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Exercise induced immune regulation and drug efficacy in rhinitis nasopharyngeal carcinoma implications for tumor microenvironment single cell immune signal transduction

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Emerging evidence reveals that exercise modulates immune signaling to enhance the efficacy of immunotherapy in diseases like allergic rhinitis (AR) and nasopharyngeal carcinoma (NPC). By influencing immune cell trafficking, reprogramming inflammatory pathways within the tumor microenvironment (TME), and altering drug pharmacokinetics, exercise improves immune responses and therapeutic outcomes. Exercise enhances immune cell activation and infiltration into tumors, modulates checkpoint and cytokine signaling cascades, and mitigates treatment-related side effects, thereby improving patient compliance. Recent advancements in single-cell technologies, such as single-cell RNA sequencing and spatial omics, provide unprecedented insights into immune cell heterogeneity and signal transduction dynamics in the TME, uncovering new targets for exercise-modulated therapies. This review explores the synergistic effects of combining exercise with immune-based therapies, particularly in cancer treatment, highlighting the role of exercise in reshaping TME inflammation, overcoming immune evasion, and enhancing immune-mediated drug bioavailability. Personalized exercise regimens, tailored to individual patient profiles, are critical for optimizing therapeutic responses. Integrating exercise with immunotherapy, guided by single-cell and systems-level analyses, may provide a transformative approach for improving the clinical outcomes of AR and NPC patients, paving the way for more effective, individualized cancer treatments.

KEYWORDS

exercise, tumor microenvironment, immune signal transduction, single cell, immunotherapy, inflammation, nasopharyngeal carcinoma, allergic rhinitis

1 Synergistic effects of exercise on drug efficacy and immunoregulation

1.1 Impact of exercise on drug metabolism

Exercise enhances drug metabolism by improving cardiac output and blood flow, facilitating tissue distribution and absorption (1, 2). This benefits targeted therapies, as shown with potassium losartan, where exercise-induced circulation improved dissolution and nasal delivery (3). Increased vascular permeability within the tumor microenvironment (TME) further optimizes intratumoral drug diffusion (4), aiding treatments for rhinitis and nasopharyngeal carcinoma (NPC) (5, 6).

Exercise also modulates the immune microenvironment, enhancing drug bioavailability and efficacy, as seen with ebastine in allergic rhinitis (7–10). By boosting T cell, B cell, and macrophage activity (11) and improving immune surveillance (12, 13), exercise supports therapeutic outcomes. Innovations such as transferosome oral films greatly increase ebastine absorption (14, 15), and when combined with exercise-induced immune activation, they strengthen targeted drug delivery for immune-related diseases, they strengthen spatiotemporal drug delivery and immune modulation at the single-cell level in immune-related diseases (16).

1.2 Immunoregulatory effects: the role of exercise in local immunity

Exercise boosts immune responses by enhancing immune cell function and migration, thereby remodeling the local TME in rhinitis and NPC (11, 17). In the nasal cavity, it improves circulation, aiding immune cell aggregation, allergen response, and drug absorption (18). For cancer, it enhances chemo- and immunotherapy efficacy inflammation regulation and single-cell immune signaling in the TME (19). Centipeda minima (CM) shows anti-inflammatory and antitumor effects, potentiated by exercise through better hemodynamics and immune activation (20, 21). In NPC, this synergy reduces immune suppression and improves tumor targeting (22). Exercise also reprograms immune tolerance in allergic rhinitis and NPC by boosting immune activity, antigen recognition, and pro-inflammatory cytokine release (23–25), thereby fostering a responsive immunotherapeutic microenvironment that can be mapped at single-cell resolution (26, 27).

1.3 Mechanisms of exercise-enhanced drug therapy

Exercise regulates inflammation, improving drug efficacy by increasing anti-inflammatory IL-10 and reducing TNF- α , IL-1 β (28), creating a favorable immune milieu for therapy. Reduced

inflammation optimizes immune function, drug permeability, and targeting (26). In rhinitis and NPC, exercise alleviates local inflammation, enhances immune cell migration/activation, and supports treatment (29, 30). Combined with immune checkpoint inhibitors like atezolizumab, it boosts tumor immune activity, improving efficacy (31). Mechanistically, exercise may modulate checkpoint pathways and antigen-presenting cell signaling cascades within the TME, thereby refining immune tolerance and mitigating immunotherapy side effects (19).

