Less Inflammatory Debris, Improved Immunity from Immune Detox: A New Perspective on the Benefits of Exercise in Chronic Disease

Asghar Abbasi (PhD), William Stringer (MD)

[1] Respiratory Research Center, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, 1124 W Carson St., Torrance, CA 90502
[2] Division of Respiratory and Critical Care Physiology and Medicine, Harbor-UCLA Medical Center, 1000 W Carson St., Torrance, CA 90509

ABSTRACT

The immunological benefits of exercise are commonly attributed to its immune-boosting effects such as the release of exercise-induced factors (e.g., exerkines) and activation of anti-inflammatory molecules. However, this may not fully explain its benefits in chronic inflammatory conditions. We propose a complementary view whereby exercise potentially functions as a biological detoxifier by removing harmful immunological debris such as damage-associated molecular patterns (DAMPs), senescent cells, dysfunctional mitochondria and pro-inflammatory extracellular vesicles (EVs) that drive chronic immune activation. We highlight key mechanisms by which exercise may reduce or remove these harmful signals, including autophagy and mitophagy activation, enhanced efferocytosis, reduced senescence burden, and modulation of EV cargo. This "immune detox" model may help explain the clinical benefits of exercise in conditions where the immune system is overactivated, not deficient. It shifts the narrative from immune boosting to restoring immune balance, and could have potentially important implications for biomarker discovery and personalized exercise prescriptions in chronic disease.

**Corresponding author:*
Asghar Abbasi, PhD
The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center
Division of Respiratory & Critical Care Physiology & Medicine
1124 W Carson St, CDCRC Building
Torrance, CA 90502
Email: asghar.abbasi@lundquist.org
Tel:+1-(310)-974-9533

INTRODUCTION

Shifting the Paradigm

The immunological benefits of exercise are widely recognized to enhance the production of beneficial signaling molecules. From the secretion of myokines such as IL-6, IL-15, and irisin, to systemic changes in catecholamines and lactate, the dominant view has been that physical activity stimulates a cascade of molecules that support immune surveillance, repair, and immune downregulation (1). This framework has been particularly influential in the field of exercise immunology, leading to a continued focus on identifying and quantifying exercise-induced biomarkers associated with anti-inflammatory or immunomodulatory effects. However, this model may be incomplete, especially in the context of chronic diseases characterized by persistent inflammation and immune dysregulation. In these persistent conditions, such as chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis (IPF) (2-6), acute lung and liver disease (7-9), diabetes mellitus (10, 11), cancer (12), Alzheimer's disease (13), autoimmune diseases (14), and aging (15, 16), immune dysfunction appears to be less about a lack of immune activation and more about the persistence of harmful signals. Damaged and senescent cells accumulate in these chronic states, releasing a spectrum of pro-inflammatory and danger-associated molecules that chronically stimulate the immune system (6, 17). The result is not immune deficiency, but an immunologically overactive system that struggles to maintain homeostasis in the face of continuous inflammatory stimuli from internal sources. In fact, an editorial by Dr Esch et al. (2020) highlights the widespread clinical use of monoclonal antibody therapies specifically designed to neutralize unregulated secretion of circulating proinflammatory cytokines for the treatment of diverse autoimmune syndromes (18). These therapeutic approaches highlight the clinical relevance of persistent inflammatory signals.

In this perspective article, we hypothesize that regular physical exercise contributes to immune rebalancing, not only by inducing beneficial exercise-induced factors, but also by reducing or removing pro-inflammatory cellular byproducts such as DAMPs, senescent signals, dysfunctional mitochondria, and inflammatory EVs, that we collectively

refer to as "inflammatory debris" or "immune clutter". This concept which we describe as "immune detox" emphasizes a "*subtractive model*" of immune regulation, where exercise promotes immune homeostasis by removing internal drivers of chronic inflammation. These terms are used metaphorically throughout the manuscript to describe biological processes that reduce harmful immunological molecules and restore balance.

The Immunological Burden on Chronic Disease

Chronic diseases are increasingly recognized as states of sustained immunological stress, driven not only by pathogens or external insults, but by the persistent accumulation of endogenous danger signals. DAMPs are released or exposed during a variety of cellular processes, including injury, necrosis, mitochondrial dysfunction, or senescence. Rather than resolving over time, DAMPs remain elevated in many chronic conditions including COPD, obesity, type 2 diabetes, autoimmune diseases and aging, resulting in prolonged immune activation and systemic inflammation. The most well described and accepted DAMPs are nucleic acids such as mitochondrial DNA (mtDNA) (13, 19-21), HMGB1 (high mobility group box 1) (18, 22), histones (23), and S100 proteins (24). Other nuclear or cytosolic components, when misplaced or mispackaged, also signal tissue damage. Given the similarities between DAMPs and pathogen-associated molecular patterns (PAMPs), it should be no surprise that DAMPs are sensed by innate immune receptors such as toll-like receptors (TLRs) and NOD-like receptors (NLRs), initiating inflammatory cascades that perpetuate low-grade but chronic immune stimulation (25-29).

Senescent cells also contribute to this inflammatory load by releasing a complex mix of pro-inflammatory factors, collectively known as senescence-associated secretory phenotype (SASP)(30), which includes cytokines (e.g., IL-6, IL-8), chemokines (e.g., CXCL1, CCL2), matrix remodeling enzymes (e.g., MMPs), and growth factors. Their persistence in tissues adds another layer to immune dysregulation, especially in the aging population (6, 11, 16). One or more SASP components likely mediate chronic inflammation and affect the growth and survival of tumor cells (30, 31). Its regulation occurs at multiple levels, including chromatin remodeling and activation of transcription factors such as C/EBP and NF-κB. Nevertheless, SASP components can also support tissue repair, immune clearance, and wound healing, making them promising targets for therapeutic modulation (31, 32).

