基于 Angiopep-2/LRP-1 治疗神经胶质瘤的研究进展

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摘要: 神经胶质瘤的治疗效果长期受限于血脑屏障导致的药物递送低效的困境。Angiopep-2 肽能主动靶向低密度脂蛋白受体相关蛋白 1, 并借助该受体介导的转胞吞作用高效穿越血脑屏障, 可实现药物向肿瘤细胞的精准高效递送, 为神经胶质瘤的治疗提供了新策略。目前, Angiopep-2 已被广泛修饰于多种载体表面, 并显著提高了药物在脑肿瘤部位的富集, 彰显了其在构建跨越血脑屏障平台中巨大的潜力, 极大地推动了脑靶向递送系统的研究。本文主要介绍了基于 Angiopep-2/LRP-1 的修饰制剂在神经胶质瘤中的应用, 按照不同载体总结了其在神经胶质瘤中的研究进展, 为后续研究提供参考。

关键词: Angiopep-2; 低密度脂蛋白受体相关蛋白 1; 血脑屏障; 神经胶质瘤; 靶向递送系统

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Research progress on Angiopep-2/LRP-1 therapy for glioma

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Abstract: The therapeutic efficacy of glioma treatment has long been constrained by the inefficiency of drug delivery due to the blood-brain barrier (BBB). Angiopep-2 peptide actively targets LDL receptor-related protein 1 and efficiently crosses the BBB *via* LRP1-mediated endocytosis, enabling precise and efficient drug delivery to tumor cells. This offers a novel therapeutic strategy for glioma treatment. Currently, Angiopep-2 has been extensively modified onto various carrier surfaces, significantly enhancing drug accumulation at brain tumor sites. This demonstrates its immense potential in constructing BBB-crossing platforms and has greatly advanced research on brain-targeted delivery systems. This paper primarily reviews the application of Angiopep-2/LRP-1-based modified formulations in glioma treatment. It summarizes research progress across different carriers in glioma, providing a reference for future studies.

Key words: Angiopep-2; low-density lipoprotein receptor-related protein 1; blood-brain barrier; glioma; targeting drug delivery system

神经胶质瘤是中枢神经系统最常见的原发性恶性脑肿瘤[1], 全球流行病学数据显示, 年新增约 2.3 万例, 年死亡超 1.5 万例[2]。患者确诊前常出现睡眠障碍、精神疲倦、头痛等非特异性前驱症状, 确诊后多表现为恶心、癫痫发作及认知功能障碍等[3,4]。根据世界卫生组织 (World Health Organization, WHO) 分级标准, 胶质瘤恶性程度分为 I～IV 级, 其中 IV 级胶质母细胞瘤

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(glioblastoma, GBM) 侵袭性强且预后极差[5]。其发病机制涉及表皮生长因子基因突变[6,7]、磷酸酶基因缺失或突变[8,9]、肿瘤区域缺氧[10]、p53 和 Rb 通路失调[11]、癌症干细胞异常[12]等。当前接受常规疗法 (手术联合化、放疗) 的患者中位生存期仍不足 2 年, 存在预后较差、高复发率、高死亡率的临床困境[13,14]。

血脑屏障 (blood-brain barrier, BBB) 及血脑肿瘤屏障 (blood brain tumor barrier, BBTB) 是阻碍胶质瘤药物递送的关键障碍[15,16]。BBB 由紧密连接的脑微血管内皮细胞 (brain microvascular endothelial cells, BMEC) 构成, 其低囊泡转运活性和外排转运蛋白, 如 P-糖蛋白 (P-glycoprotein, P-gp) 共同限制了药物渗透进入脑组织[17,18]。前有研究[19,20]表明血管肽 Angiopep-2 与低密度脂蛋白受体相关蛋白 1 (low-density lipoprotein receptor-related protein 1, LRP-1) 具有高亲和力和脑渗透性, 二者结合可高效穿透 BBB 并靶向肿瘤组织, 使其成为理想的脑靶向工具。因此, 开发高效跨越 BBB 并精准靶向肿瘤组织的递送系统, 已成为突破胶质瘤治疗瓶颈的核心研究方向。本文系统综述了经 Angiopep-2 修饰的不同类型载体的研究进展, 为后续研究提供参考。Angiopep-2 修饰制剂发展历程整合见图 1[19,21-26]。

1 Angiopep-2 靶向肽特性研究

1.1 Angiopep-2 的设计

Demeule 等[27]首次发现抑肽酶具有高效 BBB 穿透能力 (转铁蛋白的 10 倍), 其 C 端 kunitz 结构域与低密度脂蛋白受体相关蛋白家族 (low-density lipoprotein receptor-related protein, LRP) 受体配体存在同源性。研究人员通过将 Angiopep-1 第 7 位的半胱氨酸替换为丝氨酸, 消除二硫键干扰并保留 LRP 受体结合能力, 成功开发出 19 肽 Angiopep-2 (TFFYGGSRGKRNNFKTEEY), 其 BBB 穿透效率较抑肽酶提升 7 倍, 且呈现时间依赖性线性摄取[27,28]。

1.2 Angiopep-2 与 LRP-1 受体结合途径

受体介导内吞 (receptor-mediated endocytosis, RME) 是药物跨越 BBB 的核心机制[29]。LRP-1 在 BBB 内皮细胞及肿瘤细胞中高表达, 是跨越 BBB 转运的关键受体[25]。Angiopep-2 通过其 C 端与 LRP-1 的簇 II 结构域结合后引发受体聚集, 诱导网格蛋白介导的转胞吞过程, 形成内体后部分受体再体循环至膜表面, 而纳米颗粒可通过内体逃逸释放药物, 最终实现跨 BBB 递送至肿瘤细胞[30,31]。在 2022 年 Di Polidoro 等[32]通过分子对接首次揭示 Angiopep-2 与 LRP-1 相互作用的分子机制。该机制为脑靶向递送系统设计提供了重要的理论依据 (图 2)。

1.3 Angiopep-2 改性策略

Angiopep-2 作为线性多肽链, 其天然 *L*-氨基酸结构易被体内蛋白酶识别降解, 影响其靶向效果[33]。Wei 等[34]将其改造为 *D*-氨基酸逆序异构体, 可避免蛋白酶识别。此外, *L*-氨基酸在溶酶体中可被快速降解, 而 *D*-氨基酸保持稳定, 显著提升了跨 BBB 递送效率, 并在肿瘤早晚期均实现高效药物递送[35]。

1.4 Angiopep-2 修饰的靶向部位及其优化

Angiopep-2 通过特异性识别并结合在血脑屏障内皮细胞及胶质瘤细胞表面高表达的 LRP-1, 实现跨越 BBB 并靶向肿瘤的双重靶向功能。优化 Angiopep-2 在递送系统中的修饰方式, 可显著增强其与 LRP-1 受体的结合效率与靶向特异性, 从而提高药物在脑肿瘤部位的富集。