1.4 Exercise intensity, immune modulation, and drug efficacy

Exercise intensity modulates both immune function and pharmacological responses. Moderate-intensity exercise (MIE) enhances immune surveillance, attenuates inflammation, and facilitates drug absorption and distribution through increased natural killer (NK) cell activity, improved antigen presentation, and favorable cytokine shifts (11, 32). In allergic rhinitis (AR), MIE has been shown to improve intranasal drug penetration, while in nasopharyngeal carcinoma (NPC), it enhances the efficacy of immunotherapy. In contrast, high-intensity exercise (HIE) can induce transient immunosuppression, often referred to as the “open window” phenomenon (33). This state is characterized by reduced NK cell activity, decreased salivary immunoglobulin A (IgA), and elevated stress hormone levels, all of which may impair drug efficacy. From a pharmacokinetic perspective, MIE helps sustain therapeutic plasma concentrations, whereas HIE may accelerate drug clearance and consequently lower tissue drug exposure (34). Thus, exercise intensity critically dictates the balance between pro- and anti-inflammatory signaling within the TME, shaping both immune responses and drug effectiveness.

1.5 Impact of exercise on immune cell trafficking and drug resistance in NPC

Exercise modulates immune cell trafficking and overcomes immune resistance in NPC's TME by enhancing blood flow and tissue perfusion, facilitating CD8⁺ T cell and NK cell infiltration (35). It can reduce PD-L1 expression on tumor and immune cells, improving T cell function and immune surveillance, while increasing IL-6 and TNF- α to activate effector T cells. Exercise also normalizes tumor vasculature, improves oxygenation, and reduces hypoxia, enhancing drug delivery and limiting Treg/MDSC accumulation (36). At single-cell resolution, these changes highlight how exercise remodels the inflammatory and immune signal transduction landscape of the TME, strengthening immune-mediated tumor destruction and improving therapeutic responses (37).

2 Exercise in rhinitis and nasopharyngeal carcinoma: modulating immunity and enhancing drug efficacy

2.1 Exercise and immune regulation in allergic rhinitis

Allergic rhinitis (AR), affecting up to 40% globally, is an IgE-mediated nasal inflammation often comorbid with asthma, triggered by seasonal or perennial allergens (38, 39). Pharmacotherapy efficacy is limited, prompting interest in immune-regulating strategies (40). Moderate exercise enhances T, B, and NK cell activity, suppresses pro-inflammatory cytokines, and strengthens systemic/local immunity (Figure 1) (41). In the nasal cavity, it improves blood flow, immune cell aggregation, and microvascular permeability, optimizing drug delivery (42). At the immune signaling level, exercise promotes T cell migration, activation, and IL-10/TGF- β release within local mucosal niches, thereby reshaping inflammatory pathways and reducing hypersensitivity (43, 44). It also mitigates allergic sensitization, though excessive exercise may worsen airway irritation (45). Individualized intensity programs are thus essential.

2.2 Exercise enhances pharmacological efficacy in rhinitis

Exercise improves immune regulation in AR and enhances drug efficacy by boosting circulation and tissue drug delivery (11, 46), allowing lower doses and fewer side effects. Montelukast (MT), a leukotriene D4 receptor antagonist for asthma, AR, and EIB, shows variable efficacy (47, 48). Exercise may enhance MT pharmacokinetics/dynamics through improved hemodynamics and modulation of immune-related signaling pathways regulating drug transporters and metabolism (Figure 1) (49). Increased anti-inflammatory cytokines can further potentiate MT's effects, reducing dose needs (50). Pulmonary benefits, including improved ventilation, enhanced mucociliary clearance, and greater elasticity, also contribute to better responsiveness (51, 52). Thus, MT plus moderate exercise integrates drug action with immune signal regulation, making it a promising AR strategy warranting optimization studies.