Mitochondria are bacterial endosymbionts that have evolved to be vital organelles in cellular energy production. Despite this, mitochondria are frequent sources of immune-activating signals when damaged (27). Mitochondrial DNA (mtDNA), which has a bacterial-like, double-stranded circular structure, can be released into the cytosol or extracellular space under cellular stress such as ATP or LPS stimulation, where it acts as a potent DAMP that activates the innate immune system via receptors like TLR4 or TLR9 (20, 33). Among the best-characterized mitochondrial genes that trigger immune responses are *MT-ND1*, *MT-ND2*, MT-ND4 and MT-CO1 (34). Human neutrophils exposed to purified mtDNA released matrix metallopeptidases MMP-8 and MMP-9 (35), and incubation of human embryonic kidney cells with serum from acute myocardial infarction patients contains elevated levels of mtDNA induced TLR9-dependent NF-κB activity (36). Together, these findings highlight the potent immunostimulatory capacity of mitochondrial components, particularly mtDNA, and underscore their emerging role as key inflammatory mediators.

A less often discussed, but increasingly important component of this immunological milieu is EVs. Long considered vehicles of intercellular communication, EVs also serve as a mechanism for exporting unwanted or harmful cellular contents in a protected fashion. EVs often carry inflammatory cargo in chronic diseases, including damaged nucleic acids, oxidized lipids, and dysfunctional mitochondrial proteins (37). Emerging evidence suggests that these vesicles are not merely messengers but active participants in immune signaling, especially when their cargo consists of DAMP-like molecules. Several studies have demonstrated that EVs mediate inflammatory responses by delivering mtDNA (37). mtDNA levels are elevated in EVs and the release of mtDNA into EVs is suggested to coincide with an increase in the expression of markers associated with DNA damage, proinflammatory cytokines and senescence (27, 38, 39). Besides mtDNA, mitochondrial RNAs (e.g., tRNAs and rRNAs), which are recognized as key DAMPs and involved in triggering inflammation, are also carried by EVs (40, 41). Like mtDNA, mitochondrial RNAs (mtRNAs) can originate from mitochondrial fragments of stressed or damaged cells and once delivered to target cells via EVs, they can activate TLRs and trigger inflammatory pathways (42, 43). Hough and colleagues (2018) demonstrated that EVs can transfer mitochondria to target T cells and integrate with their mitochondrial network, leading to increased production of reactive oxygen species (ROS) and activation of inflammatory signaling pathways within the T cells (44). These findings suggest that the mtRNA and mtDNA content within EVs may hold clinical relevance and could serve as potential diagnostic and prognostic biomarkers for chronic inflammatory diseases.

Thus, the immune system in chronic disease settings appears to be burdened not only by defective regulation, but also by the sheer volume of inflammatory signals that sustain its activation. Addressing this "inflammatory debris" may be a more effective strategy for restoring immune balance than further stimulating a system that is already overwhelmed.

Exercise as an Immune Detoxifier

Exercise involves a diverse set of molecular and cellular pathways that enhance tissue renewal, metabolic homeostasis, and immuno-regulation. Importantly, many of these pathways directly contribute to the clearance of harmful cellular byproducts. In contrast to the conventional view of exercise as a stimulator of beneficial exerkines, an equally powerful role may lie in the potential for exercise to enhance clearance mechanisms, acting as a biological detoxifier.

A cornerstone of this detoxifying effect is the activation of autophagy and mitophagy, as shown by He et al. (2012) and Laker et al. (2017), where exercise upregulated muscle autophagy and mitochondrial quality control mechanisms, respectively (45, 46). Indeed, exercise-induced autophagy and mitophagy seem to be involved in mediating many of the beneficial effects of exercise. These conserved pathways are responsible for the degradation and recycling of damaged

organelles and proteins. Exercise, particularly aerobic and endurance-based exercise, increases autophagic capacity by upregulation of key regulators such as AMP-activated protein kinase (AMPK), forkhead box O (FOXO), transcription factor EB (TFEB), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) (47). Exercise-induced AMPK can also suppress mammalian target of rapamycin (mTOR), which is a known suppressor of autophagy (47). The role of exercise-induced autophagy has been investigated by inhibiting autophagy using the lysosomal inhibitor chloroquine, administered 5 days per week for 16 weeks in an animal model (48). This intervention has led to the development of sporadic inclusion body myositis, a condition characterized by muscle weakness and wasting (48). Resistance exercise training prevented chloroquine-induced increases in ATG6 (Beclin-1) and p62 (48), thereby improving autophagy, muscle strength, and preventing myositis.

Through mitophagy, exercise facilitates the removal of dysfunctional mitochondria, thereby reducing the leakage of ROS and mtDNA, which are both potent DAMPs that drive immune activation. This process is mediated by key molecular pathways, particularly the PINK1/Parkin axis (49). Upon mitochondrial damage, PINK1 accumulates on the outer mitochondrial membrane and recruits the E3 ubiquitin ligase Parkin, which ubiquitinates outer membrane proteins and marks the mitochondria for degradation via lysosomal autophagosomes (49). By selectively clearing damaged mitochondria, exercise-induced mitophagy preserves mitochondrial quality and supports cellular homeostasis.

Another critical mechanism is enhanced efferocytosis, the process by which phagocytic cells, particularly macrophages, clear apoptotic cells (e.g., neutrophils) to maintain tissue homeostasis. In chronic diseases such as COPD, asthma, atherosclerosis, lupus, cystic fibrosis, rheumatoid arthritis, neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), type 2 diabetes, obesity, and some cancers, efferocytosis is often impaired, resulting in secondary necrosis and the release of additional pro-inflammatory contents (50-56). While direct evidence regarding the effects of either acute or chronic exercise on macrophage efferocytosis is currently lacking, exercise training has been shown to reprogram macrophages toward a more efficient, anti-inflammatory phenotype, thereby enhancing their ability to resolve inflammation (57). Since timely clearance of apoptotic cells prevents the release of inflammatory DAMPs (58), interventions that reduce DAMPs (such as exercise) may indirectly support and improve apoptotic cell clearance.

