

Review

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Review

Exercise Reprograms PHGDH Spatial Function: A Metabolic Switch Governing Neurodegeneration via Brain-Periphery Crosstalk

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Abstract

Therapeutic stagnation in Alzheimer's disease (AD) highlights the role of non-genetic mechanisms like metabolic dysregulation. We propose a paradigm: exercise reprograms phosphoglycerate dehydrogenase (PHGDH) from a pathogenic nuclear transcription factor to a protective cytoplasmic metabolic enzyme through brain-periphery crosstalk. Under AD-associated stress, PHGDH translocate to the nucleus, where its helix-turn-helix (HHTH) domain activates pro-inflammatory genes (e.g., IKK α , HMGB1), suppresses autophagy, and accelerates A β deposition. Centrally, exercise-induced myokine irisin suppresses PHGDH nuclear translocation via AMPK/PGC-1 α signaling, preserving its metabolic role. Peripherally, exercise inhibits PHGDH in hepatic Kupffer cells, reducing systemic IL-1 β release and neuroinflammation. Notably, the HHTH-targeting inhibitor NCT-503 reduces A β plaques by 44–62% in APP-KI mice, validating this strategy. This framework positions exercise as a precision intervention, enabling novel diagnostics (e.g., PET probes for PHGDH compartmentalization) and synergistic “exercise-pharmacotherapy.”

Keywords: neurodegenerative diseases; *PHGDH*; exercise

1. Introduction

PHGDH: Redefining a Metabolic Enzyme's Paradigm in Neurodegeneration

Alzheimer's disease (AD), the most prevalent neurodegenerative disorder, is characterized by progressive cognitive decline, extracellular amyloid- β (A β) plaques, and neurofibrillary tangles composed of hyperphosphorylated tau. With global aging accelerating, AD currently affects over 55 million people worldwide, a figure projected to triple by 2050, imposing an estimated economic burden of \$1.8 trillion [1]. Despite decades of research, existing therapeutics (e.g., acetylcholinesterase inhibitors and anti-A β antibodies) offer merely symptomatic relief without halting disease progression. This therapeutic impasse stems from AD's multifactorial pathogenesis, where genetic risk factors (e.g., APOE4) explain only 30–50% of sporadic AD (sAD) cases, highlighting the critical role of non-genetic mechanisms such as metabolic dysregulation and neuroinflammation [2,3].

Phosphoglycerate dehydrogenase (*PHGDH*), the rate-limiting enzyme in de novo serine biosynthesis, has emerged as a critical node in Alzheimer's disease (AD) pathogenesis. Longitudinal multi-cohort analyses reveal that *PHGDH* expression is elevated in both brain tissue and blood of sAD patients, correlating with Braak staging and cognitive decline even in asymptomatic individuals, positioning it as a predictive biomarker for early diagnosis [4]. Beyond its canonical metabolic role, *PHGDH* exhibits a non-canonical function as a transcriptional regulator in astrocytes. Under glucose deprivation—a hallmark of AD brains—*PHGDH* undergoes p38 MAPK-mediated nuclear

translocation. Therein, its helix-helix-turn-helix (HHTH) domain binds promoters of pro-inflammatory genes (IKK α , HMGB1), acting independently of its enzymatic activity. This binding triggers NF- κ B/mTOR activation and suppresses autophagy, accelerating A β deposition in 3xTg-AD mice and human brain organoids (BOs) [3]. Crucially, enzyme-dead mutants (*PHGDH-ED*) retain this pathogenic function, confirming the dissociation of metabolic and transcriptional roles [2].

Therapeutically, the BBB-penetrant small-molecule inhibitor NCT-503 disrupts *PHGDH*'s DNA-binding capacity by targeting the HHTH domain. In APP-KI mice, NCT-503 reduces hippocampal A β plaques by 44–62% and rescues spatial memory deficits without perturbing serine metabolism, underscoring the primacy of transcriptional inhibition over metabolic modulation [2]. These findings caution against serine supplementation—an approach under clinical evaluation—as elevated *PHGDH* in AD likely augments endogenous serine production, rendering exogenous intake ineffective or potentially detrimental [4].

