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Review

Exercise Adaptation as an Immunometabolic Process: A Systems-Level Perspective on *NLRP3* Inflammasome Activation and *PPARD*-Mediated Metabolic Signaling

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Abstract

Background: Exercise adaptation is increasingly recognized as an immunometabolic process driven by coordinated interactions among inflammatory signaling, mitochondrial regulation, metabolic homeostasis, and recovery-associated physiology. Within this framework, *NLRP3* inflammasome activation and *PPARD*-mediated metabolic signaling have emerged as biologically relevant pathways potentially involved in exercise-induced physiological adaptation. However, the contribution of regulatory genetic variations linking these pathways remains poorly characterized. **Objective:** To synthesize current evidence regarding the integration of *NLRP3*- and *PPARD*-related pathways in exercise immunometabolism and adaptive physiological responses to exercise, with particular emphasis on the regulatory variants *NLRP3* rs10754558 and *PPARD* rs2267668 as potential contributors to interindividual variability in exercise adaptation. **Methods:** A structured narrative review complemented by exploratory systems-level in silico analyses was conducted using the PubMed, Scopus, and Web of Science databases until March 2026. Evidence related to exercise physiology, inflammatory regulation, metabolic adaptation, and exercise-associated phenotypes involving the *NLRP3* and *PPARD* pathways was evaluated. Complementary analyses included functional annotation, protein–protein interaction network analysis, and pathway enrichment using STRING, Reactome, KEGG, Gene Ontology, and other publicly available genomic databases. Particular attention was given to the functional and regulatory context of rs10754558 and rs2267668 within the interconnected inflammatory and metabolic pathways relevant to exercise adaptation. **Results:** The reviewed evidence identified recurrent interactions among the inflammatory and metabolic pathways involved in exercise adaptation and recovery. *NLRP3* rs10754558 and *PPARD* rs2267668 were identified as candidate regulatory variants potentially positioned at the interface between inflammatory responsiveness and metabolic flexibility, providing a biologically plausible framework for understanding the interindividual variability in exercise adaptation. Exploratory system-level analyses identified recurrent associations among inflammatory signaling, mitochondrial function, energy-sensing pathways, and metabolic regulation. These findings primarily reflect the functional annotations and system-level pathway associations identified through exploratory analyses. **Conclusions:** Current evidence supports a systems-level physiological framework in which inflammatory and metabolic pathways

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interact dynamically during exercise adaptation and recovery. *NLRP3*- and *PPARD*-related pathways, including the candidate regulatory variants rs10754558 and rs2267668, may contribute to interindividual variability in exercise-associated physiological responses and represent promising targets for future hypothesis-driven investigations in exercise immunometabolism, exercise genomics and precision exercise medicine.

Keywords: exercise immunometabolism; inflammasome signaling; *PPARD*; exercise physiology; mitochondrial regulation; oxidative stress; systems-level adaptation

1. Introduction

Exercise adaptation is increasingly recognized as a complex and dynamic physiological process resulting from coordinated interactions among metabolic regulation, inflammatory signaling, mitochondrial remodeling, tissue repair, and recovery. Rather than depending on isolated molecular determinants, interindividual variability in exercise performance, metabolic efficiency, tissue remodeling, endurance capacity, and recovery dynamics emerges through multidimensional interactions involving training load, nutritional status, sleep quality, psychosocial stress, immune regulation, and energetic homeostasis [1–4]. Accordingly, contemporary exercise physiology has progressively shifted from reductionist candidate-gene interpretations to systems-level frameworks, in which exercise-related phenotypes are understood as context-dependent physiological responses shaped by interconnected molecular and environmental regulatory networks [5–7].

Recent advances in exercise immunology and molecular physiology have highlighted inflammatory and metabolic pathways as central regulators of adaptation to repeated exercise-induced stress [8,9]. Repeated physiological stress promotes coordinated adaptive responses involving mitochondrial remodeling, substrate utilization, redox-sensitive signaling, vascular adaptation, and immune–metabolic communication [10,11]. These responses are mediated through interconnected pathways involving AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), calcium-dependent signaling, and cellular stress response systems [12,13]. Collectively, these mechanisms contribute to energetic homeostasis, physiological resilience and long-term cardiometabolic adaptation.

Although regular physical activity exerts predominantly anti-inflammatory and cardioprotective effects, elite and highly trained athletes are frequently exposed to repeated bouts of high-intensity or prolonged exercise, which can induce transient oxidative stress, tissue damage, mitochondrial perturbation, and systemic inflammatory activation [14–16]. Under appropriate recovery conditions, these responses contribute to tissue remodeling and physiological adaptations. However, excessive cumulative training load, insufficient recovery, chronic energy imbalance, and sustained physiological stress may favor maladaptive responses associated with persistent inflammation, oxidative imbalance, impaired mitochondrial regulation, and reduced adaptive capacity [17,18]. Therefore, exercise-induced inflammation should be interpreted as a context-dependent physiological response rather than an inherently detrimental process [19].

Within this physiological framework, the *NLRP3* inflammasome has emerged as a biologically relevant innate immune signaling platform linking mitochondrial dysfunction, oxidative stress, ionic imbalance, and metabolic perturbations to downstream inflammatory activation. Experimental and mechanistic evidence suggests that exercise-induced mitochondrial stress and reactive oxygen species (ROS) generation may activate inflammasome pathways. However, much of the available evidence is derived from experimental systems and inflammatory or cardiometabolic disease models, whereas direct exercise-specific

evidence remains comparatively limited. Consequently, the physiological relevance of *NLRP3*-associated signaling during exercise adaptation should be interpreted within a mechanistic and hypothesis-generating framework, rather than as a definitively established exercise-specific mechanism. These pathways are associated with caspase-1 activation and maturation of IL-1β and IL-18, cytokines involved in inflammatory regulation, endothelial adaptation, tissue remodeling, and metabolic homeostasis [20–23].

Among the metabolic regulators involved in exercise adaptation, peroxisome proliferator-activated receptor delta (*PPARD/PPARδ*) has received increasing attention because of its central role in coordinating fatty acid oxidation, oxidative metabolism, mitochondrial biogenesis, substrate utilization, and metabolic flexibility. *PPARD*-dependent signaling has been implicated in transcriptional pathways associated with endurance adaptation, mitochondrial efficiency, skeletal muscle oxidative phenotypes, and recovery physiology, although supporting evidence originates from a combination of exercise-related and experimental metabolic studies [24–26].

Within this immunometabolic context, genetic variability affecting inflammatory and metabolic signaling pathways has emerged as a potential contributor to interindividual variability in exercise-related physiological adaptation. In particular, the *NLRP3* rs10754558 polymorphism, located within the 3′ untranslated region (3′UTR), and the *PPARD* rs2267668 intronic variant have been proposed as candidate modulators of inflammatory responsiveness and metabolic regulation. Nevertheless, currently available evidence remains heterogeneous and fragmented across exercise physiology, sports genomics, immunology, metabolism, and cardiovascular research. Furthermore, direct functional evidence in athletic populations remains limited, and most available findings are derived from broader immunometabolic and cardiometabolic contexts rather than from well-characterized exercise cohorts [27,28]. The selection of rs10754558 and rs2267668 was based on their potential regulatory relevance, biological plausibility, and reported associations with inflammatory and metabolic phenotypes. These variants were specifically chosen because they represent candidate molecular interfaces linking inflammatory responsiveness and metabolic flexibility, which are two central components of exercise immunometabolism.

Importantly, accumulating evidence indicates that inflammatory and metabolic pathways interact dynamically during exercise adaptation and recovery phases. Rather than functioning as isolated biological systems, immune regulation, substrate utilization, mitochondrial activity, and cellular stress responses collectively contribute to the maintenance of physiological homeostasis and adaptive remodeling following repeated exercise exposure. Consequently, the influence of individual genetic variants should be interpreted within the context of these interconnected regulatory networks rather than as independent determinants of exercise-related phenotypes [29,30].

Despite the increasing interest in exercise immunometabolism, sports genomics, and molecular physiology, important gaps remain in our understanding of how inflammatory and metabolic pathways interact within a unified framework of exercise adaptation. Previous reviews have generally examined inflammasome signaling, mitochondrial adaptation, metabolic regulation, and exercise-associated immune responses as separate biological processes. In contrast, the present review integrates these dimensions around two candidate regulatory variants, *NLRP3* rs10754558 and *PPARD* rs2267668, while explicitly distinguishing direct exercise evidence from indirect mechanistic evidence derived from experimental and cardiometabolic studies.

2. Results

2.1. NLRP3 (rs10754558) and Exercise-Related Inflammatory Responses

The reviewed evidence identified the recurrent activation of innate immune and redox-sensitive inflammatory pathways during acute and high-intensity exercise. Experimental exercise physiology studies have consistently demonstrated that repeated physiological stress may induce transient mitochondrial perturbations, increased reactive oxygen species (ROS) generation, ATP turnover, calcium flux alterations, and activation of downstream inflammatory signaling pathways associated with tissue remodeling and recovery-associated adaptation. These responses are predominantly observed in acute exercise and skeletal muscle stress models, supporting the concept that transient inflammatory activation is part of the adaptive physiological response to repeated exercise-induced stress rather than exclusively pathological inflammation [23].

