Journal of http://www.satursonpublishing.com/
Research in Multidisciplinary Methods and Applications
ISSN 2957-3920 (Online) ISSN 3007-7060 (Print)
Volume 5, Issue 2, February 2026

Emerging Mechanistic Insights into How Physical Activity Shapes Immune Cell Function

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Abstract: Regular physical activity represents a robust, non-pharmacological means of tuning immune function. In this review, we outline the multi-layered molecular logic through which exercise reshapes immunity. At the level of cell positioning, exercise dynamically calibrates chemokine networks to steer immune-cell migration in both directions, enabling a precise balance between anti-inflammatory control and tissue repair. In parallel, exercise induces metabolic reprogramming that promotes macrophage polarization toward anti-inflammatory states and, in doing so, can imprint a form of metabolically conditioned immune memory. Meanwhile, by reconfiguring core signalling hubs—including MAPK, NF-κB and cGAS–STING—exercise contributes to an immune microenvironment that favours physiological homeostasis. Notably, metabolites generated or accumulated during exercise, such as lactate and β-hydroxybutyrate, can further act through epigenetic mechanisms, exerting sustained influence on immune-cell programmes. Beyond peripheral immune regulation, exercise also modulates systemic immunity by shaping bone-marrow haematopoiesis and dampening the progression of immunosenescence, thereby refining immune status with greater precision. Taken together, these convergent mechanisms provide a coherent scientific basis for exercise-mediated maintenance of immune homeostasis, offering conceptual support for disease prevention strategies and the design of personalized exercise prescriptions. Looking ahead, deeper integration of immune features in Chinese populations with perspectives from traditional medical thought may help drive a more locally grounded, translational agenda in exercise immunology.

Keywords: Exercise, Immunity, Metabolic reprogramming, Signaling pathway

1 INTRODUCTION

As contemporary lifestyles have undergone profound transformation, the value of regular physical activity as a non-pharmacological strategy for preventing and treating a broad spectrum of diseases has become increasingly apparent. The biological consequences of exercise extend well beyond skeletal muscle, the cardiovascular system, and metabolic–endocrine regulation; they also impinge decisively on the body's defence architecture—the immune system. Accumulating evidence over the past several years indicates that exercise-induced immunomodulation is not a collection of isolated effects, but rather a highly integrated biological programme. Signals generated across multiple layers of regulation ultimately converge on the phenotype, function, and fate decisions of immune cells, thereby enabling remarkably fine control over systemic homeostasis.

This Review aims to provide a structured synthesis of the diverse molecular and cellular mechanisms through which exercise shapes immune function. We focus on several interlocking dimensions, including chemokine-guided trafficking, metabolic reprogramming, key signalling pathways, epigenetic regulation, bone-marrow haematopoiesis, and immune ageing. By consolidating these mechanistic threads, we seek to offer a conceptual framework that may inform the development of therapeutic strategies in which the immune system itself becomes a tractable target.

2 SYSTEMIC IMMUNOMODULATION BY EXERCISE: ORCHESTRATING WHOLE-BODY IMMUNE DYNAMICS

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Physical activity exerts profound effects on immune surveillance, hematopoietic output, and long-term immune resilience. This section explores how exercise coordinately regulates immune cell trafficking, production, and aging at the organismal level.

2.1 Exercise-Mediated Regulation Of Immune Cell Chemotaxis And Migration

Exercise exerts tight control over immune-cell transport and tissue distribution by tuning an interconnected network of chemokines and adhesion molecules, thereby enabling context-specific "homing" within pathological microenvironments.

Across inflammatory and metabolic disorders, the dominant effect of exercise is to curb the infiltration of pro-inflammatory leukocytes. In asthma, for example, exercise lowers the expression of CCL5 and CCL11 as well as the adhesion molecules ICAM-1 and VCAM-1, limiting the recruitment of eosinophils and macrophages to the airways and diminishing T helper cell (Th) responsiveness to chemotactic cues[1-2]. In acute lung injury and diabetes, exercise downregulates G-CSF and endothelial adhesion programmes, respectively; similarly, in hepatic ischaemia–reperfusion injury it suppresses CXCL1, CXCL2 and CXCL5, thereby reducing detrimental neutrophil influx[3-5]. Ageing-focused studies further suggest that both aerobic and resistance training systemically reduce MCP-1 expression across multiple organs—including adipose tissue, the aorta and the liver—attenuating widespread macrophage infiltration[6]. Exercise also appears to promote lymphangiogenesis in the aged heart and improve lymphatic drainage, which in turn lessens CD3+T cell accumulation and alleviates local inflammatory tone[7].

