科学通报 2015 年 第 60 卷 第 15 期: 1339 ~ 1351
评 述 www.scichina.com csb.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS

多功能生物可降解聚合物纳米药物载体: 设计合成及在肿瘤靶向治疗上的应用

邓超[①②], 孟凤华[①②], 程茹[①②], 钟志远[①②*]

① 苏州大学生物医用高分子材料重点实验室, 苏州 215123;
② 苏州大学材料与化学化工学部, 苏州 215123
* 联系人, E-mail: zyzhong@suda.edu.cn

2015-02-07 收稿, 2015-03-10 接受, 2014-04-30 网络版发表
国家自然科学基金(51273137, 51473110)、国家杰出青年科学基金(51225302)和江苏高校优势学科建设工程资助

摘要 生物可降解聚合物纳米载体具有良好的生物相容性、较长的体内循环时间、可靶向富集到肿瘤组织、在体内可降解等优越性能, 是实现肿瘤靶向治疗最有前景的载体系统之一. 多个基于生物可降解聚合物的纳米药物已投入市场或进入不同临床试验阶段. 然而, 纳米药物虽然有效降低了药物的毒副作用, 却并没有显著提高肿瘤治疗效果. 同时, 纳米药物还存在体内稳定性差、药物易早释、肿瘤细胞内吞效率低、细胞内药物释放缓慢等问题. 因此, 提高纳米药物疗效的新策略成为国际研究的前沿和热点. 本文综述了近年来本课题组及国内外学者在构建多功能生物可降解聚合物纳米载体和肿瘤靶向治疗上的研究进展. 本文重点介绍了以下4个方面: (1) 化学或物理交联稳定的生物可降解聚合物纳米载体, 有效提高了纳米药物的体内稳定性, 抑制药物早释, 增强肿瘤靶向性能; (2) 生物响应性生物可降解聚合物纳米载体, 实现了抗癌药物在肿瘤组织和肿瘤细胞内的快速高效释放; (3) 刺激敏感可逆交联的生物可降解纳米载体, 巧妙解决了聚合物纳米载体在血液循环时需具有高稳定性、而在肿瘤细胞内需快速高效释放药物的矛盾; (4) 靶向肿瘤的生物可降解聚合物纳米载体, 促进了纳米药物在肿瘤组织处的滞留, 增强纳米药物的内吞效率和肿瘤细胞内的富集. 我们相信多功能聚合物纳米药物经过缜密设计、精确制备和系统研发, 将会陆续进入临床应用并在肿瘤靶向治疗中发挥重要作用.

关键词
纳米载体
抗癌药物
药物控制释放
靶向释放
肿瘤治疗

众多高效的化疗药物因其巨大的毒副作用而难以应用于临床肿瘤治疗. 近10多年, 各种纳米载体如脂质体、聚合物胶束、聚合物囊泡、聚合物纳米粒、聚合物纳米凝胶等被开发用于运载抗癌药物和蛋白质, 实现对肿瘤的高效低毒治疗[1~3]. 例如, 脂质体阿霉素药物(Doxil®, Myocet®, LipoDox®)已成为临床治疗晚期卵巢癌、乳腺癌、多发性骨髓瘤和卡波希氏肉瘤的常规药物[4,5]. 近年来, 多个高分子纳米抗癌药物也已进入临床或不同临床试验阶段(表1). 基于聚乙二醇-聚乳酸共聚物(PEG-PLA)的载有紫杉醇(PTX)的胶束药物(Genexol-PM)自2007年已在韩国用于临床治疗乳腺癌、肺癌和卵巢癌等[6]. 基于PEG和聚多肽的多种抗癌纳米药物(如NK 911, NK 105, NK 012, NC 6004, NC 4016, NC 6300等)已分别进入了临床I~III期的试验阶段[7~13,15]. 最近, 基于PEG-聚(*D*,*L*-乳酸)(PEG-PDLLA)和PEG-聚(乳酸-*co*-羟基乙酸)(PEG-PLGA)的第1个含靶向分子的聚合物纳米药物(BIND-014)进入了临床II期试验, 用于前列腺肿瘤和

引用格式: 邓超, 孟凤华, 程茹, 等. 多功能生物可降解聚合物纳米药物载体: 设计合成及在肿瘤靶向治疗上的应用. 科学通报, 2015, 60: 1339–1351
Deng C, Meng F H. Cheng R, et al. Multifunctional biodegradable polymeric nanocarriers: Design, synthesis, and applications in targeted tumor therapy (in Chinese). Chin Sci Bull, 2015, 60: 1339–1351, doi: 10.1360/N972015-00141

