

# PI3K/Akt/mTOR信号通路与肿瘤微环境在胶质瘤研究中的进展

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## 摘要

胶质母细胞瘤(Glioblastoma, GBM)是一种在成人中枢神经系统(Central Nervous System, CNS)常见的, 具有侵袭性的原发性脑癌。GBM的发生和发展与磷脂酰肌醇3-激酶/蛋白激酶B/雷帕霉素靶蛋白(PI3K/Akt/mTOR)信号通路的持续异常激活有密切联系。该信号通路被异常激活, 能够促进肿瘤细胞增殖。这条通路也被认为影响了肿瘤微环境(Tumor Microenvironment, TME)的免疫抑制, 比如PD-L1和IDO的表达增加, TGF- $\beta$ 和IL-10等免疫抑制因子的分泌量升高, 使得肿瘤细胞更容易逃避免疫系统的清除。PI3K/Akt/mTOR通路还会影响肿瘤相关巨噬细胞(Tumor-Associated Macrophages, TAMs)的极化, 刺激VEGF等血管生成因子的释放, 加快TME的恶化。本文主要介绍PI3K/Akt/mTOR信号通路与TME的相互作用以及基于两者的胶质瘤治疗方法, 希望为未来胶质瘤患者的治疗提供新思路。

## 关键词

胶质瘤, PI3K/Akt/mTOR, TME, 治疗策略, 免疫反应

# Advances in the PI3K/Akt/mTOR Signaling Pathway and Tumor Microenvironment in Glioma Research

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## Abstract

**Glioblastoma (GBM) is an aggressive primary brain cancer that is common in the central nervous system (CNS) in adults. The occurrence and progression of GBM is closely related to the persistent aberrant activation of phosphatidylinositol 3-kinase/protein kinase B/rapamycin target protein (PI3K/Akt/mTOR) signaling pathway. This signaling pathway is aberrantly activated to promote tumor cell proliferation. This pathway is also thought to affect the immunosuppression of the tumor microenvironment (TME), such as increased expression of PD-L1 and IDO, and increased secretion of immunosuppressive factors such as TGF- $\beta$  and IL-10, making it easier for tumor cells to evade clearance by the immune system. The PI3K/Akt/mTOR pathway also affects the polarization of tumor-associated macrophages (TAMs), stimulates the release of angiogenic factors such as VEGF, and accelerates the deterioration of TME. This article mainly introduces the interaction between PI3K/Akt/mTOR signaling pathway and TME and the treatment of glioma based on both, hoping to provide new ideas for the treatment of glioma patients in the future.**

## Keywords

**Glioma, PI3K/Akt/mTOR, TME, Therapeutic Strategies, Immune Response**

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## 1. 引言

神经胶质瘤属于 CNS 里发病率相对较高的一类肿瘤, 其中 GBM 的恶性程度高、侵袭性强、复发性高, 大多时候会出现耐药情况, 是临床治疗极具挑战性的亚型[1]。当下尽管存在不少针对新发与复发胶质母细胞瘤的治疗手段, 然而并未取得理想的临床成效, 仍有约 90% 的患者会出现复发[2]。PI3K/Akt/mTOR 信号通路在调控癌症患者细胞的迁移、增殖、存活以及代谢等生物学过程中起着关键作用[3], 未来若能更精确地调控这一通路, 或许会为 GBM 的治疗带来新的突破方向。研究说明, PI3K/AKT/mTOR 抑制剂对激素受体阳性(HR+)晚期乳腺癌有效果, 并且针对 PI3K/AKT/mTOR 抑制剂治疗 HR+晚期乳腺癌患者的诸多临床试验也已开展[4]。肿瘤微环境在癌症的发生和发展进程中同样发挥着关键作用, TME 与肿瘤细胞之间持续进行着动态的相互作用, 此过程影响了肿瘤细胞的生物学特性, 像生长、存活、侵袭转移能力以及对治疗的耐受性[5]-[7]。近年来的大量研究说明, PI3K/AKT/mTOR 信号通路与 TME 之间存在着复杂的调控与交互机制。PI3K/Akt/mTOR 通路可在 TME 背景下感知并整合来自各种环境信号的输入, 以调节免疫细胞的运输、极化及其功能特性, 从而促进肿瘤进展和转移[8], 靶向 PI3K/Akt/mTOR 通路及其与 TME 的相互作用, 有望成为一种有效的肿瘤治疗策略。

