

综述

外泌体-微小RNA调控轴介导癫痫发作后脑组织炎症微环境与神经损伤的机制研究进展

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[摘要] 外泌体是细胞间特异性信号传递的核心载体, 可封装并转运微小RNA(miRNA), 在癫痫发作后的脑组织炎症微环境调控及神经损伤进程中发挥着关键介导作用。癫痫发作后, 脑组织内的小胶质细胞、星形胶质细胞、神经元及浸润的外周免疫细胞被广泛激活, 释放的外泌体携带特征性miRNA亚群, 通过体液循环或细胞间直接作用靶向调控靶细胞功能。其核心调控模式表现为促炎miRNA(如miR-155、miR-21)表达升高, 抗炎miRNA(如miR-146a、miR-124)表达降低, 通过靶向TLR4/NF-κB、PI3K/Akt等关键通路, 参与炎症微环境的启动、放大与维持。该调控轴进一步通过诱导神经元凋亡、破坏突触结构与功能、损伤血脑屏障完整性及促进胶质瘢痕形成, 加剧神经损伤。本文综述癫痫发作后不同细胞来源外泌体-miRNA的特异性特征及调控机制的相关研究进展, 旨在为开发靶向外泌体-miRNA的癫痫炎症干预及神经保护策略提供参考。

[关键词] 外泌体; miRNA; 癫痫; 炎症微环境; 神经损伤; 血脑屏障

Research progress on the mechanism of exosome-miRNA regulatory axis mediating the formation of inflammatory microenvironment and neuronal injury in brain after epileptic seizure

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[Abstract] Exosomes, as core carriers for specific intercellular signal transmission, can encapsulate and transport microRNAs (miRNAs), playing a key mediating role in regulating the inflammatory microenvironment and neuronal injury processes in brain

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tissue after epileptic seizure. Following epileptic seizure, microglia, astrocytes, neurons, and infiltrating peripheral immune cells in the brain tissue are extensively activated. The released exosomes carry characteristic miRNA subsets, which target and regulate the functions of recipient cells through the humoral circulation or direct intercellular interactions. Their core regulatory pattern is manifested by increased expression of pro-inflammatory miRNAs (such as miR-155, miR-21) and decreased expression of anti-inflammatory miRNAs (such as miR-146a, miR-124). By targeting key pathways including TLR4/NF- κ B and PI3K/Akt, these miRNAs participate in the initiation, amplification, and maintenance of the inflammatory microenvironment. This regulatory axis further exacerbates neuronal injury by inducing neuronal apoptosis, disrupting synaptic structure and function, impairing blood-brain barrier integrity, and promoting glial scar formation. This article systematically reviews progress on the specific characteristics and regulatory mechanisms of exosomal miRNAs derived from different cell types after seizure, aiming to provide basis for the development of epilepsy inflammatory intervention and neuroprotective strategies targeting exosomal miRNAs.

[Key words] exosome; miRNA; epilepsy; inflammatory microenvironment; neuronal injury; blood-brain barrier

癫痫是一种慢性神经系统疾病，全球患者超7000万例；其中约30%会发展为难治性癫痫，患者对两种及以上抗癫痫药物无应答，且常伴随认知功能衰退、精神心理障碍、脑结构损伤及生活质量下降等严重并发症^[1]。癫痫发作不仅通过兴奋性毒性、氧化应激及钙超载直接导致神经元损伤，还会诱发持续且失控的脑组织炎症反应，形成异常炎症微环境^[2]。这一炎症微环境以小胶质细胞活化、星形胶质细胞增生、外周免疫细胞浸润及促炎因子[如肿瘤坏死因子(tumor necrosis factor, TNF)- α 、白细胞介素(interleukin, IL)-1 β 、IL-6、 γ 干扰素(interferon- γ , IFN- γ)]大量释放为核心特征，其持续存在会打破脑组织稳态，加剧神经元凋亡、突触功能紊乱及血脑屏障破坏，造成“炎症激活-神经损伤-癫痫复发”的恶性循环，是癫痫慢性化及药物抵抗的关键驱动因素^[3]。

传统研究多聚焦于癫痫发作后炎症因子直接介导的损伤效应，而近年来外泌体的发现为相关炎症调控机制研究开辟了新视角。外泌体是由细胞分泌的膜性囊泡，其膜结构富含CD9、CD63、CD81等特异性标志物，可封装微小RNA(miRNA, miRNA)、mRNA、蛋白质、脂质等多种生物活性分子^[4]。其中，外泌体所包含的miRNA是其核心功能成分之一——这类非编码RNA可被外泌体稳定包裹，通过外泌体的转运作用如表面受体结合、膜融合或内吞作用递送至靶细胞内，使其免遭体液中核酸酶、蛋白酶的降解；进入靶细胞后，miRNA通过种子序列与靶基因mRNA的3'非编码区结合，介导靶基因降解或翻译抑制，进而调控细胞增殖、分化、凋亡及炎症反应等生物学过程^[5]。外泌体-miRNA调控轴特指以“外泌体为运载体、外泌体所包含的miRNA为功能核心”的调控通路。癫痫发作后，脑组织内激活的细胞如小胶质细胞、星形胶质细胞等分泌外泌体，其携带的特异性miRNA被转运至靶细胞，通过调控靶细胞内基因表达，参与炎症反应及神经损伤相关过程^[6]。本文系统综述外泌体-miRNA

