抗肿瘤原位凝胶给药系统的研究进展

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摘要: 癌症是导致全世界死亡的主要原因之一, 2020年约1 000万死亡病例由癌症导致。原位凝胶给药系统具有良好的组织相容性、优良的可注射性、高载药量、可缓释给药及受体内环境影响较小等优点, 在药剂学与生物技术领域备受关注。原位凝胶可以结合化疗、光热治疗、化学动力学治疗、免疫治疗等多种治疗方法, 可在无需外科手术的情况下, 以较小的侵入方式将药物递送进肿瘤部位, 形成半固体凝胶状态的药物贮库, 实现肿瘤原位联合治疗。本文汇总了近10年来抗肿瘤原位凝胶给药系统的研究进展, 介绍了其常用高分子材料、分类原理及具体应用实例, 最后对关键性问题进行了总结和讨论, 以期为未来新型抗肿瘤给药系统的开发提供参考。

关键词: 原位凝胶; 给药系统; 癌症; 抗肿瘤; 联合治疗

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Research progress of anti-tumor *in situ* gel delivery system

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Abstract: Cancer is the most important leading cause of death worldwide, with about 10 million deaths caused by cancer in 2020. *In situ* gel drug delivery systems have attracted much attention in the field of pharmacy and biotechnology due to their good histo-compatibility, excellent injectability, high drug delivery capacity, slow-release drug delivery, and less influence by the *in vivo* environment. Meanwhile, *in situ* gel can be combined with chemotherapy, photo-thermal therapy, chemokinetic therapy, immunotherapy and so on to deliver drugs into the tumor site in a less invasive way without surgical operation, forming a semi-solid gel reservoir in the tumor site to realize *in situ* tumor combined therapy. In this paper, the author summarized the research progress of anti-tumor *in situ* gel delivery system in the past 10 years, introduced its commonly used polymer materials, classification principles and specific application examples, and finally summarized and discussed the key issues, in order to provide reference for the development of new anti-tumor drug delivery system in the future.

Key words: *in situ* gel; drug delivery system; cancer; anti-tumor; combination therapy

癌症是指在各种物理、化学、生物影响因素下, 人体正常细胞主动或被动转变为肿瘤细胞。癌症具有致死率高、难以治愈等特点。2020年癌症导致了约1 000万例死亡, 占全球死亡病例的六分之一, 其中, 乳腺癌、肺癌、结肠癌、直肠癌及前列腺癌发病率较高[1]。随着对肿瘤发生机制、发展过程的深入研究, 医药科研人员发现从癌前病变发展为恶性肿瘤通常是一个动态的、多水平、多因素影响的发展过程[2-4]。

目前治疗肿瘤的手段主要有手术切除[5]、放疗[6]、化疗[7]、分子靶向治疗[8]、免疫疗法[9]、中医药疗法[10,11]。其中, 手术切除是指通过外科手术切除肿瘤, 常用于起

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始阶段治疗, 可达到根治的效果。但面对比较复杂的肿瘤时, 手术治疗对于医生具有较高的专业技能要求, 术后易出现癌症复发的情况[12,13]。放疗是指放射治疗, 即通过放射线 (主要是X射线和γ射线) 杀灭恶性肿瘤细胞, 是一种非手术治疗方法, 可以弥补手术切除的不足。但人体其他正常组织在辐射作用下, 也会产生相关病变, 引起并发症[13,14]。化疗是指通过细胞毒性药物杀伤癌细胞或抑制肿瘤细胞生长, 但该方法同样会伤害体内正常细胞, 尤其是中性粒细胞等, 并且极易导致肿瘤细胞产生多药耐药性[15,16]。分子靶向治疗是指在细胞分子水平上, 通过干扰特定分子以阻止癌细胞的生长和扩散。分子靶向治疗具有较高的选择性, 可以很大程度降低化疗所带来的毒副作用。分子靶向治疗的靶标主要包括生长因子、信号分子等, 常常需要稳定可靠且具有特异性的肿瘤标志物, 在癌症治疗中具有较大的局限性[8,17,18]。免疫疗法是通过激活人体的免疫系统来攻击肿瘤细胞, 进而达到治疗癌症的方法。有效的免疫反应可以高效地根除人体内癌细胞, 达到治疗癌症的目的。但目前癌细胞已经进化出多种免疫逃逸机制, 如抗原呈递机制缺陷等, 导致免疫细胞的效应功能受阻, 部分抗肿瘤免疫反应被取消[19-21]。中医药疗法是中华民族传承下来的瑰宝, 采用中西医结合的方法治疗癌症是现在医学的一大热点。选取合适的中药可以提高肿瘤患者机体免疫力, 调节患者身体, 达到减毒增效的作用, 但单独使用该法治疗效果不明显[22-25]。在治疗癌症时, 以上6种方法分别具有各自的优点与局限性, 因此在临床上常常采用联合治疗的手段。

原位凝胶给药系统具有良好的组织相容性、优良的可注射性及长时间滞留性, 并且载药量高、可缓释给药、受体内环境影响较小, 在药剂学与生物技术领域中备受关注[26]。通过选取设计合适的高分子材料与递送载体, 原位凝胶可以同时结合化疗、光热治疗、化学动力学治疗、免疫治疗等多种方法, 在无需外科手术的情况下, 以较小侵入方式将药物递送至肿瘤部位, 形成半固体凝胶状态的药物贮库, 进而缓慢释放抗肿瘤药物, 达到杀伤肿瘤的目的, 实现原位肿瘤治疗 (图1)。

