



# A Mechanistic Framework of Exercise-induced Amelioration of Autism Spectrum Disorder *via* miR-132, miR-34a, and miR-146a\*

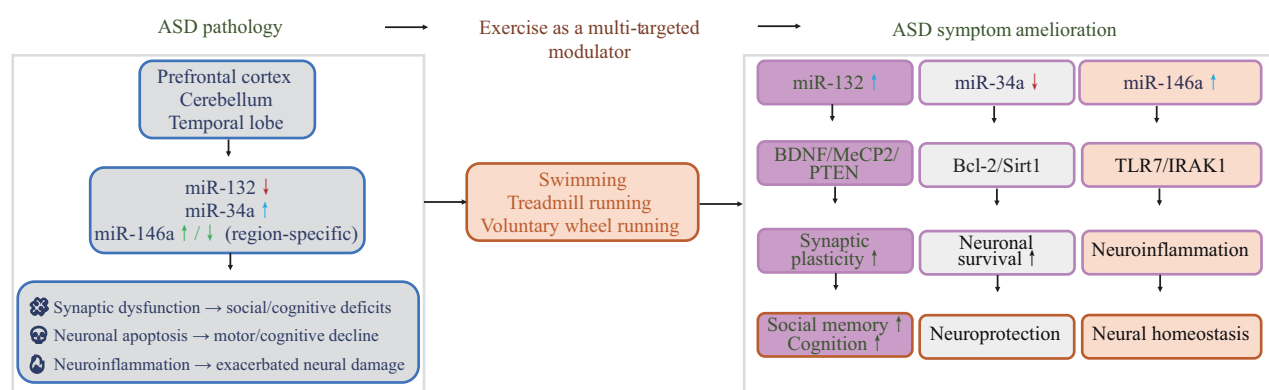
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## Graphical abstract



**Abstract** Autism spectrum disorder (ASD) is a neurodevelopmental condition with a steadily rising global prevalence, yet effective pharmacological interventions remain notably limited, highlighting an urgent need for safe, accessible, and mechanism-based therapeutic strategies. Physical exercise has emerged as a promising non-pharmacological intervention that ameliorates both core symptoms—social communication deficits and restricted repetitive behaviors—and associated features including cognitive dysfunction and motor impairments, in children and adolescents with ASD. However, the molecular mechanisms mediating these beneficial effects remain incompletely defined, impeding the development of evidence-based exercise prescriptions and biomarker-driven rehabilitation protocols. MicroRNAs (miRNAs) are evolutionarily conserved small non-coding RNAs that post-transcriptionally regulate approximately 60% of protein-coding genes. Within the central nervous system, miRNAs orchestrate diverse neurobiological processes including neural progenitor proliferation, neuronal differentiation, dendritic spine morphogenesis, synaptic plasticity, and neuroinflammatory homeostasis. Notably, miRNAs are remarkably stable in biological fluids and can be packaged into extracellular vesicles, rendering them attractive candidates as both mechanistic mediators and non-invasive peripheral

\* This work was supported by grants from Shaanxi Provincial Social Science Foundation Project (2023Q017), Shaanxi Provincial College Students' Innovation Training Program Project (S202410723043), and Weinan Normal University High-Level Talent Project (2025RC38).

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Received: May 23, 2026 Accepted: July 6, 2026

