中药活性成分协同化疗药物的纳米共载体系联合抗肿瘤现状分析

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摘要: 药物联合抗肿瘤在研究和临床中展现出独特优势。中药活性成分具有高效、低毒、作用广和靶点多等优势, 目前采用中药活性成分与化疗药物联合抗肿瘤越来越受到关注。纳米给药系统为抗肿瘤药物的有效传递提供了良好的载体平台, 基于纳米载体介导的药物联合抗肿瘤是一项很有前景的策略。本文对中药活性成分和化疗药物联合抗肿瘤的机制、药物共载纳米的优势、常用载体类型和特点进行了综述, 旨在为肿瘤治疗的有效给药方案研究提供参考。

关键词: 纳米载体; 共递送; 中药; 活性成分; 化疗药物

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2019)02-0258-11

Antitumor status analysis on the co-delivery systems regarding the active ingredients of Chinese herbs combined with chemotherapeutic drugs

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Abstract: Anti-tumor intervention using a combination of drugs shows unique advantages in research and clinical practice. Active ingredients of Chinese herbal medicines can offer many advantages, such as high efficiency, low toxicity, wide effect and multiple targets. At present, the combination active ingredients of Chinese herbal and chemotherapy drugs have attracted increased attention. Nano-drug delivery system provides a good carrier platform for anti-tumor drugs. Nano-carrier-mediated drug combination is a promising strategy. In this paper, we review the mechanisms of the anti-tumor effects of active ingredients of traditional Chinese medicine combined with chemotherapeutic drugs and consider the advantages of drug-loaded nanoparticles, the types and characteristics of carriers. The aim is to provide a reference for the research of effective regimen for anti-tumor therapy.

Key words: nanocarrier; co-delivery; Chinese herb; active ingredient; chemotherapy drug

恶性肿瘤是目前影响人类健康的最主要疾病之一, 化疗是目前肿瘤治疗的主要方式, 但大多数化疗药物水溶性较差、生物利用度不高, 且基于单一抗肿瘤机制的单药治疗作用较弱, 长时间使用可能激发肿瘤其他相关恶性增殖机制, 导致药物疗效降低、肿瘤多药耐药 (multidrug resistance, MDR)、肿瘤复发及机体不良

收稿日期: 2018-07-19; 修回日期: 2018-08-14.
基金项目: 国家自然科学基金青年科学基金资助项目 (81703718).
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DOI: 10.16438/j.0513-4870.2018-0659

反应等[1]。联合用药已成为肿瘤治疗的标准策略, 联合用药能够通过调节异常细胞的多个信号通路来获得协同治疗效果, 同时减少MDR现象的发生, 预后良好且不良反应较少[2-4]。目前基于小分子化疗药物的联合用药策略常包括以下几种类型[5]: 小分子化疗药物之间的联合、基因药物与小分子药物联合、单克隆抗体与小分子药物联合、中药 (天然) 活性成分与小分子化疗药物的联合。其中, 中药 (天然) 活性成分来源广泛, 目前已发现多种成分具有抗肿瘤的作用, 在抗肿瘤新药的研究中具有重要意义[6], 大多数毒性较小、安全性高[7,8], 具有可作用于肿瘤相关机制的多靶点、多通路的特性[9,10]。因此, 近年来随着天然药物高通量筛选技术的进步, 越来越多研究者将化疗药物的联合应用对象聚焦于中药活性成分, 以联合进行肿瘤治疗。

尽管许多联合用药方案在体外和动物实验研究中展现出显著治疗优势, 但在临床实践中往往收效甚微, 甚至造成药物毒副反应叠加。究其原因在于缺乏高效的体内药物传递。随着纳米技术在药物传递领域的积极探索, 为联合用药抗肿瘤带来了新思路。纳米粒通过粒径控制、结构改造和表面修饰等途径, 可具有较强的载药能力、体内长循环、肿瘤组织被动/主动靶向等特点, 联合药物经纳米粒递送, 可有效改善药物自身性质 (如水溶性差、体内循环时间短等), 改善药物间不同药代动力学行为导致的差异化传递, 提高肿瘤组织的药物专属性分布, 从而增强药物的治疗效果并减小毒性等。目前基于纳米载体传递的药物联合抗肿瘤常包括3种方式: 所有药物经纳米粒共载; 将不同药物采用纳米粒分别包载后再联合; 某一药物经纳米包载后与其他游离药物联合。其中, 第1种方式有利于精准控制联用药物到达肿瘤组织中的药物比例, 实现最佳比例起效。作者对中药活性成分与化疗药物联合用药的纳米递送策略, 进行了研究现状和应用特色的综述和分析, 旨在揭示基于纳米载体药物共递送联合抗肿瘤的研究意义。

1 中药活性成分与化疗药物联合抗肿瘤的机制

中药活性成分具有多靶点抗肿瘤作用特点, 可从诱导肿瘤细胞凋亡、抑制肿瘤血管的生成、诱导肿瘤细胞自噬和调节肿瘤微环境等多方面促进药物联合抗肿瘤 (图1)。

1.1 抑制肿瘤细胞增殖 肿瘤细胞具有无限增殖的特性, 中药 (天然药物) 小分子与化疗药物联合给药可从促进肿瘤细胞凋亡、诱导细胞自噬、增强氧化应激、促进增敏和阻滞细胞周期等方面抑制肿瘤细胞增殖, 从而达到治疗肿瘤的作用。Meng等[11]研究报道了雷公藤甲素和羟基喜树碱的联合给药, 其抗肿瘤机制为增强细胞凋亡, 通过调控PP2A控制ERK、p38、MAPKs和Akt信号通路。该研究以A549细胞为实验对象, 探究雷公藤甲素和羟基喜树碱联合用药的分子机制, 从参与PP2A控制的MAPKs和Akt信号通路进行了实验研究。结果表明, 联合给药使其抗肿瘤的毒性增强, 具体作用靶点为增强caspase-3和caspase-9蛋白活性、增强Bax/Bcl-2比率和释放cytochrome C等, 表明抑制了Akt信号通路, 促进了ERK和p38、MAPKs信号通路。该研究提供了一种雷公藤甲素和羟基喜树碱联合用药的机制基础, 从PP2A和PP2A控制的信号通路为出发点进行抗肿瘤研究。