1.4.1 配体修饰密度的优化 Angiopep-2 在载体表面的修饰密度直接影响 LRP-1 介导的内吞效率。Jiang

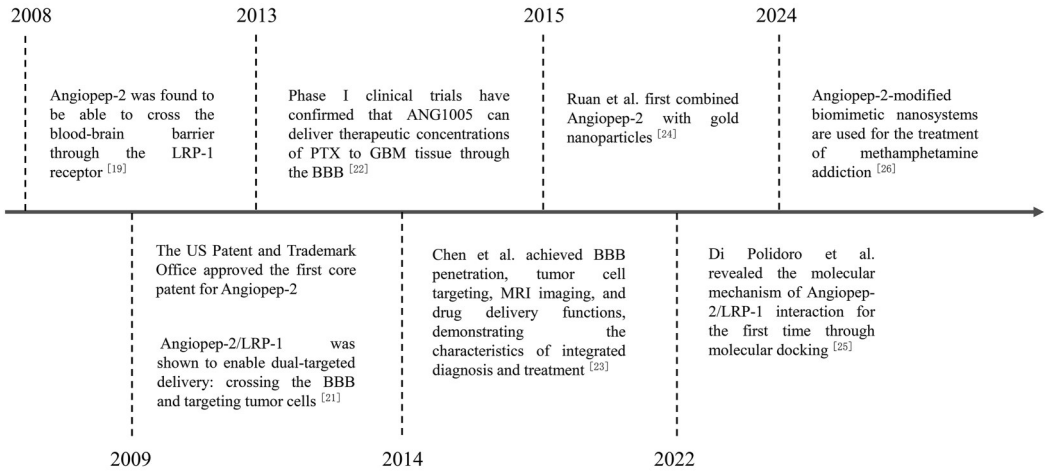


Figure 1 Chart of major historical events in the development of Angiopep-2 modified preparations. LRP-1: Low-density lipoprotein receptor-related protein 1; PTX: Paclitaxel; GBM: Glioblastoma; MRI: Magnetic resonance imaging

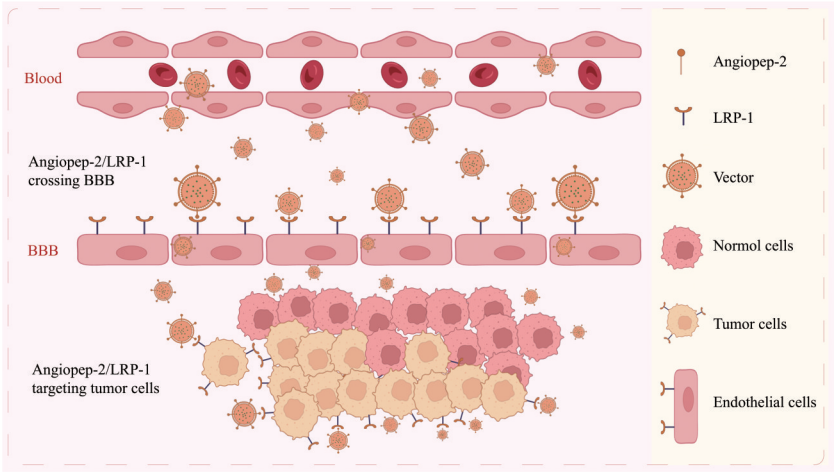


Figure 2 Mechanism of action of the Angiopep-2/LRP-1 pathway. BBB: Blood brain barrier (Created inhttps://BioRender.com)

等[36]研究显示, 当 Angiopep-2 在纳米颗粒表面的修饰密度为 20% 时, U-87 MG 细胞的摄取量较 10% 修饰密度组提升 2 倍以上, 且该摄取可被游离 Angiopep-2 竞争性抑制, 证实其摄取依赖于 LRP-1 受体介导的内吞作用。这表明通过合理调控配体密度, 可显著增强 Angiopep-2 修饰系统的靶向效率。

1.4.2 配体空间构型与暴露策略 为保障 Angiopep-2 与 LRP-1 受体的充分结合, 其空间取向与可及性至关重要。研究采用不对称嵌段共聚物, 将 Angiopep-2 连接于长链聚乙二醇 (polyethylene glycol, PEG) 末端, 利用 PEG 链的伸展性使配体充分暴露, 从而增强与 LRP-1 的识别与结合同时, PEG 链的空间屏蔽作用可减少非特异性吸附, 降低系统清除率, 延长循环时间[36]。该策略在维持靶向功能的同时, 提升了递送系统的稳定性和生物相容性。

1.4.3 与其他靶向/穿透策略的协同 为进一步提升脑内递送效率, Angiopep-2 修饰常与其他靶向或微环境响应单元联用, 形成层次化靶向策略。例如, Gao 等[37]构建了 Angiopep-2 与基质金属蛋白酶-2 (matrix metalloproteinase-2, MMP-2) 响应性可激活细胞穿透肽 (activatable cell-penetrating peptide, ACP) 共修饰的系统, Angiopep-2 负责跨越 BBB, 而在肿瘤部位高表达的 MMP-2 可激活 ACP, 增强瘤内穿透与细胞摄取。此类多级靶向设计可弥补单一配体在复杂生理环境中可能出现的受体饱和或竞争抑制问题, 提升靶向精准性与治疗效率。

综上, Angiopep-2 修饰的靶向效率不仅取决于其与 LRP-1 的固有亲和力, 亦可通过配体密度调控、空间构型优化及与其他靶向/响应元件协同等多种策略进行系统提升, 从而为构建高效、精准的脑胶质瘤靶向递送系统奠定基础。

2 ANG1005 (GRN1005) 的临床进展

2.1 ANG1005 的理化性质

Régina 团队[38]开发了一种 Angiopep-2- 紫杉醇 (paclitaxel, PTX) 偶联物 ANG1005, 其结构为 3 分子 PTX 通过可裂解的琥珀酸酯键连接至 1 分子 Angiopep-2, 分子质量为 5 109.14, 其合成通过 PTX 活化后与 Angiopep-2 的氨基端及赖氨酸残基反应完成。

制剂配制主要是将 ANG1005 粉末加入预热的非离子型表面活性剂 Solutol HS15 (65 ℃) 中, 涡旋混合。加入预热的 Ringer's HEPES 缓冲液 (65 ℃), 加热至完全溶解。通过 HPLC 验证该制剂的纯度和稳定性, HPLC 分析表明 ANG1005 保留时间 (RT = 7.2 min) 与标准品一致, 未见明显降解。