biomarkers. Among the hundreds of miRNAs expressed in the brain, three—miR-132, miR-34a, and miR-146a—have emerged as particularly relevant to ASD pathophysiology. This review focuses on these three miRNAs for the following reasons: miR-132 is a master regulator of activity-dependent synaptic plasticity through its modulation of BDNF/MeCP2/PTEN signaling and has been consistently downregulated in ASD prefrontal cortex; miR-34a functions as a pro-apoptotic factor that suppresses Bcl-2-mediated neuronal survival pathways and is upregulated in ASD cerebellum; and miR-146a serves as a key brake on neuroinflammation *via* TLR7/IRAK1 signaling and shows region-specific dysregulation in ASD temporal lobe. We first summarize evidence from human post-mortem brain tissues and ASD animal models demonstrating the consistent dysregulation of these three miRNAs. Notably, the pathological consequences of these miRNA alterations—impaired synaptic plasticity, excessive neuronal apoptosis, and sustained neuroinflammation—are interconnected and collectively contribute to the heterogeneous symptomatology of ASD. We then present a synthesis of emerging evidence demonstrating that various exercise modalities, including swimming, treadmill running, and voluntary wheel running, can concurrently reverse these ASD-like behavioral phenotypes and normalize the expression of the three key miRNAs. These data provide the first direct experimental evidence linking exercise-induced miRNA modulation to ASD symptom improvement. On the basis of these findings, we propose an integrative “exercise-miRNA-ASD” framework wherein exercise functions as a multi-targeted modulator—simultaneously enhancing synaptic plasticity, promoting neuronal survival, and attenuating neuroinflammation—through coordinated regulation of the three miRNAs. Importantly, this framework is not merely descriptive but offers testable predictions: exercise-induced miRNA changes should be dose-dependent, show temporal correlation with behavioral improvements, and be blunted by miRNA-specific antagonists or CRISPR/Cas9-mediated knockout. Beyond its specific application to ASD, this framework has broader implications. The miR-132/BDNF, miR-34a/Bcl-2, and miR-146a/TLR7 pathways are not ASD-specific but represent fundamental neural stress and repair mechanisms that are dysregulated across Alzheimer’s disease (AD), traumatic brain injury, Parkinson’s disease (PD), and major depressive disorder. Exercise has been shown to modulate these same miRNAs in several of these conditions, suggesting that the “exercise-miRNA-neural function” axis may represent a conserved neuroprotective mechanism that transcends diagnostic boundaries. Thus, we propose that ASD serves as an ideal model disease for elucidating this universal mechanism, with findings potentially generalizable to other neurological disorders. We also critically evaluate current translational barriers: the near-absence of human clinical trials with serial miRNA profiling; the undefined dose-response relationships between exercise parameters and miRNA expression; the unresolved causality issue (current evidence demonstrates association, not causation); and the uncertain correlation between peripheral exosomal miRNA levels and brain miRNA dynamics. We argue that future research must prioritize CRISPR/Cas9-based miRNA manipulation in animal models combined with longitudinal exercise interventions to establish causality, and that cross-disease validation studies are essential to determine whether exercise-induced miRNA changes represent a shared neuroprotective signature or disease-specific responses. Ultimately, we envision a paradigm where a simple blood test measuring exosomal miR-132, miR-34a, and miR-146a levels could guide personalized exercise prescriptions, enabling precision rehabilitation for individuals with ASD and potentially other neurological conditions.

**Key words** exercise, ASD, miRNA

**DOI:** 10.3724/j.pibb.2026.0283

**CSTR:** 32369.14.pibb.20260283

Autism spectrum disorder (ASD) is a prevalent neurodevelopmental condition with rising prevalence and limited pharmacological options<sup>[1-3]</sup>. Physical exercise has shown promise in alleviating core symptoms, but the molecular mechanisms remain unclear.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate approximately 60% of protein-coding genes and are critically involved in brain development, synaptic plasticity, and neuroinflammation<sup>[4-5]</sup>. In ASD, dysregulation of

specific miRNAs has been reported in multiple brain regions<sup>[6-10]</sup>. Among the hundreds of miRNAs expressed in the central nervous system, three—miR-132, miR-34a, and miR-146a—have been consistently linked to ASD pathophysiology and are the focus of this review.

This review synthesizes current evidence on the dysregulation of these three miRNAs in ASD and evaluates how physical exercise may modulate them to improve ASD-related behavioral and neurobiological deficits. We also critically discuss

current limitations, including the predominance of animal studies, lack of causal evidence, and undefined exercise parameters, and outline future directions based on our own research experience. Importantly, the three miRNA-mediated pathways discussed here—synaptic plasticity (miR-132), neuronal survival (miR-34a), and neuroinflammation (miR-146a)—represent common pathological mechanisms shared across multiple neurological disorders, including Alzheimer's disease (AD), traumatic brain injury, and depression. Thus, while this review focuses on ASD as a model disease, the mechanistic framework has broader implications for understanding exercise-induced neuroprotection in the central nervous system.