本文基于抗肿瘤原位凝胶给药系统常用高分子材料、分类原理, 结合其在抗肿瘤中的具体应用, 汇总了其近10年来的研究进展, 重点阐述其成功的关键要素和领域内尚待解决的问题, 以期为未来新型抗肿瘤原位凝胶给药系统的开发提供参考。

1 抗肿瘤原位凝胶给药系统常用的高分子材料

1.1 天然高分子材料

由于天然高分子材料具有良好的生物相容性、生物降解性、低毒性, 被广泛应用于原位凝胶的制备。常用的材料主要有蛋白和多糖, 蛋白包括胶原蛋白、纤维蛋白等, 多糖包括纤维素、透明质酸、壳聚糖、海藻酸盐、结冷胶等。

1.1.1 蛋白 胶原蛋白在自然界中广泛存在, 占大多数组织和器官 (如皮肤、骨骼、软骨、肌腱和韧带) 干重的近90%, 是一种在哺乳动物中研究最多的生物材料, 常常作为生物医学应用的水凝胶的辅料[27,28]。明胶是

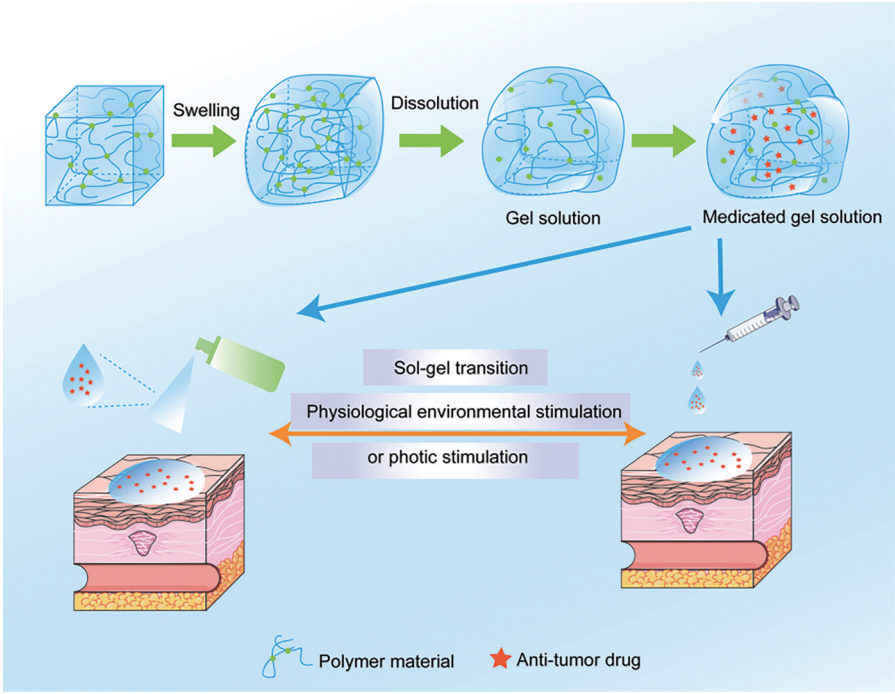

Figure 1 Schematic diagram of gel formation *in situ*

一种部分水解形式的胶原蛋白, 哺乳动物来源的明胶具有较高的胶凝温度 (～25 ℃), 而来自冷水鱼的明胶具有较低的胶凝温度 (10～12 ℃), 因此明胶或修饰后的明胶被广泛应用于温敏原位凝胶的研发[29,30]。Wang等[31]将癌症干细胞抑制剂salinomycin (SAL) 和多西紫杉醇共同包载到纳米颗粒中, 构建一种由智能明胶酶响应纳米颗粒和热敏凝胶组成的纳米复合物, 在室温下通过液体递送, 在肿瘤原位形成凝胶。

纤维蛋白胶是一种局部生物黏合剂, 由纤维蛋白原和凝血酶相互作用形成, 其效果能够模仿机体血液凝固的最后阶段, 通过凝血酶激活纤维蛋白原形成纤维蛋白凝块[32-34]。临床上作为组织胶黏剂, 主要用于加速术后凝血过程, 促进伤口愈合[35,36]。纤维蛋白胶是天然的人源性产品, 具有良好的生物相容性, 无组织毒性, 可在数秒内形成凝胶, 并于1～2周内被组织吸收, 临床上常与化疗药物、光敏剂、免疫因子混合后喷洒在肿瘤切除部位进行局部化疗[37-39]。Kuwahara等[40]使用纤维蛋白胶递送抗癌药物喜树碱衍生物 (CPT1), 在肿瘤部位缩合成凝胶, 可以有效抑制肿瘤细胞生长。

1.1.2 多糖 纤维素是一种来源于植物或微生物、不溶于水的线性有机多糖[41-43]。改性后的纤维素具有良好的水溶性、安全性、可生物降解性、凝胶特性[44]。Chen等[45]采用羟丙基纤维素设计了一种原位快速成型的可注射纤维素/白蛋白注射水凝胶递送化疗药物多柔比星 (DOX), 用于局部抗肿瘤治疗。

透明质酸是一种天然阴离子型多糖, 广泛存在于胞外组织、结缔组织、真皮组织和关节滑膜液中。透明质酸的二糖单元具有羧基、羟基和N-乙酰基, 可以与不同的官能团进行交联反应, 得到具有优异的亲水性、安全性、生物相容性和凝胶特性的改性透明质酸[46,47]。Cho等[48]采用原位可交联透明质酸凝胶向腹腔内输送顺铂, 用于卵巢癌的局部治疗。