## 2. PI3K/AKT/mTOR 信号通路与肿瘤

PI3K 由调节性亚基 p85 以及催化性亚基 p110 共同构成异源二聚体, 它的活化过程一般依赖于细胞膜表面受体传递来的激活信号[9], 当生长因子和其膜受体相结合后, 受体胞内区域的酪氨酸残基会出现自磷酸化反应, 接着 p85 调节亚基凭借其 SH2 结构域特异性识别并结合到这些磷酸化位点, 如此一来

p110 催化亚基就能作用于底物磷脂酰肌醇-4,5-二磷酸(PIP<sub>2</sub>),把它转化成脂质信号分子 PIP<sub>3</sub>。生成的 PIP<sub>3</sub> 借助和 AKT 蛋白 N 端的 PH 结构域相结合,将 AKT 招募到细胞膜。AKT 作为一种丝氨酸/苏氨酸蛋白激酶[10],其功能激活依靠两步磷酸化:3-磷酸肌醇依赖性激酶 1 也就是 PDK1 磷酸化 AKT 的 Thr308 位点,随后 mTORC2 磷酸化 Ser473 位点,形成有完全活性的 AKT 激酶[11]。活化的 PI3K-AKT 信号级联借助调控下游效应分子,促进合成代谢并且抑制分解代谢相关通路,最终协调细胞增殖、存活以及能量稳态等[12]。

PTEN 作为 PI3K-AKT 通路的关键负向调控因子,Chen 等人研究发现,CKS2 依靠抑制 PTEN 表达,解除它对 PI3K-AKT 信号通路的抑制作用,这个过程使 AKT 的磷酸化水平上升,影响小儿视网膜母细胞瘤的恶性发展过程[13]。Wang 等人的研究说明,环状 RNA PVT1 可与 miR-152-3p 发生竞争性结合,减弱 miR-152-3p 对 PI3K-AKT 信号通路的抑制效果,这一机制促进了 AKT 的磷酸化及其下游促细胞存活信号的激活,最终致使胃癌细胞对顺铂化疗药物产生耐药性[14]。Chen 等人的研究说明,在肺腺癌也就是 LUAD 中,长链非编码 RNA CCAT1 可直接与脂肪酸结合蛋白 FABP5 相互作用,提高 PI3K/AKT/mTOR 信号通路的活性。这一分子机制促进了肿瘤细胞的异常增殖、提高其侵袭能力,还诱发对化疗药物的耐受性[15]。上述过程可能还涉及了免疫细胞、成纤维细胞以及细胞外基质(ECM)等成分。在 TME 中,这些成分之间通过复杂的信号网络相互作用,共同影响着肿瘤的生长、侵袭、转移和治疗。

### 3. 肿瘤微环境

TME 是由肿瘤细胞、免疫细胞、肿瘤相关成纤维细胞(CAFs)、内皮细胞以及 ECM 等多组分构成的异质性网络,其中细胞因子、趋化因子与基质成分借助复杂的相互作用网络,共同调控肿瘤的生长、侵袭以及转移进程,并且在疾病进展中发挥关键作用[16][17]。比如 ECM 机械特性的改变,像弹性、刚度和生物物理特性等变化,可以改变癌细胞的特性[18],CAF 依靠释放促炎性细胞因子以及调控 ECM 的重构过程,较大提高肿瘤细胞的迁移潜能并激活免疫逃逸相关机制,这一双向作用对肿瘤恶性进展起到关键驱动作用[19],TAMs 可以凭借分泌促血管生成因子和抑制免疫反应来支持肿瘤进展[20]。这些促血管生成因子能够诱导新血管的形成,当肿瘤生长到 1~2 mm<sup>3</sup> 的体积时,肿瘤组织中逐渐形成缺氧、缺血、酸中毒、高间质压的微环境,释放丰富的生长因子和细胞因子,刺激肿瘤血管生成,满足肿瘤生长和代谢的需要[21]。但在肿瘤组织中,由于细胞快速增殖和血管生成不足导致缺氧区域形成,促使癌细胞通过激活 HIF-1 $\alpha$  信号通路来适应环境变化[22]。HIF-1 $\alpha$  在 TME 中的影响广泛,不仅限于肿瘤细胞本身,对免疫细胞和基质成分也有很大作用。比如, HIF-1 $\alpha$  能够调控巨噬细胞的趋化作用和表型转化,诱导其分化为 M2 型巨噬细胞,这一类型通常表现出免疫抑制的特性,反而促进了肿瘤的进展[22]。值得关注的是, HIF-1 $\alpha$  能够削弱细胞毒性 T 淋巴细胞(CTL)的功能,进一步营造免疫抑制性微环境,最终导致肿瘤免疫逃逸现象的发生[23]。事实上, TME 免疫抑制的成因复杂,不仅是因为免疫抑制性细胞增多,还与代谢竞争有很大关系。肿瘤细胞疯狂消耗葡萄糖、脂质和氨基酸,使得周围环境里的营养物质匮乏,免疫细胞不得不进行代谢重编程,这就让其抗肿瘤效果变差[24]。这种代谢重编程的过程通常涉及到 PI3K/AKT/mTOR 信号通路的异常激活,它不仅调控着肿瘤细胞的代谢过程,还影响着免疫细胞的功能状态,进一步参与调控 TME 的免疫抑制状态和肿瘤的进展[25]。