## 1 Dysregulation of 3 key miRNAs in ASD

### 1.1 miR-132: synaptic plasticity deficits

miR-132 is consistently downregulated in the prefrontal cortex of ASD patients and plays a critical role in synaptic plasticity through its regulation of the MeCP2/PTEN feedback loop. In *Mecp2*-deficient ASD models, MeCP2 downregulation leads to PTEN suppression *via* miR-137, which in turn increases miR-132 expression<sup>[11]</sup>. This miR-132 upregulation then inhibits MeCP2 through targeting its 3' untranslated region (3'UTR), affecting analgesic responses and synaptic function<sup>[12-14]</sup>. In *Shank3*-deficient models, miR-132 dysregulation has also been observed in association with impaired social memory and hippocampal structural deficits<sup>[11]</sup>. These findings position miR-132 as a central regulator of ASD-related synaptic dysfunction.

### 1.2 miR-34a: neuronal apoptosis

miR-34a is upregulated in the cerebellum of ASD patients and in sodium valproate (VPA)-induced ASD rat models, where it promotes neuronal apoptosis by inhibiting the Bcl-2 signaling pathway<sup>[15-16]</sup>. This upregulation is associated with impaired brain function and altered synaptic development. In VPA rats, increased miR-34a expression in the cerebellum correlates with reduced *Bcl-2* mRNA stability, suggesting a pro-apoptotic mechanism that may contribute to ASD pathology<sup>[17]</sup>.

### 1.3 miR-146a: neuroinflammation

miR-146a shows region-specific dysregulation in ASD. In the temporal lobe of children with ASD, miR-

146a is most prominently upregulated during early postnatal development, whereas in *Mecp2* knockout models, it is significantly reduced<sup>[18]</sup>. This bidirectional dysregulation suggests that miR-146a levels may be phenotype-dependent. Functional studies demonstrate that miR-146a regulates neural progenitor differentiation *via* TLR7 signaling; *miR-146*<sup>-/-</sup> mice exhibit impaired neurogenesis, abnormal brain structure, and severe learning and memory deficits<sup>[19]</sup>. Additionally, downregulation of miR-146a/146b increases IRAK1 expression and induces neuroinflammation in ASD models<sup>[20]</sup>.

In summary, the three miRNAs reviewed above—miR-132, miR-34a, and miR-146a—are consistently dysregulated in ASD across multiple brain regions and animal models. Mechanistically, these miRNA alterations converge on three core pathological processes that are central to ASD pathophysiology. First, miR-132 downregulation impairs BDNF/MeCP2/PTEN signaling, leading to reduced synaptic plasticity and dendritic spine density, which likely contributes to social memory deficits and cognitive impairments in ASD<sup>[21]</sup>. Second, miR-34a upregulation suppresses the anti-apoptotic Bcl-2 pathway and activates p53-mediated apoptosis, promoting neuronal loss in key brain regions such as the cerebellum, which may underlie motor and cognitive dysfunction<sup>[22]</sup>. Third, miR-146a dysregulation disrupts TLR7/IRAK1-mediated inflammatory homeostasis in microglia, resulting in sustained neuroinflammation that may exacerbate synaptic dysfunction and impair neural development<sup>[23]</sup>. Together, these 3 miRNA-mediated mechanisms—synaptic dysfunction, neuronal apoptosis, and neuroinflammation—are interconnected and collectively contribute to the heterogeneous symptoms of ASD. Additionally, other miRNAs (including miR-27a, miR-128 and miR-125b) have also been reported as dysregulated in ASD<sup>[24-26]</sup>, but their roles are less consistently linked to exercise modulation and are therefore not the focus of this review (Figure 1). Importantly, the mechanistic links described above provide a rational basis for exercise intervention, as physical activity has been shown to modulate these very same miRNAs and reverse their pathological effects, which will be discussed in detail in Section 2.