肺癌的主动靶向治疗[14]. 临床治疗结果表明, 纳米药物具有更好的药物利用率, 能很好地降低毒副作用, 极大提高了病人在治疗期间对药物的耐受性等. 尽管纳米药物在过去10多年取得了明显的进展, 但其治疗效果与人们的预期还有较大的差距[16,17]. 现有纳米药物还面临众多挑战: (1) 纳米药物注射到体内后, 由于被极大稀释及与血液中不同成分的作用而很容易分解或集聚, 导致包载的药物过早释放, 不能富集到肿瘤处[18,19]; (2) 肿瘤组织具有胞外基质硬化、组织液静水压大、肿瘤细胞与实体肿块周边组织结合紧密等特点, 导致纳米药物的肿瘤组织穿透能力差[17,20,21]; (3) 纳米药物为实现在血液循环中的长循环和肿瘤靶向效果, 通常需在表面引入PEG或葡聚糖(Dextran)等分子来避免非特异性吸附作用, 但生物惰性表面同时极大地阻碍了纳米药物进入肿瘤细胞, 使得许多细胞内作用药物(阿霉素(DOX)、PTX等)及蛋白质(细胞色素C等)无法达到预期治疗效果[22]; (4) 很多纳米药物在进入肿瘤细胞后释放药物速度太慢或释放不充分, 药物利用度低. 为了克服纳米药物面临的这些细胞内外的屏障, 同时增强化疗药物的功效, 研究人员设计制备了各种功能性生物可降解的纳米药物载体[20,22~24]. 本文将集中讨论纳米药物在肿瘤治疗中所面临的一系列挑战, 包括体内稳定性差、药物易早释、肿瘤细胞内吞效率低、细胞内药物释放缓慢等, 并针对这些挑战提出相应的解决策略.

1 化学或物理交联稳定的生物可降解聚合物纳米载体

体内研究表明, 载药纳米系统注射到体内后, 很大一部分药物迅速泄漏出来, 导致纳米药物肿瘤靶向效率低, 而且毒副作用依然显著. 纳米药物在肿瘤部位的富集通常低于5%注射百分剂量率(ID/g)[25].

过去的10多年, 人们采用了各种不同的化学交联方法提高纳米药物的体内稳定性, 抑制药物早释, 增强肿瘤靶向性能. 例如, Kataoka课题组[26]制备了PLA端甲基丙烯酸酯官能化的PEG-PLA共聚物, 然后通过自由基聚合得到了核交联的生物可降解胶束. 该胶束在表面活性剂(十二烷基磺酸钠, SDS)和有机溶剂中表现出了很好的稳定性. Kissel课题组[27]发现核交联的PEG-聚(ε-己内酯)(PEG-PCL)胶束能显著地增加PTX药物的包载效率, 同时在高倍稀释后仍保持稳定. Hennink课题组[25]用小鼠的鳞状细胞癌模型研究发现, 通过光聚合核交联的胶束在体内具有较长的循环时间, 其在肿瘤处的富集量与未交联胶束相比提高了6倍. 景遐斌课题组[28]和陈学思课题组[29]分别用侧链含肉桂基的PEG-聚谷氨酸(PEG-PGlu)制备纳米载体, 经紫外光辐射交联后能有效地抑制包载PTX药物的早释. Lecommandoux课题组[30]采用二胺和戊二醛为交联剂, 分别制备了基于聚丁二烯-PGlu(PB-PGlu)和聚顺式-1,4-异戊二烯-聚赖氨酸(PI-PLL)的壳交联胶束. 溶胀实验结果表明, 与未交联胶束相比, 壳交联胶束稳定性有很大提高. 本课题组[31,32]用PEG-聚丙烯酸酯碳酸酯-PLA(PEG-PAC-PLA)和PEG-PAC-PCL分别制备了界面光交联的生物可降解胶束载体. 界面交联方法综合了核交联和壳交联的优点: 一方面, 核交联方法可在较高胶束浓度下进行而不会导致胶束之间的交联; 另一方面, 对胶束核和壳的结构和性能影响不大. 该界面交联胶束在高倍稀释时仍保持高稳定性, 且能有效限制包载

表 1 目前用于临床及临床试验的各种高分子纳米抗癌药物

Table 1 Anticancer polymeric nanomedicines currently used in the clinics or approved for clinical trials

