DOI: 10.11844/cjcb.2026.04.0022
中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(4): 1172–1184 CSTR: 32200.14.cjcb.2026.04.0022

miRNA调控癫痫相关神经细胞铁死亡的研究进展

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摘要 近年研究表明, 微小RNA(microRNA, miRNA)通过调控铁死亡(ferroptosis)在癫痫发病机制中发挥关键作用, 尤其是在调节系统Xc^-/GSH/GPX4抗氧化轴、铁稳态和脂质过氧化等核心环节中起着至关重要的作用。有研究表明在癫痫相关动物模型中, miR-34a-5p表达上调通过靶向调控SIRT1/GPX4信号轴, 进而介导Wnt/β-catenin通路, 促进脂质过氧化和铁死亡, 加重神经元损伤; 相反, miR-211-5p表达下调可靶向*P2RX7*, 并通过MAPK/ERK通路调控GPX4/HO-1轴, 进而抑制铁死亡并改善癫痫发作表型。此外, miRNA还与多种应激和转录因子网络(如Nrf2、p53、MAPK/ERK)相互作用, 进一步调节神经元对铁死亡的易感性。鉴于miRNA不仅是神经元凋亡、兴奋/抑制平衡及突触可塑性的重要调控因子, 亦深度参与铁死亡的发生与发展, 该文重点论述经癫痫动物模型与体外神经元细胞实验验证的差异表达miRNA, 并分析其与铁死亡之间的因果关系, 以期为深入理解癫痫病理进程提供新视角, 并为未来开发癫痫治疗新靶点提供理论依据。

关键词 miRNA; 铁死亡; 癫痫; 系统Xc^-/GSH/GPX4抗氧化轴; 神经元细胞

Research Progress on miRNA Regulation of Ferroptosis in Epilepsy-Associated Neurons

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Abstract Recent studies have demonstrated that miRNAs (microRNAs) play a pivotal role in the pathogenesis of epilepsy by regulating ferroptosis, particularly in core processes such as modulating the system Xc^-/GSH/GPX4 antioxidant axis, iron homeostasis, and lipid peroxidation. Research has shown that in epilepsy-related animal models, upregulated expression of miR-34a-5p targets SIRT1/GPX4 signaling axis to mediate the Wnt/β-catenin pathway, promoting lipid peroxidation and ferroptosis, thereby exacerbating neuronal damage. Conversely, downregulated expression of miR-211-5p targets *P2RX7* to modulate the GPX4/HO-1 axis via the MAPK/ERK pathway, thereby inhibiting ferroptosis and ameliorating epileptic phenotypes. Additionally, miRNAs interact with various stress and transcription factor networks (e.g., Nrf2, p53, MAPK/ERK) to further regulate neuronal susceptibility to ferroptosis. Given that miRNAs are not only critical regulators of neuronal apoptosis, excitatory/inhibitory balance, and synaptic plasticity but

收稿日期: 2025-12-12 接受日期: 2026-02-27
黑龙江省基本科研业务费基础研究项目(批准号: 2020-KYYWF-2078)资助的课题
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Received: December 12, 2025 Accepted: February 27, 2026
This work was supported by the Basic Research Project Funded by Heilongjiang Provincial Basic Research Funds (Grant No.2020-KYYWF-2078)
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also deeply involved in the occurrence and progression of ferroptosis, this article focuses on differentially expressed miRNAs validated through epilepsy animal models and *in vitro* neuronal cell experiments, analyzing their causal relationships with ferroptosis. The aims are to provide new insights into the pathophysiological processes of epilepsy and to provide a theoretical basis for the future development of new targets for epilepsy treatment.

Keywords miRNA; ferroptosis; epilepsy; system Xc^-/GSH/GPX4 antioxidant axis; neurons

癫痫以神经元反复异常放电及进行性神经损伤为核心特征, 部分患者存在耐药性及长期脑功能受损, 这提示仍需面向其病理机制发掘新型治疗靶点。近年来研究在癫痫患者(尤其是颞叶癫痫)切除的海马/皮质组织以及多种癫痫动物与体外模型中均观察到微小RNA(microRNA, miRNA)谱系的持续性失衡, 同时外周循环miRNA亦呈现可重复的差异表达, 提示miRNA异常可能参与神经兴奋性调控、炎症反应与神经元存活等关键环节, 并与耐药及长期功能结局相关[1-3]。铁死亡是一种以铁负荷升高与脂质过氧化失控为核心特征的受调控的细胞死亡方式; 在癫痫模型中可见抗氧化防御功能受损、铁稳态紊乱与脂质过氧化增强等铁死亡相关改变, 而抑制铁死亡(如应用特异性抑制剂或通过调控铁稳态/抗氧化通路)可在一定程度上减轻癫痫发作相关的神经元损伤并改善部分行为学/认知表型[4-5]。miRNA作为转录后调控枢纽, 可通过多靶点协同重塑通路网络, 现有研究表明其与铁死亡关键分子*SLC7A11*、*GPX4*、*ACSL4*以及铁代谢节点*TFRC*、*FPN1*存在紧密的调控关联[6]。在癫痫相关动物与体外模型中, 针对特定miRNA的干预(例如抑制miR-34a-5p表达)可影响SIRT1/GPX4等轴及相关下游环节, 从而调控神经元铁死亡并改变癫痫样表型, 但在临床患者层面的直接因果证据仍需进一步积累[7]。本文围绕“miRNA如何通过调控铁死亡网络途径进而影响癫痫的发生和发展”展开归纳与凝练, 为进一步明确癫痫发病机制以及治疗策略奠定理论基础。

1 miRNA调控细胞铁死亡在癫痫发病机制中的作用

1.1 miRNA的发现及其生物学功能

miRNA为19~24 nt的内源性非编码RNA, 通常与靶mRNA 3′UTR(3′ untranslated region)结合并介导翻译抑制或mRNA降解; 其成熟与装载依赖Drosha/Dicer及RNA诱导沉默复合体(RNA-induced silencing complex, RISC)。单一miRNA可同时调控多个靶点, 且同一通路也常受多种miRNA协同调控[8-9]。鉴于癫痫病程中氧化应激与细胞死亡网络长期被激活, miRNA对铁死亡关键分子的精细调控, 已成为解析癫痫进展及实现疾病干预的全新切入点。

1.2 miRNA在癫痫中的作用

脑组织是miRNA表达最丰富的组织之一。SCHRATT等[10]率先发现, miR-134富集于树突棘, 并通过靶向LIM结构域激酶1(LIM domain kinase 1, *Limk1*)调控棘突大小与突触可塑性; 随后的工作表明, miR-124、miR-9、miR-132等神经元特异miRNA共同参与神经干细胞向神经元谱系的分化、轴突导向和活动依赖性突触重塑[11-13]。在小鼠中枢神经系统特异性敲除Dicer核酸内切酶(Dicer RNase III endonuclease, Dicer)(miRNA生物发生通路的关键加工酶, 负责将前体miRNA加工为成熟miRNA)会导致海马神经发生受阻、突触连接减少及学习记忆障碍, 提示miRNA对维持神经网络稳态具有基础性调控作用[14-15]。在癫痫研究中, HENSHALL等[1]通过高通量筛查发现, 颞叶癫痫患者海马及多种癫痫动物模型中存在miRNA(如miR-134、miR-132、miR-146a、miR-21、miR-34a等)异常表达。JIMENEZ-MATEOS等[16]证实, 抑制miR-134的表达可减轻致痫后海马神经元变性并降低自发发作频度; ZHAO等[17]和ASLANI等[18]分别从炎症与神经胶质细胞激活角度揭示miR-146a/miR-155的促炎、致痫作用; BRENNAN等[19]对现有证据进行整合, 提出“miRNA失衡–兴奋/抑制值改变–神经网络重塑–癫痫自发发作”的分子框架。

研究表明, 癫痫发作及其后续神经网络重塑伴随miRNA表达谱显著重塑, 相关miRNA可

通过影响突触可塑性、神经炎症反应及细胞死亡易感性而参与病程演变。我们前期在戊四氮(pentylenetetrazol, PTZ)慢性致痫模型中亦观察到miR-34a、miR-21等的表达水平变化与神经元损伤相关[20-22], 提示其可能参与癫痫的发生和发展进程。

1.3 铁死亡在癫痫中的作用

铁死亡是一种铁依赖、脂质过氧化驱动的受调控的细胞死亡方式, 其核心调控机制可概括为系统Xc^-/GSH/GPX4抗氧化轴、铁稳态/铁蓄积轴与脂质过氧化轴三大关键通路[23-24]。有研究已在癫痫模型中观察到抗氧化轴受损、铁稳态失衡与脂质过氧化增强等改变, 且抑制铁死亡通路可在一定程度上改善癫痫发作的相关表型, 这提示铁死亡可能参与“癫痫发作–神经元损伤–神经网络重塑”的正反馈过程[25-26]。