| Human ASD brain tissues |         |         |          | ASD animal models                  |         |         |          |                                                     |
|-------------------------|---------|---------|----------|------------------------------------|---------|---------|----------|-----------------------------------------------------|
| Brain region            | miR-132 | miR-34a | miR-146a | Model                              | miR-132 | miR-34a | miR-146a | Primary effect                                      |
| PFC                     | ↓       | —       | —        | <i>Shank3</i> <sup>-/-</sup> rats  | ↓       | —       | —        | Synaptic plasticity ↓<br>Social memory ↓            |
| Cerebellum              | —       | ↑       | —        | <i>MeCP2</i> <sup>-/-</sup> mice   | ↑       | —       | ↓        | Analgesic response abnormality<br>Neuroinflammation |
| Temporal lobe           | —       | —       | ↑        | VPA rats                           | —       | ↑       | —        | Cerebellar apoptosis ↑<br>Brain function ↓          |
| Hippocamp               | ↓       | —       | —        | <i>miR-146</i> <sup>-/-</sup> mice | —       | —       | ↓        | Neurogenesis ↓<br>Memory impairment                 |

**Fig. 1** Dysregulation of three key miRNAs in ASD brain regions and animal models

This figure integrates evidence from human post-mortem brain tissues (left panel) and animal models (right panel) regarding the expression changes of miR-132, miR-34a, and miR-146a in ASD. Downward arrows ( ↓ ) indicate downregulation, upward arrows ( ↑ ) indicate upregulation, and em dashes ( — ) indicate that expression changes have not been reported or studied. In the human brain, miR-132 is downregulated in the prefrontal cortex and hippocampus; miR-34a is upregulated in the cerebellum; miR-146a shows region-specific upregulation in the temporal lobe during early postnatal development. In animal models, *Shank3*-deficient rats exhibit miR-132 downregulation associated with synaptic deficits and impaired social memory; *Mecp2* knockout mice show feedback upregulation of miR-132 alongside miR-146a downregulation, linked to neuroinflammation; VPA-induced rats display miR-34a upregulation in the cerebellum, correlating with increased apoptosis; *miR-146a* knockout mice exhibit severe neurogenesis impairment and memory deficits. Additional miRNAs (e.g., miR-27a, miR-128, miR-181c, miR-134-5p, miR-125b) have also been reported as dysregulated in ASD but are not the focus of this review due to their less consistent links to exercise modulation.

2 Exercise modulates key miRNAs to improve ASD

Physical exercise has been shown to confer neuroprotective benefits in ASD and other neurological conditions<sup>[27-31]</sup>. Emerging evidence indicates that these beneficial effects are mediated, at least in part, through miRNA regulation. This section synthesises current evidence on how exercise modulates the 3 key miRNAs—miR-132, miR-34a, and miR-146a—to improve ASD-related deficits (Figure 2)<sup>[32-34]</sup>. The following subsections detail the specific pathways for each miRNA.

2.1 Exercise modulates miR-132 to enhance synaptic plasticity

miR-132 is a critical regulator of synaptic plasticity through its interactions with BDNF, MeCP2, and PTEN pathways<sup>[32]</sup>. In ASD, miR-132 is consistently downregulated in the prefrontal cortex and hippocampus, correlating with impaired social memory and synaptic dysfunction<sup>[35]</sup>.

Exercise has been shown to modulate miR-132 expression in multiple models. Voluntary wheel exercise improved cognitive decline in AD mice by suppressing miR-132 expression<sup>[32]</sup>.

In *Shank3*-deficient ASD rats, early swimming exercise (30 min/d, 5 d/week, for 8 weeks) significantly upregulated hippocampal miR-132

expression. This upregulation correlated with: (1) improved social memory and object recognition in behavioral tests; (2) restored hippocampal neuronal volume and number; (3) recovery of scaffold and receptor protein levels; and (4) improved water maze learning performance<sup>[11]</sup>. These findings provide the first direct evidence linking exercise-induced miR-132 modulation to ASD symptom improvement<sup>[31]</sup>.

2.2 Exercise modulates miR-34a to promote neuronal survival

miR-34a is upregulated in the cerebellum of ASD patients and VPA models, where it promotes neuronal apoptosis through inhibition of the Bcl-2 signaling pathway.

Exercise interventions have demonstrated miR-34a modulation in various disease models. Voluntary wheel running ameliorated cognitive deficits in traumatic brain injury (TBI) and aging models, at least in part, through modulation of hippocampal miR-34a expression<sup>[32-33]</sup>. Swimming exercise downregulated miR-34a and inhibited pancreatic cell apoptosis in diabetic rats *via* the miR-34a/Sirt1/p53 axis<sup>[36]</sup>. Swimming also attenuated brain aging through miR-34a-mediated autophagy regulation.

