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Review

Exercise as a Mechanobiological Signal: A Mechanometabolic Framework Linking Force Sensing to Immune Adaptation

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Abstract

Exercise is commonly classified by external dose or metabolic demand, yet each bout also imposes spatially patterned mechanical loads on muscle, vessels, extracellular matrix, stromal niches, and mobile immune cells. This review asks whether that mechanical dimension can be organised into a testable framework linking exercise to immune biology. We conducted a critical mechanistic narrative synthesis of exercise physiology, mechanotransduction, immunometabolism, immune mechanobiology, and exercise epigenetics, with structured searches updated through 31 August 2026 and targeted citation checks through 8 September 2026; the studies underpinning the principal causal claims were appraised in duplicate, and their study-level basis is reported in a supplementary evidence table. Throughout, we label whether a mechanism has been demonstrated during exercise in vivo or only in non-exercise mechanical systems. Exercise-specific mechanosensing is well supported in skeletal muscle and endothelium and supported in stromal compartments, including Piezo1-dependent muscle stromal sensing and mechanosensitive bone-marrow niches, both currently demonstrated in mice. Immune cells also possess force-sensitive machinery, but this has been established almost entirely outside exercise, and direct human evidence for durable immune-cell epigenetic change after exercise is limited, short in duration, and does not establish a mechanical mechanism. We therefore propose the Mechanometabolic Immune Interface Model of Exercise (MIIM-E), a multiroute, falsifiable model that separates endothelium-mediated from leukocyte-intrinsic haemodynamic exposure, tissue-niche mechanotransduction, and systemic biochemical signalling, and that distinguishes tests of necessity, sufficiency, mediation, and incremental explanatory value. Persistence of an immune phenotype and its attribution to a mechanical cause are treated as separate hypotheses to be tested, not as assumed consequences of exercise. Mechanical information may

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contribute to immune adaptation, but its causal role depends on cell type, route, exposure, and persistence.

Keywords: exercise; immune adaptation; mechanobiology; mechanotransduction; mechanometabolism; mechanoimmunology; Piezo1; immunometabolism; YAP/TAZ

1. Introduction

Exercise is simultaneously a behaviour, a whole-body physiological challenge, and a cell-level information system. Clinical and performance science appropriately prescribe exercise through frequency, intensity, time, type, and volume, and often interpret adaptation through energy expenditure, cardiorespiratory fitness, strength, or metabolic risk. At cellular scale, however, tissues receive local physical and chemical perturbations—tension, deformation, shear, calcium transients, ATP turnover, redox shifts, metabolites, hormones, and cytokines-that are not fully represented by external dose descriptors [1–4]. Throughout this review, mechanometabolic denotes the reciprocal coupling between the mechanical state of a cell—force, tension, deformation, adhesion, and matrix context—and its metabolic state, such that mechanical input alters metabolic and redox flux while metabolic condition in turn alters how force is generated, transmitted, and sensed [5]. The term is used in preference to a simple sequence from mechanics to metabolism precisely because the coupling runs in both directions.

The mechanical component of this signal is most explicit in muscle, tendon, and bone, where integrins, focal adhesions, the cytoskeleton, mechanosensitive channels, and YAP/TAZ-related pathways translate physical loading into biochemical responses [6–9]. Exercise mechanics also extends beyond these tissues: vascular cells experience changing shear, while leukocytes migrate, adhere, deform, and form force-dependent immune synapses [10–13]. Thus, the relevant question is not whether exercise is mechanical, but which cells receive which mechanical cues and whether those cues add information beyond metabolic and endocrine exposure.

Two lines of evidence make this reformulation especially timely. Langston and colleagues showed in mice that Piezo1-dependent mechanosensing in muscle mesenchymal stromal cells converts exercise-related mechanical stress into a local inflammatory and myogenic response [14]. Shen and colleagues demonstrated in mice that running sustains a mechanosensitive peri-arteriolar bone-marrow niche that supports lymphopoiesis through stromal Piezo1 signalling [15]. These studies do not establish direct mechanical reprogramming of circulating immune cells; they show that exercise-generated physical information can reach immune biology through intermediate tissues and niches.

A recent synthesis by Maniak, Jenkins, and Hansen reviewed how mechanical forces regulate inflammation across innate immune contexts [16]. The present review addresses a different problem: it anchors mechanical exposure to exercise dose, separates direct haemodynamic, tissue-niche, and systemic biochemical routes, distinguishes acute redistribution from persistent cell-intrinsic change, and specifies exercise experiments capable of falsifying each proposed transition. The contribution is therefore not a new catalogue of mechanosensors, but a route- and persistence-aware framework for causal inference in exercise immunobiology.

Three adjacent 2026 syntheses sharpen the boundary of this contribution. Ortiz and colleagues formalised cellular mechanometabolism as reciprocal coupling between mechanical cues and cellular metabolic state; Zubia-Aranburu and colleagues reviewed force-dependent regulation of T-cell activation, migration, and function; and Phelps and Meisel integrated exerkines, metabolites, catecholamines, and haemodynamic cues within contem-

porary exercise immunology [5,17,18]. Its specific contribution is to place them within an exercise-relevant causal architecture that requires four linked specifications: the mechanical signature of the bout, the cellular receiver and decoder, the route by which the signal reaches immune biology, and the persistence test needed to distinguish transient redistribution from durable cell-intrinsic change. What is new is not the inventory of mechanisms but the requirement that all four be specified jointly before a mechanical explanation is accepted, and the consequence that studies failing to specify them are indeterminate rather than merely incomplete. Section 7.1 gives a worked example of how these four specifications change the design and the interpretation of a specific exercise study.

This distinction is critical because exercise immunology often groups biologically different events under the words reprogramming and adaptation. We use immune adaptation as an umbrella term that must be resolved into three separable levels: a molecular response, meaning a change in transcription, chromatin state, or cellular metabolism; an altered immune function, meaning a measurable change in how cells respond to challenge ex vivo or in vivo; and a demonstrated health benefit, meaning an improved clinical, infectious, or inflammatory outcome. These levels are not equivalent; they are not automatically ordered, and a persistent molecular change is not necessarily functional, let alone beneficial. Acute exercise redistributes immune-cell subsets within minutes; repeated training changes systemic metabolic and inflammatory environments; exercise can alter haematopoietic output and tissue niches; and some studies report epigenetic or transcriptional changes [19–21]. None of these observations alone demonstrates a direct sequence from exercise-generated force to stable chromatin remodelling in a defined human immune-cell lineage. Redistribution is not reprogramming, systemic exposure is not direct mechanosensing, and mechanosensitivity shown outside exercise is not automatically exercise mechanotransduction.

Building on these distinctions, we propose the Mechanometabolic Immune Interface Model of Exercise (MIIM-E). We deliberately use the term model rather than theory: the framework organises plausible and supported routes without assuming that durable immune reprogramming has already been established. Mechanical information may reach immune biology through direct haemodynamic and migratory exposure, through mechanosensitive tissue or haematopoietic niches, or after conversion into systemic metabolic, endocrine, and exerkine signals. Persistent cell-intrinsic reprogramming is one possible downstream state within the model, not a defining premise.

Accordingly, this review asks how exercise-generated mechanical information can plausibly reach immune biology, which transitions are established, context-dependent, emerging, or speculative, and what experiments would distinguish among them. The purpose is not to replace metabolic, endocrine, or inflammatory explanations of exercise adaptation, but to determine when mechanics contributes causal information that those frameworks do not capture.

2. Evidence-Synthesis Approach

2.1. Review Design and Scope

This article is a critical mechanistic narrative review, not a systematic review or meta-analysis. The synthesis was guided by the Scale for the Assessment of Narrative Review Articles (SANRA) as a quality framework for the rationale, search transparency, referencing, scientific reasoning, and presentation of evidence [22]. The objective was to evaluate causal plausibility across mechanobiology, metabolism, and immune adaptation rather than to identify an exhaustive corpus of studies or estimate pooled effects.

The conceptual synthesis was organised around five domains: exercise-generated mechanical exposure; cellular mechanosensing; mechanometabolic and redox integration; immune-cell or immune-niche responses; and persistence versus transient change. Evidence

was interpreted at the level of each causal transition rather than according to pathway popularity or publication volume.

2.2. Literature Identification and Search Transparency

Structured searches of PubMed/MEDLINE, Web of Science Core Collection, Scopus, and the Cochrane Library were used to identify mechanistically informative literature from database inception to 30 April 2026, followed by targeted updates through 31 August 2026. A final targeted citation check on 8 September 2026 was used to capture newly published adjacent conceptual syntheses and recent exercise-immunology literature relevant to the novelty boundary of MIIM-E. Search domains included exercise and physical training, mechanotransduction, integrins and focal adhesions, Piezo1, YAP/TAZ and nuclear mechanics, vascular shear, stromal and haematopoietic niches, immune-cell mechanobiology, mitochondrial and redox signalling, metabolite-sensitive chromatin regulation, exercise epigenetics, leukocyte trafficking, and persistence after training. Database-specific search strings and the final targeted citation-check terms are provided in Supplementary Table S1.

The search was intentionally concept-driven and iterative. It was not conducted as a PRISMA-style systematic selection process; therefore, no claim is made that every eligible publication was captured, and no protocol registration was used. Landmark studies were retained when they established mechanistic principles necessary to interpret later exercise-specific findings, and reference lists of highly relevant primary studies and authoritative reviews were examined for additional mechanistic evidence.

Records were identified, screened, and selected by J.R.V.-S. during the original preparation of the review, and the reports retained for the conceptual synthesis were appraised through the usual narrative process of searching, reading, and citation. For the subset of studies that underpin the principal causal claims, a further appraisal step was applied at that same stage: K.B.T.A. and J.C.B.J. independently read each of those reports in full and extracted study-level descriptors—species or human population, experimental setting, mechanical exposure, cellular target, intervention or perturbation, immune outcome, and duration of follow-up—with any disagreement over inclusion or interpretation resolved by discussion among the three authors. This duplicate appraisal was undertaken when the review was first prepared, although it was inadvertently omitted from the Methods of the original submission. It was deliberately restricted to those studies, rather than extended to the whole reference list, because the remaining literature supports conceptual and background statements for which duplicate extraction is not informative in a narrative rather than systematic review. No language restriction was applied at any stage; all studies meeting the conceptual criteria were published in English, which reflects the composition of the retrieved mechanistic literature rather than a selection rule. No restriction was placed on publication type, although primary experimental reports were prioritised over reviews for mechanistic claims, as described in Section 2.3. Where studies reached discrepant conclusions, both findings are reported in the text together with the methodological feature—species, mechanical exposure, cell population, or sampling time—that most plausibly accounts for the discrepancy; conflicting findings were not resolved by vote counting or by preferring the larger literature. The study-level descriptors extracted for the studies underpinning the principal causal claims are reported in Supplementary Table S2.

2.3. Evidence Selection and Prioritisation

Priority was given to studies that experimentally manipulated exercise, mechanical loading, or a proposed mechanosensor and directly measured the relevant cell, tissue, or signalling route. Human exercise studies were prioritised for claims about human physiology; animal and cell models were used when they provided causal resolution not

currently feasible in humans. Reviews were used primarily to establish field context or identify primary evidence, not as substitutes for mechanistic experiments.

Evidence was interpreted more cautiously when mechanosensitivity was demonstrated outside an exercise context, when downstream immune effects were observed without measurement of the proposed upstream route, or when conclusions depended on extrapolation across tissues. Whole-blood and bulk-leukocyte studies were treated as vulnerable to compositional confounding because exercise-induced redistribution can produce apparent molecular differences without durable cell-intrinsic change [23,24].

Five ambiguities were considered explicitly throughout the review: direct versus indirect mechanosensing; tissue-specific versus systemic signalling; acute redistribution versus persistent cellular change; local versus circulating metabolite exposure; and experimentally demonstrated versus inferred epigenetic regulation.

2.4. Evidence-Maturity Framework

Each major transition was classified into one of five categories: established; supported but context-dependent; emerging; plausible but incompletely tested; or speculative. Established required convergent mechanistic and physiological evidence, including human data when the claim concerned human exercise physiology. Supported but context-dependent denoted direct evidence restricted by tissue, model, modality, or species. Emerging denoted experimentally supported mechanisms lacking complete exercise-specific or human causal validation. Plausible but incompletely tested was applied where the individual components are well described, and the overall relationship is physiologically expected, but the specific contrast has not been tested systematically; it differs from speculative in that the missing evidence is a matter of unperformed experiments rather than of an unverified causal sequence. Speculative was reserved for biologically plausible transitions for which the complete causal sequence has not been demonstrated. These five categories are used in the article. Where central claims are made in the text, the species and maturity category of the supporting evidence are stated. The categories are author-developed narrative descriptors used for interpretive transparency; they are not a validated certainty instrument, formal risk-of-bias tool, or GRADE assessment.

Evidence maturity was assigned to individual transitions rather than to MIIM-E as a whole. Mechanosensing in skeletal muscle does not establish mechanically induced chromatin remodelling in lymphocytes, and exercise-induced changes in haematopoietic progenitors do not identify mechanical loading as the upstream cause unless that route is isolated experimentally.