名称	载体	抗癌药物	病症	现状	参考文献
Genexol-PM	PEG-PLA	PTX	乳腺癌、肺癌、卵巢癌	批准销售(Samyang, Co)	[6]
NK 911	PEG-PAsp-DOX[a)] conjugate	DOX	实体瘤	II 期临床(Nippon Kayaku, Co)	[7]
NK 105	PEG-PAPB[b)]	PTX	胃癌、乳腺癌	III 期临床(Nippon Kayaku, Co)	[8]
NK 012	PEG-PGlu-SN-38[c)] conjugate	SN-38	三阴乳腺癌	II 期临床(Nippon Kayaku, Co)	[9]
NC 6004	PEG-PGlu	顺铂	胰腺癌	III 期临床(Nanocarrier, Co)	[10]
NC 4016	PEG-PGlu	奥沙利铂	实体瘤	I 期临床(Nanocarrier, Co)	[11]
NC 6300	PEG-b-poly(aspartate-hydrazone-Epi)	表柔比星	实体瘤	I 期临床(Nanocarrier, Co)	[12,13]
BIND-014	PEG-PDLLA 或 PEG-PLGA	多西紫杉醇	转移性前列腺癌、非小细胞肺癌	II 期临床(BIND Therapeutics, Inc)	[14]

a) PAsp, 聚天冬氨酸; b) PAPB, 聚天冬氨酸的 4-苯基丁醇衍生; c) PGlu, 聚谷氨酸

PTX药物的早释. 动物实验结果表明, 半乳糖靶向光交联载PTX的PEG-PAC-PCL胶束比未交联对照组能更有效地抑制肝肿瘤的生长[32].

与具有明显核壳结构的胶束不同, 纳米凝胶由亲水聚合物交联制备得到, 具有含水量高和多孔结构等特点, 可用于包载亲水药物、蛋白质及细胞等[33]. 最近, 本课题组[34]用水溶性PEG-聚(甲基丙烯酸羟乙酯-*co*-丙烯酸酯碳酸酯)嵌段共聚物(PEG-P(HEMA-*co*-AC))和胱胺原位交联, 制备得到了还原敏感纳米凝胶, 可在完全水环境下实现蛋白质药物的高效包裹. 该纳米凝胶对蛋白质药物如细胞色素C的包裹效率高达98.2%, 包载量高达48.2%, 载蛋白质纳米凝胶在生理条件下稳定, 但在细胞内还原环境下会快速解离, 实现蛋白质药物的高效细胞内释放.

除了化学交联方法, 物理交联也可用于增强聚合物纳米载体的稳定性. 例如, Leroux课题组[35]制备了等摩尔量的PEG-聚(*L*-乳酸)(PEG-PLLA)和PEG-聚(*D*-乳酸)(PEG-PDLA)通过立体复合作用交联得到的胶束, 比仅用全规或消旋的聚乳酸制备的胶束具有更好的动力学稳定性, 且在冷冻干燥后可重新分散, 不会聚集. Hennink课题组[36]将苯甲酰和萘甲酰等基团引入PEG-PCL的PCL末端, 得到π–π键交联胶束, 显著降低了临界胶束浓度, 增强了胶束的稳定性.

2 生物响应性生物可降解聚合物纳米载体

目前临床使用的聚合物药物载体通常由PEG-聚酯(PLA, PCL, PLGA等)或PEG-聚多肽(PGlu, PAsp, PLL等)等两亲性生物可降解共聚物制备得到. 它们具有良好的生物相容性, 但在体内降解缓慢, 完全降解通常需要几天到几个月, 在肿瘤处药物释放速度慢, 抗癌效果差. 近10年, 研究人员设计合成了各种不同生物响应性生物可降解聚合物纳米载体, 以实现抗癌药物在肿瘤组织和肿瘤细胞内的快速高效释放[3,37,38].

