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REVIEW

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Distinct Effects of Endurance and Resistance Exercise on Immune Regulatory Cell Subsets

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ABSTRACT

Exercise exerts profound modulatory effects on the immune system; however, its impact on regulatory immune cell subsets has not been comprehensively understood. In this narrative review, we examine how different exercise modalities—particularly endurance and resistance training—affect innate and adaptive regulatory cell populations and contribute to homeostasis, inflammation control, tissue regeneration. We outline key principles of immunoregulation and the relationship between exercise, inflammation, and infection risk, then focus on regulatory neutrophils, regulatory natural killer cells, regulatory macrophages, regulatory T cells, and regulatory B cells.

Available human and experimental data indicate that endurance exercise acutely mobilizes regulatory neutrophil subsets and transiently alters their phenotype, while long-term training may support pro-regulatory myeloid-derived suppressor cell–like populations. CD56bright NK cells are recruited to the circulation during acute endurance exercise and may contribute to anti-inflammatory adaptations with repeated training. Both endurance and resistance exercise promote M2-polarized macrophages, supporting resolution of inflammation and tissue repair, with endurance training favoring systemic effects and resistance exercise inducing local adaptations in skeletal muscle. Tregs display dynamic redistribution, with fluctuations in peripheral blood after acute exercise and accumulation in exercised tissues linked to local immunoregulation and regeneration. In contrast, Bregs show inconsistent responses, highlighting a gap in knowledge.

Overall, evidence suggests that exercise acts as a modality- and cell type–specific regulator of immunoregulatory subsets. Differential effects across neutrophil, NK, macrophage, T-cell, and B-cell populations may underlie the benefits of regular physical activity on immune balance and inflammatory risk, underscoring the need for further mechanistic and longitudinal studies.

Keywords: Exercise, immunoregulation, regulatory immune cells, endurance and resistance exercise

INTRODUCTION

An effective immune response results from coordinated interactions between antigens and the cellular and molecular components of the immune system, integrating innate and adaptive responses against pathogens, tumor cells, commensal microbiota, allergens, and self-antigens. The magnitude and duration of this response are tightly controlled by diverse regulatory mechanisms, collectively referred to as immune regulation. Disruption of the balance between effector mechanisms and immuneregulation has been associated with the development of inflammatory conditions such as allergic and autoimmune diseases (1,2). Accordingly, strategies targeting regulatory immune cells are increasingly considered potential therapeutic approaches for restoring immune tolerance (3).

Physical activity is recognized as a lifestyle-associated factor and is considered an environmental stimulus capable of influencing immune homeostasis. However, human

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studies comprehensively characterizing the relationships between physical activity levels and all subsets of immunoregulatory cell populations remain limited. Evaluating the impact of exercise on immune function is important for understanding post-exercise inflammation and infection susceptibility. One of the pioneers of exercise immunology, Georg Schulz (4), demonstrated in the 19th century, through experiments conducted using an ergometer, that acute exercise leads to an increase in circulating immune cell numbers, thereby providing the first evidence of the immunomodulatory potential of exercise (5).

Today, it is widely accepted that the immunomodulatory effects of exercise contribute to the prevention of numerous chronic diseases associated with low-grade systemic inflammation, including cardiovascular diseases, cancer, and type 2 diabetes (5). Nevertheless, according to the World Health Organization (WHO) 2024 report, 31% of adults and 80% of adolescents worldwide do not meet the recommended levels of physical activity (6). If physical inactivity persists at current levels, the projected cost to global health systems between 2020 and 2030 is estimated to reach approximately 300 billion USD, with a substantial proportion allocated to pharmacological treatments (7). This projection further underscores the importance of exercise as a preventive and therapeutic strategy. However, optimal intensity and duration of exercise remain unclear, because immune responses vary by modality, duration, and intensity.

Exercise intensity is commonly classified based on metabolic equivalent of task (MET) values. Accordingly, light-intensity activities (<3.0 METs) include slow walking and light household tasks; moderate-intensity activities (3.0–5.9 METs) encompass brisk walking, tennis, and gardening; and vigorous-intensity activities (≥6.0 METs) include running, heavy load carrying, and high-intensity fitness training (8). In general, low-to-moderate intensity exercise is associated with immune-supportive effects, whereas prolonged, high-intensity exercise may lead to a transient post-exercise reduction in immune responsiveness described as "open window" and a higher short-term infection risk (9,10). Moderate-intensity exercise can enhance immune surveillance, promote anti-inflammatory effects, and lower the risk of chronic inflammatory diseases, potentially through reduced visceral adiposity, increased release of anti-inflammatory myokines from skeletal muscle, and exercise-induced changes in immune cell number, function, and surface marker expression (11-13). However, the precise molecular pathways underlying these adaptations remain incompletely defined.