While direct evidence in ASD models remains limited, the convergence of findings across multiple neurological conditions suggests that exercise-induced miR-34a downregulation may promote neuronal survival and reduce apoptosis. Given that miR-34a

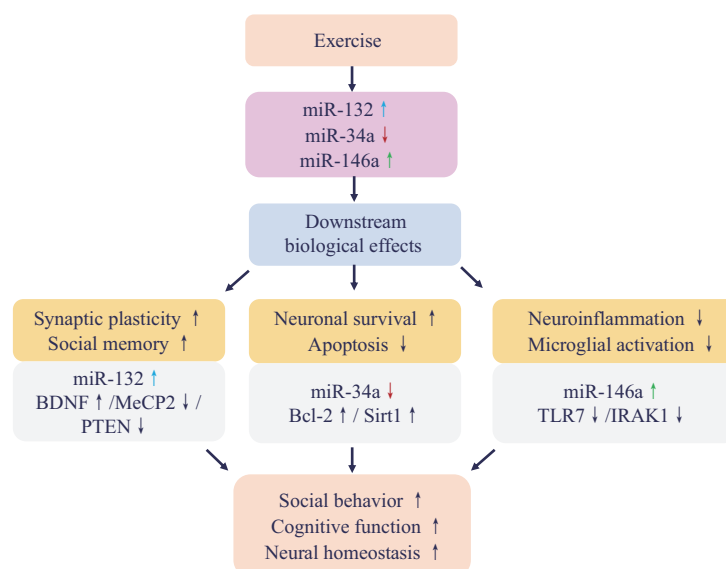


**Fig. 2 Proposed miRNA-mediated mechanisms underlying the beneficial effects of exercise in autism spectrum disorder (ASD)**

This schematic illustrates the integrative “exercise-miRNA-ASD” axis. Physical exercise interventions modulate the expression of three key miRNAs: miR-132, miR-34a, and miR-146a. Blue upward arrows indicate upregulation, red downward arrows indicate downregulation, and green upward arrows indicate normalization/upregulation. Solid arrows represent experimentally validated pathways; dashed arrows represent hypothesized pathways requiring further validation. miR-132 primarily regulates synaptic plasticity through BDNF/MeCP2/PTEN signaling; miR-34a modulates neuronal survival and apoptosis *via* the Bcl-2/Sirt1 pathway; miR-146a attenuates neuroinflammation through TLR7/IRAK1 signaling. Collectively, these miRNA-mediated pathways contribute to improved cognitive function, social behavior, and neural homeostasis in ASD. Of note, the majority of supporting evidence is derived from animal models, and direct validation in human ASD studies remains a critical priority. BDNF: brain-derived neurotrophic factor; MeCP2: methyl-CpG-binding protein 2; PTEN: phosphatase and tensin homolog; Bcl-2: B-cell lymphoma 2; Sirt1: sirtuin 1; TLR7: toll-like receptor 7; IRAK1: interleukin-1 receptor-associated kinase 1; ASD: autism spectrum disorder.

upregulation is a consistent feature of ASD pathology, exercise-mediated miR-34a reduction represents a promising therapeutic mechanism that warrants direct validation in ASD-specific studies.

### 2.3 Exercise modulates miR-146a to attenuate neuroinflammation

miR-146a regulates neuroinflammation through TLR7 and IRAK1 signaling pathways<sup>[34, 37]</sup>. In ASD, miR-146a shows region-specific dysregulation and is implicated in neural progenitor differentiation and neurogenesis<sup>[38]</sup>.

Exercise has been shown to modulate neuroinflammation-related miRNAs. Long-term aerobic exercise (16 weeks of treadmill training) increased brain expression of exosomal miR-532-5p and improved blood-brain barrier function in AD mice by targeting EPHA4<sup>[39]</sup>. Exercise also altered miR-21, miR-92a, miR-874, miR-138, let-7c, and miR-124 expression in TBI models, many of which are involved in neuroinflammatory pathways<sup>[40]</sup>.