Across the analyzed literature, recurrent pathway associations linked *NLRP3*-related signaling with mitochondrial stress responses, ROS-sensitive regulation, NF-κB activation, inflammasome-associated cytokine maturation and recovery-associated inflammatory modulation. Exercise-related studies directly support the activation of inflammatory and oxidative stress pathways following intense or prolonged physiological stress exposure, whereas complementary mechanistic evidence derived from inflammatory and cardiometabolic studies further reinforces the role of *NLRP3*-associated immune signaling [21,24].

Functional annotation analyses consistently identified rs10754558 within the 3′ untranslated region (3′UTR) of the *NLRP3* gene, a non-coding regulatory region potentially involved in post-transcriptional modulation and mRNA stability. Evidence supporting the potential functional relevance of this variant was mainly derived from inflammatory and cardiometabolic contexts rather than direct exercise physiology investigations. Consequently, the current evidence is insufficient to establish direct associations between rs10754558 and exercise performance, recovery efficiency, or endurance-related phenotypes in athletic populations [27].

Collectively, the available evidence supports the involvement of *NLRP3*-associated inflammatory signaling in the immunometabolism of exercise. However, most supporting data originate from mechanistic, inflammatory, and cardiometabolic studies, whereas direct functional evidence in athletes is limited. Current evidence is insufficient to establish a direct association between rs10754558 and exercise-related physiological outcomes [28].

2.2. PPARD rs2267668 and Metabolic Adaptation

PPARD-related signaling pathways have emerged as biologically relevant components of metabolic adaptation during exercise because of their involvement in fatty acid oxidation, mitochondrial biogenesis, substrate utilization, and energy homeostasis. Across the reviewed literature, *PPARD*-associated mechanisms were consistently linked to oxidative skeletal muscle metabolism and endurance-related physiological adaptation, particularly under conditions of prolonged energy demand and repeated exercise-induced stress exposure [31].

Exercise-related studies and complementary experimental models have consistently linked *PPARD*-associated signaling to oxidative phosphorylation, fatty acid utilization, metabolic flexibility, and mitochondrial adaptation. These pathways involve coordinated interactions with AMPK, PGC-1α, and SIRT1, which contribute to substrate utilization efficiency, maintenance of energetic homeostasis, and adaptive responses to repeated physiological stressors. While direct exercise-based evidence supports the relevance of these mechanisms, additional support is derived from metabolic and cardiometabolic studies, emphasizing the role of *PPARD* as a component of broader metabolic adaptation networks rather than an isolated determinant of exercise responsiveness [32].

Functional annotation analyses identified rs2267668 as an intronic regulatory variant within the *PPARD* gene, potentially associated with transcriptional modulation and metabolic pathway regulation. Although direct physiological evidence in athletic populations remains limited, previous studies suggest that *PPARD*-related variants may influence pathways associated with oxidative metabolism, mitochondrial efficiency, and endurance-related adaptations. However, most of the currently available evidence is derived from broader metabolic and cardiometabolic research rather than direct athlete-based investigations. Consequently, the physiological interpretation of rs2267668 should remain restricted to biological plausibility and hypothesis generation rather than deterministic prediction of exercise performance or exercise responsiveness [33].

However, the available evidence does not establish an independent effect of *PPARD* rs2267668 on athletic performance or exercise capacity. Metabolic adaptation is a highly multifactorial process influenced by the training load, nutritional status, mitochondrial function, recovery physiology, environmental exposure, and broader polygenic interactions. Overall, current evidence supports the biological plausibility of *PPARD*-mediated metabolic regulation as a contributor to exercise adaptation and recovery. Nevertheless, direct evidence linking rs2267668 to exercise-related phenotypes remains limited, and its physiological significance requires further investigation in exercise-specific settings.

2.3. Integrated Inflammatory–Metabolic Pathways Linking NLRP3 and PPARD

The reviewed evidence supports the existence of interconnected inflammatory and metabolic pathways involved in exercise-induced physiological adaptations and stress responses. Rather than functioning independently, inflammatory signaling and metabolic regulation appear to converge through coordinated mechanisms associated with mitochondrial perturbation, redox-sensitive signaling, substrate utilization, and adaptive cellular responses during repeated exercise [34,35].

Mitochondrial signaling may represent a central biological interface linking inflammatory activation and metabolic adaptation during exercise. Through mechanisms involving redox-sensitive signaling, energetic stress sensing, and substrate utilization, mitochondrial pathways contribute to the coordination of immune and metabolic responses associated with exercise-induced physiological stress [34,36].

Although support for these interactions is derived from both exercise-based and mechanistic studies, the strength of evidence varies across pathways and should be interpreted according to the evidence classification framework adopted in this review.

Within this framework, *NLRP3*-related signaling was predominantly associated with inflammatory responsiveness and innate immune activation, whereas *PPARD*-associated pathways were mainly linked to oxidative substrate utilization and metabolic regulation. Importantly, current evidence does not support deterministic interpretations of the isolated physiological influence of *NLRP3* rs10754558 or *PPARD* rs2267668 on exercise performance or athletic phenotypes. Instead, these pathways should be interpreted as interconnected modulatory components within broader physiological networks influenced by training load, recovery dynamics, nutritional status, mitochondrial function, environmental exposure and polygenic interactions.

Collectively, these findings support a biologically plausible framework linking inflammatory signaling and metabolic regulation during exercise adaptation and its recovery. Because the evidence supporting *NLRP3*- and *PPARD*-related pathways originates from heterogeneous research contexts, including human exercise studies, experimental models, and non-exercise inflammatory or cardiometabolic investigations, the available literature was categorized according to the evidence classification framework described in the Meth-

ods section. The strength and origin of the evidence supporting the principal biological mechanisms discussed in this review are summarized in Table 1.

Table 1. Strength and origin of evidence supporting the involvement of *NLRP3*- and *PPARD*-related pathways in exercise immunometabolism.

Biological Mechanism	Direct Exercise Evidence (Level 1)	Experimental Exercise-Related Evidence (Level 2)	Indirect Mechanistic Evidence (Level 3)	Overall Strength of Exercise-Specific Evidence
NLRP3 inflammasome activation	Human studies reporting transient inflammasome-related responses following acute or high-intensity exercise	Exercise-induced skeletal muscle stress models and murine exercise studies evaluating inflammasome signaling	Obesity, insulin resistance, cardiovascular disease, chronic inflammatory disorders	Moderate
ROS-mediated signaling	Human exercise interventions demonstrating transient oxidative stress responses and redox-sensitive adaptation	Cellular and animal models investigating ROS-dependent signaling pathways	Oxidative stress-related diseases and inflammatory disorders	Strong
Mitochondrial adaptation and remodeling	Training studies showing mitochondrial biogenesis and oxidative adaptation in skeletal muscle	Experimental models evaluating mitochondrial stress responses and bioenergetic regulation	Metabolic disorders, mitochondrial dysfunction syndromes	Strong
PPARD-mediated metabolic regulation	Human endurance and exercise-training studies reporting associations with oxidative metabolism and substrate utilization	Skeletal muscle and animal models examining *PPARD*-dependent metabolic signaling	Cardiometabolic diseases, obesity, dyslipidemia, insulin resistance	Moderate
Fatty acid oxidation and metabolic flexibility	Exercise interventions and athlete-based studies evaluating substrate utilization during prolonged exercise	Experimental models of oxidative metabolism and metabolic adaptation	Obesity and insulin resistance studies	Strong
Integrated immunometabolic regulation	Limited direct evidence simultaneously evaluating inflammatory and metabolic pathways in athletes	Systems biology studies, mechanistic models, and exercise-related experimental investigations	Chronic inflammatory and cardiometabolic disease models	Limited-to-moderate

Evidence classification framework: Level 1, direct exercise evidence derived from human exercise interventions, athlete cohorts, and training studies; Level 2, experimental exercise-related evidence derived from animal, skeletal muscle, or cellular models relevant to exercise adaptation; Level 3, indirect mechanistic evidence derived from inflammatory, metabolic, cardiovascular, or chronic disease contexts. The strength of evidence was classified as strong (multiple human exercise studies), moderate (limited direct human evidence plus experimental support), or limited (predominantly indirect evidence).

A schematic representation of this interconnected immunometabolic model is shown in Figure 1.

