)
RRMS patients	10 female; (32.15 ± 7.57) years old; EDSS score ≤ 4	Stretch training, aerobic exercises, endurance and resistance training	ND	55~65 min/session, 3 sessions/week for 8 weeks	Blood	PBMC-derived INF-γ and IL-17 ↓; IL-4 →; Fitness ↑; Clinical scores ↓	(215)
	31 female/7 males; 19~40 years old; EDSS: 1~4.5	Cycling	60%~70% VO _{2max}	30 min/session, 3 sessions/week for 8 weeks	Blood	GFAP and NFL ↓	(216)

(Continued)

TABLE 2 Continued

Subjects		Intervention program			Region	Mode of action	References
Model	Characteristics	Type	Intensity	Duration			
CPMS and RRMS patients	12 female/10 male; (46.0 ± 2.0) years old; EDSS score < 6	Endurance training (ET) (walking and cycling) combined with strength training (ST) (resistance exercise)	ET: 65% HRR; ST: 70% 1RM	A single bout	Blood	(i) Immediate post-exercise: Monocytes and granulocyte number ↑; cDC and pDC number ↑; CD62L ⁺ cDC and CD62L ⁺ pDC number ↑; CCR5 ⁺ cDC and CCR5 ⁺ pDC number ↑; MIP-1α →; Flt3L ↑; MMP-9 → (ii) 2 hours post-exercise: Monocytes number →; Granulocyte number ↑; cDC number →; pDC number ↑; CD62L ⁺ cDC ↑; CD62L ⁺ pDC number →; CCR5 ⁺ cDC and CCR5 ⁺ pDC number ↑; MIP-1α →; Flt3L →; MMP-9 ↑	(95)
	16 female/13 male; (46.0 ± 2.0) years old; EDSS score: (3 ± 0.2)	Endurance training (cycling and treadmill walking or running) combined with strength training (resistance exercise)	ND	5 sessions/2 weeks for 12 weeks	Blood	pDC number and proportion ↑; cDC number →; CD80 ⁺ pDC number and proportion ↑; CCR7 ⁺ pDC number ↓; CD62L ⁺ pDC number ↑; CD62L ⁺ , CCR5 ⁺ , and CCR7 ⁺ cDC number →; The fold change of CCR5 ⁺ cDC and TNF-α and MMP-9 secretion upon LPS and IFN-γ stimulation ↓; The fold change of CD86 ⁺ and HLA-DR ⁺ cDC and IL-1β, IL-6, IL-12p70, IFN-α, and caspase-1 secretion upon LPS and IFN-γ stimulation ↓; The fold change of HLA-DR ⁺ pDC upon IQ stimulation ↑; The fold change of CCR5 ⁺ and CD86 ⁺ pDC and IL-6, IL-12p70, TNF-α, IFN-α, caspase-1, and MMP-9 upon IQ stimulation →	(96)
SPMS and RRMS patients	42 female/26 male; (50.3 ± 10.2) years old; EDSS score: 3–6	High-intensity interval training (HIIT) or moderate continuous training (MCT)	(i) HIIT: 95%–100% HR _{max} (ii) MCT: 65% HR _{max}	3 sessions/week for 3 weeks	Blood	(i) HIIT: NLR ↓; Systemic immuneinflammation index ↓ (ii) MCT: NLR →; Systemic immuneinflammation index ↑	(182)
PwMS	22 female/8 male; 43.5 ± 10.1) years old; EDSS score: 2–3	High-intensity aerobic training	40%, 60%, and 80% peak power	3 session/week for 16 weeks	Blood	GFAP, BDNF, and NFL →	(217)
PwMS treated with either ATZ, FTY, or NAT	17 female/13 male	Climbing stairs at normal speed (CN) or fast (CF) or cycling (C)	C: 1, 2 Watt per kilogram BW	CN: ND CF: ND C: 20 min	Blood	(i) CN: Absolute NK cells number ↑ (ii) CF: Absolute NK cells number ↑ (iii) C: Absolute NKT cells and NK cells number ↑	(99)