2.3 Immune evasion mechanisms in nasopharyngeal carcinoma tumor microenvironment

Nasopharyngeal carcinoma (NPC) exhibits strong immune evasion within the tumor microenvironment (TME), driven by tumor-immune-stroma interactions (53). Key mechanisms include upregulation of immune checkpoints such as PD-1/PD-L1 and CTLA-4, with PD-1 binding to PD-L1 inducing T cell exhaustion and weakening antitumor immunity. NPC also secretes TGF- β and IL-10, promoting regulatory T cell (Treg) and myeloid-derived

suppressor cell (MDSC) infiltration, further suppressing immunity (54). Additionally, tumor-associated fibroblasts and endothelial cells release matrix metalloproteinases (MMPs) and remodel the extracellular matrix, hindering immune cell infiltration and reinforcing an immunosuppressive niche. These mechanisms reshape immune signal transduction networks within the TME, limiting effector cell function and promoting tumor persistence.

2.4 Exercise and immune checkpoint inhibitors in nasopharyngeal carcinoma

Immune checkpoint inhibitors (ICIs), including anti-PD-1/PD-L1 and anti-CTLA-4, improve NPC treatment by reactivating CTLs and NK cells, though efficacy is limited by the immunosuppressive TME (55). Exercise enhances ICI effects through modulation of immune signaling, boosting T cell function, increasing CD8⁺ T and NK cell infiltration into the TME, reducing PD-1/CTLA-4 expression, alleviating hypoxia, and improving blood flow, thereby promoting antigen recognition (35). Clinical studies show exercise during ICI therapy improves OS, PFS, and immune profiles, while reducing fatigue and adverse events (56). Preclinical data suggest exercise delays NPC growth and shifts the TME toward immunostimulation, overcoming resistance. Combining exercise with ICIs refines immune signal transduction within the TME, offering a promising strategy to enhance efficacy and patient outcomes (57).

2.5 Exercise, tumor oxygenation, and immunotherapy enhancement in nasopharyngeal carcinoma

In NPC, tumor hypoxia drives immune evasion, therapy resistance, and aggressiveness (58). Aerobic/endurance exercise alleviates hypoxia by enhancing cardiovascular output, angiogenesis, and vascular normalization (59), reducing interstitial fluid pressure and improving oxygen diffusion, thereby lowering HIF-1 α activity (60). This reversal decreases immunosuppressive myeloid-derived suppressor cells and Tregs, reprograms macrophages toward anti-tumor activity, and boosts CD8⁺ T cell infiltration and survival. At the single-cell level, improved oxygenation synergizes with PD-1/PD-L1 inhibitors, cancer vaccines, and adoptive T cell transfer by enhancing antigen presentation, limiting T cell exhaustion, and increasing effector cytokine production (61). Preclinical NPC studies support structured aerobic exercise as a non-pharmacological adjuvant to immunotherapy.

2.6 Exercise as an adjunct in nasopharyngeal carcinoma immunotherapy

Immunotherapy, particularly ICIs such as anti-PD-1/PD-L1 agents, has transformed treatment landscapes in multiple cancers,