Two labelling conventions follow from this framework and are applied throughout. First, every mechanistic claim is marked according to whether the supporting evidence was generated during exercise in vivo, in a non-exercise mechanical system such as isolated cells, engineered matrices, direct tissue loading, or pharmacological channel activation, or by inference across the two. Demonstrating that a cell can respond to force is not equivalent to demonstrating that the forces generated during exercise engage that response at physiological magnitude and duration, and in most non-exercise systems the applied forces have not been calibrated against exercise exposures. Second, the persistence of an immune phenotype and its attribution to a mechanical cause are classified separately, because a change may be convincingly durable while its upstream cause remains unidentified, and a cause may be convincingly mechanical while the resulting change is transient. Consequently, some of the representations constructed to illustrate our findings present persistence and attribution to a mechanical cause as distinct assessments, rather than as a single, unified status.

2.5. Mechanistic Synthesis and Causal Interpretation

For each proposed transition we asked: what signal was manipulated; which cell or tissue received it; whether the proposed sensor or mediator was measured or perturbed; whether the phenotype persisted beyond acute exposure; and which alternative explanations remained plausible. Causal claims were narrowed whenever the available evidence did not resolve these questions.

Accordingly, circulating metabolite changes were not treated as evidence of equivalent nuclear exposure in immune cells; skeletal-muscle epigenetic responses were not used as surrogates for immune-cell chromatin; and shifts in circulating leukocyte composition were not interpreted as persistent reprogramming without cell-resolved evidence. This conservative approach is central to the model: uncertainty is retained as an experimental target rather than resolved by a linear pathway diagram.

The resulting evidence hierarchy is summarised in Section 7.2; the study-level basis of the transitions carrying the strongest causal claims is provided in Supplementary Table S2; and the full search strategies are provided for transparency in Supplementary Table S1.

2.6. Use of Generative Artificial Intelligence

OpenAI ChatGPT (GPT-5.6 Sol; OpenAI, San Francisco, CA, USA) was used during manuscript preparation for three distinct purposes: (1) language refinement of author-written text; (2) structural editing and consistency checking of terminology and cross-references; and (3) assistance with the graphical layout and rendering of the schematic Figures 1–4. Anthropic Claude (Claude Opus 5; Anthropic, San Francisco, CA, USA) was used before submission to check internal consistency, figure and table cross-references, and formatting, and to draft minor text revisions. During revision following peer review, Anthropic Claude was additionally used to support text editing, to assist an audit of citation–claim alignment, and to draft the structure of Supplementary Table S2. Every entry in that table was subsequently verified against the full text of the primary report by the authors, and the remaining citation–claim pairs were checked against their cited sources; the authors validated or rejected each suggestion. Neither tool was used to generate data, and no tool is an author. The figures are qualitative conceptual schematics that contain no quantitative data; they were produced by the authors, whose scientific content was defined by the authors. The authors reviewed all AI-assisted text and take full responsibility for the manuscript.

3. Exercise as a Multiscale Mechanobiological Perturbation

3.1. Mechanical Information Is Distributed Across Tissues

Exercise generates multiple mechanical variables simultaneously. Muscle experiences active tension and matrix strain, tendons transmit load, and bone senses strain and fluid movement [6,9,25,26]. At the same time, vascular cells experience changing shear and pressure, while stromal and mobile immune cells encounter changes in geometry, adhesion, deformation, and interstitial flow [10,12,16]. The relevant mechanical dose is therefore spatially distributed and cell-specific.

These components scale differently across exercise modalities, although the magnitude of each depends on the specific protocol rather than on the modality label. Resistance exercise emphasises local contractile tension and matrix strain, with the highest tensile exposures occurring at heavy relative loads, of the order of 70–90% of one-repetition maximum, and during the eccentric phase, while vascular shear is comparatively modest and intermittent because work periods are short and the pressor response dominates. Continuous running at moderate-to-vigorous intensity, of the order of 65–85% of maximal oxygen uptake, adds repetitive impact and ground-reaction loading together with sustained elevations in conduit-

artery shear. Cycling at a comparable relative intensity preserves rhythmic contractile and vascular loading with substantially lower impact, which is why it is frequently chosen as the lower-impact comparator in matched-workload designs. Aquatic and low-impact land-based exercise should not be treated as interchangeable: immersion adds hydrostatic compression and a central redistribution of blood volume that non-immersed low-impact exercise does not, whereas both reduce ground-reaction loading relative to running. Metabolic intensity therefore cannot be assumed to represent mechanical intensity [12,27,28].

Figure 1 summarises these differences as qualitative, protocol-conditional hypotheses rather than as fixed properties of each modality.

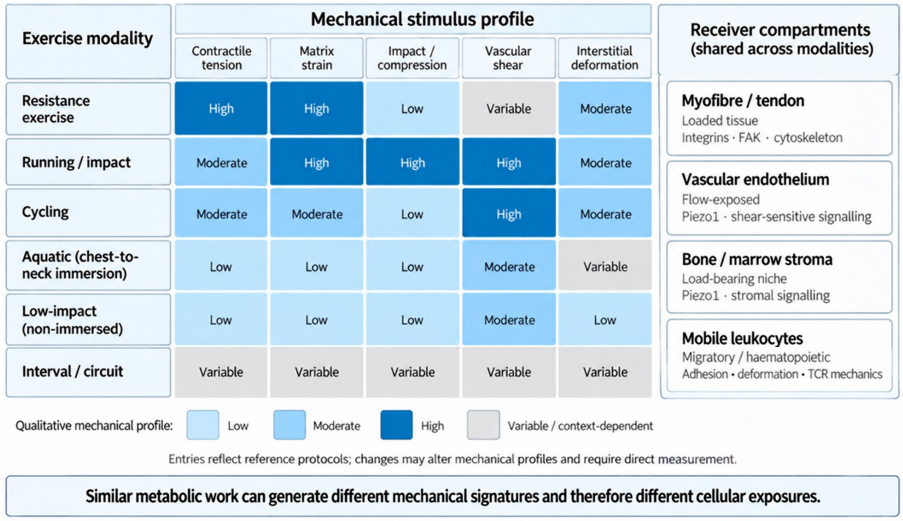


Figure 1. Conceptual, protocol-conditional mechanical signatures of exercise. Exercise modalities differ in their relative contributions of contractile tension, matrix strain, impact and compression, vascular shear, and interstitial deformation. Entries are qualitative hypotheses, not quantitative dose estimates, and are conditional on the reference protocols assumed here: resistance exercise at approximately 70–90% of one-repetition maximum, for which vascular shear is marked variable because it is not determined by relative load alone; running and cycling at approximately 65–85% of maximal oxygen uptake performed continuously; and aquatic exercise at chest-to-neck immersion. Entries that cannot be assigned without further protocol detail are marked variable, and interval or circuit exercise is shown as protocol-dependent throughout because its mechanical profile cannot be inferred from interval structure alone. Aquatic and low-impact exercise are presented as distinct categories because immersion adds hydrostatic compression and central blood-volume shifts that non-immersed low-impact exercise does not. The receiver panel lists a shared set of compartments and candidate mechanosensory systems available in principle to every modality; its horizontal alignment with the modality rows is presentational only and does not indicate a modality-specific or exclusive mapping, and no downstream immune outcome is assigned. Similar metabolic work can therefore produce different cellular mechanical exposures. Abbreviations: FAK, focal adhesion kinase; Piezo1, Piezo-type mechanosensitive ion channel component 1; TCR, T-cell receptor. Category assignments reflect the authors' qualitative synthesis of the modality-specific literature cited in Section 3.1 [10,12,25–28] and should be read as hypotheses for measurement rather than as established rankings.

The entries assume the reference protocols stated in the legend; changes in relative load, cadence, contraction mode, immersion depth, or work-to-rest ratio may alter their qualitative classifications, but the direction and magnitude of these changes cannot be specified without direct measurement. Entries that cannot be assigned without sufficient protocol detail are marked as variable. Vascular shear is marked variable for resistance exercise rather than assigned a fixed category, because it depends strongly on the protocol: heavy-load, short-set schemes have a brief duty cycle and an intramuscular pressure that intermittently impedes perfusion, whereas higher-repetition, shorter-rest schemes generate

a substantially greater shear stimulus. Interstitial deformation is classified as variable during aquatic exercise because chest-to-neck immersion changes hydrostatic pressure and fluid distribution without establishing the magnitude of local interstitial tissue deformation. Non-immersed low-impact exercise is presented separately because it lacks immersion-related hydrostatic loading. Interval structure alone cannot define a mechanical profile, because cycling-, running-, and circuit-based interval protocols load tissues differently. The receiver compartments shown alongside the modalities are a shared set available in principle to every modality, not a modality-specific assignment: no exclusive mapping between a given modality and a given receiver is implied or supported by the cited evidence.

Each of these dimensions can, in principle, be measured rather than inferred, provided the measured quantity is not confused with the biological variable of interest. External load and joint torque are proxies for local contractile exposure rather than measurements of it, because the force actually experienced by a given fibre, adhesion complex, or matrix domain depends on muscle architecture, moment arm, regional recruitment, and local tissue compliance. Tissue strain should be distinguished from tissue stiffness assessed by elastography: ultrasound speckle tracking or elastographic strain imaging estimates how much a tissue deforms under a given load, whereas shear-wave elastography estimates a material property of the tissue that conditions how any load is converted into deformation. The two can move in opposite directions, and a stiffer tissue exposed to the same external load experiences less strain. Impact and compression can be indexed by ground-reaction force magnitude and loading rate. For the vasculature, Doppler ultrasound yields blood velocity and arterial diameter, from which wall shear rate is calculated; wall shear stress is the product of wall shear rate and blood viscosity and therefore requires viscosity to be measured or assumed, so studies that do not measure viscosity should report wall shear rate rather than describe their outcome as shear stress [10,12]. Interstitial deformation remains the least tractable and is currently approached only indirectly, through changes in tissue pressure, volume, or fluid flow. Studies that report these internal mechanical variables alongside external dose and metabolic demand are needed to test whether the qualitative profiles in Figure 1 hold.

3.2. Mechanotransduction Is Not Restricted to Muscle Fibres

In skeletal muscle, integrin/focal-adhesion complexes, the cytoskeleton, mechanosensitive channels, and YAP/TAZ-related systems couple tissue loading to intracellular signalling [6–8]. Comparable principles operate in other mechanically exposed cells, but the relevant sensor architecture differs by cell type and microenvironment [11,29–31].

Langston and colleagues provided direct exercise-specific evidence in mice, using a single 90-min moderate-intensity treadmill bout and two weeks of voluntary wheel running, that muscle mesenchymal stromal cells sense mechanical stress through Piezo1 and use that information to shape local inflammatory and myogenic responses, with Piezo1 deleted conditionally in the PDGFRα-positive stromal compartment [14] (mouse; exercise in vivo; supported but context-dependent). The result is important because it locates mechanosensing in an immune-relevant stromal compartment rather than only in the myofibre, while also showing that transient inflammatory signalling can be adaptive rather than intrinsically pathological [14,16]. The study does not, however, show direct mechanosensing by an immune cell: the mechanosensing cell is a resident stromal population, not a circulating leukocyte, so the immune consequence is an indirect one, and the demonstration is in mice.

A related architecture is evident in bone marrow. In mice, voluntary running sustains osteolectin-positive peri-arteriolar stromal cells and common lymphoid progenitors in load-bearing bone, whereas unloading or Piezo1 deletion in the osteogenic progenitor population disrupts the niche [15] (preclinical; supported but context-dependent). The immune

consequence therefore arises through a mechanically regulated stromal intermediate rather than direct loading of mature lymphocytes.

Together, these findings argue against a universal "exercise mechanosensor". The same physical perturbation can be decoded differently by myofibres, endothelial cells, stromal progenitors, or immune cells; mechanotransduction is a property of the cell–microenvironment system, not of the stimulus alone [8,11,29,30].

3.3. Mechanical and Metabolic Signals Are Generated Together

Mechanical work and metabolic demand are physiologically coupled. Cross-bridge cycling consumes ATP, excitation–contraction coupling generates calcium transients, perfusion alters substrate delivery, and mitochondrial and redox signalling change within the same bout [1–3]. MIIM-E therefore treats mechanics as an additional information dimension, not as a universal chronological event that necessarily precedes metabolism.

The decisive experimental question is whether changing mechanics, while holding competing exposures as constant as feasible, changes downstream biology. Matching metabolic demand is a necessary but not a sufficient condition for isolating a mechanical mechanism. Exercise conditions that differ mechanically also commonly differ in the muscle mass recruited, contraction mode, tissue damage, perfusion and reperfusion kinetics, core and local temperature, catecholamine and cortisol responses, and the time course of metabolite appearance. A credible dissociation design must therefore measure these competing exposures rather than assume that matching external or metabolic work has equalised them. Designs that dissociate eccentric from concentric loading in contralateral limbs of the same participant, alter vascular shear directly by cuff, or selectively perturb a mechanosensor in an exercise-relevant cell population are consequently more informative than simple pre-to-post comparisons [12,14,15,27]; worked examples of a human and a mechanistic design built on this principle are developed in Section 8.