Conversely, exercise can also promote the trafficking of immune cells in ways that are clearly beneficial. In models of cerebral ischaemia, exercise engages the CXCL12–CXCR4 axis to enhance the recruitment of regulatory T cells (Tregs) to injured brain tissue, where they contribute to repair processes[8]. Under physiological conditions, exercise similarly draws immune cells into skeletal muscle to support adaptive remodelling. This can occur through upregulation of the chemokine CX3CL1, which facilitates neutrophil recruitment, or via PGC-1α–dependent induction of multiple chemokines that attract macrophages and thereby promote angiogenesis within muscle[9-10]. In tumour settings, exercise increases intratumoural expression of CCL5 and CXCL10 in lung cancer models, and elevates CXCL9 and CXCL11 in breast cancer, collectively amplifying CD8+T-cell infiltration and fostering a shift from immunologically "cold" to "hot" tumours[11-12].

Taken together, these findings highlight the bidirectionality of exercise-mediated control over immune-cell migration. The overarching outcome is a redistribution of immune populations that enables more precise immunomodulation and functional optimization.

2.2 Impact Of Exercise On Bone Marrow Hematopoiesis

Exercise can directly tune immune-cell abundance and lineage output by reshaping bone-marrow haematopoiesis. Mechanistically, exercise reduces leptin expression in adipose tissue, which in turn limits CXCL12 production by bone-marrow stromal cells; this suppresses haematopoietic progenitor activity and lowers circulating leukocyte numbers[13]. The direction of this effect, however, is contingent on context. Under infectious conditions, exercise can instead bolster emergency haematopoiesis in the marrow, with measurable improvements in outcome[13]. Beyond myeloid control, exercise also increases the proportion of common lymphoid progenitors (CLPs), thereby strengthening antiviral immune capacity[14]. Collectively, these studies argue that exercise achieves unusually precise control over systemic immune status by dynamically regulating bone-marrow haematopoietic programmes.

2.3 Exercise As A Strategy To Counteract Immunosenescence

Ageing is accompanied by declining immune competence alongside a persistent, low-grade inflammatory state. A growing body of work suggests that exercise exerts a measurable anti-ageing influence on the immune system: sustained training reduces the proportion of senescent T cells in older adults, reflected by a lower frequency of CD28-CD57+cells in peripheral blood[15]. In parallel, exercise is associated with reduced scores for the senescence-associated secretory phenotype (SASP) across multiple immune-cell populations in the bone marrow, pointing to broadly distributed anti-senescent effects rather than changes confined to a single lineage[16].

Thymic involution represents another hallmark of immune ageing, and exercise appears to counter this trajectory. By inducing the release of thymic trophic factors such as IL-7, physical activity can oppose thymic atrophy and increase the proportion of thymic emigrants[17]. Consistent with improved thymopoiesis, exercise increases the fraction of thymic CD4+CD8+ double-positive T cells and lowers senescence-related gene-expression scores in T/NK-cell compartments[16].

Importantly, exercise dose may determine the extent of immune rejuvenation. Moderate-intensity continuous training increases circulating naïve T cells and thymic emigrants in older women, whereas high-intensity interval training does not produce an equivalent effect[18]. This distinction provides a key mechanistic foothold for designing precise, efficient anti-ageing exercise interventions. Given the practical limits on exercise capacity in older populations, it is of clear translational value to delineate the molecular basis of exercise-driven immune rejuvenation—and to determine whether these benefits are sustained through long-lived, epigenetically encoded "memory."

3 Cell-Intrinsic Immunomodulation By Exercise: Reprogramming Immune Responses At The Cellular Level

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Beyond systemic effects, exercise directly fine-tunes the functional state of individual immune cells through metabolic, signaling, and epigenetic remodeling. This section delves into the intracellular adaptations that underlie exercise-induced immunomodulation.