Epidemiological studies consistently demonstrate that physical activity reduces AD incidence by 45% and decelerates cognitive decline in prodromal stages, with aerobic exercise (AE) identified as the most effective modality for enhancing global cognition in elderly AD patients [5–7]. Single-nucleus RNA sequencing reveals that exercise restores neuroprotective astrocyte subpopulations (e.g., CDH4⁺ cells) in AD mice, enhancing neurovascular coupling and A β phagocytosis, while simultaneously augmenting disease-associated microglial gene expression (e.g., TREM2) to promote amyloid clearance [8,9]. Notably, exercise-induced reactivation of the metabolic gene *ATPIF1* promotes neuronal survival and synaptic plasticity, accounting for 64% of transcriptional repair in oligodendrocyte precursor cells [8,9]. Clinically, moderate-intensity continuous training (e.g., 4,000 steps/day) increases hippocampal volume by 2%, effectively reversing age-related atrophy and correlating with a 25–50% risk reduction for AD conversion [6,7].

For patients with advanced frailty, pharmacological mimetics targeting exercise-activated pathways (e.g., NCT-503 inhibiting *PHGDH* transcriptional activity) reduce A β plaques by 44–62% and improve spatial memory, offering potential “exercise-in-a-pill” strategies [2].

2. The Metabolic and Transcriptional Duality of *PHGDH* in Astrocytes: A Bifunctional Regulator in Neurodegenerative Pathogenesis

Phosphoglycerate dehydrogenase (*PHGDH*), the gatekeeper of the serine biosynthesis pathway, is canonically defined by its catalytic conversion of 3-phosphoglycerate (3-PG) to 3-phosphohydroxypyruvate (3-PHP), a process integral to one-carbon metabolism and nucleotide biosynthesis [10]. This traditional view is now being challenged by the revelation of a non-canonical, moonlighting function for *PHGDH* as a transcriptional regulator, a role that is especially pronounced in astrocytes—the principal glial population of the central nervous system (CNS) [2]. This functional duality situates *PHGDH* at the confluence of metabolic reprogramming and epigenetic regulation, positioning it as a pivotal player in the pathogenesis of neurodegenerative diseases, notably Alzheimer's disease (AD) [10,11]. In the context of AD, astrocytes—long relegated to the status of metabolic support cells for neurons—undergo a pathological reprogramming characterized by aberrant *PHGDH* expression. Strikingly, the magnitude of this dysregulation scales with Braak staging and parallels cognitive deterioration [11].

2.1. Metabolic Functions: Serine Synthesis and Beyond

In astrocytes, phosphoglycerate dehydrogenase (*PHGDH*) is the master regulator of de novo serine synthesis, yielding D-serine—an essential co-agonist of NMDA receptors for synaptic plasticity (Figure 1). Genetic ablation of *PHGDH* in murine models depletes D-serine pools, thereby impairing long-term potentiation (LTP) and spatial memory [14]. Beyond its role in neurotransmission, *PHGDH*-derived serine fuels the folate cycle, which produces S-adenosylmethionine (SAM). SAM serves as the universal methyl donor for reactions governing histone modifications (e.g., H3K27me3) and DNA stability in neurons [12].

Under conditions of glucose deprivation—a hallmark of Alzheimer’s disease (AD) brains—PHGDH undergoes dynamic subcellular redistribution. Specifically, p38 MAPK phosphorylates PHGDH at Ser371, triggering its nuclear translocation (Figure 1) [10]. Concurrently, AMPK-mediated phosphorylation at Ser55 reprograms PHGDH’s catalytic activity to utilize alternative substrates like malate. This metabolic shift generates NADH to sustain redox homeostasis [10]. Such metabolic plasticity enables astrocytes to maintain the NAD⁺/NADH balance during energetic stress, a process elegantly visualized using nuclear-targeted SoNar/Frex biosensors [10].