1RM, repetition maximum; ATZ, alemtuzumab; BDNF, brain-derived neurotrophic factor; CCR, chemokine C-C-Motif receptor; cDC, conventional dendritic cells; CPMS, chronically progressive MS; CPZ, cuprizone; CXCL, chemokine (C-X-C motif) ligand; EAE, experimental autoimmune encephalomyelitis; EC_{max}: maximal exercise capacity; EDSS, Expanded Disability Status Scale; Flt3L, FMS Like Tyrosine Kinase 3 Ligand; FTY, Fingolimod; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GPx, glutathione peroxidase; HLA-DR, human leukocyte antigen DR; HR_{max}: maximal heart rate; HRR, heart rate reserve; IFN, interferon; IL-10, interleukin-10; IQ, imiquimod; LPS, lipopolysaccharide; MIP-1α: macrophage inflammatory protein 1 α; MMP, matrix metalloproteinase; MOG, myelin oligodendrocyte glycoprotein; NAT, natalizumab; ND, not determined; NFL, neurofilament light; NGF, nerve growth factor; NLR, neutrophil to lymphocyte ratio; Nr2, nuclear factor (erythroid-derived 2)-like 2; PBMC, peripheral blood mononuclear cell; pDCs: plasmacytoid DCs; PwMS, patients with MS; TGF-β, transforming growth factor-β; Th, T helper cells; TNF-α, tumor necrosis factor-α; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS. ↑, significantly increased or improved; ↓, significantly decreased or reduced; →, no significant change.

patients with RRMS. However, a subsequent investigation by Gravesteijn et al. (217) found no statistically significant changes in serum levels of GFAP, brain-derived neurotrophic factor (BDNF), and NFL in PwMS following a 16-week cycling intervention. The

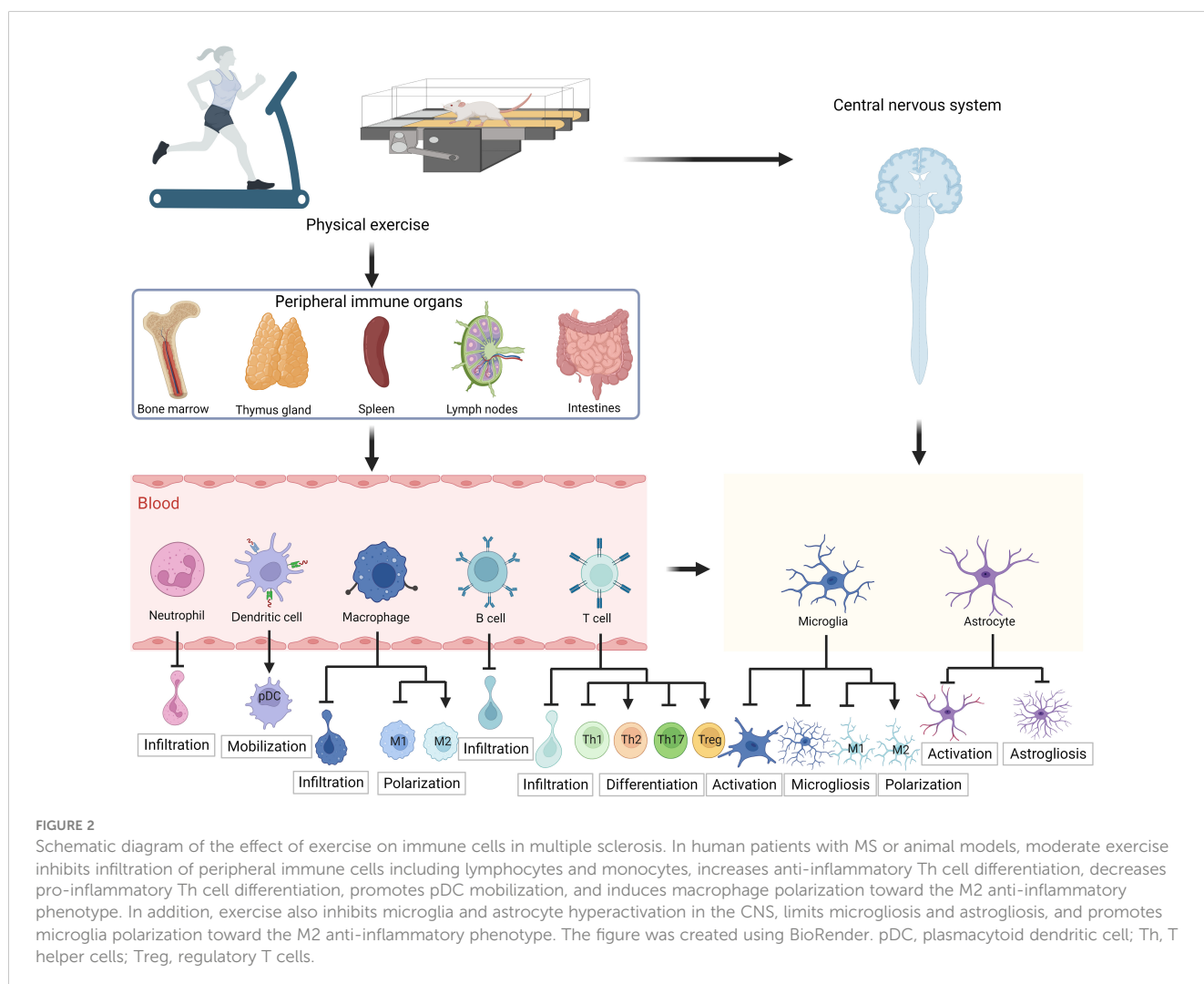
amount of relevant research available is restricted and there is a lack of consistency in the results obtained from human trials. Additional research is necessary to obtain a more comprehensive understanding of this issue.