3.4. Repetition Converts Perturbation into a Training History

A single bout changes regulated variables; repeated bouts change the response to subsequent bouts. Training remodels mitochondrial content, vascular function, extracellular matrix, and transcriptional responsiveness, creating a history-dependent substrate for later mechanosensing [3,32].

That history is clinically relevant because ageing and chronic disease alter matrix composition, fibrosis, vascular function, and stromal state. The same external exercise prescription may therefore produce different intracellular mechanical information in compliant versus stiff or inflamed tissues [25,33–35]. This provides a mechanobiological route to response heterogeneity without assuming that all variation is genetic or behavioural.

4. From Force Sensing to Nuclear and Metabolic Regulation

4.1. Integrins, Focal Adhesions, and the Cytoskeleton Form a Continuous Force-Transmission Network

Mechanotransduction begins when physical forces alter molecular conformation, membrane tension, receptor clustering, or cytoskeletal organisation. Integrins link extracellular-matrix proteins to actin through focal-adhesion complexes that recruit focal adhesion kinase, Src-family kinases, and Rho-family GTPases; in muscle, costameric structures couple the contractile apparatus to the extracellular matrix, whereas in stromal and endothelial cells analogous adhesion complexes integrate matrix stiffness, shear, and cell shape [6,8,27,36]. Cytoskeletal tension can propagate to the nucleus through linker of nucleoskeleton and cytoskeleton complexes, altering nuclear shape, nuclear pore transport, and chromatin organisation; YAP/TAZ is one of the clearest examples of a transcriptional system sensitive

to cell geometry, substrate rigidity, and actomyosin tension [8]. A force imposed at tissue scale can therefore, in principle, influence transcription without first being converted into a circulating endocrine signal [30,31].

How far this direct force-to-nucleus route operates in vivo depends on the target cell: a myofibre in contracting tissue, an endothelial cell exposed to shear, and a lymphocyte moving through blood do not share the same force-transmission architecture. MIIM-E therefore treats cellular mechanical context as a necessary explanatory variable rather than assuming a single-cell template.

4.2. Piezo1 Converts Membrane Mechanics into Calcium-Dependent Information

Piezo1 is a particularly relevant exercise mechanosensor because it couples membrane tension directly to cation influx; the resulting calcium signal engages calmodulin-dependent kinases, phosphatases, cytoskeletal remodelling, mitochondrial function, and transcriptional regulators. Exercise-relevant Piezo1 signalling has been described in skeletal-muscle stromal cells, bone-marrow osteogenic progenitors, and endothelial cells responding to activity-related haemodynamics [14,15,29,37]. Piezo1 is not a universal gatekeeper of exercise adaptation; rather, it illustrates that forces are decoded by receptors whose distribution is cell-specific, so exercise mechanosensing should be tested at the level of a defined receptor–cell pair rather than a generic whole-tissue marker.

4.3. YAP/TAZ and Nuclear Mechanics Link Physical Context to Transcriptional Competence

YAP/TAZ signalling is often presented as a linear mechanical pathway, but its activity integrates matrix stiffness, cell spreading, polarity, cytoskeletal tension, growth-factor signalling, and metabolic state [8]. The supporting evidence is cell-type specific and is attributed accordingly below. In skeletal muscle, YAP participates in mechanotransduction and growth-related programmes [7,36], and injury-induced stiffening persistently activates muscle stem cells through YAP and TAZ [38] (mouse and ex vivo; non-exercise mechanical system). In T cells, matrix stiffening arising from collagen fibril density and alignment modulates YAP-mediated immune suppression in three-dimensional culture [39], and force-dependent regulation of T-cell activation and migration has been reviewed comprehensively [17]; in tumour-infiltrating regulatory T cells, a stiff matrix alters YAP-dependent mitochondrial metabolism [40] (human and mouse cells in vitro and in tumour models; non-exercise). In macrophages, YAP-mediated mechanotransduction tunes the inflammatory response to substrate stiffness [41] (mouse macrophages in vitro; non-exercise). None of these systems applied an exercise stimulus, and none calibrated the applied forces against those generated during exercise. The implication for exercise is therefore not that every bout drives YAP into immune-cell nuclei, but that exercise-induced remodelling of matrix organisation, stromal activity, and vascular function may change the mechanical niche, and thus the transcriptional competence, of immune cells that enter or reside in those tissues—a proposition that remains to be tested directly [16].

4.4. Mechanotransduction and Metabolism Converge at Mitochondria and Chromatin-Regulatory Systems

Force sensing rapidly intersects with energetic and redox signalling. AMPK responds to cellular energetic stress; calcium-sensitive pathways communicate contraction patterns; mitochondrial flux changes NADH/NAD+ balance, reactive oxygen species, and metabolite availability; and YAP/TAZ itself can interact with metabolic programmes. Exercise therefore generates a coupled mechanometabolic state rather than independent “mechanical” and “metabolic” streams [3,42–44].

MIIM-E extends this logic to epigenetic regulation: NAD+, acetyl-CoA, lactate, α-ketoglutarate, succinate and fumarate can influence sirtuins, histone acetylation, DNA/histone demethylation or other chromatin-associated processes under appropriate cellular conditions [45–48]. Human skeletal muscle studies show that acute and chronic exercise can alter DNA methylation and histone-related processes, establishing that exercise can indeed reach the epigenetic layer in a mechanically and metabolically active tissue [49–51].

The inferential limits of this coupling are, however, strict. Mitochondrial acetyl-CoA does not simply diffuse into a lymphocyte nucleus; lactate accumulation in blood does not prove histone lactylation in an immune-cell subset; and skeletal-muscle methylation cannot be used as a surrogate for immune chromatin. Nuclear metabolite pools are compartmentalised, transporter expression differs by cell type, and chromatin effects depend on concentration and exposure duration. Figure 2 therefore depicts mechanometabolic coupling as a set of conditional gates rather than a guaranteed linear cascade, and shows the reciprocal arm of the relationship explicitly: metabolic and redox state feed back on cytoskeletal tension, adhesion turnover, matrix remodelling, and mechanosensor expression, so the left-to-right arrangement of the panel is a reading order and not a claim of unidirectional causality [44,52–54].

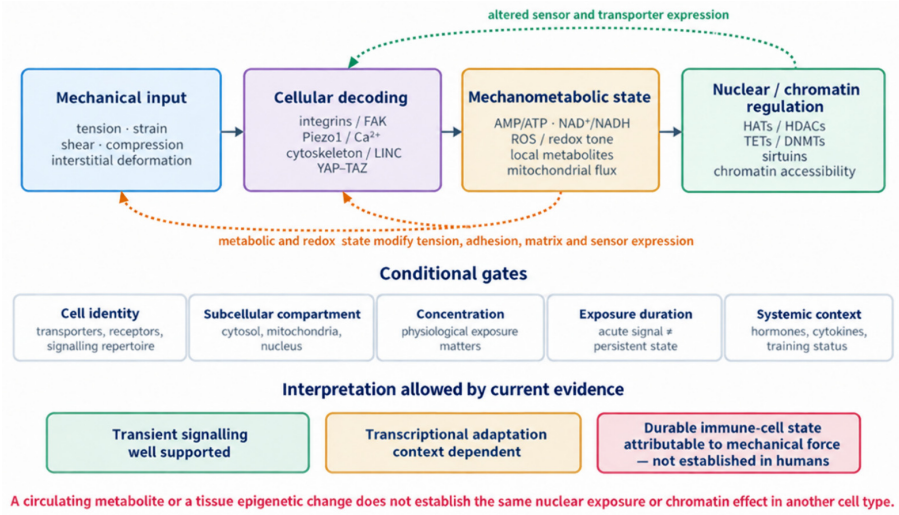


Figure 2. Conditional and reciprocal coupling between mechanosensing, metabolism, and chromatin regulation. Mechanical signals can be converted into calcium-dependent, cytoskeletal, mitochondrial, redox, and metabolic responses, but downstream chromatin effects are not automatic. The coupling is bidirectional: metabolic and redox state in turn modify cytoskeletal tension, adhesion dynamics, matrix remodelling, and mechanosensor expression, and the feedback arrows indicate that the panels must not be read as a one-directional cascade from mechanics to chromatin. Mechanometabolic and epigenetic coupling depends on cell identity, transporter and receptor expression, subcellular compartmentalisation, metabolite concentration, exposure duration, and systemic context; consequently, metabolite changes measured in one tissue cannot be assumed to reproduce equivalent nuclear effects in another. The statement that a durable immune-cell state is not established in humans refers specifically to persistence attributable to a mechanical cause, which is distinguished throughout from the separate question of whether exercise-associated persistence occurs at all. Abbreviations: AMP/ATP, adenosine monophosphate and adenosine triphosphate; Ca^{2+}, calcium ion; DNMT, DNA methyltransferase; FAK, focal adhesion kinase; HAT, histone acetyltransferase; HDAC, histone deacetylase; LINC, linker of nucleoskeleton and cytoskeleton; NAD+/NADH, oxidised and reduced nicotinamide adenine dinucleotide; Piezo1, Piezo-type mechanosensitive ion channel component 1; ROS, reactive oxygen species; TET, ten-eleven translocation methylcytosine dioxygenase; YAP–TAZ, Yes-associated protein and transcriptional coactivator with PDZ-binding motif.

5. How Exercise Mechanics Can Reach Immune Biology

5.1. Route I: Direct Haemodynamic and Migratory Forces

Route I groups two causal sequences that share a haemodynamic origin but differ in where the force is actually sensed, and MIIM-E therefore subdivides it. In Route Ia the mechanical signal is received by the endothelium, which subsequently alters leukocyte behaviour through adhesion-molecule expression, nitric oxide and prostanoid release, glycocalyx remodelling, and chemokine presentation; the immune cell in this sequence responds to a biochemical and adhesive output of endothelial mechanotransduction rather than to force itself. In Route Ib, the circulating or marginated leukocyte is itself the mechanosensor, deforming under shear, adhesive tethering, and passage through capillaries and constricted interstitial spaces. The distinction matters because the two sequences predict different experiments: Route Ia is tested by perturbing endothelial sensing or its soluble and adhesive output; Route Ib only by a leukocyte-restricted perturbation. Endothelial shear sensing during exercise is well characterised in humans [10,12,28,55] (human; exercise in vivo; established), whereas the independent contribution of leukocyte mechanosensing during exercise has not been isolated in any species.

The haemodynamic exposure itself is substantial. Increased cardiac output modifies blood velocity, vascular shear, pressure, and endothelial adhesion dynamics. Exercise also rapidly changes catecholamine concentrations and vascular margination, mobilising leukocyte subsets with strong dependence on cell phenotype and adrenergic sensitivity [56,57]. Cells subsequently deform as they traverse capillaries, adhere to endothelium, extravasate, and migrate through mechanically heterogeneous tissues [10,12,58,59].

These events make direct mechanical effects plausible, but difficult to separate from endothelial mediation, neuroendocrine signalling, and trafficking. The evidence that acute exercise alters leukocyte trafficking is strong and reproducible, yet it does not establish that leukocytes sense exercise forces directly, because catecholamine-driven demargination and endothelial activation predict the same observation. Distinguishing Route Ia from Route Ib therefore requires either a leukocyte-restricted perturbation of a candidate sensor or a design in which endothelial output and adrenergic drive are measured and separated analytically from the shear exposure itself. A further confound is compositional: a post-exercise blood sample can show a large shift in gene expression simply because the proportions of naïve, effector-memory, natural killer, or monocyte subsets have changed. Unless studies purify defined cell populations and account for redistribution, apparent reprogramming can be a compositional artefact. This is one reason why evidence for exercise-induced immune-cell epigenetic change must be interpreted more cautiously than tissue-level exercise epigenetics [19,20,23,24].

5.2. Route II: Mechanosensitive Tissue and Haematopoietic Niches

The strongest new support for a mechanics-to-immunity pathway lies in tissue intermediates. In muscle, Piezo1-dependent mechanosensing by mesenchymal stromal cells converts exercise-related mechanical stress into local inflammatory activation and contributes to the timing of myogenic responses [14] (preclinical; supported but context-dependent). In bone marrow, mechanical stimulation of osteolectin-positive stromal cells supports a lymphopoietic niche: four weeks of voluntary running increased, and two weeks of hindlimb unloading decreased, common lymphoid progenitors in load-bearing bone, through a mechanism requiring inducible Piezo1 deletion in osteolectin-positive cells to abolish [15] (preclinical; supported but context-dependent). These are mechanistically distinct systems, but they share a crucial architecture: exercise mechanics is first decoded by a resident structural/stromal cell, which then modifies an immune-relevant microenvironment [16].

This route offers a plausible way to explain how mechanical loading can influence immunity without requiring direct mechanical reprogramming of mature circulating lymphocytes. It also helps reconcile apparently contradictory exercise effects. Local inflammation initiated by mechanosensing may be adaptive when temporally resolved and linked to repair, whereas chronic tissue stiffness and persistent mechanosensory activation during ageing can contribute to inflammatory dysregulation [14]. The relevant outcome is therefore not "more" or "less" inflammation, but whether the mechanical response is appropriately timed, spatially restricted and resolved [16,38,60].

