张弩副教授团队在Molecular Cancer杂志发表恶性胶质瘤研究成果

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日前，我院神经外科张弩副教授团队的研究论文“A Novel Tumor Suppressor Protein Encoded by Circular AKT3 RNA Inhibits Glioblastoma Tumorigenicity by Competing with Active Phosphoinositide-Dependent Kinase-1”在Molecular Cancer在线发表，我院为第一作者单位和唯一通讯作者单位，第一作者为我院2017级博士生夏昕，李西西和李凡滢，唯一通讯作者为神经外科张弩副教授。

该研究通过对临床样本进行测序结合生物信息学分析，发现可能具有翻译蛋白质潜能的环状RNA。在这些候选环状RNA中，研究团队发现AKT3基因的第 3-7号外显子环化后可形成524nt的环状RNA，课题组将其命名为circ-AKT3。课题组通过对circ-AKT3进行预测分析，发现该环状RNA序列中包含一个进化上高度保守的开放阅读框。通过针对特定序列的抗体检测和质谱分析，张弩课题组证实环状RNA circ-AKT3通过内部核糖体插入位点序列IRES驱动翻译一个由174个氨基酸组成的全新蛋白质，并将其命名为AKT3-174aa。临床研究结果显示，AKT3-174aa蛋白在肿瘤中表达显著下调，且有别于全长AKT3蛋白，AKT3-174aa表达与高级别胶质瘤患者的预后存在显著相关性，提示circ-AKT3具有独立于其母基因发挥抑癌基因功能的可能性。机制研究发现AKT3-174aa通过竞争性结合磷酸肌醇依赖性蛋白激酶-1(p-PDK1)，负性调控下游PI3K/AKT信号通路，进而抑制恶性胶质瘤的发生和发展。该研究为恶性胶质瘤的诊疗手段提供了新思路。

此项研究得到国家重点研发计划青年科学家项目“环状RNA翻译蛋白质的调控过程与生物学功能”、国家自然科学基金优秀青年基金、国家自然科学基金面上项目以及广东省自然科学杰出青年基金等项目的资助。唯一通讯作者张弩副教授主攻方向为中枢神经系统肿瘤，获得广东省特支计划青年拔尖人才、广东省高等学校优秀青年教师以及我院“三个三”工程的支持。（神经外科）

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A novel tumor suppressor protein encoded by circular AKT3 RNA inhibits glioblastoma tumorigenicity by competing with active phosphoinositide-dependent Kinase-1

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Abstract

Background: The RTK/PI3K/AKT pathway plays key roles in the development and progression of many cancers, including GBM. As a regulatory molecule and a potential drug target, the oncogenic role of AKT has been substantially studied. Three isoforms of AKT have been identified, including AKT1, AKT2 and AKT3, but their individual functions in GBM remain controversial. Moreover, it is not known if there are more *AKT* alternative splicing variants.

Methods: High-throughput RNA sequencing and quantitative reverse transcription-PCR were used to identify the differentially expressed circRNAs in GBM samples and in paired normal tissues. High throughput RNA sequencing was used to identify circ-AKT3 regulated signaling pathways. Mass spectrometry, western blotting and immunofluorescence staining analyses were used to validate AKT3-174aa expression. The tumor suppressive role of AKT3-174aa was validated in vitro and in vivo. The competing interaction between AKT3-174aa and p-PDK1 was investigated by mass spectrometry and immunoprecipitation analyses.

Results: Circ-AKT3 is a previously uncharacterized *AKT* transcript variant. Circ-AKT3 is expressed at low levels in GBM tissues compared with the expression in paired adjacent normal brain tissues. Circ-AKT3 encodes a 174 amino acid (aa) novel protein, which we named AKT3-174aa, by utilizing overlapping start-stop codons. AKT3-174aa overexpression decreased the cell proliferation, radiation resistance and in vivo tumorigenicity of GBM cells, while the knockdown of circ-AKT3 enhanced the malignant phenotypes of astrocytoma cells. AKT3-174aa competitively interacts with phosphorylated PDK1, reduces AKT-thr308 phosphorylation, and plays a negative regulatory role in modulating the PI3K/AKT signal intensity.

Conclusions: Our data indicate that the impaired circRNA expression of the *AKT3* gene contributes to GBM tumorigenesis, and our data corroborate the hypothesis that restoring AKT3-174aa while inhibiting activated AKT may provide more benefits for certain GBM patients.

Keywords: circRNA, AKT3, PDK1, Glioblastoma

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