Senescence is another target of exercise-mediated immune detox. Studies in aging and metabolic disease models have demonstrated that regular exercise reduces the number of exhausted/senescent cells as well as circulating SASP factors (59, 60). In addition, increased cardiorespiratory fitness can protect against the production/accumulation of senescent cells, including immune cell populations (60, 61). For example, it has been demonstrated that individuals with an above-average cardiorespiratory fitness measured by VO_2max (47.3 ml/kg/min) had 37% fewer KLRG1+/CD57+ and KLRG1+/CD28− senescent T cells than individuals with an average or below-average VO_2max (43.0 and 34.4 ml/kg/min, respectively) (62). Whether reduced senescent cells are due to direct effects on cellular senescence or enhanced immune clearance of senescent cells remains under investigation, but the result is a measurable reduction in pro-inflammatory signaling (63, 64).

A particularly intriguing detoxification pathway involves the modulation of EVs. As previously noted, beyond transporting secreted exerkines and immunoregulatory molecules, EVs can also carry harmful cargo including mtDNA, pro-inflammatory cytokines and chemokines, nuclear debris, and dysfunctional proteins, all of which contribute to immune activation. Exercise has been shown to change not only the abundance of circulating EVs, but also their molecular cargo (65-68). In both animal models and human studies, exercise appears to shift EV profiles away from pro-inflammatory content toward those enriched in regulatory or restorative molecules (69-72). This may reflect a functional reorganization of the EV system, shifting from disseminating inflammatory signals to exporting intracellular waste, depending on physiological context. Recently, we observed a reduction in the EV content of mitochondrially encoded transcripts, including *MT-ND1*, *MT-ND2*, *MT-NDP28*, *MT-ND3* and *MT-RNR1*, at peak exercise compared to rest, following exercise training interventions in two different patient groups (COPD and long COVID) (*Abstract published* (73), and *manuscripts currently under review*). These findings support the idea that exercise facilitates the clearance or suppression of harmful mitochondrial-derived EV cargo, representing a potential mechanism for immune restoration. In addition, exercise-induced EVs may contribute to macrophage efferocytosis. EVs can enhance macrophage efferocytosis by modulating macrophage polarization, thereby improving apoptotic cell clearance and promoting inflammation resolution (74, 75). Specifically, EVs may increase the expression of efferocytosis receptors such as Tim4 on macrophages, enhancing their capacity to engulf apoptotic cells (74). EVs can also deliver functional molecules like milk fat globule-EGF factor 8 (MFGE8), which further promote efferocytosis (76). Notably, we recently found that C1q proteins are elevated in serum EVs from smoke-exposed mice following 1 hour of aerobic exercise compared to their non-exercised counterparts (*Abstract published* (77)). C1q, a well-known component of the classical complement system, also acts as a pro-efferocytic signal, enhancing the uptake of apoptotic cells while limiting TNFα production by mouse and human macrophages (78-80). The unpublished data from our lab, although preliminary, add empirical support to the proposed detoxification hypothesis, and are the focus of ongoing mechanistic investigations.

Collectively, these mechanisms illustrate how exercise acts as a biological clean-up mechanism (see *Figure 1*), leading to reduced immune activation. Rather than merely introducing beneficial factors, exercise also diminishes the presence of harmful or inflammatory ones. In principle, this could alleviate chronic immune stimulation and allow the system to return to a more responsive and regulated state. We hypothesize that exercise, including acute bouts, reduces the EV content of mitochondrially-encoded RNAs (e.g., *MT-ND1*, *MT-ND2*, *MT-ND3*, *MT-RNR1*, *MT-RNR2*) by enhancing mitochondrial quality control via coordinated activation of AMPK, PGC-1α, FOXO, and SIRT1 signaling pathways. Although direct