壳聚糖是唯一天然来源的阳离子多糖, 具有相当大的生物活性, 如抗氧化 (清除自由基、螯合金属离子、调节抗氧化酶活性和减少脂质过氧化)、抗肿瘤、抗炎、抗菌、免疫调节等[49-51]。Kurakula等[52]采用泊洛沙姆和壳聚糖开发了一种包被辛伐他汀纳米颗粒的原位凝胶, 有望有效治疗舌癌。Bragta等[53]将装载卡铂的聚ε-己内酯纳米颗粒与壳聚糖-β-甘油磷酸凝胶合并, 用于肿瘤内给药, 增强黑色素瘤的治疗效果, 减小药物对正常细胞的毒性。

海藻酸钠是从褐藻类海带或马尾藻中提取碘和甘露醇之后的副产物, 能够螯合二价阳离子, 形成水凝胶, 其中钙离子是形成海藻酸钠凝胶最常用的阳离子。海藻酸钠及其衍生物的物理性质取决于M和G嵌段在生物聚合物中的相对比例 (图2)[54]。凝胶形成是由G块之间的相互作用引起的, 在二价阳离子存在下G块紧密结合形成相互作用的节点, 水凝胶稳定性随G块占比增加而提高[54,55]。

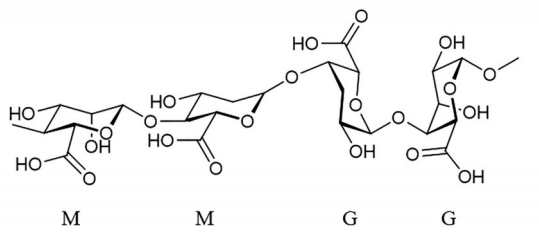

Figure 2 Structure of alginates: conformation of the oligosaccharide chain (cited with reference 54)

结冷胶是一种天然来源的阴离子胞外多糖, 具有高分散性和透明性。在接触金属离子 (如K^+、Ca^{2+}) 时, 表现出离子响应凝胶特性。由于其无毒且具有良好生物降解性, 被广泛用于离子敏感型原位凝胶的研发[56,57]。

1.2 合成高分子材料

经常用于制备温敏原位凝胶的合成高分子材料主要为泊洛沙姆, 是一种由极性 (聚环氧乙烷)和非极性 (聚环氧丙烷) 形成的一类水溶性非离子三嵌段共聚物 (图3)[58], 具有良好的两亲性、安全性。目前热敏水凝胶主要有两种类型, 一种通过冷却到临界凝胶温度 (UCGT) 以下进行凝胶化, 另一种通过加热到临界凝胶温度 (LCGT) 以上进行凝胶化。通过调整泊洛沙姆分子量和疏水亲水比, 可以制备具有不同性质的热敏水凝胶[59,60]。

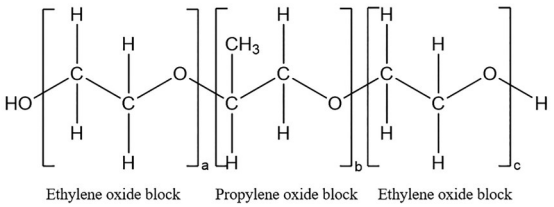

Figure 3 Schematic of the chemical structure of poloxamers (cited with reference 58)

Li等[61]通过使用羟丙基甲基纤维素、泊洛沙姆188和泊洛沙姆407, 制备了原位热敏harmine (HM) 凝胶制剂, 用于治疗结肠癌。HM凝胶可以延长HM在肿瘤部位的停留时间, 减少毒副作用, 并对肿瘤生长和转移表现出明显的抑制作用, 显著延长荷瘤小鼠的生存期。Xie等[62]使用泊洛沙姆开发了一种去甲斑蝥素热敏原位凝胶, 具有缓释性和特异靶向性。通过小鼠H22肝癌模型研究表明, 去甲斑蝥素热敏原位凝胶可

以明显降低去甲斑蝥素的肾毒性, 并且中、高剂量能显著诱导肿瘤消退, 抑制血管内皮生长因子和CD44表达, 提高荷瘤小鼠存活率。

2 抗肿瘤原位凝胶给药系统的分类

根据原位凝胶刺激响应性不同, 可以将其分为两种, 一种是基于生理环境刺激响应自发形成的抗肿瘤原位凝胶给药系统, 另一种是基于可见光或紫外光照射时原位形成的抗肿瘤凝胶给药系统[63,64]。

2.1 基于生理环境刺激响应自发形成的抗肿瘤原位凝胶给药系统

基于生理环境刺激响应自发形成的抗肿瘤原位凝胶给药系统是指通过使用相应的聚合物材料, 使其在给药前为低黏度的溶液状态, 给药后由于体内温度、pH或离子浓度与外界不同, 该溶液自发变为半固体凝胶状态, 在肿瘤部位形成药物贮库, 进而释放抗肿瘤药物, 达到杀伤肿瘤的目的。

2.1.1 温度响应型抗肿瘤原位凝胶给药系统 温度响应型抗肿瘤原位凝胶给药系统是目前研究最广泛、使用最多的一类凝胶给药系统。Lin等[65]开发了一种温度响应型抗肿瘤原位凝胶给药系统, 用于递送亲水性表柔比星和疏水性紫杉醇 (PTX), 并掺入牛血清白蛋白纳米颗粒, 共同发挥抗肿瘤作用。Zhan等[66]使用温敏材料泊洛沙姆407、泊洛沙姆188制备了PTX微球-原位温敏凝胶。该凝胶能较好降低微球突释的风险, 使药物缓慢释放, 并且只需一次给药就能达到Taxol给药3次的效果, 至优于Taxol的药效, 显著降低了Taxol毒副作用。