2.2 ANG1005 细胞、动物实验

Régina 等[38]通过细胞实验证实 ANG1005 对 GBM U-87 MG 细胞表现出与 PTX 相似的细胞毒性, IC_{50} 值为 2.7×10^{-9}～8.3×10^{-9} mol·L^{-1}。其通过免疫荧光实验证实, ANG1005 与紫杉醇类似, 能诱导 β-微管蛋白聚合形成稳定的微管束; 流式细胞术显示, ANG1005 处理 U-87 MG 细胞 24 h 后, 52% 细胞停滞于 G2/M 期 (对照组 19%, 紫杉醇组 68%), 表明其通过干扰微管动力学阻断有丝分裂。此外, MDCK-MDR1 细胞模型显示 ANG1005 在 P-gp 过表达细胞中的积累不受 P-gp 抑制剂环孢素 A 影响, 证明其可绕过 P-gp 介导的外排。在小鼠原位脑灌注实验中, ANG1005 在 CD-1 小鼠脑中的摄取量比游离 PTX 高 4.5 倍, 且 65% 以上分布于脑实质中。在 MDR1A 缺陷小鼠中, 紫杉醇组小鼠脑摄取增加 2.2 倍, 而 ANG1005 摄取量与正常小鼠无差异, 证实其不依赖 P-gp 转运。皮下胶质瘤 U-87 MG 模型中, 40 mg·kg^{-1} 腹腔注射 ANG1005 组的肿瘤生长抑制率 (tumor growth inhibition, TGI) 为 107%, 且在原位脑肿瘤模型中延长

中位生存期15%。

Thomas等[39]通过大鼠原位脑灌注测试其BBB穿透效率实验中显示, ANG1005的脑摄取速率较游离PTX高86倍, 且70%以上分布于脑实质。在乳腺癌脑转移模型中, 正常脑组织和转移灶中ANG1005的浓度较PTX浓度分别增长54和4倍。

以上结果表明, ANG1005在体内外模型中均表现出较强的抗肿瘤活性。二者研究均缺乏灵长类评估、未分析长期毒性、疗效及药物蓄积效应及免疫缺陷小鼠模型微环境失真等问题, 可能影响临床转化预测的准确性等。

2.3 I期临床进展

Drappatz等[40]设计了一种通过化学偶联技术将Angiopep-2-PTX制成的冻干粉针剂——GRN1005。临床使用时以无菌注射用水或生理盐水复溶, 静脉输注1 h。其优点在于冻干制剂便于保存, 可避免液态下药物降解。此外, 在临床以体表面积计算剂量 (mg·m^{-2}), 可确保血药浓度可控。本期临床纳入63例复发性恶性胶质瘤患者进行I期临床试验研究, 其中有效患者数为46例 (接受至少2次治疗并至少有一次治疗后MRI评估)。I期临床试验主要目的为评估其安全性, 因此入组患者均为重度预处理的复发性高级别胶质瘤患者 (68%为WHO 4级, 29%为WHO 3级)。通过剂量递增30～700 mg·m^{-2}静脉注射 (每3周一次), 结果表明700 mg·m^{-2}剂量组出现剂量限制性毒性 (3级黏膜炎1例、4级中性粒细胞减少1例), 这也成为650 mg·m^{-2}剂量组为最大耐受剂量 (maximal tolerance dose, MTD)的关键依据[41,42] (表1)。

Table 1 Efficacy evaluation from a phase I clinical trial

Therapeutic endpoint	Dose /mg·m^{-2}	Number of cases /total number of cases	Percentage /%	Median survival time/d
Completely dissolution	700	1/46	2.2%	−
Partial dissolution	420, 650	2/46	4.3%	−
Disease stable	≥ 420	8/27	29.6%	51

该试验结果表明, 在安全剂量下, ANG1005对恶性GBM具有一定的治疗效果, 并且耐受性良好。但对于重度预处理人群的客观溶解率 (objective response rate, ORR) 较低, 仅4.8%且剂量在≥ 420 mg·m^{-2}的27例患者中, 仅8例达到疾病稳定, 其原因可能为试验人群多为重度预处理患者 (54%接受≥3线化疗、35%接受贝伐珠单抗治疗), 这可能导致肿瘤异质性增加、改变BBB通透性和LRP-1受体表达等影响疗效评估。此外, 该临床试验存在血液系统毒性, 表现为中性粒细胞减少78%、白细胞减少89%, 以及疲劳44%等不良反应[21]。

2.4 II期临床进展

Dmello等[21]开展了关于ANG1005治疗高级别胶质瘤的II期临床转化研究, 基于I期临床试验, 研究将剂量调整至600 mg·m^{-2}以平衡疗效与耐受性。该试验采用三臂设计: Arm 1纳入24例未接受过贝伐珠单抗治疗的复发性GBM患者; Arm 2纳入16例贝伐珠单抗耐药的复发性GBM患者; Arm 3纳入33例未使用贝伐珠单抗的WHO 3级渐变性胶质瘤患者。研究主要以ORR、无进展生存期 (progression free survival, PFS)、总生存期 (overall survival, OS) 为主要疗效终点 (表2)。

Table 2 Efficacy evaluation from a phase II clinical trial. ORR: Objective response rate; PFS: Progression free survival; OS: Overall survival

Group	ORR/%	PFS/%			OS/month
		3 months	6 months	12 months	
Arm 1	13.3	33.3	26.7	13.3	13.4
Arm 2	0	0	0	0	5.8
Arm 3	3.6	35.7	35.7	26.8	18.2

Arm 1和Arm 3的数据表明, ANG1005在未接受贝伐珠单抗治疗的复发性胶质瘤患者中具有疾病控制作用, 但ORR较低, 提示药物可能主要通过稳定疾病而非显著缩瘤发挥疗效。Arm 2疗效受限归因于: ① 耐药GBM侵袭性强伴随血管异常和药物外排机制增强, 导致化疗药物难以有效蓄积; ② LRP-1受体可能因血管异常而下调或功能受损, 影响药物递送效率; ③ 缺乏耐药后分子标志物分析, 无法排除分子亚型对疗效的影响。

该研究存在研究样本量小, 可能导致统计效力不足和选择偏倚; 患者在入组前已接受多种治疗, 可能影响药物反应评估; 缺乏长期随访数据限制了疗效的持续性判断; 未直接验证药物浓度与疗效关系, 无法直接验证其穿透效率与疗效的关系等局限性, 未来研究应扩大样本量同时整合分子分型以探索潜在人群。

