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M2 型巨噬细胞在胶质母细胞瘤中代谢机制和临床管理

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摘要：胶质母细胞瘤是一种棘手的神经系统恶性肿瘤，由于其较高的侵袭性、异质性、代谢率，患者中位生存期通常只有 12~15 个月。[2]在胶质瘤中，肿瘤相关巨噬细胞甚至占到 30%~50%,先前研究表明，巨噬细胞极化为 M1 表型巨噬细胞 （经典激活巨噬细胞）和 M2 表型巨噬细胞 （替代激活巨噬细胞）。后者多具有促进肿瘤生长的作用。通过加入细胞因子改变肿瘤微环境，促进 M2 型肿瘤相关巨噬细胞向 M1 型巨噬细胞转化是当前治疗的一种策略。近年研究发现肿瘤细胞和微环境通过调控基因信号通路参与巨噬细胞向 M2 型极化的过程。处于不同的微环境下巨噬细胞的行为和物质代谢得以揭示，临床试验也取得许多进展，运用纳米技术作为药物载体来进入到传统手术无法切除的游离肿瘤细胞,基因编辑肿瘤细胞，采用光动力疗法传递药物，靶向治疗的基础上采用多种方法联合治疗，从而延长患者生存期。文章综述了 M2 巨噬细胞在胶质瘤中的代谢机制，并分析相关临床研究，为今后基础研究和临床治疗提供方向。

关键词： 极化;增殖;信号

引言：神经胶质瘤是常见的脑肿瘤，胶质母细胞瘤(GBM）是被世界卫生组织 WHO 定义为 IV 级胶质瘤，具有高度恶性，治疗较为困难，预后较差[1]。巨噬细胞在免疫系统应答中承担重要工作，也是构成肿瘤微环境 (TME）的重要组成部分。然而肿瘤相关巨噬细胞 （TAM）却在肿瘤的演进过程中起着积极作用，在缺氧条件下，M2 巨噬细胞分泌生长因子诱导蛋白(TGFBI）来维持胶质瘤干细胞（GSC）的自我更新[2]。有趣的是，同样在缺氧条件下，胶质瘤细胞衍生的外体中 MiR-25-3P/MiR-6733-5P 基因高表达，转移到巨噬细胞中激活了 PIP3/IGF2BP3-AKT 信号通路诱导巨噬细胞向 M2 表型极化[3, 4]。作为正反馈环的一部分会加速胶质瘤细胞朝着恶性方向演变 (图 1）。

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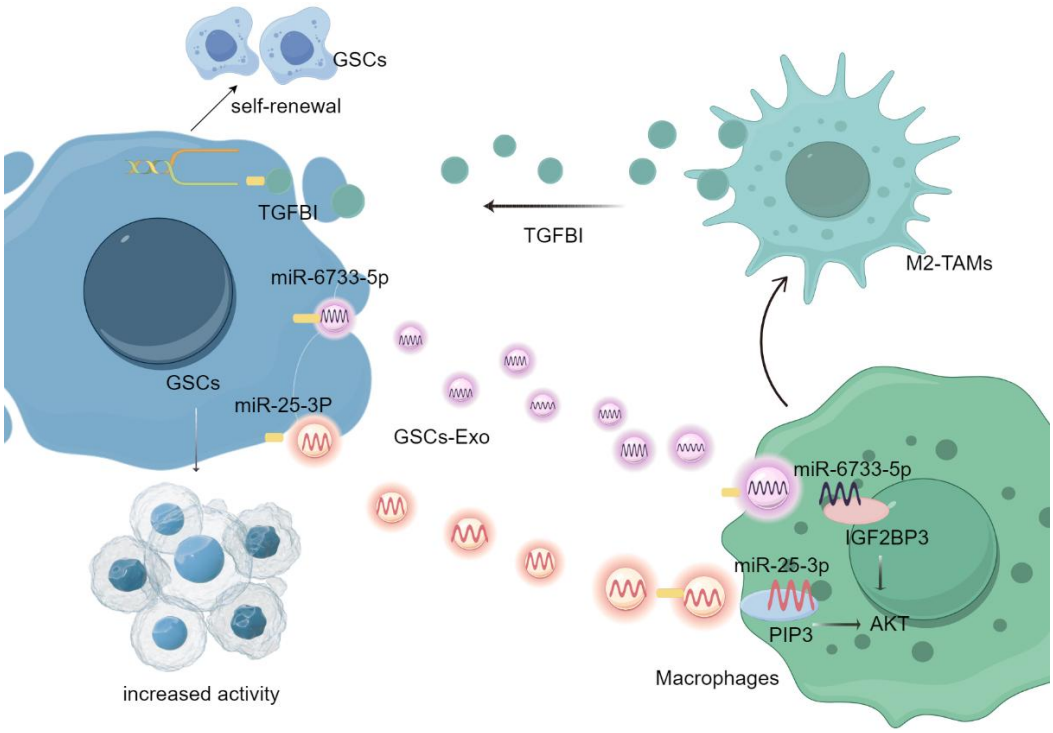