Exercise-induced leukocyte changes have attracted scientific interest for nearly a century. One of the earliest systematic observations was reported by Ralph Larrabee in 1902, who documented increased leukocyte counts in Boston Marathon runners (14). Single bouts of exercise induce marked but transient alterations in leukocyte mobilization and cause leukocytosis which can reach up to four times the baseline level during exercise (15). Exercise performed at more than approximately 70% of maximal oxygen uptake and lasting longer than one hour has been reported to prolong this leukocytotic response. Endurance activities such as marathon running, cross-country skiing, and open water swimming elicit more robust cellular immune responses and greater leukocyte shifts than resistance exercises such as weightlifting, bodyweight strength training, and resistance band exercises (16). Innate immune cells, particularly neutrophils and natural killer (NK) cells, exhibit the most prominent mobilization, and after prolonged intense exercise, some leukocyte subsets may take up to 48 hours to return to baseline (17). While granulocyte counts remain elevated for several hours, lymphocytes typically show a brief post-exercise increase followed by a rapid decline below baseline levels. This transient lymphopenia is primarily attributed to NK cells and effector-memory T cells, whereas divergent responses may be observed in B cells. Monocytes increase during exercise and generally return to baseline within approximately three hours (18). Although a single bout of exercise elicits acute immune responses, it is equally important to consider the cumulative immunological adaptations that develop over time in response to repeated training stimuli, as these adaptations are likely to underlie the long-term effects of regular exercise on immune function (19).

Tissue-specific immune responses do not always run parallel to peripheral blood parameters. Given that circulating leukocytes constitute only approximately 2% of the total leukocyte pool and most of the immune cells are located in lymphoid tissues (20), blood-based analyses may not fully reflect exercise-induced immune changes at the tissue level. Moreover, exercise induces the release of metabolites, growth factors, cytokines, and hormones, collectively termed "exerkines", that activate multiple molecular signaling pathways and can alter the extracellular matrix composition, and interstitial pH (21,22). During eccentric and high-resistance exercise, microstructural damage

occurs leading to release of damage-associated molecular patterns (DAMPs), such as mitochondrial DNA, ATP, tenascin C, and HMGB-1, which subsequently trigger inflammatory responses with parallels to type I inflammation seen after infection or trauma (23–28). While repeated bouts may transiently promote a pro-inflammatory milieu, long-term training generally induces compensatory anti-inflammatory adaptations (29). Immunoregulatory cells likely contribute to this balance, although mechanisms remain unclear, and responses vary by age, sex, lifestyle, and baseline health status.

Within this framework, the present review aims to evaluate the effects of exercise on immune regulation from an integrative perspective, focusing on regulatory neutrophils, regulatory NK cells, regulatory macrophages, regulatory T cells, and regulatory B cells, key players in the modulation of innate and adaptive immune responses (Table I). In addition, the potential implications of exercise-induced alterations in these cell populations for human health will be discussed.

METHODS

This narrative review was developed through a structured literature search of PubMed, Web of Science, and Scopus databases for studies published up to January 2026. MeSH terms and free-text keywords were used in PubMed, and corresponding keyword combinations were adapted

Table I: Immune Cells in Acute and Chronic Resistance and Endurance Exercise

Cell Type	Subtype / Characteristic	Acute Resistance Exercise	Chronic Resistance Exercise	Acute Endurance Exercise	Chronic Endurance Exercise	Functional Role
Neutrophil	$CD16^{dim}CD62L^{bright}$, LDN, G-MDSC	🟢 Rapid mobilization	🟢 Inflammation control with regular exercise	🟢 Comparable mobilization	🟢 Inflammation control with regular exercise	Pro-inflammatory & regulatory; T/NK interaction
NK cell	$CD56^{bright}$regulatory NK cell $CD56^{dim}$cytotoxic NK cell	🟢 $CD56^{dim}$ ↑ cytotoxicity	🟢 $CD56^{bright}$ ↑ homeostasis	🟢 $CD56^{dim}$ ↑ cytotoxicity	🟢 $CD56^{bright}$ ↑ homeostasis	Antiviral/ antitumor defense, cytokines
Macrophage	M1, M2, Mreg	🟢 M1 onset → M2 shift	🟢 M2/Mreg ↑ Tissue regeneration and anti-inflammatory regulation	🟢 M1 onset → M2 shift	🟢 M2/Mreg ↑ Tissue regeneration and anti-inflammatory regulation	Tissue repair, inflammation control
Treg cell	CD4+CD25+FoxP3+, Tr1, iTreg	🟡 Transient mobilization	🟢 Activity ↑	🟡 Mobilization; transient lymphopenia	🟢 ↑ muscle regeneration	Suppression of adaptive immunity
Breg cell	IL-10, IL-35, TGF-β^{+} B cell	🟡 Limited	🟢 Anti-inflammatory support	🟡 Limited	🔴 ↓ in elderly	T-cell regulation, immune balance
T cell (overall)	CD8+ cytotoxic T cell, γδ T cell, CD4+ helper T cell	🟢 Lymphocytosis CD8+, γδ T	🟢 Memory adaptation	🟢 Similar	🟢 Memory adaptation	Adaptive immunity, effector function
B cell (overall)	Naïve, memory, mature B cell	🟡 Immature ↑	🟡 Minimal change	🟡 Similar	🟡 Minimal change	Antibody production, regulation

Immune regulatory cell responses to acute and chronic resistance and endurance exercise are summarized.

