综述

环状 RNA 作为脑肿瘤潜在生物学标志物的研究进展

杜毅超，楼美清
（上海市第一人民医院，上海 200080）

摘　要：环状 RNA（circular RNA，circRNA）是一类无游离 5′端和 3′端的共价闭合的非编码 RNA，具有丰富性、稳定性、保守性和组织特异性等结构特点，circRNA 与细胞增殖、凋亡、血管生成和转移等方面都有着密不可分的联系。脑肿瘤因为其独特的微环境造成了其发生发展机制的特殊性。研究 circRNA 与脑肿瘤发生发展的机制，必将促进对脑肿瘤诊断、治疗预后等多方面的发展。全文综述 circRNA 在常见脑肿瘤（胶质瘤、垂体瘤和髓母细胞瘤）中的表达情况及其靶向 miRNA 和后续信号通路，并概述其作用结果，总结 circRNA 作为多种脑肿瘤的潜在生物学标志物。

主题词：环状 RNA；脑肿瘤；生物学标志物
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Research Progress on Circular RNA as a Potential Biomarker of Brain Tumors

DU Yi-chao，LOU Mei-qing
（*Shanghai General Hospital*，*Shanghai* 200080，*China*）

Abstract：Circular RNA (circRNA) is a class of covalently closed non-coding RNA that without 5′ cap and 3′ poly A tail. They have the characteristics such as richness，stability，high conservatism and tissue specificity. With the in-depth study of the mechanism of circRNA in tumorigenesis and development，we found that circRNA is closely related to cell proliferation，apoptosis，angiogenesis and metastasis. Brain tumors have the specific mechanism of tumorigenesis and development because of their unique microenvironment. The study of the mechanism of circRNA with the tumorigenesis and development of brain tumors will promote the progress of diagnosis，treatment and prognosis of brain tumors. This article reviews the expression of circRNA in some common brain tumors (such as glioma，pituitary adenoma and medulloblastoma) and their targeting miRNA and related signal pathways，and summarizes the functions of circRNA in the tumors. Finally we concludes that circRNA may act as potential biomarkers for commom brain tumors.
Subject words：circular RNA；brain tumors；biomarker

环状 RNA（circular RNA，circRNA）最早于 1976 年由 Sanger 团体研究 RNA 病毒时发现[1]。circRNA 最初被认为是 RNA 剪接过程中产生的无功能产物，但随着高通量测序技术和生物信息学的快速发展，circRNA 在基因转录、转录后修饰以及翻译调控中的作用逐渐被证实[2]。研究表明 circRNA 广泛参与细胞的增殖、凋亡、血管生成和转移等多种病理生理过程，并与神经系统肿瘤在内的多种肿瘤的发病机制有关[3]。明确 circRNA 与脑肿瘤发生发展以及预后的相关性，从而为脑肿瘤提供新的治疗策略具有重要的临床意义。

通信作者：楼美清，E-mail：Loumq68128@sina.com
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1　circRNA 概述

1.1　circRNA 产生与分类

与线性 RNA 分子不同的是，circRNA 是由特殊的 mRNA 前体（pre-mRNA）通过非经典的方式反剪接而成的。circRNA 根据 pre-mRNA 的不同，可分为

4 类：外显子 circRNA、内含子 circRNA、外显子-内含子 circRNA 和线粒体编码的 circRNA[4]。目前有 3 种模型解释 circRNA 的形成机制[5]：(1)套索驱动的环化：一个外显子的 3′剪接供体与另一个外显子的 5′剪接受体共价结合后切除内含子，然后形成 circRNA。(2)内含子配对驱动的环化：由 2 个内含子先通过碱基互补配对形成环状结构，再切除内含子，最后形成 circRNA。(3)RNA 结合蛋白(RNA-binding protein,RBP)依赖性的环化：一些 RBP 能够结合到 pre-mRNA 某些内含子序列的特定位点上，从而代替内含子中反向重复序列或者互补序列，拉近剪接供体和剪接受体的距离，进而使相邻外显子连接环化，最终形成 circRNA[6]。circRNA 的形成机制尚未完全阐明，有待进一步深入研究。

1.2 circRNA 特点

circRNA 具有如下特点：(1)丰富性：circRNA 种类多，含量丰富，在各种组织、细胞和细胞组分(如外泌体等)、体液(如血液、唾液等)中都有丰富的表达[7]。(2)稳定性：因为 circRNA 具有独特的共价闭合环状结构，缺乏 5′帽和 3′polyA 尾结构，从而不易被核酸外切酶降解，导致 circRNA 半衰期更长，比与之相对应的线性 RNA 更加稳定[8]。(3)保守性：circRNA 在不同物种间具有高度保守性，部分人类 circRNA 可在其他物种基因组中找到相应的同源序列[9]。(4)组织特异性：circRNA 在中枢神经系统中高度富集，具有高度特异性[10]。此外，circRNA 在包括神经系统肿瘤在内的多种肿瘤细胞中差异性表达[11]，以上特点使 circRNA 有望成为肿瘤有效的生物学标志物。