Exercise can also modify haematopoiesis through non-mechanical systemic routes. Frodermann and colleagues showed in mice that voluntary running decreased inflammatory leukocyte production by altering adipose leptin signalling to the bone-marrow niche, with persistent transcriptomic and epigenomic effects in haematopoietic progenitors after wheel withdrawal [21] (mouse; exercise in vivo; durable, but without mechanical attribution). This study does not establish a direct mechanical mechanism, and the identified mediator is explicitly metabolic rather than mechanical; it is nonetheless important for MIIM-E because it demonstrates that exercise can produce durable upstream changes in immune-cell production. Read together with the mechanically regulated peri-arteriolar niche described by Shen and colleagues, it indicates that the bone marrow integrates both mechanically derived and systemic metabolic information, and that the two can be dissociated experimentally [15,21].

5.3. Route III: Systemic Mechanometabolic and Exerkine Signalling

An exercise bout simultaneously generates mechanical and metabolic perturbations that can be translated into biochemical signals far beyond the loaded tissue. Contracting muscle releases myokines and metabolites; adipose tissue, liver, endothelium, bone and other organs contribute to the circulating exerkine network; and catecholamines, cortisol, lactate, free fatty acids and cytokines alter immune-cell state [4,61–63]. In this route, the immune target is exposed to soluble or metabolic signals generated during exercise rather than to the original tissue force itself [64]. Whether the mechanical component is causally necessary for any specific systemic mediator must be established experimentally.

This distinction preserves causal clarity. If a lymphocyte changes because it was exposed to catecholamines, lactate, or IL-6 during exercise, the biological effect is exercise-dependent but does not by itself demonstrate lymphocyte mechanotransduction. MIIM-E therefore separates systemic biochemical communication during coupled mechanical-metabolic exercise exposure from direct immune-cell mechanosensing. Both can contribute to the final phenotype, but they make different predictions and require different experiments.

5.4. Immune Cells Are Mechanosensitive, but Exercise-Specific Validation Remains Incomplete

Independent of exercise, immune cells are demonstrably mechanosensitive, although the evidence is strongly cell-type specific and almost entirely non-exercise. In T cells, receptor signalling is force-dependent; catch-bond behaviour and receptor deformation contribute to antigen discrimination, and cytoskeletal tension shapes immune-synapse function [11,13,17,65–69]. In myeloid cells, the relevant evidence is separate: Piezo1 transduces cyclical force in monocytes and macrophages and is required for normal innate immune function in vivo [70]; Piezo1 also modulates macrophage polarisation and substrate-stiffness sensing [71]; matrix stiffness tunes the macrophage inflammatory response through YAP-mediated mechanotransduction [41]; and stiffness regulates macrophage polarisation through a Piezo1–YAP axis [72]. Extracellular-matrix properties likewise influence leukocyte migration and activation [16,39].

The logical error would be to treat this general mechanosensitivity as proof that exercise-derived forces directly reprogramme those cells in vivo. The relevant mechanical environ-

ment during exercise must be specified: blood shear, endothelial contact, tissue stiffness, interstitial flow, immune-synapse force, or migration through constricted spaces. It is also necessary to establish whether the magnitude and duration of those forces are sufficient to produce persistent functional change rather than transient activation, and whether the forces applied in the non-exercise systems cited above fall within the range generated during exercise. In most cases, that comparison has not been attempted, and until it is, the inference from mechanosensitivity to exercise mechanotransduction remains an extrapolation [13,16,68,69].

Figure 3 integrates these three routes.

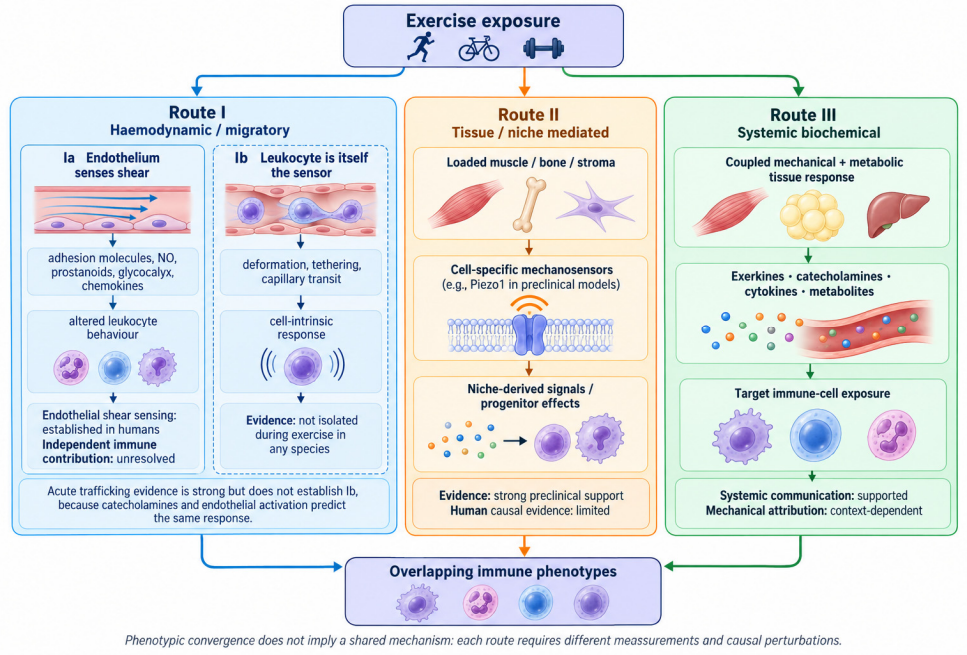


Figure 3. Mechanistically distinct routes by which exercise-associated mechanical information may influence immune biology. Route I represents direct haemodynamic exposure and is subdivided into Route Ia, in which the endothelium senses shear and pressure and subsequently alters leukocyte behaviour through adhesive and soluble output, and Route Ib, in which the circulating or marginated leukocyte is itself the mechanosensor. Endothelial shear sensing is established in humans, whereas an independent immune contribution from this route during exercise remains unresolved. Route II represents mechanotransduction within loaded tissues and haematopoietic or stromal niches. Route III represents systemic biochemical communication arising during coupled mechanical and metabolic exercise exposure. Evidence for acute exercise-induced leukocyte trafficking is strong; however, because catecholamine-driven demargination and endothelial activation predict the same response, that evidence does not establish an independent contribution of leukocyte mechanosensing, and Route Ib accordingly remains unresolved during exercise. Whether the upstream cause of a Route III mediator is mechanical, metabolic, or both remains context-dependent and requires experimental attribution. Although these routes may converge on overlapping immune phenotypes, they require different measurements and causal perturbations and must not be treated as mechanistically interchangeable. Abbreviations: NO, nitric oxide; Piezo1, Piezo-type mechanosensitive ion channel component 1.

The distinction between them determines what should be measured, which cell should be isolated, and which causal perturbation would be informative.

6. From Redistribution to Durable Immune Reprogramming: The Causal Bottleneck

Exercise immunology has an extensive literature on changes in circulating leukocyte number, subset distribution, and function. Acute exercise preferentially mobilises highly

differentiated CD8+ and NK-cell populations through haemodynamic and catecholamine-dependent mechanisms [56,57,59]. These responses are biologically meaningful for surveillance and trafficking, but their rapid reversibility means that they should not be labelled durable cellular reprogramming.

A stricter definition of reprogramming requires persistence beyond the initiating exposure and evidence that the altered state is cell intrinsic rather than a consequence of changing cell composition, replacement from bone marrow, or continued systemic exposure. Relevant readouts include chromatin accessibility, locus-specific DNA methylation, histone modifications, persistent metabolic state, altered response to ex vivo restimulation, or stable transcriptional programmes in purified cell populations [19,20,23,24].

Operationally, three mechanisms should be distinguished. Redistribution changes which cells are present in blood without requiring a durable change within any cell. Replacement changes the circulating population through altered production, survival, or tissue egress. Reprogramming is the strongest claim: a defined cell population retains a molecular or functional state after the initiating exercise environment has resolved. These mechanisms can coexist, but they are not interchangeable, and blood-level molecular change cannot identify which one occurred without cell-resolved sampling and temporal follow-up [19,20,23,24].

Direct human evidence in mature immune cells remains limited, and the two principal studies address different questions. Zimmer and colleagues reported increased histone H4K5 acetylation and NKG2D expression in natural killer cells isolated after an official half-marathon, with the change still detectable at 24 h, providing proof-of-principle that an exercise bout can be associated with an epigenetic change in a defined immune population [73] (human; exercise in vivo; emerging). The cohort comprised 14 cancer survivors and 14 sex- and age-matched healthy controls of about 51 years, so it is not a general healthy population; the sample was small; no mechanical variable was measured or manipulated; and persistence to 24 h is not equivalent to long-term cellular memory.

Schenk and colleagues reported genome-wide DNA-methylation changes in natural killer cells after acute aerobic exercise [19]. Its design requires specific qualification. It was an explicitly designated pilot in five healthy women aged 61.4 ± 8.0 years, who performed an incremental cycle-ergometer test to exhaustion, and blood was drawn immediately before and one minute after the bout. A sample taken one minute after exercise captures the acute response and cannot, by design, address persistence at any level; neither can it distinguish a methylation change occurring within the sampled cells from the arrival in the circulation, during the same bout, of a differently methylated population. The authors did measure natural killer subset composition, which is the appropriate control and makes this study more informative than a whole-blood analysis. Nevertheless, because exercise mobilises CD56dim and CD56bright subsets differentially and within precisely this time frame, a residual compositional contribution to a bulk methylation signal cannot be excluded in a sample of this size, and sorting at the level of the broad natural killer gate does not resolve heterogeneity within it. The study is therefore best described as evidence of an acute, exercise-associated methylation signal in a defined immune population, with persistence untested and mechanical attribution absent. Comparable qualifications, with the additional problem of unmeasured subset composition, apply to leukocyte epigenetic and non-coding-RNA studies performed in mixed populations [20,74].

These limitations motivate an explicit four-level classification of what has actually been demonstrated, which should be applied before any finding is described as persistent. Level 1 is acute epigenetic change, detectable during or immediately after a bout, as in Schenk et al. [19]. Level 2 is delayed post-exercise change, detectable hours to days later, once acute trafficking and catecholamine effects have resolved, as partially addressed by Zimmer et al.

at 24 h [73]. Level 3 is persistence after training withdrawal, which requires a detraining or wheel-removal interval and has been demonstrated to date only in mice and only at the progenitor level [21]. Level 4 is persistence that survives cell isolation and ex vivo functional restimulation, the standard applied in the trained-immunity literature [53,54] and not yet met by any human exercise study. Evidence at one level must not be promoted to the next without the corresponding temporal and cell-resolved test. This classification concerns persistence alone; mechanical attribution is a separate judgement, and no study at any of the four levels has yet isolated a mechanical cause.

Findings in haematopoietic progenitors should be reported separately from findings in mature immune cells, because the two support different biological claims: a change in what the marrow produces, as against a state retained within an existing differentiated cell. At the progenitor level, Frodermann and colleagues provide the strongest evidence for durability, in mice: six weeks of voluntary wheel running altered haematopoietic progenitor activity, and transcriptomic and chromatin-accessibility effects persisted through three weeks of wheel withdrawal [21] (mouse; Level 3 persistence; mechanical attribution absent). The identified upstream mediator was reduced adipose leptin signalling rather than mechanical loading, so this is a durable exercise-induced change without a demonstrated mechanical cause. Together with the mechanically regulated niche described by Shen and colleagues [15], it shows that bone marrow can integrate both mechanically derived and systemic metabolic information without requiring direct mechanical reprogramming of mature lymphocytes. No equivalent Level 3 evidence exists for mature human immune cells.

Independent trained-immunity studies further show that transient metabolic environments can leave persistent chromatin states. Lactate-dependent metabolic rewiring has been linked experimentally to histone lactylation and enhanced secondary responses, while persistent histone lactylation has been associated with long-term innate immune memory [53,54]. These studies do not establish an exercise mechanism; they establish biological plausibility for persistence once the appropriate cellular and epigenetic conditions are met.

Cell purification is necessary but not sufficient as a control, and its value should not be overstated. Sorting broad populations—CD8+ T cells, natural killer cells, classical monocytes—substantially reduces compositional confounding relative to whole blood, but it does not eliminate heterogeneity within the sorted gate, and exercise mobilises subsets differentially within such gates. More fundamentally, purification at a single time point cannot distinguish a molecular state retained by cells that were already present from the replacement of those cells by newly produced or newly recruited cells carrying a different state. Resolving that ambiguity requires single-cell rather than bulk profiling, repeated sampling combined with markers of replication history or cell age, or designs that track the same cells over time.

The three alternative explanations defined above—redistribution, replacement, and continued systemic exposure—must each be excluded before human immune reprogramming is inferred. Sorted-cell or single-cell analyses, repeated sampling after acute signals have resolved, and ex vivo functional testing are therefore not optional refinements but the minimum conditions for identifying the biological level at which any persistence resides [23,24].