3 Angiopep-2修饰制剂的类型及应用

3.1 纳米药物递送系统

3.1.1 脂质体 脂质体由两亲性磷脂分子自组装形成双分子层囊泡, 其载药效率取决于脂质组成、粒径及制备工艺, 可同时包载亲水性及疏水性药物兼具良好的生物相容性、可降解性和低毒性等[22,43-45]。Yang等[46]开发Angiopep-2/TLyP-1双肽修饰脂质体共载VEGF siRNA与多西他塞 (docetaxel, DTX), 肿瘤体积缩小50%, 凋亡指数提升8.5倍, 但在载药优化和体内稳定性方面仍需改进; Du等[47]通过调控PEG链长 (10 kDa)延长循环时间与内化效率, 并促进BBB穿透。这些研

究体现从单一靶向到多元调控、从化疗单用到联合治疗的演进思路, 为后续多机制协同的纳米载体设计提供了重要参考, 但如何平衡靶向性与系统毒性仍是未来研究的重点。未来研究可探索刺激响应性配体暴露或可脱落 PEG 修饰以平衡长循环与高效靶向。

3.1.2 固体脂质纳米粒 固体脂质纳米粒 (solid lipid nanoparticles, SLNs) 是由固体脂质构成的 10～1 000 nm 颗粒, 其紧密晶体结构可能导致药物泄漏, 是优化载药时需考虑的理化特性[48,49]。Kadari 等[50]构建 Angiopep-2-SLN 负载 DTX, 克服 P-gp 外排限制, 实现高效脑靶向递送, 细胞凋亡率 45.9%, 生存期延长至 39 天; Ak 等[51]研究负载卡莫司汀和替莫唑胺的 SLNs 通过靶向单羧酸转运蛋白 1 (monocarboxylate transporter 1, MCT1) 实现 GBM 靶向递送, 肿瘤凋亡率提升 26.3 倍。二者分别通过 LRP-1 及 MCT1 靶向通路提供互补策略。Kadari 等[50]的 LRP-1 递送系统实现了 BBB 的跨越和肿瘤的靶向, 而他们的 MCT-1 靶向系统虽在体外效果显著, 但尚需进一步的体内验证。这两项研究为克服 BBB 和增强肿瘤靶向提供了互补性的解决方法, 未来研究可探索二者的协同应用, 例如开发双靶向系统。

3.1.3 纳米结构脂质载体 纳米结构脂质载体 (nanostructured lipid carriers, NLCs) 由固/液态脂质混合形成非晶态基质, 可增加药物容纳空间, 显著提高负载效率、减少药物逃逸, 并能通过表面修饰实现肿瘤主动靶向。Cai 等[52]通过 Angiopep-2 偶联至液晶纳米粒载体表面, 共载顺铂 (cisplatin, CDDP)/替莫唑胺 (temozolomide, TMZ), BBB 穿透率提升 10%, 脑蓄积量增加 3 倍。Basso 等[53]采用“质量源于设计”框架优化匹伐他汀-NLCs, 包封率达 97.5% 且稳定性长达 6 个月。在治疗 GBM 上, 二者分别代表了被动优化与主动靶向的策略差异。Cai 等[52]的研究在靶向性和穿透性上更具优势, 但 Basso 等[53]研究工艺成熟度、成本及稳定性方面更突出, 对于转化意义重大。未来研究可通过 QbD 优化靶向载体, 并利用微流控器官芯片加速临床前评估。

3.1.4 PEG 聚合物 PEG 是一种生物相容性良好的线性聚合物, 低免疫原性和优异的水溶性能有效降低药物载体的免疫反应和毒性[54,55]。其亲水特性可在药物载体表面形成保护层, 减少非特异性吸附, 延长体内循环时间[56]。但 PEG 在体内易受 pH 和酶活性影响而降解, 导致细胞摄取减少, 称为“PEG 困境”[57]。因此, 在利用 PEG 延长循环时间的同时, 如何克服其对细胞摄取的负面影响, 是 PEG 化递送系统设计中的一个关键考量。在此背景下, Angiopep-2 与 PEG 的结合提供了一种有效的解决思路。Xin 等[58]开发的 Angiopep-2 修饰纳米粒 (ANG-PEG-NP) 显著穿透 BBB, 使胶质瘤体积减少至 35.2%, 肿瘤富集量提高 3 倍且中位生存期延长 15 天。验证了该 PEG 化靶向系统的治疗潜力。为实现跨越血脑屏障后的瘤内深度渗透。Gao 等[37]开发了更先进的双功能系统, 同步修饰了 Angiopep-2 和 MMP-2 响应型细胞穿透肽。该设计使纳米粒在肿瘤微环境中被激活, 穿透肽暴露, 从而极大促进了在 C6 胶质瘤细胞中的摄取 (在 MMP-2 存在下提升约 2.3 倍)。在体内, 此智能系统显著抑制肿瘤生长, 将小鼠中位生存期从 19 天延长至 32 天, 疗效优于单靶向组, 体现了从基础靶向向“环境触发–级联穿透”的演进。

3.1.5 PLGA 纳米粒 PLGA 是一种 FDA 批准的可降解聚合物, 具有良好的生物相容性、可降解性和表面修饰灵活性, 可通过代谢途径安全排出体外[59,60]。但其疏水性导致载药效率较低, 需通过 PEG 化等表面修饰增强亲水性以延长循环时间[61]。此外, 结合肿瘤微环境特征 (如弱酸性) 设计 pH 响应型释药系统 (如使用腙键), 可实现药物的靶向控制释放[62]。Wang 等[59]开发了 Angiopep-2 修饰的 PLGA 递送系统 (ANG/PLGA/DOX/siRNA) 可抑制胶质瘤细胞的增殖, 脑部浓度提高 30%, 使小鼠中位生存期延长 47.8 天。Martins 等[63]首次整合酸响应性释药与双阶段靶向, 使细胞摄取率提高 12 倍, 脑部积累提高 3 倍, 小鼠中位生存期延长至 54 天, 长期存活率提高 50%。二者均通过 Angiopep-2 修饰 PLGA NPs 改进 GBM 的治疗, 但 Martins 等在靶向层次化和微环境响应性设计上更先进, 而 Wang 等在共同递送策略为联合基因治疗提供了早期范式。Martins 等的研究弥补了 Wang 等缺乏酸响应性或肿瘤微环境靶向设计的不足, 未来研究可结合二者优势。

