·综述·

*miRNA-145*调控胶质瘤恶性生物学行为研究进展

王军成 李欣龙 马东明 潘亚文

【摘要】 胶质瘤因其恶性增殖、侵袭、耐药性、免疫抑制等复杂的生物学特性，使临床治疗面临极大困难。尽管手术联合放化疗使患者生存率有一定提高，但总体疗效仍不显著。微小RNA（miRNA）作为一种非编码RNA，参与调控多种肿瘤（包括胶质瘤）的生物学过程，抑癌基因*miRNA-145*通过多种途径在胶质瘤发生与进展中发挥调控作用，尤其是作为靶向药物通过纳米载体运送至肿瘤区域治疗肿瘤成为当前研究热点。本文总结*miRNA-145*在胶质瘤病理分级、肿瘤微环境、胶质瘤干细胞调控、胶质瘤耐药性及胶质瘤预后中的作用，旨在为胶质瘤的诊断与治疗提供参考。

【关键词】 神经胶质瘤； 微RNAs； 生物标记； 综述

Research progress on the regulation of malignant biological behavior of glioma by *miRNA-145*

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【Abstract】 Glioma is the most malignant brain tumor with high mortality. Due to its complex biological characteristics such as malignant proliferation, invasion, drug resistance, and immunosuppression, the clinical treatment faces great difficulties. Although the survival rate has improved under surgery combined with radiotherapy and chemotherapy, the overall curative effect is still not obvious. As a kind of non coding RNA (ncRNA), microRNA (miRNA) which has been extensively studied in recent years is involved in the regulation of biological processes of normal tissues and various tumors (including glioma) in human. As a cancer suppressor gene, *miRNA-145* plays a regulatory role in the progression of glioma through a variety of pathways, especially as a targeted drug transported to the tumor area through nanocarriers to treat tumors, becoming a current research hotspot. This article summarizes the role of *miRNA-145* in pathological grading, tumor microenvironment, the regulation of glioma stem cells, drug resistance, and the prognosis of glioma, aiming to provide the reference for the diagnosis and treatment of glioma.

【Key words】 Glioma; MicroRNAs; Biomarkers; Review

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脑胶质瘤是中枢神经系统最常见的原发性恶性肿瘤，占颅内肿瘤的40%～50%[1]；胶质瘤生物学特性复杂，复发率和病死率较高，中位生存期为14.6个月，5年生存率＜10%[2]。胶质瘤的病理分级为WHO 1～4级，分级越高、预后越差[3-5]。其中，胶质母细胞瘤（WHO 4级）是最具侵袭性的亚型，约占胶质瘤的50%，1年总生存率＜3%，平均总生存期（OS）＜12个月[6-7]。胶质瘤的治疗以手术切除后辅以药物化疗或同步放化疗为主，尽管诊断策略与积极治疗取得显著进展，3年总生存率仍较低，特别是胶质母细胞瘤，替莫唑胺化疗后3年无进展生存率仅28%[8]。胶质母细胞瘤发病机制复杂，目前尚未完全阐明，肿瘤细胞内和肿瘤细胞间存在遗传学、表观遗传学、分子生物学和代谢异质性[9]。因此，有研究者将注意力转向胶质母细胞瘤潜在分子机制研究，致力于探寻新的生物学标志物，用于肿瘤的早期诊断、监测及预后评估。微小RNA（miRNA）是一种内源性、长度为20个核苷酸序列的非编码RNA（ncRNA），广泛分布于细胞内，通过沉默或降解靶基因在信使RNA（mRNA）转录的调控中发挥主要作用[10-11]。近年发现，miRNA不仅调控正常组织细胞的生理学过程，还参与调控多种肿瘤细胞的生物学过程，包括肿瘤细胞增殖、凋亡、代谢、迁移、耐药性、异质性等[12]。这一特性使miRNA成为肿瘤诊断、治疗或预后评估的生物学标志物被广泛研究，研究显示，外源性调控miRNA有可能成为胶质瘤的潜在治疗靶点[13]。本文拟对*miRNA-145*在胶质瘤病理分级、肿瘤微环境（TME）、胶质瘤干细胞（GSCs）调控、胶质瘤耐药性以及胶质瘤预后中的作用进行总结，并对miRNA（包括*miRNA-145*）作为胶质瘤诊断与治疗靶点的潜在功能以及特异性miRNA（或miRNA联合化疗药物）外泌体治疗胶质瘤的潜在价值进行讨论，以为胶质瘤的诊断与治疗提供参考。