The central unresolved experiment is consequently straightforward to state but technically demanding: does repeated exercise induce persistent chromatin and functional changes in purified human immune-cell populations that can be causally attributed, wholly or partly, to a defined mechanical route? Addressing it requires longitudinal interventions, cell-resolved sampling, control for redistribution, paired haemodynamic/mechanical and endocrine/metabolomic measures, and epigenomic assays such as ATAC-seq or CUT&Tag/CUT&RUN [75–77]. A positive persistence signal would still not establish a me-

chanical mechanism unless the candidate mechanical route were independently measured or perturbed.

7. A Mechanometabolic Immune Interface Model of Exercise

MIIM-E is proposed as a heuristic and falsifiable model, not as a mature theory of immune reprogramming. Its purpose is to organise where mechanical information may enter exercise immunobiology, which cells decode it, through which route it reaches immune outcomes, and whether any resulting change persists. The model therefore accommodates both supported and speculative transitions without treating the latter as established facts.

Four premises organise the model: exercise has a mechanically structured dimension that is not reducible to metabolic workload; mechanical cues are decoded by cell- and tissue-specific sensor architectures; mechanical and metabolic information interact rather than travel in isolated cascades; and immune consequences can arise through direct haemodynamic exposure, tissue/niche intermediates, or systemic biochemical communication. Persistent cell-intrinsic reprogramming is a possible endpoint within this architecture, not a prerequisite for the model.

These premises generate five experimentally discriminable predictions (Figure 4).

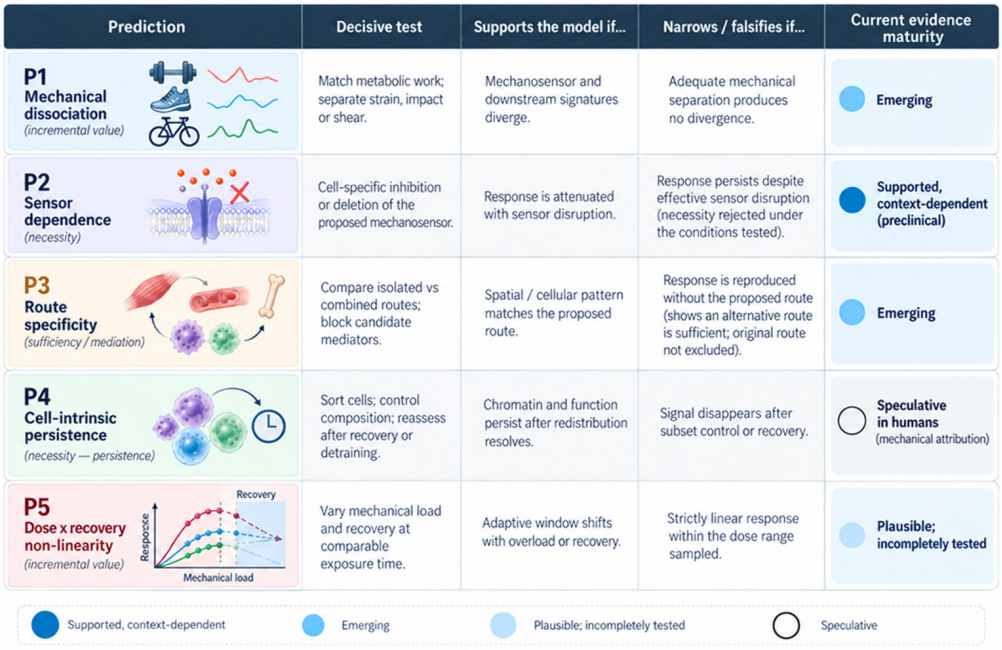


Figure 4. Falsifiability matrix for the Mechanometabolic Immune Interface Model of Exercise (MIIM-E). Five predictions—mechanical dissociation, sensor dependence, route specificity, cell-intrinsic persistence, and dose-by-recovery non-linearity—are paired with decisive tests, supportive observations, narrowing or falsifying outcomes, and the current maturity of the evidence. Maturity labels are drawn from the categories defined in Section 2.4, the colour key shows the four categories that occur among these five predictions. Each prediction is additionally identified in Section 8 as a test of necessity, sufficiency, mediation, or incremental explanatory value; most negative results narrow the scope of a prediction under the conditions tested rather than falsifying the underlying mechanism. The classification of cell-intrinsic persistence as speculative in humans refers to persistence attributable to a mechanical cause; whether exercise-associated persistence occurs at all is a separate question, classified as emerging. The figure is intentionally conservative. Abbreviations: P1–P5, predictions 1 to 5.

Figure 4 summarises the decisive tests and the observations that would support, narrow, or falsify each prediction; Section 8 develops the experimental logic in detail.

7.1. What MIIM-E Adds to Existing Frameworks

MIIM-E does not replace exercise-metabolism, exerkine, exercise-immunology, cellular mechanometabolism, mechanoimmunology, or general mechanobiology frameworks. Instead, it asks a narrower causal question: when does the mechanical structure of exercise explain variance that metabolic workload or systemic biochemical exposure cannot? Cellular mechanometabolism establishes that force and metabolic state are reciprocally coupled, T-cell mechanobiology defines force-sensitive immune mechanisms, and contemporary exercise immunology integrates haemodynamic and biochemical mediators [5,17,18]. MIIM-E adds four exercise-specific constraints: the initiating mechanical signature must be tied to an exercise exposure; the receiving cell or tissue must be specified; the route from the cue to the immune phenotype must be identified; and persistence must be distinguished from acute redistribution, replacement, or continuing systemic exposure. The model therefore uses these adjacent frameworks as mechanistic components rather than presenting them as discoveries of MIIM-E.

A worked example makes the practical difference concrete. Consider a design of a kind that is common in the literature: older adults complete twelve weeks of moderate-intensity continuous cycling; blood is sampled at rest before and after the programme; peripheral blood mononuclear cell DNA methylation and inflammatory gene expression shift favourably; and the result is interpreted as exercise-induced immune reprogramming. Read through MIIM-E, four specifications are missing from this design, and each implies a concrete change. First, the mechanical signature was neither manipulated nor measured: cycling was selected for tolerability rather than as a mechanical contrast, so the study cannot separate mechanical from metabolic contribution. Adding a second arm matched for oxygen uptake and session duration but differing in mechanical exposure—cycling with intermittent cuff-restricted limb shear, or a resistance-based protocol at matched metabolic cost—converts a single-dose study into a dissociation test. Second, the receiver is unspecified: peripheral blood mononuclear cells are a mixture, and both samples are subject to redistribution and replacement, so the analysis should be performed in sorted populations with subset composition reported at every time point. Third, the route is unidentified: without paired measurement of conduit-artery shear, catecholamine and cortisol responses, and circulating exerkines, the observation is equally compatible with Routes Ia, Ib, and III. Fourth, persistence is untested beyond the post-training resting sample: adding a sample after two to four weeks of detraining, and an ex vivo restimulation assay, would place the finding at Level 3 or Level 4 rather than leaving it undefined. The same study, redesigned under these four constraints, would permit a stronger test of a causal hypothesis than an additional positive association provides. Causal attribution would still depend on the assumptions set out in Section 8: verified separation of the mechanical exposure, measurement of the competing exposures, and, for attribution to a mechanical route, an independent perturbation of that route. This is the sense in which the model is additional to the frameworks listed in Table 1.

Table 1 positions MIIM-E relative to adjacent exercise, mechanometabolic, and mechanoimmunological frameworks without ranking them. Its purpose is to show which explanatory problem each framework addresses and which uncertainty remains when the question is specifically how exercise mechanics reaches immune biology.

Table 1. Relationship of MIIM-E to adjacent exercise frameworks.

Framework	Primary Focus	What it Explains Well	Unresolved for This Question	Relationship to MIIM-E
Exercise metabolism	Energetic demand, substrate flux, AMP/ATP balance	Metabolic sensing and adaptation	Does not specify tissue-specific mechanical exposure	Provides the metabolic context against which mechanical information must add explanatory value
Exerkine biology	Exercise-induced circulating mediators	Inter-organ biochemical communication	Does not identify whether an initiating tissue signal was mechanical, metabolic, or both	Represents systemic biochemical communication after tissue-level signal generation
Exercise immunology	Leukocyte mobilisation, trafficking, inflammatory responses	Acute and training-related immune physiology	Redistribution can be mistaken for persistent cell-intrinsic change	Provides immune endpoints that MIIM-E separates by route and persistence
Mechanobiology	Force, stiffness, shear, deformation, mechanosensors	Cellular conversion of physical cues into signalling	Often studied outside whole-body exercise	Provides candidate sensors and causal perturbations for exercise-specific testing
Cellular mechanometabolism	Reciprocal coupling between mechanical cues and cellular metabolic state	How ECM, cytoskeleton, force and metabolism influence one another	Not exercise-specific and does not by itself identify an immune route or persistence	Provides the mechanometabolic coupling principle embedded within MIIM-E [5]
Mechanoimmunology	Force-dependent immune-cell activation, migration and function	TCR mechanics, cytoskeletal force sensing and matrix-dependent immune behaviour	Mostly not linked to exercise-specific mechanical exposure or persistence	Provides immune-cell force-sensing mechanisms that MIIM-E requires to be validated during exercise [17]
MIIM-E	Mechanical signature × cellular decoder × route × persistence	Organises competing exercise-to-immune routes into falsifiable contrasts	Does not establish transitions that remain untested, especially durable human immune-cell reprogramming	Exercise-specific model for causal discrimination rather than a replacement for adjacent frameworks

MIIM-E is an integrative model for causal discrimination, not a claim that mechanical signalling supersedes metabolic, endocrine, exerkine, or conventional exercise-immunology explanations.

7.2. Evidence Maturity Within the Model

Evidence is not equally mature across transitions, and the maturity of a transition's persistence must not be conflated with the maturity of its mechanical attribution. Direct mechanosensing in mechanically loaded tissues is established in humans; exercise-specific Piezo1-dependent stromal sensing is supported but context-dependent and derived from mouse models; immune-cell mechanosensitivity is established outside exercise but incompletely validated as an exercise mechanism; exercise-associated persistent change in immune

cells is emerging, with human evidence confined to Levels 1 and 2 and mouse evidence at Level 3 confined to progenitors; and the attribution of any such persistence to exercise-generated force remains speculative [19–21,29,41,73]. Table 2 reports these judgements using the five categories defined in Section 2.4, identifies the representative primary studies in each row, and separates persistence from mechanical attribution in the final rows. Supplementary Table S2 provides the study-level basis—species, experimental setting, mechanical exposure, cellular target, intervention or perturbation, immune outcome, and duration of follow-up—for the studies underpinning the strongest causal claims.

Table 2. Evidence maturity of critical MIIM-E transitions, with representative primary studies. Maturity categories are those defined in Section 2.4, as in Figure 4. "Human evidence" denotes direct exercise-related human evidence, indirect human evidence, or predominantly preclinical evidence. "Causal perturbation" denotes whether the proposed upstream mediator has been experimentally manipulated. Persistence and mechanical attribution are reported as separate judgements in the final two rows. Study-level details for selected primary studies underpinning the principal causal claims are provided in Supplementary Table S2. These are author-developed narrative descriptors for transparency, not validated certainty grades.

Critical Transition	Representative Evidence	Human Evidence	Causal Perturbation	Current Status	Most Informative Next Experiment
Exercise → loaded-tissue mechanosensing	Skeletal muscle, endothelium and load-bearing tissues [6–10,12,25–28]	Direct	Partial	Established	Mechanical dissociation at matched metabolic demand
Exercise → stromal Piezo1 signalling	Muscle mesenchymal stromal cells; Piezo1 deletion in mice [14]	Preclinical	Demonstrated	Supported, context-dependent	Human validation of cell-specific mechanosensing
Mechanical loading → haematopoietic niche regulation	Load-bearing bone and marrow stromal niches; running and unloading in mice [15]	Preclinical	Demonstrated	Supported, context-dependent	Longitudinal human niche/progenitor studies with loading contrasts
Immune-cell mechanosensitivity	TCR force sensing and cytoskeletal mechanics [11,13,17,65–69]; myeloid Piezo1 and stiffness sensing [41,70–72]; matrix-dependent T-cell responses [39]; all outside exercise	Indirect	Demonstrated outside exercise	Established outside exercise; emerging within exercise	Exercise-specific quantification or perturbation of immune mechanical exposure
Exercise → persistent immune-cell change (persistence only)	Human NK-cell studies at Level 1 and Level 2 [19,73]; mouse progenitor epigenomics after wheel withdrawal, Level 3 [21]	Direct (limited)	Not demonstrated for a mechanical route	Emerging for persistence; mechanical attribution not assessed	Sorted-cell longitudinal epigenomics after training and detraining
Exercise mechanics → durable immune chromatin reprogramming (mechanical attribution)	No study has combined an exercise mechanical exposure with cell-specific sensor perturbation and purified-cell epigenomics [14,15,19,21,73]	Indirect	Not demonstrated	Speculative	Mechanical exposure + cell-specific perturbation + purified-cell epigenomics
Exercise dose × recovery → adaptation/maladaptation	Broad physiological and recovery evidence [38,60,78]	Direct	Partial	Plausible; incompletely tested	Factorial manipulation of mechanical load and recovery with molecular endpoints

This uneven maturity is the central reason to frame MIIM-E as a model rather than a theory. By locating weak transitions explicitly, the framework turns uncertainty into an

experimental agenda. Table 2 summarises the status of each critical transition and the experiment most capable of changing that status.