调控轴在癫痫后脑组织炎症微环境形成及神经损伤中作用机制的相关研究进展，旨在为开发靶向外泌体-miRNA的癫痫后神经保护策略提供理论参考。

1 外泌体与miRNA的生物学特性及在癫痫发作后的表达特征

1.1 外泌体分泌机制及功能

在神经系统中，神经元和多种胶质细胞及外周免疫细胞均可分泌外泌体，且不同细胞来源的外泌体在成分与功能上存在显著特异性。神经元源性外泌体富含突触相关蛋白如突触素、突触后致密蛋白95(postsynaptic density protein 95, PSD-95)与神经营养因子相关miRNA，参与突触功能调控与神经保护；小胶质细胞源性外泌体富集炎症相关分子如Toll样受体4(toll-like receptor 4, TLR4)、促炎miRNA，在免疫炎症反应中发挥关键作用；星形胶质细胞源性外泌体高表达胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)及纤维化相关miRNA，参与血脑屏障维护与胶质瘢痕形成；外周免疫细胞源性外泌体携带免疫调节分子，可通过血脑屏障浸润至脑组织，参与炎症放大^[7-9]。

癫痫发作后，脑组织中增多的外泌体具有明确的细胞来源倾向性，其中小胶质细胞、星形胶质细胞和外周免疫细胞是主要贡献者。癫痫发作引发的兴奋性毒性、氧化应激及早期炎症信号，可快速激活小胶质细胞从静息态转变为促炎表型，激活核因子- κ B(NF- κ B)通路及钙依赖的囊泡释放机制，大量分泌含促炎miRNA(如miR-155、miR-223)的外泌体，这是癫痫后早期外泌体增多的主要来源^[10]；星形胶质细胞作为脑组织中数量最多的胶质细胞，在癫痫发作后受炎症因子及谷氨酸兴奋性毒性刺激，会快速增生并增强外泌体分泌，其释放的外泌体富含miR-21、miR-19a等纤维化及炎症相关分子，是癫痫中晚期外泌体持续增多的关键来源^[11]。此外，癫痫发作导致血脑屏障通透性增加，外周免疫细胞可浸润至脑组织，其分泌的外泌体携带miR-155、miR-223等促炎成分，进一步增加了脑组织中外泌体的总

量，且与中枢固有细胞来源的外泌体协同放大炎症反应^[12]。相比之下，神经元及少突胶质细胞受自身损伤及功能抑制影响，其外泌体分泌量的增幅低于上述三类细胞，对癫痫发作后外泌体总量增多的贡献有限。

1.2 miRNA 的生物学功能与调控网络 miRNA 由 RNA 聚合酶 II 转录生成初级 miRNA，经 Drosha 酶剪切形成前体 miRNA，再通过输出蛋白 5 (exportin-5) 转运至细胞质，经 Dicer 酶进一步剪切生成成熟 miRNA^[13]。成熟 miRNA 通过种子序列与靶基因 mRNA 的 3' 非编码区结合，介导靶基因的降解或翻译抑制，从而调控基因表达^[14]。一个 miRNA 可靶向调控多个靶基因，而一个靶基因也可被多个 miRNA 调控，形成复杂的 miRNA-靶基因调控网络^[15]。

在炎症反应中，miRNA 通过调控炎症通路关键分子的表达，参与炎症反应的启动、放大与消退。促炎 miRNA (如 miR-155、miR-21、miR-223) 可通过靶向抑制抗炎因子或炎症通路负调控分子，增强促炎反应；抗炎 miRNA (如 miR-146a、miR-124、miR-132) 可通过抑制促炎通路关键分子如 TLR4、NF- κ B、TNF- α 的表达，减轻炎症损伤^[16]。例如，miR-155 可通过靶向抑制抗炎因子 IL-10 及细胞因子信号传导抑制因子 1 (suppressor of cytokine signaling 1, SOCS1)，激活 NF- κ B 通路，放大促炎反应；而 miR-146a 可通过靶向抑制 TLR4、IL-1 受体相关激酶 1 (interleukin-1

receptor-associated kinase 1, IRAK1)、TNF 受体相关因子 6 (TNF receptor-associated factor 6, TRAF6) 等分子，阻断 TLR4/NF- κ B 通路，抑制炎症激活^[17-18]。