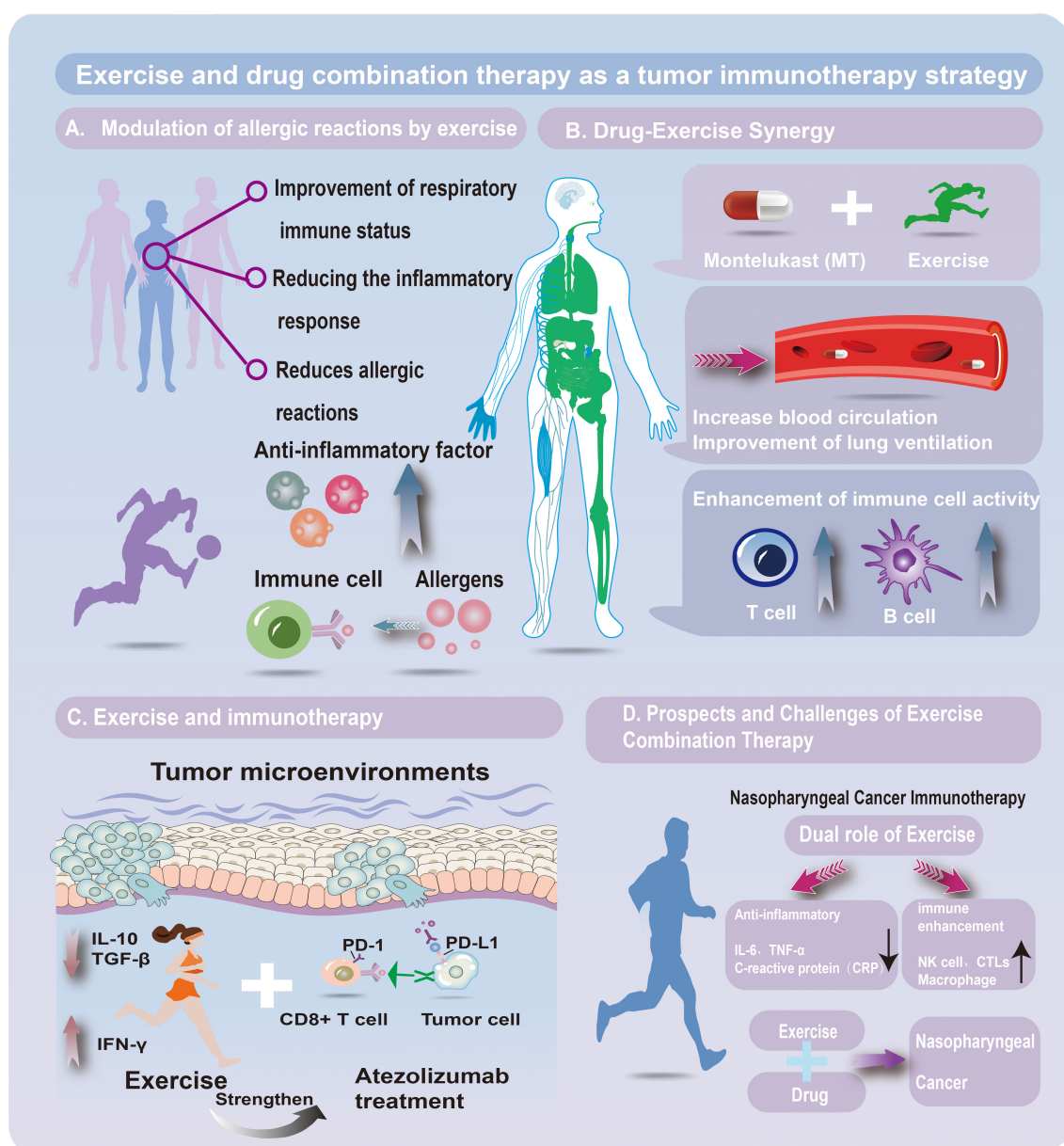


FIGURE 1

Exercise–drug combination therapy in tumor immunotherapy. (A) Exercise and allergy modulation. Exercise enhances respiratory immunity, lowers inflammation, and reduces allergic reactions via anti-inflammatory mediators and allergen-responsive immune cells. (B) Drug–exercise synergy. Combining montelukast (a leukotriene receptor antagonist) with exercise improves circulation and ventilation, boosting T- and B-cell activity and strengthening immune defense against tumors and inflammation. (C) Exercise and immunotherapy. Exercise reshapes the tumor microenvironment by regulating cytokines (e.g., IL-10, TGF- β , IFN- γ), enhancing antitumor responses. It complements atezolizumab (a PD-L1 inhibitor) by counteracting PD-1/PD-L1 immune evasion. (D) Prospects and challenges. In nasopharyngeal cancer, exercise reduces IL-6, TNF- α , and CRP while activating NK cells, CTLs, and macrophages. Integrating exercise with drug therapy holds promise for improving therapeutic efficacy.