2.1.2 pH响应型抗肿瘤原位凝胶给药系统 pH响应型抗肿瘤原位凝胶给药系统是指由于肿瘤低pH的微环境[67], pH敏感型凝胶在给药后由溶液状态在肿瘤部位变为半固体凝胶状态。寡磺胺二甲嘧啶 (OSM) 是一种pH响应性低聚物, 在pH > 7.4时溶解性较好, 但在肿瘤的生理条件 (pH 5.6～6.8) 下易析出。Kang等[68]将OSM引入明胶骨架, 合成明胶-OSM偶联物, 结合抗癌药物PTX, 制备了一种基于明胶衍生物的温度和pH响应原位水凝胶, 用以防止脑肿瘤复发。

2.1.3 离子浓度响应型抗肿瘤原位凝胶给药系统 离子响应型抗肿瘤原位凝胶给药系统是指由于肿瘤微环境中高钾离子[69]的存在, 离子响应凝胶给药后在肿瘤部位由溶液变为半固体凝胶状态。Zhou等[70]通过化学反应合成谷胱甘肽-结冷胶偶联物, 调节结冷胶胶凝温度, 之后以此装载抗肿瘤药物盐酸多柔比星, 开发了一种温度-离子-pH三重响应原位水凝胶, 用于癌症长效治疗。

2.2 基于可见光或紫外光照射时原位形成的抗肿瘤凝胶给药系统

基于可见光或紫外光照射时原位形成的抗肿瘤凝胶给药系统是指在可见光或紫外光的照射下, 光敏化合物在光引发剂的影响下相互作用, 产生自由基, 进而引发聚合在给药部位形成交联水凝胶[71]。

乳腺癌术后复发与术后伤口诱发的炎症肿瘤微环境密切相关, 化疗药物虽然杀死残留肿瘤细胞, 但同时分泌的多种炎性细胞因子易导致肿瘤复发[72,73]。Wang等[74]采用光催化方法, 开发了一种包载DOX和Toll样受体4 (TLR4) 拮抗剂 (TAK-242) 的原位光交联水凝胶 (D/T凝胶), 是一种可以在短时间内完美覆盖乳腺癌手术伤口的胶束交联凝胶植入物。D/T凝胶直接将治疗药物输送到手术伤口, 通过提高肿瘤部位DOX和TAK-242的浓度并重塑TLR4激活诱导的促炎微环境, 减弱DOX和手术损伤引起的双重炎症反应, 从而大大增强其预防术后肿瘤复发的功效 (图4)。

Meng等[75]以光敏剂修饰的过氧化氢酶 (Ce6-

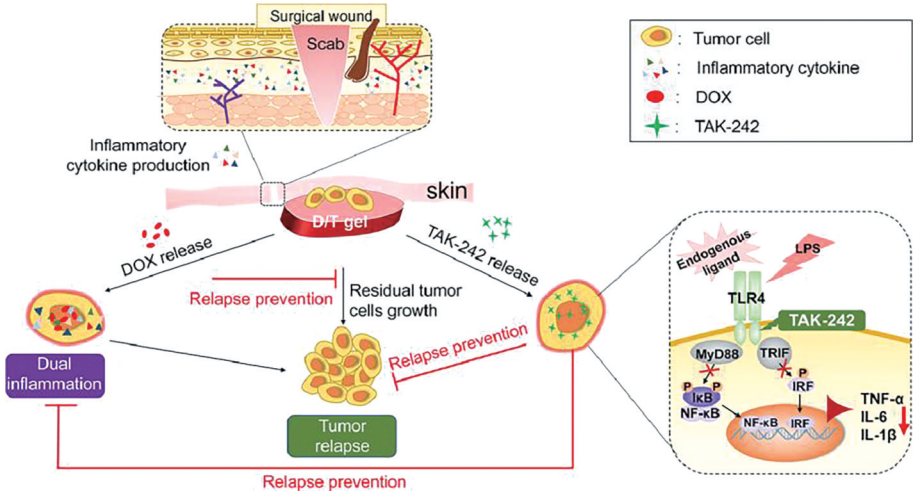

Figure 4 Schematic of the *in situ* photo-crosslinked hydrogel (D/T gel) (cited with permission from reference 74)

CAT) 和聚乙二醇二丙烯酸酯 (PEGDA) 为凝胶基质, 与咪喹莫特 (R6) 的聚乳酸-乙醇酸共聚物 (PLGA) 纳米颗粒 (RPNPs) 充分结合后, 构建了一种光触发原位凝胶系统。将其局部注射到肿瘤部位, 并采用 6 nm 红光照射后, 光引发剂产生活性氧, 进而引发 PEGDA 的聚合, 使原位凝胶化, 水凝胶中的 CAT 通过分解肿瘤内源性 H_2O_2 产生 O_2, 改善肿瘤微环境缺氧的情况, 逆转肿瘤微环境中的免疫抑制。并且光动力免疫疗法触发的免疫原性细胞死亡后的肿瘤细胞碎片, 可以作为肿瘤相关抗原, 与 RPNPs 一起作为免疫佐剂, 引起强烈的抗肿瘤免疫应答。这种独特的光触发原位凝胶可以通过多轮光触发光动力免疫疗法反复激活免疫系统, 实现高效的光动力免疫治疗。