8. Falsifiable Predictions and Decisive Experiments

A useful model must generate outcomes that are not guaranteed by the generic proposition that exercise is beneficial. MIIM-E makes five predictions, each of which can fail independently, so that part of the model may be rejected without requiring acceptance or rejection of the framework as a whole. Because the model explicitly allows multiple, non-exclusive routes, the inferential status of each test must be declared before it is run.

We therefore distinguish four questions. A test of necessity asks whether removing a proposed component abolishes or attenuates the outcome under the conditions tested. A test of sufficiency asks whether reproducing the component in isolation reproduces the outcome. A test of mediation asks what proportion of an established exercise effect is transmitted through the proposed route while the exercise stimulus itself remains intact. A test of incremental explanatory value asks whether adding the mechanical specification improves prediction of the outcome beyond the metabolic and endocrine exposures already measured. These are not interchangeable, and in a multiroute model the first two are the most frequently over-interpreted: demonstrating that an alternative route is sufficient does not eliminate the contribution of the original route, and demonstrating that a component is dispensable does not show that it contributes nothing when present.

Claims resting on negative findings carry three additional conditions. The first is demonstrated target engagement: evidence that the sensor was in fact disrupted, or that the mechanical exposure in fact differed, measured rather than assumed. The second is meaningful exposure separation: a difference in the mechanical variable large enough to be biologically relevant, reported as achieved rather than as intended. The third is estimation precise enough to exclude a biologically relevant effect, rather than a failure to detect one. In the absence of all three, a negative result is only weakly informative and should be reported as inconclusive rather than as evidence against the mechanism.

Prediction 1—mechanical dissociation (a test of incremental explanatory value). If mechanical information contributes independently to adaptation, exercise conditions matched as closely as feasible for metabolic demand but differing in local strain, impact, or shear should produce different mechanosensor activation and different downstream signatures. Repeated failure to observe such divergence, under verified mechanical separation and with competing exposures measured, would show that the mechanical specification adds no explanatory value for that outcome under those conditions. It would not show that the tissue is mechanically insensitive, nor that mechanics is irrelevant at other doses [12,27,28].

Prediction 2—sensor dependence (a test of necessity, under the conditions tested). If a proposed exercise effect requires a given mechanosensor, selective disruption of that sensor in the relevant cell population should attenuate the response without abolishing the broader exercise stimulus. The Shen and Langston studies satisfy this logic in bone-marrow and muscle stromal compartments [14,15]; equivalent exercise-specific evidence is largely absent for mature immune cells. Persistence of the outcome despite verified sensor disruption would reject the necessity of that sensor in that cell population under those conditions. It would not exclude mechanical regulation as such, because compensatory mechanosensors, parallel force-transmission pathways, and developmental adaptation to constitutive deletion can each preserve the outcome. Inducible, cell-restricted, adult-onset disruption, together with a second and independent sensor perturbation, is required before any broader conclusion is drawn.

Prediction 3—route specificity (tests of sufficiency and of mediation). If an immune effect is niche-mediated, it should track the mechanically engaged tissue and its stromal sig-

nals. If it is predominantly systemic, it should be reproducible in unloaded compartments when the relevant biochemical milieu is reproduced. The inferential limit here follows directly from the multiroute structure of the model and is easily overlooked: reproducing the immune response without the proposed route establishes only that an alternative route is sufficient under those conditions. It does not establish that the original route contributes nothing during intact exercise, when both operate simultaneously. Quantifying the contribution of a route therefore calls for mediation analysis within an intact exercise stimulus—measuring the candidate mediator and the outcome while the route is attenuated—rather than substitution experiments alone [10,28]. Because the mediator itself is not randomised in such designs, these analyses rest on assumptions about unmeasured confounding that the data cannot verify, and their estimates should be reported as exploratory.

Prediction 4—cell-intrinsic persistence (a test of necessity for the persistence claim only). Durable immune change should remain detectable after acute catecholamine and trafficking effects have resolved and after cell composition has been controlled, that is, at Level 3 or Level 4 as defined in Section 6. If the signal disappears in purified populations or after subset correction, redistribution or replacement is the more parsimonious explanation. A positive result at these levels establishes persistence alone; attributing that persistence to mechanics requires that a mechanical route be independently measured or perturbed within the same design [19,20,23,24].

Prediction 5—dose by recovery non-linearity (a test of incremental explanatory value). Mechanosensitive pathways should not be uniformly beneficial across doses. Excessive or poorly recovered loading should shift the response toward tissue damage, unresolved inflammatory signalling, or maladaptive matrix remodelling, and age, disease, matrix state, and recovery capacity should modify that relationship [38,60,78]. A linear response observed within the range actually sampled constrains only that range and cannot exclude non-linearity at higher loads, shorter recoveries, or in more vulnerable populations. Studies testing this prediction should therefore state the dose range sampled and treat any extrapolation beyond it as untested rather than as excluded.

Two worked designs make these principles concrete, one in humans and one mechanistic. The proposed human study is a randomised, counterbalanced crossover in healthy middle-aged adults comparing three exercise conditions matched as closely as feasible for systemic oxygen uptake and session duration: conventional upright cycling; upright cycling with unilateral thigh-cuff compression intended to attenuate local conduit-artery shear; and a circuit of multi-joint resistance exercises producing a different contractile-loading profile at comparable metabolic demand. The cuff intervention is informed by the forearm handgrip model of Tinken and colleagues [12], but its haemodynamic effects cannot be assumed to transfer directly to cycling or to the lower limb. Accordingly, a preliminary feasibility phase would establish whether the selected cuff pressure produces a reproducible, tolerable separation in femoral arterial shear rate, verified by bilateral Doppler ultrasound measurements of blood velocity and arterial diameter. Wall shear stress would be estimated only if blood viscosity were also assessed. Cuff-related changes in regional perfusion, muscle oxygenation, recruitment, interstitial pressure, and local metabolite kinetics would be measured or characterised as potential competing exposures rather than assumed to remain constant. Matching whole-body oxygen uptake would therefore not be interpreted as matching local mechanical or metabolic conditions.

The principal mechanical contrasts would be the measured differences in arterial shear rate between the cuffed and contralateral limbs and the differences in contractile loading between exercise conditions, quantified through appropriate biomechanical measurements rather than modality labels alone. The vascular endothelium would be the candidate receiver

for the haemodynamic contrast, with endothelial responses assessed through flow-mediated dilation and circulating endothelial markers. Sorted CD8+ T cells, CD56dim natural killer cells, and classical monocytes would represent downstream immune populations, without assuming that they directly sense the manipulated haemodynamic stimulus. PIEZO1-related signalling and YAP/TAZ-associated transcriptional responses in these populations would be considered exploratory mechanistic correlates rather than evidence of endothelial sensor engagement. The primary immune outcome would be chromatin accessibility at prespecified inflammatory loci in sorted CD8+ T cells, with ex vivo cytokine responses and natural killer-cell cytotoxicity as secondary outcomes. Sampling would occur at rest, immediately after exercise, and at 3 h, 24 h, and 72 h, with adequate washout between crossover conditions. Where technically feasible, paired limb venous sampling would complement systemic blood measurements. Catecholamines, cortisol, temperature, lactate, circulating metabolites, muscle-damage indices, and leukocyte-subset composition would be assessed to characterise competing physiological explanations.

Analyses would first establish whether the intended mechanical exposure separation had actually been achieved and would then examine associations between measured exposure and immune outcomes, reporting effect estimates and their precision. Mediation analyses would remain exploratory and would distinguish competing exposures from potential downstream mediators of mechanotransduction. Because cuff compression can modify several local physiological variables simultaneously, differences between conditions would not, by themselves, establish endothelial mechanotransduction as the cause of an immune response. Similarly, the absence of an immune difference would not exclude a mechanical mechanism unless exposure separation, measurement sensitivity, and statistical precision were adequate. The human experiment could therefore assess feasibility and generate exposure–response evidence, whereas testing the necessity of a specific mechanosensor would require the complementary cell-specific perturbation experiment described below.

The complementary mechanistic experiment tests necessity under the conditions examined. It also addresses receiver compartments that the human design does not: the human crossover manipulates a haemodynamic exposure whose immediate receiver is the endothelium, that is Route Ia, whereas deleting a sensor in a leukocyte tests the leukocyte-intrinsic Route Ib. The two examples are therefore complementary rather than interchangeable, and the mechanistic experiment is specified with arms addressing both. In mice, Piezo1 is deleted inducibly and cell-restrictedly in the endothelium, which addresses the same receiver as the human design and for which an exercise-relevant model already exists [29], and, in separate arms, in the myeloid compartment and in mature T cells, which address Route Ib. Each arm is combined with voluntary wheel running and with a non-exercise mechanical control such as passive limb loading. The mechanical contrasts are running against sedentary housing and loaded against unloaded limb; the receiver cell is defined by the Cre driver; the candidate sensor is deleted in adulthood to avoid developmental compensation, with target engagement verified at transcript and functional level; and the competing exposures—leptin, corticosterone, catecholamines, and body composition—are measured, because the leptin-dependent pathway operates in the same model [21]. The primary outcome is the chromatin and functional state of the relevant immune population after a detraining interval and after ex vivo restimulation, that is, Level 4 persistence; in the leukocyte arms, this is the deleted population itself, whereas in the endothelial arm it is the sorted immune populations downstream of the manipulated route, since the predicted effect there is indirect. A second, independent mechanosensor perturbation is required before any negative result is interpreted as excluding mechanical regulation.

A distinction that must be preserved in both designs is that between a competing explanation and a downstream mediator. Catecholamine release, core temperature, and

perfusion are plausible competing explanations, and measuring and adjusting for them is appropriate. A soluble mediator generated by mechanotransduction—an exerkine released from a mechanically activated stromal cell, for instance—is not a competing explanation but a component of the causal pathway, and adjusting for it would remove precisely the effect under study. Whether a given mediator belongs in one category or the other is an empirical question, best settled by testing whether its release survives disruption of the candidate mechanosensor. Where it cannot be settled, the analysis should be presented both with and without adjustment rather than defaulting to adjustment, and the resulting estimates treated as exploratory.

More generally, human studies designed to test these predictions should combine external exercise dose with internal haemodynamic and biochemical exposure, isolate defined immune populations, sample both acute and delayed recovery, and pair mechanosensor measurements with sorted-cell or single-cell molecular profiling. Mechanistic models should use cell-specific perturbation of the most plausible sensor or intermediate tissue rather than relying on whole-body knockout or descriptive pathway activation [64,75,76,79]. Negative results are informative when the three conditions set out above are met: failure of a predicted route under an adequately powered and mechanically discriminating design should narrow the model rather than be absorbed as unexplained heterogeneity.

A staged validation strategy is therefore preferable to a single omnibus experiment. First, establish that two exercise exposures create meaningfully different mechanical signatures. Second, show that the relevant cellular decoder changes accordingly. Third, demonstrate route-specific downstream effects. Only then should persistence be tested after redistribution and systemic exposure have resolved. This sequence prevents a durable molecular endpoint from being retrospectively attributed to mechanics when the upstream mechanical link was never established.

9. Translational Relevance, Boundary Conditions, and Medical Implications

The translational relevance of MIIM-E lies in recognising that chronic disease changes the physical environment in which exercise signals are received. Ageing, obesity, type 2 diabetes, cardiovascular disease, cancer, and chronic inflammatory disorders alter matrix composition, vascular mechanics, stromal phenotype, mitochondrial function, and inflammatory tone, so an identical external prescription may not generate an identical intracellular mechanical signal [35,55,80,81].

In ageing, matrix stiffening, fibrosis, endothelial dysfunction, impaired regeneration, and altered stromal or haematopoietic niches offer a testable explanation for response heterogeneity that is distinct from reduced fitness or metabolic capacity alone [33–35,38]. In obesity and type 2 diabetes, extracellular-matrix remodelling, endothelial dysfunction, metabolic inflexibility, and chronic low-grade inflammation may alter both mechanical and biochemical signal transmission; MIIM-E predicts that baseline tissue state will modify which mechanosensors and stromal programmes are engaged by a standardised external dose [80–83].

In cardiovascular disease, exercise haemodynamics are intrinsically mechanical: blood flow, pulsatility, and shear regulate endothelial signalling and leukocyte–endothelial interactions, so modalities with different haemodynamic profiles may be biologically non-interchangeable despite comparable energy expenditure [10,12,29,55]. Cancer and chronic inflammatory disease are more complex boundary conditions, in which pathological matrix stiffness, stromal signalling, and immune-cell exclusion shape immune migration and function [40,41,72]; MIIM-E does not imply that exercise mechanically reverses these ab-

normalities, only that exercise-induced changes in perfusion, tissue mechanics, or stromal signalling can be tested as modifiers.