🟢 indicates an increase or functional adaptation, 🟡 a limited or transient response, and 🔴 a decrease in cell frequency or function.

CD: cluster of differentiation, **LDN:** low-density neutrophils, **G-MDSC:** Granulocytic-Myeloid-derived suppressor cells, **Mreg:** regulatory macrophages, **Tr1:** Type 1 regulatory cells, NK cell: **natural killer cell, γδ T cells:** gamma delta T cells, IL-**10:** interleukin 10, **IL-35:** interleukin 35, **TGF-β:** Transforming growth factor β

for Web of Science and Scopus. Search terms included combinations of "exercise," "physical activity," "exercise training," "endurance exercise," "aerobic exercise," "resistance exercise," "strength training," "immune regulation," "regulatory neutrophils," "suppressive neutrophils," "low-density neutrophils," "myeloid-derived suppressor cells," "CD56bright natural killer cells," "regulatory macrophages," "M2-like macrophages," "regulatory T cells," and "regulatory B cells. Articles were selected based on relevance to the scope of the review, with emphasis on mechanistic, translational, and clinical evidence linking exercise to immune regulatory pathways. Original research articles, systematic reviews, and meta-analyses published in English were considered. Studies focusing exclusively on pharmacological or disease-driven immune modulation without an exercise component were excluded. Given the narrative and concept-driven aim of this review, protocol registration and formal risk-of-bias evaluation were not undertaken.

Overview of Innate Immune Responses to Exercise

The innate immune response constitutes the first line of defense against pathogens and is composed of cellular components such as granulocytes, macrophages, NK cells, and dendritic cells (DCs), as well as soluble factors including complement proteins. Neutrophils rapidly migrate to inflammatory sites and release granular enzymes (30). Acute exercise, depending on its duration and intensity, induces a rapid neutrophilia followed by a delayed second rise, and may also contribute to skeletal muscle inflammation after high-intensity activity (31,32). Functionally, acute exercise can enhance neutrophil degranulation, oxidative burst, and phagocytic activity, potentially amplified by endurance-related increases in complement factors such as C5a that promote chemotaxis (33,34).

Monocytes can infiltrate damaged tissues, and differentiate into macrophages or DCs and exert key functions including phagocytosis, antigen presentation, and cytokine production. Acute exercise has been shown to induce a transient monositosis lasting approximately two hours, with preferential mobilization of pro-inflammatory $CD14^{+}/CD16^{+}$ subsets (35). Although data is limited, approximately fourfold increase in monocyte-derived DCs (mo-DCs) following a bout of running exercise was reported (36). Given their capacity to cross-present viral and tumor antigens, exercise-associated increases in DC numbers may have favorable implications for overall immune system functionality.

NK cells are key cytotoxic effectors against virus-infected, and malignant cells and are rapidly mobilized by acute exercise, predominantly within the CD56dim subset (37). The functional response of NK cells appears to be highly dependent on exercise intensity; low-to-moderate bouts may enhance cytotoxicity, whereas prolonged strenuous exercise may transiently reduce per-cell cytotoxic activity, potentially contributing to post-exercise infection (37).

Taken together, these findings indicate that evaluating the responses of innate regulatory cell populations to exercise beyond exercise-induced quantitative and functional changes in innate immune cells is essential for achieving a more comprehensive understanding of immune regulation.

Neutrophil Regulatory Cells and Exercise

Recent research indicates that neutrophils comprise functionally distinct subtypes, including populations with regulatory or suppressive properties capable of dampening inflammation through cell–cell interactions and the secretion of immunomodulatory mediators. Nevertheless, these regulatory neutrophil populations remain incompletely characterized, and no universally accepted phenotypic marker set has been established. Although phenotypes such as $CD16^{bright}CD62L^{dim}$ have been associated with suppressive functions in specific experimental settings, these markers have not achieved universal consensus across different physiological and pathological contexts (38,39).

A major suppressive neutrophil-like population is granulocytic myeloid-derived suppressor cells (G-MDSCs), within the broader MDSC family (monocytic M-MDSCs vs granulocytic G-MDSCs) (40-42). Functionally, among suppressive neutrophil-related populations, granulocytic myeloid-derived suppressor cells (G-MDSCs) are the best-characterized subset. G-MDSCs primarily mediate immunosuppression through reactive oxygen species (ROS) and arginase-1 (Arg1), whereas monocytic MDSCs (M-MDSCs) more commonly rely on inducible nitric oxide synthase (iNOS)-dependent nitric oxide production, together with Arg1-mediated mechanisms (43).