Although direct evidence for exercise-induced miR-146a modulation in ASD is currently lacking, the established role of miR-146a in neuroinflammation and its dysregulation in ASD, combined with the well-documented anti-inflammatory effects of exercise, support the hypothesis that exercise may restore miR-146a homeostasis and reduce microglial activation. This represents a critical direction for future research.

### 2.4 Integrated mechanistic framework

The evidence reviewed above supports an integrative model wherein exercise modulates 3 key miRNAs to improve ASD pathophysiology. These miRNA-mediated mechanisms contribute to improved cognitive function, social behavior, and neural homeostasis in ASD. However, it is important to emphasize that the majority of mechanistic evidence is derived from non-ASD models, and direct causal validation in ASD-specific experimental paradigms remains a critical priority (Figure 3).

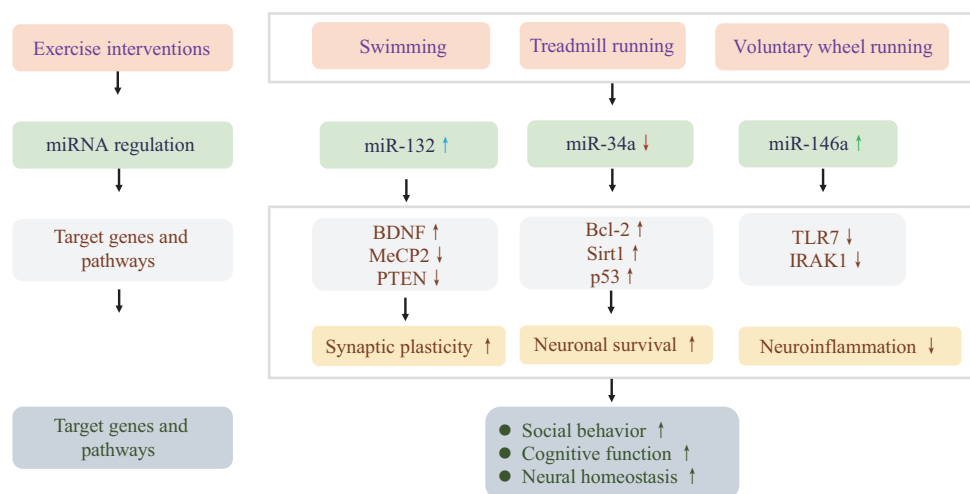


**Fig. 3 Proposed miRNA-mediated mechanisms underlying the beneficial effects of exercise on autism spectrum disorder (ASD)**

Physical exercise interventions, including swimming, treadmill training, and voluntary wheel running, may modulate the expression of key miRNAs such as miR-132, miR-34a, and miR-146a. These miRNAs are implicated in regulating neurobiological processes including synaptic plasticity (*via* BDNF-related pathways), neuronal survival and apoptosis, and neuroinflammation. Through these mechanisms, exercise may contribute to improved cognitive function, social behavior, and overall neural homeostasis in ASD. It should be noted that most supporting evidence is derived from animal models, and further validation in human studies is required.

### 3 Conclusion and future perspectives

#### 3.1 Summary of main findings

The findings reviewed here demonstrate that physical exercise ameliorates core deficits in ASD through modulation of three key miRNAs—miR-132, miR-34a, and miR-146a. These exercise-induced miRNAs function through regulating distinct but interconnected neurobiological processes: miR-132 enhances synaptic plasticity *via* BDNF/MeCP2/PTEN signaling; miR-34a promotes neuronal survival through Bcl-2/Sirt1 pathway inhibition; miR-146a attenuates neuroinflammation *via* TLR7/IRAK1 suppression. The convergence of evidence around this three-miRNA axis provides a coherent mechanistic framework for understanding how exercise benefits the ASD brain. Our own laboratory's findings in *Shank3*-deficient rats—demonstrating that early swimming exercise upregulates hippocampal miR-132, correlating with improved social memory and restored hippocampal structure—support the translational potential of early exercise intervention for ASD.

#### 3.2 Limitations and future directions

However, this field is still in its infancy and faces

several critical challenges.

First, the current body of evidence is predominantly derived from animal studies, with a notable scarcity of human research. To date, no registered clinical trials have specifically examined exercise-induced miRNA changes in ASD populations, representing a critical knowledge gap. Longitudinal human studies that incorporate serial miRNA profiling before, during, and after structured exercise interventions are urgently needed to validate the preclinical findings discussed in this review.