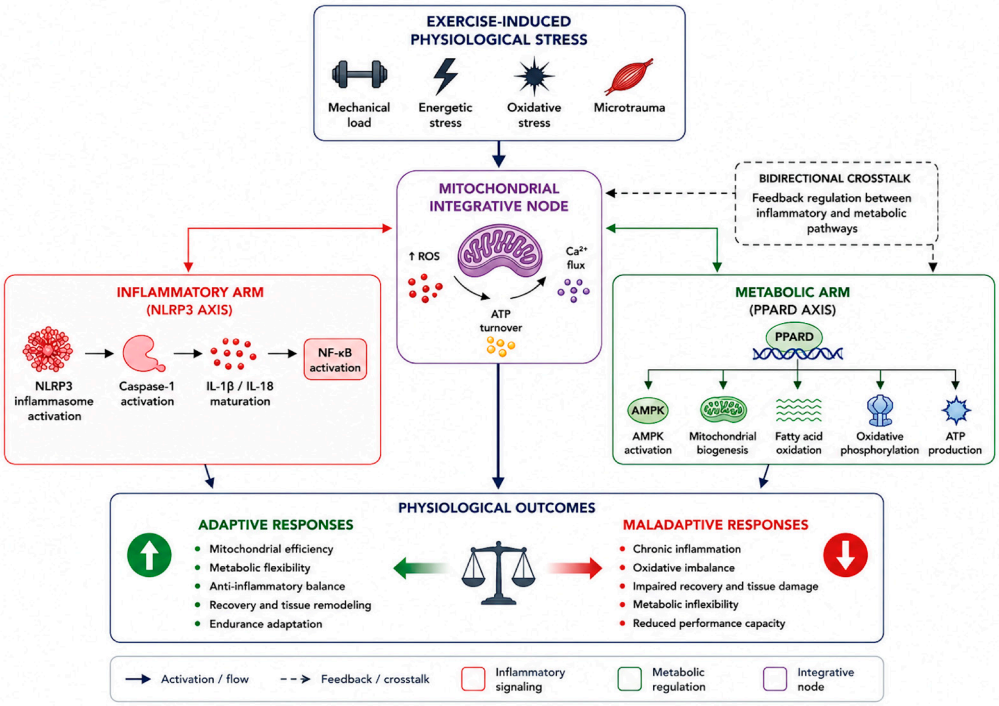


Figure 1. Integrated inflammatory–metabolic pathways linking *NLRP3* (rs10754558) and *PPARD* (rs2267668) in exercise immunometabolism. The schematic model illustrates the interactions between exercise-induced physiological stress, inflammatory signaling, mitochondrial regulation, and metabolic adaptation during exercise and recovery. Acute physiological stress promotes ROS generation, ATP turnover, and stress-responsive signaling, linking inflammatory (*NLRP3/NF-κB*) and metabolic (*PPARD/AMPK/PGC-1α*) pathways together. Shared mechanisms involving mitochondrial regulation, oxidative metabolism, and energy-sensing pathways contribute to the adaptive physiological responses and recovery following repeated exercise exposure. The proposed framework represents a biologically plausible systems-level model and should not be interpreted as evidence of deterministic exercise-related effects. The interactions illustrated represent biologically plausible relationships derived from direct exercise evidence and complementary mechanistic evidence and should not be interpreted as experimentally validated causal relationships.

2.4. Functional Annotation and Exercise-Related Evidence for NLRP3 rs10754558 and PPARD rs2267668

Functional annotation analyses were performed to explore the potential biological relevance of *NLRP3* rs10754558 and *PPARD* rs2267668 within inflammatory and metabolic pathways associated with exercise adaptation and physiological stress responses. Publicly available genomic and regulatory databases, including dbSNP, Ensembl, GTEx, RegulomeDB, and LDlink, were consulted to evaluate genomic localization, predicted regulatory context, potential transcriptional relevance, and broader genomic architecture [37–40].

NLRP3 rs10754558 is a non-coding regulatory variant located within the 3′ untranslated region (3′UTR) of the *NLRP3* gene, which is implicated in post-transcriptional regulatory processes involving mRNA stability and microRNA-mediated regulation. Previous evidence derived primarily from inflammatory, autoimmune, and cardiometabolic contexts suggests that this variant may influence inflammasome-related signaling responsiveness under conditions of oxidative or metabolic stress [41,42].

In contrast, *PPARD* rs2267668 is an intronic regulatory variant located within the *PPARD* locus and is associated with pathways involved in oxidative metabolism, substrate utilization, mitochondrial function, and metabolic flexibility [43].

Importantly, neither rs10754558 nor rs2267668 should be assumed to represent the sole functional variant within their respective genomic regions. The functional effects

attributed to these polymorphisms may reflect broader regulatory architectures, including linkage disequilibrium with neighboring variants influencing gene expression, chromatin accessibility, or regulatory activity. Consequently, these variants should be interpreted within the broader regulatory architecture of their respective genes.

However, direct exercise-specific evidence for these variants remains limited. Among the two polymorphisms, rs2267668 has been evaluated in selected studies investigating training responsiveness, aerobic exercise adaptation, and exercise-related metabolic phenotypes, suggesting its potential role in modulating metabolic responses to physical activity. In contrast, direct evidence linking rs10754558 to exercise-related outcomes remains scarce, and its relevance to exercise adaptation is primarily inferred from its established involvement in inflammatory regulation and broader cardiometabolic processes. Consequently, the available literature supports different levels of evidence for the two variants, with rs2267668 demonstrating limited direct exercise-related support and rs10754558 being largely supported by mechanistic plausibility and indirect biological evidence.

From an exercise physiology perspective, these observations are biologically relevant because repeated exercise induces transient inflammatory activation, mitochondrial perturbation, oxidative stress response, and metabolic remodeling. Therefore, the physiological processes influenced by *NLRP3*- and *PPARD*-related pathways represent plausible mechanistic interfaces through which regulatory genetic variation could contribute to interindividual variability in adaptive responses to exercise. However, direct experimental validation in athletic populations is insufficient.

A summary of the current genomic annotation, regulatory evidence, exercise-related findings, and translational considerations for rs10754558 and rs2267668 is provided in Supplementary Table S3. Importantly, current evidence does not support deterministic conclusions regarding exercise performance, athletic capacity, or training responsiveness based on the isolated genetic variants. Instead, rs10754558 and rs2267668 should be interpreted as potential modulatory components within broader interconnected inflammatory–metabolic networks influenced by training load, nutritional status, mitochondrial function, recovery physiology, environmental exposure, and complex polygenic interactions.

Collectively, the available evidence supports the relevance of rs10754558 and rs2267668 as candidate regulatory variants potentially linking inflammatory and metabolic pathways involved in exercise immunometabolism. Current evidence is primarily derived from functional annotation studies and complementary mechanistic investigations. The principal functional annotations and physiological interpretations are summarized in Table 2.

Table 2. Functional annotation and physiological relevance of *NLRP3* rs10754558 and *PPARD* rs2267668 in exercise immunometabolism.

Variant/Gene	Genomic Localization	Predicted Regulatory Relevance	Recurrently Associated Biological Pathways	Potential Biological Relevance in Pathways Associated with Exercise Adaptation
NLRP3 rs10754558	3′ untranslated region (3′UTR)	Non-coding regulatory variant potentially associated with post-transcriptional modulation, mRNA stability, and microRNA-mediated regulation	Inflammasome activation, innate immune signaling, NF-κB-associated inflammatory pathways, ROS-sensitive signaling, mitochondrial stress responses	Modulation of inflammatory adaptation, recovery-associated immune regulation, tissue remodeling, oxidative stress responsiveness, and exercise-associated immunometabolic adaptation

Table 2. *Cont.*

Variant/Gene	Genomic Localization	Predicted Regulatory Relevance	Recurrently Associated Biological Pathways	Potential Biological Relevance in Pathways Associated with Exercise Adaptation
PPARD rs2267668	Intronic regulatory region	Predicted transcriptional regulatory variant potentially associated with oxidative metabolic signaling and mitochondrial regulation	Fatty acid oxidation, oxidative phosphorylation, mitochondrial biogenesis, AMPK signaling, PGC-1α-mediated pathways, metabolic flexibility	Regulation of substrate utilization, mitochondrial adaptation, oxidative metabolism, energetic homeostasis, endurance-associated metabolic regulation, and recovery-related metabolic adaptation
Integrated inflammatory–metabolic interaction	Systems-level physiological interface	Coordinated interaction between inflammatory and metabolic regulatory systems during physiological stress adaptation	AMPK signaling, ROS-sensitive pathways, NF-κB signaling, oxidative metabolism, mitochondrial remodeling, energy-sensing pathways	Integration of inflammatory signaling, metabolic flexibility, mitochondrial resilience, tissue repair, recovery physiology, and adaptation to repeated exercise-induced stress

The table summarizes the genomic localization, predicted regulatory relevance, recurrent biological pathways, and potential physiological implications of *NLRP3* rs10754558 and *PPARD* rs2267668 in exercise immunometabolism. Functional annotations were derived from publicly available genomic and regulatory databases and interpreted within an exploratory, systems-level physiological framework. The proposed interpretations should not be considered as evidence of deterministic exercise-related phenotypes. Abbreviations: AMPK, AMP-activated protein kinase; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; 3′UTR, 3′ untranslated region.

2.5. Systems-Level Pathway Enrichment and Immunometabolic Integration

Pathway enrichment analyses and system-level evidence integration supported the existence of coordinated inflammatory, metabolic, mitochondrial, and redox-sensitive signaling pathways associated with exercise-induced physiological responses. Rather than functioning as isolated biological systems, these interconnected mechanisms converge through coordinated immunometabolic regulation involving mitochondrial regulation, inflammatory signaling, substrate utilization, and cellular stress responses [44].

Among the most consistently enriched pathways were oxidative phosphorylation, fatty acid β-oxidation, AMPK signaling, *PPAR*-associated metabolic regulation, PGC-1α-mediated mitochondrial biogenesis, ROS-sensitive signaling, NF-κB-associated inflammatory responses, and inflammasome-related pathways. Collectively, these interconnected pathways contribute to energetic homeostasis, mitochondrial remodeling, inflammatory modulation, and substrate utilization efficiency during repeated exercise-induced stress exposure. The recurrent enrichment of mitochondrial and metabolic pathways further supports the physiological relevance of coordinated bioenergetic regulation in exercise-induced immunometabolism [45].

Integrated pathway profiles identified recurrent convergence among *NLRP3* inflammasome signaling, IL-1 family pathways, NF-κB-associated inflammatory regulation, oxidative phosphorylation, mitochondrial stress response pathways, fatty acid oxidation, and energy-sensing mechanisms [46]. These findings support the interpretation that exercise adaptation emerges through coordinated immunometabolic regulation rather than isolated inflammatory or metabolic pathway activation. Instead, these pathways should be interpreted as modulatory components within broader interconnected physiological networks

influenced by training load, recovery physiology, nutritional status, mitochondrial function, environmental exposure, and polygenic interactions [47,48].