2.1 pH响应性生物可降解聚合物纳米载体

肿瘤组织微环境呈弱酸性, 其pH为6.5~7.2. 肿瘤细胞内涵体和溶酶体酸性更低, pH可达4.0~6.5. 肿瘤组织和肿瘤细胞内的微酸环境为聚合物纳米载体的触发释放提供了理想的内在刺激, 被广泛应用于抗癌纳米药物的肿瘤靶向释放[39]. 例如, Kataoka课题组[40~42]用抗癌药物DOX的羰基与PEG-PAsp嵌段共聚物的酰肼基通过酸敏的酰腙键相连, 制备了pH敏感的聚多肽前药胶束. 腙键在生理条件下(pH 7.4)相对稳定, 但在类似内涵体和溶酶体的酸性条件下会快速断裂, 从而快速释放出键合的抗癌药物. 最近, 本课题组[43,44]制备了基于PEG-聚(甲基丙烯酸羟乙酯-*co*-甘氨酸乙酯基甲基丙烯酰胺)嵌段共聚物(PEG-P(HEMA-*co*-EGMA))的酸敏感DOX前药纳米粒, 其酸响应速度快, DOX在48 h内实现完全定量释放, 释放行为与水溶的大分子DOX前药相似.

除了通过腙键构建pH敏感聚合物纳米载体前药, 酸敏感的乙缩醛键也常用于制备pH敏感可降解纳米载体和前药. 例如, 本课题组[45]将PTX通过乙缩醛键接枝到PEG-聚丙烯酸聚合物(PEG-PAA)上, 构建了内涵体酸敏感的高载药量(21.6%~42.8%)前药胶束. 体外释放实验结果表明, 该前药胶束的释放具有明显的pH敏感性, 在pH分别为5.0, 6.0和7.4时, 48 h分别释放了86.9%, 66.4%和29.0%的PTX药物. 细胞存活率分析结果显示, 该pH敏感的前药胶束对KB, HeLa和耐PTX的A549耐药细胞具有高抗肿瘤效果. 同时, 该前药胶束可以同时包裹抗癌药物DOX, 在弱酸的条件下同时释放PTX和DOX 2种抗癌药物. 通过设计含乙缩醛键的环碳酸酯(TMBPEC)单体, 我们制备了酸敏感生物可降解聚合物胶束, 可包裹DOX和PTX等抗癌药物[46]. 体外释放实验结果表明, 可通过环境pH来控制药物释放速率. Haag课题组[47]利用基于超支化聚甘油(dPG)的含乙缩醛炔基和叠氮衍生物, 通过纳米沉淀法制备纳米粒, 原位点击化学交联制备了pH敏感的纳米凝胶, 其可高效包裹蛋白质药物(包裹效率100%). 体外释放研究结果表明, 包裹的天冬酰胺酶在pH 7.4下35 h内很少释放, 但在pH 4.0和5.0环境下, 蛋白质分别在5和35 h内几乎完全释放.

基于硼酸-儿茶酚酯的化学键在生理条件下稳定, 而在类内涵体和溶酶体的弱酸条件下容易断裂, 因而也被用于制备pH敏感的聚合物纳米载体. 例如, Feng课题组[48]依次将儿茶酚、胆固醇苯硼酸盐衍生物接枝到PEG-PLL共聚物上, 制备得到pH敏感的聚多肽纳米胶束; 载DOX胶束的肿瘤细胞致死率与自由药相当. Levkin课题组[49]将硼酸接枝到葡聚糖的邻位双羟基上制备得到酸敏感的纳米粒, 载DOX纳米粒在pH 5.0弱酸性条件下释放的药量是在生理pH条件下释放量的4倍. Herrera-Alonso课题组[50]将含二醇

的抗癌药物卡培他滨(capecitabine, CAPE)键合到硼酸接枝的聚碳酸酯上, 得到了pH敏感的前药胶束, 其在中性条件下稳定, 弱酸性条件下能快速释放键合药物.

聚合物囊泡具有类脂质体的结构, 其亲水内腔通过疏水薄膜与外界环境分隔, 不但可用于疏水药物而且可用于亲水药物的控制释放. 聚合物囊泡通过两亲性大分子自组装形成, 通常具有比脂质体更厚的疏水膜(5~30 nm)、更高的稳定性、增强的力学强度和更低的药物渗透性. 聚合物囊泡在亲水物质(DOX·HCl、蛋白质、siRNA、DNA等)和憎水物质(PTX、DOX、量子点等)的包裹和响应性释放中都展现了巨大潜力[51,52]. 近年来, 人们设计制备了各种生理环境(如pH、还原)响应聚合物囊泡, 实现抗癌药物和蛋白质药物的高效细胞内释放[53~55]. 例如, 本课题组[56]制备了pH敏感生物可降解聚合物囊泡, 可同时包载亲水药物(DOX·HCl)和憎水药物(PTX). 体外释放实验结果表明, 载药囊泡在pH 7.4较为稳定, 而在pH 4.0和5.0时会快速降解, 有效增强了包裹药物的释放. Bae课题组[57]用pH敏感PEG-聚组氨酸聚合物囊泡包载亲水药物, 在pH 7.4下药物释放缓慢, 而在pH低于6.8时药物释放速度显著加快.