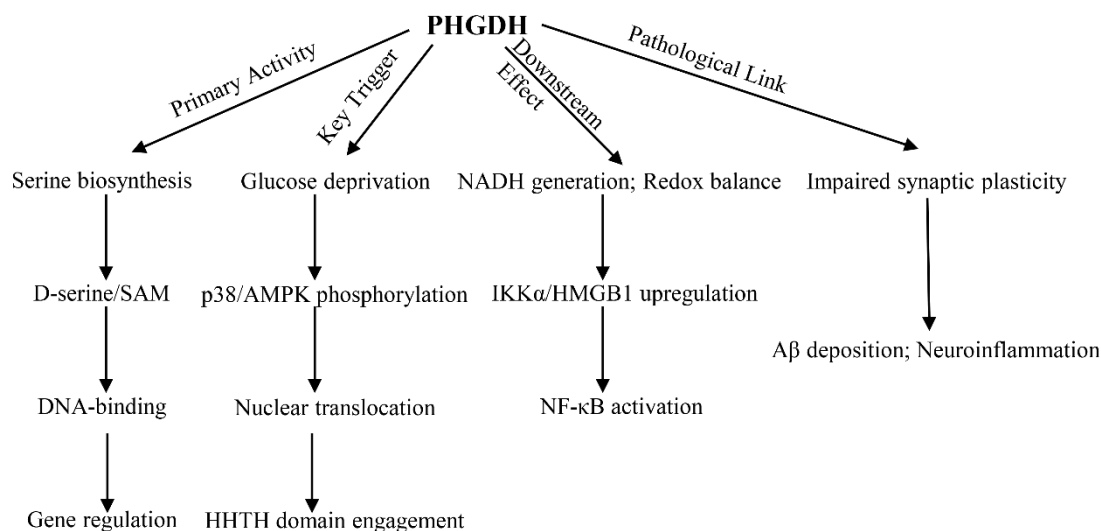


Figure 1. Duality of *PHGDH* Functions in Astrocytes. **Canonical metabolic function of PHGDH:** Under healthy physiological conditions, PHGDH is primarily located in the cytoplasm, where it serves as the rate-limiting enzyme of the serine synthesis pathway. This pathway generates D-serine, a co-agonist of NMDA receptors that supports synaptic plasticity and cognitive function. Concurrently, serine metabolism fuels the production of S-adenosylmethionine (SAM), a methyl donor for epigenetic modifications (e.g., histone methylation) that maintains neuronal homeostasis. **Pathological mode of PHGDH (Non-canonical transcriptional function):** Under pathological conditions such as Alzheimer’s disease (AD), particularly during glucose deprivation, PHGDH is phosphorylated by p38 MAPK and translocates from the cytoplasm to the nucleus. Within the nucleus, its HHTH domain acts as a transcription factor, directly binding to and activating the promoters of pro-inflammatory genes, such as *IKKα* and *HMGB1*. This function is independent of its enzymatic activity, leading to the inhibition of autophagy via the NF- κ B pathway, accelerated amyloid-beta ($A\beta$) deposition, and ultimately, neurodegeneration.

2.2. Transcriptional Regulation: The Non-Canonical Paradigm

In astrocytes within the Alzheimer’s disease (AD) brain, *PHGDH* assumes a novel, non-canonical role in the nucleus, functioning independently of its well-characterized metabolic activity. Utilizing its helix-helix-turn-helix (HHTH) domain, PHGDH acts as a DNA-binding protein, as demonstrated by chromatin immunoprecipitation sequencing (ChIP-seq) which identified its occupancy at promoter regions. This binding directly drives the expression of key pro-inflammatory genes, *IKKα* and *HMGB1* (Figure 1) [10]. The downstream effects are profoundly pathogenic: *IKKα* potentiates NF- κ B signaling, while *HMGB1* disrupts the autophagic removal of amyloid-beta ($A\beta$), establishing a self-perpetuating cycle that amplifies amyloid deposition [11].

This dual functionality is unequivocally demonstrated by the finding that enzyme-dead PHGDH mutants (e.g., *PHGDH-ED*) retain their transcriptional capabilities, confirming a clear dissociation between its metabolic and gene-regulatory functions (Figure 1) [10]. The HHTH domain (residues 210–310) is the critical mediator of this activity, as its deletion via mutagenesis prevents PHGDH from activating *IKKα* and *HMGB1*, even when the protein is overexpressed to pathological levels [10]. Furthermore, the structural homology of this domain to established transcription factors

provides the molecular basis for its ability to engage in sequence-specific DNA recognition, specifically targeting CpG-rich sites near neuroinflammatory gene promoters [10].