3.1 Metabolic Reprogramming Of Immune Cells During Exercise

Immune cells accommodate exercise-induced shifts in energy availability by rewiring their metabolic circuitry, with direct consequences for their functional state and lineage trajectory. Broadly speaking, M1 macrophages and effector T cells are strongly glycolysis-dependent, whereas M2 macrophages and Tregs rely more heavily on oxidative phosphorylation and fatty-acid β-oxidation. In this context, exercise suppresses macrophage HIF-1α and phosphofructokinase-2 expression, dampening glycolytic flux and NF-κB activity while biasing cellular energetics toward oxidative phosphorylation—a shift that favours M2 polarization[19]. Exercise also downregulates CD36 and SREBP1, accelerating lipid catabolism in microglia and promoting their transition toward an anti-inflammatory programme[20]. Alongside these changes, exercise enhances macrophage production of specialized pro-resolving mediators (SPMs), engages AMPK, and thereby strengthens mitochondrial metabolism and oxidative phosphorylation capacity[21].

Adaptive immunity shows analogous plasticity. Exercise drives Treg cells to upregulate genes involved in fatty-acid uptake and β-oxidation, reinforcing their immunosuppressive function[22]. With sustained aerobic training, CD8+T cells likewise exhibit improved mitochondrial performance, a bioenergetic upgrade that translates into greater tumouricidal activity[23].

Notably, metabolic reprogramming may also give rise to a form of “trained immunity”, opening a fresh window onto the emerging concept of metabolic–immune memory. Exercise has been shown to shift hepatic Kupffer cells away from glycolysis and toward oxidative phosphorylation, accompanied by increased itaconate; upon a subsequent challenge, these cells display a stronger propensity to polarize toward an anti-inflammatory state[24]. Complementing this, an ATAC-seq–based study reported that exercise enriches cEBPβ motif accessibility in bone-marrow–derived macrophages and increases chromatin openness at M2-associated loci, consistent with the induction of a durable anti-inflammatory programme[19].

3.2 Modulation Of Intracellular Signaling Pathways In Response To Exercise

Immune cells interpret external cues through densely interconnected signalling networks that, in turn, reconfigure transcriptional programmes. Exercise, in broad terms, dampens pro-inflammatory signalling while engaging pathways linked to metabolic improvement and inflammation resolution—an architecture that underlies its protective effects across inflammatory, metabolic and ischaemic disorders. Exercise training reduces activation of several canonical cascades, including p38 MAPK[25], NF-κB[26], JAK1–STAT1[27], TLR4[28] and cGAS–STING[29], thereby limiting inflammatory mediator release and favouring tissue repair. In a middle cerebral artery occlusion model, exercise upregulates microglial circFndc3b, restraining NLRP3 inflammasome–driven pyroptosis; this is accompanied by a smaller infarct burden and improved neurological recovery[30].

At the same time, the signalling effects of exercise are not monolithic but can be tuned to disease context. In heart failure, exercise activates the STAT3–S100A9 axis to expand myeloid-derived suppressor cells (MDSCs), attenuating cardiac inflammation and fibrosis[31]. In diabetes, it suppresses STAT3–RORγt signalling, thereby limiting Th17 differentiation[32]. Following cardiac injury, exercise increases expression of the inhibitory B-cell receptor FcγRIIB, effectively lowering BCR pathway activation[33].

Through this multi-target remodelling of intracellular signalling circuitry, exercise helps shape an immune microenvironment that is permissive for repair and supportive of homeostatic maintenance.

3.3 Exercise-Induced Epigenetic Modifications In Immune Cells

Epigenetic rewiring sits at a deeper stratum of exercise-induced immunomodulation. One route is metabolite-driven chromatin modification, in which exercise-associated metabolites serve directly as substrates or donors for epigenetic marks. Lactate, for instance, can promote histone H3K18 lactylation and thereby enhance macrophage expression of Arg1[34]. Likewise, β-hydroxybutyrate supports histone H3 acetylation at the Foxp3 promoter and the conserved non-coding sequence 1 (CNS1), strengthening the immunosuppressive programme of Treg cells[22]. A second route involves direct effects on epigenetic enzymes. High-intensity interval training upregulates the demethylase KDM6B, reduces H3K27me3 levels, and promotes microglial expression of brain-derived neurotrophic factor and IL-4, thereby restraining pro-inflammatory activation[35]. Together, these observations suggest that exercise “sculpts” immune-cell identity and function through precisely targeted epigenetic mechanisms.