1.2 抑制肿瘤细胞转移 肿瘤细胞转移是恶性肿瘤的主要特征, 是引起癌症患者死亡的首要因素。肿瘤细胞释放各种蛋白水解酶, 破坏其黏附部位的组织, 即破坏细胞外基质和血管壁的基底膜, 实现浸润转移和新生血管的生成[12]。而在这一过程中, 基质金属蛋白酶家族 (matrix metalloproteinase, MMP) 及其抑制剂发挥了重要的作用。Zhang等[13]前期研究了从促进细胞凋亡和抗血管新生两方面实现姜黄素和多柔比星联合治疗肝癌的作用, 表现出更高效地诱导细胞凋亡, 良好的抑制肿瘤血管生成的作用, 包括抑制人脐静脉血管内皮细胞 (human umbilical vein endothelial ceils, HUVEC) 增殖、转移、侵袭和血管内皮生长因子 (vascular endothelial growth factor, VEGF) 通路。Zhang等[14]研究报道了冬凌草甲素和顺铂联合给药逆转肿瘤MDR, 该联合给药不仅可以抑制肿瘤移行和侵袭, 并且从MMP2和MMP9蛋白的表达方面阐述了抑制肿瘤MDR的机制。

1.3 抗肿瘤多药耐药 肿瘤MDR是指肿瘤细胞在对1种化疗药产生耐药的情况下同时对一系列不同结构和不同机制的化疗药产生耐药的现象, 是临床上导致化疗失败的重要原因[15,16]。MDR发生机制复杂, 包括细胞内因和肿瘤微环境改变等, 其发生机制的复杂性为克服肿瘤耐药带来挑战[17,18]。采用纳米载体共递送化疗药物和中药活性成分的一大优势就体现在能够逆转MDR。Zhang等[19]研究表明藤黄酸和顺铂联合用药可下调多药耐药相关蛋白2 (multidrug resistance-associated protein 2, MRP2) 和肺耐药蛋白 (lung resistance protein, LRP) 的表达, 达到治疗肿瘤的作用。其中藤黄酸可阻滞细胞周期G0/G1, 并且上调caspase-3和Bax蛋白的表达, 下调pro-caspase-9和Bcl-2蛋白表达; 当两药合用后, 其细胞凋亡作用增强, 减小抗肿瘤药物顺铂耐药指数。Zou等[20]研究了将冰片与紫杉醇联合用于逆转MDR, 体外细胞实验发现, 联合用药可提高紫杉醇在A2780/PTX细胞内的浓度、细胞摄取, 细胞毒性增强, 减少MMP蛋白和增强细胞凋亡。