聚合物囊泡虽然可以运载亲水药物(包括蛋白质), 但其包载量和包封率通常较低[58]. 为提高聚合物囊泡对亲水药物的包载能力, 人们设计合成了具有离子化膜的囊泡[59], 采用的制备方法有梯度法[60]和纳米沉淀[61]等. 本课题组[62]通过设计ABC不对称三嵌段共聚物, 构建了具有不对称膜结构的聚合物囊泡, 其中较短的亲水链为聚电解质, 主要位于囊泡内腔, 可与亲水药物产生静电或氢键作用, 从而有效提高聚合物囊泡对亲水药物的载药能力. 我们还设计制备了酸敏感的具有不对称膜结构的PEG-PTTMA-PAA聚合物囊泡, 发现其可高效包载DOX·HCl, 药物包载量高达15.9%(质量百分比), 包封率高达88.8%, 疏水膜层在细胞内涵体低pH条件下会快速水解, 导致囊泡溶胀和分解, 高效释放出药物, 产生高抗癌活性. 该设计同时解决了囊泡载药效率低和在细胞内药物释放缓慢等难题[63].

2.2 还原响应性生物可降解聚合物纳米载体

还原响应性聚合物纳米载体响应速度快、细胞内药物释放效率高, 近几年成为药物释放领域的研究热点[64~66]. 肿瘤细胞质和细胞核内是强还原环境, 谷胱甘肽(glutathione, GSH)的浓度高达2~10 mmol/L, 其还原能力是细胞外基质和血液的100~1000倍. 因此, 还原响应性纳米药物在血液循环过程中可保持稳定, 但在细胞内会快速释放药物. 本课题组[67,68]设计制备了还原敏感壳可摘弃的PEG-SS-PCL和Dextran-SS-PCL聚合物胶束, 其在10 mmol/L二硫苏糖醇(dithiothreitol, DTT)还原环境下, 12 h内定量释放出包裹的DOX药物. 相同条件下, 非还原敏感的胶束释放出的药物很少. 细胞实验表明, 该还原响应胶束可高效地将药物释放到细胞质和细胞核, 有效地增强抗肿瘤效果. 王均课题组[69]报道了还原敏感壳可摘弃PCL-SS-聚磷酸酯(PEEP)胶束, 其在GSH存在情况下快速释放DOX, 很好地抑制了A549肿瘤细胞的生长. 随后的研究还发现载药PCL-SS-PEEP胶束能有效地抑制耐药肿瘤细胞的生长[70]. 研究表明, 基于不同聚合物(如聚多肽、透明质酸等)的还原敏感型壳可摘弃胶束都实现了抗癌药物(DOX, PTX等)的肿瘤细胞内触发释放[71,72]. 通过调节还原敏感壳的量, 可精确控制胶束药物细胞内的释放量和释放速率, 控制抗癌活性[73]. 除了构建壳可摘弃胶束, 二硫键也被引入到共聚物憎水链段的主链或侧链, 构建还原敏感核可降解胶束[74~76]. 基于Gal-PEG-PCL-聚二乙胺基乙基甲基丙烯酸酯(PDEA)、PEG-PCL-PDEA和 PEG-SS-PCL, 本课题组[77]还设计制备了半乳糖修饰、还原敏感、具有不对成膜结构的生物可降解聚合物囊泡. 该多功能囊泡可高效包载蛋白质药物如细胞色素C和果粒酶B(包封率>90%), 有效靶向到肝癌细胞, 并在细胞内快速释放出蛋白质药物, 有效杀死肝癌细胞(半抑制率IC_{50}为2.7 nmol/L).