1.3 癫痫发作后外泌体与 miRNA 的表达特征及调控因素 癫痫发作可通过兴奋性毒性、氧化应激、钙超载及炎症激活等多重机制，诱导脑组织内多种细胞分泌外泌体，同时显著改变外泌体中 miRNA 的表达谱，且这些变化具有细胞来源特异性、病程依赖性及亚型差异性。

1.3.1 外泌体含量与释放动力学变化 一项临床队列研究显示，癫痫患者脑脊液及外周血中外泌体浓度显著高于健康人，且与癫痫发作频率、发作持续时间及严重程度呈正相关^[19]。一项临床病例对照研究显示，难治性癫痫外泌体升高幅度显著高于药物敏感型癫痫^[20]。在戊四氮 (PTZ) 致痫大鼠模型的研究显示，大鼠癫痫发作后 6 h 即可检测到海马区外泌体分泌量升高，24~72 h 达到峰值，慢性期仍维持在较高水平^[21]；海人藻酸 (kainic acid, KA) 致痫模型中，外泌体升高持续时间更长，且皮质区与海马区外泌体含量差异显著^[22]。

1.3.2 miRNA 表达谱的异常特征 癫痫后外泌体中 miRNA 表达呈现“促炎 miRNA 升高、抗炎 miRNA 降低”的特征，且不同细胞来源外泌体的 miRNA 表达存在显著差异 (表 1)。

表 1 癫痫发作后不同细胞来源外泌体中微小 RNA (miRNA) 表达谱异常特征

Tab.1 Abnormal expression profiles of miRNAs in exosomes derived from different cell types after epileptic seizure

外泌体来源细胞	差异表达 miRNA 类别	具体 miRNA 分子	表达变化	核心功能关联
小胶质细胞 ^[23]	促炎 miRNA	miR-155	升高	激活炎症通路、促进神经兴奋性毒性、加剧神经元凋亡
		miR-223	升高	调控免疫细胞浸润、参与突触吞噬、放大中枢炎症
		miR-125b	升高	抑制抗炎因子表达、加重神经炎症反应
	抗炎 miRNA	miR-146a	降低	负向调控核因子 κ B 通路、抑制促炎因子释放的作用减弱
星形胶质细胞 ^[24]	促炎/纤维化相关 miRNA	miR-21	升高	靶向调控纤维化通路、破坏血脑屏障紧密连接、抑制突触修复
		miR-19a	升高	减弱抑制性突触传递、打破神经兴奋-抑制平衡
		miR-92a	升高	参与炎症反应调控、加剧血脑屏障损伤
神经元 ^[25]	抗炎/神经保护相关 miRNA	miR-124	降低	调控小胶质细胞活化、维持神经元代谢稳态的作用减弱
		miR-132	降低	抑制兴奋性突触过度传递、促进突触修复的功能受损
		miR-219	降低	维持神经元膜稳定性、保护神经功能的作用减弱
外周免疫细胞 ^[26]	巨噬细胞源性 miRNA	miR-155	升高	跨越血脑屏障、放大中枢炎症反应、加重神经损伤
	中性粒细胞源性 miRNA	miR-223	升高	浸润脑组织、激活胶质细胞炎症、破坏血脑屏障完整性

1.3.3 调控外泌体-miRNA 表达的关键因素 癫痫发作后，外泌体分泌及 miRNA 表达谱异常受多重因素调控：(1) 兴奋性毒性。谷氨酸过度释放激活 N-甲基-D-天冬氨酸 (NMDA) 受体，导致钙超载，促进多囊泡体与细胞膜融合，增加外泌体释放^[27]；(2) 炎症激

活。促炎因子 TNF- α 、IL-1 β 可通过激活 NF- κ B 通路，上调外泌体分泌相关基因的表达^[28]；(3) 氧化应激。癫痫发作后活性氧 (ROS) 大量产生，可诱导细胞内 miRNA 表达谱重构，进而改变外泌体中 miRNA 的封装与释放^[29]；(4) 抗癫痫药物。部分抗癫痫药物

如丙戊酸钠可抑制炎症通路,下调促炎 miRNA 表达,而难治性癫痫患者对药物的应答不足,导致外泌体-miRNA 异常持续存在^[30]。

2 外泌体-miRNA 调控轴介导癫痫发作后脑组织炎症微环境的机制

2.1 小胶质细胞源性外泌体-miRNA 炎症微环境的“启动者” 小胶质细胞是脑组织内固有免疫细胞,占脑细胞总数的 10%~15%,癫痫发作后可迅速从静息态分支状转变为活化态阿米巴状,并分泌大量外泌体,通过 miRNA 调控启动炎症反应,是炎症微环境形成的“启动者”。