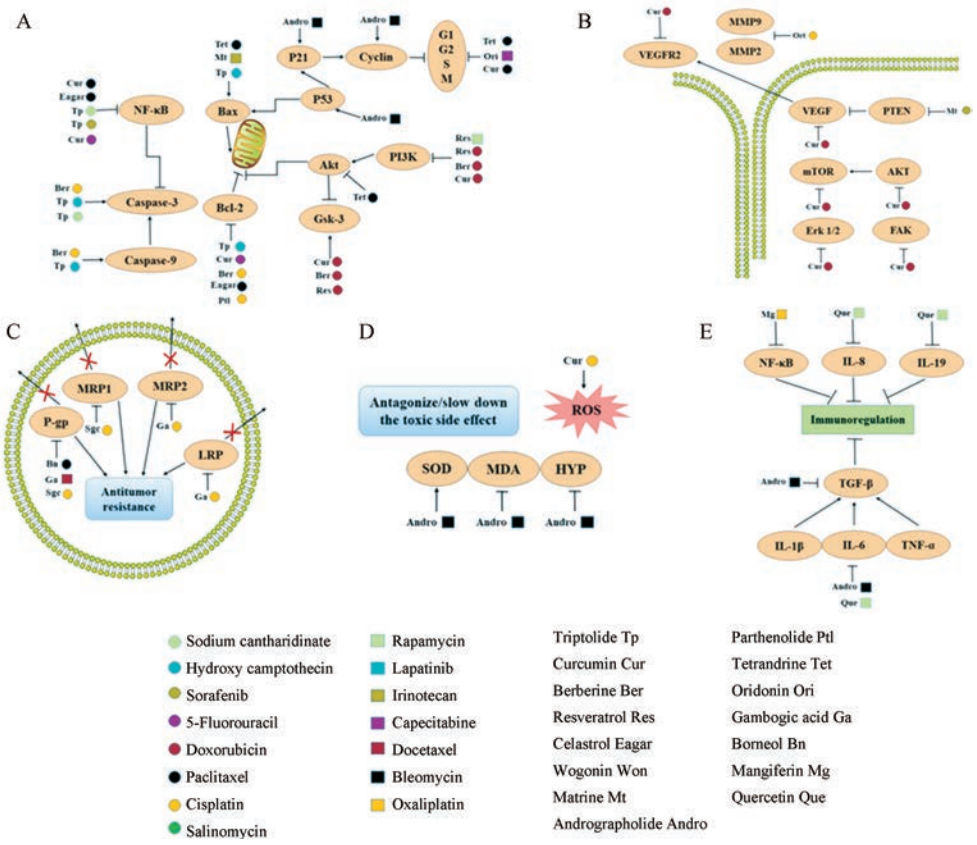

Figure 1 The advantages of combining active ingredients of Chinese herbs with small-molecule anticancer drugs. A: Proliferation inhibition; B: Metastasis inhibition; C: Antitumor resistance; D: Antagonize/slow down the toxic side effect; E: Immunoregulation

1.4 拮抗/减缓毒副作用 化疗药物在治疗肿瘤的同时也会损伤机体正常组织或细胞, 采用中药 (天然药) 联合化疗药物使用, 可以从多靶点、多途径作用于肿瘤组织, 减少化疗药物的用量从而降低其毒性, 并且有些中药 (天然药) 能够减缓化疗药物所造成的毒副作用, 联合使用能提高临床用药安全性。Guo 等[21]利用中药穿心莲的有效成分穿心莲内酯与博来霉素联合用药, 不仅增强抗肿瘤的作用, 还可减缓博来霉素长期使用对机体产生的毒性。实验结果表明, 将穿心莲内酯与博来霉素联合给药后, 使博来霉素单独用药造成的肺纤维化得到缓解, 具体表现在激活超氧化物歧化酶 (superoxide dismutase, SOD)、抑制丙二醛 (malondialdehyde, MDA) 和羟脯氨酸 (hydroxyproline, HYP) 的产生, 同时衰减一些炎症因子的蛋白表达。Cheng 等[22]利用姜黄素能够增敏化疗药物对 HCC 细胞的作用, 研究了姜黄素和顺铂两种药物的联合使用, 姜黄素能够减轻顺铂药物单独使用时所造成的毒副作用 (肾毒性、耳毒性和神经毒性), 提高了临床上合理用药的可能性。

1.5 免疫调节 机体的免疫功能状态对肿瘤的发生和发展影响很大, 肿瘤免疫治疗能通过调节患者自身的免疫能力达到识别肿瘤细胞、杀伤肿瘤细胞的目的, 具有能将毒性降至最小的特点。Quagliariello 等[23]研究雷帕霉素和槲皮素的联合用药, 发现可明显降低 IL-8、IL-6 和 IL-19 细胞因子水平, 提示该联合用药可调节机体免疫状态, 增强肿瘤免疫; 并且可下调 VEGF、MMP2 和 MMP9, 表明该联合用药可抑制肿瘤细胞转移。Guo 等[21]研究发现穿心莲内酯和博来霉素联用不仅可以增强博来霉素抗肿瘤的疗效, 而且可以减轻毒副作用, 还可衰减 IL-1β、TNF-α、IL-6 和 TGF-β1 细胞因子水平, 调节肿瘤细胞的免疫状态, 表明穿心莲内酯可成为博来霉素的辅助治疗药物。

目前, 多种中药活性成分联合化疗药物的抗肿瘤的研究报道见表 1[11,13,14,19,21-44]。

2 药物联合纳米共载的优势

2.1 增加药物肿瘤专属性 具有合适粒径的纳米药物载体可通过渗透滞留效应 (enhanced permeability and retention effect, EPR) 增加化疗药物在肿瘤部位的蓄积。因此, 与游离药物比较, 采用载体递送药物可达到更好地逆转 MDR 的作用[45]。Hu 等[46]将槲皮素和替莫唑胺共载于脂质体中, 发现该纳米体系可显著增强药物进入脑组织。再者, 纳米载体还可通过表面修饰,

Table 1 Antitumor of active ingredients of Chinese herbs combined with chemotherapeutic drugs. IGF: Insulin-like growth factor; EGFR: Epidermal growth factor receptor; COX: Cyclooxygenase; VEGF: Vascular endothelial growth factor; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; MMP: Matrix metalloproteinase; LRP: Lung resistance protein; SOD: Superoxide dismutase; MDA: Malondialdehyde; HYP: Hydroxyproline; ROS: Reactive oxygen species