### 4. PI3K/AKT/mTOR 通路激活对胶质瘤 TME 的调控

PI3K/Akt/mTOR 通路在 GBM 的恶性进展中起着重要作用[26]。该通路激活后,通过调控多个下游靶点,介导广泛的促癌效应,导致细胞存活能力增强、增殖速度加快、蛋白质合成持续激活,肿瘤细胞的迁移能力增加[27]。研究表明,GBM 中 PI3K/Akt/mTOR 通路异常的主要原因,通常是上游信号节点的遗

传变异,比如 PTEN 的缺失、EGFR 扩增或者突变等,这些分子层面的变化已被认为是 GBM 的核心分子特征[27] [28]。PTEN 基因缺失通过激活 PI3K-AKT 信号轴,驱动 GBM 免疫抑制性微环境的形成[29]。此外,PI3K/Akt/mTOR 通路可以直接影响 PTEN 缺乏 GBM 的 TME。PTEN 基因作为重要的抑癌因子,其编码产物通过磷酸酶活性催化 PIP3 去磷酸化,维持细胞内 PIP3 稳态以拮抗 PI3K/Akt 信号传导。当 PTEN 发生功能缺失性突变时,PIP3 异常蓄积将导致 Akt 持续磷酸化,进而通过解除 TSC 复合体对 Rheb 蛋白的抑制,激活 mTORC1 信号轴,最终驱动肿瘤细胞的增殖活化和凋亡逃逸[30]。

在 GBM 的低氧微环境里,HIF-1 $\alpha$  的稳定性明显提高,凭借核转位激活自身转录功能,形成与 PI3K/Akt/mTOR 信号通路的双向调控网络,一方面,低氧诱导产生的 HIF-1 $\alpha$ ,依靠结合 GLUT1、HK2 和 LDHA 等糖酵解基因的启动子区域,驱动 Warburg 效应维持能量代谢,借助产生大量乳酸来调节 TME[31]。另一方面,激活的 PI3K/AKT 信号会使 HIF-1 $\alpha$  的转录和翻译上调,延长其半衰期并提高转录活性[32],形成正反馈调节环路。这种协同作用促使 HIF-1 $\alpha$  与 mTORC1 共同上调 VEGF 及其受体的表达,刺激内皮细胞异常增殖以及血管通透性增加[33],最终致使 GBM 标志性的血管过度增生表型出现[34]。高浓度的 VEGF 也可以增加血管通透性,导致血管渗漏、血流缓慢和间质压力升高。这些复杂的调控机制使得 GBM 的治疗面临巨大挑战,同时也为靶向治疗提供了潜在的切入点,有助于开发更精准有效的治疗策略,抑制肿瘤的恶性进展,从而改善 GBM 患者的预后。

## 5. 基于 PI3K/AKT/mTOR 与 TME 的胶质瘤治疗策略

TME 帮助癌细胞躲避宿主免疫,引发肿瘤发生、进展以及转移[35],在此进程中,PI3K/AKT/mTOR 通路大多时候被癌症过度激活[36],靶向 TME 和 PI3K/AKT/mTOR 通路是颇具前景的肿瘤治疗策略。已有研究说明,GBM 来源的细胞外囊泡(EVs)被证实有促进肿瘤细胞及髓源性神经干细胞(mNPC)增殖与迁移的生物学效应[37]。这一现象暗示 GBM-EVs 可能借助调控 mNPC 的表型重编程,重塑 TME 的细胞组成以及功能特征。PI3K 抑制剂 Wortmannin 可较大抑制 EVs 诱导的 mNPCs 增殖迁移提高表型,证实该通路在 EVs 介导的 TME 调控中有关键作用[36]。Cui 等人发现阿托伐他汀(AVT)可借助下调趋化因子受体 4 的表达,抑制人脑胶质瘤细胞增殖、侵袭和迁移,促进细胞凋亡,其机制与调控 miR-146a/PI3K/Akt 信号通路相关[38]。但上述药物仍处于实验室研究阶段,未获批准用于人体临床治疗,目前临床上针对 PI3K/AKT/mTOR 信号通路异常激活的癌症患者,已有多种靶向抑制剂获批上市,主要覆盖以下两类:mTOR 抑制剂,包括 everolimus、sirolimus、temsirolimus,PI3K 抑制剂,有 Alpelisib、Duvelisib、Copanlisib、Idelalisib、Umbralisib [34]。AKT 抑制剂的 III 期临床试验已在癌症中开展[39] [40]。然而药物耐药性问题仍是其临床应用面临的一大挑战,随着癌症患者数量持续上升,开发更高效的靶向药物变得极为迫切。