2.1.1 miR-155 的促炎调控作用 活化的小胶质细胞分泌的外泌体中 miR-155 含量显著升高,其可通过多重途径促进炎症微环境形成。(1)靶向抑制含 SH2 结构域的肌醇 5'-磷酸酶 1(SH2-containing inositol 5'-phosphatase 1, SHIP1)的表达,激活磷酸肌醇 3-激酶(phosphoinositide 3-kinase, PI3K)/蛋白激酶 B(protein kinase B, Akt)/NF- κ B 信号通路,促进小胶质细胞自身活化,释放 TNF- α 、IL-1 β 、IL-6 等促炎因子,同时抑制 IL-10 等抗炎因子分泌^[31];(2)被星形胶质细胞摄取后,靶向抑制 SOCS1,增强信号转导与转录激活因子 3(signal transducer and activator of transcription 3, STAT3)信号通路活性,促进星形胶质细胞增生与促炎因子 CXC 基序趋化因子配体 1(CXC motif chemokine ligand 1, CXCL1)、C-C 基序趋化因子配体 2(C-C motif chemokine ligand 2, CCL2)分泌,招募更多免疫细胞浸润^[32];(3)进入神经元后,抑制神经元内抗炎因子转化生长因子 β (transforming growth factor- β , TGF- β)及抗凋亡蛋白 B 细胞淋巴瘤-2(B-cell lymphoma 2, BCL-2)的表达,降低神经元对炎症损伤的抵抗力^[33]。Li 等^[34]发现,向正常大鼠脑内注射富含 miR-155 的小胶质细胞源性外泌体,可诱发脑组织炎症反应,表现为促炎因子水平升高、小胶质细胞活化,而抑制 miR-155 表达则可显著减轻这一效应。

2.1.2 miR-223 的协同促炎作用 小胶质细胞源性外泌体中的 miR-223 可通过靶向抑制 RhoGTP 酶激活蛋白 15(Rho GTPase activating protein 15, ARHGAP15)的表达,增强小胶质细胞的迁移与浸润能力,使其向损伤部位聚集^[35];同时,miR-223 可抑制 Toll 样受体 2(Toll-like receptor 2, TLR2)的表达,调控小胶质细胞活化表型转换,促进其从 M2 抗炎型向 M1 促炎型转变,进一步放大炎症反应^[36]。Selene 等^[37]发现,难治性癫痫患者脑脊液中小胶质细胞源性外泌体 miR-223 表达与脑组织炎症浸润程度呈正相关。

2.1.3 miR-125b 的辅助调控作用 在脊髓损伤的大

鼠模型研究显示,miR-125b 在小胶质细胞源性外泌体中表达升高,可通过靶向抑制 TNF- α 的负调控因子肿瘤坏死因子 α 诱导蛋白 3(TNF- α induced protein 3, TNFAIP3),增强 TNF- α 信号通路活性,促进促炎因子释放,同时抑制神经元存活信号通路,加剧炎症损伤^[39]。

2.2 星形胶质细胞源性外泌体-miRNA: 炎症微环境的“放大器” 星形胶质细胞是脑组织中数量最多的胶质细胞,占脑细胞总数的 40%~50%,癫痫发作后可被炎症因子与兴奋性毒性激活,分泌外泌体参与炎症微环境的维持与放大,同时促进胶质瘢痕形成。

2.2.1 miR-21 的促炎与纤维化作用 星形胶质细胞源性外泌体中 miR-21 表达显著升高,是炎症微环境放大与胶质瘢痕形成的关键调控因子。miR-21 可靶向抑制磷酸酶与张力蛋白同源物(phosphatase and tensin homolog, PTEN)的表达,激活 Akt/NF- κ B 通路,促进星形胶质细胞分泌 IL-6、CXCL1 等促炎因子,同时抑制 IL-10 的释放,加剧炎症失衡^[40];还可靶向调控 TGF- β 1/Sma 和 Mad 相关蛋白(Sma-and Mad-related proteins, Smad)通路,促进星形胶质细胞增生与 GFAP 表达,加速胶质瘢痕形成,这一过程不仅会机械性阻碍神经修复,还会通过瘢痕微环境加剧局部炎症反应^[41];miR-21 被小胶质细胞摄取后,可增强后者的促炎活性,形成“星形胶质细胞-小胶质细胞”炎症正反馈循环,持续放大炎症信号^[42]。Samões 等^[43]发现,难治性癫痫患者脑组织中星形胶质细胞源性外泌体 miR-21 表达与胶质瘢痕面积、炎症因子水平呈正相关。

2.2.2 miR-146a 的抗炎代偿作用减弱 正常状态下,星形胶质细胞源性外泌体中的 miR-146a 可通过靶向抑制 TLR4、IRAK1、TRAF6 等分子,抑制 NF- κ B 通路激活,减轻炎症反应^[44]。但癫痫发作后,星形胶质细胞源性外泌体中 miR-146a 表达显著降低,其抗炎代偿作用减弱,无法有效抑制炎症通路的过度激活,从而加剧脑组织炎症微环境的形成^[45]。Carlos 等^[46]发现,向癫痫模型小鼠脑内补充 miR-146a 可显著降低星形胶质细胞与小胶质细胞的活化水平。