including NPC (62, 63). However, response rates to ICIs in NPC remain modest due to immune escape and an immunosuppressive TME (64). This immunosuppressive TME is shaped by dynamic interactions among tumor-associated immune cells, which can now be characterized at single-cell resolution to dissect resistance-related signal transduction. Exercise increases CD8⁺ T cell infiltration, reduces immunosuppressive factors like TGF- β and IL-10, and improves oxygenation in hypoxic tumor regions, thereby amplifying cytotoxic immune responses (Figure 1) (65). It also

fine-tunes inflammatory and immune signaling pathways, promoting anti-tumor cytokine secretion and systemic immune activation (66). In NPC specifically, combining Atezolizumab with exercise may improve outcomes by reversing tumor immune evasion. This could involve enhanced antigen presentation and improved spatial organization of immune infiltrates, both of which are crucial for immunotherapy efficacy. Moreover, exercise could potentiate the effects of nano-platform photodynamic therapies that induce immunogenic cell death, further enhancing treatment synergy (67).

2.7 Clinical trials and real-world evidence

Clinical studies, including randomized trials and real-world evidence, show that exercise improves immune regulation in AR and NPC, enhancing therapeutic outcomes and quality of life. In AR, RCTs have demonstrated that moderate-intensity exercise reduces airway inflammation, relieves nasal congestion, and boosts the effects of antihistamines and nasal corticosteroids by increasing anti-inflammatory cytokines (IL-10) and decreasing pro-inflammatory cytokines (TNF- α). Real-world studies also suggest that higher physical activity levels correlate with fewer rhinitis exacerbations and less need for medical interventions. In NPC, clinical trials indicate that structured exercise combined with immunotherapy enhances immune responses, with increased T-cell infiltration and reduced PD-1/PD-L1 expression, suggesting synergy between exercise and immunotherapy. Cohort studies also highlight that single-cell immune profiling reveals exercise-induced shifts in TME composition, linking clinical benefit to rewired immune signal transduction (68, 69).

2.8 Clinical translation and emerging combinatorial strategies

Although Atezolizumab monotherapy has shown limited efficacy in NPC (ORR ~5%) in Chinese cohorts, combining it with chemotherapy improves outcomes (70). Exercise may complement such combinatorial strategies by improving drug delivery through enhanced perfusion and reprogramming immune cell signal transduction in the tumor milieu (71). These effects are increasingly appreciated through spatial transcriptomics and multi-omics analyses, which reveal how localized perfusion and immune cell positioning impact drug response. In addition to ICIs, new therapeutic agents such as Camrelizumab and the natural compound cinobufagin have shown promise in NPC. Cinobufagin induces cell cycle arrest and apoptosis in NPC cells and may be a candidate for integration into multimodal treatment strategies (72). Exercise could potentially enhance these agents' efficacy by improving immune surveillance and systemic metabolism (73). Combining exercise with immune-activating compounds may remodel the tumor immune landscape, making it more responsive to targeted agents. Together, these findings point toward a multimodal, patient-specific approach that integrates ICIs, novel agents, and exercise-based interventions to improve NPC outcomes (74).

2.9 Challenges and future perspectives in exercise-drug integration

While the immunomodulatory potential of exercise is clear, its integration with pharmacological therapies presents several challenges. Exercise has a dual role: it can reduce tumor-promoting inflammation and enhance immune activation, but excessive intensity or duration may lead to immune suppression and treatment resistance (75). The key lies in tailoring exercise regimens to individual patient profiles, including cancer type, treatment phase, and physical

condition (76). Interindividual variability in treatment response, tolerance to physical activity, and underlying comorbidities further complicate standardization (77). For example, frail patients may experience adverse effects from even mild exertion, while fitter patients may require higher intensity to achieve benefits. Personalized prescriptions, ideally integrated into routine care and synchronized with treatment windows, may optimize outcomes (78). Patient compliance also remains a hurdle. Fatigue, psychological burden, and side effects of treatment often limit adherence to structured exercise programs (79). Incorporating behavioral support, supervised group programs, and flexibility in exercise formats could help sustain participation and improve treatment adherence (80). Future research should leverage single-cell and systems-level analyses to refine exercise-drug integration strategies, ensuring alignment with immune signal transduction mechanisms in the TME.