图 1 缺氧下巨噬细胞极化与胶质瘤干细胞的正反馈环

研究已经表明，缺氧本身作为信号促进胶质瘤的增殖和转移，HIF-1α缺氧诱导因子扮演关键作用[2, 5, 6]。更进一步的研究发现，在低氧的肿瘤微环境（TME）中，tph-1 衍生的静息巨噬细胞 M0 依赖 HIF-1α的调节诱导向 M2 型巨噬细胞极化，M2 巨噬细胞分泌含有环状 RNACICR000317 的囊泡（EVS），进入胶质瘤中的调节 PTBP1/PLOD3 促进胶质瘤的上皮间充质转化(EMT)，肿瘤细胞的紧密型和粘附性下降，从而促进肿瘤转移[7]。缺氧信号显示胶质瘤细胞中的 LNCRNA 的调控也能引起肿瘤相关巨噬细胞（TAM）的渗透和 M2 极化，其中的长非编码 RNA （TP73-AS1）具有代表性[8]。最新的研究发现肿瘤缺氧区富含一些含有特定 mRNA 亚型的肿瘤相关巨噬细胞（TAM）和多倍体巨癌细胞[9, 10]。同时乳酸转运蛋白（SLC16A1/A3）也作为中介参与缺氧调节的炎症反应和肿瘤转移[11]。目前，胶质瘤的治疗仍以手术为主，并联合替莫唑胺(TMZ）进行放化疗。研究人员在常规治疗基础上探索多种方法来提高疗效。Yang 等人采用注射粒细胞集落刺激因子(GM-CSF）联合替莫唑胺(TMZ)化疗，和对照组相比，粒细胞集落刺激因子（GM-CSF）能明显提高术后生存率，与化疗有关血小板和中性粒细胞的减少[12]。此外研究人员开展了病毒对胶质母细胞瘤(GBM)的临床试验[13-19]。Batich 等人发现用树突细胞(DC)联合巨细胞病毒，和剂量增强的替莫唑胺(TMZ）以及粒细胞集落刺激因子（GM-CSF）联合治疗能显著延长患者生存期，治疗的新发胶质母细胞瘤(GBM）患者中位无进展生存期（PFS）和整体生存期(OS）分别延长至 25.3 个月和 41.1 个月。研究证实巨细胞病毒对胶质瘤的治疗起到较好的疗效[14]。为了确定更为有效的治疗方案，我们不仅要了解在缺氧环境下 M2 巨噬细胞的代谢机制，更要找到肿瘤相关巨噬细胞（TAM）在不同的肿瘤微环境(TME）的作用机制和代谢通路，找到共同的信号传递路径，研究表面抗原、细胞因子和肿瘤耐药性，结合当下临床研究，为如何干预肿瘤的进展提供更好方案。