2.2.3 miR-19a/miR-92a 的协同调控作用 细胞实验研究显示,星形胶质细胞源性外泌体中 miR-19a、miR-92a 表达升高,可靶向抑制 PTEN 及炎症抑制因子,增强 Akt 通路活性,促进星形胶质细胞增殖与促炎因子分泌,同时抑制免疫细胞凋亡,延长炎症反应持续时间^[47-48]。

2.3 神经元源性外泌体-miRNA: 炎症微环境的“双重调控者” 神经元在癫痫发作后可释放外泌体,通过 miRNA 调控炎症反应,其功能具有双重性:既

可能参与炎症抑制与神经保护,也可能在持续损伤下加剧炎症失衡,具体取决于癫痫发作的严重程度与病程阶段。

2.3.1 miR-124的抗炎保护作用 神经元源性外泌体富含 miR-124,正常状态下是炎症反应的关键“负调控因子”:可靶向抑制小胶质细胞表面的TLR4及下游信号分子如髓样分化原发反应蛋白88(MyD88)的表达,阻止小胶质细胞活化^[49];促进小胶质细胞向抗炎的M2型转换,增强抗炎因子IL-10、TGF- β 分泌,减轻炎症损伤,调控星形胶质细胞功能,抑制其过度增生与促炎因子释放,维持脑组织稳态^[50]。癫痫发作后,神经元损伤导致神经元源性外泌体分泌减少,miR-124传递不足,其抗炎保护作用减弱,难以抑制炎症反应的启动与放大^[51]。Wang等^[52]报道,向癫痫模型大鼠脑内注射负载miR-124的外泌体,可显著减轻小胶质细胞活化与炎症因子释放。

2.3.2 miR-132的功能失衡 miR-132在神经元源性外泌体中高表达,正常状态下可靶向抑制PTEN,促进神经元存活与突触修复^[53]。但癫痫发作后,持续的兴奋性毒性导致miR-132表达异常升高,进而激活星形胶质细胞内的细胞外信号调节激酶1/2(extracellular signal-regulated kinase 1/2, ERK1/2)通路,促进促炎因子分泌,反而加剧炎症微环境形成;同时,miR-132过度表达可抑制神经干细胞分化,阻碍神经修复^[54-55]。

2.3.3 miR-219的神经保护作用减弱 神经元源性外泌体中的miR-219可通过靶向抑制电压门控钙通道,减少钙离子内流,减轻神经元兴奋性毒性,同时抑制小胶质细胞活化^[56]。Hamamoto等^[57]发现,癫痫患者发作后miR-219表达降低,其神经保护与抗炎作用减弱,进一步加剧神经元损伤与炎症激活。

2.4 外周免疫细胞源性外泌体-miRNA:炎症微环境的“参与者” 癫痫发作后血脑屏障通透性增加,外周免疫细胞可浸润至脑组织,分泌外泌体参与炎症微环境调控,成为连接外周免疫与中枢炎症的关键“桥梁”。

2.4.1 巨噬细胞源性外泌体-miR-155 癫痫大鼠模型的研究显示,浸润的巨噬细胞分泌的外泌体富含miR-155,可靶向抑制SOCS1,增强NF- κ B通路活性,促进促炎因子释放,同时激活脑组织内固有免疫细胞,放大炎症反应^[58];Fu等^[59]在脊髓损伤小鼠的研究显示,巨噬细胞源性外泌体还可携带TNF- α 、IL-1 β 等促炎因子,直接加剧炎症损伤。

2.4.2 中性粒细胞源性外泌体-miR-223 中性粒细胞分泌的外泌体中miR-223是一种高度富集于胶质细胞,可通过外泌体分泌的关键调控分子;其不仅能在细胞间传递信号,还可调控神经元炎症因子的表

达。Mellios^[60]的细胞培养研究显示,miR-223可靶向抑制神经元谷氨酸离子受体的表达,并与炎症因子表达呈正相关,与 γ -氨基丁酸(γ -aminobutyric acid, GABA)能基因表达呈负相关;中性粒细胞源性外泌体还可释放弹性蛋白酶等蛋白酶,降解脑组织细胞外基质,破坏血脑屏障完整性与神经组织结构,加剧氧化应激介导的中枢神经损伤。Pan等^[61]在神经母细胞瘤细胞的研究显示,miR-223可靶向抑制叉头框转录因子O3/硫氧还蛋白互作蛋白(FOXO3/TXNIP)轴,降低ROS水平、增强超氧化物歧化酶(SOD)活性并减少丙二醛(MDA)蓄积,抑制氧化应激,减轻神经元凋亡。这种“促炎损伤与抗氧化保护并存”的双向特性,使miR-223可能成为癫痫后炎症-氧化应激耦联调控网络中的潜在调控节点。