1.4 miRNA靶向调控铁死亡通路参与癫痫的发生和发展

随着铁死亡研究深入, miRNA与铁死亡的交叉调控逐渐成为热点。现有证据表明, miRNA可靶向*SLC7A11*、*GPX4*、*FPN1*、*TFRC*、*ACSL4*等关键分子, 参与构建转录后调控网络。多篇系统综述指出, miRNA可通过抑制系统Xc^-/GSH/GPX4抗氧化轴、影响铁蛋白自噬与铁外排, 或调节脂质合成与过氧化相关酶活性, 从而在多种肿瘤、心脑血管疾病及神经退行性疾病中调控铁死亡敏感性[6,27-29]。有研究发现众多“铁死亡相关miRNA”, 其中miR-15/16、miR-34a、miR-214等可通过靶向*GPX4*/*NRF2*或系统Xc^-提高铁死亡易感性, 促进细胞损伤; 而miR-137、miR-29家族、miR-124-3p等更倾向于增强神经元的抗氧化与铁缓冲能力继而防止细胞损伤[28]。

在神经系统疾病方面, 近期的综述与实验结果提示, miRNA通过介导铁死亡参与调控脑缺血再灌注、脑外伤和神经退行性病变等过程[29]。而癫痫领域的研究还处于初级阶段, 但已有研究工作描绘“miRNA-铁死亡–癫痫表型”的关系, 并将系统Xc^-/GSH/GPX4轴、铁稳态/铁蓄积轴与炎症、凋亡通路一并纳入miRNA调控网络[30]。基于现有研究, 我们提出“miRNA-铁死亡–癫痫表型”的整合性概念模型: miRNA可能通过调控抗氧化轴、铁稳态与脂质代谢等改变神经细胞对铁死亡的易感性; 铁死亡相关的神经元丢失与胶质细胞反应可能参与中枢神经环路重塑并影响癫痫表型。需要强调的是, 当前直接证据主要来自动物与体外模型, 且集中于证据链相对完整的少数miRNA; 仍需在癫痫模型中进一步验证靶点、铁死亡、癫痫结局三者之间的因果关联。

综上, “miRNA-铁死亡–癫痫”轴这一视角既为难治性癫痫中神经元进行性丢失提供了新的解释, 也为以miRNA及铁死亡通路为双重调控靶点的联合干预策略奠定了理论基础。后续章节将围绕具体miRNA亚型、系统Xc^-/GSH/GPX4抗氧化轴、铁稳态轴、脂质过氧化轴及应激转录网络等展开讨论。

2 癫痫相关miRNA在铁死亡中的调控作用及其对癫痫的影响

脑组织中表达的miRNA数量众多, 本文仅讨论与癫痫相关的核心miRNA, 且本文将同时关联靶点、铁死亡终点及癫痫相关表型的miRNA作为重点研究对象展开论述。

2.1 miR-142-5p

miR-142-5p在多种癫痫动物模型中普遍表达上调, 其可促进神经细胞损伤, 并与线粒体功能受损、氧化应激增强及铁死亡相关改变相关。ZHANG等[31]在匹罗卡品诱导的小鼠癫痫持续状态模型中发现, 癫痫发作后海马组织中miR-142-5p表达上调而靶蛋白线粒体Rho GTP酶1(mitochondrial Rho GTPase 1, Miro1)表达下调; 抑制miR-142-5p的表达可逆转线粒体转运相关蛋白表达、改善线粒体功能并减少神经元死亡, 同时延迟癫痫发作起始、减轻发作程度。该研究结果提示, miR-142-5p/Miro1轴可能会提高神经元对铁依赖性脂质过氧化的易感性。更直接的铁死亡证据来自体外模型。ZHANG等[32]在无镁诱导的海马神经元细胞癫痫样放电模型中发现, FTX(five prime to Xist)表达下调伴随miR-142-5p表达上调与GABPB1(GA-binding protein transcription factor subunit B1)表达水平下降, 同时出现Fe^{2+}水平升高、脂质过氧化增强及GPX4等抗铁死亡蛋白表达下调; 过表达FTX可下调miR-142-5p, 从而抑制铁死亡并减少癫痫样放电, 而过表达miR-142-5p可抵消FTX对神经细胞的保护作用。WU等[33]进一步报道, Lin-28同源蛋

白(Lin-28 homolog, LIN28)水平降低与miR-142-5p水平升高并行，伴随GPX活性及GPX4表达水平下降、氧化损伤加重和细胞活力下降；上调LIN28表达可抑制miR-142-5p表达并恢复GPX4表达，从而逆转铁死亡相关改变(图1)。

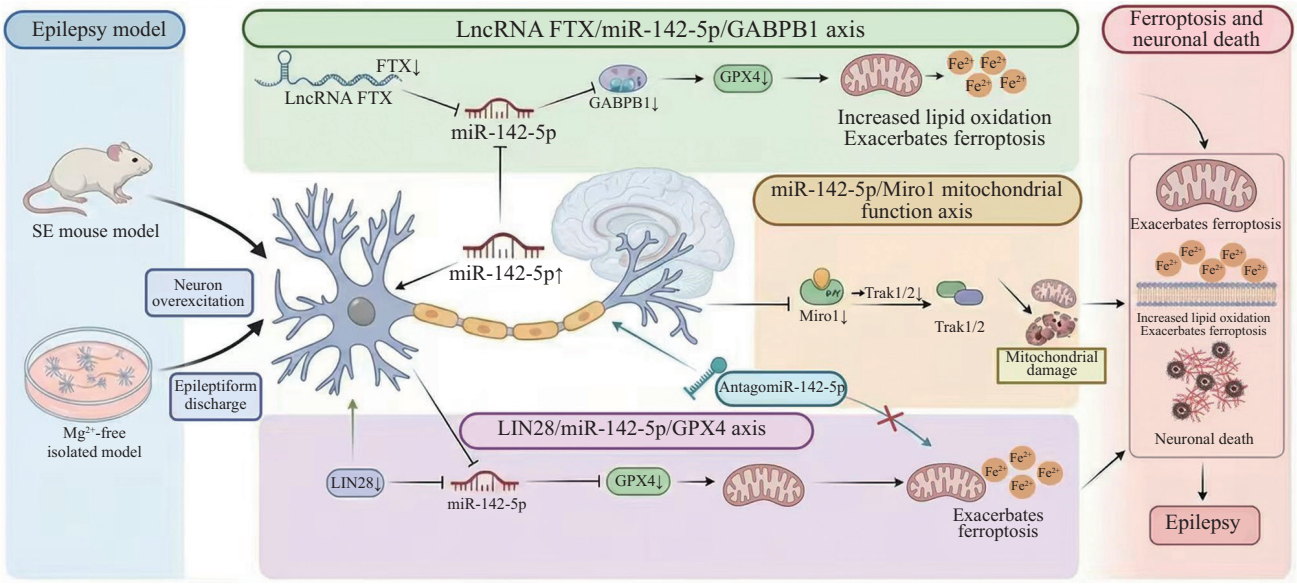
总体来看，癫痫状态下miR-142-5p的病理性上调可能通过两类机制推动铁死亡相关损伤：一是靶向Miro1导致线粒体稳态受损并放大氧化应激；二是通过FTX/miR-142-5p/GABPB1及LIN28/miR-142-5p/GPX4轴削弱GPX4介导的抗铁死亡防线，促进Fe^{2+}积聚与脂质过氧化。然而，现有证据仍以啮齿类与体外模型为主，细胞类型特异性及不同发作类型/病程阶段的动态规律尚待系统阐明。基于现有研究线索，围绕miR-142-5p抑制干预(如antagomir)，或通过上调FTX/LIN28实现对miR-142-5p的间接调控，并与铁死亡抑制相关策略联合开展深入探索，仍具有重要的后续研究价值与临床转化潜力。

2.2 miR-211-5p

miR-211-5p近年来被视为癫痫相关miRNA中较具代表性的保护性分子，可能与氧化应激及铁死亡调控相关。于海艳等[34]的临床研究报道，癫痫患者血清miR-211-5p水平低于健康对照，且其下降与脑电图(electroencephalogram, EEG)异常程度显著相关，提示miR-211-5p减少可能与癫痫发作及严重性有关。LI等[35]在化学致痫小鼠模型中发现，癫痫状态下海马miR-211-5p水平降低，可解除其对P2RX7的抑制并激活MAPK/ERK信号，继而抑制GPX4/HO-1抗氧化轴，伴随脂质过氧化相关指标恶化，呈现铁死亡表型；脑内上调miR-211-5p或沉默*P2RX7*均可改善癫痫表型。PANT等[36]从非编码RNA(non-coding RNA, ncRNA)网络层面同样指出，miR-211-5p的抗癫痫效应与其抑制铁死亡密切相关，并将其列入潜在的表观遗传治疗靶点。与此一致的是，ENGEL等[37]报道P2X7R过度活化与癫痫发作严重程度及药物不敏感相关，拮抗或沉默*P2X7R*在多种实验性癫痫模型中可降低发作强度并具有疾病修饰潜力，从侧面支持miR-211-5p/P2RX7轴的干预价值。