3.1.6 聚合物胶束 聚合物胶束 (polymer micelles, PM) 是由两亲性嵌段共聚物 (疏水核心和亲水外壳) 自组装成的纳米颗粒[64], 兼具提高难溶性药物的溶解度、抑制 P-gp 外排增强靶向性、载药方式灵活及利用增强渗透与滞留效应 (enhanced permeability and retention effect, EPR) 被动靶向肿瘤组织等优势[65]。但存在载药量较低、体内易解离导致药物提前释放等问题[66,67]。同时, 纳米载体可借助肿瘤组织的 EPR 效应实现被动靶向积累[68]。Jiao 等[69]开发了双靶向及微环境响应性胶束系统, 用于递送基因治疗药物 Dbait 以增强 GBM 对放疗的敏感性, 细胞摄取量增加 164.9%, 细胞凋亡率 15.72% 且无明显毒性。Jiang 等[70]设计了一种基于组织蛋白酶 B (cathepsin B, CTSB) 响应的胶束系统 (D&R-HM-MCA), 用于 GBM 的化疗–免疫联合治疗, 使瘤区荧光信号增强 4.95 倍, 生存期延至 36 天。前者 MMP-2 触发 R8 穿透肽暴露, 实现“被动蓄积–主动穿透”的创新性层级递送。后者展示了微环境重编程, 凸显了

Angiopep-2修饰制剂从单一靶向到“BBB穿透−微环境触发−多靶点协同”治疗的智能递送技术演变。

3.1.7 金纳米颗粒 金纳米颗粒 (gold nanoparticles, AuNPs) 是由金原子构成的纳米材料 (1～100 nm)[71]。兼具高生物相容性与低毒性, 因其惰性化学性质而稳定性高[72], 表面易修饰 (如PEG化) 以延长循环时间, 同时兼具光热治疗和光学成像功能[72,73]。但长期蓄积于肝脾网状内皮系统可引发慢性炎症, 且在生理环境中随pH的变化导致的聚集可能加剧其毒性[74]。Ruan等[75]成功构建了一种基于Angiopep-2/AuNPs的pH响应性纳米递送系统 (AN-PEG-DOX-AuNPs)。肿瘤靶向率较未修饰组提高2倍, 酸性条件下DOX释放速率是生理pH的4倍 (82%∶21.9%), 中位生存期达55天, 延长2.89倍。Hsu等[76]研究开发了一种多功能纳米平台 (Ang-Fe-Au NPs), 主要通过LRP-1靶向、磁热疗和MRI成像实现胶质瘤的诊疗一体化, 兼具高特异性和低不良反应, 细胞存活率降至5%, 肿瘤体积进一步缩小至72.1 mm^3, 较对照组减少了约75.9%, 中位生存期延长至33天, 正常细胞存活率 > 90%。前者主要创新在于pH响应性递送药物, 然后者突破性地将磁热疗与靶向成像结合, 避免了传统化疗的不良反应。

3.1.8 介孔硅纳米颗粒 介孔硅纳米颗粒 (mesoporous silica nanoparticles, MSNs) 2001年, 研究人员首次将介孔硅纳米颗粒应用于药物递送系统[77]。MSNs具有有序的孔道结构和高比表面积, 这为其实现高载药量提供了理想平台。其载药效率受粒径、孔径及表面化学性质的显著调控, 例如, 小粒径 (如20 nm) MSNs因更高的比表面积而表现出更优的载药能力[24,78-81]。Heggannavar等[82]构建了一种MSNs负载DOX, PLGA负载PTX的双载药系统 (ANG-PTX-DOX-MSNs), 双药协同使疗效提升30～50倍, IC_{50}为0.026 5 μg·mL^{-1}, 96 h后癌细胞死亡率89.94%。Tao等[83]开发的pH响应释药系统 (ANG-LP-PAA-MSN@ATO) 使48 h释药率达77.3%, 肿瘤体积缩小75.8%, 中位生存期延长至49.5天。二者研究均通过Angiopep-2提升靶向性, 前者的双药策略需进一步优化释放动力学与体内靶向验证, 较侧重药物组合的协同效应; 然而后者在释放控制、技术方法和体内验证上更系统, 突出了环境响应性释药和药代动力学监测的创新性, 未来可结合研究并引入多模态成像进行验证。

3.1.9 磁性纳米颗粒 磁性纳米颗粒 (magnetic nanoparticles, MNPs) 是由磁性核心 (如铁、氧化铁等) 与功能性涂层 (如聚合物、二氧化硅等) 组成, 涂层可赋予其生物相容性、稳定性、表面可修饰性等特性[84]。可通过吸附、包埋或共价连接负载药物[85]。未经修饰易被肝脾等RES快速清除, 导致血液循环时间短, 靶向效率低, 难以有效穿透BBB[86,87]。Pucci等[88]开发了一种通过溶酶体膜通透性和化疗药物联合作用的纳米递送系统, 可针对GBM的选择性杀伤, 72 h细胞存活率降至0.2%。Thirumurugan等[89]制备了金包裹的铁肽核壳结构药物递送系统 (FeTi@Au-ANG NPs)。其通过Angiopep-2介导的靶向递送和磁热疗协同作用, 使原位胶质瘤体积缩减99%。前者存在药物负载率低、封装效率低及溶酶体膜透化机制不明确等不足, 磁热疗诱导的溶酶体膜透化虽能增强化疗效果, 但长期效应不明。后者递送系统可升温至55 ℃, 但局部温度控制的精准性不足, 可能会损伤正常脑组织, 仍存在临床转化挑战。图3整合了Angiopep-2修饰制剂的药物递送载体类型。

3.2 基因递送系统

3.2.1 病毒载体 病毒载体是经基因工程改造的病毒颗粒, 保留感染机制但删除致病基因, 失去复制能力, 兼具安全性和高效递送特性[90]。其优势包括: 高效递送能力[91,92]; 组织靶向性[93]; 长期基因表达[94]。但存在免疫原性可能引发免疫反应[95]、生产工艺复杂[96], 以及随机整合宿主基因组致突变风险等局限性[97]。Jiang等[36]基于Angiopep-2与天然蛋白毒素——皂草素 (saponin, SAP) 研发了一种病毒模拟聚合物囊泡 (ANG-PS-SAP), 由于游离SAP无法有效进入细胞, 而经Angiopep-2修饰囊泡其 $IC_{50} > 30.2\times10^{-9}$ mol·L^{-1}, 显著抑制肿瘤细胞迁徙, 中位生存期延长至43天且系统毒性低, 经Angiopep-2修饰解决了蛋白毒素体内递送的关键技术瓶颈。但未进行长期毒性的评估及实验中仅使用免疫缺陷小鼠模型, 未验证免疫系统影响, 临床转化存在局限性。Zhu等[98]研发了一种双功能修饰递送系统 (Ang/TAT-sEVs-DOX), 其克服了单一靶向肽的受体饱和问题, 细胞摄取率提高6倍, 中位生存期延长至52天, 生物发光成像显示肿瘤荧光强度约减少83.3%, 但该递送系统体内实验对肝脏有显著的截留作用, 增加肝毒性的风险, 且未分析长期免疫原性或重复给药可能引发的免疫原性, 因此存在临床转化障碍等不足。