2.3. Pathogenic Implications in Neurodegenerative Diseases

Elevated RNA and protein levels of *PHGDH* in astrocytes have been consistently demonstrated in multi-cohort analyses of late-onset Alzheimer's disease (LOAD), with these levels positively correlating with amyloid-beta ($A\beta$) burden and Braak staging [11]. This relationship is further supported by functional studies in 3xTg-AD mice, where astrocyte-specific overexpression of *PHGDH* resulted in a 2.3-fold increase in $A\beta$ plaques. In contrast, *PHGDH* knockdown led to a substantial reduction of 60–70% in plaque formation [11]. At the mechanistic level, the *PHGDH*-*IKK α* -*HMGB1* axis contributes to $A\beta$ accumulation by suppressing autophagy and enhancing the activity of β -secretase (*BACE1*) [11].

The function of nuclear *PHGDH* extends to the integration of metabolic stress with immune responses. Under conditions of low glycolytic flux, such as the depletion of 3-phosphoglycerate (3-PGA), *PHGDH* promotes the assembly of a *PHGDH*-*AXIN*-*HIPK2* complex. This complex facilitates the phosphorylation of p53 at Serine 46, initiating pro-apoptotic pathways in astrocytes under duress [16]. On the other hand, through its role in producing S-adenosylmethionine (SAM), *PHGDH* fuels the trimethylation of H3K27 (H3K27me3) at the promoters of key neuroprotective genes like *BDNF*, leading to their transcriptional silencing and a subsequent increase in neuronal vulnerability [11,12].

3. Multi-Organ *PHGDH* Network Remodeling Underlies Systemic Benefits of Exercise Training

3.1. Exercise-Induced Irisin Modulates the Brain Metabolic Landscape via AMPK/*PGC-1 α* -Mediated Suppression of *PHGDH* Nuclear Translocation

Physical exercise emerges as a potent non-pharmacological intervention that consistently demonstrates neuroprotective benefits across clinical and preclinical studies. Intriguingly, the muscle-brain endocrine axis has been implicated as a critical mediator of exercise-induced neuroprotection, with the myokine irisin serving as a key signal transducer. This review posits a novel hypothesis: Exercise-derived irisin activates the AMPK/*PGC-1 α* axis to suppress nuclear translocation of phosphoglycerate dehydrogenase (*PHGDH*), thereby reprogramming brain metabolism and attenuating neurodegenerative pathology [13,14].

Skeletal muscle functions as a dynamic endocrine organ during physical activity, secreting myokines that communicate with distant organs, including the brain. Irisin, a cleaved fragment (~12 kDa) of the membrane protein fibronectin type III domain-containing protein 5 (*FNDC5*), is robustly upregulated by exercise via the *PGC-1 α* -dependent pathway in contracting muscle. Upon release into circulation, irisin crosses the blood-brain barrier (BBB) via saturable transport mechanisms, achieving physiologically relevant concentrations in the hippocampus, cortex, and cerebrospinal fluid. Crucially, irisin deficiency exacerbates synaptic loss and cognitive impairment in AD models, whereas its administration rescues neurogenesis deficits [14]. This establishes irisin as a principal exercise-derived mediator of central nervous system (CNS) adaptation.

Irisin initiates a neuroprotective signaling cascade by binding to integrin $\alpha V/\beta 5$ receptors on the surface of neurons and glial cells. This interaction triggers the activation of AMP-dependent protein kinase (AMPK), a master cellular energy sensor that is phosphorylated at Thr172 in response to irisin-induced shifts in the cellular AMP:ATP ratio. Once active, AMPK directly phosphorylates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC-1 α*) at Ser538, which enhances its stability as a transcriptional coactivator and promotes its retention within the nucleus [15]. In turn, *PGC-1 α* orchestrates a transcriptional program that favors mitochondrial biogenesis—mediated by *NRF1* and *TFAM*—and bolstered antioxidant defenses through *SOD2* and *CAT*. Notably, activation of the AMPK/*PGC-1 α* axis has demonstrated neuroprotective effects in ischemic

stroke models, correlating with improved mitochondrial membrane potential and enhanced ATP generation [15].