Neutrophils are also classified by density into low-density (LDNs) and high-density neutrophils (HDNs) (44,45). In some experimental tumor models, HDNs have been associated with N1-like antitumor properties, whereas certain LDN subsets exhibit N2-like, tumor-promoting features. However, the LDN population is heterogeneous,

and density-based classification should not be considered equivalent to the N1/N2 functional framework. N2/LDNs can suppress $CD8^+$ T-cell proliferation, dampen inflammatory mediator expression and promote metastasis via TGF-β/tumor-derived G-CSF and suppress T-cell responses via arginase-dependent mechanisms (45-47). Additionally, they can facilitate recruitment of immunosuppressive cells such as Treg cells via the secretion of CCL2/CCL5, and promote angiogenesis and tumor growth via mediators like oncostatin-M (48). Beyond oncology, a pregnancy-associated LDN subset expressing CD63 and arginase-1 has been reported to contribute immunetolerance by metabolizing L-arginine and inducing T-cell unresponsiveness (46,47). Regulatory neutrophils have also been linked to the production of IL-10 and IL-22, and may support intestinal barrier integrity (49,50).

Finally, G-MDSCs can suppress NK-cell activation, reducing NKp30, CD69, and CD137 expression and IFN-γ production, through ROS-mediated mechanisms (48,51).

Exercise is a strong physiological stimulus for neutrophil mobilization. During exercise, the number of neutrophils demarginating from the endothelial surface increases, and this elevation may persist for 2–3 hours afterwards, consistent with a "delayed second neutrophilia" associated with additional bone marrow release (52). The magnitude of this response depends on exercise duration and intensity, and mediated by stress hormones (cortisol, catecholamines), and adrenergic mechanisms. Robson et al. demonstrated that exhaustive cycling at 80% VO_2max elicited a greater neutrophil increase than longer-duration exercise at 55% VO_2max (53).

Following prolonged exercise, immature neutrophils ($CD16^{dim}CD62L^{bright}$) released from the bone marrow. In contrast, immunosuppressive neutrophils ($CD16^{bright}CD62L^{dim}$) constitute a smaller post-exercise fraction and have been linked to increased susceptibility to post-exercise infections (54-56). Accordingly, exercise-induced shifts in neutrophil surface receptor expression may represent a potential biomarker for monitoring immune balance during prolonged and repetitive exercise regimens.

Data on MDSC responses to exercise are limited. In a 20-week moderate-to-vigorous exercise program in older individuals with rheumatoid arthritis Anderson et al. reported no significant differences in MDSC frequencies compared with controls, and a trend toward reduced $CD15^+$ MDSCs did not reach significance (57). Although $CD15^+$ MDSCs tend to accumulate with age and may contribute to infections and cancer susceptibility, current evidence does not indicate that exercise meaningfully reduces MDSC numbers (58).

Consequently, regulatory neutrophils represent one of the least explored components of exercise immunology, and defining their phenotype and functional adaptations to acute and chronic exercise may represent an important frontier in understanding exercise-induced immune regulation.

Natural Killer Regulatory (NKreg) Cells and Exercise

NK cells constitute key components of the early immune response in conditions such as tumor development, viral infections, and organ transplantation. NK cells eliminate target cells either through perforin- and granzyme-containing cytolytic granules or via apoptosis-inducing surface molecules such as TRAIL and FasL (59–61). In addition, they have been shown to mediate antibody-dependent cellular cytotoxicity (ADCC) (62). By secreting IFN-γ, GM-CSF, and TNF-α, NK cells also contribute to the regulation of both innate and adaptive immune responses (63).

Human NK cells can be subdivided into several CD56/CD16-defined subsets which are broadly classified into immature $CD56^{bright}CD16^-$ cells that comprise 5–10% of circulating NK cells and are relatively enriched in tissues and secondary lymphoid organs and mature, highly cytotoxic $CD56^{dim}CD16^+$ cells account for approximately 90–95% of peripheral blood NK cells (64–67). Because of their strong cytokine-producing capacity (IFN-γ, GM-CSF, and TNF-α) $CD56^{bright}$ NK cells are widely considered the prototypic regulatory NK (NKreg) cell population (64,67).

$CD56^{bright}$ NK cells can trigger T-cell death via granzyme K–dependent mechanisms (68) or promote autologous T-cell apoptosis through increased perforin and granzyme B (69). $CD56^{bright}CD16^-$ NKreg cells can also halt the effector T-cell cycle through cell–cell contact and exert an indirect suppressive effects via Treg modulation through IL-10 (70–73). These cells have been proposed to assume protective or neurotoxic roles in neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (74). The presence of NK cells within the brain parenchyma and blood–brain barrier makes the $CD56^{bright}$ and $CD56^{dim}$ NK cell subsets potential therapeutic targets (75,76).