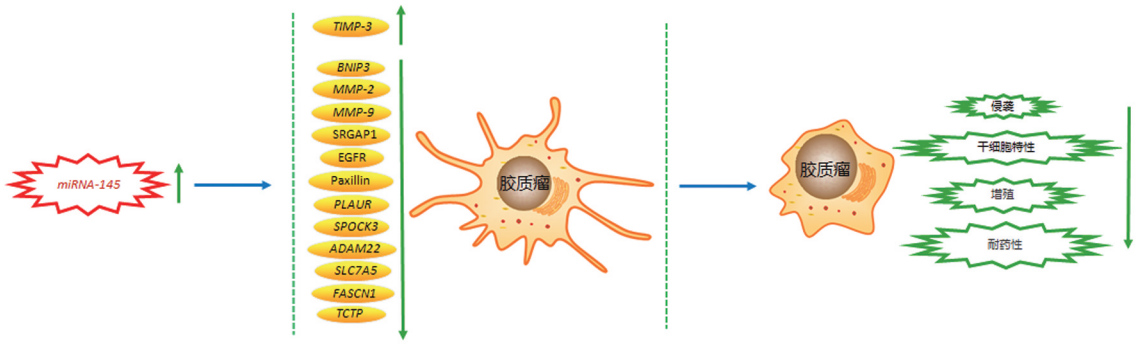
一、*miRNA-145*的生物学特性

*miRNA-145*定位于染色体5q32，包括*miRNA-145-5p*和*miRNA-145-3p*两种亚型，可在大多数体液中检测到[14]，且*miRNA-145-5p*表达量显著高于*miRNA-145-3p*[15]。*miRNA-145*在多种肿瘤中表达下调，作为抑癌基因被广泛关注[16-17]，但在少数肿瘤中表达上调，作为癌基因发挥作用[14]。*miRNA-145*在胶质瘤中呈低表达，且病理分级越高、表达量越低，患者预后越差、总生存期越短；此外，*miRNA-145*表达量还与胶质瘤耐药性密切相关[17]。总之，*miRNA-145*通过多种分子机制调控胶质瘤进展，作为一种新型非编码RNA，成为胶质瘤领域的研究热点，在肿瘤诊断、治疗及预后中具有潜在价值。

二、*miRNA-145*调控胶质瘤的恶性生物学行为

1. *miRNA-145*通过靶向下游癌基因调控胶质瘤细胞生长　*miRNA-145*通过多种路径调控胶质瘤细胞增殖、凋亡、迁移、侵袭等特性。有研究者在人和大鼠胶质瘤组织和胶质瘤细胞系中发现，*BNIP3*基因表达上调、*miRNA-145*表达下调，后者通过结合*BNIP3* mRNA的3'非翻译区（3′UTR）抑制*BNIP3*基因表达，进而通过调控Notch信号转导通路关键分子促进胶质瘤细胞系U87和U251凋亡[18]。将$CD133^+$GSCs（即U251细胞分离出的$CD133^+$胶质瘤干细胞）进行体外培养，分别以*miRNA-145*抑制剂和*miRNA-145*拟似物转染，结果显示，过表达*miRNA-145*可上调$CD133^+$GSCs中*TIMP-3*基因的表达，下调*MMP-2*和*MMP-9*基因的表达，抑制U251细胞的侵袭能力；抑制*miRNA-145*，则*TIMP-3*和*MMP-2*、*MMP-9*表达逆转，增强U251细胞的侵袭能力[19]。通过构建胶质母细胞瘤细胞侵袭性亚群（IM3），包括U87-IM3细胞和U251-IM3细胞，在体外转染及共培养过程中上调*miRNA-145*表达，发现*miRNA-145*经Slit-Robo信号转导通路靶向作用于Slit-Robo Rho GTP酶激活蛋白1（SRGAP1），使其在U87-IM3和U251-IM3细胞中表达下调，抑制肿瘤细胞侵袭；反之下调*miRNA-145*表达，促进肿瘤细胞侵袭[20]。有研究探讨*EGFR*基因在胶质母细胞瘤及新生微血管中的表达差异，发现表皮生长因子受体（EGFR）在胶质母细胞瘤中呈高表达，活化的EGFR可促进肿瘤细胞增殖、抑制其凋亡，*miRNA-145-5p*靶向作用于EGFR，抑制EGFR翻译，靶向抑制胶质母细胞瘤细胞增殖[21]。*miRNA-145*亦可通过调控桩蛋白（paxillin）等细胞间黏附分子（ICAM）的表达，调节胶质瘤细胞迁移、侵袭[22]。*miRNA-145*过表达可导致*PLAUR*、*SPOCK3*、*ADAM22*、*SLC7A5*和*FASCN1*等肿瘤转移相关基因表达下调，显著抑制U87和U373细胞迁移、侵袭[23]。由此可见，*miRNA-145*作为抑癌基因，可以通过调控下游多种癌基因的表达发挥抗肿瘤效应（图1）。