2.3 双重或多重响应性生物可降解聚合物纳米载体

为了更精准控制药物释放行为, 近年来人们研发了pH和还原双重响应及多重响应聚合物纳米载体[78]. 基于PEG-SS-聚(2,4,6-三甲氧基苯甲缩醛季戊四醇碳酸酯)嵌段共聚物(PEG-SS-PTMBPEC), 本课题组[79]制备了pH和还原双重响应性胶束, 实现了高效细胞内DOX释放(图1). 体外释放实验结果表明, 胶束药物在生理条件下, 21 h内仅释放约24.5%药物; 在pH 5.0弱酸或10 mmol/L GSH还原条件下, DOX释放速度明显加快, 21 h内分别释放62.8%和

74.3%药物；在弱酸且还原的条件下，10 h内药物释放高达94.2%. 研究发现，模拟细胞内运输过程中的不同微环境，即在pH 5.0环境中2~4 h(内涵体或溶酶体环境)，然后在pH 7.4和10 mmol/L GSH条件下(细胞质环境)，显著加速了药物释放. 汪长春课题组[80]通过腙键将DOX接枝到PEG-PMMA聚合物上制得前药胶束，然后再用二巯基二乙酸交联得到pH和还原双敏感胶束，其在弱酸和还原条件下可高效释放键合的药物. 刘世勇课题组[81]通过二硫代双(丙酰二肼)交联胶束壳上的醛基，制得pH和还原双敏感胶束，可高效地将抗癌药物喜树碱(camptothecin，CPT)和DOX释放到细胞核，有效杀死肿瘤细胞. Haag课题组[82]综合利用纳米沉淀法和点击化学制备得到pH和还原双敏感的聚乙烯醇纳米凝胶，促进了纳米药物的内吞和细胞内快速释放. 用共聚焦激光扫描显微镜(CLSM)观察到，引入pH敏感的乌头酸基团的纳米凝胶在肿瘤的弱酸条件下(pH 6.5~6.8)能发生电荷翻转，纳米凝胶表面电位由负电转变为正电，有效促进肿瘤细胞内吞. 体外释放实验表明，在模拟内涵体的弱酸环境和细胞内的还原环境时，纳米凝胶能快速、完全地释放出包裹的DOX药物. 我们简单地通过将PEG-SS-PDEA聚合物水溶液的pH从5.5升高到7.4就制备了pH和还原双敏感聚合物囊泡[83]. 载蛋白质囊泡在pH 7.4时稳定，8 h释放的蛋白质药物少于20%，但在弱酸或细胞内还原环境中蛋白质快速释放. 王均课题组[84]基于PEG和聚磷酸酯制备了双重pH响应的聚合物前药纳米粒，其在肿瘤组织的微酸环境下(pH 6.8)，表面电荷发生反转，由负电变成正电，促进了纳米粒内吞进入细胞. 在细胞内，经腙键接枝到聚磷酸酯上的DOX在内涵体/溶酶体的弱酸环境下可快速释放出来，有效地抑制了耐药SK-3rd肿瘤干细胞的生长. 李子臣课题组[85]用寡聚聚乙二醇丙烯酸酯、含酸敏感原酸酯的丙烯酸酯和含二硫键的双丙烯酸酯通过细乳液聚合法制备得到温度、pH和还原三重响应性纳米凝胶. 该纳米凝胶在升温至37 ℃时，粒径迅速缩小到17~35 nm；而在弱酸性(pH 4~6)或还原(20 mmol/L DTT)环境中，会分别因原酸酯的水解和二硫键的断裂而溶胀. 体外释放实验表明，在中性和非还原条件下包裹在纳米凝胶中的PTX、尼罗红、DOX释放速度较慢，但在弱酸和还原条件下释放速度明显加快.

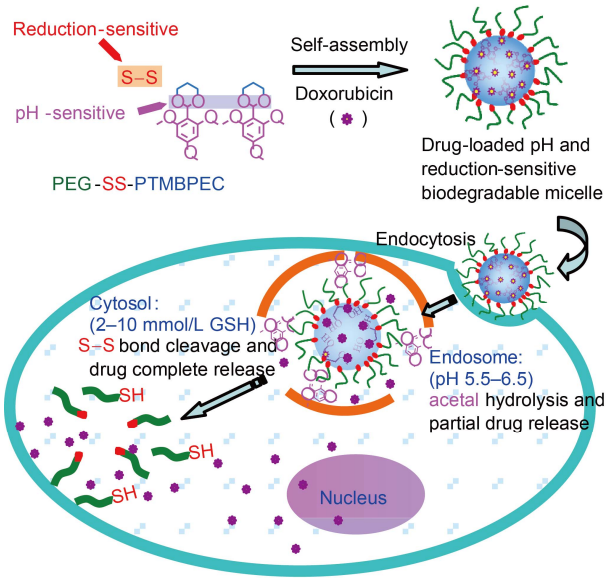

图 1 (网络版彩色)还原和 pH 双重敏感的 PEG-SS-PTMBPEC 胶束用于抗癌药物的细胞内触发释放[79]