二、胶质母细胞瘤 （GBM）中的 PI3K-AKT 信号通路

PI3K-AKT 信号通路参与多种生理过程，尤其是肿瘤发展的重要信号途径，能调控细胞存活、转移和新陈代谢，在血管生成和炎症因子募集中发挥作用。上文中 XUE 的研究显示了巨噬细胞中 PI3K-AKT 信号的激活促进向 M2 表型极化[3]。在胶质瘤的肿瘤微环境(TME) 中既包括组织驻留小胶质细胞，也包括骨髓

来源的巨噬细胞，Qiu 等人利用纳米技术平台沉默骨髓来源巨噬细胞 TRME-2 基因发现，巨噬细胞等通过该基因表达实现胶质母细胞瘤 （GBM）的放射抗性和免疫逃脱，并且该基因通过调节 （HMGB1）形成正反馈回路，级联激活 TOLL 样受体 4 （TLR4）从而激活 PIP3-AKT 通路，抑制该基因可促进 M1 经典抗炎巨噬细胞增多[20]。其他研究也发现一些基因通过 AKT 通路促进巨噬细胞 M2 表型的极化[21-23]。

在临床治疗中，胶质瘤会产生对替莫唑胺（TMZ）的耐药性，WEI 等人发现巨噬细胞迁移抑制因子（MIF）其中起到作用，在替莫唑胺治疗（TMZ）的胶质瘤中，巨噬细胞迁移抑制因子（MIF）在抗替莫唑胺（TMZ）的肿瘤细胞被提升，从而转移了药物敏感肿瘤细胞的抵抗。研究发现这一过程依赖 TIP3 下调和 PI3K-AKT 的激活[24]。因此 W 等人发明一种靶向抑制巨噬细胞迁移抑制因子的药物--伊布地利斯特 （IBIDIILST），和替莫唑胺（TMZ）联合作用于患者肿瘤细胞衍生物，实验发现肿瘤细胞周期停止并凋亡，这无疑为胶质瘤的临床治疗又打开了一扇窗[25]。在耐药性的研究中，Ji 等人发现白介素 18 （IL-18）在胶质瘤中被提高，白介素 18 （IL-18）通过 PIP3-AKT 通路激活使得胶质母细胞瘤具有耐药性[26]。

目前关于 AKT 抑制剂来阻断肿瘤进展设计药物有许多，但是受限于靶点较多毒副作用。有关 AKT 在胶质母细胞瘤的表型演化过程仍不清晰，但是设计 AKT 抑制剂与胶质瘤细胞的基础实验，这条通路相关与之联系机制的作用靶点，阻滞上游激活因子或许能给治疗胶质瘤带来新的路径。

三、巨细细胞免疫表型与胶质母细胞瘤（GBM）结局

现有研究表明不同的白细胞分化抗原的巨噬细胞都会对胶质瘤患者的预后产生直接或间接的影响[26-40]。其中 CD68 和 CD163 通常被分别看作肿瘤相关巨噬细胞 M1 型和 M2 型特殊的免疫标志[31]。 通过对肿瘤相关巨噬细胞（TAM）免疫表型的分析， WU 等人发现 CD163 的表达通常和 M2 型巨噬细胞介导的免疫抑制有关，其抗原的高表达还与分泌白细胞介素 IL-6、IL-10 有关[29]。Annovazzi 等人也发现当 CD163 在巨噬细胞中高表达时意味着胶质瘤的生存率下降[39]。有趣的是，Kemmerer 等人发现在高级别胶质瘤(HGG）患者中 CD68 巨噬细胞中高表达，相关巨噬细胞在血管周围显著丰富，然而 CD68 通常被看作是 M1 型巨噬细胞特征[34]。显然，如果仅仅依靠 CD68 和 CD163 作为独立的免疫标志来判断肿瘤的预后是不完美的。这就必须依靠其他的抗原标记来更好评估肿瘤相关巨噬细胞 （TAM）的极化程度。在高级别胶质瘤 （HGG）中，XU 等人发现 CD74 高度表达在免疫细胞中，例如巨噬细胞、树突状细胞和中性粒细胞。CD74 表达越高其胶质瘤患者存活率越低，因此 CD74 对高级别胶质瘤的预后判断具有重要价值[35]。Sorensen 等人利用纳米技术对胶质母细胞瘤（GBM）细胞骨髓转录体分析发现 CD204 表达的巨噬细胞多聚集于血管周围，与肿瘤的侵袭有关，也可以作为患者预后不良的一个独立的免疫标志[33]。Xiao 等人发现 CD44 存在于恶性胶质瘤的 M2 型巨噬细胞中，通过基因组学分析，其高表达不仅与肿瘤的免疫抑制有关，还与肿瘤的程序死亡性受体与配体 PD- 1 和 PDL-1 蛋白有关，这种结果扩大了胶质瘤的免疫学特征[36]。为了更深层次研究这种受体，Xing 等人利用单细胞 RNA 测序技术发现表达 SPP1 蛋白的肿瘤相关巨噬细胞（TAM-SPP1+）与表达 CD44 受体的 T 细胞结合，这一效应可能与巨噬细胞由 M1 型极化为 M2 型有关。除此以外，Peres 等人利用神经网络分析 CD86 在肿瘤相关巨噬细胞中的高表达也是胶质瘤患者预后不良的标志之一[27]。