Following exercise, a transient lymphopenia lasting up to six hours may occur, with lymphocyte counts falling to <50% of resting levels, due to redistribution of NK cells and effector-memory T cells. NK cells are highly sensitive to exercise, increasing 50–400% shortly after initiation (77), this response being closely related to circulating catecholamine levels (78,79). Within the first 15 minutes post-exercise, NK cells migrate from the circulation into peripheral tissues, and after prolonged and strenuous endurance exercise, circulating NK cells may drop by approximately 40% (80). Exercise mainly mobilizes the cytotoxic $CD56^{dim}$ subset and NK cytotoxicity typically rises for 1–2 hours after a single bout, especially with aerobic and high-intensity exercise (81,82).

Across studies, responses vary by protocol, intensity and duration (83). Acute high-intensity exercise preferentially mobilizes CD16high/CD56 NK cells, and most data indicate stronger mobilization of $CD56^{dim}$ than $CD56^{bright}$ cells (84). Short or moderate bouts can increase one or both subsets, whereas very prolonged efforts (e.g., ultra-endurance or extended running) may reduce both $CD56^{bright}$ and $CD56^{dim}$ counts below baseline (85,86). Suzui et al. Showed that during short-term incremental exercise, only the proportion of $CD56^{dim}$ NK cells increased (87). Timmons et al. Demonstrated that 60 minutes of exercise at 70% VO_2max increased both $CD56^{bright}$ and $CD56^{dim}$ NK cell proportions, with a more pronounced response in the $CD56^{dim}$ subset (88,89). Training studies are mixed but meta-analytic evidence suggests no consistent change in resting NK counts (90). Within 30–60 minutes post-exercise, both subsets approached baseline levels, with $CD56^{bright}$ cells remaining slightly elevated and $CD56^{dim}$ cells slightly reduced. During recovery, the CD56bright-to-CD56dim (83) ratio may transiently increase, largely reflecting the more rapid decline in circulating CD56dim cells, however, the functional significance of this shift remains uncertain. (91). Exercise-associated increase in $CD56^{bright}$ NK cells is considered supportive evidence for the beneficial effects of exercise on immune system health (92).

Regulatory Macrophages (Mreg) and Exercise

Macrophages are highly plastic phagocytic cells that regulate inflammatory processes, antigen presentation, wound healing and angiogenesis. Functionally, macrophages are broadly divided as classically activated (M1; pro-inflammatory) and alternatively activated (M2; anti-inflammatory) phenotypes (with M2 subtypes) (93). Regulatory macrophages (Mreg) characterized by immunosuppressive properties, can be induced by Toll-like receptor ligands (94,95), and mediators such as TGF, IL-10, or glucocorticoids (96). Mreg cells typically produce high IL-10 and low IL-12 secretion, and can inhibit M1 macrophage activity and suppressing T-cell proliferation (93,97-99). Most exercise-related studies have examined pro-inflammatory versus reparative/M2-like macrophage states rather than specifically defined Mreg populations.

The phenotypic and functional properties of macrophages are strongly influenced by the tissue microenvironment (100). Several studies have demonstrated that moderate exercise can alter cytokine and chemokine profiles and thereby influence macrophage polarization (101–103). During exercise, mobilized monocytes migrate into tissues and differentiate into macrophages, supporting tissue repair and angiogenesis. Following acute muscle injury, an early M1-skewed phase contributes to tissue repair by debris clearance and pro-inflammatory signaling (e.g., IL-1β, TNF-α, oncostatin M), and may also facilitate the recruitment of Treg cells to the injured site (104-107). This phase is followed by a shift toward pro-regenerative M2 macrophages producing mediators such as IL-10 and amphiregulin that promote resolution of inflammation, angiogenesis, extracellular matrix remodeling, and myogenesis (108,109). These transitions are driven by sensing of DAMPs/PAMPs through receptors such as TLRs and other environmental cues (110). Moreover, monocarboxylate transporter 1 (MCT1) has been shown to induce a pro-angiogenic macrophage phenotype during skeletal muscle regeneration (111).

Adipose tissue is regarded as a key immunoregulatory organ that orchestrates the interplay between inflammation and metabolism (112). In white adipose tissue (WAT), the accumulation of M1 macrophages has been associated with obesity and insulin resistance (113). In contrast, M2 macrophages predominate in lean WAT and display anti-inflammatory properties (114). Adrenergic signaling modulates macrophage polarization. Alpha-adrenergic pathways tend to promote pro-inflammatory responses, while β_2-adrenergic activation supports M2 polarization and IL-10 production and suppresses TNF-α (114,115). Accordingly, moderate-to-high intensity exercise has been proposed to support M2 macrophage polarization, although responses may differ between acute and chronic exercise. In contrast, physical inactivity has been shown to reverse these adaptive responses and dysregulated polarization is implicated in chronic diseases, with excessive M1

activity linked to cardiometabolic pathology and excessive M2 dominance associated with tumor-promoting microenvironments (116-118).