3 Preclinical and clinical evidence on exercise-drug synergy in rhinitis and nasopharyngeal carcinoma

3.1 Animal studies on exercise-enhanced drug efficacy

Preclinical studies highlight the potential of combining exercise with pharmacological interventions to enhance immune regulation in AR and NPC. In AR models, exercise activates immune cells (CD4⁺, CD8⁺ T cells, dendritic cells) and shifts the immune response toward Th1 dominance, reducing Th2-mediated allergic reactions (Figure 2) (26, 81).

Exercise also promotes anti-inflammatory cytokines like IL-10 and TGF- β , amplifying drug efficacy (82). In NPC models, exercise reprograms the tumor microenvironment (TME) by modulating inflammatory signaling and immune infiltration, reducing immunosuppressive mechanisms and boosting anti-tumor immune cell activity (83). Single-cell RNA sequencing (scRNA-seq) provides insights into the molecular effects of exercise, revealing how exercise reshapes immune signal transduction in cell subsets in AR (e.g., Tregs, Th2 cells) and NPC (e.g., cytotoxic CD8⁺ T cells, TAM reprogramming) (84–86).

Exercise also enhances immune checkpoint inhibitor efficacy by reducing MDSCs and Tregs, improving immune balance and therapeutic response (Figure 2) (81). Aerobic exercise reduces chronic inflammation, improving immunotherapy outcomes (66) and induces epigenetic and transcriptional changes within immune pathways, sensitizing tumors to treatments (87). Imaging studies show exercise improves tumor perfusion and vessel normalization, enhancing drug delivery.

3.2 Clinical insights into exercise and immunotherapy

Preliminary clinical studies suggest that exercise is a beneficial adjuvant in cancer immunotherapy, especially with checkpoint