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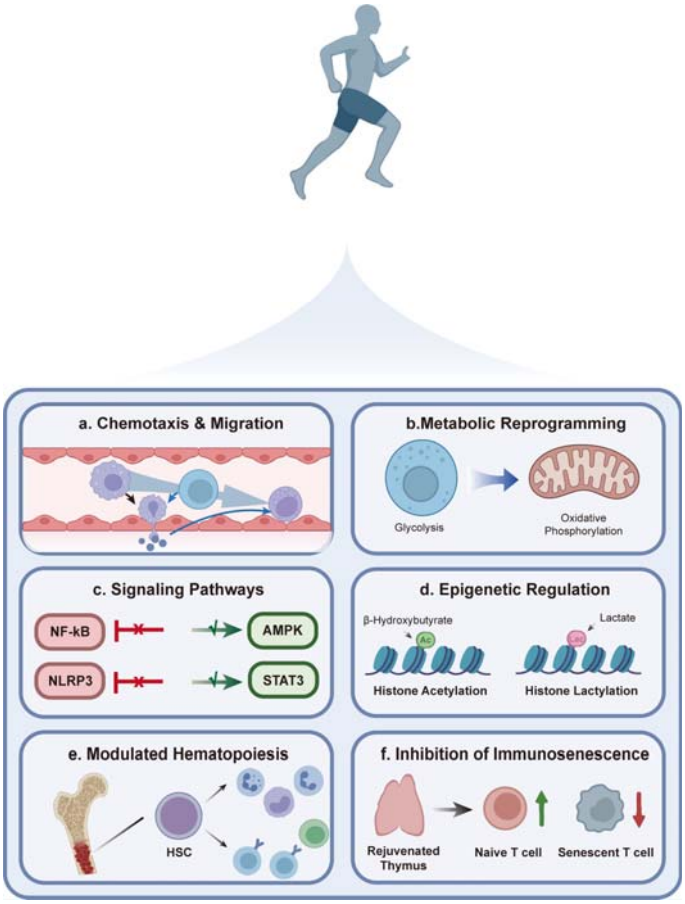

FIGURE 1: THE UNDERLYING MECHANISM OF EXERCISE IN REGULATING THE IMMUNE CELLS

4 CONCLUSIONS

Taken together, exercise training remodels immune function through multiple, intersecting routes—chemokine-guided trafficking, metabolic reprogramming, signalling rewiring, epigenetic modification, bone-marrow haematopoiesis and the modulation of immunosenescence—thereby mediating biological effects across physiological settings and a range of disease states (Fig. 1). Although exercise immunology has advanced appreciably, an integrated portrait of exercise–immune features in Chinese populations remains to be established. Differences in genetic background, lifestyle patterns, environmental exposures and prevalent disease spectra relative to many Western cohorts may plausibly confer distinct immune responses to exercise.

There is also a conceptual resonance worth exploiting. Traditional Chinese medicine places emphasis on holistic regulation and the maintenance of balance—often framed as "yin–yang equilibrium" and the harmonization of "qi and blood"—ideas that align closely with the homeostatic orientation of modern immunology. Traditional mind–body practices such as tai chi, Baduanjin and Wuqinxi may engage the immune system in characteristic ways. Compared with conventional aerobic exercise, these modalities tend to be gentler and safer, making them particularly suitable for older adults and potentially valuable as complementary approaches for immune modulation.

Looking ahead, the field would benefit from a deeper synthesis of local medical traditions with population-specific immunological characteristics. Strengthening basic and clinical research at the interface of "exercise–traditional medicine–immunity" could help build an exercise-immunology framework with distinctive Chinese features. Such efforts would not only inform exercise guidelines that better reflect national realities, but also provide a scientific foundation for broader public-health priorities, including the Healthy China initiative.

FUNDING

This work was supported by grants from the National Natural Science Foundation of China (No.82470296 to XN)

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