Mechanism	Drug	Cell type	Pathway	Ref
Proliferation inhibition	Triptolide + sodium cantharidinate	SMMC 7721	Down-regulated the expression of NF-κB p65 and up-regulated the expression of caspase-3	[24]
	Triptolide + hydroxycamptothecin	A549	Up-regulated the expression of caspase-3, caspase-9, Bax/Bcl-2, release cytochrome C	[11]
	Triptolide + sorafenib	HuH-7, PLC/PRF/5	Decrease NF-κB activity	[25]
	Curcumin + 5-fluorouracil	-	NF-κB, IGF-1, EGFR, COX-2, phosphatase and tensin homolog and Bcl-2	[26]
	Curcumin + doxorubicin	MIA-PaCa-2	Modulate the activities of the PI3K/PTEN/AKT/mTORC1/GSK-3	[27]
	Curcumin + paclitaxel	MCF-7, B16F10	NF-κB, Akt, G2/M	[28]
	Berberine +doxorubicin	MIA-PaCa-2, MCF-7	Modulate the activities of the PI3K/PTEN/AKT/mTORC1/GSK-3	[27]
	Berberine + cisplatin	MCF-7	Increase capase-3, caspase-9 activity, decrease Bcl-2 activity	[29]
	Resveratrol + doxorubicin	MIA-PaCa-2	Modulate the activities of the PI3K/PTEN/AKT/mTORC1/GSK-3	[27]
	Resveratrol + salinomycin	MCF-10A, MCF-7	Modulate MAPK pathway	[30]
	Resveratrol + rapamycin	$TSC1^{-/-}$ MEF	Inhibiting mTOR and PI3K signaling	[31]
	Celastrol + lapatinib	MDA-MB-453	HER2/neu-overexpressing	[32]
	Celastrol + paclitaxel	8505C, SW1736	Down-regulated the expression of Bcl-2, modulate the activities of the NF-κB and Akt	[33]
	Wogonin + sorafenib	Hep3B, Bel-7402, HepG2, SMMC-7721	Apoptosis potentiation and autophagy inhibition	[34]
	Matrine + irinotecan	HT29	Upregulation of the TOPO I, Bax and caspase-3 protein expression	[35]
	Andrographolide + bleomycin	H22	P53/P21/cyclin pathways	[21]
	Parthenolide + 5-fluorouracil	SW620	Down-regulated the expression of Bcl-2	[36]
	Tetrandrine + paclitaxel	MCF-7/ADR	G1 and G2	[37]
	Tetrandrine + paclitaxel	BGC-823	Down-regulated the expression of p-Akt and Bcl-2, up-regulated the expression of Bax	[38]
	Tetrandrine + paclitaxel	A2780/PTX	Down-regulated the expression of p-Akt, Akt and Bcl-2, up-regulated the expression of Bax	[39]
	Oridonin + capecitabine	MDA-MB-231	S and G2/M	[40]
Metastasis inhibition	Curcumin + doxorubicin	SMMC 7721	Modulate VEGF pathway	[13]
	Matrine + sorafenib	HepG2, Hep3B	Decrease PTEN	[41]
	Oridonin + cisplatin	AML	Down-regulated the expression of MMP2 and MMP9	[14]
Antitumor resistance	Gambogic acid + cisplatin	A549/DDP	Downregulating MRP2 and LRP expression	[19]
	Borneol + paclitaxel	A2780/PTX	Downregulating P-gp expression	[42]
	Gambogic acid + docetaxel	MCF-7/ADR	Downregulating P-gp expression	[42]
	Oridonin + cisplatin	SGC7901/DDP	Downregulating P-gp, MRP1, cyclin D1 and PP2A expression	[43]
Antagonize/slow down the toxic side effect	Andrographolide + bleomycin	H22	SOD, MDA and HYP	[21]
	Curcumin + cisplatin	HepG2	ROS	[22]
Immunoregulation	Andrographolide + bleomycin	H22	Decrease IL-1β, TNF-α, IL-6, TGF-β1, downregulating TGF-β, α-SMA, p-Smad2/3 expression, increase Smad7 activity	[21]
	Mangiferin + oxaliplatin	HT29	Downregulating NF-κB	[44]
	Quercetin + rapamycin	MCF-7	Downregulating IL-8, IL-6, IL-19, decrease VEGF, downregulating MMP2, MMP9 expression, decrease CD44	[23]

利用靶头分子与肿瘤细胞表面特异性高表达的受体结合, 达到靶向递送药物[47]。常见的靶向修饰分子包括叶酸[48]、透明质酸[49]、细胞穿膜肽[50]、转铁蛋白[51]和生物素[52]等。Baek 等[53]采用多功能脂质纳米粒共递送姜黄素和紫杉醇以逆转肿瘤 MDR, 通过结构外侧接有叶酸分子, 可靶向到肿瘤部位的叶酸受体, 该主动靶向可显著地逆转肿瘤 MDR。

2.2 保证联合药物最佳比例 联合给药的药物比例对抗肿瘤效果的发挥起关键作用, 不合适的药物比例甚至可能会使联合作用的药物产生拮抗作用, 降低治疗效果。将不同药物共载于同一纳米载体, 可改变药物原有药动学特征, 从而确保联用药物以恒定比例进入肿瘤细胞, 有利于发挥药物间协同作用[54]。Houdaihed 等[55]研究了一种共递送紫杉醇和依维莫司最优比例的聚合物纳米粒, 由于这两种药物具有显著不同的药代动力学行为, 临床联合用药效果不理想, 因此制备

了一种纳米体系, 使紫杉醇和依维莫司能够在体内维持最优比率1∶0.5, 从而改善了由于体内药代动力学行为不同造成的联用疗效弱, 精准地控制联合用药在肿瘤部位的比率。

2.3 增强药物瘤内/细胞内多层次作用 纳米给药系统可以通过调节联用药物在不同刺激下的释放响应机制和释放速率, 从而控制药物联合治疗的顺序和时程, 以实现更为精准的给药过程, 提高联合作用的效果和特异性[56]。Ruttala等[28]制备了一种能够按顺序释放姜黄素和紫杉醇的脂质体, 先将紫杉醇–白蛋白制成纳米粒, 再利用姜黄素包封此纳米粒, 形成内外两层结构, 从而使姜黄素能够下调NF-*κ*B和Akt信号通路, 增加紫杉醇的治疗作用。在生理条件下带正电荷的物质容易被机体消除, 因此Yang等[57]制备了一种可以多级pH响应的纳米胶束, 该胶束能够实现电荷翻转, 当胶束在机体循环的时候呈电中性, 到达肿瘤组织时电荷翻转为正电荷, 通过静电相互作用促进肿瘤细胞对载体的吞噬。