3.2.2 非病毒载体 非病毒载体是一类不依赖病毒结构, 通过物理或化学方法将基因、药物、RNA导入靶细胞[99]。具有低免疫原性、易生产、负载灵活等优势, 但转染率较低, 且需克服细胞摄取及内体逃逸等障碍[100]。Huang等[101]研究了一种以聚酰胺胺树状大分子为载体的递送系统 (PAMAM-PEG-Angiopep/pORF-TRAIL NPs), 中位生存期延长至61天, 在300 μg·mL^{-1}浓度下细胞存活率仍达50%。Sun等[102]构建了一种以阳离子脂质体为载体的递送系统 (ANG-CLP/PTX/

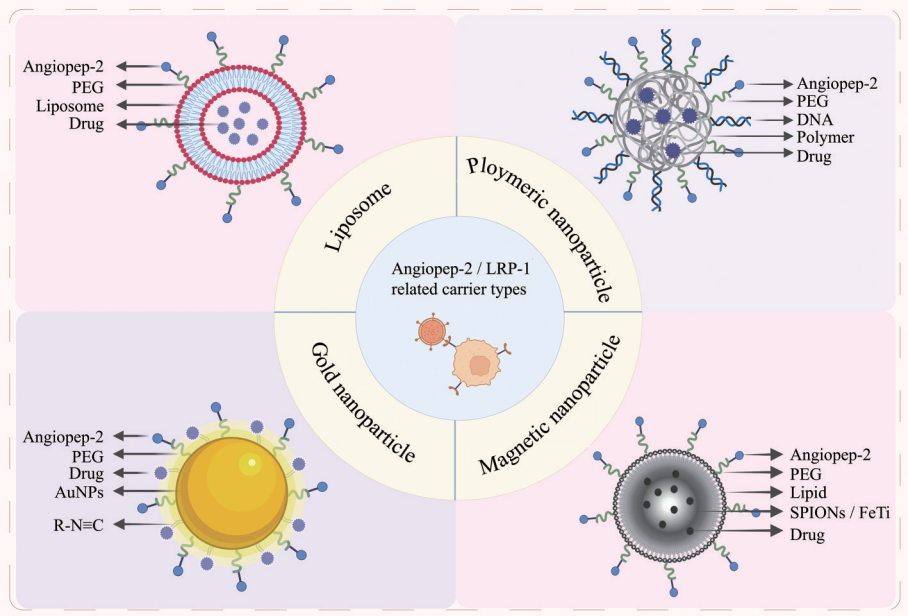


Figure 3 Types of nanocarriers utilizing the Angiopep-2/LRP-1 pathway. PEG: Polyethylene glycol; AuNPs: Gold nanoparticles; Spions: Superparamagnetic iron oxide nanoparticles; FeTi: Iron-titanium alloy (Created in https://BioRender.com)

pEGFP-hTRAIL), 中位生存期延长至 69.5 天, U-87 MG 细胞凋亡率达 81.99%, 低细胞毒性允许多次给药。该研究通过基因疗法与化疗药物的协同作用克服了单药耐药性问题。二者均在肝脏明显蓄积, 可能引发肝毒性的风险, 缺乏长期安全性验证。后者虽证实 PTX 与 TRAIL 具有协同效率, 但未明确两者最佳剂量比例及未检测长期治疗中肿瘤耐药性变化。

3.3 其他治疗剂

3.3.1 光敏剂 光敏剂 (photosensitizer, PS) 是一类能吸收光能并转化为活性氧 (reactive oxygen species, ROS), 从而选择性杀伤病变组织的分子[103]。其兼具非侵入性[104]与高肿瘤选择性[105], 但也存在疏水性强、易聚集导致 ROS 产率降低[106], 可能引发皮肤光过敏[55]及依赖氧气[107]等局限。Pucci 等[108]构建了 Angiopep-2 修饰的 NLCs 光动力系统 (Ang-Ce6-NLCs)。该系统可有效保护 Ce6 的光学性质并在生理环境中稳定释放。低功率 LED 照射后肿瘤细胞存活率降至 (1.7 ± 0.9)%, 氧化应激表达增加 2.4 倍。但该系统在酸性环境中 Ce6 释放效率低且荧光强度随时间下降, 存在长期稳定性不足等问题。Li 等[109]开发了一种仿生纳米平台 (AM-NP), 通过 Angiopep-2 修饰的巨噬细胞膜包裹吲哚菁绿 (indocyanine green, ICG) 及化疗药物 SN38 与近红外激活技术的结合实现 GBM 的双靶向协同治疗。在 Angiopep-2 修饰下, 纳米颗粒穿透 BBB 能力提升 2 倍, 较未修饰组的肿瘤细胞摄取量提高 45%。ICG 在 808 nm 激光照射下产生光热效应, 同时触发 SN38 在酸性肿瘤微环境中的累积释放 64.7%, 使肿瘤体积缩减 60% 且未造成主要器官损伤, 并延长中位生存期 7 天, 这一设计突破了 BBB 的限制, 实现了化疗–光热协同治疗。研究虽未明确损伤阈值, 但 48.6 ℃的高热可能损伤正常脑组织, 且未评估长期免疫效应, 肿瘤异质性响应及联合策略仍需进一步探索。

3.3.2 免疫检查点抑制剂 由于 GBM 的高免疫抑制肿瘤微环境和 BBTB 限制了抗程序性死亡配体 1 (anti-programmed death-ligand 1, aPD-L1) 等免疫检查点抑制剂的疗效[110,111]。Xu 等[112]开发一种经 Angiopep-2 修饰的巨噬细胞膜仿生纳米囊泡 (A2-MPC) 联合递送 CXCL10 和 aPD-L1 以增强 GBM 的免疫治疗。二者协同使肿瘤区域 aPD-L1 累积提升 19.75 倍, $CD8^+$ T 细胞浸润增加 3.85 倍, 体外模型中转运效率提高 2.45 倍, 显著抑制肿瘤生长。Galstyan 等[113]开发的 Angiopep-2/LRP-1 纳米免疫偶联物可高效递送 aCTLA-4 和 aPD-1 抗体至脑瘤, 瘤内荧光信号强度超游离组 10 倍以上; 诱导 $CD8^+$ T 细胞浸润增加 3.5 倍, 中位生存期延长 40% 且未造成器官损伤。前者长期免疫效应评估虽可持续 45 天, 但仍存在未开展大规模动物实验验证其临床转化潜力及载药率等问题。后者尽管通过抗组胺和 PAF 拮抗剂减轻了过敏反应, 但重复给药仍可能引发免疫相关不良反应, 需进一步评估长期毒性。