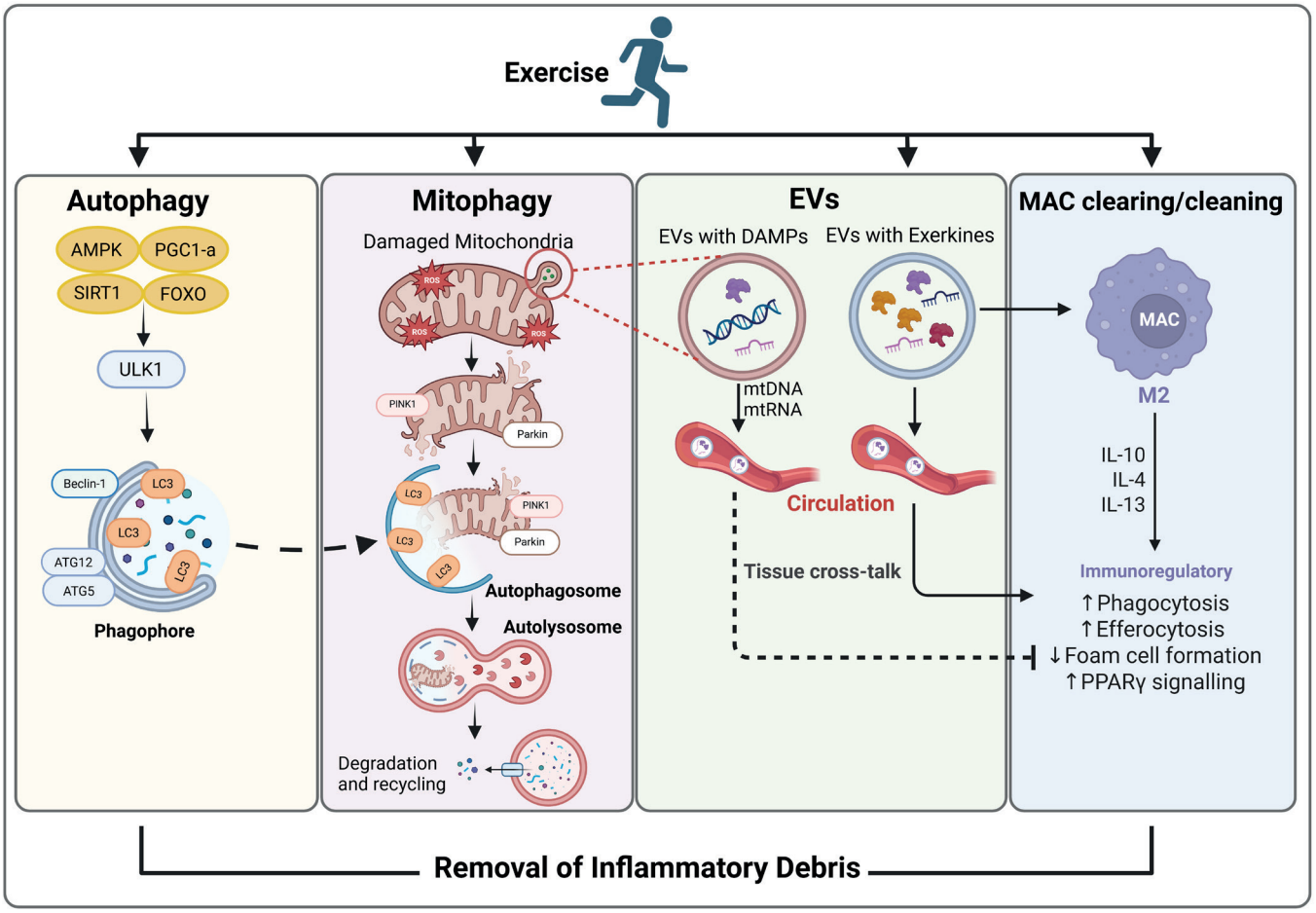

Figure 1. Exercise-induced autophagy, mitophagy, macrophage pro-resolving function and modulation of EV content contribute to cellular detoxification and immune resolution. Exercise activates key signaling molecules such as AMPK, PGC-1α, SIRT1, and FOXO, which initiate the ULK1–Beclin-1–LC3 autophagy machinery. This promotes the formation of autophagosomes and enhances mitophagy, mitochondria-specific autophagy. Dysfunctional mitochondria produce excess reactive oxygen species (ROS) and release mitochondrial DAMPs such as mtDNA and mtRNAs, which may be exported via EVs. Exercise reduces the abundance of EVs and DAMPs, while increasing the production of EVs laden exerkines that influence immune cells. In particular, exercise-induced EVs can promote macrophage polarization toward an M2-like phenotype, enhancing phagocytosis, efferocytosis, and PPARγ signaling, while reducing foam cell formation. Collectively, these pathways support a coordinated detoxification response, contributing to improved mitochondrial quality and immune homeostasis by removing inflammatory debris. EV: Extracellular vesicles; MAC: macrophage; DAMP: danger-associated molecular patterns; ROS: reactive oxygen species.

evidence is currently lacking, it is plausible that exercise-induced activation of signaling molecules such as AMPK, PGC-1α, FOXO, or SIRT1 contributes to the observed reduction in mtRNA and mtDNA content in EVs. This reduction may reflect improved mitochondrial integrity, turnover, or reduced cellular stress, rather than direct pathway-specific modulation. Future studies are needed to dissect these mechanisms.

Reframing the Concept of Exercise-Induced Benefits

If we embrace the view that exercise reduces harmful inflammatory immunological burden rather than simply enhancing beneficial signals, it will require a fundamental shift in how we understand, study, and prescribe physical activity, particularly in the context of chronic disease. The traditional narrative has emphasized the "addition" model, in which exercise increases anti-inflammatory cytokines, mobilizes immune cells, and releases myokines and metabolites that enhance host defense and tissue repair. While these phenomena are well-documented, they do not appear to fully account for the therapeutic effects observed in individuals with chronic inflammatory conditions. In such individuals, the immune system is overactive, bombarded by DAMPs, senescent signaling, and pro-inflammatory EVs. In this context, the value of exercise may lie in its potential to remove the drivers of this chronic activation, essentially dampening the background noise so that productive immune responses can emerge. This subtractive or detoxifying model reframes exercise not as a simple immune stimulant, but as a homeostatic regulator that clears internal debris and restores equilibrium.

This perspective may also help explain why modest doses of exercise, sometimes even below the recommended thresholds, can result in profound clinical improvements in populations with chronic illness or immunosenescence. These populations may not need more immune activation; they need less immune distraction. By reducing the load of pro-inflammatory signals, exercise may restore immune precision and functional reserve. Importantly, this conceptual shift has implications for biomarker development and exercise prescription. Biomarkers of benefit should not be limited to increased levels of known anti-inflammatory mediators but should also include reductions in molecules that reflect immune clutter (e.g., circulating

mtDNA, senescence-associated transcripts, SASP factors, and inflammatory EVs). Similarly, exercise prescriptions could be personalized not only by intensity and volume, but also by the individual's inflammatory burden and capacity to engage in immune restoration.

In sum, this reframing opens the door for a more nuanced, mechanism-informed understanding of exercise in chronic disease. It positions physical activity as a systemic regulator of immune tone, not merely by boosting the system, but rather by clearing the path for it to function effectively.