Second, the optimal parameters of exercise (type, intensity, duration, frequency) for effectively modulating miRNA networks remain largely unexplored. Future studies must systematically compare different exercise modalities (aerobic vs. resistance training), as well as varying intensities, durations, and frequencies, to delineate dose-response relationships between exercise and miRNA expression. Defining these parameters is crucial for translating preclinical findings into standardized, evidence-based exercise prescriptions for individuals with ASD.

Third, and most critically, the causal relationship between exercise, specific miRNA changes, and functional improvements in ASD requires rigorous

demonstration. Our current findings, including our own *Shank3*-deficient rat data, demonstrate association rather than causation. Employing genetic tools, such as CRISPR/Cas9-mediated miRNA modulation (*e. g.*, *miR-132* knockout or overexpression) in animal models, combined with longitudinal exercise interventions, will be essential to definitively establish whether specific miRNAs functionally mediate the therapeutic effects of exercise.

Fourth, the translatability of peripheral miRNA measurements remains uncertain—it is unclear whether changes in circulating exosomal miRNAs accurately reflect brain miRNA dynamics. Systematic validation of this correlation is required before exosomal miRNAs can be reliably used as non-invasive biomarkers for monitoring exercise efficacy.

### 3.3 General implications for neurological disorders

Beyond ASD, the three miRNA pathways reviewed here are fundamental mechanisms of neural function and dysfunction that operate across a wide spectrum of neurological and psychiatric disorders. miR-132 dysregulation has been documented not only in ASD but also in AD, schizophrenia, and major depressive disorder, where it similarly affects synaptic plasticity and dendritic spine density<sup>[41-42]</sup>. miR-34a is upregulated in AD and aging-related cognitive decline, contributing to neuronal apoptosis through Bcl-2 suppression. miR-146a is a well-established regulator of neuroinflammation in multiple sclerosis, ischemic stroke, and TBI, modulating microglial activation *via* TLR7/IRAK1 signaling<sup>[43]</sup>.

Encouragingly, exercise has been shown to modulate these miRNAs in several of these conditions. Voluntary wheel running suppressed miR-132 in AD models<sup>[44]</sup>, treadmill exercise rescued blood-brain barrier function *via* exosomal miR-532-5p in AD mice<sup>[45]</sup>, and exercise altered miR-138 expression in TBI models<sup>[46]</sup>. These findings suggest that the “exercise-miRNA-neural function” axis may represent a conserved neuroprotective mechanism that transcends disease-specific boundaries.

Therefore, the integrative framework proposed here—though built on ASD evidence—may offer a conceptual foundation for designing exercise-based interventions across various neurological disorders. Future research should systematically evaluate

whether exercise-induced miRNA changes are disease-specific or represent a shared response to neural stress and repair, which would inform the development of broadly applicable exercise prescriptions for brain health. Additionally, the biomarker potential of exosomal miRNAs may be equally applicable to monitoring exercise efficacy in AD, PD, TBI, and other conditions, warranting cross-disease validation studies.

From a clinical perspective, we envision a future where a simple blood test measuring exosomal miR-132, miR-34a, and miR-146a levels could guide personalized exercise prescriptions for individuals with ASD and potentially other neurological conditions. Achieving this vision will require multidisciplinary collaboration among exercise physiologists, neuroscientists, and clinicians, as well as rigorous validation through large-scale, longitudinal human studies.

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# 运动通过miR-132/miR-34a/miR-146a改善孤独症谱系障碍的机制框架\*