此外，其他中枢疾病模型也提示miR-211-5p在海马区具有神经保护倾向。LI等[38]在慢性应激抑郁模型中观察到齿状回miR-211-5p下调与神经发生减少、凋亡增加相关，而上调miR-211-5p可通过抑制Dyrk1A/STAT3通路促进神经再生并改善相关表型(图2)。

综上，miR-211-5p可能是连接癫痫表型、氧化应激与铁死亡的关键节点，其相关通路(miR-211-

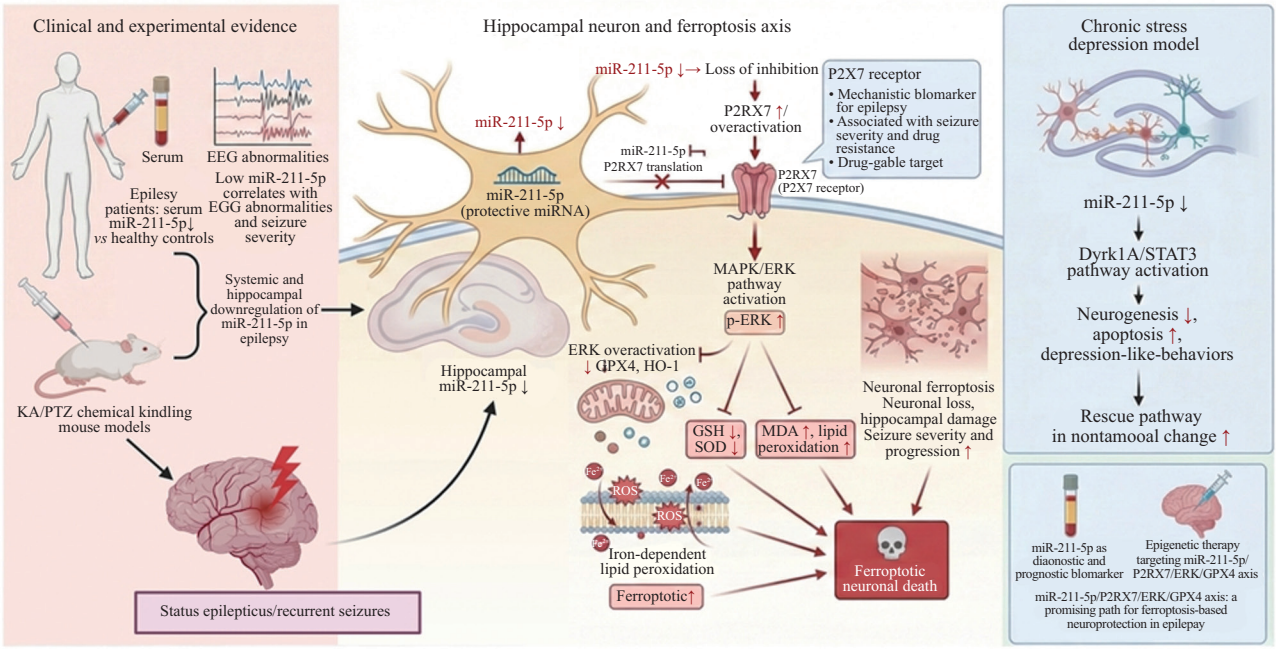


向上箭头: 上调; 向下箭头: 下调; T形: 抑制; 叉号: 阻断。

Upward arrow: upregulation; downward arrow: downregulation; T shape: inhibition; cross: block.

图1 miR-142-5p在癫痫中的调控作用示意图

Fig.1 Schematic diagram of the regulatory role of miR-142-5p in epilepsy



GPX4: 谷胱甘肽过氧化物酶4; GSH: 还原型谷胱甘肽; SOD: 超氧化物歧化酶; MDA: 丙二醛; Dyrk1A: 双特异性酪氨酸磷酸化调节激酶1A; STAT3: 信号转导及转录激活因子3。向上箭头: 上调; 向下箭头: 下调; T形: 抑制; 叉号: 阻断。

GPX4: glutathione peroxidase 4; GSH: reduced glutathione; SOD: superoxide dismutase; MDA: malondialdehyde; Dyrk1A: dual-specificity tyrosine phosphorylation-regulated kinase 1A; STAT3: signal transducer and activator of transcription 3. Upward arrow: upregulation; downward arrow: down-regulation; T shape: inhibition; cross: block.

图2 miR-211-5p在癫痫中的调控作用示意图

Fig.2 Schematic diagram of the regulatory role of miR-211-5p in epilepsy

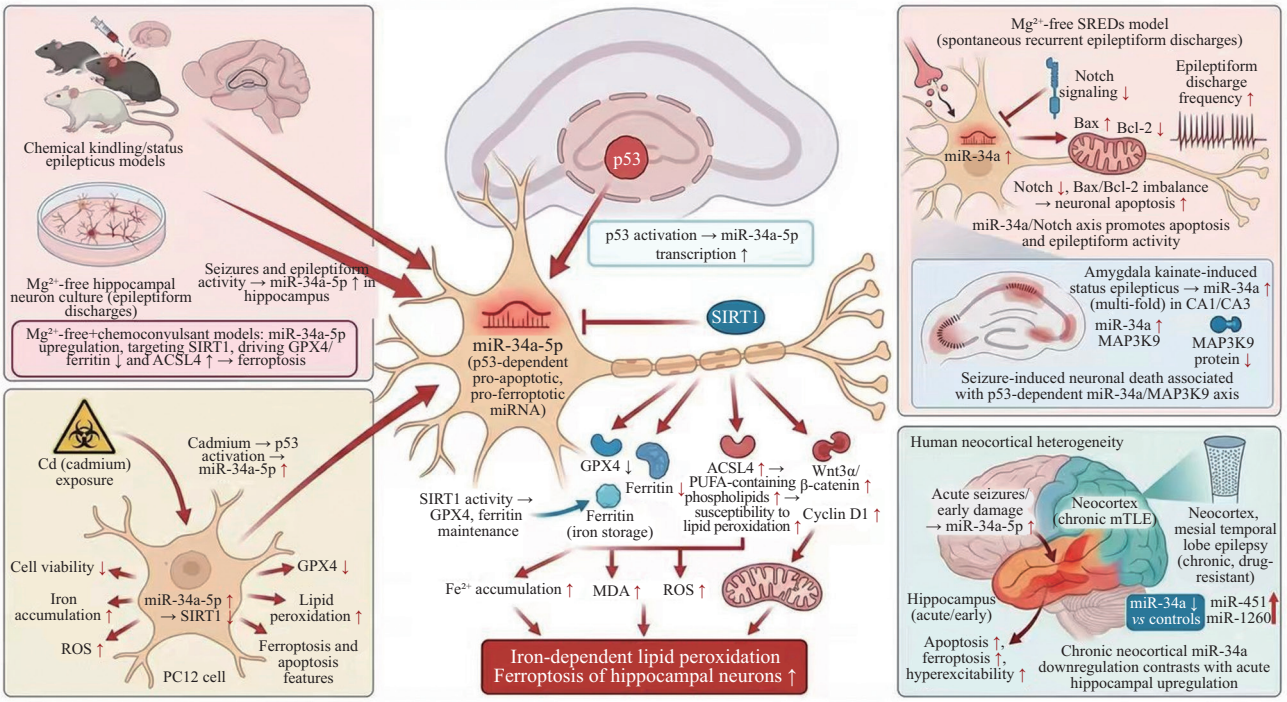
5p/P2RX7/ERK/GPX4)为癫痫的生物标志物与干预靶点研究提供了思路, 但该通路在患者层面的稳定性与可转化性仍需进一步验证。