From a translational perspective, the integrated pathway profiles support the potential relevance of multidimensional physiological approaches that combine inflammatory, metabolic, mitochondrial, and recovery-associated biomarkers, rather than isolated molecular indicators. Future investigations integrating exercise physiology, mitochondrial phenotyping, inflammatory profiling, metabolomics, transcriptomics, and longitudinal recovery assessment may contribute to a more comprehensive understanding of adaptive and maladaptive responses to repeated physiological stress exposure.

Enrichment findings should be interpreted as exploratory functional associations derived from the publicly available biological databases. These analyses provide a functional context for interpreting the relationships among inflammatory, metabolic, and mitochondrial pathways. The principal enriched pathways associated with exercise immunometabolism and physiological adaptation are summarized in Table 3, and the system-level pathway interaction model derived from the enrichment analyses is illustrated in Figure 2.

Table 3. Principal enriched pathways associated with exercise immunometabolism and physiological adaptation.

Enriched Pathway	Principal Physiological Role	Recurrent Integrative Mechanisms	Potential Relevance in Exercise Adaptation
Oxidative phosphorylation	ATP production and mitochondrial respiration	Mitochondrial respiratory complexes, oxidative metabolism, energetic stress adaptation	Energetic efficiency and endurance performance
Fatty acid metabolism	Lipid utilization and substrate flexibility	*PPARD*-associated signaling, β-oxidation pathways, oxidative metabolic regulation	Sustained energy supply during prolonged exercise
AMPK signaling	Cellular energy sensing and metabolic regulation	Energetic stress signaling, mitochondrial adaptation, substrate utilization control	Metabolic homeostasis during exercise stress
PGC-1α-mediated mitochondrial biogenesis	Mitochondrial remodeling and oxidative adaptation	Mitochondrial transcriptional regulation, oxidative metabolism, mitochondrial plasticity	Enhanced oxidative capacity
ROS-sensitive signaling	Redox-sensitive adaptation and stress regulation	Reactive oxygen species signaling, oxidative stress responses, redox regulation	Adaptive cellular signaling
NF-κB-associated inflammatory signaling	Inflammatory regulation and immune activation	Cytokine-mediated signaling, stress-responsive inflammatory pathways	Exercise-related inflammatory modulation
Inflammasome activation pathways	Innate immune sensing and inflammatory responsiveness	*NLRP3* signaling, IL-1β and IL-18 maturation, stress-associated inflammatory activation	Regulation of inflammatory responses to physiological stress
Mitochondrial stress-response pathways	Maintenance of mitochondrial homeostasis during physiological stress	Redox-sensitive signaling, ATP turnover, calcium flux regulation	Cellular adaptation to energetic demand
Metabolic flexibility pathways	Dynamic regulation of substrate utilization	*PPARD* signaling, oxidative metabolism, energy-sensing mechanisms	Efficient fuel selection during variable exercise conditions

Table 3. *Cont.*

Enriched Pathway	Principal Physiological Role	Recurrent Integrative Mechanisms	Potential Relevance in Exercise Adaptation
Systems-level inflammatory–metabolic integration	Coordinated interaction between inflammatory and metabolic systems	AMPK, NF-κB, ROS-sensitive pathways, mitochondrial signaling	Integrated physiological adaptation

Principal enriched pathways identified through exploratory systems-level analyses of *NLRP3*- and *PPARD*-associated networks. Pathways were derived from the STRING, Reactome, KEGG, and Gene Ontology databases and grouped according to their predominant physiological functions. Functional interpretations represent biologically plausible mechanisms associated with exercise immunometabolism and should be interpreted within an exploratory framework, rather than as direct evidence of exercise-specific pathway activation.

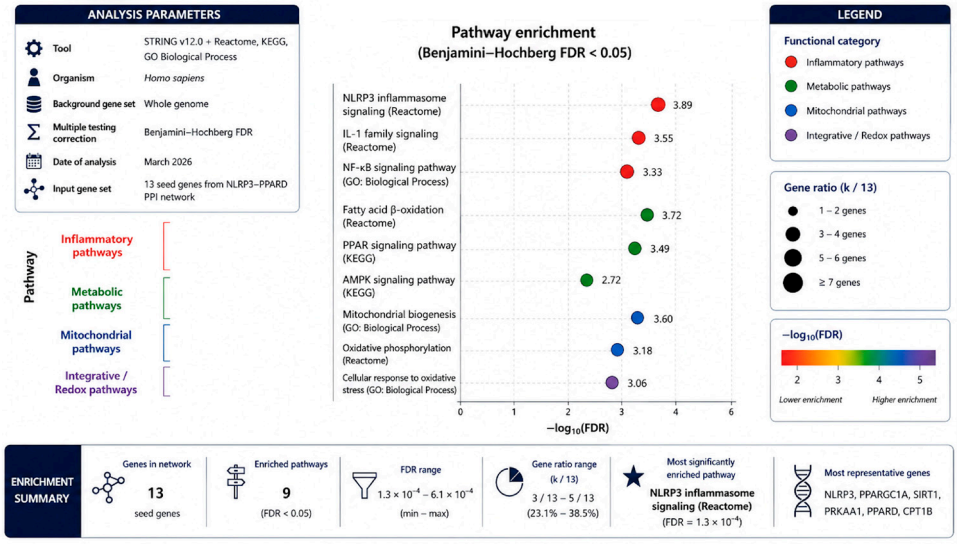


Figure 2. Pathway enrichment analysis of the exercise immunometabolism gene network. Exploratory systems-level analyses were performed using a predefined 13-gene set associated with inflammatory regulation, metabolic adaptation, mitochondrial function, and exercise immunometabolism (*NLRP3*, *PPARD*, *IL1B*, *IL18*, *CASP1*, *NFKB1*, *TNF*, *PRKAA1*, *PPARGC1A*, *SIRT1*, *AKT1*, *MTOR*, and *PPARA*). Protein–protein interaction networks were generated using STRING v12.0 under *Homo sapiens* settings and subsequently analyzed using the Reactome, Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Ontology Biological Process databases. Pathways were ranked according to Benjamini–Hochberg false discovery rate (FDR)-adjusted *p*-values, and only pathways with FDR < 0.05 were retained for interpretation. Functional categories were grouped into inflammatory, metabolic, mitochondrial, and integrative redox-related pathways. The dot size represents the proportion of genes within the input gene set contributing to each enriched pathway (gene ratio), whereas the color intensity reflects the enrichment significance −log10(FDR). Because enrichment analyses are dependent on existing biological annotations and database coverage, the identified pathways should be interpreted as exploratory and hypothesis-generating functional associations rather than as direct evidence of exercise-specific physiological regulation.

3. Discussion

This review supports a systems-level interpretation of exercise adaptation, in which inflammatory and metabolic regulatory pathways interact dynamically during repeated physiological stress exposure. The recurrent identification of mitochondrial and redox-sensitive pathways across evidence domains further supports their potential integrative role in exercise immunometabolism [36,47,48].

A central finding of this review is that exercise-induced inflammation should be interpreted as a context-dependent physiological response. Acute and transient inflammatory activation may contribute to tissue remodeling, immune surveillance, vascular adaptation, and recovery after repeated training stimuli. However, excessive or insufficiently com-

pensated physiological stress may favor maladaptive responses associated with persistent inflammation, oxidative imbalance, impaired mitochondrial regulation and reduced adaptive capacity [49–51]. This interpretation aligns with contemporary exercise physiology models, in which adaptation depends on the balance between physiological stress exposure and recovery capacity, rather than isolated molecular pathway activation.

Within this framework, the *NLRP3* inflammasome represents a relevant inflammatory interface linking mitochondrial perturbation, reactive oxygen species generation, ionic imbalance, danger-associated molecular signals and downstream cytokine maturation. Exercise-induced mitochondrial stress may transiently activate inflammasome-related pathways that contribute to immune regulation, tissue remodeling, and recovery-associated physiological responses in skeletal muscle. These mechanisms may participate in the adaptive response to repeated exercise exposure through interactions with the mitochondrial and metabolic regulatory systems [7,10].

Therefore, the functional relevance of *NLRP3* rs10754558 should be interpreted cautiously. Although this variant is located in the 3′ untranslated region and may influence post-transcriptional regulation, mRNA stability, or inflammatory responsiveness, direct evidence in athletic populations remains limited. Most mechanistic support derives from inflammatory, cardiometabolic, and oxidative stress contexts rather than from longitudinal exercise cohorts. Consequently, *NLRP3* rs10754558 should be considered a potential modulatory marker of inflammatory responsiveness and not a deterministic predictor of exercise performance, recovery capacity or maladaptive outcomes [45,52].

The reviewed evidence suggests the potential physiological relevance of *PPARD*-associated metabolic regulation in exercise adaptation. *PPARD*-related pathways appear to be closely linked to substrate utilization efficiency, oxidative metabolic adaptation, mitochondrial function, and maintenance of energetic balance during prolonged physiological demand. Through interactions with AMPK, PGC-1α, and SIRT1, these mechanisms may contribute to adaptive metabolic responses that support endurance physiology, metabolic flexibility, and exercise-associated energy homeostasis [9,32,50,53].