3 抗肿瘤原位凝胶给药系统常见的给药方式及其具体应用

3.1 原位凝胶喷射给药

原位凝胶喷射给药具有黏附力强、载药量高等特点, 可以使药物较好地停留在给药部位, 提高药效, 是抗肿瘤原位凝胶给药系统一种常见的给药方式[76,77]。目前, 在癌症的治疗手段中, 手术切除仍是第一选择。但研究人员发现, 患者在手术切除肿瘤后的 12 至 18 个月常常面临肿瘤转移性复发的风险[78,79]。Krall 等[80]开发了一种基于绿色荧光蛋白在 D2A1 小鼠乳腺癌细胞中异位表达的免疫肿瘤学模型, 证明手术后诱导的全身炎症反应促进了肿瘤的转移和复发, 在手术期后进行抗炎治疗可以有效降低癌症的复发和转移。

Chen 等[81]使用纤维蛋白凝胶材料开发了一种原位喷雾生物反应性免疫治疗凝胶。在肿瘤切除部位喷洒形成原位治疗凝胶, 预装有抗 CD47 抗体的碳酸钙纳米颗粒被封装在纤维蛋白凝胶中并在手术伤口中清除氢离子, 调节酸性和发炎的肿瘤切除环境。释放的抗 CD47 抗体阻断癌细胞中的“不要吃我”信号, 从而增加巨噬细胞对癌细胞的吞噬作用。巨噬细胞可以促进有效的抗原呈递, 并启动 T 细胞介导的免疫反应, 控制肿瘤生长 (图 5)。

Si 等[82] 构建了一种装有抗 OX40 抗体 (iSGels@aOX40) 的原位喷雾双功能免疫治疗凝胶, 用于结直肠癌术后治疗。其中 iSGel 通过单宁酸 (TA) 和聚 (*L*-谷氨酸)-g-甲氧基聚乙二醇/苯硼酸 (PLG-g-mPEG/PBA) 交联, 在喷涂后可立即形成黏附能力很强的凝胶。TA 可通过抑制环加氧酶-2 的活性来缓解术后免疫抑制的微环境, aOX40 作为一种免疫激动抗体, 可在 20 天内持续从凝胶中释放出来。iSGels@aOX40 凝胶可以在治愈小鼠的体内建立免疫记忆效应, 完全抑制肿瘤复发, 并且还可以抑制腹部转移肿瘤的生长。

Li 等[83]基于固有的代谢重编程, 即异柠檬酸脱氢酶 1 (IDH1) (R132H) 细胞对低浓度的葡萄糖和高浓度的活性氧 (ROS) 敏感, 开发了一种原位喷雾饥饿/化学动力学治疗凝胶, 用于 IDH1 (R132H) 胶质瘤的术后治疗。首先采用原位仿生矿化方法将葡萄糖氧化酶 (GOx) 与锰掺杂的磷酸钙矿化, 形成 GOx@MnCaP 纳米颗粒, 之后将这些纳米颗粒封装到纤维蛋白凝胶 (GOx@MnCaP@fibrin) 中。手术腔内喷洒凝胶后, GOx@MnCaP 在酸性肿瘤微环境中逐渐溶解并释放 GOx 和 Mn^{2+}, GOx 催化残留 IDH1 (R132H) 细胞中葡萄糖的氧化并产生 H_2O_2, 生成的 H_2O_2 通过 Mn^{2+} 催化, 进一步转化为高致死性羟基自由基, 可以杀死残留的 IDH1 (R132H) 细胞。

3.2 原位注射凝胶给药

传统的给药系统总是表现出固有的局限性, 具有

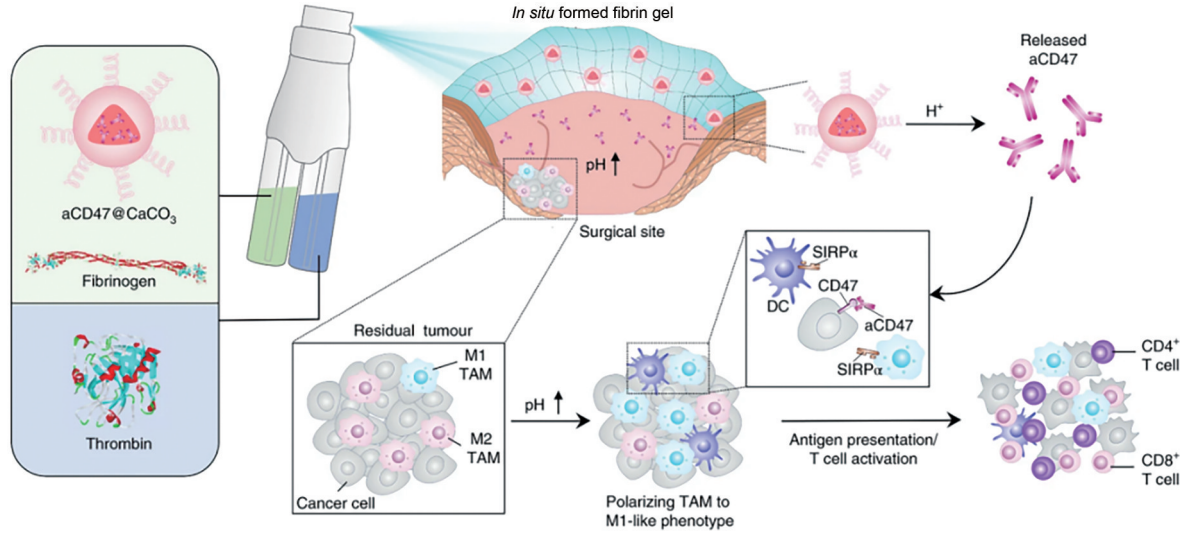

Figure 5 Schematic of the *in situ* formed immunotherapeutic fibrin gel (cited with permission from reference 81)

非特异性分布、生物利用度差、血液清除快和在生理环境中的溶解度差等缺点[84,85]。原位注射凝胶给药系统可以将药物主动递送至给药部位, 具有缓释性、空间可控性、显著提高生物利用度等优点, 在生物医学领域获得了巨大的吸引力[61,86,87]。