2.3 miR-34a-5p

miR-34a-5p是典型的p53依赖性促凋亡miRNA, 在癫痫与铁死亡研究中常被作为促损伤分子, 其可能通过miR-34a-5p/SIRT1/GPX4/ACSL4轴影响铁依赖性脂质过氧化与细胞死亡。GAO等[7]在化学致痫大鼠及无镁培养海马神经元细胞中证实, 发作/癫痫样放电可诱导海马miR-34a-5p表达上调, 且*SIRT1*为其直接靶点; 过表达miR-34a-5p抑制SIRT1表达后, GPX4与铁蛋白表达下调、ACSL4表达上调, 同时出现Fe^{2+}负荷增加、脂质过氧化增强等铁死亡表型; 该研究同步呈现了miRNA干预、铁死亡终点变化与惊厥结局的对应关系, 为“miRNA-铁死亡–癫痫表型”的调控机制提供了较直接的实验证据。HAO等[39]在PC12细胞中亦观察到镉暴露可上调miR-34a-5p表达并抑制SIRT1表达, 伴随GPX4水平下降与氧化损伤/脂质过氧化加重。

从电生理改变与细胞凋亡的关联角度分析, WANG等[40]在无镁诱导自发性复发性癫痫样放电(spontaneous recurrent epileptiform discharges, SREDs)海马神经元模型中发现miR-34a上调伴随Notch信号抑制与促凋亡分子表达上调; miR-34a抑制剂可激活Notch、减少凋亡并降低放电频率, 提示其促损伤效应与癫痫样放电相互耦联。SANO等[41]在杏仁核内红藻氨酸诱导的小鼠癫痫持续状态模型中观察到海马CA1/CA3区miR-34a显著上调并伴随靶基因丝裂原活化蛋白激酶激酶激酶9(mitogen-activated protein kinase kinase kinase 9, *MAP3K9*)表达下调, 且p53抑制剂可抑制miR-34a水平升高; 脑室内注射miR-34a拮抗剂虽可部分调节凋亡信号, 但对重症模型中的神经元死亡的抑制效果仍较为有限, 提示miR-34a可能同时联结凋亡、铁死亡等多条信号通路[39]。

值得注意的是, 人类组织存在差异。ORGANISTA-JUÁREZ等[42]在药物难治性内侧颞叶癫痫患者颞叶新皮质样本中发现miR-34a表达下调, 同时miR-451、miR-1260等表达上调并与发作频率及



向上箭头: 上调; 向下箭头: 下调; T形: 抑制。

Upward arrow: upregulation; downward arrow: downregulation; T shape: inhibition.

图3 miR-34a-5p在癫痫中的调控作用示意图

Fig.3 Schematic diagram of the regulatory role of miR-34a-5p in epilepsy

用药量相关, 提示miR-34a-5p可能具有脑区与病程阶段的时空异质性(图3)。总体而言, 现有证据更支持miR-34a-5p在模型研究中呈促损伤倾向, 但其在不同脑区/细胞类型/病程阶段的精细谱系及其对铁死亡的相对贡献仍需系统验证, 以评估其作为干预靶点的稳定性与可转化性。

2.4 其他相关miRNA

癫痫相关miRNA并非随机发挥作用, 而是在转录后调控层面对铁死亡不同环节产生分工效应; 但不同miRNA的证据链完整程度差异明显。本文因此将证据链相对完整者作为重点展开介绍(见2.1~2.3); 其余miRNA目前多停留在候选关联层面(证据来自非癫痫模型或缺乏干预–表型闭环证据), 为避免造成它们“均为核心因子”的误读, 仅将其他相关miRNA统一汇总于表1供读者查阅。

3 癫痫相关的miRNA调控铁死亡通路的机制

3.1 癫痫相关的miRNA调控系统Xc^-/GSH/GPX4轴

系统Xc^-/GSH/GPX4轴是神经元抵御铁死亡的关键抗氧化通路。SLC7A11转运胱氨酸以支持GSH合成, GSH与GPX4共同清除脂质过氧化物; 当该轴受到抑制时, GSH耗竭、GPX4失活, 加之脂质过氧化与Fe^{2+}累积, 共同促发铁死亡。

相关研究提示, 该轴失衡可能参与癫痫的“兴奋毒性–氧化应激–铁死亡”链条。前文已述miR-34a-5p在癫痫模型中表达上调并可通过SIRT1/GPX4通路加重脂质过氧化与铁死亡。在非癫痫神经毒性模型中, HAO等[39]在$CdCl_2$处理的PC12细胞中同样观察到miR-34a-5p水平升高与去乙酰化酶SIRT1(sirtuin 1)表达下调并行, 敲低miR-34a-5p可恢复SIRT1蛋白的表达及活性并减轻铁死亡相关损伤, 支持其通过SIRT1/GPX4通路促进铁死亡。

除miR-34a-5p外, 直接靶向系统Xc^-的miRNA亦被报道。LI等[49]在创伤性脑损伤(traumatic brain injury, TBI)小鼠及HT22细胞中证实, miR-128-3p可下调SLC7A11表达并促进铁死亡; 氨茶碱通过降低miR-128-3p水平、恢复SLC7A11/GSH/GPX4轴减轻TBI后功能障碍。LUO等[50]在阿尔茨海默病模型中进一步提示, 特定miRNA介导IGFBP-2过表达可抑制核因子E2相关因子2(nuclear factor erythroid

表1 miRNA靶向铁死亡通路并关联癫痫相关表型的研究汇总

Table 1 Summary of miRNA targeting ferroptosis pathways and their association with epilepsy-related phenotypes

第一作者/发表年份 First author/year of publication	miRNA	表达趋势 Expression trend	来源/作用条件 Source/conditions of action	靶向的通路 Target pathway	主要作用机制 Main mechanism of action
XIE et al [43], 2023	miR-124-3p	Dowregulation	Exosomes derived from M2 microglia	NCOA4	Reduction of ferritin autophagy and Fe^{2+} release, elevation of GSH/GPX4 levels, and alleviation of neuronal ferroptosis
DONG et al [44], 2024	miR-219-5p	Dowregulation	Exosomes derived from bone marrow mesenchymal stem cells	UBE2Z/NRF2 pathway	Relieve UBE2Z's inhibition of NRF2, upregulation GPX4, SLC7A11, reducing oxidative stress and ferroptosis
XIAO et al [45], 2019	miR-212-5p	Dowregulation	Traumatic brain injury model	COX2	Directly inhibits COX2, reduces lipid peroxidation and iron overload, alleviates ferroptosis, and improves cognitive function
WANG et al [46], 2024	miR-30a-5p	Upregulation	Chronic cerebral hypoperfusion model	SIRT1/NRF2 pathway	Inhibition of the SIRT1/NRF2 pathway leads to reduced GPX4, promoting ferroptosis in hippocampal neurons and cognitive impairment
ZHU et al [47], 2023	miR-27a	Upregulation	cerebral ischemia-reperfusion model	SLC7A11	Direct targeting of SLC7A11 leads to impaired GSH synthesis and downregulation of GPX4, exacerbating ferroptosis and infarction
WANG et al [48], 2022	miR-378a-3p	Upregulation	Exosomes derived from astrocytes (lead exposure model)	SLC7A11	After uptake by neurons, SLC7A11 is inhibited, leading to decreased GSH levels, elevated lipid ROS, and induction of ferroptosis

2-related factor 2, Nrf2)表达并下调SLC7A11与GPX4表达，从而加重铁负荷与脂质过氧化；干预相关miRNA或下调IGFBP-2表达可部分逆转铁死亡与认知下降，提示“miRNA→Nrf2/SLC7A11/GPX4”轴具有放大效应。

与“促铁死亡miRNA”相对，部分研究通过恢复该轴功能实现神经保护。ZHANG等[51]在缺血性脑卒中模型中发现，H_2S可降低miR-27a水平并解除其对SLC7A11的抑制，进而提升SLC7A11、GSH与GPX4水平并降低铁死亡标志物水平；过表达miR-27a可部分抵消H_2S的保护效应。WANG等[52]在自然衰老大鼠及Erastin诱导的HT22细胞中证明，叶酸可上调SLC7A11、GPX4和FTH1表达并降低铁负荷与脂质过氧化程度；当SLC7A11表达下调时叶酸的保护作用基本消失。尽管文献[52]未直接涉及miRNA，但可与文献[49,51]相互印证，提示多种外源干预可能最终汇聚至“恢复SLC7A11/GPX4”这一共同终点。

综上，系统Xc^-/GSH/GPX4轴为miRNA介入癫痫相关铁死亡提供了明确枢纽：miR-34a-5p、miR-128-3p等可削弱抗氧化防线并提高铁死亡敏感性；下调miR-27a、miR-128-3p表达或间接恢复该轴则有望减少铁死亡并改善结局。WANG等[53]亦强调靶向“miRNA→SLC7A11/GSH/GPX4”轴可能成为串联铁死亡与神经损伤的策略，这与癫痫中的氧化应激与铁稳态失衡相契合。当前仍缺乏在癫痫分型、病程及脑区层面的系统比较研究，且对miRNA间的协同与拮抗关系尚未深入解析；若结合递送平台实现精准干预，或可为难治性癫痫提供新的切入点。相关内容见表2。