Similarly, *PPARD* rs2267668 may represent a regulatory variant with potential relevance to metabolic adaptation. The interpretation of non-coding variants remains complex because regulatory effects may be influenced by tissue-specific expression patterns and linkage disequilibrium with neighboring functional loci. Consequently, longitudinal exercise studies integrating transcriptomic, epigenetic, and functional genomic approaches are required to clarify the biological relevance of rs10754558 and rs2267668 in adaptive responses to training [49].

Evidence supporting the involvement of *NLRP3*- and *PPARD*-related pathways in exercise immunometabolism is heterogeneous. Direct evidence is derived mainly from human exercise interventions, athlete-based studies, and physiological investigations assessing inflammatory, metabolic, and mitochondrial responses to exercise. Additional support comes from animal and cellular models, whereas a substantial part of the mechanistic framework is extrapolated from the contexts of inflammatory, metabolic, and cardiometabolic diseases. Therefore, the interpretation of the proposed *NLRP3*–*PPARD* interaction should consider the heterogeneous origin and strength of the currently available evidence.

A major contribution of this review is the integration of inflammatory and metabolic regulation within the exercise immunometabolism framework [54]. Pathway enrichment analyses identified associations among inflammatory signaling, mitochondrial regulation, substrate utilization, and energy-sensing pathways, supporting the interpretation that adaptive exercise responses involve coordinated immunometabolic regulation rather than isolated molecular mechanisms [12,53].

The proposed framework may have important implications for recovery physiology. Efficient recovery following repeated exercise exposure likely depends on coordinated regulation of inflammatory resolution, energetic restoration, tissue repair, and metabolic recovery processes [52,55]. When appropriately regulated, these adaptive responses may contribute to improved physiological resilience and the restoration of homeostasis. Conversely, impaired recovery regulation may favor maladaptive responses associated with persistent fatigue, oxidative imbalance, and reduced physiological adaptation [56].

The proposed framework may also help explain interindividual variability in exercise adaptation. Individuals exposed to similar training stimuli may exhibit distinct physiological responses because adaptation is influenced by training history, nutritional status, sleep quality, inflammatory tone, mitochondrial function, environmental exposure, sex, age, and broader genetic background [57]. Consequently, isolated candidate gene interpretations are insufficient to explain the complexity of exercise-related phenotypes, reinforcing the need for integrative approaches that combine physiological, molecular, metabolic, and recovery-related assessments [58,59].

From a translational perspective, these findings support the potential value of integrated biomarker panels over single genetic markers. Future studies should evaluate whether combined inflammatory, metabolic, mitochondrial, and recovery-associated signatures can help identify adaptive or maladaptive responses to exercise training. Such approaches could contribute to precision exercise physiology, athlete monitoring, recovery optimization, and the prevention of maladaptive responses associated with excessive cumulative physiological stress. Nevertheless, these applications remain exploratory and require rigorous longitudinal validation before clinical or performance-related implementation [49,50].

An additional consideration is the growing evidence that inflammatory and metabolic responses to exercise may differ between males and females. Sex hormones influence immune regulation, substrate utilization, mitochondrial function, and recovery-associated physiology, potentially contributing to [57]. Emerging evidence suggests that females may exhibit distinct inflammatory responses, enhanced lipid utilization, and differences in mitochondrial regulation compared with males, although the underlying mechanisms remain incompletely understood [58,59].

From the perspective of exercise immunometabolism, these observations highlight the possibility that the biological effects of *NLRP3*-associated inflammatory signaling and *PPARD*-mediated metabolic regulation may vary according to sex-specific physiological context. However, direct evidence evaluating the sex-dependent effects of rs10754558 and rs2267668 in exercise settings remains limited. Future studies integrating genetic, hormonal, metabolic, and exercise response data will be important for clarifying the potential sex-specific mechanisms underlying interindividual variability in exercise adaptation [57–59].

This study has several limitations. First, this review was designed as a structured narrative synthesis rather than a formal systematic review or meta-analysis. Accordingly, the literature search was intended to identify and integrate relevant evidence sources rather than provide exhaustive study retrieval or formal evidence synthesis procedures.

Second, the available literature is heterogeneous in terms of exercise protocols, populations, training status, molecular outcomes, inflammatory biomarkers, metabolic endpoints and recovery measures. Third, direct evidence simultaneously evaluating *NLRP3*- and *PPARD*-related pathways in well-characterized athletic cohorts is limited. Fourth, the in silico analyses were based on public databases and pathway annotations, which are useful for biological contextualization but cannot establish causality or functional validation. Finally, the interpretation of *NLRP3* rs10754558 and *PPARD* rs2267668 remains hypothesis-generating and should not be used for deterministic or predictive conclusions.

Future research should prioritize longitudinal multicenter studies integrating standardized exercise protocols, repeated physiological testing, mitochondrial phenotyping, inflammatory and metabolic biomarkers, multi-omics profiling, and recovery assessment. Particular attention should be paid to sex-specific responses, ancestry diversity, training status, nutritional context, and environmental modifiers. Experimental validation in skeletal muscle, immune cells, and vascular tissues is necessary to clarify whether *NLRP3*- and *PPARD*-related pathways directly modulate exercise-induced adaptation or primarily reflect broader immunometabolic states [57].

In conclusion, the evidence synthesized in this review supports a biologically plausible systems-level framework in which exercise adaptation emerges through coordinated immunometabolic regulation, involving interconnected inflammatory and metabolic pathways. *NLRP3*-associated inflammatory signaling and *PPARD*-mediated metabolic regulation may contribute to the interindividual variability in exercise-related physiological responses and recovery processes. However, the strength of the available evidence is heterogeneous, and a substantial proportion of the proposed mechanistic framework is derived from experimental models and cardiometabolic disease contexts rather than direct exercise-based investigations. Consequently, current evidence remains insufficient to support deterministic genetic predictions or causal interpretations of exercise adaptation. Future longitudinal studies on athletes, controlled exercise interventions, and mechanistic validation studies integrating molecular, physiological, and multi-omics approaches are necessary to clarify the direct role of *NLRP3*- and *PPARD*-related pathways in exercise physiology and adaptive responses to training.

4. Materials and Methods

4.1. Study Design and Reporting Framework

This study was designed as a structured narrative review integrating systems-level physiological and immunometabolic perspectives, complemented by exploratory in silico functional annotation, protein–protein interaction (PPI) network analysis, and pathway enrichment analysis. The primary objective was to synthesize the current evidence regarding the potential contribution of *NLRP3* rs10754558 and *PPARD* rs2267668 to inflammatory and metabolic regulation associated with exercise adaptation and the interconnected immunometabolic regulation.

Given the substantial heterogeneity across exercise protocols, study populations, molecular outcomes, inflammatory biomarkers, metabolic endpoints, and recovery-related physiological measures, a formal systematic review or meta-analysis approach was not methodologically appropriate. Instead, this study prioritized integrative physiological interpretation and systems-level contextualization of inflammatory and metabolic pathways associated with exercise immunometabolism.

The study design integrated three complementary analytical components: (i) a structured literature synthesis focused on inflammatory, metabolic, mitochondrial, and exercise physiology pathways; (ii) functional annotation of *NLRP3* rs10754558 and *PPARD* rs2267668 using publicly available genomic and regulatory databases; and (iii) exploratory systems-level analyses, including protein–protein interaction networks and pathway enrichment analyses, to identify recurrent biological processes associated with inflammatory signaling, oxidative metabolism, mitochondrial adaptation, energetic stress sensing, and recovery-associated physiological regulation.

The reporting strategy was developed to align with the contemporary recommendations for narrative and integrative reviews in molecular physiology and exercise biology. Particular emphasis was placed on distinguishing direct evidence derived from exercise physiology investigations from complementary mechanistic evidence originating from

inflammatory, metabolic, mitochondrial, and cardiometabolic research. Additionally, the interpretation of functional annotations and pathway enrichment findings was intentionally restricted to biological plausibility and hypothesis generation rather than causal inference or predictive exercise-related interpretations.

Because the analyses incorporated publicly available databases, literature-derived annotations, and previously published studies, no human participants, biological samples, or identifiable personal data were directly involved in this investigation. Therefore, institutional ethics committee approval and informed consent were not required for this study.

Accordingly, the present review should be interpreted as a structured physiological synthesis integrating mechanistic and translational evidence, rather than a quantitative evidence-grading review.

4.2. Eligibility Criteria

Eligibility criteria were established to identify studies relevant to inflammatory regulation, metabolic adaptation, mitochondrial physiology, exercise immunometabolism, and the potential biological relevance of *NLRP3*- and *PPARD*-related pathways during exercise-induced physiological stress and recovery.

Studies were considered eligible if they met at least one of the following criteria: (i) evaluated inflammatory, mitochondrial, metabolic, oxidative stress, or recovery-associated responses related to exercise physiology; (ii) investigated *NLRP3* inflammasome signaling, *PPARD*-associated metabolic regulation, or interconnected immunometabolic pathways associated with exercise adaptation; (iii) examined molecular, physiological, or biomarker responses associated with mitochondrial remodeling, oxidative metabolism, substrate utilization, energetic stress sensing, or metabolic flexibility; or (iv) provided mechanistic, translational, or systems-level evidence relevant to exercise-induced physiological adaptation, recovery physiology, or cardiometabolic regulation.