1.3 circRNA 功能

circRNA 生物学功能主要是以下 4 种：(1)作为 miRNA 分子海绵。circRNA 具有不同类型和数量的 miRNA 结合位点，这些位点能够特异性与 miRNA 结合，从而消除 miRNA 对其靶基因的抑制作用，上调相应靶基因的表达[12]。(2)调节 RBP。RBP 对调节转录后基因表达起着重要的作用，可发挥 RNA 选择性剪接、维持 RNA 稳定、RNA 转运和翻译等多种生物学功能，并参与细胞的增殖、分化、转运、衰老、凋亡及衰老等多种活动。circRNA 可以与 RBP 直接特异性相互作用，调控基因表达与多种生物活动[13]。(3)翻译蛋白。传统观点认为，circRNA 作为非编码 RNA，不具有编码蛋白的功能，而近来的研究表明 circRNA 可编码蛋白从而发挥生物学效应，例如 Qu 等[14]研究证实了一种编码 Spike 蛋白受体结合域的 circRNA 疫苗，其可有效增强疫苗中和抗体的能力，从而更有效地对抗 SARS-CoV-2 病毒。(4)参与基因表达的调控。circRNA 可通过多种途径参与基因表达的调控，例如前文提及的 circRNA 作为 miRNA 分子海绵或者通过与 RBP 相互作用，调控基因表达。此外，线性 RNA 通常是由 pre-mRNA 剪接而成，而 circRNA 是经特定的 pre-mRNA 反向剪切形成的，所以 circRNA 合成通常与其线性 mRNA 之间存在竞争关系[15]，从而影响 mRNA 相应靶基因的表达。因此，circRNA 可以通过多种途径参与基因的表达与调控。

2 circRNA 与脑肿瘤的关系

2.1 circRNA 与胶质瘤

胶质瘤是中枢神经系统中最常见的恶性肿瘤，且具有恶性程度高、肿瘤切除术后易复发等特点，故胶质瘤具有极高的致残率和病死率[16]。越来越多的研究表明 circRNA 是胶质瘤发生发展的重要生物学标志物，参与胶质瘤增殖、侵袭和迁移等多种病理生理过程[17-39](Table 1)。

据报道，七氟醚可以抑制胶质瘤细胞的生长、侵袭，并诱导胶质瘤细胞的凋亡。本文总结出七氟醚通过 5 种途径抑制胶质瘤的发生发展[40-44](Table 2)。

2.2 circRNA 与垂体瘤

垂体腺瘤约占脑肿瘤的 17%[45]。已有一些研究表明 circRNA 是垂体腺瘤发生发展的重要生物学标志物。本文总结出 circRNAs 通过 5 种途径调节垂体腺瘤的发生发展[46-50](Table 3)。

2.3 circRNA 与髓母细胞瘤

髓母细胞瘤(medulloblastoma,MB)是最常见的儿童恶性脑肿瘤，占所有儿童中枢神经系统恶性肿瘤的 15%~20%[51]。Zhao 等[52]研究发现 circ-SKA3(hsa_circ_0029696)在 MB 中高表达，通过靶向抑制 miR-326，进而上调 ID3，从而促进 MB 的增殖、迁移和侵袭。Lv 等[53]研究发现 33 个 circRNA 在 MB 组织中差异表达后证实 circ-SKA3 和 circ-DTL(hsa_circ_0000179)在 MB 中高表达，调节 MB 的发