3 联合抗肿瘤的常用纳米载体类型及特点

3.1 脂质体 脂质体的水相和脂质双分子层可以包载多种药物, 如亲水性的药物可以包封于亲水性的核心, 疏水性的药物可以包载于脂质膜层中, 两性药物可定位于水相和膜内部的磷脂上, 蛋白质类抗体还可修饰于脂质体表面赋予其靶向性[58,59]。Hu等[46]利用二硬脂酰基磷脂酰乙醇胺–聚乙二醇2000 (1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000], DSPE-PEG2000) 材料制备了一种新型脂质体, 共载替莫唑胺和槲皮素用于耐药细胞株神经胶质瘤U87。透射电子显微镜法揭示, 替莫唑胺–槲皮素共载脂质体纳米粒具有较小的粒径; 体外细胞实验表明, 该脂质体有利于药物细胞摄取, 从而实现替莫唑胺的给药量减少而疗效不减的效果。

3.2 纳米粒 脂质纳米粒的性质稳定、制备较简便, 具有一定的缓释作用, 主要适合于难溶性药物的包裹, 被用作静脉注射或局部给药达到靶向定位和控释作用的载体。Xu等[42]制备了一种聚乳酸–羟基乙酸共聚物[poly(lactic-co-glycolic acid), PLGA]脂质纳米粒, 用于多西他赛和藤黄酸的共递送, 首先筛选多西他赛和藤黄酸的最优比率将其包封到PLGA脂质纳米粒, 细胞凋亡实验和免疫印迹分析结果表明, 该共载纳米粒可通过下调P-gp的表达而增强细胞的凋亡, 有效地抑制了肿瘤细胞的MDR。

此外, 为了改善纳米载体的靶向性及稳定性, 近年来国内外学者不断尝试对其表面进行功能化修饰, 以更好地达到主动靶向的目的。Cui等[60]制备了一种具有双重靶向性的纳米粒 (图2A), 该体系同时具有磁性导向和T7转铁蛋白受体。首先合成NH_2-PEG_{3500}-T7材料 [图2B(a)], 再制备负载药物的磁性PLGA-PEG-T7纳米粒 [图2B(b)]。实验结果表明, 该系统提高了神经胶质瘤的治疗效果。另外, 也研究了具有叶酸受体[61]、表皮生长因子受体[62]主动靶向性的纳米粒。

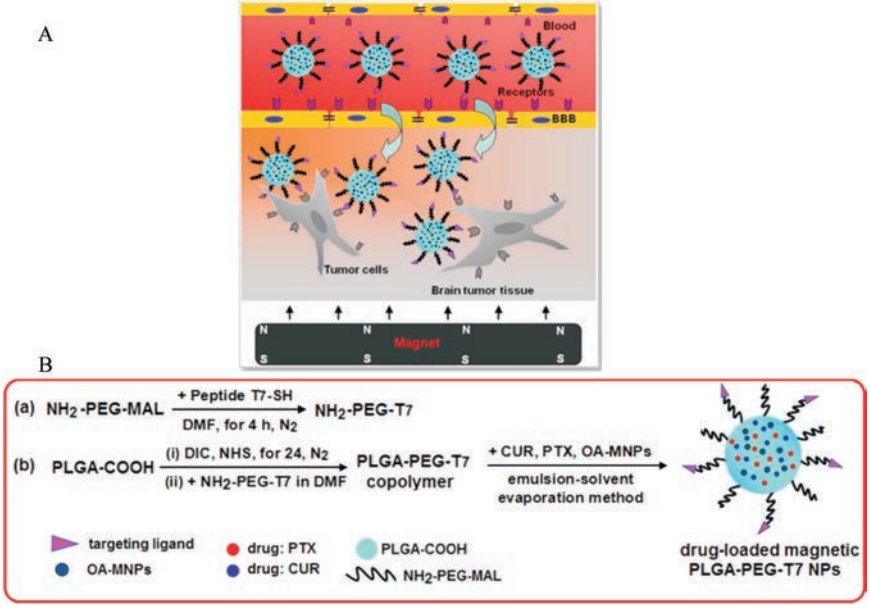

Figure 2 Schematic illustration of blood-brain barrier (BBB)-penetrating andtumor-targeting delivery *via* the T7-mediated and magnetic-guided, dual-targeting MNP/T7-PLGA NPs (A). Synthesis of PLGA-PEG-T7 polymer (a) and drug-loaded MNP/T7-PLGA NPs (b) (B)[60]. PTX: Paclitaxel; CUR: Curcumin

利用肿瘤组织和肿瘤细胞内涵体/溶酶体内的酸性微环境, 研发了pH敏感的聚合物纳米载体以实现抗癌药物在肿瘤处的高效快速释放。Peng等[63]研究采用一步制成聚丙烯酸-碳酸钙 (polyacrylic acid-calcium carbonate, PAA-$CaCO_3$) 纳米粒包封多柔比星和姜黄素两种药物, 当此纳米体系到达肿瘤部位时, 在肿瘤部位的微酸性条件下, pH敏感键断裂, 结构破坏, 从而释放出所载药物。