Both experimental and observational studies were considered eligible, including human exercise studies, athlete-based investigations, mechanistic physiological studies, molecular biology studies, and relevant translational or experimental investigations involving inflammatory and metabolic regulation. Complementary evidence derived from mitochondrial biology, immunology, metabolism, and cardiometabolic research was also included when relevant to exercise adaptation and immunometabolic regulation.

Review articles, mechanistic reviews, and systems biology studies were also considered if they provided relevant conceptual or physiological integration regarding inflammatory–metabolic interactions, mitochondrial adaptation, energetic regulation, or exercise recovery physiology. Publicly available genomic, regulatory, and pathway databases used for functional annotation and enrichment analyses, including dbSNP, Ensembl, GTEx, RegulomeDB, STRING, Reactome, KEGG, and Gene Ontology databases, were also considered eligible sources for exploratory in silico analyses. All database searches were performed up to March 2026.

Studies were excluded if they (i) lacked relevance to exercise physiology, inflammatory regulation, mitochondrial adaptation, oxidative metabolism, or metabolic physiology; (ii) focused exclusively on unrelated pathological conditions without physiological or mechanistic relevance to exercise adaptation; (iii) did not provide sufficient methodological or mechanistic information for physiological interpretation; or (iv) represented duplicate publications, conference abstracts without accessible full data, editorials, or non-scientific reports.

No strict restrictions regarding participant sex, age, ancestry, or training status were applied because the objective of this review was to capture broad physiological and mechanistic evidence related to exercise immunometabolism and inflammatory–metabolic integration. However, studies directly involving exercise interventions, athletic populations,

skeletal muscle physiology, mitochondrial adaptation, inflammatory biomarkers, and exercise-associated metabolic regulation were prioritized during evidence synthesis.

Because the present study aimed to provide a systems-level physiological interpretation rather than quantitative pooled estimates, the study selection prioritized mechanistic relevance, physiological integration, and biological plausibility over formal risk-of-bias stratification or evidence grading.

Studies were considered eligible if they addressed one or more of the following domains: (i) *NLRP3*-associated inflammatory signaling; (ii) *PPARD*-related metabolic regulation; (iii) exercise physiology, exercise adaptation, or exercise immunometabolism; (iv) mitochondrial, inflammatory, metabolic, or recovery-associated pathways relevant to exercise adaptation; and (v) functional, regulatory, or translational evidence related to rs10754558 or rs2267668.

Studies were excluded if they lacked relevance to exercise physiology, immunometabolism, inflammatory regulation, metabolic adaptation, or the biological pathways investigated in this review. Conference abstracts without sufficient methodological information, duplicate reports, and studies lacking relevance to the predefined thematic framework were also excluded. Eligibility decisions were guided by thematic relevance to the review objectives and the predefined evidence domains used to structure the narrative synthesis.

4.3. Information Sources and Search Strategy

A structured literature search was conducted to identify studies related to exercise immunometabolism, inflammatory regulation, mitochondrial adaptation, oxidative metabolism, metabolic flexibility, recovery-associated physiology, and the potential biological relevance of *NLRP3*- and *PPARD*-related pathways in exercise-induced physiological stress. The search strategy was designed to capture mechanistic, physiological, translational, and systems-level evidence relevant to inflammatory–metabolic integration in exercise adaptation.

The literature search was performed using the electronic databases PubMed/MEDLINE, Scopus, and Web of Science from database inception to March 2026. Additional complementary searches were conducted through manual screening of reference lists from relevant review articles and primary studies to identify potentially eligible publications not captured during the initial database search.

The search terms combined controlled vocabulary and free-text keywords related to exercise physiology, immunometabolism, mitochondrial adaptation, inflammatory signaling, metabolic regulation, and candidate pathways associated with *NLRP3* and *PPARD*. The principal search strategy included combinations of the following terms: "exercise immunometabolism," "exercise physiology," "exercise adaptation," "exercise-induced stress," "NLRP3 inflammasome," "*PPARD*" OR "*PPARδ*," "mitochondrial adaptation," "oxidative phosphorylation," "fatty acid oxidation," "metabolic flexibility," "AMPK signaling," "PGC-1α," "oxidative stress," "ROS signaling," "exercise recovery," and "recovery physiology." Boolean operators ("AND," "OR") were applied to optimize search sensitivity and specificity according to database requirements.

Representative search combinations included: ("exercise adaptation" AND "*NLRP3*"), ("exercise physiology" AND "*PPARD*"), ("exercise immunometabolism" AND "mitochondrial adaptation"), ("oxidative metabolism" AND "exercise recovery"), ("NLRP3 inflammasome" AND "oxidative stress" AND "exercise"), and ("*PPARD*" OR "*PPARδ*") AND ("fatty acid oxidation" OR "metabolic flexibility") AND ("exercise adaptation"). Detailed Boolean combinations and database-specific search strategies used during literature retrieval are provided in Supplementary Table S1 to enhance methodological transparency and reproducibility. The search strategy was intended to identify relevant evidence sources

and support the development of a structured narrative synthesis, rather than to perform a formal systematic review, scoping review, or quantitative evidence synthesis. Consequently, no predefined study selection flow diagram, risk of bias assessment, or quantitative pooling procedures were applied. The retrieved literature was evaluated according to its relevance to exercise physiology, exercise immunometabolism, inflammatory regulation, metabolic adaptation, and the proposed *NLRP3–PPARD* framework of this review.

The literature retrieval strategy was designed to support a systems-level physiological synthesis integrating inflammatory signaling, mitochondrial adaptation, metabolic flexibility, oxidative metabolism, redox-sensitive regulation, and recovery physiology within the exercise immunometabolism framework. The principal physiological domains, conceptual search categories, representative search terms, and their biological relevance to exercise adaptation are presented in Table 4.

Table 4. Conceptual framework for evidence retrieval and systems-level integration in exercise immunometabolism.

Physiological Domain	Principal Biological Processes	Representative Search Terms	Physiological Relevance
Exercise immunometabolism	Interaction between inflammatory and metabolic regulation during exercise adaptation	"Exercise immunometabolism", "exercise inflammation", "exercise metabolism", "exercise adaptation"	Integrated physiological responses to repeated exercise-induced stress
Inflammatory regulation	Inflammasome activation, cytokine signaling, and innate immune responses	"*NLRP3*", "inflammasome", "NF-κB", "IL-1β", "exercise inflammation"	Modulation of inflammatory responses associated with physiological stress and adaptation
Mitochondrial adaptation	Mitochondrial biogenesis and energetic regulation	"Mitochondrial adaptation", "oxidative phosphorylation", "PGC-1α"	Energetic efficiency and adaptive regulation during repeated exercise exposure
Metabolic flexibility	Oxidative metabolism and substrate utilization	"*PPARD*", "fatty acid oxidation", "energy metabolism"	Regulation of substrate utilization and energetic homeostasis during exercise
Redox-sensitive signaling	Reactive oxygen species generation and oxidative stress responses	"Oxidative stress", "ROS signaling", "redox signaling"	Cellular stress adaptation and physiological signaling during exercise exposure
Systems-level physiological integration	Interaction among inflammatory, metabolic, and mitochondrial pathways	"systems biology", "exercise systems physiology", "immunometabolic regulation"	Integrated regulation of exercise adaptation and physiological homeostasis

The table summarizes the principal physiological domains and conceptual categories used for evidence retrieval and systems-level integration in this structured narrative review. The selected domains were organized to support the interpretation of interconnected inflammatory, metabolic, mitochondrial, and redox-sensitive pathways associated with exercise adaptation and immunometabolic regulation. Search terms were derived from exercise physiology, immunology, metabolism, and systems biology literature and were used to guide structured evidence retrieval across the PubMed, Scopus, and Web of Science databases. Abbreviations: ROS, reactive oxygen species; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; *PPARD*, peroxisome proliferator-activated receptor delta.

The search strategy prioritized studies published in peer-reviewed journals and written in English only. No strict restriction regarding publication year was initially applied because foundational mechanistic studies related to mitochondrial physiology, inflammatory regulation, oxidative metabolism, and exercise adaptation were considered relevant for a systems-level physiological interpretation. However, particular emphasis was placed

on contemporary literature addressing exercise immunometabolism, mitochondrial remodeling, and inflammatory and metabolic integration.

In parallel, publicly available genomic and regulatory resources were consulted to perform exploratory analyses of *NLRP3* rs10754558 and *PPARD* rs2267668, including dbSNP, the Ensembl Genome Browser, GTEx Portal, RegulomeDB, STRING v12.0, Reactome, KEGG, and Gene Ontology databases. These resources were used to evaluate genomic localization, regulatory features, protein–protein interaction profiles, and biological pathways associated with inflammatory and metabolic processes relevant to the exercise physiology.

Potentially relevant studies were assessed according to predefined thematic domains and grouped into categories related to inflammatory regulation, metabolic adaptation, mitochondrial biology, exercise responsiveness, recovery-associated physiology, functional genomics, and system-level regulation. This framework facilitates evidence integration across complementary biological disciplines while avoiding formal evidence grading or quantitative synthesis.

The overall selection strategy emphasized physiological relevance, mechanistic consistency, and translational interpretation, rather than exhaustive evidence retrieval. Nevertheless, literature identification and study selection procedures were conducted systematically to enhance transparency, reproducibility, and consistency throughout the evidence-synthesis process.