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**摘要** 孤独症谱系障碍(ASD)是一种全球患病率持续上升的神经发育疾病,目前有效药物干预手段十分有限,迫切需要探索安全、可行且具有明确机制基础的干预策略。体育运动作为一种前景广阔的非药物干预手段,已被证实能够改善ASD儿童及青少年的核心症状——包括社交沟通缺陷和限制性重复行为以及认知功能障碍和运动障碍等共病表现。然而,介导这些改善效应的分子机制至今尚未被充分阐明,这阻碍了循证运动处方的制定和基于生物标志物的康复方案开发。微小RNA(miRNA)是进化上高度保守的小分子非编码RNA,在转录后水平调控约60%的蛋白质编码基因。在中枢神经系统中,miRNA协调多种神经生物学过程,包括神经前体细胞增殖、神经元分化、树突棘形态发生、突触可塑性以及神经炎症稳态。但miRNA在体液中异常稳定,并可被包装进入细胞外囊泡,使其既可作为机制介导因子,又可作为非侵入性外周生物标志物。脑内表达的数百种miRNA中,有3个——miR-132、miR-34a和miR-146a——与ASD病理生理的关联尤为密切。本综述聚焦于这3个miRNA。miR-132通过调控BDNF/MeCP2/PTEN信号通路成为活动依赖性突触可塑性的核心调控因子,在ASD前额叶皮层中呈现一致性下调;miR-34a作为促凋亡因子,通过抑制Bcl-2介导的神经元存活通路发挥促凋亡作用,在ASD小脑中表达上调;miR-146a则通过TLR7/IRAK1信号通路充当神经炎症的关键“刹车”,在ASD颞叶中呈现区域性失调。本文首先系统总结了来自人脑死后组织和ASD动物模型的证据,证实这3个miRNA在ASD中呈现一致的表达异常。值得注意的是,这些miRNA异常所导致的病理后果——突触可塑性受损、神经元过度凋亡和持续性神经炎症——相互关联,共同促成ASD的异质性症状谱。其次,本文对新近证据进行了综合分析,表明多种运动方式(包括游泳、跑台运动和自主跑轮运动)能够同时逆转这些ASD样行为表型,并使上述3个关键miRNA的表达恢复正常。这些数据是运动诱导的miRNA调控与ASD症状改善之间存在关联的直接实验证据。基于上述发现,本文提出了一个“运动-miRNA-ASD”整合框架。在该框架中,运动通过协同调控3个miRNA,同时发挥增强突触可塑性、促进神经元存活和减轻神经炎症的多靶点调节作用。重要的是,该框架不仅是描述性的,还提出了可检验的预测:运动诱导的miRNA变化应呈现剂量依赖性,应与行为改善呈时间相关性,并应被miRNA特异性拮抗剂或CRISPR/Cas9介导的基因敲除所阻断。该框架在ASD的具体应用之外,具有更广泛的启示意义。miR-132/BDNF、miR-34a/Bcl-2和miR-146a/TLR7通路并非ASD特有,而是代表着在阿尔茨海默病、创伤性脑损伤、帕金森病和重度抑郁症等多种疾病中普遍失调的神经应激与修复机制。运动在上述多种疾病中已被证实可调控相同的miRNA,提示“运动-miRNA-神经功能”轴可能代表一种超越疾病界限、在进化上保守的神经保护机制。因此,ASD可作为阐明这一普适机制的理想模型,其研究发现可能具有向其他神经系统疾病推广的潜力。本文同时对当前的转化瓶颈进行了批判性评估:缺乏开展连续miRNA检测的人体临床试验;运动参数与miRNA表达之间的量效关系尚未明确;因果关系尚待证实(现有证据仅支持相关性而非因果性);以及外周血分泌体miRNA水平与脑内miRNA动态之间的相关性尚不确定。这表明未来研究应优先采用CRISPR/Cas9介导的miRNA操控联合长期运动干预的动物实验设计以确立因果关系,同时有必要开展跨疾病验证研究,以明确运动诱导的miRNA变化究竟是具有疾病特异性的“标签”还是共享的神经保护“信号”。最终,我们展望这样一种范式:通过简单的血液检测测定分泌体miR-132、miR-34a和miR-146a水平,即可指导个性化运动处方的制定,从而为ASD患者乃至其他神经系统疾病患者实现精准康复。

**关键词** 运动,孤独症谱系障碍,微小RNA

**中图分类号** Q95-336, R742.8+9

**DOI:** 10.3724/j.pibb.2026.0283

**CSTR:** 32369.14.pibb.20260283

\* 陕西省社会科学基金(2023Q017),陕西省大学生创新计划项目(S202410723043)和渭南师范学院人才项目(2025RC38)资助。

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收稿日期: 2026-05-23, 接受日期: 2026-07-06