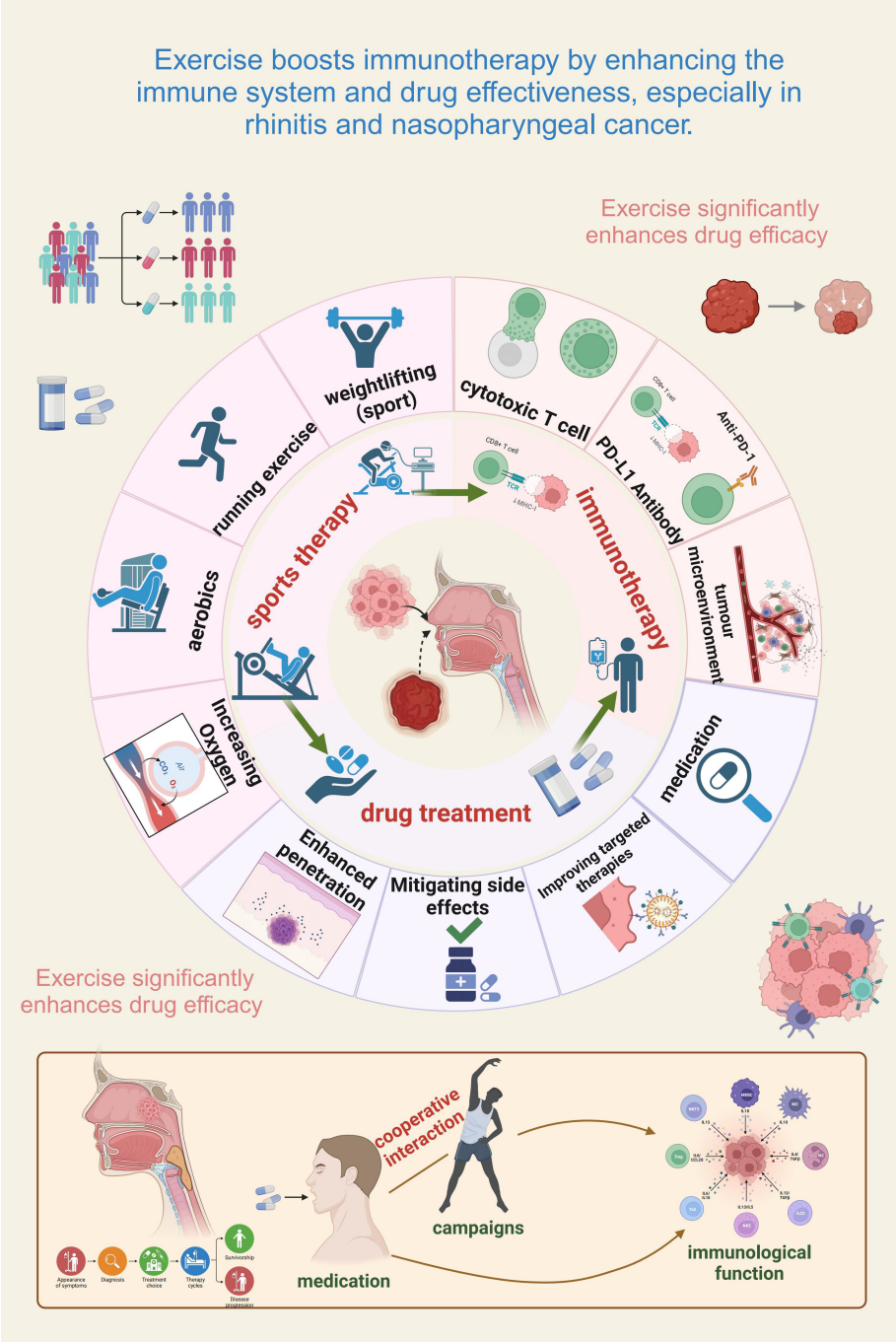


FIGURE 2 Exercise enhances immunotherapy efficacy by modulating immunity and drug effectiveness in rhinitis and nasopharyngeal cancer. Exercise strengthens immune function and improves drug treatment outcomes in immune-related conditions. The figure highlights the interplay of physical activity, immune modulation, and drug therapy in optimizing efficacy. Different exercise forms (e.g., running, weightlifting, aerobics) enhance oxygenation, drug delivery, and cytotoxic T cell activity. Exercise also synergizes with immunotherapy by fostering anti-tumor immunity, fortifying the tumor microenvironment, and boosting PD-L1 antibody effectiveness. In addition, it mitigates side effects, facilitates targeted therapy, and increases immune checkpoint inhibitor efficiency. The lower panel illustrates the cooperative interaction of exercise and medication, underscoring physical activity as a valuable adjunct to conventional treatment.

inhibitors (e.g., anti-PD-1/PD-L1) (56). For instance, moderate-intensity aerobic exercise alongside checkpoint inhibition in non-small cell lung cancer patients boosts immune surveillance, enhances CD8⁺ T cell activation, and reduces immunosuppressive cell populations such as Tregs and MDSCs (88). Similar trends in NPC trials show that exercise enhances NK and dendritic cell function, improves drug delivery, and reduces immune suppression (89). Exercise likely modulates TME intercellular signaling and chemokine-mediated communication (e.g., CXCL9/10), thereby regulating immune cell infiltration (90). In allergic

rhinitis, exercise restores immune balance disrupted by chronic allergens, enhancing immune responses, reducing inflammation, and improving drug efficacy in symptom management (Figure 2) (91). Advances in single-cell profiling provide tools to map cell-type-specific immune signaling changes induced by combined exercise and immunotherapy (92). Despite promising results, challenges remain in defining optimal exercise regimens (type, intensity, duration, timing) for individual patients. The ACSM guidelines recommend moderate-intensity aerobic exercise (60–70% HRmax, 30–60 min) as safe (93), with personalized prescriptions and real-time monitoring tools enhancing tailored interventions (94).

3.3 Clinical potential of exercise combined with immunotherapy in NPC

Emerging clinical evidence shows significant synergy between exercise and immunotherapies like Atezolizumab (anti-PD-L1 antibody) in NPC. Exercise enhances immune cell activation, promotes tumor infiltration, and reduces common side effects, such as fatigue, improving patient compliance and outcomes (95). Clinical studies also show that combined exercise interventions improve physical endurance, psychological well-being, and immune response (96). Exercise enhances tumor perfusion and oxygenation, increasing drug bioavailability and efficacy, addressing limitations of single-agent immunotherapy (65). Furthermore, exercise-induced changes in the tumor microenvironment (TME) may overcome primary and acquired resistance to immune checkpoint inhibitors. Additionally, exercise mitigates treatment-related side effects, supports overall health, and enables sustained drug administration. Clinical data also demonstrate exercise's positive effects on emotional well-being and long-term treatment adherence, underscoring its broader clinical utility.