4.4. Study Selection and Evidence Integration

The literature retrieval process identified 420 potentially relevant records from the PubMed/MEDLINE, Scopus, and Web of Science databases, including additional studies identified through manual reference screening. After duplicate removal and title and abstract screening, 185 articles were selected for full-text evaluation based on their relevance to exercise physiology, immunometabolism, inflammatory regulation, mitochondrial adaptation, oxidative metabolism, metabolic flexibility, and recovery-related physiological responses. Of these, 87 studies were considered sufficiently relevant for inclusion in the final evidence synthesis.

Because this study was designed as a structured narrative review rather than a formal systematic review, the study selection was intended to identify representative, mechanistically informative, and physiologically relevant evidence sources rather than to provide exhaustive literature retrieval according to the PRISMA methodology. Consequently, the selection process prioritized studies that offered direct experimental, mechanistic, translational, or exercise-related biological insights relevant to inflammatory and metabolic adaptation.

Particular emphasis was placed on investigations involving exercise interventions, skeletal muscle physiology, mitochondrial remodeling, substrate utilization, oxidative metabolism, inflammatory signaling, energetic stress responses, and recovery-associated adaptive processes. When available, evidence derived directly from exercise physiology studies was prioritized in this review. However, as studies simultaneously evaluating *NLRP3* rs10754558, *PPARD* rs2267668, and exercise-associated physiological outcomes remain scarce, complementary evidence from related biological fields was incorporated to support mechanistic interpretation and physiological contextualization.

Accordingly, additional evidence derived from inflammatory biology, mitochondrial physiology, metabolism, cardiometabolic research, and systems biology was included when relevant to exercise immunometabolism and adaptive regulation of exercise. The final evidence integration strategy emphasized physiological relevance, mechanistic consistency, translational coherence, and a systems-level interpretation of exercise adaptation. Functional relationships were interpreted within the broader context of interconnected

inflammatory and metabolic pathways while avoiding causal inference or deterministic conclusions based on isolated candidate-gene associations.

Data Extraction and Evidence Synthesis

Information extracted from eligible studies included the study design, study population, biological pathways investigated, exercise-related outcomes, genetic findings, inflammatory markers, metabolic markers, and principal conclusions. The extracted information was organized into predefined thematic categories relevant to exercise immunometabolism.

Evidence synthesis was conducted narratively through the thematic integration of inflammatory regulation, metabolic adaptation, mitochondrial biology, exercise responsiveness, recovery-associated physiology, and systems-level physiological interactions. Because the primary objective of this review was conceptual and mechanistic integration rather than quantitative evidence synthesis, no formal risk-of-bias assessment or evidence-grading framework was applied. The initial screening and thematic categorization were performed by the first author and subsequently reviewed by the co-authors. Potential disagreements regarding study relevance or evidence interpretation were resolved through consensus.

4.5. Exploratory Systems-Level Analyses

4.5.1. Gene Selection and Enrichment Parameters

Exploratory systems-level analyses were conducted to provide biological contextualization of the inflammatory and metabolic pathways potentially involved in exercise immunometabolism. The analyses were centered on the candidate genes *NLRP3* and *PPARD*, which were selected based on their reported relevance to inflammasome signaling, metabolic regulation, mitochondrial adaptation, and exercise-associated physiological responses.

To capture the broader biological networks potentially linking inflammatory and metabolic regulation during exercise adaptation, the initial candidate genes were expanded through literature-guided selection of functionally related genes with established relevance to inflammatory signaling, mitochondrial biology, oxidative stress responses, energy sensing, and metabolic homeostasis. The final gene set used for network construction included *NLRP3*, *PPARD*, *IL1B*, *IL18*, *CASP1*, *NFKB1*, *TNF*, *PRKAA1 (AMPK)*, *PPARGC1A (PGC-1α)*, *SIRT1*, *AKT1*, *MTOR*, and *PPARA* genes. The biological rationale supporting the inclusion of each gene in the exploratory systems-level analyses is summarized in Supplementary Table S2.

These genes were selected because of their documented involvement in interconnected pathways related to inflammasome activation, cytokine regulation, energy sensing, mitochondrial biogenesis, substrate utilization, oxidative metabolism, and physiological adaptation during exercise. This predefined 13-gene set served as the input for protein–protein interaction network construction and subsequent pathway enrichment analysis.

Because system-level enrichment analyses depend on existing biological annotations and literature representation, the resulting findings were interpreted as exploratory and hypothesis-generating rather than direct evidence of exercise-specific physiological regulation.

4.5.2. Functional Annotation Analysis

Functional annotation analyses were performed to characterize the genomic localization, regulatory context, and potential biological relevance of *NLRP3* rs10754558 and *PPARD* rs2267668 polymorphisms. Publicly available genomic and regulatory resources, including dbSNP, Ensembl, GTEx, RegulomeDB, and LDlink, were consulted to evaluate the genomic position, predicted regulatory function, expression quantitative trait loci (eQTL) evidence, tissue-specific annotation patterns, and broader genomic context of each variant.

Particular attention was given to evidence potentially relevant to exercise physiology, including tissues involved in metabolic regulation and physiological adaptation, such

as skeletal muscle, adipose tissue, the liver, and vascular tissues. Available annotations were reviewed to identify potential regulatory mechanisms associated with non-coding variation, including transcriptional regulation, post-transcriptional regulation, chromatin accessibility, and possible linkage disequilibrium with neighboring functional loci.

The objective of this analysis was to provide a biological context for interpreting rs10754558 and rs2267668 within interconnected inflammatory and metabolic pathways potentially involved in exercise immunometabolism. Because functional annotations are derived from publicly available genomic resources and computational predictions, the resulting interpretations were considered descriptive and hypothesis-generating rather than evidence of direct physiological effects or causal relationships in the exercise settings.

Accordingly, the functional annotation results were integrated with evidence from exercise physiology, inflammatory biology, metabolic regulation, and systems-level analyses to support the broader conceptual framework proposed in this review.

4.5.3. Protein–Protein Interaction Network Analysis

Protein–protein interaction (PPI) networks were generated using STRING (version 12.0) and GeneMANIA to explore potential functional relationships among the predefined exercise immunometabolism gene set described in Section 4.5.1. Analyses were restricted to *Homo sapiens* and incorporated interactions supported by experimental evidence and curated database annotations available within the STRING platform.

Network construction was performed using a minimum STRING interaction confidence score of 0.40 (medium confidence level). Interactions were restricted to the predefined gene set, and network interpretation focused on experimentally supported and biologically plausible associations relevant to inflammatory signaling, metabolic regulation, mitochondrial function, oxidative stress responses, and exercise-associated physiological adaptations.

The resulting PPI networks were examined to identify recurrent functional clusters and interconnected biological modules associated with inflammasome activation, energy sensing, mitochondrial biogenesis, substrate utilization, oxidative metabolism, and inflammatory–metabolic crosstalk. Particular attention was given to interactions that potentially link *NLRP3*-mediated inflammatory signaling with *PPARD*-associated metabolic regulation within the broader framework of exercise immunometabolism.

Because PPI networks are dependent on existing biological knowledge, database curation, and annotation density, the identified interactions should be interpreted as representations of functional associations rather than direct evidence of exercise-specific physiological regulation. Accordingly, network analyses are considered exploratory and hypothesis-generating approaches intended to provide a systems-level biological context for the mechanisms discussed throughout this review.

4.5.4. Pathway Enrichment Analysis

Pathway enrichment analyses were conducted using the Reactome, Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Ontology Biological Process databases to identify biological pathways overrepresented within the predefined exercise immunometabolism gene set and the associated protein–protein interaction network.

Enrichment significance was evaluated using the Benjamini–Hochberg false discovery rate (FDR) correction procedure to account for multiple tests. Pathways with FDR-adjusted p-values < 0.05 were considered significantly enriched and retained for biological interpretation. The enriched pathways were subsequently grouped according to their primary biological functions, including inflammatory, metabolic, mitochondrial, and integrative redox-related pathways.

The enrichment results were used to identify recurrent biological themes potentially linking inflammatory signaling, mitochondrial regulation, energy sensing, oxidative metabolism, and metabolic adaptation in exercise immunometabolism. However, because enrichment analyses reflect statistically overrepresented functional annotations derived from existing biological databases, the identified pathways should be interpreted as hypothesis-generating functional associations rather than as direct evidence of exercise-specific physiological regulation. The principal enriched pathways identified through Reactome, KEGG, and Gene Ontology analyses are shown in Figure 2.

4.6. Statistical Considerations

Because this study was conducted as a structured narrative review complemented by exploratory systems-level in silico analyses, no formal meta-analysis, quantitative evidence synthesis, or inferential statistical analyses involving primary experimental datasets were performed in this study.

For pathway enrichment analyses, statistical significance was evaluated using Benjamini–Hochberg false discovery rate (FDR)-adjusted p-values, and pathways with FDR-adjusted p-values < 0.05 were considered significantly enriched. These statistical procedures were applied exclusively to exploratory enrichment analyses and did not represent direct evidence of exercise-specific physiological regulation.

Accordingly, the system-level findings should be interpreted as exploratory and hypothesis-generating rather than as confirmatory evidence of causal or exercise-specific biological mechanisms. The results are intended to provide a biological context and support the conceptual integration of the inflammatory and metabolic pathways discussed throughout this review.

4.7. Evidence Classification Framework

To improve the transparency of the interpretation of the reviewed literature, all evidence discussed in this review was classified according to its proximity to exercise physiology. Three hierarchical levels of evidence were defined and applied throughout this study (Table 1). Level 1 corresponded to direct exercise evidence, including human exercise interventions, athlete-based studies, training studies, and investigations evaluating exercise-induced physiological, metabolic, inflammatory, mitochondrial, recovery-related and genetic responses.