2.4.3 T细胞源性外泌体-miR-142-3p Tung等^[62]在小鼠实验中发现,浸润的T细胞分泌的外泌体中miR-142-3p表达升高,可被小胶质细胞摄取,靶向抑制抗炎因子IL-10的表达,增强促炎反应,同时促进小胶质细胞向T细胞呈递抗原,激活适应性免疫反应,延长炎症持续时间。

3 外泌体-miRNA调控轴介导癫痫发作后神经损伤的下游机制

外泌体-miRNA调控轴可通过多途径介导癫痫发作后神经损伤,可激活凋亡通路、干扰神经元代谢与兴奋性毒性,诱导神经元凋亡;抑制突触相关蛋白与神经营养因子,破坏突触结构功能;破坏血脑屏障紧密连接,促进内皮炎症与基底膜降解;还可抑制神经干细胞分化迁移、促进胶质瘢痕形成。最终通过多环节恶性循环加剧神经损伤(图1)。

3.1 神经元凋亡与功能障碍 外泌体-miRNA可通过诱导凋亡、干扰代谢稳态及增强兴奋性毒性等多重途径,导致神经元凋亡与功能障碍。细胞共培养实验中,小胶质细胞与星形胶质细胞源性外泌体中的miR-155、miR-21可被神经元摄取,分别靶向抑制抗凋亡蛋白BCL-2、PTEN的表达,激活胱天蛋白酶(caspase)-3、caspase-9凋亡通路,促进神经元凋亡^[63];同时,miR-155可抑制神经元内DNA修复相关基因,如辐射敏感蛋白51(RADiation sensitive 51, RAD51)的表达,增强氧化应激介导的DNA损伤,进一步加剧凋亡^[64]。Zhu等^[65]在人海马神经元癫痫细胞模型的研究显示,神经元凋亡率与外泌体miR-155、miR-21表达呈正相关,而抑制这些miRNA可降低神经元凋亡率。外泌体-miRNA可通过调控神经元代谢相关基因的表达,破坏代谢稳态。miR-21可抑制神经元内葡萄糖转运蛋白3(Glucose Transporter 3, GLUT3)的表达,导致葡萄糖摄取减少和能量代谢障