3.4 Personalized exercise interventions: tailoring approaches for clinical efficacy

Personalization of exercise interventions remains essential, considering variability in patient demographics, comorbidities, tumor biology, and treatment regimens. Comprehensive pre-exercise evaluations incorporating medical history, physical capability assessments, and disease staging are critical for effective customization of exercise prescriptions (97). For patients with cardiovascular or respiratory comorbidities, low-intensity aerobic activities such as walking or Tai Chi are recommended initially, with gradual intensity escalation (98). Patients with diabetes require close blood glucose monitoring combined with carefully timed aerobic and resistance exercises (99). Individuals experiencing musculoskeletal pain may benefit from low-impact exercises like aquatic therapy (100). These exercises can relieve pain while maintaining muscle strength and joint flexibility. Future strategies should also consider integrating exercise training with other supportive care modalities, such as nutritional interventions or

psychosocial counseling, to improve adherence and holistic patient outcomes. Importantly, integrating personalized exercise with immune monitoring at the single-cell level may optimize safety and efficacy (37).

3.5 Future directions and challenges

Future research should focus on the molecular and cellular mechanisms by which exercise regulates immune function in cancer and allergic diseases. Investigating how exercise affects immune cell subsets, cytokine profiles, and metabolic pathways will help optimize exercise regimens to enhance drug efficacy and reduce side effects (19).

Identifying and validating biomarkers to predict treatment response is essential. Integrating genomics, transcriptomics, proteomics, and advanced single-cell and spatial approaches (e.g., spatial CITE-seq, CRISPR screening) offers powerful strategies to uncover immune signaling mechanisms and design personalized interventions (101). However, challenges remain, including individual variability in response to exercise. Personalized interventions are needed to prevent immune overstimulation or excessive exercise-induced stress (102). Balancing exercise intensity to optimize immune regulation without exacerbating side effects or immune-related adverse events is key (103). Systematic research and well-designed clinical trials are required to define optimal parameters for combining exercise with drug therapies, ensuring safe and effective clinical translation (104).

4 Conclusion

The interplay between exercise and immune signaling is a promising, yet underexplored, pathway for enhancing the effectiveness of immunotherapy, particularly in conditions such as allergic rhinitis (AR) and nasopharyngeal carcinoma (NPC). Current evidence suggests that exercise influences immune cell activation, remodels inflammatory signaling within the tumor microenvironment (TME), and improves drug pharmacokinetics, collectively contributing to better therapeutic outcomes. Recent advances in single-cell technologies have highlighted the substantial heterogeneity in immune cell states and immune signal transduction pathways within the TME. Exercise-induced changes in immune cell distribution and function likely reshape these dynamic signaling processes at single-cell resolution. However, the precise molecular mechanisms by which exercise influences immune signaling and intercellular communication remain largely unknown. To address this, future research should integrate exercise immunology with single-cell transcriptomics and spatial omics technologies. These approaches will provide high-resolution insights into how exercise modulates immune cell populations and their interactions within disease-relevant tissues. Such integration could uncover new regulatory pathways and therapeutic targets, facilitating the development of personalized interventions that combine physical activity with immune-based

treatments. By bridging exercise science with cutting-edge immune profiling technologies, researchers can uncover novel mechanisms supporting exercise as an adjunct to immunotherapy. This interdisciplinary strategy, focused on inflammation and immune signal transduction in the TME, may ultimately lead to more effective, individualized treatments for cancer and other immune-mediated diseases.

Author contributions

GH: Conceptualization, Formal analysis, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. WB: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. JY: Formal analysis, Resources, Validation, Writing – original draft, Writing – review & editing. XG: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. WL: Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. XJ: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SG: Conceptualization, Software, Supervision, Writing – original draft, Writing – review & editing. RW: Conceptualization, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. YC: Conceptualization, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

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