The balance between M1 and M2 macrophages appears to be critical for optimal health, and exercise may represent an important tool for maintaining or restoring this balance. In this context, structured exercise programs tailored to specific disease groups are proposed to possess therapeutic potential.

Adaptive Immune Regulatory Cells and Exercise

The adaptive immune response is shaped by regulatory molecules and specialized cellular subsets that constrain both the magnitude and the duration. Immunoglobulins (Ig) can amplify immune responses through anti-idiotypic interactions or immune complex formation, while also providing negative feedback on B cells. Regulatory T-cell subsets (CD4/CD8) suppress immune activity through IL-10 and TGF-β, and surface receptor–mediated mechanisms. While, regulatory B cells (Bregs) have been reported to help restrain excessive inflammation and maintain immune homeostasis in healthy individuals.

Acute exercise affects the adaptive immune system through transient shifts in lymphosite number and function. A brief lymphocytosis that occurs during or immediately after exercise is thought to reflect mobilization of immune cells from the marginal pool, spleen, and other lymphoid tissues, whereas post-exercise lymphopenia has been attributed to redistribution of cells to peripheral tissues and, at least in part, to apoptotic processes (119).

Exercise-induced T-cell mobilization appears to depend on the differentiation status of the cells. Highly differentiated T cells exhibit a more pronounced mobilization response to acute exercise compared with less differentiated subsets (120,121). In contrast, B-cell mobilization is less dependent on effector status, with the greatest relative increases reported for immature B cells, followed by memory and naive B-cell populations (122). During exercise-associated lymphocytosis, marked increases are particularly evident in $CD8^+$ cytotoxic and γδ T cells, with smaller changes in $CD4^+$ helper T cells and Treg populations, although memory T cells can also be substantially mobilized (123).

Within 30–60 minutes post-exercise, lymphopenia predominates, driven primarily by reductions in $CD8^+$ cytotoxic T cells and γδ T cells, followed by $CD4^+$ helper T cells (119,124).

Regulatory T Cells and Exercise-Associated Immunoregulation

Regulatory T cells (Tregs) are central mediators in the maintenance of immune homeostasis, the limitation of autoimmune responses, and the control of excessive inflammation. Forkhead box protein 3 (Foxp3), functions as a key transcription factor underlying their regulatory activity (125) and PD-1, CTLA-4 are critical for the effectiveness of their suppressive functions (126). Immune suppression is mediated either through cell–cell contact or via the secretion of inhibitory cytokines including IL-10, IL-35, and TGF-β (127). Classically defined as $CD4^+$CD25 high cells with strong IL-2 responsiveness via STAT5 signaling, additional CD25-negative subsets with memory/effector-like features have also been described (128,129). Tregs can arise as natural (nTreg) or induced (iTreg) populations, including IL-10–producing Tr1 cells, TGF-β–producing Tregs, $CD8^+$ Tregs, and IL-35–dependent iTr35 cells (130).

The suppressive actions of Tregs can be broadly categorized into five principal mechanisms: inhibitory cytokine production, cytolysis (granzyme/perforin-mediated), metabolic disruption (e.g., CD39/CD73-dependent adenosine generation), inhibition of dendritic cell maturation (e.g., CTLA-4–CD80/86 interactions), and Treg-specific vesicular pathways (131,132).

Beyond their role in adaptive immunity, Tregs also modulate innate immune cell functions, by promoting resolution of inflammation and tissue repair, including effects on neutrophils and macrophage polarization toward anti-inflammatory phenotypes (133-135). They additionally restrain autoreactive B-cell responses, and the direct inhibition of effector B cells via PDL-1 and PDL-2 expression is also an established function of Tregs (136).

The effects of exercise on Treg cells vary with age, exercise intensity, duration and sampling time (137–139). Higher VO_2max in young elite athletes has been associated with increased Treg frequency (137), whereas marathon runners may exhibit reduced peripheral Treg levels following competition, likely reflecting redistribution to tissues and/or increased apoptosis (138-141). High-intensity exercise can enhance Treg mobilization (142), a phenomenon relevant to both transient immune suppression and broader immunoregulatory processes (143), but several

endurance studies report decreases in Treg proportions and Foxp3 expression during recovery. This cannot be fully explained by post-exercise lymphopenia alone and may be linked to the high sensitivity of Tregs to extracellular ATP, with exercise-induced ATP release potentially promoting early ATP-mediated cell death (144). However, the short half-life of ATP renders it insufficient to fully explain prolonged Treg suppression (138).

Low-intensity exercise modalities, such as Tai Chi, have been associated with increased Treg levels, while experimental models suggest more robust Treg expansion with high-intensity stimuli than with moderate exercise (145). In skeletal muscle, following acute muscle injury Treg accumulation peaks around days 3–4 and supports the transition from the inflammatory to the reparative phase (146,147). Post-exercise increases in Treg density have been demonstrated in several muscle groups and may persist beyond active training, through mechanisms not solely dependent on IL-6 signaling (148-150).