Level 2 corresponds to experimental mechanistic evidence derived from animal models, skeletal muscle models, cellular systems, and in vitro studies investigating the biological mechanisms relevant to exercise adaptation.

Level 3 corresponds to indirect mechanistic evidence derived from inflammatory, metabolic, cardiometabolic, obesity-related, insulin resistance, or chronic disease contexts. These studies were used to support biological plausibility but were not interpreted as direct evidence of exercise adaptation or athletic performance.

This framework was applied throughout the review to distinguish direct exercise-related findings from extrapolated mechanistic evidence and facilitate the interpretation of the available literature. Accordingly, discussions involving *NLRP3* rs10754558 and *PPARD* rs2267668 were contextualized according to the origin and strength of the supporting evidence, and causal, deterministic, or predictive interpretations were avoided when direct exercise-specific evidence was lacking.

Functional Annotation of Genetic Variants

Functional annotation analyses were performed as exploratory systems-level approaches to characterize the genomic localization, regulatory context, and potential biological relevance of *NLRP3* rs10754558 and *PPARD* rs2267668 polymorphisms. Publicly

available genomic and regulatory resources, including dbSNP (NCBI), Ensembl, GTEx, RegulomeDB, and LDlink, were consulted to evaluate genomic position, regulatory classification, expression quantitative trait loci (eQTL) evidence, predicted transcriptional relevance, and broader genomic context of the variants.

Particular attention was given to regulatory features potentially relevant to exercise physiology, including non-coding functional annotation, tissue-specific regulatory patterns, and potential linkage disequilibrium with neighboring loci. Functional annotations were reviewed in the context of inflammatory signaling, metabolic regulation, mitochondrial biology, and exercise immunometabolism.

NLRP3 rs10754558 was evaluated as a regulatory variant located within the 3′ untranslated region (3′UTR) of the *NLRP3* gene, whereas *PPARD* rs2267668 was evaluated as an intronic regulatory variant within the *PPARD* locus. The functional annotation strategy focused on identifying biologically plausible regulatory mechanisms and contextualizing both variants within pathways potentially relevant to inflammatory and metabolic adaptations.

Because these analyses relied on publicly available genomic resources and computational annotations, the resulting interpretations were considered descriptive and hypothesis-generating rather than evidence of direct physiological effects or causal relationships in the exercise settings.

4.8. Protein–Protein Interaction Network and Enrichment Analyses

Protein–protein interaction network and pathway enrichment analyses were performed to provide systems-level biological contextualization of the inflammatory and metabolic mechanisms discussed throughout this review. Using the predefined exercise immunometabolism gene set described in Section 4.5.1, the analyses explored potential functional relationships linking inflammasome signaling, metabolic regulation, mitochondrial function, energy sensing, and physiological adaptation to the exercise.

The resulting interaction networks and enrichment profiles were used to identify recurrent biological themes and interconnected signaling pathways potentially relevant to exercise-induced immunometabolism. Particular attention was given to inflammatory–metabolic interfaces involving *NLRP3*-associated signaling, *PPARD*-mediated metabolic regulation, AMPK signaling, mitochondrial biogenesis, oxidative metabolism, and stress-responsive pathways because of their recognized physiological relevance to exercise adaptation.

The findings were interpreted within a systems-level framework intended to facilitate the conceptual integration of the available literature. Because the analyses relied on publicly available databases and functional annotations rather than direct experimental validation in athletic populations, the resulting interaction profiles and enriched pathways should be considered exploratory and hypothesis generating. Accordingly, they were used to provide a biological context for the proposed inflammatory–metabolic framework rather than evidence of causal molecular mechanisms or predictive exercise-related phenotypes. Accordingly, the observed pathway convergence should be interpreted as reflecting biologically plausible functional relationships supported by existing annotations, rather than the discovery of novel molecular mechanisms.

4.9. Methodological Considerations and Limitations

Several methodological considerations should be acknowledged when interpreting the findings of the present review and complementary systems-level analyses.

First, this study was conducted as a structured narrative review rather than a formal systematic review or a quantitative meta-analysis. Consequently, the objective was to

provide conceptual integration and biological contextualization of the available literature rather than a quantitative estimation of effect sizes or formal evidence grading.

Second, the literature addressing exercise immunometabolism remains heterogeneous with respect to study design, participant characteristics, exercise modalities, training status, molecular methodologies and physiological endpoints. This heterogeneity limited direct comparability across studies and precluded quantitative synthesis.

Third, direct evidence specifically evaluating *NLRP3* rs10754558 and *PPARD* rs2267668 in well-characterized athletic or exercise-trained populations remains limited. Much of the available evidence derives from inflammatory, metabolic, cardiometabolic, or mechanistic research contexts and requires cautious interpretation when extrapolating the findings to exercise physiology.

Fourth, functional annotation, protein–protein interaction, and pathway enrichment analyses relied on publicly available genomic and biological databases, including STRING, Reactome, KEGG, Gene Ontology, GTEx, Ensembl, RegulomeDB, and dbSNP. Although these resources provide valuable biological context, they are dependent on existing annotations, curated datasets, previously reported molecular interactions, and the current representation of biological knowledge in public databases. Consequently, they cannot establish causality, tissue-specific physiological effects, or direct functional validation in exercise settings.

An additional limitation of systems-level analyses is that pathway enrichment results may preferentially identify extensively studied biological pathways because enrichment significance is influenced by annotation density and database coverage. Therefore, recurrent enrichment of inflammatory, metabolic, mitochondrial, and energy-sensing pathways may partly reflect the structure of existing biological knowledge rather than the identification of novel exercise-specific mechanisms of action. Accordingly, the enrichment results should be interpreted as providing biological contextualization and support for conceptual integration, rather than as evidence of previously unrecognized mechanistic pathways.

Despite these limitations, the integrative framework adopted in this review is a strength. The combination of structured literature synthesis, functional annotation, protein–protein interaction networks, and pathway enrichment analyses facilitated the identification of biologically plausible interfaces linking inflammatory and metabolic regulation within the exercise immunometabolism.

Overall, the findings should be interpreted as exploratory and hypothesis-generating. Future longitudinal studies integrating exercise physiology, functional genomics, transcriptomics, metabolomics, proteomics, mitochondrial phenotyping, and exercise intervention designs are necessary to clarify the physiological relevance of *NLRP3*- and *PPARD*-related pathways and the potential contribution of rs10754558 and rs2267668 to interindividual variability in exercise adaptation.

5. Conclusions

The evidence synthesized in this review supports a biologically plausible, systems-level framework linking inflammatory and metabolic processes involved in exercise immunometabolism. Rather than operating as isolated mechanisms, these pathways appear to interact dynamically to shape physiological responses to exercise and recovery.

Within this framework, *NLRP3*-associated inflammatory signaling and *PPARD*-mediated metabolic regulation emerge as biologically relevant components of interconnected immunometabolic networks that may contribute to the interindividual variability in exercise-related physiological responses. However, the available evidence remains heterogeneous in origin and is derived from a combination of direct exercise studies, experimental models, and indirect cardiometabolic research. Consequently, the proposed biological in-

teractions should be interpreted as mechanistically plausible and hypothesis-generating, rather than as definitively established exercise-specific mechanisms.

Importantly, current evidence is insufficient to support deterministic interpretations of the physiological effects of *NLRP3* rs10754558 or *PPARD* rs2267668 on exercise performance, endurance capacity, or athletic phenotypes. Neither variant should be considered an independent predictor of exercise adaptation, as adaptive responses are influenced by multiple interacting biological and environmental factors.

The systems-level framework proposed in this review may contribute to future research investigating the biological basis of exercise responsiveness and interindividual adaptation. Although the integration of inflammatory and metabolic biomarkers may eventually inform precision exercise physiology approaches, these translational applications remain exploratory and require rigorous validations. Future research should incorporate sex-specific physiological, hormonal, and molecular factors when investigating the roles of inflammatory and metabolic pathways in exercise adaptation. Growing evidence indicates that biological sex may influence immune regulation, substrate utilization, mitochondrial function, and recovery-related responses to exercise, highlighting the importance of considering sex as a relevant source of interindividual variability in exercise immunometabolism.

Beyond the synthesis of inflammatory and metabolic pathways, this review highlights the potential value of integrating regulatory genetic variations into contemporary models of exercise immunometabolism. Within this framework, rs10754558 and rs2267668 emerged as regulatory variants of potential relevance for understanding the interindividual variability in adaptive responses to exercise. Although current evidence remains insufficient to support predictive or deterministic interpretations, these variants represent promising targets for future hypothesis-driven research in exercise physiology, genomics, and precision exercise medicine. In addition, longitudinal studies in athletes, controlled exercise interventions, and integrative multi-omics investigations combining genomic, transcriptomic, metabolic, and physiological assessments are required to clarify the functional relevance of *NLRP3*- and *PPARD*-related pathways. Such approaches may help determine how these interconnected inflammatory and metabolic networks contribute to adaptive and maladaptive responses to exercise in diverse physiological contexts.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/physiologia6020042/s1, Table S1: Detailed Boolean search strategy used for literature retrieval and evidence identification; Table S2: Biological rationale for gene selection in exploratory systems-level analyses; Table S3: Current genomic, regulatory, and exercise-related evidence supporting *NLRP3* rs10754558 and *PPARD* rs2267668.

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