2. *miRNA-145*作为环状RNA靶点调控胶质瘤细胞生长　环状RNA（circRNA）于20世纪70年代末在病毒及类病毒中被发现，是一类在转录过程中



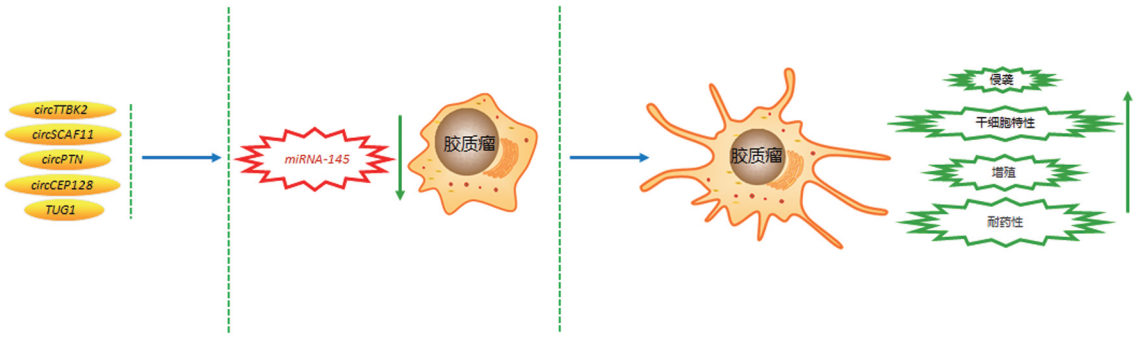
↑，过表达；↓，表达抑制或功能抑制

图1　*miRNA-145*过表达调控胶质瘤细胞生长示意图

Figure 1　The mechanism of overexpression of *miRNA-145* in regulating the growth of glioma cells.