It is important to recognize that the immune-activating and immune-detoxifying effects of exercise are not mutually exclusive but may function synergistically depending on the physiological context. For instance, during acute infection or immunosuppression, the stimulatory effects of exercise on immune surveillance and effector functions may be advantageous. In contrast, in chronic disease conditions (which are characterized by sustained immune activation and systemic inflammation) the ability of exercise to attenuate immunological burden through clearance of pro-inflammatory mediators may be more therapeutically relevant. This integrated framework acknowledges that exercise exerts both immunostimulatory and immunoregulatory effects, with their relative predominance shaped by factors such as disease type, biological age, physical fitness, and metabolic status.

While the detox model presents a compelling framework, it is important to recognize its potential limitations. Under certain conditions, excessive autophagy or mitophagy may be maladaptive, leading to cellular dysfunction or energy depletion (81-85). Furthermore, in some chronic diseases, clearance pathways such as efferocytosis or autophagy may be too impaired to fully respond to exercise stimuli, limiting the detox potential (11, 20, 51, 86). Finally, if immune activity is overly affected, it could potentially suppress essential immune surveillance. These limitations underscore the need for mechanistic validation and the identification of optimal exercise thresholds that balance immune restoration with necessary immune vigilance.

Future Directions and Therapeutic Potential

The idea that exercise promotes immune health by reducing cellular waste and inflammatory burden presents a number of promising avenues for future research and therapeutic innovation. While preclinical and *in vitro* studies have provided strong foundational evidence, direct clinical validation of these detoxification mechanisms, particularly exercise-induced EV cargo modulation and enhanced efferocytosis, in human populations remains limited. Future studies in animal models and human populations with chronic diseases are needed to confirm whether these mechanisms translate into measurable therapeutic effects.

As this detoxification framework gains traction, several key areas deserve focused investigation. First, the development of biomarkers of immune inflammatory debris or clutter could greatly enhance our ability to assess exercise responsiveness in chronic disease populations. Current research predominantly measures increases in exercise-induced factors, but equally important may be reductions in circulating DAMPs (e.g., HMGB1, mtDNA), senescence-associated transcripts (e.g., p16, IL-6, CXCL1), dysfunctional mitochondria markers, and pro-inflammatory EVs. Standardizing these metrics could help identify individuals most in need of "immune unloading" and track their physiological response to training.

Second, this perspective opens the possibility for therapeutic synergy. Interventions aimed at reducing immune burden such as senolytics, mitophagy enhancers, or anti-inflammatory diets may act synergistically with exercise to accelerate immune restoration. Rather than viewing exercise as a standalone tool, it could be strategically integrated into multi-modal treatment plans that combine physical activity with agents targeting cellular senescence, mitochondrial health, or vesicle biogenesis.

Third, understanding individual variability in "immune detox" capacity will be essential. Some individuals, due to age, disease state, or genetic predisposition, may exhibit impaired efferocytosis (e.g., in COPD), sluggish autophagy, or dysregulated EV release. These individuals might require longer or differently structured training regimens to achieve the same immunological benefits. Investigating the molecular "non-responder" phenotype in this context could be particularly valuable.

Finally, the detox model has clear relevance in emerging areas such as long COVID, immunosenescence, and cancer-related immune exhaustion. These conditions are all marked by a buildup of internal danger signals and impaired immune resolution. Exercise interventions tailored to reduce this load may provide a safe and scalable strategy to restore immune resilience in diverse clinical populations. Together, these directions underscore the potential of a more refined, mechanism-based application of exercise as a therapeutic agent, not just to stimulate immunity, but to improve removal of inflammatory debris.

CONCLUSION

The conventional narrative of exercise as an immune booster has advanced our understanding of how physical exercise supports health. However, in the context of chronic diseases characterized by immune overactivation and persistent inflammation, this perspective may be incomplete. We propose that a major, underappreciated benefit of exercise lies in its ability to reduce harmful cellular byproducts, what we term 'inflammatory debris' or clutter. By promoting autophagy, enhancing efferocytosis, reducing senescence, and reshaping extracellular vesicle cargo, exercise acts as a biological detoxifier that restores immune balance. This framework offers a compelling explanation for the broad clinical benefits of exercise rehabilitation, especially in populations where the immune system is not underperforming, but is overactive. Although promising, this model remains a hypothesis and further clinical validation is essential. Recognizing and measuring this detoxifying role opens the door for new biomarkers, personalized interventions, and therapeutic strategies that position exercise and exercise rehabilitation as a precision tool for immune restoration.