In dystrophic muscle disease models, Tregs appear protective (151,152). Experimental Treg depletion worsens inflammation by enhancing IFN-γ production from $CD4^+$ effector T cells and intensifying macrophage-driven inflammation, tissue damage, and pro-fibrotic signaling (146,153). These findings suggest that exercise-induced increases in intramuscular Treg content and concomitant reductions in IFN-γ levels may represent a potential therapeutic strategy for dystrophic muscle disorders; however, supporting clinical data in humans remain limited.

Recent studies reporting elevated Treg levels in athletes suggest that the anti-inflammatory properties of these cells may help counterbalance excessive immune suppression during periods of intense training (139). Accordingly, the controlled integration of exercise into therapeutic strategies for autoimmune and autoinflammatory diseases may represent a promising avenue for future intervention approaches.

Regulatory B Cells and Exercise-Associated Immunoregulation

Regulatory B (Breg) cells, which differentiate from B-cell precursors, are defined as an important subpopulation involved in the control of inflammatory responses. They represent a small B-cell subset (approximately 0.5%) that helps control inflammation (154), with particular relevance in allergic disease; conversely, impaired Breg function has been linked to autoimmunity, malignancy, and transplant rejection.

Bregs exert immunosuppressive effects mainly through cytokines such as IL-10, IL-35, and TGF-β, which inhibit $CD4^+$ T-cell proliferation, dampen Th1 responses, and promote Treg expansion (139-160). Furthermore, they can also suppress T cells via cell–cell interactions through surface-expressed PDL-1 and FasL molecules and their corresponding receptors, PD-1 and Fas, on T cells (159,160). Recent studies have revealed that Breg cells may also employ alternative regulatory mechanisms involving molecules and metabolites such as CD39, CD73, the aryl hydrocarbon receptor (AhR), and γ-aminobutyric acid (GABA) (161–164). However, unlike Treg cells, the absence of a Breg-specific defining transcription factor suggests that their regulatory properties are largely shaped by environmental cues, and there is no universally accepted classification scheme for Breg cells. Although they have been studied across many disease models, clinical cell-based Breg therapies are not yet established.

The number of studies examining the effects of exercise on Breg cells is limited. This limitation is thought to stem from the relatively lesser focus on B-cell mobilization in exercise-induced immune response studies compared with T and NK cells. Accordingly, current knowledge regarding the responses of B-cell subsets to exercise has not yet been fully clarified.

In one study, a 20-week moderate-to-high-intensity exercise in individuals aged ≥65 years with rheumatoid arthritis resulted in a reduction in Breg cell frequency and serum IL-10 levels without changing CRP (57).

Several studies have shown that the mobilization effect of exercise on B cells is lower than that observed for T and NK cells. Overall, low-intensity and resistance exercise often show minimal effects on B-cell counts, and available studies report that exercise may increase, decrease, or have no effect on B cell counts after training.

To elucidate exercise-related changes in B cell and Breg numbers and function, and their potential effects on the treatment of inflammatory and autoimmune diseases, better-designed studies are required, particularly in physically active populations. These studies could form the basis for the future development of personalised, exercise-based treatment strategies (165).

INTEGRATED OVERVIEW OF REGULATORY IMMUNE RESPONSES TO EXERCISE

Overall, exercise is a strong immunomodulatory stimulus, and regulatory immune-cell responses differ by modality, intensity, and duration. Endurance (aerobic) exercise, transiently mobilizes regulatory/immature neutrophil phenotypes from the bone marrow, whereas prolonged and chronic exercise supports the pro-regulatory characteristics of myeloid-derived suppressor cell (MDSC) subtypes. NK regulatory (NKreg) cells, particularly the $CD56^{bright}$ subset, are mobilized into the peripheral circulation during short-term endurance exercise, while chronic adaptations promote their accumulation in muscle and lymphoid tissues, where they exert anti-inflammatory effects. Macrophage polarization shifts toward tissue-repair programs, with endurance exercise favoring broader M2/Mreg-associated patterns, while resistance exercise more prominently supports local M2 accumulation within skeletal muscle. Treg cells may decrease in the peripheral blood during endurance exercise while accumulating in muscle tissue to suppress inflammation; during resistance exercise, short-term mobilization enhances local anti-inflammatory effects. In contrast, Breg cells display relatively low mobilization compared with Treg and NK cells under both exercise modalities; their numbers generally remain stable or show a slight reduction, and their anti-inflammatory functions appear to be only modestly affected. Further studies are required to clarify the relationship between exercise and Breg cells. (Figure 1).