Zhang等[88]通过使用聚乙二醇 (MW 200或400) 和磷酸盐缓冲液 (PBS), 基于其粒子间的非共价力、氢键相互作用和π-π堆积作用, 开发了一种新型PTX自组装可注射凝胶。注射后PTX凝胶可在原位停留40天以上, 与生理盐水和PTX (静脉内和原位给药) 相比, 皮下注射PTX凝胶不仅降低了药物在正常器官中的毒性, 而且维持了PTX在肿瘤附近的持续释放, 显示出优异的抗肿瘤活性 (图6)。

Li等[89]开发了一种由热敏水凝胶和ROS响应纳米凝胶组成的肿瘤微环境适应复合材料, 将选择性转化生长因子β (TGF-β) 抑制剂LY3200882 (LY) 封装在ROS响应纳米凝胶中, 并将其与瑞戈非尼 (REG) 均匀分散在热敏水凝胶 (Gel/(REG+NG/LY)) 中。原位注射给药后, REG优先从水凝胶中释放, 以抑制肿瘤生长并促进ROS生成, 从而触发纳米凝胶中按需释放LY。LY有助于防止TGF-β升高诱导的肿瘤细胞的上皮−间充质转化和免疫逃逸。在皮下和原位结直肠瘤小鼠模型中, Gel/(REG+NG/LY) 通过增加CD8 T细胞的肿瘤浸润, 减少肿瘤相关巨噬细胞和髓源性抑制细胞的募集, 促进巨噬细胞从M2型向M1型的极化, 有效抑制肿瘤生长和肝转移, 证明了精准控制药物释放顺序在恶性肿瘤联合治疗方面的潜力。

Tan等[90]设计了一种用于骨肉瘤治疗和骨再生的可注射姜黄素−微球/IR820共载杂化甲基纤维素原位水凝胶 (Cur-MPs/IR820水凝胶)。在体外, K7M2wt骨肉瘤细胞被热疗和姜黄素根除, 姜黄素的持续释放促进了碱性磷酸酶的表达和骨间充质干细胞的钙沉积。在体内, 这种杂化水凝胶被注射到肿瘤部位, 由于热敏性而变成水凝胶。在808 nm激光的照射下, 51 min内产生局部热疗 (约5 ℃) 以消融肿瘤。同时, 热疗加速姜黄素释放和热增加的细胞膜通透性使肿瘤细胞凋亡。光热共化疗组肿瘤从治疗后第2天起成功抑制, 之后持续释放的姜黄素促进骨重建。Cur-MPs/IR820水凝胶的化学共热功效和成骨能力为治疗骨肉瘤提供了一种有前途的方法, 并为治疗骨肿瘤和修复骨组织提供了启发 (图7)。

Wang等[91]以纳米氧化石墨烯 (NGO) 为光敏剂, 甘草次酸 (GA) 为靶分子, 盐酸小檗碱 (BH) 为模型药物, 制备了基于甘草次酸 (GA) 改性纳米氧化石墨烯 (NGO) 的注射原位热敏水凝胶 (GA-BH-NGO-Gel) (图8)。GA-BH-NGO-Gel在体外呈现出持续且温度依赖性的药物释放效果, 在体内具有很强的抗恶性肝细胞肿瘤活性, 可靶向分布到肿瘤组织, 当与808 nm激光照射相结合时, GA-BH-NGO-Gel的抑制效果增强。本研究将化学−光热联合疗法应用于肿瘤治疗, 可为恶性肿瘤的临床治疗提供一定的理论依据和研究思路。

Wang等[92]开发了一种原位缓释水凝胶递送系统,

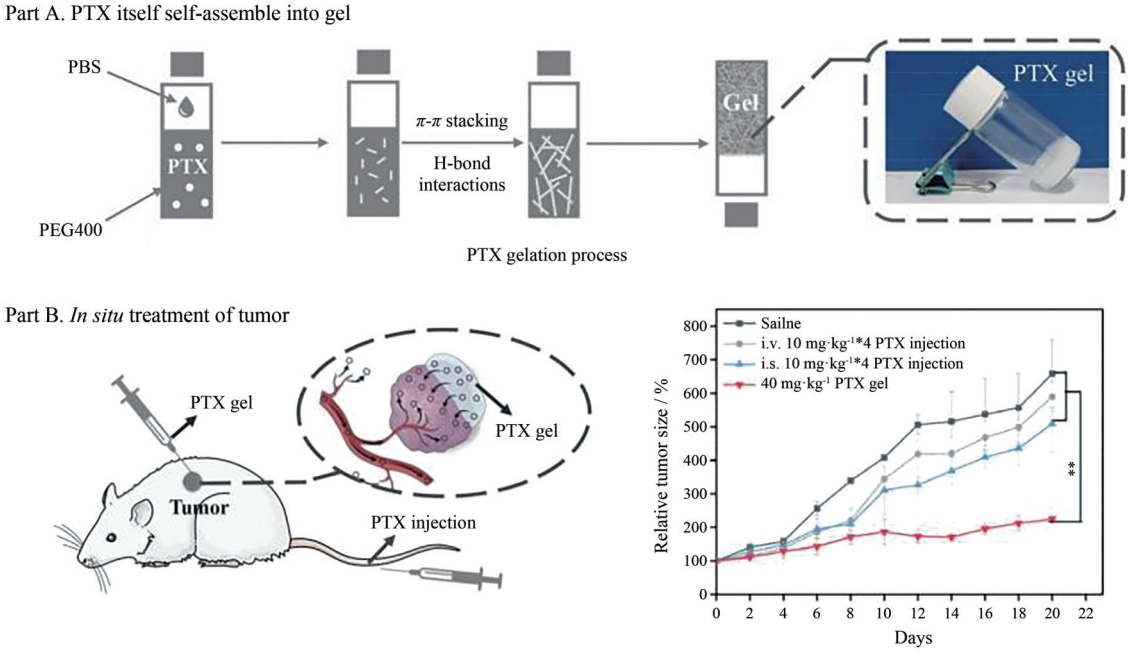

Figure 6 Schematic of the injectable gel self-assembled by paclitaxel (PTX) itself for *in situ* inhibition of tumor growth (cited with permission from reference 88)