Figure 1 (Color online) Illustration of reduction and pH-sensitive biodegradable micelles based on PEG-SS-PTMBPEC copolymer for dually activated release of anticancer drugs[79]

3 可逆交联稳定的生物可降解聚合物纳米载体

如上所述，聚合物纳米载体经化学或物理交联后可有效改善纳米药物的体内稳定性. 然而，交联在提高纳米药物稳定性的同时，往往进一步减少药物在肿瘤部位的释放，降低肿瘤治疗效果. 近几年，研究人员采用含二硫键、腙键、缩醛或缩酮键的响应性交联剂，制备得到刺激敏感可逆交联的生物可降解纳米载体，巧妙解决了聚合物纳米载体在血液循环时需具有高稳定性，而在肿瘤细胞内需快速高效释放药物的矛盾.

研究人员分别用含二硫键的交联剂(如胱胺、胱胺衍生物和胱氨酸*N*-羧酸内酸酐)制备得到还原敏感可逆交联的聚合物纳米载体[86~89]. 该载体具有明显增强的稳定性，在细胞内还原条件下能迅速释放出包载的药物. 本课题组[90]用PEG-PAA-聚(*N*-异丙基丙烯酰胺)温敏性三嵌段共聚物(PEG-PAA-PNIPAM)和胱胺交联，制备得到了温度和还原敏感可逆交联的聚合物囊泡. 该聚合物囊泡在高倍稀释、有机溶剂、高浓度盐溶液和变温条件下保持结构稳定；但在10 mmol/L DTT还原环境下，囊泡在1.5 h内完全分解，快速释放出包裹的葡聚糖. 通过调节PAA/

PNIPAM的比例可以将聚合物的低临界溶解温度(LCST)调节到38~39℃[91], 其在温和条件下可高效包裹各种不同的蛋白质药物(牛血清蛋白、溶菌酶、细胞色素C、白蛋白). 交联使载蛋白囊泡在生理条件下十分稳定, 但在模拟细胞内还原条件时很快分解, 释放出蛋白质药物.

二硫键交联也可通过氧化聚合物纳米载体上的自由巯基来实现, 巯基可存在于亲水链段(聚(*L*-半胱氨酸))[92]或憎水链段(聚磷酸酯、聚碳酸酯、聚丙烯酸酯、聚多肽、超支化聚合物等)[93~97]. 接种卵巢癌的老鼠研究结果发现, 二硫键交联的胶束药物相对于PTX自由药和未交联胶束药物, 在体内展现出更好的肿瘤选择性和治疗效果[96]. 本课题组[98]通过氧化PEG-PAA-PDEA巯基衍生(PEG-PAA(SH)-PDEA)囊泡界面上的巯基制备得到还原敏感可逆交联的聚合物囊泡, 并在极温和条件下实现了对蛋白质药物(牛血清白蛋白、细胞色素C)的高效装载. 载蛋白囊泡在生理环境下稳定, 但在细胞内还原条件下会快速解离, 释放出蛋白药物, 促使肿瘤细胞(MCF-7, HeLa, 293T)凋亡.

还原敏感可逆交联聚合物纳米载体可通过引入硫辛酸(lipoic acid, LA)衍生物方便地制备得到[99~101]. LA是人体内存在的天然氧化剂, 具有一个含二硫键的五元环, 环上的二硫键因环张力在催化剂DTT作用下可开环聚合, 形成线型的聚二硫化物. 研究结果发现, 基于LA的二硫键交联的纳米载体具有很好的生物相容性; 在体内循环时稳定, 能很好地抑制药物泄漏; 在细胞内可快速释放药物, 产生高抗肿瘤活性. 本课题组[102]最近报道了基于LA和顺式1,2-环己烷二羧酸(CCA)接枝PEG-PLL的pH和还原双重敏感可逆交联聚多肽胶束(图2), 可高效包载DOX. 体外释放研究表明, 在生理条件下, 24 h内DOX释放量少(<20%), 而在10 mmol/L GSH还原条件下, 24 h内DOX释放量在pH 7.4和5.0分别达86%和96.7%. 载DOX交联胶束对HeLa和HepG2等肿瘤细胞具有显著的细胞毒性(IC_{50}~12.5 μg DOX当量/mL). He课题组[103]将含六元环二硫键的反式-4,5-二羟基-1,2-二噻烷(*O*-DTT)分子引入聚氨酯, 制备了核可逆交联的聚氨酯胶束. 载DOX胶束在体内表现出比自由药和未交联的载药胶束更强的抗癌效果和更低的毒副作用.