Phosphoglycerate dehydrogenase (*PHGDH*), which catalyzes the rate-limiting step of de novo serine biosynthesis, diverts glycolytic flux toward amino acid production and one-carbon metabolism. Under pathological stress conditions, such as exposure to amyloid-beta ($A\beta$) oligomers, *PHGDH* undergoes translocation to the nucleus. Within the nucleus, it locally generates serine to support histone methylation (specifically H3K27me3), leading to the repression of genes essential for neurogenesis. This elevation of nuclear *PHGDH* correlates with impaired hippocampal neurogenesis and deficits in memory consolidation in models of Alzheimer's disease (AD). We hypothesize that exercise-induced irisin signaling suppresses this aberrant nuclear localization. To mechanistically validate this axis, we will investigate whether exercise intervention fails to suppress *PHGDH* nuclear translocation in *Fndc5* murine models, thereby exacerbating tau hyperphosphorylation through the amplification of this pathological cascade.

3.2. Exercise-Mediated Suppression of Hepatic Macrophage *PHGDH* Attenuates Neuroinflammation via the Liver-Brain Immune Axis

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by progressive neuronal loss and neuroinflammation driven by microglial activation and cytokine dysregulation (e.g., IL-1 β , TNF- α). While central mechanisms have been extensively studied, recent evidence highlights the liver as a critical peripheral regulator of brain immunity via the "liver-brain immune axis" [16,17]. This axis orchestrates systemic metabolic and immune homeostasis, wherein hepatic macrophages (Kupffer cells) act as key sentinels. Intriguingly, physical exercise—a non-pharmacological intervention—modulates this axis by suppressing phosphoglycerate dehydrogenase (*PHGDH*) in hepatic macrophages, thereby reducing IL-1 β production and mitigating neuroinflammation [2,17].

PHGDH catalyzes the rate-limiting step in de novo serine synthesis, a pathway linked to inflammatory responses. In aged or metabolically stressed livers, *PHGDH* is upregulated in Kupffer cells, promoting serine flux toward IL-1 β biosynthesis via the NLRP3 inflammasome. Serine-derived metabolites fuel mitochondrial respiration, enhancing ROS generation and caspase-1 activation, which cleaves pro-IL-1 β into its active form [2]. Elevated IL-1 β enters systemic circulation, crosses the compromised blood-brain barrier (BBB) in neurodegeneration, and activates microglia, exacerbating $A\beta$ /tau pathology in AD and α -synuclein aggregation in PD [18]. Critically, *PHGDH* inhibition reduces IL-1 β by >40% in murine models, confirming its pro-inflammatory role [2].

Exercise induces multi-organized crosstalk that converges on hepatic *PHGDH* regulation (Figure 2):

- **AMPK/SIRT1 Activation:** Exercise initiates a powerful metabolic signal by releasing myokines (IL-6, irisin) from skeletal muscle that activate hepatic AMPK and SIRT1. These enzymes orchestrate a two-pronged attack on *PHGDH*: AMPK flags *PHGDH* for destruction by phosphorylating it at Ser49, while SIRT1 suppresses *PHGDH* gene transcription by deacetylating NF- κ B [16,19].
- **Gpld1-Mediated Signaling:** The liver counters inflammation through the exercise-induced hepatokine Gpld1. Gpld1 disrupts inflammatory signaling in Kupffer cells by cleaving GPI-anchored proteins, which directly halts *PHGDH*-driven serine synthesis and blocks IL-1 β maturation. This pathway is so crucial that its absence in Gpld1-deficient mice renders the anti-inflammatory effects of exercise completely ineffective [16,19].
- **Gut-Liver Axis Modulation:** Exercise also reshapes the gut ecosystem, fostering beneficial bacteria like *Bifidobacterium*. These microbes generate short-chain fatty acids, notably butyrate, which act as epigenetic regulators. In Kupffer cells, butyrate inhibits histone deacetylases, effectively silencing the expression of key inflammatory genes, *PHGDH* and IL1B [16].