表 3 整合了 Angiopep-2 修饰的载体类型及应用, 按照载体类型分类, 列举了其配体、受体、载药及主要创新点和相关数据等关键信息。

Table 3 Types and applications of Angiopep-2-conjugated formulations. TLyP-1: Luciferase-yellow fluorescent protein Puro 1; VEGF siRNA: Vascular endothelial growth factor small interfering ribonucleic acid; DTX: Docetaxel; DiO: Dioxygen; DiD: 1,1'-Dioctadecyl-3,3,3', 3'-tetramethylindodicarbocyanine perchlorate; SLNs: Solid lipid nanoparticles; NLCs: Nanostructured lipid carriers; CDDP: *cis*-Dichlorodiammineplatinum (II); TMZ: Temozolomide; MMP-2: Matrix metalloproteinase-2; ACP: Ammonium cerium (IV) nitrate; DiR: 1,1'-Dioctadecyl-3,3,3',3'-tetramethylindotricarbocyanine iodide; DOX siRNA: Doxorubicin small interfering ribonucleic acid; LAT-1: *L*-Type amino acid transporter 1; PMs: Polymeric micelles; Dbait: DNA double-strand break bait; MAN: Mannosylated; PD-L1 siRNA: Programmed death-ligand 1 small interfering ribonucleic acid; DOX: Doxorubicin; MSNs: Mesoporous silica nanoparticles; ATO: Arsenic trioxide; MNPs: Magnetic nanoparticles; SAP: Saponin; pORF-TRAIL: Plasmid open reading frame encoding tumor necrosis factor-related apoptosis-inducing ligand; Ce6: Chlorin e6; SN38: 7-Ethyl-10-hydroxycamptothecin; ICG: Indocyanine green; CXCL10: C-X-C motif chemokine ligand 10; aPD-L1: Anti-programmed death-ligand 1 antibody; PD-L1: Anti-programmed cell death protein 1 antibody; aCTLA-4: Anti-cytotoxic T-lymphocyte-associated protein 4 antibody

Carrier type	Receptor	Ligand	Drug	Innovative point	Main efficacy point	Ref.
Liposomes	LRP-1	Angiopep-2, TLyP-1	VEGF siRNA, DTX	Dual ligand modification can enhance BBB penetration and tumor targeting	Apoptosis index ↑ 8.5 times; tumor suppression rate ↑ 72%	[46]
	LRP-1	Angiopep-2	DiD, DiO	It was first demonstrated that long-chain PEG can prolong circulation time and promote BBB penetration	Brain tumor fluorescence intensity ↑ 50%; phagocytosis efficiency ↑ 3 times	[47]
SLNs	LRP-1	Angiopep-2	DTX	Overcoming P-gp efflux to increase drug loading capacity	Median survival time was 39 days; drug load ↑ 2.3 times	[50]
NLCs	LRP-1	Angiopep-2	CDDP, TMZ	Co-loading chemotherapy drugs, synergistic enhancement	BBB permeability ↑ 10 times; tumor uptake and accumulation ↑ 3 times	[52]
PEG polymer	LRP-1	Angiopep-2	PTX	It systematically verified the biocompatibility of the drug delivery system for the first time	Tumor volume ↓ 35.2%; inhibition rate 65.6%; median survival time ↑ 48%	[58]
	LRP-1, MMP-2	Angiopep-2, ACP	DTX, coumarin-6, DiR	Addressing issues such as insufficient permeability of traditional delivery systems by increasing MMP-2 response	Median survival time extended to 32 days; an increase of 1.68 times; IC_{50} 1.03 μg·mL^{-1}	[37]
PLGA polymer	LRP-1	Angiopep-2	DOX siRNA	Gene-chemotherapy co-delivery	Apoptosis rate 38.4%; brain concentration ↑ 30%; median survival time 47.8 days	[59]
	LRP-1, LAT-1	Angiopep-2	DTX	Acid-triggered drug release could enhance targeting of the tumor microenvironment	Cell uptake rate ↑ 12 times; brain accumulation ↑ 3 times; long-term survival rate ↑ 50%	[63]
PMs	LRP-1	Angiopep-2	Dbait	Acid-responsive micelles could enhance permeability	Cell uptake ↑ 164.9%; apoptosis rate 15.72%	[69]
	LRP-1	Angiopep-2, MAN	DOX, PD-L1 siRNA	Chemotherapy-immunotherapy combination therapy	Median survival extended to 36 days	[70]
AuNPs	LRP-1	Angiopep-2	DOX	pH-responsive drug release and photothermal therapy	Drug release rate ↑ 3.75 times, median survival time 55 days	[75]
	LRP-1	Angiopep-2	/	Achieving integrated diagnosis and treatment of glioma through LRP-1 targeting, magnetothermal therapy, and MRI imaging	Tumor cell survival rate ↓ to 5%; tumor volume ↓ 4 times	[76]
MSNs	LRP-1	Angiopep-2	DOX, PTX	Full-chain research on material design, targeted modification, and mechanism verification	Therapeutic efficacy ↑ 30 times − 50 times; cancer cell mortality rate 89.94%	[82]
	LRP-1	Angiopep-2, PEG2000	ATO	Combining environmentally responsive drug delivery and pharmacokinetic monitoring	Tumor volume ↓ 75.8%; median survival time 49.5 days	[83]
MNPs	LRP-1	Angiopep-2	Nutlin-3a	Receptor-targeted, magnetothermal, and chemotherapy triple synergistic treatment	Cell uptake rate ↑ 20 times; penetration rate ↑ 16.7 times	[88]
	LRP-1	Angiopep-2	/	Integration of receptor targeting, AMF responsiveness, heat generation, and dual-mode MRI functional synergistic enhancement	C6 cell killing rate 82%; tumor volume ↓ 99%	[89]
Viral vector	LRP-1	Angiopep-2	SAP	Combining the advantages of protein toxins' low off-target toxicity and high cytotoxicity (limited to intracellular activation) with the targeting properties of nanocarriers	Tumor suppression rate 84%; median survival time extended by 95% (43 days)	[36]