3.2 癫痫相关miRNA对神经细胞铁死亡中铁稳态/铁蓄积轴的调控

铁死亡对细胞内游离Fe^{2+}的积累高度敏感。铁稳态主要由三环节共同决定：TFRC介导铁摄取、FPN1(SLC40A1)介导铁外排，以及Ferritin(FTH1/FTL)储存与NCOA4介导的铁蛋白自噬共同调控“流动铁池”。当FPN1表达下调或铁蛋白储存/自噬失衡时，自由铁水平上升并促进Fenton反应与脂质过氧化，降低铁死亡阈值，在神经系统中表现为神经元更易受损并可能加重癫痫相关损伤。

在“促铁过载/促铁死亡”方面，SANGOKOYA等[54]提出miR-485-3p具有“铁感应”特性，可直接结合*FPN1* 3′UTR并抑制其翻译，限制铁外排并提高细胞对铁死亡的敏感性，伴随铁积聚与氧化损伤/脂质过氧化程度同步升高。YANG等[55]在肿瘤模型中发现，miR-29a-5p可下调FTH1表达，削弱

表2 相关miRNA通过系统Xc^-/GSH/GPX4信号通路调控铁死亡对癫痫的影响

Table 2 Effects of ferroptosis regulated by relevant miRNAs through the system Xc^-/GSH/GPX4 signaling pathway on epilepsy

miRNA	功能 Function	靶蛋白 Target protein	作用 Affect
miR-34a-5p [39]	Promote ferroptosis	SIRT1, GPX4, ACSL4	By inhibiting miR-34a-5p to restore SIRT1 and GPX4, ferroptosis is alleviated and epileptic symptoms are improved
miR-128-3p [49]	Promote ferroptosis	SLC7A11	Inhibiting miR-128-3p restores the activity of the SLC7A11/GSH/GPX4 axis, thereby alleviating neurological dysfunction following TBI (traumatic brain injury)
miR-27a [50]	Inhibition of ferroptosis	SLC7A11	Enhance the anti-apoptotic effect of the SLC7A11/GSH/GPX4 axis by upregulating miR-27a
miR-128-3p [51]	Promote ferroptosis	SLC7A11	By restoring SLC7A11 and its associated antioxidant axis, ferroptosis is reduced, thereby alleviating neural damage
miR-211 [52]	Inhibition of ferroptosis	SLC7A11, GPX4	By upregulating miR-211 or its target proteins, the activity of the system Xc^- axis is enhanced, thereby inhibiting ferroptosis

铁缓冲能力, 使更多铁进入流动铁池, 进而加重铁死亡表型; 在应激条件下miR-29a-5p上调更易打破铁稳态。在缺血–再灌注模型中, ZHU等[47]提示miR-27a上调可通过靶向SLC7A11等关键节点, 引发GSH水平下降、Fe^{2+}蓄积与脂质过氧化增强的铁死亡表型, 并加重脑损伤; antagomiR-27a或Ferrostatin-1干预可减少铁死亡并改善结局。综合上述研究可见miR-485-3p、miR-29a-5p等miRNA通过“抑制铁外排或削弱铁缓冲”, 推动流动铁池扩大并放大脂质过氧化, 具有促铁死亡倾向, 在癫痫背景下其潜在的促惊厥效应也值得警惕。

与之相对, 部分miRNA对铁稳态具有“刹车”作用。XIE等[43]在脑缺血模型中发现, miR-124-3p上调可抑制NCOA4表达并减少铁蛋白自噬, 从而减少Fe^{2+}释放与减轻脂质过氧化, 促进细胞存活; 而抑制miR-124-3p表达则相反。在脊髓损伤模型中, DONG等[44]报道骨髓间充质干细胞外泌体递送miR-219-5p至神经元, 靶向UBE2Z并促进*NRF2*及其下游SLC7A11、GPX4表达, 伴随Fe^{2+}与脂质ROS水平下降及神经元功能恢复; miR-219-5p虽更偏“抗氧化通路”, 但从整体效果来看同样有利于限制铁蓄积并抑制铁死亡。

总体来看, miRNA介入TFRC/FPN1/Ferritin/NCOA4轴, 使铁稳态模块成为连接铁死亡与癫痫的重要支点: 一类miRNA(如miR-485-3p、miR-29a-5p、miR-210-3p)更可能通过抑制FPN1或削弱Ferritin缓冲推动铁过载; 另一类miRNA(如miR-124-3p、miR-219-5p)可通过限制铁蛋白自噬或增强NRF2-抗氧化防线, 间接稳定铁稳态并降低铁死亡风险。需要指出的是, 目前癫痫模型中的直接证据仍有限, 部分结论来自缺血–再灌注或其他神经损伤模型的类比; 后续应在不同癫痫类型、病程阶段与脑区系统中检测FPN1、Ferritin/NCOA4及相关miRNA的时空变化, 并结合条件性干预或递送手段验证其对发作结局、神经元丢失与网络重塑的影响。相关miRNA通过TFRC-FPN1-Ferritin/NCOA4通路调控铁死亡对癫痫的影响见表3。

3.3 癫痫相关miRNA对神经细胞铁死亡中脂质过氧化轴的调控

脂质过氧化轴是铁死亡的核心驱动力之一。ACSL4将多不饱和脂肪酸(polyunsaturated fatty acid, PUFA)活化并促进其进入膜磷脂, 在溶血磷脂酰胆碱酰基转移酶3(lysophosphatidylcholine acyltransferase 3, LPCAT3)等参与下完成膜重塑, 随后赖氨酰氧化酶(lysyl oxidase, LOX)家族在铁离子与ROS水平升高的背景下推动磷脂过氧化, 造成膜结构破坏并触发铁死亡。JIA等[56]强调, ACSL4通过改变细胞膜PUFA组成来调节脂质过氧化, 因而是决定铁死亡敏感性的关键因子, 尤其在神经系统损伤/疾病中的意义突出。相关机制在多巴胺能神经元中亦得到支持: 研究显示PUFA富集与铁离子共同推动脂质过氧化并启动铁死亡, 抑制ACSL4或LOX(如ALOX15/ALOX15B)表达可明显减少神经元死亡[57]。

在miRNA层面, 有研究指出神经元特异miRNA与脂质过氧化/氧化应激耐受性密切相关。WANG等[58]在神经元损伤模型中发现miR-21上调可促进ACSL4及部分LOX家族成员表达, 推动PUFA富集并

表3 相关miRNA通过TFRC/FPN1/Ferritin/NCOA4信号通路调控铁死亡对癫痫影响

Table 3 Effects of ferroptosis regulated by TFRC/FPN1/ferritin/NCOA4 signaling pathway on epilepsy through related miRNAs

miRNA	功能 Function	靶蛋白 Target protein	作用 Affect
miR-485-3p [54]	Promote ferroptosis	FPN1 (SLC40A1)	By inhibiting FPN1 translation, it increases intracellular Fe^{2+} load, thereby promoting iron overload and ferroptosis
miR-29a-5p [55]	Promote ferroptosis	FTH1 (ferritin heavy chain)	Downregulation of FTH1 disrupts iron buffering, increases the flow of Fe^{2+} in the iron pool, and promotes ferroptosis
miR-210-3p [47]	Promote ferroptosis	SLC7A11	By upregulating miR-210-3p, it promotes the accumulation of Fe^{2+}, enhances oxidative stress, and induces ferroptosis
miR-124-3p [43]	Inhibition of ferroptosis	NCOA4 (ferritin autophagy)	By inhibiting NCOA4-mediated ferritin autophagy, the release of Fe^{2+} is reduced, thereby enhancing the protective effect against ferroptosis
miR-219-5p [44]	Inhibition of ferroptosis	UBE2Z, NRF2	By enhancing NRF2 expression and upregulating downstream SLC7A11 and GPX4, it reduces Fe^{2+} accumulation and lowers the risk of ferroptosis
miR-485-3p, miR-29a-5p, miR-210-3p [47,54-55]	Iron homeostasis/iron accumulation regulation	TFRC, FPN1, ferritin/NCOA4	By regulating FPN1 and ferritin autophagy, it promotes Fe^{2+} flow, increases the risk of ferroptosis, and may exacerbate epilepsy and neurological damage
miR-124-3p, miR-219-5p [43-44]	Iron homeostasis/iron accumulation regulation	Ferritin-NCOA4, NRF2	Maintain iron homeostasis, inhibit ferroptosis, and exert neuroprotective effects by regulating ferritin autophagy or activating antioxidant pathways