## 6. PI3K/AKT/mTOR 与免疫检查点抑制剂联用治疗策略

针对 PI3K-AKT 抑制剂与免疫检查点抑制剂联用治疗所开展的研究发现,整合素  $\alpha 5$  (ITGA5)可依靠重塑 TAMs 的免疫表型,提升抗 PD-1 免疫检查点抑制剂对 GBM 的治疗效果[41],ITGA5 抑制剂与 PD-1 阻断剂的协同作用或许会成为克服免疫治疗耐药性的有效策略。

然而,免疫疗法在 GBM 的治疗里应用依然面临着诸多挑战,GBM 的 TME 有高度异质性以及动态性,主要覆盖免疫细胞、肿瘤细胞、ECM 以及各种可溶性分子[42]。其中 TAMs 和 MDSCs 是 GBM 微环境中的主要免疫抑制细胞,它们依靠分泌免疫抑制因子比如转化生长因子- $\beta$ 、白细胞介素-10 等,抑制 T 细胞的活性[43] [44]。GBM 的 TME 还有肿瘤突变负荷以及 T 细胞浸润不足的特性,导致免疫检查点抑制剂在 GBM 治疗中的效果不尽如人意[45]。

近些年研究者们一直在努力探寻突破 GBM 治疗瓶颈的办法,PI3K/Akt/mTOR 信号通路的抑制剂在临

床前研究中呈现出一定的抗肿瘤效果, 不过其在临床应用里耐药性较强, 药物很难完全穿透血脑屏障[3]。近期免疫治疗的联合应用取得了关键进步, 新辅助三联免疫治疗(PD-1 抑制剂 + CTLA-4 抑制剂 + LAG-3 抑制剂)在动物实验以及临床案例中显示出较为较大的疗效, 可明显提高肿瘤浸润淋巴细胞的数量以及活性, 改变 TME 的免疫状态, 提高抗肿瘤免疫反应[45]。目前多项临床试验也在研究 PI3K/AKT/mTOR 抑制剂与免疫检查点抑制剂的联合应用。一项 II 期试验(NCT03961698)正在研究 eganelisib (PI3K- $\gamma$  抑制剂)与 atezolizumab (PD-L1 抑制剂)和白蛋白结合型紫杉醇联合用于局部晚期或转移性 TNBC 患者的一线治疗。最新结果显示, 这种联合治疗在 TNBC 患者中具有可管理的毒性, 无论 PD-L1 表达状态如何, 客观缓解率(ORR)均达到 55.3%, 显示出良好的安全性[46]。另外脂质的纳米载体的应用也为 GBM 患者的治疗提供了新的思路。脂质体作为药物递送系统, 可提高药物的溶解度, 降低药物的毒性以及非特异性不良反应, 还可以避免药物在储存和给药过程中被提前降解[47]。未来的研究仍需继续探索具体的联合方案和临床试验数据, 以优化治疗策略, 提高治疗效果。

## 7. 研究现状与展望

GBM 是 CNS 中发病率最高的恶性肿瘤之一, 治疗上一直是神经肿瘤学领域的重大挑战[1]。目前常采用手术、放疗和化疗等常规治疗方法, 但患者的总体生存率差[47]。最近几年关于 GBM 的 TME, 以及 PI3K/Akt/mTOR 信号通路研究得越来越多, 人们对 GBM 的发病机制、肿瘤进展甚至耐药这些问题都逐渐有了更深的理解。

在 GBM 中, PI3K/Akt/mTOR 信号通路大多时候呈现出持续性的异常活化状态, 借助磷酸化级联反应对下游效应分子加以调控, 驱动肿瘤细胞出现异常增殖、迁移侵袭以及促血管生成等一系列恶性表型[33][48][49]。该通路还会与 TME 里的多种细胞和分子相互产生作用, 共同促使 GBM 的恶性进展[32]。PI3K/Akt/mTOR 信号通路的异常活化是凭借诱导肿瘤细胞分泌多种细胞因子以及趋化因子, 募集骨髓来源的抑制性细胞(MDSCs)和调节性 T 细胞(Tregs)等免疫抑制细胞向 TME 迁移, 构建起免疫抑制性微环境, 对免疫细胞的抗肿瘤活性造成明显抑制[50]。在治疗 GBM 的进程中, 将 PI3K/Akt/mTOR 通路抑制与 TME 重编程策略联合起来, 有望突破 GBM 传统治疗存在的局限性, 为个体化精准治疗提供全新方向。

PI3K/Akt/mTOR 通路与 TME 在 GBM 的发生、发展以及治疗方面发挥着关键作用, 但目前关于两者在 GBM 中的研究相对较少, 未来的研究应当深入剖析这两者之间的关联, 找到更多有效的靶点药物以及免疫治疗切入点, 改善 GBM 患者的总体生存率。

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