REFERENCES

1. Chow LS, Gerszten RE, Taylor JM, Pedersen BK, van Praag H, Trappe S, et al. Exerkines in health, resilience and disease. Nat Rev Endocrinol. 2022;18(5):273-89.
2. Pouwels SD, Heijink IH, ten Hacken NH, Vandenabeele P, Krysko DV, Nawijn MC, et al. DAMPs activating innate and adaptive immune responses in COPD. Mucosal Immunol. 2014;7(2):215-26.
3. Dong L-L, Liu Z-Y, Chen K-J, Li Z-Y, Zhou J-S, Shen H-H, et al. The persistent inflammation in COPD: is autoimmunity the core mechanism? European Respiratory Review. 2024;33(171):230137.
4. Peebles RS, Jr., Aronica MA. Proinflammatory pathways in the pathogenesis of asthma. Clin Chest Med. 2019;40(1):29-50.
5. Huang X, Tan X, Liang Y, Hou C, Qu D, Li M, et al. Differential DAMP release was observed in the sputum of COPD, asthma and asthma-COPD overlap (ACO) patients. Sci Rep. 2019;9(1):19241.
6. Barnes PJ, Baker J, Donnelly LE. Cellular senescence as a mechanism and target in chronic lung diseases. Am J Respir Crit Care Med. 2019;200(5):556-64.
7. Kuipers MT, van der Poll T, Schultz MJ, Wieland CW. Bench-to-bedside review: Damage-associated molecular patterns in the onset of ventilator-induced lung injury. Critical care. 2011;15:1-11.
8. Marques PE, Amaral SS, Pires DA, Nogueira LL, Soriani FM, Lima BH, et al. Chemokines and mitochondrial products activate neutrophils to amplify organ injury during mouse acute liver failure. Hepatology. 2012;56(5):1971-82.
9. Huidobro C, Martín-Vicente P, López-Martínez C, Alonso-López I, Amado-Rodríguez L, Crespo I, et al. Cellular and molecular features of senescence in acute lung injury. Mech Ageing Dev. 2021;193:111410.
10. Shin JJ, Lee EK, Park TJ, Kim W. Damage-associated molecular patterns and their pathological relevance in diabetes mellitus. Ageing Res Rev. 2015;24(Pt A):66-76.
11. Palmer AK, Tchkonia T, LeBrasseur NK, Chini EN, Xu M, Kirkland JL. Cellular senescence in type 2 diabetes: a therapeutic opportunity. Diabetes. 2015;64(7):2289-98.
12. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822-32.
13. Wilkins HM, Carl SM, Greenlief AC, Festoff BW, Swerdlow RH. Bioenergetic dysfunction and inflammation in Alzheimer's disease: a possible connection. Front Aging Neurosci. 2014;6:311.
14. Romerio A, Peri F. Increasing the chemical variety of small-molecule-based TLR4 modulators: an overview. Front Immunol. 2020;11:1210.
15. Kapetanovic R, Bokil NJ, Sweet MJ. Innate immune perturbations, accumulating DAMPs and inflammasome dysregulation: A ticking time bomb in ageing. Ageing Res Rev. 2015;24(Pt A):40-53.
16. van Deursen JM. The role of senescent cells in ageing. Nature. 2014;509(7501):439-46.
17. Ma KC, Schenck EJ, Pabon MA, Choi AMK. The role of danger Signals in the pathogenesis and perpetuation of critical illness. Am J Respir Crit Care Med. 2018;197(3):300-9.
18. Esch T, Stefano GB, Ptacek R, Kream RM. Emerging roles of blood-borne intact and respiring mitochondria as bidirectional mediators of pro- and anti-inflammatory processes. Med Sci Monit. 2020;26:e924337.
19. Simmons JD, Lee YL, Mulekar S, Kuck JL, Brevard SB, Gonzalez RP, et al. Elevated levels of plasma mitochondrial DNA DAMPs are linked to clinical outcome in severely injured human subjects. Ann Surg. 2013;258(4):591-6; discussion 6-8.
20. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol. 2011;12(3):222-30.
21. Nakahira K, Kyung SY, Rogers AJ, Gazourian L, Youn S, Massaro AF, et al. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. PLoS Med. 2013;10(12):e1001577; discussion e.
22. Lotze MT, Tracey KJ. High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal. Nat Rev Immunol. 2005;5(4):331-42.
23. Silk E, Zhao H, Weng H, Ma D. The role of extracellular histone in organ injury. Cell Death Dis. 2017;8(5):e2812.
24. Ryckman C, Vandal K, Rouleau P, Talbot M, Tessier PA. Proinflammatory activities of S100: proteins S100A8, S100A9, and S100A8/A9 induce neutrophil chemotaxis and adhesion. J Immunol. 2003;170(6):3233-42.
25. Yu M, Wang H, Ding A, Golenbock DT, Latz E, Czura CJ, et al. HMGB1 signals through toll-like receptor (TLR) 4 and TLR2. Shock. 2006;26(2):174-9.
26. Karikó K, Ni H, Capodici J, Lamphier M, Weissman D. mRNA is an endogenous ligand for Toll-like receptor 3. J Biol Chem. 2004;279(13):12542-50.
27. Giordano L, Gregory AD, Pérez Verdaguer M, Ware SA, Harvey H, DeVallance E, et al. Extracellular release of mitochondrial DNA: triggered by cigarette smoke and detected in COPD. Cells. 2022;11(3).
28. Krishnaswamy JK, Chu T, Eisenbarth SC. Beyond pattern recognition: NOD-like receptors in dendritic cells. Trends Immunol. 2013;34(5):224-33.
29. Roh JS, Sohn DH. Damage-associated molecular patterns in inflammatory diseases. Immune Netw. 2018;18(4):e27.
30. Wang B, Han J, Elisseeff JH, Demaria M. The senescence-associated secretory phenotype and its physiological and pathological implications. Nat Rev Mol Cell Biol. 2024;25(12):958-78.
31. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010;5:99-118.
32. Takasugi M, Yoshida Y, Ohtani N. Cellular senescence and the tumour microenvironment. Mol Oncol. 2022;16(18):3333-51.
33. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity. 2012;36(3):401-14.
34. Lin X, Zhou Y, Xue L. Mitochondrial complex I subunit *MT-ND1* mutations affect disease progression. Heliyon. 2024;10(7):e28808.
35. Zhang Q, Itagaki K, Hauser CJ. Mitochondrial DNA is released by shock and activates neutrophils via p38 map kinase. Shock. 2010;34(1):55-9.
36. Bliksøen M, Mariero LH, Torp MK, Baysa A, Ytrehus K, Haugen F, et al. Extracellular mtDNA activates NF-κB via toll-like receptor 9 and induces cell death in cardiomyocytes. Basic Res Cardiol. 2016;111(4):42.
37. Liao Z, Tong B, Ke W, Yang C, Wu X, Lei M. Extracellular vesicles as carriers for mitochondria: biological functions and clinical applications. Mitochondrion. 2024;78:101935.
38. Vikramdeo KS, Anand S, Khan MA, Khushman M, Heslin MJ, Singh S, et al. Detection of mitochondrial DNA mutations in circulating mitochondria-originated extracellular vesicles for potential diagnostic applications in pancreatic adenocarcinoma. Sci Rep. 2022;12(1):18455.