Table 1 Expression and function of circRNA in glioma

circRNA	Expression in glioma	Target gene/pathway	Function	Reference
circCPA4 (hsa_circ_0082374)	Upregulated	let-7/CPA4	Promote the proliferation and metastasis of glioma	[17]
circ_0074026	Upregulated	miR-1304/ERBB4	Idem	[18]
circ-U2AF1 (hsa_circ_0061868)	Upregulated	hsa-miR-7-5p/NOVA2	Idem	[19]
hsa_circ_0072389, hsa_circ_0072386, hsa_circ_0008621, hsa_circ_0072387, hsa_circ_0072391	Upregulated	miR-338-5p/IKBIP	Idem	[20]
circ-E-Cad	Upregulated	C-E-Cad/EGFR	Promote the proliferation and metastasis of glioblastoma	[21]
hsa_circ_0088732	Upregulated	miR-661/RAB3D	Promote the proliferation, invasion and epithelial-mesenchymal transition and inhibit apoptosis of glioma cell	[22]
circ-CREBBP	Upregulated	miR-375/glutaminase	Promote cell tumorigenesis and glutamine catabolism in glioma	[23]
circ-PTN	Upregulated	miR-432-5p/RAB10	Promote cell proliferation, invasion and glycolysis in glioma	[24]
circ-SHKBP1	Upregulated	miR-544a/FOXP1, miR-379/FOXP2	Regulate the angiogenesis of glioma-exposed endothelial cells	[25]
circ-CEP128	Upregulated	miR-145-5p	Enhance temozolomide resistance of glioma cells and promote the proliferation and metastasis of glioma	[26]
circ_0005198	Upregulated	miR-1294, miR-198/ TRIM14	Idem	[27-28]
hsa_circ_0000936	Upregulated	miR-1294	Enhance temozolomide resistance of glioma cells	[29]
circ_0072083	Upregulated	miR-1252-5p/ALKBH5, Nanog	Idem	[30]
hsa_circ_0110757	Upregulated	miR-1298-5p/ITGA1	Idem	[31]
circ_0043949	Upregulated		Regulate temozolomide resistance of glioblastoma	[32]
circ-ATP8B4	Upregulated	miR-766	Regulate radioresistance of glioma	[33]
circ-VCAN	Upregulated	miR-1183	Idem	[34]
hsa_circ_0001017	Downregulated	hsa-let-7g-3p/NDST3	Regulate the proliferation and metastasis of glioma	[35]
hsa_circ_0000915, hsa_circ_0127664, hsa_circ_0008362, hsa_circ_0001467	Downregulated	FAIM2, DLGAP2, ATP1B1 and RALYL	Idem	[36]
circ-EPB41L5	Downregulated	miR-19a/ EPB41L5/ p-AKT	Regulate the proliferation and metastasis of glioblastoma	[37]
hsa_circ_0072309	Downregulated	p53	Enhance autophagy and temozolomide sensitivity in glioblastoma	[38]
circ-SHPRH	Downregulated	Encode SHPRH-146aa	SHPRH-146aa suppresses glioma tumorigenesis	[39]

Table 2 Sevoflurane inhibit the tumorigenesis and development of glioma by regulating circRNA

circRNA	Expression in glioma	Target gene/pathway of sevoflurane	Reference
circ_0012129	Upregulated	circ_0012129/miR-761/TGIF2	[40]
circ_0000215	Upregulated	circ_0000215/miR-1200/NCR3LG1	[41]
circ_0079593	Upregulated	circ_0079593/miR-633/ROCK1	[42]
circ_0002755	Upregulated	circ_0002755/miR-628-5p/MAGT1	[43]
circ-RELN	Downregulated	circ-RELN/miR-1290/RORA	[44]

Table 3　Expression and function of circRNA in pituitary adenoma(PA)

circRNA	Expression in PA	Target gene/pathway	Function	Refenence
circNFIX (hsa_circ_0005660)	Upregulated	miR-34a-5p/ CCNB1	Promote cell invasion, migration and proliferation in PA	[46]
hsa_circ_0000066, hsa_circ_0069707		Modulate the response of transport vesicles and cells to unfolded proteins	Predict tumor recurrence in non-functioning pituitary adenoma(NFPA)	[47]
circOMA1 (hsa_circRNA_0002316)	Upregulated	mir-145-5p/ TPT1	Promote cell invasion, migration and proliferation in NFPA	[48]
hsa_circ_0001368	Upregulated	Correlate with pituitary-specific transcription factor Pit-1	Promote the proliferation, invasion and growth hormone secreting level of growth hormone-secreting pituitary adenoma	[49]
hsa_circ_102597	Downregulated		Predict tumor progression and recurrence in NFPA	[50]

生发展。Lee 等[54]通过研究MB 患者脑脊液中 RNA 表达的差异，发现 circ_463 是脑脊液中表达最丰富的 circRNA，提示 circ_463 可能与 MB 的发生发展有关。

3　总结与展望

随着分子生物学和检测技术的快速发展，circRNA 现已成为分子生物学领域的研究热点。近年来对 circRNA 的研究不断深入，其在恶性肿瘤发生发展中的作用机制也越发明确。circRNA 可以充当 miRNA 海绵，并通过调节多种与肿瘤相关基因的转录，蛋白质的翻译和选择性剪接来参与肿瘤的发生进展，与细胞增殖、凋亡、血管生成、转移和耐药等方面有着密不可分的联系，circRNA 具有成为肿瘤生物标志物的潜力。本文综述了 circRNA 在胶质瘤、垂体瘤和髓母细胞瘤中的表达情况及其靶向 miRNA 和后续信号通路，并概述了其作用结果，总结出以胶质瘤为主的多种脑肿瘤的潜在生物标志物。但如何从中筛选出特异度更高，灵敏度更高，诊断、预后预测效果更好，并可作为治疗靶点的生物标志物；circRNA 之间及后续靶向信号通路之间是否存在协同作用或抵抗作用，他们之间是如何互相影响；干预 circRNA 及后续信号通路表达情况是否影响疾病转归等问题需要进一步的大样本、多中心研究。circRNA 在脑肿瘤的发生发展中具有重要作用，在众多的 circRNA 中找到发挥关键作用的分子任重而道远，对 circRNA 不同作用模式的深入研究，有助于更精准地实现对脑肿瘤的诊断治疗及预后评估。

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