TIME	Immune phenotype	Author	References
2024	CD86	peres N	[27]
2024	CD47	Du R	[28]
2024	CD163	Wu M	[29]
2024	CD44	Xing J	[30]
2024	CD274	Ji H	[26]
2022	CD204	Sorensen MD	[33]
2022	CD276	Zhang H	[32]
2021	CD68	Kemmerer CL	[34]
2021	CD74	Xu S	[35]
2021	CD44	Xiao Y	[36]
2019	CD47	Giholamin S	[37]
2018	CD8	Malo CS	[38]
2018	CD45 CD98	Annovazzi	[39]
2017	CD206	Achyut BR	[40]

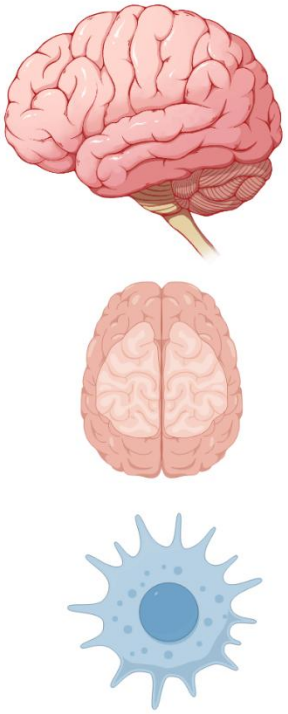

图 2 胶质瘤及相关免疫细胞表型发现及研究时间

一系列新型胶质瘤免疫细胞抗原受体被发现，其作用的深层机制值得进一步探究，结合新兴的嵌合抗原受体 T 细胞免疫疗法（CAR-T）可能为胶质瘤患者带来益处。

四、基因层面分析神经胶质瘤的生长增殖和存活

肿瘤基因功能的作用机制研究是胶质瘤科研者们研究的重点，一系列的基因可能控制着肿瘤细胞的增殖、凋亡和转移等。通过观察肿瘤在体内的生长情况，分析基因相关的分子机制、信号通路和蛋白表达情况，为肿瘤基因治疗提供潜在的治疗靶点是当前的一种研究思路。An 等人通过基因组图和细胞实验发现恶性胶质瘤患者中相关表达人唾液结合免疫球蛋白样凝集素 7（siglec-7）可以促进巨噬细胞向 M2 型极化[41]。同样与巨噬细胞 M2 极化相关的肿瘤细胞高表达基因还有 HH1、CLEC7A、ST3GAL4、PVT1、DHX9 基因等[42-45]。Xia 等人的研究发现神经钙蛋白 1 相关基因的表达可以促进 M2 巨噬细胞在胶质瘤中的浸润，并能促进胶质瘤细胞体外增殖和迁移的能力[46]。关于 M2 巨噬细胞在原发性胶质瘤和复发性胶质瘤中的表达情况，You 等人利用肿瘤细胞构建了单细胞图谱，发现复发性胶质瘤亚群的 M2 型肿瘤相关巨噬细胞明显增多。恶性胶质瘤复发与几种癌通路和细胞间相互作用相关基因的升高调节有关。此外,M2 样的肿瘤相关巨噬细胞（M2-TAMs） 可以激活恶性胶质瘤细胞的 PI3K/AKT/HIFF-1A/CA9 通路[47]。