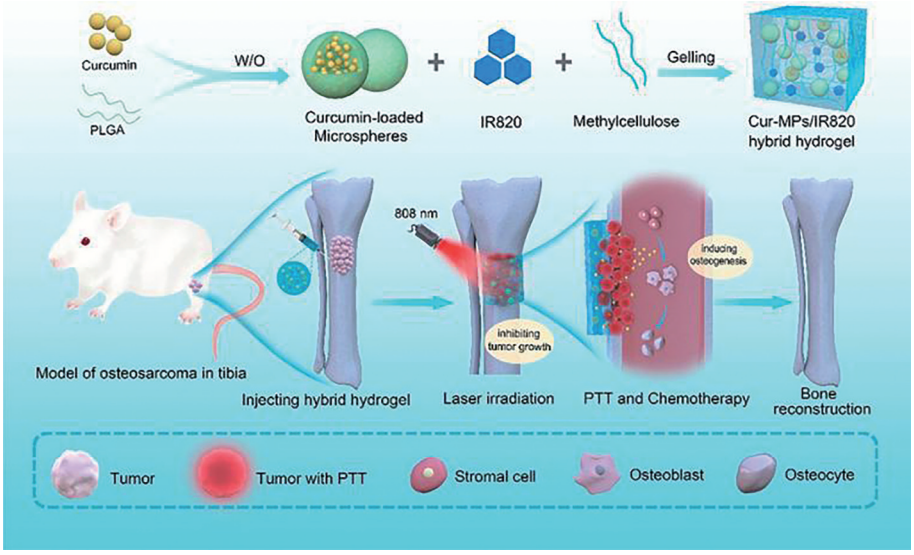

Figure 7 Schematic of the curcumin-microsphere/IR820 hybrid bifunctional hydrogels for *in situ* osteosarcoma chemo-co-thermal therapy and bone reconstruction (cited with permission from reference 90)

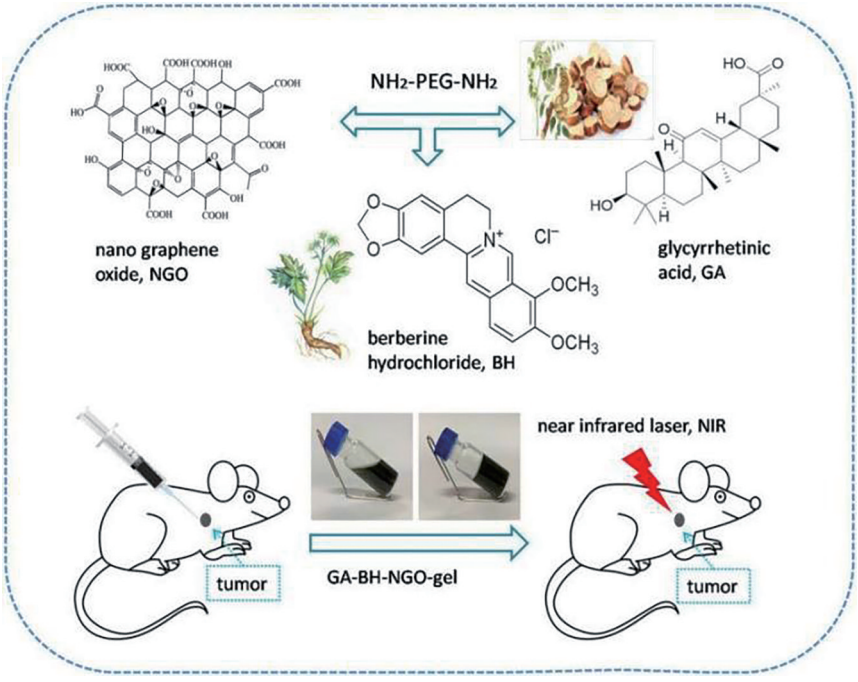

Figure 8 Schematic illustration of injectable *in situ* intelligent thermo-responsive hydrogel with glycyrrhetinic acid-conjugated nano graphene oxide for chemo-photothermal therapy of malignant hepatocellular tumor (cited with permission from reference 91)

通过手术切除腔局部递送, 用于胶质瘤化学免疫联合治疗。简而言之, Pep-1 修饰 PTX 靶向纳米颗粒 (PNP_{PTX}) 和甘露醇化免疫佐剂靶向纳米颗粒 (MNP_{CpG}) 嵌入到 $PLGA_{1750}$-PEG_{1500}-$PLGA_{1750}$ 热敏水凝胶框架 (PNP_{PTX}&MNP_{CpG}@ Gel) (图 9)。该给药系统注射到胶质瘤切除腔中时, 可以立即形成凝胶药物储液库, 缓释 PNP_{PTX} 可以靶向残留浸润的胶质瘤细胞并产生肿瘤抗原, MNP_{CpG} 可以靶向并激活抗原呈递细胞, 增强肿瘤抗原呈递能力, 激活 CD8 T 和 NK 细胞从而逆转胶质瘤微环境的免疫抑制。该研究采用联合治疗法, 同时结合化疗和免疫治疗, 显著增强胶质瘤的治疗效果。