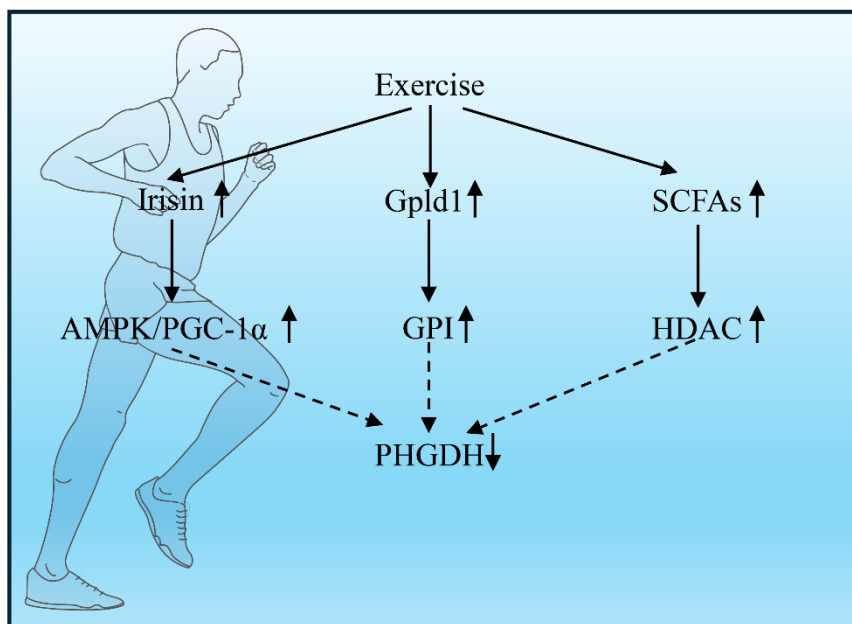


Figure 2. Molecular Pathways Linking Exercise to Hepatic *PHGDH*-IL-1 β Suppression. Central pathway (Intra-brain): Exercise induces the release of the myokine irisin from skeletal muscle. Irisin crosses the blood-brain barrier and activates the AMPK/PGC-1 α signaling pathway in the brain (primarily in astrocytes), thereby inhibiting PHGDH nuclear translocation and retaining it in the cytoplasm to perform its beneficial metabolic functions. **Peripheral pathway (Liver-brain axis):** Exercise modulates hepatic immunity by suppressing PHGDH in liver macrophages (Kupffer cells), reducing the systemic release of the pro-inflammatory cytokine IL-1 β , which in turn mitigates neuroinflammation in the brain.

4. Precision Exercise Intervention: Diagnostic and Therapeutic Innovations Targeting PHGDH

Addressing the critical unmet need for novel therapeutics in neurodegenerative disorders, we propose to establish a comprehensive experimental framework for *PHGDH*-targeted precision exercise interventions. This initiative is founded on three highly innovative and synergistic components, each supported by a rigorous and systematic experimental design.

Aim 1: Pioneering a Diagnostic PET Probe for *PHGDH* Subcellular Dynamics. Our first objective is to develop a revolutionary molecular imaging tool: a PET probe engineered with the HHTH structural domain to quantify the *PHGDH* nuclear-to-cytoplasmic ratio (N/C ratio). This technology will, for the first time, allow for in vivo, high-resolution spatiotemporal mapping of *PHGDH* compartmentalization. By providing a quantitative biomarker of *PHGDH* activation states, this probe will transform early disease detection and enable the precise stratification of patients for personalized therapeutic interventions.

Aim 2: Validating a Synergistic Exercise-Pharmacotherapy Strategy. We will investigate the synergistic potential of combining aerobic exercise with pharmacotherapy, specifically testing the hypothesis that exercise enhances the blood-brain barrier permeability and central nervous system (CNS) bioavailability of the *PHGDH* inhibitor NCT-503. To validate this premise, we will execute a systematic experimental program encompassing: (1) the development and characterization of transgenic animal models with robust, disease-relevant phenotypes; (2) detailed pharmacokinetic and pharmacodynamic (PK/PD) profiling of NCT-503 under controlled exercise conditions; and (3) the application of multidimensional behavioral batteries to assess functional outcomes.

Aim 3: Translational Optimization of Combinatorial Parameters. The final phase of our research will be to translate these findings into an optimized therapeutic protocol. We will systematically determine the ideal combinatorial parameters, including the most effective dosing regimens for NCT-

503 and the optimal intensity, duration, and timing of exercise interventions. This will establish a comprehensive, clinically actionable framework for PHGDH-targeted precision exercise therapy.