Given the high sensitivity of regulatory cell populations to microenvironmental cues, the immunoregulatory effects of exercise are thought to be mediated predominantly through functional reprogramming rather than simple changes in cell numbers. Thus, exercise should be viewed neither as purely immunosuppressive nor purely immunostimulatory, but as a context-dependent regulator that can enhance immune homeostasis and tissue regeneration. Considering the limited availability of human data and the substantial methodological heterogeneity across studies, advanced mechanistic and longitudinal investigations are required to establish causal relationships between exercise and immune regulation. Nevertheless, the current body of evidence suggests that exercise may represent a rational adjunctive therapeutic strategy, particularly in inflammatory, autoimmune, and musculoskeletal disorders, by targeting microenvironment-immune cell interactions.

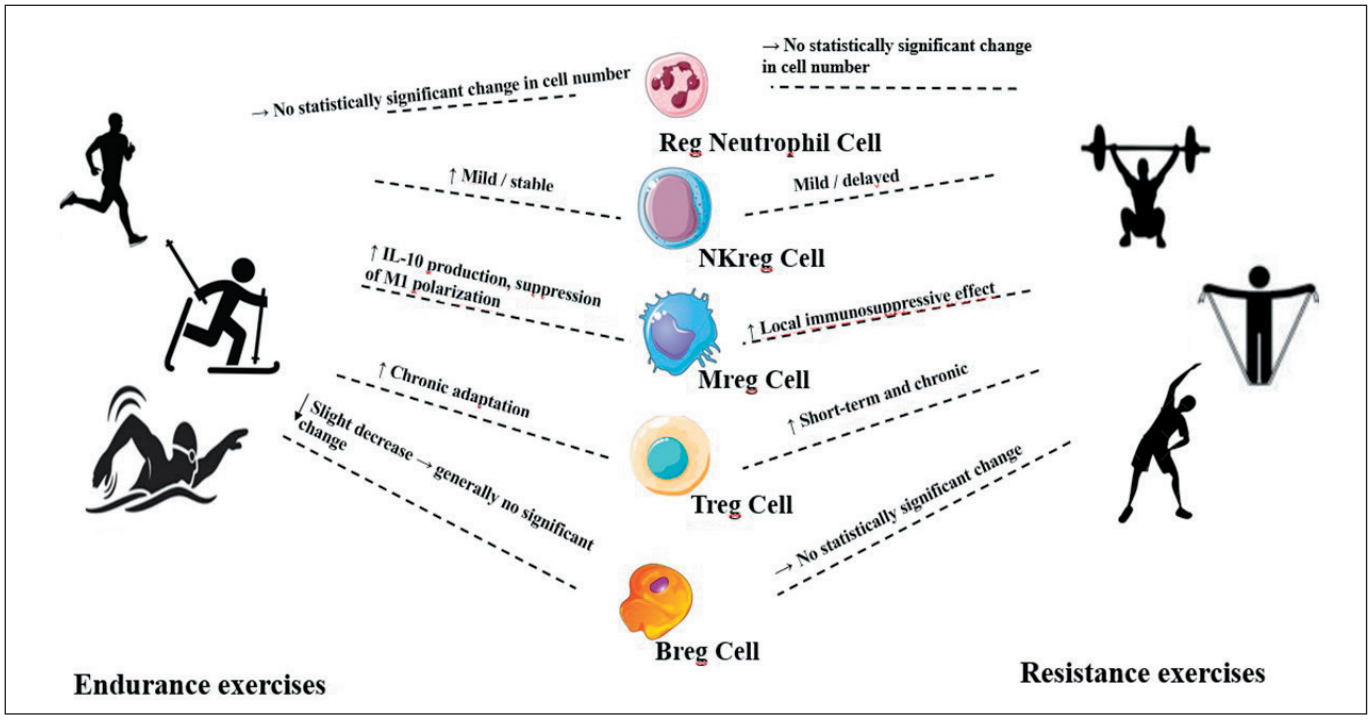

Figure 1: Immune regulatory cells in acute and chronic resistance and endurance exercise
Reg Neutrophil cell: Regulatory neutrophil, **NKreg cell:** regulatory natural killer (NK) cell, **Mreg cell:** regulatory macrophage (M2/Mreg), **Treg cell:** regulatory T cell (Treg), **Breg cell:** regulatory B cell (Breg).

CONCLUSION

Exercise exerts broad immunomodulatory effects through coordinated changes in regulatory immune-cell networks. Although responses differ according to exercise modality, intensity, and duration, the available evidence suggests that exercise promotes immune homeostasis and tissue repair through functional adaptation of regulatory immune populations. Despite substantial methodological heterogeneity and limited human mechanistic data, these findings support the incorporation of exercise as a complementary strategy in the prevention and management of chronic inflammatory and metabolic diseases. Future longitudinal and mechanistic studies are needed to better define causal pathways and optimize exercise-based immunomodulatory interventions.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Concept: **SD, SK, ZCS,** Design: **SD, SK, ZCS,** Analysis or Interpretation: **SD, SK, ZCS,** Literature search: **SD, SK,** Writing: **SD, SK, BED, ZCS,** Approval: **SD, SK, BED, ZCS.**

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