加剧脂质过氧化与铁死亡; 而抑制miR-21可部分逆转上述改变。

与上述促铁死亡机制相对应, 药理与分子层面的证据支持抑制脂质过氧化轴具有神经保护意义。HUANG等[59]提出铁超载、脂质过氧化与抗氧化系统失衡构成的铁死亡过程, 可能参与癫痫相关神经元损伤与发作后的神经病理改变, 且在动物/细胞模型中抑制铁死亡可产生保护效应。由此可见, ACSL4/LPCAT3/LOX轴为miRNA介入铁死亡提供了重要入口: 一类miRNA(如miR-21, 结合前文所述miR-34a-5p的相关研究线索)可能通过上调ACSL4和/或LOX推动PUFA富集与脂质过氧化, 加重铁死亡与神经元损伤; 而对ACSL4/LOX的抑制, 以及未来可能被发现的抗脂质过氧化miRNA, 有望从源头削弱铁死亡反应并稳定神经网络。目前“癫痫-miRNA-ACSL4/LPCAT3/LOX”的直接证据仍有限, 后续需在不同癫痫模型中开展更系统的时空验证, 并评估miRNA靶向干预在控制发作与减轻长期脑损伤方面的真实潜力。相关内容见表4。

3.4 癫痫相关miRNA神经细胞铁死亡中应激与转录网络的调控

应激与转录因子网络位于“氧化应激–铁稳态–铁死亡”上游, 是决定神经元铁死亡阈值的重要枢纽。现有研究最集中于Nrf2/HO-1、HIF-1α、p53以及MAPK/ERK等通路: Nrf2/HO-1多表现为抗氧化、限铁负荷与抗铁死亡; HIF-1α在缺氧与能量应激背景下可通过HO-1、FPN1等靶点影响铁稳态; p53及其上游应激信号常通过抑制SLC7A11表达削弱系统Xc^-/GSH/GPX4抗氧化功能而促进铁死亡; MAPK/ERK则更像把应激信号“放大”为脂质过氧化输出的信号平台[60-63]。这些通路并非各自独立作用, 其与miRNA的交互调控被认为共同决定了铁死亡易感性[64-65]。

在保护性网络中, Nrf2/HO-1是证据最充分的一条主轴。相关综述与实验研究一致认为, Nrf2不仅可上调*HO-1*、*NQO1*、*GCLC*等抗氧化基因表达来降低ROS, 还可诱导铁转运/铁储存相关分子调控, 从而在多个层面限制铁依赖性脂质过氧化; 在多种中枢神经系统疾病与损伤模型中, 激活Nrf2/HO-1常与铁死亡减轻和神经保护相伴[60-63]。与之相连的HIF-1α/HO-1轴近年也被引入癫痫相关研究: 有研究提出HIF-1α/HO-1可能通过调控铁代谢与氧化应激参与癫痫进展, 缺血模型中亦有证据显示HIF-1α可通过促进*FPN1*转录并与Nrf2/HO-1通路联动而减少铁死亡[64-65]。不过, HIF-1α在不同阶段可能呈现“促铁负荷”或“排铁+抗氧化”的双相效应, 癫痫模型中仍缺少对其因果链条的直接闭环验证。

表4 相关miRNA通过ACSL4/LPCAT3/LOX信号通路调控铁死亡对癫痫的影响

Table 4 Effects of ferroptosis regulated by relevant miRNAs through the ACSL4/LPCAT3/LOX signaling pathway on epilepsy

miRNA	功能 Function	靶蛋白 Target protein	作用 Affect
miR-128-3p[58]	Promote neuronal ferroptosis	SLC7A11	Increased cortical iron load and reduced GPX4 levels lead to exacerbated behavioral impairment and ferroptosis
miR-27a[59]	Inhibition of ferroptosis	SLC7A11	Improving neurological function after stroke and reducing markers of lipid peroxidation and ferroptosis

与保护性通路相反, p53/系统Xc^-常被视为促铁死亡的经典范式。关键研究显示*p53*可转录抑制*SLC7A11*, 减少半胱氨酸摄取与降低GSH水平, 从而提高铁死亡敏感性; 同时p53作用也具有情境依赖的“双向性”, 应激强度、细胞类型及上游非编码RNA状态都可能改变其最终的调控效果[66-68]。值得注意的是, p53与miRNA/lncRNA的互作被认为是其调控铁死亡的重要环节: miRNA既可作为p53下游效应分子, 也可反向调节p53/系统Xc^-/GPX4轴, 进而改变铁死亡阈值[66-68]。在神经元模型中, JNK/p38-MAPK激活与ATM/p53轴协同将DNA损伤信号转化为铁死亡执行的证据,也进一步提示“应激激酶-p53”耦合在神经元铁死亡中可能具有关键意义[69]。

在MAPK/ERK相关网络方面, 研究普遍认为神经元因高代谢水平与膜富含PUFA而对铁死亡更敏感, ERK、JNK、p38等MAPK家族可整合多类应激并推动脂质过氧化输出[70]; 与此同时, MAPK与AMPK之间并非简单同向改变, AMPK在部分情境下可通过FoxO3、Nrf2/HO-1等通路产生抑制铁死亡的效果, 二者的耦合关系可能决定铁死亡强弱[71-72]。更宏观地看, 炎症相关信号(如JAK-STAT、NF-κB、MAPK)与铁死亡之间存在相互促进作用: 炎症因子可放大铁死亡, 而铁死亡释放的损伤相关分子模式(damage-associated molecular patterns, DAMPs)又可反过来激活炎症反应[73]; 结合癫痫的慢性炎症背景, 这种正反馈链路值得在癫痫模型中被更直接地检验。

总体而言, 应激与转录网络为miRNA介入癫痫相关铁死亡提供了更高层级的调控平台: 以Nrf2/HO-1、HIF-1α为代表的“抗氧化/排铁”路径可能降低铁负荷并提高抗氧化能力, 而以p53/系统Xc^-与MAPK家族为代表的网络更可能放大脂质过氧化并推动铁死亡。现有证据仍多来自肿瘤、缺血–再灌注及其他神经损伤模型, 直接聚焦“癫痫-miRNA-应激/转录网络–铁死亡”的系统性研究仍不足; 后续需在不同癫痫综合征、病程阶段与脑区中进行更一致的时空谱系描绘, 并结合递送平台开展多轴联合验证, 以评估miRNA在抑制铁死亡与稳定神经网络活动方面的真实价值。

4 总结与展望

近年来众多研究表明, miRNA可通过靶向SLC7A11、GPX4、ACSL4等关键节点, 调控系统Xc^-/GSH/GPX4抗氧化防线、铁稳态与脂质过氧化等生物学过程, 从而改变神经细胞对铁死亡的易感性, 并可能参与癫痫相关的神经元损伤与病程进展。以miR-34a-5p、miR-142-5p、miR-211-5p等为代表的临床前研究提示, 部分miRNA干预策略与铁死亡水平、癫痫发作及神经损伤表型呈同向关联; 但目前仍缺乏临床患者层面的直接循证证据, 需进一步围绕因果调控链开展机制验证与转化研究。相较既往更多聚焦凋亡或兴奋/抑制失衡的综述, 本文以“miRNA调控神经细胞铁死亡”为主线, 进一步将其置于*Nrf2*、*MAPK*/*ERK*、*p53*等应激转录网络中讨论, 以便更清晰地呈现“上游应激–铁死亡执行–癫痫表型”的可能连接路径。

目前仍存在三方面瓶颈: 现有证据主要来自动物与体外模型, 患者层面缺少“miRNA变化/干预–铁死亡终点–发作结局”的直接证据链; 不同癫痫类型、病程阶段与脑区的时空异质性尚未理清; miRNA-应激网络–铁死亡之间的因果结构及动态演化仍缺乏系统解析。后续研究应优先推进临床样本miRNA谱系与表型关联, 并在动物模型中开展更严格的因果验证(靶点、铁死亡终点与癫痫结局三者同向改变); 同时聚焦miRNA与Nrf2/HO-1、p53、MAPK/ERK等关键

信号节点的互作机制，结合外泌体或纳米载体等递送手段，探索可转化的靶向与联合干预策略，以期在抑制铁死亡的同时，改善癫痫发作控制情况，降低长期脑损伤风险。

参考文献 (References)

[1] HENSHALL D C, HAMER H M, PASTERKAMP R J, et al. MicroRNAs in epilepsy: pathophysiology and clinical utility [J]. Lancet Neurol, 2016, 15(13): 1368-76.

[2] WANG J L, ZHAO J H. MicroRNA dysregulation in epilepsy: from pathogenetic involvement to diagnostic biomarker and therapeutic agent development [J]. Front Mol Neurosci, 2021, 14: 650372.