39. Byappanahalli AM, Noren Hooten N, Vannoy M, Mode NA, Ezike N, Zonderman AB, et al. Mitochondrial DNA and inflammatory proteins are higher in extracellular vesicles from frail individuals. Immun Ageing. 2023;20(1):6.
40. Di Florio DN, Sin J, Coronado MJ, Atwal PS, Fairweather D. Sex differences in inflammation, redox biology, mitochondria and autoimmunity. Redox Biol. 2020;31:101482.
41. Koupenova M, Clancy L, Corkrey HA, Freedman JE. Circulating platelets as mediators of immunity, inflammation, and thrombosis. Circ Res. 2018;122(2):337-51.
42. Lee JH, Shim YR, Seo W, Kim MH, Choi WM, Kim HH, et al. Mitochondrial double-stranded RNA in exosome promotes interleukin-17 production through toll-like receptor 3 in alcohol-associated liver injury. Hepatology. 2020;72(2):609-25.
43. Kim KM, Meng Q, Perez de Acha O, Mustapic M, Cheng A, Eren E, et al. Mitochondrial RNA in Alzheimer's disease circulating extracellular vesicles. Front Cell Dev Biol. 2020;8:581882.
44. Hough KP, Trevor JL, Strenkowski JG, Wang Y, Chacko BK, Tousif S, et al. Exosomal transfer of mitochondria from airway myeloid-derived regulatory cells to T cells. Redox Biol. 2018;18:54-64.
45. He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. Nature. 2012;481(7382):511-5.
46. Laker RC, Drake JC, Wilson RJ, Lira VA, Lewellen BM, Ryall KA, et al. AMPK phosphorylation of Ulk1 is required for targeting of mitochondria to lysosomes in exercise-induced mitophagy. Nat Commun. 2017;8(1):548.
47. Halling JF, Pilegaard H. Autophagy-dependent beneficial effects of exercise. Cold Spring Harb Perspect Med. 2017;7(8).
48. Kwon I, Lee Y, Cosio-Lima LM, Cho JY, Yeom DC. Effects of long-term resistance exercise training on autophagy in rat skeletal muscle of chloroquine-induced sporadic inclusion body myositis. J Exerc Nutrition Biochem. 2015;19(3):225-34.
49. Guan Y, Drake JC, Yan Z. Exercise-induced mitophagy in skeletal muscle and heart. Exerc Sport Sci Rev. 2019;47(3):151-6.
50. Eltboli O, Bafadhel M, Hollins F, Wright A, Hargadon B, Kulkarni N, et al. COPD exacerbation severity and frequency is associated with impaired macrophage efferocytosis of eosinophils. BMC Pulm Med. 2014;14:112.
51. Hodge S, Hodge G, Ahern J, Jersmann H, Holmes M, Reynolds PN. Smoking alters alveolar macrophage recognition and phagocytic ability: implications in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2007;37(6):748-55.
52. McCubbrey AL, Curtis JL. Efferocytosis and lung disease. Chest. 2013;143(6):1750-7.
53. Wootton DG, Diggle PJ, Court J, Eneje O, Keogan L, Macfarlane L, et al. Recovery from pneumonia requires efferocytosis which is impaired in smokers and those with low body mass index and enhanced by statins. Thorax. 2016;71(11):1052-4.
54. Vandivier RW, Henson PM, Douglas IS. Burying the dead: the impact of failed apoptotic cell removal (efferocytosis) on chronic inflammatory lung disease. Chest. 2006;129(6):1673-82.
55. Cohen PL, Caricchio R, Abraham V, Camenisch TD, Jennette JC, Roubey RA, et al. Delayed apoptotic cell clearance and lupus-like autoimmunity in mice lacking the C-mer membrane tyrosine kinase. J Exp Med. 2002;196(1):135-40.
56. Khanna S, Biswas S, Shang Y, Collard E, Azad A, Kauh C, et al. Macrophage dysfunction impairs resolution of inflammation in the wounds of diabetic mice. PLoS One. 2010;5(3):e9539.
57. Leung A, Gregory NS, Allen LH, Sluka KA. Regular physical activity prevents chronic pain by altering resident muscle macrophage phenotype and increasing interleukin-10 in mice. Pain. 2016;157(1):70-9.
58. Poon IK, Lucas CD, Rossi AG, Ravichandran KS. Apoptotic cell clearance: basic biology and therapeutic potential. Nat Rev Immunol. 2014;14(3):166-80.
59. Simpson RJ, Lowder TW, Spielmann G, Bigley AB, LaVoy EC, Kunz H. Exercise and the aging immune system. Ageing Res Rev. 2012;11(3):404-20.
60. Donovan T, Bain AL, Tu W, Pyne DB, Rao S. Influence of exercise on exhausted and senescent T Cells: a systematic review. Front Physiol. 2021;12:668327.
61. Shimizu K, Suzuki N, Imai T, Aizawa K, Nanba H, Hanaoka Y, et al. Monocyte and T-cell responses to exercise training in elderly subjects. J Strength Cond Res. 2011;25(9):2565-72.
62. Spielmann G, McFarlin BK, O'Connor DP, Smith PJ, Pircher H, Simpson RJ. Aerobic fitness is associated with lower proportions of senescent blood T-cells in man. Brain Behav Immun. 2011;25(8):1521-9.
63. Xu M, Tchkonia T, Ding H, Ogrodnik M, Lubbers ER, Pirtskhalava T, et al. JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. Proc Natl Acad Sci U S A. 2015;112(46):E6301-10.
64. Robbins PD, Jurk D, Khosla S, Kirkland JL, LeBrasseur NK, Miller JD, et al. Senolytic drugs: reducing senescent cell viability to extend health span. Annu Rev Pharmacol Toxicol. 2021;61:779-803.
65. Whitham M, Parker BL, Friedrichsen M, Hingst JR, Hjorth M, Hughes WE, et al. Extracellular vesicles provide a means for tissue crosstalk during exercise. Cell Metab. 2018;27(1):237-51.e4.
66. Chong MC, Shah AD, Schittenhelm RB, Silva A, James PF, Wu SSX, et al. Acute exercise-induced release of innate immune proteins via small extracellular vesicles changes with aerobic fitness and age. Acta Physiol (Oxf). 2024:e14095.
67. Vechetti IJ, Jr., Valentino T, Mobley CB, McCarthy JJ. The role of extracellular vesicles in skeletal muscle and systematic adaptation to exercise. J Physiol. 2021;599(3):845-61.
68. Xhuti D, Nilsson MI, Manta K, Tarnopolsky MA, Nederveen JP. Circulating exosome-like vesicle and skeletal muscle microRNAs are altered with age and resistance training. J Physiol. 2023;601(22):5051-73.
69. Wang T, Zhang Y, Taaffe DR, Kim JS, Luo H, Yang L, et al. Protective effects of physical activity in colon cancer and underlying mechanisms: a review of epidemiological and biological evidence. Crit Rev Oncol Hematol. 2022;170:103578.
70. Apostolopoulou M, Mastrototaro L, Hartwig S, Pesta D, Straßburger K, de Filippo E, et al. Metabolic responsiveness to training depends on insulin sensitivity and protein content of exosomes in insulin-resistant males. Sci Adv. 2021;7(41):eabi9551.
71. Castaño C, Mirasierra M, Vallejo M, Novials A, Párrizas M. Delivery of muscle-derived exosomal miRNAs induced by HIIT improves insulin sensitivity through down-regulation of hepatic FoxO1 in mice. Proc Natl Acad Sci U S A. 2020;117(48):30335-43.
72. Gallo-Villegas J, Aristizabal JC, Estrada M, Valbuena LH, Narvaez-Sanchez R, Osorio J, et al. Efficacy of high-intensity, low-volume interval training compared to continuous aerobic training on insulin resistance, skeletal muscle structure and function in adults with metabolic syndrome: study protocol for a randomized controlled clinical trial (Intraining-MET). Trials. 2018;19(1):144.