5. Precision Exercise Targeting PHGDH in Neurodegenerative Diseases: Challenges, and Future Experimental Designs

To further explore the therapeutic potential of gene-exercise crosstalk, we will employ AAV-mediated delivery of a constitutively active *PHGDH*-S553D gene variant, engineered to mimic exercise-induced phosphorylation. This innovative strategy requires a sophisticated experimental framework that incorporates: (1) quantitative evaluation of transduction efficiency using advanced molecular techniques, (2) longitudinal therapeutic monitoring through multimodal imaging and functional assays, and (3) rigorous safety profiling to assess potential off-target effects. Through an interdisciplinary collaboration integrating biomedical engineering, molecular neuroscience, and clinical neurology, we anticipate achieving transformative breakthroughs in mitigating the progression of motor neuron degeneration.

A central objective of our future experimental design is to elucidate a fundamental question: how does exercise specifically regulate the HHTH domain of *PHGDH* without affecting its canonical enzymatic activity? To comprehensively dissect this complex mechanism, we have devised two complementary experimental strategies.

First, we will leverage cutting-edge spatial omics technologies, integrating single cell sequencing with subcellular proteomics, to map the comprehensive landscape of the *PHGDH* interactome following exercise. This approach will enable us to identify key proteins that dynamically interact with the *PHGDH* HHTH domain across different cell types and subcellular compartments, thereby revealing the specific regulatory mechanisms engaged during physical activity.

Second, we will construct organoid models, specifically by introducing a *PHGDH*-luc reporter gene into late-onset Alzheimer's disease brain organoids (LOAD-BOs), to simulate and study the regulatory effects of exercise on *PHGDH*. This platform will serve to screen pharmacological compounds capable of mimicking the beneficial effects of exercise. Such screening will not only validate the generalizability of our mechanistic findings but also identify promising therapeutic targets and lead compounds for future drug development. We are confident that the synergistic combination of these two strategies will open new avenues for elucidating the molecular mechanisms by which exercise regulates *PHGDH*.

6. Conclusions

In conclusion, this review fundamentally reframes our understanding of how physical exercise confers neuroprotection, identifying PHGDH as a pivotal metabolic switch whose spatial function is reprogrammed through brain-periphery crosstalk. We have elucidated a dual regulatory mechanism: centrally, exercise-induced irisin activates the AMPK/PGC-1 α axis in astrocytes, suppressing the pathological nuclear translocation of PHGDH and thereby preserving its beneficial metabolic role while inhibiting its non-canonical function as a pro-inflammatory transcription factor. Peripherally, exercise modulates the liver-brain immune axis by suppressing PHGDH activity in hepatic Kupffer cells, which curtails the systemic release of IL-1 β and mitigates neuroinflammation.

These findings collectively transcend the conventional view of PHGDH as merely a metabolic enzyme, establishing it as a bifunctional regulator linking metabolic stress directly to gene expression and immune dysregulation in neurodegeneration. This paradigm shift not only provides a unified mechanistic explanation for the well-documented neuroprotective effects of exercise but also opens new avenues for therapeutic intervention. The demonstrated efficacy of selectively targeting PHGDH's non-canonical HHTH domain with inhibitors like NCT-503, which reduces amyloid pathology without disrupting serine metabolism, validates the promise of precision medicine strategies that decouple these dual functions.

Looking ahead, our proposed framework—encompassing the development of a novel PET probe to quantify PHGDH subcellular dynamics and the validation of synergistic exercise-pharmacotherapy regimens—charts a clear course for translational research. By establishing the principles of PHGDH spatial regulation, this work lays the groundwork for a new era of “precision exercise medicine,” offering tangible hope for altering the trajectory of Alzheimer’s disease and other neurodegenerative disorders.

Author Contributions: Wen Guo and Liang Guo conceived and designed the “Exercise-CTSS-AD Axis” hypothesis and framework. Dong Yang performed the literature search, data synthesis, and figure creation, and drafted the initial manuscript. Wen Guo and Liang Guo critically reviewed and edited the manuscript for important intellectual content. All authors read and approved of the final manuscript. Wen Guo, Liang Guo, and Bihan Wang are the co-corresponding authors.

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