除了胶质瘤中一些基因促进巨噬细胞 M2 极化外，某些基因可能是患者预后不良的独立标志，例如 FAM 基因、TP53l13 基因，与不良的生存结果有关[48, 49]。 Sajjadi 等人利用单细胞 RNA 测序技术分析不同部位的胶质瘤转移瘤，与原发部位的胶质瘤转移瘤进行肿瘤相关微环境对比，分析发现脑部原位转移瘤的 CD4 抗原受体表达相对上升，CD8 下降。这或是原发癌一项有潜力的鉴定标志物[50]。Ptp4A2 蛋白是一种蛋白酪氨酸磷酸酶，在刺激细胞从有丝分裂期间从 G1 期进入 S 期发挥着重要作用，调控下游信号分子如 AKT 和 MAPK 影响细胞增殖，通常作为肿瘤的启动子出现。Kim 等人的研究发现 MAPK/ERK 信号

与在复发性胶质母细胞瘤 （GBM）的抗 pd1 和抗 ctla-4 治疗后的整体存活率有关[51]。Chouleur 等人发现 Ptp4A2 蛋白相关基因的高表达在胶质瘤中可促进肿瘤增长，降低小鼠存活率[52]。Mistry 等人发现在复发性胶质母细胞瘤 （rGBM）中，肿瘤相关巨噬细胞脂肪代谢基因表达活跃[53],这或许和新研究发现巨噬细胞吞噬髓鞘中胆固醇合成脂质的关系值得去进一步探究[54]。为了研究不同基因组的胶质瘤细胞的预后结果，Zhang 等人建立基于神经胶质细胞相关的基因(ARG)的预后信号，发现相关的巨噬细胞也有所不同，高 ARG 与免疫细胞高度浸润有关，并且巨噬细胞亚群分别与其具有通路联系[55]。Pereira 等人研究发现胶质瘤中免疫细胞浸润程度往往与预后呈负相关[56]。

为了研究巨噬细胞不同亚群之间基因表达上的区别，研究人员建立模型对巨噬细胞的关键基因进行分析并验证预后，并从差异表达的特征巨噬细胞中发现与肿瘤预后不良呈正相关。这些基因可能成为未来治疗的靶点[57-59]。同样地，为了深入了解胶质瘤细胞特异基因表达与巨噬细胞特征基因之间的关联，Chen 等人首次发现了具有胶质免疫双重特征的中淋巴-2 型 (中 2 型)GBM 亚群,该亚群癌基因 EZH2 在与增殖基因、细胞周期转录因子和类似激活的标志性途径一致的恶性细胞和免疫细胞中表现出异质性。在与肿瘤相关的巨噬细胞(TAMS)亚群中,EZH2 与细胞周期基因和巨噬细胞 M2-PH 型基因的转录酶组动力学的类似变化高度表达[60]。在治疗方面，Müller 等人从另一个视角出发提出巨噬细胞和小胶质细胞在治疗角度的观点，从小鼠和人体实验分析得出恶性胶质瘤中血源性巨噬细胞比例上升，治疗前的血液来源巨噬细胞虽然不符合胶质瘤表型，但更倾向于表达免疫抑制细胞因子，他不赞成关于肿瘤相关巨噬细胞的治疗，提出有针对地去治疗血液衍生的免疫抑制性巨噬细胞[61]。除了巨噬细胞外，在肿瘤微环境(TME)中，细胞外囊泡在不同的肿瘤细胞亚群中也具有异质性，研究发现 IDH 突变可以决定胶质瘤细胞的亚型，在小鼠实验中，Ludwig 等人将 IDH 突变型小鼠的胶质瘤细胞外囊泡（TEX）注入野生型小鼠体内时，发现野生型小鼠的肿瘤生长率和死亡率快速增加[62]。Hu 等人研究显示肌萎缩相关基因 ATRX 的失活能引起胶质瘤细胞 IDH 突变，并导致肿瘤的免疫抑制[63]。PD-L1 是一种肿瘤抗原，通过与免疫细胞上的程序性死亡受体-1（PD-1 受体）结合，传递抑制信号，降低免疫细胞活性，从而使得癌细胞有机会逃脱免疫系统的监控和清楚。Wang 等人研究发现胶质母细胞瘤中 Met 过度表达可能会引起肿瘤相关巨噬细胞（TAM）介导的原发性胶质瘤母细胞（GBM）的 4-PD-L1 信号激活，并与肿瘤的预后不良有关[64]。研究进一步发现抗 PD1 阻断治疗的过程可以使肿瘤相关巨噬细胞（TAM）向 M1 型极化[65]。