形成的端端连接的环状非编码RNA，高通量测序发现其稳定存在于人体组织和体液中[24]；虽然circRNA含量明显低于miRNA，但circRNA富含miRNA结合位点，发挥miRNA海绵（miRNA sponge）作用，抑制miRNA对目标mRNA的调控，从而上调靶基因的表达，通过这一内源性竞争机制，circRNA参与调控多种肿瘤的发生与进展[25-26]。小鼠异种移植实验显示，*circTTBK2*通过对*miRNA-145-5p*进行海绵样吸附，促进胶质瘤细胞增殖、迁移、侵袭和糖酵解，抑制*miRNA-145-5p*可减轻*circTTBK2*敲低对胶质瘤细胞恶性行为的影响[27]。在体外研究中，胶质瘤组织和细胞中*circSCAF11*表达上调、*miRNA-145-5p*表达下调，双荧光素酶报告基因检测（Dual-Luciferase Reporter Assay）和RNA免疫共沉淀实验发现，*circSCAF11*是*miRNA-145-5p*的海绵，罗哌卡因通过抑制*circSCAF11*对*miRNA-145-5p*的海绵样吸附以抑制胶质瘤生长[28]；*circPTN*通过与*miRNA-145-5p*结合，促进胶质瘤生长，同时，体外增加*circPTN*的表达，可抵消*miRNA-145-5p*过表达对胶质瘤细胞增殖的抑制作用，*circPTN*还可通过海绵样吸附*miRNA-145-5p*促进自我更新，当*miRNA-145-5p*中*circPTN*结合位点发生突变时，*circPTN*的调控作用消失[29]。*miRNA-145-5p*亦为*circCEP128*的靶点，后者在胶质瘤组织和耐药胶质瘤细胞系中表达上调，*miRNA-145-5p*在胶质瘤细胞和替莫唑胺耐药的胶质瘤细胞中均呈低表达，过表达*miRNA-145-5p*可抑制替莫唑胺耐药U251细胞增殖，敲除*circCEP128*后*miRNA-145-5p*表达上调，从而增强替莫唑胺在胶质瘤细胞中的毒性作用，进一步抑制细胞增殖[30]。由此可见，*miRNA-145*作为多种circRNA靶点被circRNA海绵样吸附，从而失去对下游癌基因的抑制作用（图2）。

3. *miRNA-145*调控胶质瘤干细胞生长　胶质瘤干细胞是胶质瘤中CD133和巢蛋白（Nes）阳性且具有正常干细胞特性的一类细胞，可导致肿瘤广泛切除后复发[31-32]，而复发性胶质母细胞瘤的中位生存期仅24～44周[33]。近年随着对胶质母细胞瘤发生与进展相关分子机制研究的深入，发现其属于基因失调性疾病，过表达、激活多个癌基因以及抑癌基因功能丧失导致正常细胞无限增殖、异常分化、局部侵袭[34]。因此，探寻胶质母细胞瘤恶性进展相关分子靶点，尤其是胶质瘤干细胞进展关键分子，对胶质母细胞瘤的靶向治疗具有重要意义[35]。体外研究显示，*TCTP*基因在原代胶质瘤干细胞（pGSCs）中表达显著上调，将其沉默可抑制肿瘤细胞增殖，促进其凋亡；*miRNA-145-5p*在原代胶质瘤干细胞中呈低表达，通过生物信息学和荧光素酶靶向分析证实*miRNA-145-5p*表达上调通过直接抑制*TCTP*的表达以发挥抑制原代胶质瘤干细胞增殖的作用[36]（图1）。国内一项双荧光素酶报告基因检测显示，转录因子*TWIST*通过靶向结合*miRNA-145*以促进胶质瘤干细胞迁移、侵袭[37]。在胶质母细胞瘤生长过程中，胶质瘤干细胞可以产生分化的胶质瘤细胞（DGCs），后者在特定情况下可以转化为胶质瘤干细胞，以维持稳定的肿瘤微环境。核糖体分析、转录组和RNA m^6A甲基化测序研究显示，在胶质瘤干细胞分化过程中，*miRNA-145*起关键作用，与*RRACH*异位结合的*miRNA-145*可诱导m^6A丢失，并在抑癌



↑,功能增强;↓,表达抑制

图2 抑制*miRNA-145*表达调控胶质瘤细胞生长示意图

Figure 2 The mechanism of inhibition of *miRNA-145* in regulating the growth of glioma cells.