The biologically optimal stimulus is not synonymous with the largest tolerable mechanical load: excessive strain, inadequate recovery, fibrosis, or unresolved inflammation may shift adaptive signalling toward injury or non-resolution [38,60,78]. MIIM-E therefore points to a direction for precision exercise research rather than an immediately deployable clinical algorithm. Candidate measurements include haemodynamic exposure, tissue stiffness or deformation, circulating mediators, cell-resolved mechanosensor activation, immune phenotype, and delayed persistence; their clinical value will depend on explaining response heterogeneity beyond workload, fitness, and energy expenditure [64,79,84].

10. Conclusions

Exercise is not only a metabolic challenge but a spatially distributed mechanometabolic perturbation whose biological meaning depends on which cells receive the load, how they decode it, which route carries the signal to immune biology, and whether the response persists. The strongest evidence currently supports mechanotransduction in mechanically engaged tissues and stromal or haematopoietic intermediates [14,15,29].

The major unresolved transition lies downstream. Immune cells possess sophisticated mechanosensory machinery, but this has been established almost entirely outside exercise, and no study has yet shown that a defined exercise mechanical exposure produces durable, cell-intrinsic chromatin reprogramming in purified human immune populations [19,20,41,73]. Persistence and its attribution to mechanics remain separate and separately unanswered questions, and the analytic distinctions set out in Section 6 are the minimum required to address either.

MIIM-E therefore makes a deliberately constrained claim: exercise generates tissue- and cell-specific mechanical information that can influence immune biology through direct haemodynamic exposure, niche-mediated mechanotransduction, and systemic biochemical communication arising during coupled mechanical-metabolic exercise exposure. The model does not assume that these routes are interchangeable, that the mechanical component is necessary for every systemic mediator, or that durable immune reprogramming is an established endpoint.

The value of the model will depend on its ability to fail. Mechanical dissociation, sensor dependence, route specificity, cell-intrinsic persistence, and dose-by-recovery interactions provide explicit criteria by which individual components can be supported, narrowed, or rejected. Progress will come from experiments that isolate mechanical information, identify the responsible cell and route, control competing systemic signals, and test persistence after the acute exercise environment has resolved.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medsci14070724/s1, Table S1, complete database-specific search strategies and final targeted citation-check terms for the mechanistic narrative review; Table S2, study-level evidence summary for the studies underpinning the principal causal claims, reporting species or population, experimental setting, mechanical exposure, cellular target, intervention or perturbation, immune outcome, and duration of follow-up.

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References

1. Egan, B.; Zierath, J.R. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab.* **2013**, *17*, 162–184. [CrossRef]
2. Hargreaves, M.; Spriet, L.L. Skeletal muscle energy metabolism during exercise. *Nat. Metab.* **2020**, *2*, 817–828. [CrossRef]
3. Smith, J.A.B.; Murach, K.A.; Dyar, K.A.; Zierath, J.R. Exercise metabolism and adaptation in skeletal muscle. *Nat. Rev. Mol. Cell Biol.* **2023**, *24*, 607–632. [CrossRef]
4. Chow, L.S.; Gerszten, R.E.; Taylor, J.M.; Pedersen, B.K.; van Praag, H.; Trappe, S.; Febbraio, M.A.; Galis, Z.S.; Gao, Y.; Haus, J.M.; et al. Exerkines in health, resilience and disease. *Nat. Rev. Endocrinol.* **2022**, *18*, 273–289. [CrossRef]
5. Ortiz, I.; Lopez, S.; Kondapaneni, R.V.; Hernandez, J.V.; Boone, K.; Reinhart-King, C.A. Cellular mechanometabolism: Stimuli and implications. *EMBO Rep.* **2026**, *27*, 2853–2864. [CrossRef]
6. Boppart, M.D.; Mahmassani, Z.S. Integrin signaling: Linking mechanical stimulation to skeletal muscle hypertrophy. *Am. J. Physiol.-Cell Physiol.* **2019**, *317*, C629–C641. [CrossRef]
7. Fischer, M.; Rikeit, P.; Knaus, P.; Coirault, C. YAP-mediated mechanotransduction in skeletal muscle. *Front. Physiol.* **2016**, *7*, 41. [CrossRef]
8. Panciera, T.; Azzolin, L.; Cordenonsi, M.; Piccolo, S. Mechanobiology of YAP and TAZ in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 758–770. [CrossRef]
9. Kjaer, M.; Langberg, H.; Heinemeier, K.; Bayer, M.L.; Hansen, M.; Holm, L.; Doessing, S.; Kongsgaard, M.; Krogsgaard, M.R.; Magnusson, S.P. From mechanical loading to collagen synthesis, structural changes and function in human tendon. *Scand. J. Med. Sci. Sports* **2009**, *19*, 500–510. [CrossRef]
10. Green, D.J.; Hopman, M.T.E.; Padilla, J.; Laughlin, M.H.; Thijssen, D.H.J. Vascular adaptation to exercise in humans: Role of hemodynamic stimuli. *Physiol. Rev.* **2017**, *97*, 495–528. [CrossRef]
11. Huse, M. Mechanical forces in the immune system. *Nat. Rev. Immunol.* **2017**, *17*, 679–690. [CrossRef]
12. Tinken, T.M.; Thijssen, D.H.J.; Hopkins, N.; Dawson, E.A.; Cable, N.T.; Green, D.J. Shear stress mediates endothelial adaptations to exercise training in humans. *Hypertension* **2010**, *55*, 312–318. [CrossRef]
13. Liu, B.; Chen, W.; Evavold, B.D.; Zhu, C. Accumulation of dynamic catch bonds between TCR and agonist peptide-MHC triggers T cell signaling. *Cell* **2014**, *157*, 357–368. [CrossRef]
14. Langston, P.K.; Vijaya Raghavan, J.; Benoist, C.; Mathis, D. Piezo1-dependent activation of stromal cells ignites muscle inflammation in exercise and injury and is associated with inflammaging. *Nat. Immunol.* **2026**, *27*, 543–555. [CrossRef]
15. Shen, B.; Tasdogan, A.; Ubellacker, J.M.; Zhang, J.; Nosyreva, E.D.; Du, L.; Murphy, M.M.; Hu, S.; Yi, Y.; Kara, N.; et al. A mechanosensitive peri-arteriolar niche for osteogenesis and lymphopoiesis. *Nature* **2021**, *591*, 438–444. [CrossRef]

16. Maniak, M.K.; Jenkins, S.J.; Hansen, C.G. Mechanobiology of inflammation: Pulling the strings of innate immunity. *J. Exp. Med.* **2026**, *223*, e20252269. [CrossRef]
17. Zubia-Aranburu, J.; Zhang, L.; Dong, M. T-cell mechanobiology: How molecular forces shape immune function. *J. Cell Biol.* **2026**, *225*, e202601058. [CrossRef]
18. Phelps, C.M.; Meisel, M. The immunology of exercise: Mechanisms, mediators, and therapeutic opportunities. *Immunity* **2026**, *59*, 1794–1810. [CrossRef]
19. Schenk, A.; Koliamitra, C.; Bauer, C.J.; Schier, R.; Schweiger, M.R.; Bloch, W.; Zimmer, P. Impact of acute aerobic exercise on genome-wide DNA-methylation in natural killer cells—A pilot study. *Genes* **2019**, *10*, 380. [CrossRef]
20. Denham, J.; Marques, F.Z.; Bruns, E.L.; O'Brien, B.J.; Charchar, F.J. Epigenetic changes in leukocytes after 8 weeks of resistance exercise training. *Eur. J. Appl. Physiol.* **2016**, *116*, 1245–1253. [CrossRef]
21. Frodermann, V.; Rohde, D.; Courties, G.; Severe, N.; Schloss, M.J.; Amatullah, H.; McAlpine, C.S.; Cremer, S.; Hoyer, F.F.; Ji, F.; et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat. Med.* **2019**, *25*, 1761–1771. [CrossRef]
22. Baethge, C.; Goldbeck-Wood, S.; Mertens, S. SANRA—A scale for the quality assessment of narrative review articles. *Res. Integr. Peer Rev.* **2019**, *4*, 5. [CrossRef]
23. Jones, M.J.; Islam, S.A.; Edgar, R.D.; Kobor, M.S. Adjusting for cell type composition in DNA methylation data using a regression-based approach. *Methods Mol. Biol.* **2017**, *1589*, 99–106. [CrossRef]
24. Shiwa, Y.; Hachiya, T.; Furukawa, R.; Ohmomo, H.; Ono, K.; Kudo, H.; Hata, J.; Hozawa, A.; Iwasaki, M.; Matsuda, K.; et al. Adjustment of cell-type composition minimizes systematic bias in blood DNA methylation profiles derived by DNA collection protocols. *PLoS ONE* **2016**, *11*, e0147519. [CrossRef]
25. Mavropalias, G.; Boppart, M.; Usher, K.M.; Grounds, M.D.; Nosaka, K.; Blazevich, A.J. Exercise builds the scaffold of life: Muscle extracellular matrix biomarker responses to physical activity, inactivity, and aging. *Biol. Rev.* **2023**, *98*, 481–519. [CrossRef]
26. Robling, A.G.; Niziolek, P.J.; Baldridge, L.A.; Condon, K.W.; Allen, M.R.; Alam, I.; Mantila, S.M.; Gluhak-Heinrich, J.; Bellido, T.M.; Harris, S.E.; et al. Mechanical stimulation of bone in vivo reduces osteocyte expression of Sost/sclerostin. *J. Biol. Chem.* **2008**, *283*, 5866–5875. [CrossRef]
27. Franchi, M.V.; Ruoss, S.; Valdivieso, P.; Mitchell, K.W.; Smith, K.; Atherton, P.J.; Narici, M.V.; Flück, M. Regional regulation of focal adhesion kinase after concentric and eccentric loading is related to remodelling of human skeletal muscle. *Acta Physiol.* **2018**, *223*, e13056. [CrossRef]
28. Newcomer, S.C.; Thijssen, D.H.J.; Green, D.J. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: Role of exercise-induced hemodynamics. *J. Appl. Physiol.* **2011**, *111*, 311–320. [CrossRef]
29. Rode, B.; Shi, J.; Endesh, N.; Drinkhill, M.J.; Webster, P.J.; Lotteau, S.J.; Bailey, M.A.; Yuldasheva, N.Y.; Ludlow, M.J.; Cubbon, R.M.; et al. Piezo1 channels sense whole body physical activity to reset cardiovascular homeostasis and enhance performance. *Nat. Commun.* **2017**, *8*, 350. [CrossRef]
30. Wang, S.; Stoops, E.; Cp, U.; Markus, B.; Reuveny, A.; Ordan, E.; Volk, T. Mechanotransduction via the LINC complex regulates DNA replication in myonuclei. *J. Cell Biol.* **2018**, *217*, 2005–2018. [CrossRef]
31. Guilluy, C.; Osborne, L.D.; Van Landeghem, L.; Sharek, L.; Superfine, R.; Garcia-Mata, R.; Burridge, K. Isolated nuclei adapt to force and reveal a mechanotransduction pathway in the nucleus. *Nat. Cell Biol.* **2014**, *16*, 376–381. [CrossRef]
32. MoTrPAC Study Group. Temporal dynamics of the multi-omic response to endurance exercise training. *Nature* **2024**, *629*, 174–183. [CrossRef]
33. Garg, K.; Boppart, M.D. Influence of exercise and aging on extracellular matrix composition in the skeletal muscle stem cell niche. *J. Appl. Physiol.* **2016**, *121*, 1053–1058. [CrossRef]
34. Gumpenberger, M.; Wessner, B.; Graf, A.; Narici, M.V.; Fink, C.; Braun, S.; Hoser, C.; Blazevich, A.J.; Csapo, R. Remodeling the skeletal muscle extracellular matrix in older age—Effects of acute exercise stimuli on gene expression. *Int. J. Mol. Sci.* **2020**, *21*, 7089. [CrossRef]
35. Yeung, C.-Y.C.; Nyström, A. The extracellular matrix as a central regulator of aging and tissue adaptation to exercise. *Am. J. Physiol.-Cell Physiol.* **2026**, *331*, C98–C100. [CrossRef]
36. Goodman, C.A.; Dietz, J.M.; Jacobs, B.L.; McNally, R.M.; You, J.-S.; Hornberger, T.A. Yes-associated protein is up-regulated by mechanical overload and is sufficient to induce skeletal muscle hypertrophy. *FEBS Lett.* **2015**, *589*, 1491–1497. [CrossRef]
37. Beech, D.J. Endothelial Piezo1 channels as sensors of exercise. *J. Physiol.* **2018**, *596*, 979–984. [CrossRef]
38. Silver, J.S.; Günay, K.A.; Cutler, A.A.; Vogler, T.O.; Brown, T.E.; Pawlikowski, B.T.; Bednarski, O.J.; Bannister, K.L.; Rogowski, C.J.; Mckay, A.G.; et al. Injury-mediated stiffening persistently activates muscle stem cells through YAP and TAZ mechanotransduction. *Sci. Adv.* **2021**, *7*, eabe4501. [CrossRef]
39. Sapudom, J.; Alatoom, A.; Tipay, P.S.; Teo, J.C.M. Matrix stiffening from collagen fibril density and alignment modulates YAP-mediated T-cell immune suppression. *Biomaterials* **2025**, *315*, 122900. [CrossRef]