3 Conclusions and perspectives

Both peripheral and CNS immunity are essential for maintaining the proper CNS function. Physical exercise provides direct neuroprotective benefits and induces immunomodulatory effects. However, additional research is necessary to fully understand the impact of physical exercise on autoimmune diseases. In animal models and PwMS, the aberrant functioning of immune cells has been identified as a significant pathological mechanism. The implementation of a moderate exercise program has been shown to effectively limit the infiltration of various peripheral immune cell types, including T lymphocytes, B lymphocytes, neutrophils, dendritic cells, and macrophages, into the CNS. This physiological phenomenon can be attributed to the fact that physical exercise can modify the quantity, functionality, and migratory potential of immune cells and contribute to the establishment of immune cell homeostasis from a pro-inflammatory phenotype to an anti-inflammatory phenotype. For instance, studies have indicated that exercise can promote the differentiation of Treg cells, while inhibiting the differentiation of Th1/Th17 cells, thereby leading to a reduction in IFN- γ and IL-17 production, and an increase in IL-10 and TGF- β production.

Additionally, physical exercise has been observed to modulate the structure of the BBB, consequently improving integrity and decreasing permeability. In addition, physical exercise has an impact on resident innate immune cells, specifically microglia and astrocytes in the CNS. This impact mainly manifests as a reduction in the activation of microglia and astrocytes induced by pathological stimuli, as well as a decrease in microgliosis and astrogliosis and the synthesis of pro-inflammatory cytokines (Figure 2). The immunomodulatory responses elicited by exercise may constitute a vital mechanism by which exercise ameliorates myelin and axonal damage, alleviates disease symptoms, and abates clinical scores.

The regulation of immune cells in MS through exercise has attracted growing attention. However, some immune cells, including γ - δ T cells, MAIT cells, and natural killer cells, among others, have not yet been investigated. Additionally, current research has some potential limitations. Firstly, so far, most studies have only described alterations in cellular phenotype. Few studies have been undertaken regarding the molecular mechanisms that underlie the effects of exercise on immune cells in MS. Although it has been proposed that exercise could modulate immune cell function by altering immunometabolism in MS (240), the current evidence is insufficient. Furthermore, many



transcription factors, including peroxisome proliferator-activated receptor γ (PPAR- γ) (241), and regulators of signaling pathways, such as nuclear factor kappa-B (NF- κ B) (242) are involved in regulating immune cell plasticity but have not been explored in MS. Secondly, it is essential to give more consideration to the interaction between the immunomodulatory mechanisms linked to exercise improvement and other mechanisms, such as the release of neurotrophic factors, mitochondrial dysfunction, and oxidative stress. Thirdly, exploration of the disparities in immunomodulatory mechanisms induced by varied experimental protocols in animal studies, such as disease prevention via pre-training, disease progression inhibition via concurrent training, functional improvement through training during remission, presents a fascinating future research topic. Additionally, the effects of exercise alone and exercise combined with other interventions should be actively explored. Finally, despite extensive research and notable advancements in studying animal models, it is important to acknowledge that these models cannot fully replicate the entire spectrum of MS and its clinical manifestations due to significant heterogeneity observed in various disease courses. Therefore, further empirical studies are imperative to validate the efficacy of exercise interventions in ameliorating the disease across diverse types, durations, intensities, and cycles. During the clinical translational phase, it is crucial to provide personalized exercise programs to PwMS to improve functional recovery.

Author contributions

BZ: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation. FY: Writing – original draft, Writing – review & editing. XZ: Investigation, Writing – review & editing. WZ: Investigation,

Writing – review & editing. SL: Writing – review & editing. LL: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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