五、肿瘤相关巨噬细胞（TAM）与微环境之间的联系网

胶质母细胞瘤（GBM）的演进离不开肿瘤微环境 （TME）提供能量。Kloosterman 等人通过单细胞技术发现巨噬细胞吞噬富含胆固醇的髓鞘碎片，衍生脂质为肿瘤细胞提供能量[54]。脂质液滴(LDS）在脑肿瘤胶质母细胞瘤（GBM）中并不罕见[66]。Chen 等人利用靶向纳米技术发现抑制与脂肪代谢相关的 ALOX5 花生四烯酸 5 脂氧合酶能减弱巨噬细胞 M2 极化，通过小鼠实验联合 PD1 治疗能提高疗效[67]，针对胶质母细胞瘤 (GBM）摄入脂质获取能量的行为，Zhong 等人发现靶向抑制谷氨酰胺转运蛋白(Asct2），能有效抑制谷氨酰胺的代谢与脂肪合成，胶质瘤细胞在体内体外死亡[68]。Ye 等人研究发现脂质磷酸酶 PRL1 和 PRL3 在促进细胞膜生成同时也与胶质瘤细胞的增殖有关[69]。从代谢角度来看，脂肪和葡萄糖都是脑细胞主要来源，而在胶质母细胞瘤（GBM）中，脂肪酸的含量很高[70]。

针对肿瘤脂代谢靶向抑制无疑是一项具有潜力的新兴治疗，但是脂肪代谢的抑制可能会影响正常脑细胞的生理活性，其研究前景和临床转化仍然具有很大价值。胶质瘤细胞和巨噬细胞依赖肿瘤微环境（TME）相互作用，现有研究表明通过改变肿瘤微环境可以间接影响巨噬细胞和肿瘤细胞状态和亚群[71, 72]。而白细胞介素作为一种炎症因子，对肿瘤微环境的改变已被证实[6, 17, 26, 34, 73, 74]。Si 等人发现肿瘤微环境（TME）缺氧因素通过缺氧诱导因子 HIF-1-α调节 IL-1 的分泌促进胶质瘤细胞的增殖迁移能力[6]。Zhai 等人发现跨白细胞介素 6(IL-6)-可溶性 IL-6 受体(SL-6R)-转录信号传感器和激活剂 3(STT3)信号传递是胶质瘤细胞中某些高表达基因维持巨噬细胞极化的中介，运用小分子抑制剂可以改变巨噬细胞的极化状态从而抑制肿瘤的发展[75]。在这些研究中，改变微环境实现对肿瘤相关巨噬细胞（TAM）的重编程来控制肿瘤进展是当前研究的热点方向，但是许多通路之间的联系仍不清晰，研究不同极化状态时巨噬细胞的调节通路，构建成一张动态的网络，寻找共同的作用靶点，存在着巨大的研究价值和临床意义。