40. Bai, J.; Yan, M.; Xu, Y.; Wang, Y.; Yao, Y.; Jin, P.; Zhang, Y.; Qu, Y.; Niu, L.; Li, H. YAP enhances mitochondrial OXPHOS in tumor-infiltrating Treg through upregulating Lars2 on stiff matrix. *J. Immunother. Cancer* **2024**, *12*, e010463. [CrossRef]
41. Meli, V.S.; Atcha, H.; Veerasubramanian, P.K.; Nagalla, R.R.; Luu, T.U.; Chen, E.Y.; Guerrero-Juarez, C.F.; Yamaga, K.; Pandori, W.; Hsieh, J.Y.; et al. YAP-mediated mechanotransduction tunes the macrophage inflammatory response. *Sci. Adv.* **2020**, *6*, eabb8471. [CrossRef]
42. Cantó, C.; Auwerx, J. PGC-1α, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. *Curr. Opin. Lipidol.* **2009**, *20*, 98–105. [CrossRef]
43. Yu, X.; Li, S. Specific regulation of epigenome landscape by metabolic enzymes and metabolites. *Biol. Rev.* **2024**, *99*, 878–900. [CrossRef]
44. Izzo, L.T.; Trefely, S.; Demetriadou, C.; Drummond, J.M.; Mizukami, T.; Kuprasertkul, N.; Farria, A.T.; Nguyen, P.T.T.; Murali, N.; Reich, L.; et al. Acetylcarnitine shuttling links mitochondrial metabolism to histone acetylation and lipogenesis. *Sci. Adv.* **2023**, *9*, eadf0115. [CrossRef]
45. Etchegaray, J.P.; Mostoslavsky, R. Interplay between metabolism and epigenetics: A nuclear adaptation to environmental changes. *Mol. Cell* **2016**, *62*, 695–711. [CrossRef]
46. Li, X.; Egervari, G.; Wang, Y.; Berger, S.L.; Lu, Z. Regulation of chromatin and gene expression by metabolic enzymes and metabolites. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 563–578. [CrossRef]
47. Wellen, K.E.; Hatzivassiliou, G.; Sachdeva, U.M.; Bui, T.V.; Cross, J.R.; Thompson, C.B. ATP-citrate lyase links cellular metabolism to histone acetylation. *Science* **2009**, *324*, 1076–1080. [CrossRef]
48. Zhang, D.; Tang, Z.; Huang, H.; Zhou, G.; Cui, C.; Weng, Y.; Liu, W.; Kim, S.; Lee, S.; Perez-Neut, M.; et al. Metabolic regulation of gene expression by histone lactylation. *Nature* **2019**, *574*, 575–580. [CrossRef]
49. McGee, S.L.; Fairlie, E.; Garnham, A.P.; Hargreaves, M. Exercise-induced histone modifications in human skeletal muscle. *J. Physiol.* **2009**, *587*, 5951–5958. [CrossRef]
50. Barrès, R.; Yan, J.; Egan, B.; Treebak, J.T.; Rasmussen, M.; Fritz, T.; Caidahl, K.; Krook, A.; O'Gorman, D.J.; Zierath, J.R. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab.* **2012**, *15*, 405–411. [CrossRef]
51. Lim, C.; Shimizu, J.; Kawano, F.; Kim, H.J.; Kim, C.K. Adaptive responses of histone modifications to resistance exercise in human skeletal muscle. *PLoS ONE* **2020**, *15*, e0231321. [CrossRef]
52. Bulusu, V.; Tumanov, S.; Michalopoulou, E.; van den Broek, N.J.; MacKay, G.; Nixon, C.; Dhayade, S.; Schug, Z.; Voorde, J.V.; Blyth, K.; et al. Acetate recapturing by nuclear acetyl-CoA synthetase 2 prevents loss of histone acetylation during oxygen and serum limitation. *Cell Rep.* **2017**, *18*, 647–658. [CrossRef]
53. Cai, H.; Chen, X.; Liu, Y.; Chen, Y.; Zhong, G.; Chen, X.; Rong, S.; Zeng, H.; Zhang, L.; Li, Z.; et al. Lactate activates trained immunity by fueling the tricarboxylic acid cycle and regulating histone lactylation. *Nat. Commun.* **2025**, *16*, 3230. [CrossRef]
54. Ziogas, A.; Novakovic, B.; Ventriglia, L.; Galang, N.; Tran, K.A.; Li, W.; Matzaraki, V.; van Unen, N.; Schlüter, T.; Ferreira, A.V.; et al. Long-term histone lactylation connects metabolic and epigenetic rewiring in innate immune memory. *Cell* **2025**, *188*, 2992–3012.e16. [CrossRef]
55. Cheng, C.K.; Wang, N.; Wang, L.; Huang, Y. Biophysical and biochemical roles of shear stress on endothelium: A revisit and new insights. *Circ. Res.* **2025**, *136*, 752–772. [CrossRef]
56. Campbell, J.P.; Riddell, N.E.; Burns, V.E.; Turner, M.; van Zanten, J.J.C.S.V.; Drayson, M.T.; Bosch, J.A. Acute exercise mobilises CD8+ T lymphocytes exhibiting an effector-memory phenotype. *Brain Behav. Immun.* **2009**, *23*, 767–775. [CrossRef]
57. Simpson, R.J.; Bigley, A.B.; Agha, N.; Hanley, P.J.; Bollard, C.M. Mobilizing immune cells with exercise for cancer immunotherapy. *Exerc. Sport Sci. Rev.* **2017**, *45*, 163–172. [CrossRef]
58. Kendall, A.; Hoffman-Goetz, L.; Houston, M.; MacNeil, B.; Arumugam, Y. Exercise and blood lymphocyte subset responses: Intensity, duration, and subject fitness effects. *J. Appl. Physiol.* **1990**, *69*, 251–260. [CrossRef]
59. Witard, O.C.; Turner, J.E.; Jackman, S.R.; Tipton, K.D.; Jeukendrup, A.E.; Kies, A.K.; Bosch, J.A. High-intensity training reduces CD8+ T-cell redistribution in response to exercise. *Med. Sci. Sports Exerc.* **2012**, *44*, 1689–1697. [CrossRef]
60. Peake, J.M.; Neubauer, O.; Della Gatta, P.A.; Nosaka, K. Muscle damage and inflammation during recovery from exercise. *J. Appl. Physiol.* **2017**, *122*, 559–570. [CrossRef]
61. Pedersen, B.K.; Febbraio, M.A. Muscle as an endocrine organ: Focus on muscle-derived interleukin-6. *Physiol. Rev.* **2008**, *88*, 1379–1406. [CrossRef]
62. Brooks, G.A. Lactate as a myokine and exerkine: Drivers and signals of physiology and metabolism. *J. Appl. Physiol.* **2023**, *134*, 529–548. [CrossRef]
63. Walzik, D.; Wences Chirino, T.Y.; Zimmer, P.; Joisten, N. Molecular insights of exercise therapy in disease prevention and treatment. *Signal Transduct. Target. Ther.* **2024**, *9*, 138. [CrossRef]
64. Noone, J.; Mucinski, J.M.; DeLany, J.P.; Sparks, L.M.; Goodpaster, B.H. Understanding the variation in exercise responses to guide personalized physical activity prescriptions. *Cell Metab.* **2024**, *36*, 702–724. [CrossRef]

65. Rossy, J.; Laufer, J.M.; Legler, D.F. Role of mechanotransduction and tension in T cell function. *Front. Immunol.* **2018**, *9*, 2638. [CrossRef]
66. Jeffreys, N.; Brockman, J.M.; Zhai, Y.; Ingber, D.E.; Mooney, D.J. Mechanical forces amplify TCR mechanotransduction in T cell activation and function. *Appl. Phys. Rev.* **2024**, *11*, 011304. [CrossRef]
67. Das, D.K.; Feng, Y.; Mallis, R.J.; Li, X.; Keskin, D.B.; Hussey, R.E.; Brady, S.K.; Wang, J.-H.; Wagner, G.; Reinherz, E.L.; et al. Force-dependent transition in the T-cell receptor β-subunit allosterically regulates peptide discrimination and pMHC bond lifetime. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 1517–1522. [CrossRef]
68. Feng, Y.; Reinherz, E.L.; Lang, M.J. αβ T cell receptor mechanosensing forces out serial engagement. *Trends Immunol.* **2018**, *39*, 596–609. [CrossRef]
69. Wu, P.; Zhang, T.; Liu, B.; Fei, P.; Cui, L.; Qin, R.; Zhu, H.; Yao, D.; Martinez, R.J.; Hu, W.; et al. Mechano-regulation of peptide-MHC class I conformations determines TCR antigen recognition. *Mol. Cell* **2019**, *73*, 1015–1027.e7. [CrossRef]
70. Solis, A.G.; Bielecki, P.; Steach, H.R.; Sharma, L.; Harman, C.C.D.; Yun, S.; de Zoete, M.R.; Warnock, J.N.; To, S.D.F.; York, A.G.; et al. Mechanosensation of cyclical force by PIEZO1 is essential for innate immunity. *Nature* **2019**, *573*, 69–74. [CrossRef]
71. Atcha, H.; Jairaman, A.; Holt, J.R.; Meli, V.S.; Nagalla, R.R.; Veerasubramanian, P.K.; Brumm, K.T.; Lim, H.E.; Othy, S.; Cahalan, M.D.; et al. Mechanically activated ion channel Piezo1 modulates macrophage polarization and stiffness sensing. *Nat. Commun.* **2021**, *12*, 3256. [CrossRef]
72. Mei, F.; Guo, Y.; Wang, Y.; Zhou, Y.; Heng, B.C.; Xie, M.; Huang, X.; Zhang, S.; Ding, S.; Liu, F.; et al. Matrix stiffness regulates macrophage polarisation via the Piezo1-YAP signalling axis. *Cell Prolif.* **2024**, *57*, e13640. [CrossRef]
73. Zimmer, P.; Bloch, W.; Schenk, A.; Zopf, E.M.; Hildebrandt, U.; Streckmann, F.; Beulertz, J.; Koliamitra, C.; Schollmayer, F.; Baumann, F. Exercise-induced Natural Killer Cell Activation is Driven by Epigenetic Modifications. *Int. J. Sports Med.* **2015**, *36*, 510–515. [CrossRef]
74. Kotewitsch, M.; Waranski, M.; Schmitz, B.; Mooren, F.C. Non-coding RNAs in exercise immunology: A systematic review. *J. Sport Health Sci.* **2024**, *13*, 311–338. [CrossRef]
75. Buenrostro, J.D.; Giresi, P.G.; Zaba, L.C.; Chang, H.Y.; Greenleaf, W.J. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. *Nat. Methods* **2013**, *10*, 1213–1218. [CrossRef]
76. Kaya-Okur, H.S.; Wu, S.J.; Codomo, C.A.; Pledger, E.S.; Bryson, T.D.; Henikoff, J.G.; Ahmad, K.; Henikoff, S. CUT&Tag for efficient epigenomic profiling of small samples and single cells. *Nat. Commun.* **2019**, *10*, 1930. [CrossRef]
77. Meers, M.P.; Bryson, T.D.; Henikoff, J.G.; Henikoff, S. Improved CUT&RUN chromatin profiling tools. *eLife* **2019**, *8*, e46314. [CrossRef]
78. Proske, U.; Morgan, D.L. Muscle damage from eccentric exercise: Mechanism, mechanical signs, adaptation and clinical applications. *J. Physiol.* **2001**, *537*, 333–345. [CrossRef]
79. Ross, R.; Goodpaster, B.H.; Koch, L.G.; Sarzynski, M.A.; Kohrt, W.M.; Johannsen, N.M.; Skinner, J.S.; Castro, A.; A Irving, B.; Noland, R.C.; et al. Precision exercise medicine: Understanding exercise response variability. *Br. J. Sports Med.* **2019**, *53*, 1141–1153. [CrossRef]
80. Sun, K.; Li, X.; Scherer, P.E. Extracellular matrix (ECM) and fibrosis in adipose tissue: Overview and perspectives. *Compr. Physiol.* **2023**, *13*, 4387–4407. [CrossRef]
81. Catalán, V.; Gómez-Ambrosi, J.; Rodríguez, A.; Frühbeck, G. Role of extracellular matrix remodelling in adipose tissue pathophysiology: Relevance in the development of obesity. *Histol. Histopathol.* **2012**, *27*, 1515–1528. [CrossRef]
82. Nait Irahal, I. Adipose tissue extracellular matrix remodeling: A driver of obesity and insulin resistance. *Cell Biochem. Funct.* **2026**, *44*, e70188. [CrossRef]
83. Böhm, A.; Weigert, C.; Staiger, H.; Häring, H.-U. Exercise and diabetes: Relevance and causes for response variability. *Endocrine* **2016**, *51*, 390–401. [CrossRef]
84. Hrubeniuk, T.J.; Bonafiglia, J.T.; Bouchard, D.R.; Gurd, B.J.; Sénéchal, M. Directions for exercise treatment response heterogeneity and individual response research. *Int. J. Sports Med.* **2022**, *43*, 11–22. [CrossRef]

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