3.3 聚合物胶束 聚合物胶束具有疏水性的核心, 常用于包载水溶性较差或疏水性药物, 并且能够提高包载药物的生物利用度, 避免药物在体内被快速降解[59]。Yao等[64]设计了一种能够共载紫杉醇和姜黄素的胶束 (图3), 结果表明该胶束对于疏水性药物的递送具有很大的应用价值。为了更好地控制药物在肿瘤部位的释放, Yang等[57]研制了一种多级pH响应的胶束, 此胶束共递送了紫杉醇和姜黄素用于乳腺癌干细胞的治疗, 具有良好的效果。此胶束所用的材料为聚乙二醇-苯亚胺-聚*γ*-苄基-*L*-天冬氨酸-聚乙烯基咪唑 [poly(ethylene glycol)-benzoic imine-poly(*γ*-benzyl-*L*-aspartate)-*b*-poly(1-vinylimidazole), mPEG-PBLA-PVIm], 可实现表面电荷由中性到阳性的智能转换, 并且粒径的减小有利于长时间的血液循环和从肿瘤血管的溢出, 促进细胞的摄取和更好的肿瘤渗透率。Sarisozen等[65]为了实现纳米载体对肿瘤部位具有更好的靶向性, 利用转铁蛋白-聚乙二醇-聚乙烯 (transferrin-polyethylene glycol-polyethylene, TF-PEG-PE) 等材料制备了一种具有转铁蛋白主动靶向的混合胶束。Fang等[66]制备了一种磁性胶束用于共递送多柔比星和姜黄素, 此共载体系具有乳铁蛋白靶向和磁性响应的性质, 此体系相比单一递送任何一种药物, 不仅延长了药物在肿瘤部位的停留时间, 并且更有效地抑制了肿瘤。

3.4 聚合物-药物结合物 聚合物-药物结合物在机体内转运过程中保持稳定, 通过对连接基团进行合理设计, 获得生理环境如pH值、酶、温度及磁等敏感性质, 从而实现肿瘤靶向部位有效释放药物[67]。Xue等[68]制备了一种能够维持体外细胞毒性和具有多功能纳米医学特征的自组装前药纳米粒, 采用还原敏感键将香茅醇和卡巴他塞两种药物连接, 制得的纳米粒能响应肿瘤细胞的高生物还原剂谷胱甘肽 (glutathione, GSH) 浓度 (图4)。Zhang等[69]设计了PEG-DOX-CUR前体药物纳米粒, 用于同时递送多柔比星 (DOX) 和姜黄素 (CUR), 通过希夫碱反应将多柔比星连接到PEG上制得多柔比星前体药物, 通过自组装将姜黄素包封在纳米粒内部形成PEG-DOX-CUR NPs。实验结果表明, 此系统具有酸敏感性, 到达肿瘤内部使结构破坏从而释放出多柔比星和姜黄素两种药物, 能够使其到达肿瘤细胞的细胞核和细胞质中, 发挥抗肿瘤的作用。Cui等[70]采用转铁蛋白修饰纳米粒用于共递送多柔比星和姜黄素两种药物, 首先合成pH敏感的Tf-PEG-CUR前体药物, 再将多柔比星包在Tf-PEG-CUR NPs中制得Tf-PEG-CUR/DOX NPs体系。此体系具有主动靶向性, 并能够响应肿瘤部位微酸性而实现药物的释放。

3.5 其他纳米载体 纳米笼和纳米水凝胶也可用于共递送化疗药物。Zhang等[71]利用生物素聚乙二醇巯基 (biotin PEG thiol, biotin-PEG-SH) 制备了一种具有近红外响应的金纳米笼, 共递送多柔比星和槲皮素治疗乳腺癌。该体系应用生物素修饰金纳米笼使其具有

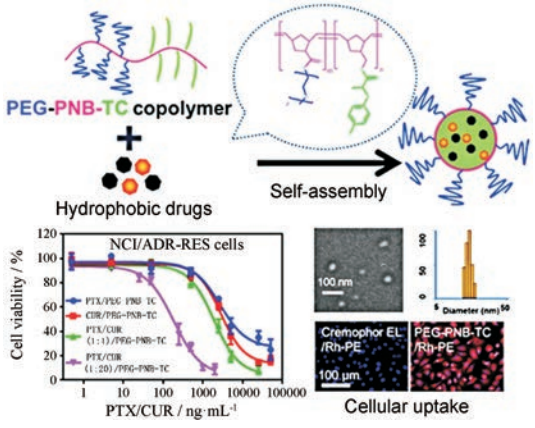

Figure 3 Scheme of the bottlebrush PEG-PNB-TC polymericmicelles. The combination of PTX and CUR showed synergistic anticancer effect in both the drug mixture and drug coloaded micelles[64]. PTX: Paclitaxel

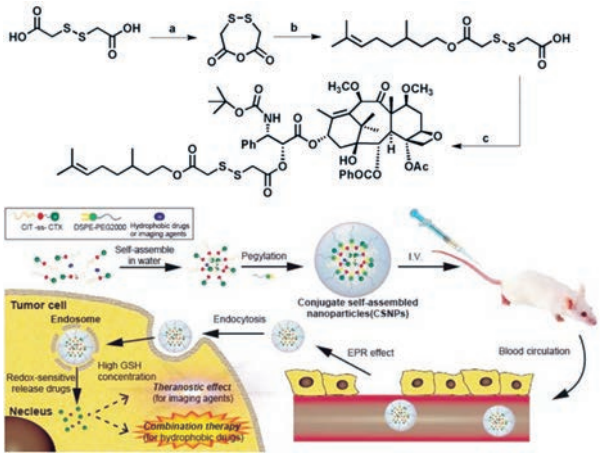

Figure 4 Synthesis of citronellol-cabazitaxel (CIT-ss-CTX) conjugate self-assembled noparticles (CSNPs). It has a promising perspective as a multifunctional nanomedicine for combination therapy and theranostics attribute to its long circulation property, redox-sensitive mechanism and high drug co-loading capability[68]