六、铁死亡（Ferroptosis）与巨噬细胞极化联系

铁死亡（Ferroptosis）是一种新型铁依赖性细胞程序性死亡，有研究表明缺铁死亡相关基因在胶质母细胞瘤（GBM）中同样表达，并且与 M1 型巨噬细胞向 M2 型巨噬细胞极化、肿瘤细胞 IDH 突变、胶质瘤患者不良预后有关[76-78]。进一步的研究，Li 等人发现铁蛋白轻链（FTL）在铁死亡（Ferroptosis）诱导巨噬细胞极化过程中起到关键的作用，抑制铁蛋白轻链（FTL）相关基因的表达，可能会抑制巨噬细胞 M2 的极化，并且可促进 PD-1 靶向的效果[79]。铁死亡（Ferroptosis）相关基因在胶质瘤的涉及多种信号通路，抑制相应的靶点可能对延长生存期带来希望，巨噬细胞在铁死亡介导下的具体作用形式随着技术的进步有待于揭示。

七、 胶质瘤多模式下的临床治疗

目前已知手术切除后替莫唑胺（TMZ）化疗是胶质瘤治疗的金标准，但是大部分患者面临着肿瘤复发等问题。为此在传统疗法的基础上研究人员采用多种方法针对胶质瘤联合治疗，取得了一定的疗效[12, 14, 24-26, 37, 71, 74, 80-84]。在联合治疗方面 Yang 等人发现替莫唑胺（TMZ）联合粒细胞集落刺激因子受体（GM-CSF）进行放疗可以提高胶质瘤患者的化疗疗效，并且能明显改善与化疗相关的血小板减少和中性粒细胞下降[12]。Hou 等人通过组学研究发现肠道微生物参与胶质母细胞瘤 GBM）的发展，联合抗生素治疗可以增加替莫唑胺（TMZ）的疗效[83]。靶向联合传统化疗也是当前临床实验的新方向，抑制相应的白介素受体、抗原识别受体和信号传递因子，可以获得更好的预后[24-26, 37, 74]。粒细胞集落刺激因子 （GM-CSF）是由巨噬细胞等免疫细胞分泌的蛋白质，近年来被广泛研究用于癌症的免疫治疗，通过刺激免疫系统增强对癌细胞的攻击。这种疗法在临床实验中被多种治疗联合应用和改进。疫苗和病毒联合该种治疗都产生了较好的疗效[12, 14, 82, 85]。CSF-1R 是巨噬细胞集落刺激因子-1-受体，是一种在免疫系统中起重要作用的受体参与巨噬细胞的生长增殖等生理过程。CSF-1R 抑制剂主要靶向 CSF-1R 受体的小分子化合物和抗体等，近年来在胶质瘤领域逐渐实验和应用[73, 86-92]。Watson 等人发现虽然粒细胞集落刺激因子（GM-CSF）治疗能取得良好的疗效，但是在实验中仍有 50%的小鼠复发，通过解剖发现这一现象与纤维瘢痕有关，纤维区包裹住幸存的肿瘤细胞促进休眠和免疫抑制，这是由周围血管纤维母细胞对神经炎症激活和转化生长因子（TGF）信号所介导，抑制纤维化反应可促进疗效[86]。Almahariq 等人发现抑制粒细胞集落刺激因子-1 受体（CSF-1R）联合放疗可提高胶质瘤小鼠的生存期，在体外减少放疗诱导的 M2 巨噬细胞的浸润[89]。针对粒细胞集落刺激因子-1 受体 （CSF-1R）的靶向治疗，研究发现不同的肿瘤细胞亚群的敏感性不同，这是由于胶质母细胞瘤的亚特异性所决定的，肿瘤细胞的遗传因素决定肿瘤相关巨噬细胞（TAM）的功能以及对粒细胞集落刺激因子-1-受体 （CSF-1R）抑制反应的敏感性[88, 92]。研究人员除了在治疗方式上的改进，其他如放射影像学核医学和新型靶向等领域也取得了一定进展[73, 84, 93-101]。Christie 等人利用巨噬细胞作为光动力学治疗的光敏剂传递系统来更好地去切除肿瘤细胞[98]。Foray 等人利用示踪剂结合 PET/MRI 成像能更好地评估靶向治疗下胶质瘤的生长状态[73]。Thomas 等人使用 CXCR4 抑制剂联合放射治疗提高了胶质母细胞瘤患者（GBM）的生存期，抑制了放疗后肿瘤依赖基质细胞衍生因子/CXCR4 轴的再血管化[93]。Miao 等人研究发现成纤维活化蛋白α可促进肿瘤的进展,在体外缺能抑制肿瘤上皮——间充质分化[100]。Giordano 等人将磁共振显像 （MRI）与系统单核细胞检测相结合，利用核磁共振评估了与流式细胞仪数据吻合的肿瘤形态学特征，分析循环单核细胞中 pd-l1 表达与 MRI 肿瘤坏死评分相关性，这项研究更有利于胶质瘤患者病情的精细化评估和判断[94]。Chen 等人在高级别胶质瘤（HGG）中开发出一种非侵入性的放射学信号,以预测肿瘤相关巨噬细胞(TAMS)的绝对密度，利用造影后增强 T1 加权(T1CE)成像验证了 11 个特征的 M2 样肿瘤相关巨噬细胞（M2-TAM）辐射模型[97]。虽然传统的放化疗是治疗胶质瘤的金标准，Lecoultre 等人发现经过放化疗的胶质瘤细胞的上清液中虽然巨噬细胞吞噬活性增加，分泌细胞相关的受体被升高调节,这种效应可能有害于抗胶质母细胞瘤（GBM）的免疫应答。