73. Abbasi A, Hutchins E, Meechoovet B, Hall M, Garcia-Mansfield K, Soriano A, et al. Greater enrichment of biological pathways in circulating extracellular vesicles of controls than COPD following exercise. Eur Respir J. 2023;62(suppl 67):PA2273.
74. Bhattacharya P, Dhawan UK, Hussain MT, Singh P, Bhagat KK, Singhal A, et al. Efferocytes release extracellular vesicles to resolve inflammation and tissue injury via prosaposin-GPR37 signaling. Cell Rep. 2023;42(7):112808.
75. Panahi S, Yazdi Z, Sanchouli M, Sajadi F, Motavasselian F, Maghareh Abed H, et al. The role of extracellular vesicles in efferocytosis. Mini Rev Med Chem. 2024;24(6):634-41.
76. Ma Z, Sun Y, Yu Y, Xiao W, Xiao Z, Zhong T, et al. Extracellular vesicles containing MFGE8 from colorectal cancer facilitate macrophage efferocytosis. Cell Commun Signal. 2024;22(1):295.
77. Abbasi A, Vitorino SA, Okerblom J, Hertz JPZ, Wolf A, Indralingam C, et al. Proteomic analysis unveiled exercise-induced changes in extracellular vesicles from BALF And blood In cigarette smoke exposed mice: 3095. Medi Sc Sports Exerc. 2024;56(10S):1122-3.
78. Galvan MD, Foreman DB, Zeng E, Tan JC, Bohlson SS. Complement component C1q regulates macrophage expression of Mer tyrosine kinase to promote clearance of apoptotic cells. J Immunol. 2012;188(8):3716-23.
79. Benoit ME, Clarke EV, Morgado P, Fraser DA, Tenner AJ. Complement protein C1q directs macrophage polarization and limits inflammasome activity during the uptake of apoptotic cells. J Immunol. 2012;188(11):5682-93.
80. Hulsebus HJ, O'Conner SD, Smith EM, Jie C, Bohlson SS. Complement component C1q programs a pro-efferocytic phenotype while limiting TNFα production in primary mouse and human macrophages. Front Immunol. 2016;7:230.
81. Alsina D, Lytovchenko O, Schab A, Atanassov I, Schober FA, Jiang M, et al. FBXL4 deficiency increases mitochondrial removal by autophagy. EMBO Mol Med. 2020;12(7):e11659.
82. Subramaniam S. Exaggerated mitophagy: a weapon of striatal destruction in the brain? Biochem Soc Trans. 2020;48(2):709-17.
83. Kubli DA, Gustafsson Å B. Mitochondria and mitophagy: the yin and yang of cell death control. Circ Res. 2012;111(9):1208-21.
84. Mizumura K, Cloonan SM, Nakahira K, Bhashyam AR, Cervo M, Kitada T, et al. Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. J Clin Invest. 2014;124(9):3987-4003.
85. Hariharan N, Ikeda Y, Hong C, Alcendor RR, Usui S, Gao S, et al. Autophagy plays an essential role in mediating regression of hypertrophy during unloading of the heart. PLoS One. 2013;8(1):e51632.
86. Wong CK, Smith CA, Sakamoto K, Kaminski N, Koff JL, Goldstein DR. Aging impairs alveolar macrophage phagocytosis and increases influenza-induced mortality in mice. J Immunol. 2017;199(3):1060-8.