近红外响应性, 再用十四醇填补中空的载体使其能在39 ℃融化从而控制药物释放。Quagliariello等[23]制备了一种纳米水凝胶用于共载雷帕霉素和槲皮素, 该研究是基于CD44主动靶向策略将雷帕霉素和槲皮素有效递送至乳腺癌组织。

目前, 中药活性成分联合化疗药物抗肿瘤的常用纳米载体类型及特点的研究报道见表2[13,23,28,42,46,53,57,61,63,65,66,69-88]。

Table 2 The researches of several nanoparticles used to co-deliver two different drugs. EPR: Enhanced permeability and retention effect; DSPE-PEG: 1, 2-Distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)]; PLGA: Poly(lactic-co-glycolic acid); PEI-IPDI-PEA: Branched polyethylenimine-isophorone diisocyanate-poly(*L*-lactide)-PEI; PAA: Polyacrylic acid; GMS-TPGS-SA-FA: Glyceryl monostearate-*D*-alpha tocopherol acid polyethylene glycol succinate-stearic acid and folate; PVDF: Poly(vinylidene fluoride); PAE: Polyamide epichiorobydrin; PVA: Polyvinyl alcohol; PLMS: PEGylated lipid bilayer coated mesoporous silica; ETP-CUR-NLC: Etoposide and curcumin loaded nanostructured lipid carriers; mPEG-PBLA-PVIm: Poly(ethylene glycol)-benzoic imine-poly (*γ*-benzyl-*L*-aspartate)-*b*-poly (1-vinylimidazole); Tf: Transferrin; MePEG/PCL: Methoxy poly(ethylene glycol)-*ε*-poly(caprolactone) diblock copolymers

Nanoparticle	Nanocarrier type	Nanocarrier composition	Feature	Drug	Cell type	Ref
Liposome	Liposome	DSPE-PEG2000	EPR	Temozolomide + quercetin	U87	[46]
	Liposome	PEG	EPR	Paclitaxel + curcumin	subG1	[72]
Nanoparticle	PLGA-lipid nanoparticle	DSPE-PEG2000, PLGA	EPR	Docetaxel + gambogic acid	MCF-7/ADR	[42]
	Phytosome nanoparticle	Phytosomes	EPR	Doxorubicin + quercetin	MCF-7	[73]
	PLGA nanoparticle	CHO-hyd-PEG-AA/PLGA	EPR	Doxorubicin + resveratrol	MDA-MB-231/ADR and MCF-7/ADR	[74]
	PLGA nanoparticle	PEI-IPDI-PEA	EPR	Doxorubicin + curcumin	4T1	[75]
	Polymer-lipid nanoparticle	DSPE-PEG2000	EPR	Paclitaxel + curcumin	MCF-7 and B16F10	[28]
	Lipid-polyacrylic acid calcium carbonate nanoparticle	PEG-PAA-$CaCO_3$	pH-sensitive	Doxorubicin + curcumin	HepG2	[63]
	Lipid nanoparticle	GMS-TPGS-SA-FA	Folate receptor targeted	Paclitaxel + curcumin	MCF-7/ADR	[53]
	Lipid-polymer hybrid nanoparticle	PLGA/PEG-DSPE	EPR	Cisplatin + curcumin	HeLa	[76]
	Lipid nanoparticle	PVDF	EPR	Doxorubicin + curcumin	BEL7402/5-FU	[77]
	Polymeric nanoparticle	TPGS-PAE	pH-sensitive	Doxorubicin + curcumin	SMMC7721	[13]
	Polymeric nanoparticle	PLGA/PEG-DSPE	EPR	Cisplatin + curcumin	HeLa	[76]
	Polymeric nanoparticle	PLGA-PVA	EPR	Camptothecin + curcumin	Colon-26	[78]
	Mesoporous silica nanoparticle	PLMS	EPR	Paclitaxel + curcumin	7364	[79]
	Magnetic nanoparticle	$FeCl_3 \cdot 6H_2O/FeCl_2 \cdot 4H_2O$	Magnetic targeted	Temozolomide + curcumin	T-98G	[80]
	Lipid nanoparticulate	ETP-CUR-NLC	EPR	Etoposide + curcumin	SGC7901	[81]
Polymeric micelle	Micelle	mPEG-PBLA-PVIm	pH multistage responsive	Paclitaxel + curcumin	MCF-7	[57]
	Micelle	(PEG-PE)/vitamin E	EPR	Paclitaxel + curcumin	SK-OV-3	[82]
	Micelle	Tf-PEG-PE	Transferrin-targeted	Paclitaxel + curcumin	SK-OV-3	[65]
	Micelle	TPGS-PEG-DSPE	EPR	Doxorubicin + curcumin	MCF7 and MCF7/Adr	[83]
	Amphiphilic copolymeric micelle	PEG-PLA	EPR	Doxorubicin + curcumin	MCF-7/ADR	[61]
	Magnetic micelle	PVA/PAA	Lactoferrin (Lf)-tethered magnetic targeted	Doxorubicin + curcumin	RG2	[66]
	Magnetic micelle	MePEG/PCL	Magnetic targeted	Rapamycin + curcumin	T98G	[84]
Polymer-drug conjugate	Prodrug nanoparticle	PEG-DOX-CUR	pH-sensitive	Doxorubicin + curcumin	HepG2	[69]
	Prodrug nanoparticle	Tf-PEG-CUR	pH-sensitive, transferrin-targeted	Doxorubicin + curcumin	MCF-7	[70]
	Prodrug lipid nanoparticle	Tf-PEG-hz-GMS	pH-sensitive, transferrin targeted	Docetaxel + baicalein	Lung cancer	[85]
Other types	mPEG-PLGA copolymer	mPEG-PLGA	EPR	Doxorubicin + quercetin	MDA-MB231	[86]
	Nanohydrogel	FA-HA	CD44 targeted	Rapamycin + quercetin	MCF-7	[23]
	Lipid-polymeric nanocarrier	PLGA-cholesterol-stearic acid-PEG2000-DSPE	EPR	Vincristine + quercetin	Human Burkitt's lymphoma	[87]
	Gold nanocage	Biotin-PEG-SH	Near-infrared (NIR)-responsive	Doxorubicin + quercetin	MCF-7/ADR	[71]
	Nanostructured lipid	HA, solid lipids, liquid lipids	CD44 targeted	Doxorubicin + baicalein	MCF-7/ADR	[88]