八、总结与展望

M2 型巨噬细胞在胶质瘤中代谢机制和信号通路随着技术的发展得以被逐渐揭示。我们构建了低氧环境

下 M2 型巨噬细胞和胶质瘤演进的正反馈环，发现了关于肿瘤相关巨噬细胞（TAM）的极化途径和相关通路，以及影响极化的上游控制的基因、细胞免疫抗原的表型。除此以外我们还发现 M2 型巨噬细胞和耐药性、能量代谢之间的联系。鉴于肿瘤微环境随着肿瘤演进的过程时刻变化是一个动态构成，仍然需要大量的工作去分析。虽然当下我们已经取得了一定进展，但是离真正意义上去彻底揭开胶质瘤机制的终点还是有一段要走的距离。从基因到代谢层面以及临床应用，我们需要构建一个庞大的网络从时间和空间层面上描述这个过程。临床治疗方面，基因编辑技术在小鼠实验上已经初显疗效，多种方式联合治疗是提高胶质瘤患者生存率的有效途径。一系列新兴技术有望在临床试验中得到转化。相信随着研究的进展和技术的进步，我们可以在不久的将来揭开胶质瘤这层神秘的面纱。

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M2 macrophage metabolism and clinical management in glioblastoma

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Abstract： Glioblastoma is a difficult neurological malignancy, and the median survival of patients are usually only 12 to 15 months due to its high invasiveness, heterogeneity, and Metabolic rate. In gliomas, tumor-associated macrophages account for even 30% to 50%, and previous studies have shown that macrophages polarize into M1 phenotype macrophages (classically activated macrophages) and M2 phenotype macrophages (alternatively activated [1]Macrophages). Most of the latter have the effect of promoting tumor growth. Changing the tumor microenvironment by adding cytokines to promote the transformation of M2 tumor associated Macrophages into M1 macrophages is a current strategy for treatment. Recent studies have found that tumor cells and microenvironment participate in the process of Macrophage polarization to M2 through gene regulatory signaling pathways. The behavior and substance metabolism of macrophages in different microenvironments have been revealed, and many advances have also been made in clinical trials, using nanotechnology as a drug carrier to enter free tumor cells that cannot be removed by traditional surgery, gene edited tumor cells, using photodynamic therapy to deliver drugs, and using a combination of Methods on the basis of targeted therapy, thereby prolonging patient survival. This article reviews the metabolic mechanism of M2 macrophages in glioma and analyzes the relevant Clinical studies to provide directions for basic research and clinical treatment in the future.

Keywords： polarization; proliferation; signal