[3] BRENNAN G P, BAUER S, ENGEL T, et al. Genome-wide microRNA profiling of plasma from three different animal models identifies biomarkers of temporal lobe epilepsy [J]. Neurobiol Dis, 2020, 144: 105048.

[4] CHEN K N, GUAN Q W, YIN X X, et al. Ferrostatin-1 obviates seizures and associated cognitive deficits in ferric chloride-induced posttraumatic epilepsy via suppressing ferroptosis [J]. Free Radic Biol Med, 2022, 179: 109-18.

[5] SONG Y, GAO M J, WEI B Y, et al. Mitochondrial ferritin alleviates ferroptosis in a kainic acid-induced mouse epilepsy model by regulating iron homeostasis: involvement of nuclear factor erythroid 2-related factor 2 [J]. CNS Neurosci Ther, 2024, 30(3): e14663.

[6] MAHMOUDI-LAMOUKI R, KADKHODA S, HUSSEN B M, et al. Emerging role of miRNAs in the regulation of ferroptosis [J]. Front Mol Biosci, 2023, 10: 1115996.

[7] GAO F, YANG Z L, LI J Z. The miR-34a-5p promotes hippocampal neuronal ferroptosis in epilepsy by regulating SIRT1 [J]. Neurochem Res, 2025, 50(2): 124.

[8] HA M J, KIM V N. Regulation of microRNA biogenesis [J]. Nat Rev Mol Cell Biol, 2014, 15(8): 509-24.

[9] KIM V N. MicroRNA biogenesis: coordinated cropping and dicing [J]. Nat Rev Mol Cell Biol, 2005, 6(5): 376-85.

[10] SCHRATT G M, TUEBING F, NIGH E A, et al. A brain-specific microRNA regulates dendritic spine development [J]. Nature, 2006, 439(7074): 283-9.

[11] MAKEYEV E V, ZHANG J W, CARRASCO M A, et al. The microRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing [J]. Mol Cell, 2007, 27(3): 435-48.

[12] LOOHUIS N F M O, KOS A, MARTENS G J M, et al. MicroRNA networks direct neuronal development and plasticity [J]. Cell Mol Life Sci, 2012, 69(1): 89-102.

[13] IM H I, KENNY P J. MicroRNAs in neuronal function and dysfunction [J]. Trends Neurosci, 2012, 35(5): 325-34.

[14] EDBAUER D, NEILSON J R, FOSTER K A, et al. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132 [J]. Neuron, 2010, 65(3): 373-84.

[15] 刘高澳, 彭小忠, 舒鹏程. Dicer1缺失对小鼠早期神经发育的影响[J]. 基础医学与临床(LIU G A, PENG X Z, SHU P C. Effect of Dicer1 ablation on early neurodevelopment of mice [J]. Basic and Clinical Medicine), 2021, 41(6): 818-24.

[16] JIMENEZ-MATEOS E M, ENGEL T, MERINO-SERRAIS P, et al. Silencing microRNA-134 produces neuroprotective and prolonged seizure-suppressive effects [J]. Nat Med, 2012, 18(7): 1087-94.

[17] ZHAO W, SPIERS J G, VASSILEFF N, et al. microRNA-146a modulates behavioural activity, neuroinflammation, and oxidative stress in adult mice [J]. Mol Cell Neurosci, 2023, 124: 103820.

[18] ASLANI M, MORTAZAVI-JAHROMI S S, MIRSHAFIEY A. Efficient roles of miR-146a in cellular and molecular mechanisms of neuroinflammatory disorders: an effectual review in neuroimmunology [J]. Immunol Lett, 2021, 238: 1-20.

[19] BRENNAN G P, HENSHALL D C. microRNAs in the pathophysiology of epilepsy [J]. Neurosci Lett, 2018, 667: 47-52.

[20] 金绍静, 马巍, 张淑红, 等. miR34a在戊四氮致癫痫大鼠中通过下调Bcl-2导致神经元凋亡[J]. 中风与神经疾病杂志(JIN S J, MA W, ZHANG S H, et al. MiR34a induces neuronal apoptosis by downregulating Bcl-2 in rats with epilepsy induced by PTZ [J]. Journal of Apoplexy and Nervous Diseases), 2018, 35(7): 617-21.

[21] 刘东海, 赵天宁, 杨嘉琦, 等. miRNA21在戊四氮致癫痫大鼠马神经元中的作用及其机制的研究[J]. 海南医学院学报(LIU D H, ZHAO T N, YANG J Q, et al. The role of miRNA21 in hippocampal neurons of rats with pentylenetetrazol-induced epilepsy and its mechanism [J]. Journal of Hainan Medical University), 2019, 25(10): 744-9.

[22] 顿圆圆, 扈清云, 冯燕, 等. 丹皮酚对癫痫大鼠的治疗作用及miRNA-34a/Bcl-2通路的影响[J]. 郑州大学学报(医学版)(DUN Y Y, HU Q Y, FENG Y, et al. Effects of paeonol on rats with epilepsy and miRNA-34a/Bcl-2 pathway [J]. Journal of Zhengzhou University, Medical Sciences), 2025, 60(4): 569-72.

[23] STOCKWELL B R, FRIEDMANN ANGELI J P, BAYIR H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease [J]. Cell, 2017, 171(2): 273-85.

[24] JIANG X, STOCKWELL B R, CONRAD M. Ferroptosis: mechanisms, biology and role in disease [J]. Nat Rev Mol Cell Biol, 2021, 22(4): 266-82.

[25] FU R T, FANG L Y, LIU J H, et al. Mitochondrial-associated endoplasmic reticulum membranes (MAMs) drive ferroptosis via redox signaling: a key potential mechanism in epilepsy [J]. Neurobiol Dis, 2026, 218: 107248.

[26] XU J, DONG X N, YUAN M, et al. Ferroptosis and epilepsy: bidirectional pathogenic links and therapeutic implications [J]. Front Neurol, 2025, 16: 1635441.

[27] RAZI S, KHOJINI J Y, NORIOUN H, et al. MicroRNA-mediated regulation of ferroptosis: implications for disease pathogenesis and therapeutic interventions [J]. Cell Signal, 2025, 125: 111503.

[28] CANDIA PLATA M D C, MARTÍNEZ SOTO J M, ARREDONDO DAMIÁN J G, et al. Ferroptosis-associated microRNAs: systematic review [J]. Cell Mol Biol, 2025, 71(4): 1-14.

[29] JIN S K, LIU P S, ZHENG D H, et al. The interplay of miRNAs and ferroptosis in diseases related to iron overload [J]. Apoptosis, 2024, 29(1/2): 45-65.

[30] XU Y J, JIA B W, LI J, et al. The interplay between ferroptosis and neuroinflammation in central neurological disorders [J]. Antioxidants, 2024, 13(4): 395.

[31] ZHANG H F, LIAN Y J, XIE N C, et al. Antagomirs targeting

miR-142-5p attenuate pilocarpine-induced status epilepticus in mice [J]. Exp Cell Res, 2020, 393(2): 112089.

[32] ZHANG G L, GAO Y, JIANG L X, et al. LncRNA FTX inhibits ferroptosis of hippocampal neurons displaying epileptiform discharges *in vitro* through the miR-142-5p/GABPB1 axis [J]. Neuroscience, 2023, 526: 48-60.

[33] WU X K, SHI M M, CHEN Y, et al. Effect and mechanism of LIN28 on ferroptosis in Mg^{2+}-free rat hippocampal neuron model of epilepsy [J]. Neurochem Res, 2024, 49(7): 1655-64.

[34] 于海艳, 孔慧, 王瑞. 癫痫患者血清miR-128-3p和miR-211-5p水平及其与脑电图异常程度的相关性研究 [J]. 中国临床新医学 (YU H Y, KONG H, WANG R. Study on levels of serum miR-128-3p and miR-211-5p in epilepsy patients and their correlations with the degree of electroencephalogram abnormalities [J]. Chinese Journal of New Clinical Medicine), 2025, 18(9): 1027-31.

[35] LI X Y, QUAN P S, SI Y, et al. The microRNA-211-5p/P2RX7/ERK/GPX4 axis regulates epilepsy-associated neuronal ferroptosis and oxidative stress [J]. J Neuroinflammation, 2024, 21(1): 13.

[36] PANT K, SHARMA A, MENON S V, et al. Exploring ncRNAs in epilepsy: from oxidative stress regulation to therapy [J]. Brain Res, 2024, 1841: 149089.

[37] ENGEL T. The P2X7 receptor as a mechanistic biomarker for epilepsy [J]. Int J Mol Sci, 2023, 24(6): 5410.