4 药物联合纳米共载的主要方式

4.1 共载原理 纳米载药体系递送药物的原理可以是简单的物理包封, 如脂质体通常是将两种水溶性的药物载入其亲水性的内核, 聚合纳米粒倾向于在其疏水内核中同时包裹两种脂溶性药物。Lin等[79]制备了一种具备双分子层结构的介孔硅纳米粒用于共递送姜黄素和紫杉醇, 该结构采用物理包载的方式将姜黄素和紫杉醇包封在双分子层结构内, 从而提高其对肿瘤细胞的细胞毒性。与脂质体或胶束等主要依靠物理作用包封药物不同, 聚合物–药物结合物是通过化学键共价作用实现载体与药物的连接, 由高分子聚合物与药物键合形成的化合物受到广泛关注, 这类化合物被称为“聚合物前药”。与传统纳米药物输送系统相比具有合成方法灵活、性质及构成广泛多样性、载药率确定、稳定性高和爆释现象小等优点。Cui等[70]设计了一种具有pH敏感的姜黄素前药, 同时将转铁蛋白修饰在纳米载体的表面以帮助制剂实现转铁蛋白介导的肿瘤主动靶向; 并且依靠聚乙二醇–姜黄素前药两亲性结构实现自组装, 将多柔比星包裹在其中。

4.2 共载形式 采用纳米粒共载药物具有多种形式, 可以将两种药物均包封在纳米核内。Li等[76]制备了两种不同材料的纳米粒用于递送顺铂和姜黄素, 一种为脂质–聚合物混合纳米粒, 另一种为聚合物纳米粒, 两种纳米粒均是通过物理包载的方式将两种药物包封在纳米材料内部, 对HeLa细胞均具有较高的细胞毒性。结果表明, 采用纳米载体将药物包载在核内能较好地提高抗肿瘤作用。也可利用核壳形式将药物分层包载, Guo等[75]制备了一种具有核壳结构的共载多柔比星和姜黄素的纳米粒, 姜黄素包载于聚乳酸 (poly(*L*-lactide), PLLA) 疏水内核, 将多柔比星吸附于亲水的纳米粒壳表面, 从而实现了分层载药。结果表明, 该设计可增强联合给药的抗肿瘤疗效, 并且降低了多柔比星对心脏组织的病理损伤。Wu等[89]制备了一种具有核壳的PLGA纳米粒, 该纳米粒的外层为透明质酸, 可主动靶向到肿瘤部位的CD44细胞, 结构的内层为PLGA包载的紫杉醇, 采用核壳形式达到了主动靶向到肿瘤部位和治疗肿瘤的作用。因此, 纳米共载的形式是多种多样的, 根据纳米材料的性质结合药物的物理性质和作用机制, 设计更有效的纳米载体形式是科学工作者的使命。

5 结语与展望

随着肿瘤发生、发展机制研究的不断深入, 药物联合治疗方案在肿瘤治疗中展现出显著优势, 而纳米技术在药剂学领域的发展更是为其带来了广阔的应用前景。但目前联合用药纳米体系在制剂设计、制备工艺和评价等方面依然面临诸多挑战, 如依靠纳米粒尺寸效应带来的被动靶向或受体介导的主动靶向特性, 尽管在细胞或动物模型上可观察到肿瘤趋向性, 但仍难以取得真正的临床效果; 如何在共载纳米制备过程实现预设载药量和两种 (多种) 药物配比不变, 并稳定传递入肿瘤组织; 联合用药方案中不同药物可能存在不同作用位点, 如何控制共载体系在肿瘤组织具有良好的释放特性; 随着对纳米技术生物安全性的逐渐关注, 纳米材料的毒理性质也逐渐被人们重视, 但对于在体内纳米粒是否会导致机体损伤仍不明确等。目前国内外学者不断尝试对纳米载体表面进行功能化修饰, 以更好地达到主动靶向的目的; 利用肿瘤复杂微环境中低氧、低pH、间质高压和免疫抑制等生物学特征, 进行纳米结构的改造以实现药物的多步骤多空间的肿瘤组织内释放特性, 均表现出更好的抗肿瘤效果。相信随着中药活性成分作用机制的不断揭示和纳米技术的不断发展, 纳米载体共载中药活性成分和化疗药物以联合抗肿瘤将为肿瘤临床治疗带来惊喜和希望。

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