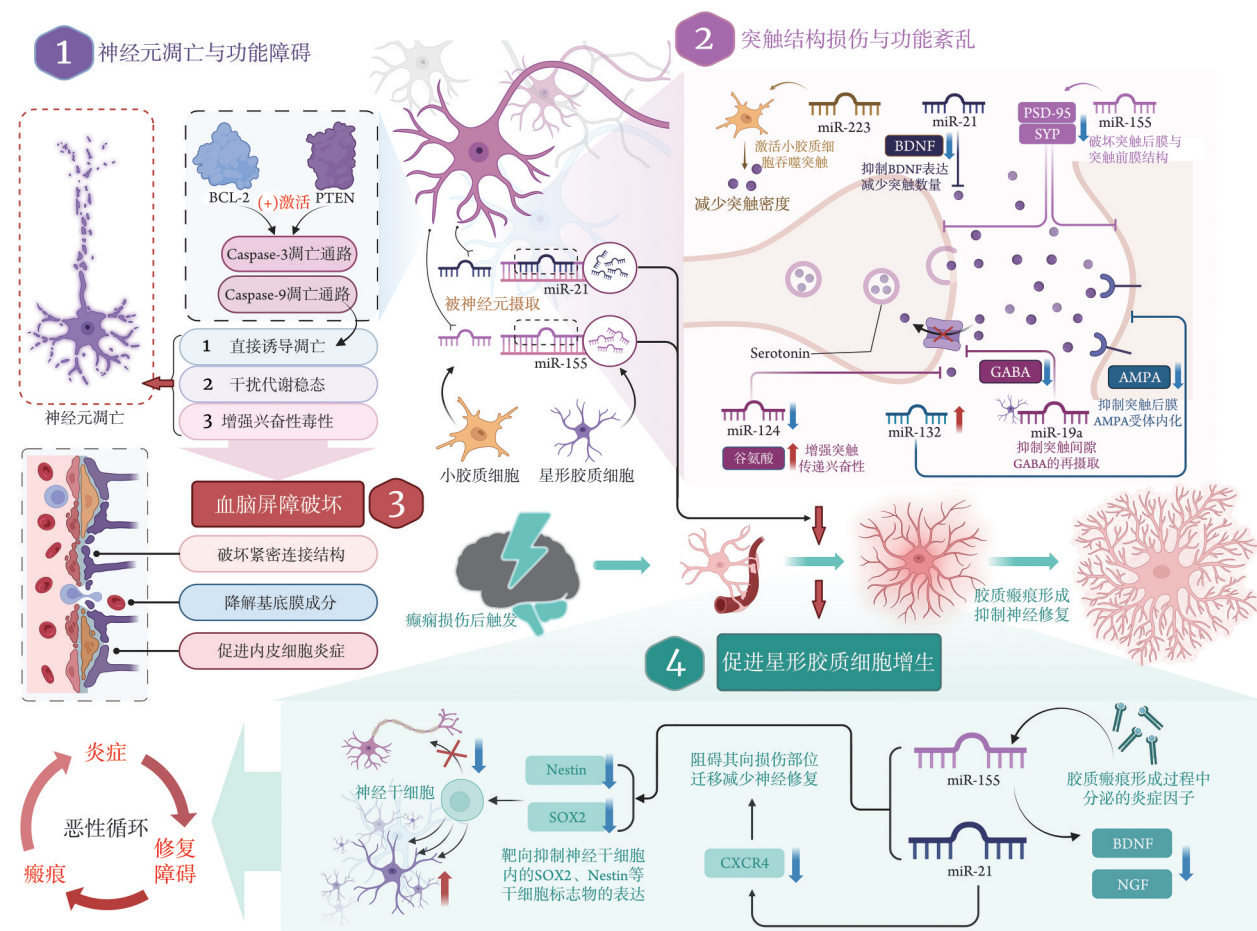


图1 外泌体-miRNA调控轴介导癫痫发作后神经损伤的下游机制

Fig.1 Downstream mechanism diagram of exosome-miRNA regulatory axis mediating post-epileptic neuronal injury

本图采用BioRender构建,自行绘制。BCL-2.抗凋亡蛋白B细胞淋巴瘤-2; PTEN.磷酸酶及张力蛋白同源物; caspase.胱天蛋白酶; PSD-95.突触后致密蛋白-95; SYP.突触素; BDNF.脑源性神经营养因子; GABA.γ-氨基丁酸; AMPA.α-氨基-3-羟基-5-甲基-4-异恶唑丙酸; Nestin.巢蛋白; SOX2.SRY相关高迁移率族盒蛋白2; CXCR4.C-X-C趋化因子受体4; NGF.神经生长因子

碍^[66];神经元源性外泌体miR-124表达降低,可导致小胶质细胞活化释放的炎症因子损伤线粒体功能,ATP生成减少,进而加剧神经元功能障碍^[67]。外泌体-miRNA还可通过调控谷氨酸转运体与受体的表达,加剧中枢兴奋性毒性。星形胶质细胞源性外泌体miR-21可抑制星形胶质细胞谷氨酸转运体1 (glutamate transporter 1, GLT-1)的表达,减少突触间隙谷氨酸清除,导致谷氨酸蓄积^[68];小胶质细胞源性外泌体miR-155可增强神经元NMDA受体的表达与活性,促进钙离子内流,加剧兴奋性毒性损伤^[69];神经元源性外泌体miR-132过度表达,可抑制GABA受体的表达,减弱抑制性神经信号,进一步增强神经元兴奋性^[70]。

3.2 突触结构损伤与功能紊乱 突触是神经元间信号传递的关键结构,外泌体-miRNA可调控突触相关分子的表达,破坏突触结构与功能,导致神经网络信号传递异常。例如,miR-155可抑制PSD-95、突触素的表达,破坏突触后膜与突触前膜结构^[71-72];

miR-21可抑制脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF)的表达,减少突触再生与修复,导致突触数量减少^[73];小胶质细胞源性外泌体miR-223可激活小胶质细胞吞噬突触,进一步降低突触密度^[74]。Ludhiadch等^[75]发现,癫痫患者脑组织中PSD-95、BDNF表达降低,且与外泌体miR-155、miR-21表达水平呈负相关。外泌体-miRNA可通过调控突触传递相关分子,干扰突触功能。神经元源性外泌体miR-124表达降低,可导致突触前膜谷氨酸释放增多,增强突触传递兴奋性^[76];miR-132过度表达可抑制突触后膜α-氨基-3-羟基-5-甲基-4-异恶唑丙酸 (AMPA)受体的内化,增强兴奋性突触传递,导致神经元异常同步化放电^[77];星形胶质细胞源性外泌体miR-19a可抑制突触间隙GABA的再摄取,减弱抑制性突触传递,打破兴奋-抑制平衡^[78]。