基因*CLIP3* mRNA上形成*FTO/AGO1/ILF3/miRNA-145*化合物,促进*CLIP3*的翻译,抑制*miRNA-145*可以维持*CLIP3*的*RRACH* m^6A水平,最终抑制胶质瘤干细胞向分化的胶质瘤细胞的转化[38]。动物实验显示,胶质瘤干细胞中Notch1激活可以特异性诱导长链非编码RNA(lncRNA)*TUG1*的表达,后者通过在细胞质中吸附*miRNA-145*,协同促进胶质瘤干细胞的自我更新,静脉注射靶向*TUG1*的反义寡核苷酸药物可以诱导胶质瘤干细胞分化,并有效抑制其生长[39](图2)。中药在胶质瘤的治疗中亦发挥重要作用。体外研究显示,去甲氧基姜黄素可以抑制胶质瘤干细胞增殖并诱导其凋亡,*miRNA-145*在体内外均可提高胶质瘤干细胞对去甲氧基姜黄素的敏感性,促进去甲氧基姜黄素对胶质瘤干细胞增殖的抑制和凋亡的诱导;同时,*miRNA-145*和去甲氧基姜黄素通过miRNA-145/Y染色体性别决定区相关高迁移率组盒蛋白2(SOX2)-Wnt/β-连环蛋白信号转导通路发挥作用,过表达*SOX2*可降低*miRNA-145*联合去甲氧基姜黄素处理后胶质瘤干细胞对增殖抑制的抵抗性[40]。另一项研究对患者来源的胶质母细胞瘤球(PDGS)予以异丹叶大黄素干预,发现异丹叶大黄素可诱导*miRNA-145*表达,并与*SOX2* mRNA 3'非翻译区结合,抑制SOX2蛋白的翻译,同时下调细胞周期素D1(CCND1),导致G_0/G_1期阻滞,抑制PDGS的非锚定依赖性生长[41]。胶质瘤干细胞作为胶质瘤手术后复发的重要因素之一,抑制其生长对提高胶质瘤治愈率和患者生存率具有重要意义;*miRNA-145*直接参与调控胶质瘤干细胞的生长,亦可提高其对中药的敏感性,为胶质瘤的治疗提供参考。

4.*miRNA-145*调控胶质瘤细胞对化疗药物的敏感性　目前,药物化疗仍是胶质母细胞瘤的最主要治疗方法,既往数十年,卡莫司汀、洛莫司汀、长春新碱、顺铂、贝伐珠单抗、替莫唑胺等化疗药物被广泛研究并应用于胶质母细胞瘤的治疗[42]。其中,替莫唑胺通过诱导碱基错配、DNA修复畸变、DNA链断裂导致肿瘤细胞死亡,并可透过血脑屏障,成为最有效的化疗药物之一[43]。然而,仅约45%的胶质瘤患者对替莫唑胺短期有效,替莫唑胺治疗后5年生存率仍<10%[44],这是由于胶质瘤细胞固有性和获得性替莫唑胺耐药所导致[43]。近年相关研究显示,*miRNA-145*对增强胶质瘤细胞对化疗药物的敏感性具有积极作用。通过构建对DMC-BH(双脱甲氧基姜黄素衍生物)耐药的胶质母细胞瘤细胞株(U87/DMC-BH和U251/DMC-BH)发现,*miRNA-145-5p*在U87/DMC-BH和U251/DMC-BH细胞中的表达水平低于非耐药U87和U251细胞;同时还发现,*TCTP*在U87/DMC-BH和U251/DMC-BH细胞中呈过表达,但转染*miRNA-145-5p*后,*TCTP*表达显著下降,提示*miRNA-145-5p*通过抑制*TCTP*增强耐药胶质瘤细胞对DMC-BH的敏感性[45]。一项纳入90例胶质瘤手术患者的临床研究根据术后替莫唑胺疗效分为有效组和无效组,有效组化疗前血清*miRNA-145-5p*相对表达量高于无效组,提示血清*miRNA-145-5p*水平是影响化疗敏感性的因素,即高水平*miRNA-145-5p*可增强替莫唑胺化疗的敏感性[46]。体外研究和动物实验均证实,*miRNA-145-5p*通过靶向抑制*RAD18*表达,增强替莫唑胺的化疗效果[47]。体外构建聚氨酯短支聚乙烯亚胺(PU-PEI)载体,介导*miRNA-145*进入$CD133^+$胶质母细胞瘤细胞,抑制

其对替莫唑胺的耐药性；进一步的动物实验结果发现，PU-PEI-*miRNA-145*可提高原位移植CD133⁺胶质母细胞瘤细胞的免疫缺陷小鼠的存活率[48]。亦有研究利用*miRNA-145*拟似物和抑制剂联合替莫唑胺干预U251细胞，发现*miRNA-145*通过增强U251细胞对替莫唑胺的敏感性，抑制其恶性生长[49]。由此可见，胶质瘤化疗后产生的耐药性是其无法根治的重要原因，*miRNA-145*通过调控多种耐药基因的表达，增强胶质瘤细胞对化疗药物的敏感性，为提高胶质瘤化疗效果提供了实验基础。