4 总结与展望

目前, 已上市或者即将上市的原位凝胶制剂主要用于黏膜给药[93,94] (如口腔[95]、鼻腔[63]、眼部[96,97]), 应用于抗肿瘤研究领域的原位凝胶递送系统主要停留在实验室的研究阶段, 尚未进入临床研究。其原因可能是: ① 虽然众多研究者认为天然高分子材料安全性良

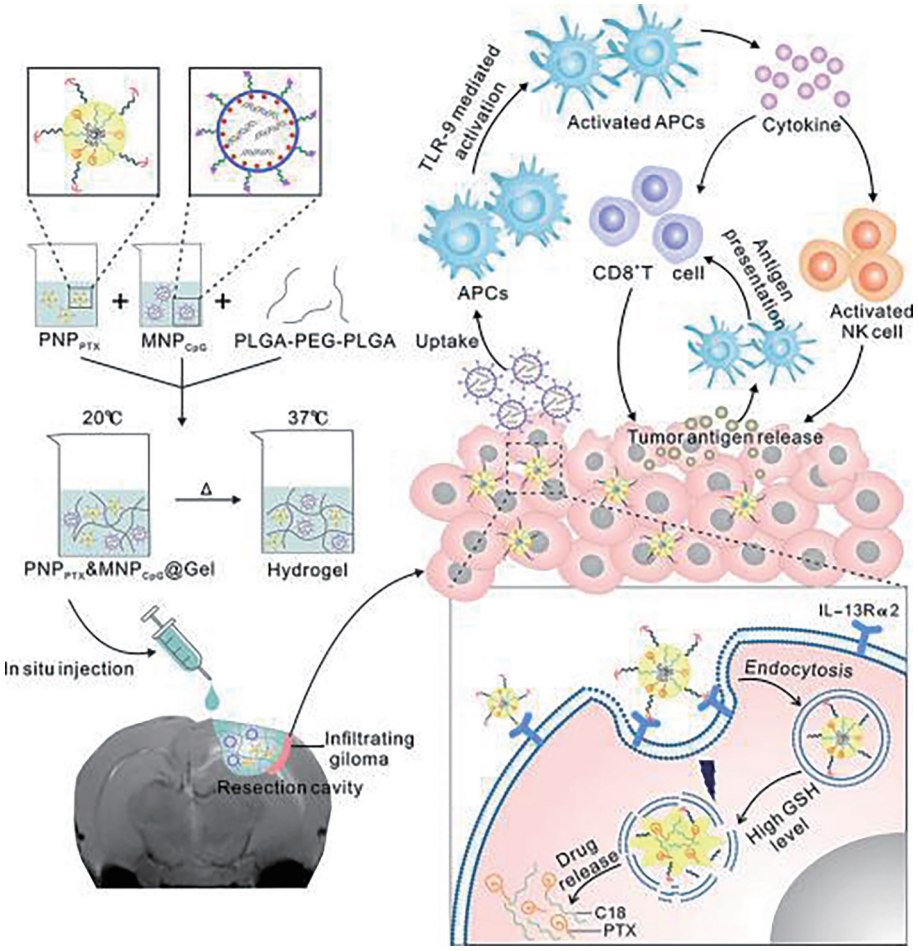

Figure 9 Scheme design of PNP$_{PTX}$&MNP$_{CpG}$@Gel for localized chemo-immunotherapy after surgical resection of glioma (cited with permission from reference 92)

好[98], 但其体内行为、安全性及降解性需进一步研究与验证。据报道, 低分子质量的透明质酸易诱导体内免疫应答反应, 高分子量的透明质酸则不会; 含有10～100个二糖单位的透明质酸可以促进肿瘤生长, 而含有超过100个单位的透明质酸可能会抑制肿瘤生长[99,100]。② 部分高分子材料在体内不易降解, 或其降解产物可能易产生与药效相反的毒副作用, 因此高分子材料的研究仍需要不断优化[101,102]。③ 制剂处方工艺研究复杂, 如通常需要灭菌和去除有机溶剂等操作。④ 制剂开发缺乏相关质量评价规范, 易导致质量参差不齐。⑤ 所涉及的生物制剂稳定性不佳, 需要进一步优化。⑥ 根据制剂体内行为分析: 体内溶液-凝胶转变时间可能过长, 以免影响其药效及后续开发, 需着重优化改善。⑦ 喷射给药、注射给药等一次给药体积有限, 常常需多次给药。⑧ 联合多种疗法治疗时, 其安全性有待考察, 如光化疗协同作用时, 光引发剂及其光聚合反应副反应的安全性有待考察[103]。⑨ 从处方优化到最终上市, 所涉及的是一个耗时耗力耗钱的过程, 需要大量科研工作和资金投入。

综上所述, 抗肿瘤药物原位凝胶递送系统的成功开发离不开材料科学家、药剂科研工作者、医生的共同努力及密切合作, 相信随着时间的推移, 会有越来越多抗肿瘤药物原位凝胶递送系统可以由“实验室”这一研究平台转移至“临床研究平台”, 最后直至成功上市。

作者贡献: 冯靖、赵鹤鸣负责文献和图片的收集整理; 肖聪聪负责阅读、文章构思、撰写和修改; 刘陈霏、陈丽青、金明姬负责内容讨论、审阅和校对; 黄伟和高钟镐负责论文选题、指导、审阅和修改。

利益冲突: 无任何利益冲突。

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