Continued

Carrier type	Receptor	Ligand	Drug	Innovative point	Main efficacy point	Ref.
	LRP-1	Angiopep-2	DOX	Dual peptide-modified sEVs could achieve efficient BBB penetration and tumor targeting	Cell uptake rate ↑ 6 times; median survival time ↑ 2 times (52 days); tumor growth inhibition rate ↑ 2 times − 6 times	[98]
Non-viral vector	LRP-1	Angiopep-2	pORF-TRAIL	Significantly improve the efficacy of GBM treatment through the dual-targeting and selective killing effects of the TRAIL gene	Median survival time was 67 days; and the nanoparticles maintained a 50% cell survival rate at a concentration of 300 μg·mL^{-1}	[101]
	LRP-1	Angiopep-2	pEGFP-hRRAIL PTX	Synergistic effects of Angiopep-2, hTRAIL, and PTX	Median survival time 69.5 days; apoptosis rate 81.99%	[102]
Photosensitizer	LRP-1	Angiopep-2	Ce6	Under the synergistic action of photodynamic therapy, NLCs, and chlorine e6, targeting can be significantly improved and side effects reduced	Cell survival rate ↓ 44%; oxidative stress expression ↑ 2.4 times	[108]
	LRP-1	Angiopep-2, macrophage membrane	SN38, ICG	Using near-infrared light-triggered chemotherapy-photothermal synergistic therapy for GBM	Cell uptake rate ↑ 45%; tumor penetration depth ↑ 2 times; tumor volume ↓ 60%	[109]
Immune checkpoint inhibitors	LRP-1	Angiopep-2, macrophage membrane	CXCL10, aPD-L1	Their biomimetic design addressed the dual challenges of BBB penetration and immune microenvironment modulation in GBM treatment	Intratumoral antibody accumulation increased by 19.75-fold; and $CD8^+$ T cell infiltration increased by 3.85-fold	[112]
	LRP-1	Angiopep-2	aCTLA-4, aPD-1	For the first time, efficient delivery of immune checkpoint inhibitors to brain tumors and reshaping of the immune microenvironment have been achieved	$CD8^+$ T cell infiltration ↑ 3.5 times; median survival ↑ 40%	[113]

4 优势与挑战

Angiopep-2 修饰制剂的核心优势在于: ① 通过靶向 LRP-1 受体, 可同时实现高效穿透 BBB 和特异性富集肿瘤组织的双重靶向能力。研究证实, ANG1005 在脑组织的摄取量是游离紫杉醇的 4.5 倍, 并超过 65% 分布于脑实质[38]。② 高靶向性, 研究发现, 经 Angiopep-2 修饰的递送系统在小鼠脑肿瘤中荧光信号较未修饰组提高 9.1 倍, 细胞凋亡率提高 100%[114]。③ Angiopep-2 具有良好的载体适配性, 可灵活修饰脂质体[115]、多种聚合物等[116]纳米递送系统, 不仅为化疗药物, 也为基因递送和免疫治疗等新策略拓展了应用前景。

然而, 在实际应用中仍面临一些关键挑战。① LRP-1 受体存在竞争性抑制问题, 这将影响 Angiopep-2 的靶向效率。针对这一问题, 研究人员设计了 Angiopep-2/CD133 抗体双靶向系统, 通过多靶点协同机制可以有效规避受体竞争问题[117]; 或通过优化配体比例, 将 Angiopep-2 与纳米颗粒以 1∶3 摩尔比结合, 也可降低竞争性抑制风险[118]。② 纳米颗粒进入体内后可能会形成“蛋白冠”, 使靶向配体被物理屏蔽, 导致 BBB 穿透效率出现个体差异[119-121]。研究通过采用添加卵磷脂涂层[122]或设计 pH/酶响应性材料[120]是有效缓解蛋白管形成的手段。③ Angiopep-2 作为多肽的一种, 可能存在潜在的免疫原性[123], 可通过 PEG 化减弱免疫原性[102]、序列优化, 剔除非必要片段[20]及临床监测降低风险。

5 总结及展望

Angiopep-2 作为靶向 LRP-1 的功能性肽段, 为解决胶质瘤治疗中 BBB 和 BBTB 的核心递送障碍提供了有效策略。其基于 LRP-1 受体介导的转胞吞作用机制, 显著提升了治疗药物在脑肿瘤组织的靶向递送效率与蓄积浓度, 已成为胶质瘤靶向治疗研究的重要工具。在临床转化方面, ANG1005 的 I/II 期临床试验证实了该策略的初步安全性与耐受性。值得注意的是, 其在未接受贝伐珠单抗治疗的复发性 GBM 患者中显示出疾病稳定作用。然而, II 期临床试验结果也凸显了挑战, 特别是在 Arm 2 中疗效有限。这提示肿瘤微环境的病理改变及既往高强度治疗累积的毒性, 可能显著影响药物的有效递送。

目前, 国内学者研究中药有效成分对于 GBM 的治疗也提供了不同的治疗思路。Chen 等[124]通过微流控芯片技术筛选出半枝莲中 6 种黄酮类活性成分, 证实其可通过抑制细胞增殖、迁移并诱导凋亡发挥抗 GBM 作用, 其中柚皮素、芹菜素和木犀草素与替莫唑胺展现出协同疗效; Wang 等[125]总结了中药挥发油可通过调控肿瘤微环境、诱导细胞凋亡等机制治疗 GBM 的潜力等。

基于以上国内外的研究, 未来研究应聚焦于以下方向: ① 智能化递送系统: 开发整合多重肿瘤微环境

信号 (如蛋白酶、氧化还原梯度、局部温度等) 的智能响应系统, 优化时空精准释药 (如 MMP-2 响应型 ACP[37]、CTSB 响应胶束[70]); ② 协同治疗与免疫微环境重塑: 深入拓展 Angiopep-2 在免疫调节剂 (如 CXCL10、aPD-L1 抗体[112])、肿瘤抗原或溶瘤病毒递送中的应用, 联合放化疗、抗血管生成等疗法形成协同增效; ③ 克服治疗抵抗, 针对贝伐珠单抗耐药等临床难点 (如 II 期 Arm 2), 探索 Angiopep-2 与其他靶向分子联用的双靶向/多靶向系统或病理血管适应性载体 (如酸响应设计增强肿瘤滞留[63]); ④ 推动精准医学与转化研究: 建立 LRP-1 表达水平、肿瘤分子特征等生物标志物与疗效的关联性, 推动个体化用药, 并着重优化耐药人群的治疗策略。未来应优化临床试验设计, 扩大样本量并采用更贴近人体的临床前模型; ⑤长期安全性评价: 因其潜在免疫原性问题故需长期监测免疫原性风险, 系统评估载体材料的生物安全性、内在降解动力学及器官特异性蓄积、潜在慢性毒性等问题, 为安全、可持续的临床转化提供充分依据。

综上所述, Angiopep-2 修饰的靶向递送系统为突破胶质瘤治疗的 BBB 壁垒提供了关键技术支持。通过持续创新载体设计 (智能化、多功能化、克服耐药)、拓展治疗模态 (协同免疫治疗)、践行精准医疗理念 (生物标志物指导) 并夯实长期安全性基础, 该策略有望引领胶质瘤靶向治疗迈向新的高度。

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