[38] LI Y, FAN C Q, GAO R, et al. Hippocampal miR-211-5p regulates neurogenesis and depression-like behaviors in the rat [J]. Neuropharmacology, 2021, 194: 108618.

[39] HAO R L, GE J L, SONG X Y, et al. Cadmium induces ferroptosis and apoptosis by modulating miR-34a-5p/Sirt1 axis in PC12 cells [J]. Environ Toxicol, 2022, 37(1): 41-51.

[40] WANG J L, ZHENG Y, CHENG X, et al. Inhibition of microRNA-34a suppresses epileptiform discharges through regulating Notch signaling and apoptosis in cultured hippocampal neurons [J]. Neurochem Res, 2019, 44(5): 1252-61.

[41] SANO T, REYNOLDS J P, JIMENEZ-MATEOS E M, et al. MicroRNA-34a upregulation during seizure-induced neuronal death [J]. Cell Death Dis, 2012, 3(3): e287.

[42] ORGANISTA-JUÁREZ D, JIMÉNEZ A, ROCHA L, et al. Differential expression of miR-34a, 451, 1260, 1275 and 1298 in the neocortex of patients with mesial temporal lobe epilepsy [J]. Epilepsy Res, 2019, 157: 106188.

[43] XIE K, MO Y, YUE E L, et al. Exosomes derived from M2-type microglia ameliorate oxygen-glucose deprivation/reoxygenation-induced HT22 cell injury by regulating miR-124-3p/NCOA4-mediated ferroptosis [J]. Heliyon, 2023, 9(7): e17592.

[44] DONG J J, GONG Z Q, BI H C, et al. BMSC-derived exosomal miR-219-5p alleviates ferroptosis in neuronal cells caused by spinal cord injury via the UBE2Z/NRF2 pathway [J]. Neuroscience, 2024, 556: 73-85.

[45] XIAO X, JIANG Y J, LIANG W B, et al. miR-212-5p attenuates ferroptotic neuronal death after traumatic brain injury by targeting Ptgs2 [J]. Mol Brain, 2019, 12(1): 78.

[46] WANG L H, LI M J, LIU B, et al. miR-30a-5p mediates ferroptosis of hippocampal neurons in chronic cerebral hypoperfusion-induced cognitive dysfunction by modulating the SIRT1/NRF2 pathway [J]. Brain Res Bull, 2024, 212: 110953.

[47] ZHU L J, FENG Z R, ZHANG J, et al. MicroRNA-27a regulates ferroptosis through SLC7A11 to aggravate cerebral ischemia-reperfusion injury [J]. Neurochem Res, 2023, 48(5): 1370-81.

[48] WANG W X, SHI F, CUI J M, et al. MiR-378a-3p/ SLC7A11 regulate ferroptosis in nerve injury induced by lead exposure [J]. Ecotoxicol Environ Saf, 2022, 239: 113639.

[49] MANRUI L, XU Y, LIU J Y, et al. Aminophylline targets miR-128-3p/Slc7a11 axis to attenuate neuronal ferroptosis after traumatic brain injury [J]. Cell Mol Life Sci, 2025, 82(1): 87.

[50] LUO C L, WU G Y, XIAO Z, et al. Role of miRNA regulation in IGFBP-2 overexpression and neuronal ferroptosis: insights into the Nrf2/SLC7A11/GPX4 pathway in Alzheimer's disease [J]. Int J Biol Macromol, 2025, 287: 138537.

[51] ZHANG Y, LÜ H B, CHEN C, et al. Hydrogen sulfide modulates the miR-27a/SLC7A11 axis to inhibit ferroptosis and reduce neuronal damage in ischemic stroke [J]. J Radiat Res Appl Sci, 2025, 18(4): 102035.

[52] WANG Y, ZHANG J W, WANG Z H, et al. Folic acid ameliorates neuronal ferroptosis in aging by up-regulating SLC7A11-GSH-GPX4 antioxidant pathway and increasing cystine levels [J]. Int J Mol Sci, 2025, 26(14): 6669.

[53] WANG C, LIU H H, XU S, et al. Ferroptosis and neurodegenerative diseases: insights into the regulatory roles of SLC7A11 [J]. Cell Mol Neurobiol, 2023, 43(6): 2627-42.

[54] SANGOKOYA C, DOSS J F, CHI J T. Iron-responsive miR-485-3p regulates cellular iron homeostasis by targeting ferroportin [J]. PLoS Genet, 2013, 9(4): e1003408.

[55] YANG G, PAN Q, LU Y, et al. miR-29a-5p modulates ferroptosis by targeting ferritin heavy chain FTH1 in prostate cancer [J]. Biochem Biophys Res Commun, 2023, 652: 6-13.

[56] JIA B W, LI J, SONG Y T, et al. ACSL4-mediated ferroptosis and its potential role in central nervous system diseases and injuries [J]. Int J Mol Sci, 2023, 24(12): 10021.

[57] BOUCHAOUI H, MAHONEY-SANCHEZ L, GARCON G, et al. ACSL4 and the lipoxygenases 15/15B are pivotal for ferroptosis induced by iron and PUFA dyshomeostasis in dopaminergic neurons [J]. Free Radic Biol Med, 2023, 195: 145-57.

[58] WANG H H, LIU X D, CHEN Y, et al. The regulatory role of miR-21 in ferroptosis by targeting FTH1 and the contribution of microglia-derived miR-21 in exosomes to arsenic-induced neuronal ferroptosis [J]. J Hazard Mater, 2024, 478: 135580.

[59] HUANG L M, LIU H Y, LIU S Y. Insight into the role of ferroptosis in epilepsy [J]. J Integr Neurosci, 2024, 23(6): 113.

[60] XIANG Y, SONG X H, LONG D X. Ferroptosis regulation through Nrf2 and implications for neurodegenerative diseases [J]. Arch Toxicol, 2024, 98(3): 579-615.

[61] SHAKYA A, MCKEE N W, DODSON M, et al. Anti-ferroptotic effects of Nrf2: beyond the antioxidant R response [J]. Mol Cells, 2023, 46(3): 165-75.

[62] YAN R H, LIN B Y, JIN W W, et al. NRF2, a superstar of ferroptosis [J]. Antioxidants, 2023, 12(9): 1739.

[63] PARK J S, LEEM Y H, PARK J E, et al. Neuroprotective effect of β-lapachone in MPTP-induced Parkinson's disease mouse model: involvement of astroglial p-AMPK/Nrf2/HO-1 signaling pathways [J]. Biomol Ther, 2019, 27(2): 178-84.

[64] LIANG Z, ZHENG Z S, GUO Q, et al. The role of HIF-1α/HO-1 pathway in hippocampal neuronal ferroptosis in epilepsy [J]. iScience, 2023, 26(11): 108098.

[65] YAO H Q, TIAN J N, CHENG S, et al. The mechanism of hy-

poxia-inducible factor-1α enhancing the transcriptional activity of transferrin ferroportin 1 and regulating the Nrf2/HO-1 pathway in ferroptosis after cerebral ischemic injury [J]. Neuroscience, 2024, 559: 26-38.

[66] JIANG L, KON N, LI T Y, et al. Ferroptosis as a p53-mediated activity during tumour suppression [J]. Nature, 2015, 520(7545): 57-62.

[67] LEI G, ZHANG Y L, HONG T, et al. Ferroptosis as a mechanism to mediate p53 function in tumor radiosensitivity [J]. Oncogene, 2021, 40(20): 3533-47.

[68] PUNZIANO C, TROMBETTI S, GROSSO M, et al. The molecular interplay between p53-mediated ferroptosis and non-coding RNAs in cancer [J]. Int J Mol Sci, 2025, 26(14): 6588.

[69] GU W P, PAN T T, WANG X D, et al. Sevoflurane exposure triggers ferroptosis of neuronal cells initiated by the activation of ATM/p53 in the neonatal mouse brain via JNK/p38 MAPK-mediated oxidative DNA damage [J]. Int Immunopharmacol, 2025, 158: 114866.

[70] JACQUEMYN J, RALHAN I, IOANNOU M S. Driving factors of neuronal ferroptosis [J]. Trends Cell Biol, 2024, 34(7): 535-46.

[71] WANG X Y, TAN X, ZHANG J P, et al. The emerging roles of MAPK-AMPK in ferroptosis regulatory network [J]. Cell Commun Signal, 2023, 21(1): 200.

[72] ZHONG S F, CHEN W J, WANG B C, et al. Energy stress modulation of AMPK/FoxO3 signaling inhibits mitochondria-associated ferroptosis [J]. Redox Biol, 2023, 63: 102760.

[73] CHEN Y, FANG Z M, YI X, et al. The interaction between ferroptosis and inflammatory signaling pathways [J]. Cell Death Dis, 2023, 14(3): 205.