3.3 血脑屏障破坏 血脑屏障完整性是维持脑组织稳态的关键。外泌体-miRNA可通过破坏紧密连接结构、促进内皮细胞炎症反应及降解基底膜成分,加

剧血脑屏障损伤。小胶质细胞源性外泌体中的 miR-155 可被血脑屏障内皮细胞摄取, 靶向抑制紧密连接蛋白 occludin、ZO-1、claudin-5 的表达, 导致紧密连接结构松散, 血脑屏障通透性增大^[79]; 同时, 星形胶质细胞源性外泌体 miR-21 可通过激活 Akt/基质金属蛋白酶 9(MMP-9) 通路, 促进 MMP-9 分泌, 降解紧密连接蛋白, 进一步破坏屏障结构^[80]。Aloi 等^[81]发现, 抑制外泌体-miR-155 表达可使癫痫模型小鼠 occludin、ZO-1 表达水平增高, 血脑屏障通透性降低。外泌体-miR-155、miR-223 可激活血脑屏障内皮细胞内的 NF- κ B 通路, 促进促炎因子表达, 增强外周免疫细胞与内皮细胞的黏附与浸润, 机械性破坏血脑屏障^[18]; 同时, miR-155 可抑制内皮细胞抗凋亡蛋白 BCL-2 的表达, 促进内皮细胞凋亡, 导致屏障完整性进一步丧失^[82]。外泌体-miRNA 还可促进蛋白酶分泌, 降解血脑屏障基底膜成分。小胶质细胞源性外泌体 miR-155 可激活小胶质细胞分泌 MMP-9, 降解基底膜的胶原蛋白 IV、层黏连蛋白, 破坏血脑屏障的机械支撑结构^[83]; 中性粒细胞源性外泌体可携带弹性蛋白酶, 直接降解基底膜成分, 加剧屏障损伤^[84]。血脑屏障破坏后, 更多外周免疫细胞与有害物质进入脑组织, 进一步放大炎症反应与神经损伤, 形成恶性循环^[85]。

3.4 胶质瘢痕形成与神经修复障碍 星形胶质细胞过度增生形成的胶质瘢痕, 是阻碍癫痫后神经修复的重要因素; 外泌体-miRNA 在这一过程中发挥关键调控作用。神经干细胞培养和小鼠脑出血模型研究显示, 外泌体-miR-155、miR-21 可靶向抑制神经干细胞内的 SRY 相关高迁移率族盒蛋白 2(SRY-related HMG-box 2, SOX2)、巢蛋白(nestin)等干细胞标志物的表达, 抑制神经干细胞向神经元方向分化, 同时促进其向胶质细胞分化^[86]; 细胞实验显示, miR-21 可抑制神经干细胞表面 CXC 趋化因子受体 4(CXC chemokine receptor 4, CXCR4)的表达, 阻碍其向损伤部位迁移, 减少神经修复^[87]; Nyoman 等^[88]的大鼠脊髓损伤模型研究显示, 胶质瘢痕形成过程中分泌的炎症因子可通过外泌体-miRNA 进一步抑制神经修复相关基因 BDNF、神经生长因子(nerve growth factor, NGF)的表达, 形成“瘢痕-炎症-修复障碍”的恶性循环。胶质瘢痕形成后, 其致密的纤维网络可机械性阻碍神经轴突生长与突触重建, 同时瘢痕微环境中高浓度的炎症因子与抑制性分子如硫酸软骨素蛋白多糖, 可进一步抑制神经修复, 导致神经功能长期受损^[89-90]。

4 总结与展望

外泌体-miRNA 调控轴是介导癫痫发作后脑组织

炎症微环境形成与神经损伤的核心分子机制。癫痫发作通过兴奋性毒性、氧化应激及早期炎症激活, 诱导脑组织固有细胞及外周免疫细胞分泌外泌体, 且显著重构外泌体中 miRNA 表达谱, 呈现“促炎 miRNA 富集、抗炎 miRNA 耗竭”的特征性改变。小胶质细胞源性外泌体-miR-155、miR-223 是炎症微环境的关键启动者, 星形胶质细胞源性外泌体-miR-21、miR-19 推动炎症信号放大与胶质瘢痕形成, 同时神经元源性外泌体-miR-124、miR-132 的抗炎保护作用减弱, 外周免疫细胞源性外泌体则通过跨血脑屏障浸润进一步加剧中枢炎症。这些异常 miRNA 通过靶向调控炎症通路关键分子及神经功能相关基因, 从多维度诱导神经元凋亡、突触损伤、血脑屏障破坏及神经修复障碍, 最终推动癫痫慢性化与药物抵抗。

基于外泌体-miRNA 调控轴在癫痫发病中的核心作用, 当前针对癫痫发作后外泌体-miRNA 的靶向干预已形成多种潜在策略: (1)通过 miRNA 拮抗剂直接抑制促炎 miRNA 活性, 或补充抗炎 miRNA 模拟物纠正表达失衡; (2)利用工程化外泌体构建靶向递送系统, 提升干预分子的中枢靶向性与生物利用度; (3)通过调控外泌体分泌关键分子如 Rab27a、神经酰胺合成酶或封装机制, 从源头减少异常外泌体-miRNA 的释放与传递。

综上, 外泌体-miRNA 调控轴为癫痫发病机制研究提供了全新的外周-中枢跨系统调控视角, 其中 miR-155、miR-21、miR-124 及 TLR4/NF- κ B 通路可作为癫痫炎症干预的潜在靶点。未来通过开发外泌体靶向递送系统、miRNA 模拟物或拮抗剂, 有望打破“炎症-神经损伤”恶性循环, 为难治性癫痫提供新的治疗策略。同时, 外泌体中特征性 miRNA 亚群也具备作为癫痫诊断、病情评估及预后预测生物标志物的潜力, 值得进一步研究乃至临床转化。

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