5. *miRNA-145*通过囊泡转运调控胶质瘤微环境　外泌体是细胞胞吞作用产生的膜源性囊泡，直径30～100 nm，功能性外泌体包含脂质、核酸（DNA、mRNA、miRNA等）和蛋白质等，参与细胞与微环境间的信息传递，通过触发特殊的细胞内级联反应影响受体细胞的基因表达，肿瘤细胞分泌的功能性外泌体参与肿瘤生长、血管生成、免疫逃逸、耐药性和转移等诸多生物学行为[50-51]。*miRNA-145-5p*作为肿瘤抑制因子，通过细胞外囊泡转运方式在胶质母细胞瘤细胞与内皮细胞之间进行信息传递，改变肿瘤微环境中的分子分布，调控胶质母细胞瘤细胞和内皮细胞的增殖[52]。通过转染*miRNA-145-5p* mimics构建可分泌*miRNA-145-5p*囊泡的人骨髓间充质干细胞（*miRNA-145-5p* hMSCs），将其与U87细胞体外共培养，建立*miRNA-145-5p* hMSCs细胞与U87细胞的共聚体，再将该共聚体植入器官型大鼠脑组织切片纹状体，发现U87细胞的侵袭性明显受到抑制[53]。可见*miRNA-145*作为小分子ncRNA，通过外泌体形式参与调控胶质瘤微环境，抑制胶质瘤细胞生长，未来研究中如果将其与特定的纳米载体相结合，研发可透过血脑屏障的新型纳米载体药物模型，对提高胶质瘤的治疗效果具有重要意义。

三、展望

ncRNA提供的生物学信息虽仅占非编码基因组（non-coding genome）转录信息的小部分，但在研究生物生长发育及疾病治疗领域取得了显著成果，使得对生物复杂分子调控网络有了进一步认识[54]。miRNA广泛存在于体液中，其靶向治疗在胶质瘤基础研究中取得了良好效果，提示其作为胶质瘤生物学标志物和分子治疗方法的巨大潜力和广阔应用前景，准确识别其分子靶点、了解其作用机制，对克服胶质瘤耐药性、防止肿瘤复发具有重要意义[55]。由于血脑屏障的存在，胶质瘤的药物化疗受到极大限制[56]。新型纳米载体药物模型的构建虽使药物在肿瘤组织中的传递有了极大改观，但因其自身毒性、稳定性、有效性和靶向性等问题，在临床转化过程中仍存在困难[55]；而以患者来源的外泌体作为药物载体更兼容、更安全，外泌体ncRNA被选择性地包装、分泌并在细胞之间转移，通过调节肿瘤微环境，应用于肿瘤的靶向治疗[57]，但在胶质瘤治疗领域中的研究较少。*miRNA-145*作为新型ncRNA，通过多种途径干扰下游癌基因的表达；亦作为靶点被抑制，调控胶质瘤细胞的增殖、迁移、侵袭和胶质瘤干细胞的分化，同时通过多条信号转导通路参与胶质瘤微环境及耐药性的调节。因此，探寻可以有效透过血脑屏障、靶向性强的外泌体，构建特异性*miRNA-145*外泌体载体，或富集其他靶向性药物（诊断相关特异性ncRNA以及药物联合特异性ncRNA），或与新型特异性纳米载体（毒性小、稳定性好）相融合，使其成为优秀的诊断和靶向治疗药物，是未来研究趋势。

利益冲突　无

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《疼痛外科学》出版

由首都医科大学宣武医院功能神经外科胡永生教授主编的国内首部《疼痛外科学》（ISBN：978-7-5659-3092-8）已于2024年3月由北京大学医学出版社出版发行。该书由我国疼痛医学创始人韩济生院士题词、著名神经外科专家赵继宗院士作序，凝聚了全国20余家知名医学单位30余位疼痛外科学领域权威专家的宝贵经验和集体智慧。

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