Lee等人[104]用含酸敏感的缩酮交联剂制备得到界面交联的PEG-PAsp-PPhe聚多肽胶束, 交联胶束在SDS溶液中较稳定, 但在类内涵体pH条件下因缩酮键的断裂会很快释放出包裹的DOX药物, 可有效抑制MCF-7乳腺癌细胞的生长. 本课题组[105]通过PEG与含乙缩醛键和可光交联丙烯酸酯基团的聚碳酸酯嵌段共聚物(P(TMBPEC-*co*-AC)), 构建了核交联pH敏感胶束. 该交联胶束在pH 7.4时非常稳定, 能有效地抑制药物早释. 然而, 在pH 4.0和5.0环境下, 23 h内分别有90.9%和78.1%的药物释放出来. Li等人[106]

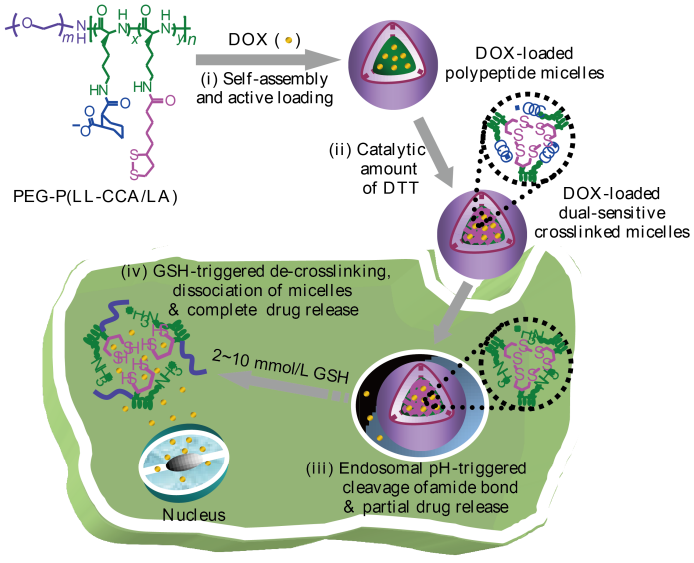

图 2 (网络版彩色) 还原和 pH 双敏感核交联的 PEG-P(LL-CCA/LA)胶束用于抗癌药物 DOX 的高效包裹和细胞内触发释放[102]

Figure 2 (Color online) Illustration of reduction and pH dual-sensitive core-crosslinked PEG-P(LL-CCA) micelles for active loading and triggered intracellular release of DOX[102]

用含硼酸和儿茶酚的超支化聚合物，制备得到酸和顺式二醇双敏感的交联胶束用于药物靶向释放. 该交联胶束在中性条件下能很好地抑制药物早释，而在弱酸环境或甘露醇存在的条件下能迅速地释放出包裹的抗癌药物.

4 靶向肿瘤的生物可降解聚合物纳米载体

为了避免肾小球排除和肝网状内皮组织(reticuloendothelial systems, RES)的吞噬、增强纳米药物通过高渗透长滞留(EPR)效应在肿瘤的富集，纳米载体表面通常需要引入有屏蔽效应的PEG或葡聚糖等分子. 然而，屏蔽效应同时也会大大降低肿瘤细胞对纳米药物的内吞效率. 通过在纳米载体表面引入与肿瘤细胞有特异性结合的靶向分子(如多肽、单糖、多糖、叶酸、抗体、抗体片段等)，可促进纳米药物在肿瘤组织处的滞留，增强纳米药物的内吞效率和肿瘤细胞内的富集[107].

本课题组[108,109]将半乳糖靶向分子引入还原敏感型PEG-SS-PCL和PCL-g-SS-LBA(LBA: 乳糖酸)纳米载体，能明显促进纳米载体内吞进入表达无唾液酸糖蛋白受体(asialoglycoprotein, ASGP-R)的HepG2细胞，并在4~8 h内快速高效地将DOX药物释放到细胞核. 细胞存活率分析显示，半乳糖修饰后的PEG-SS-PCL胶束药物对HepG2细胞的细胞毒性与自由药相当，是不含靶向分子胶束的6倍多[108]. 最近，本课题组[110]报道了半乳糖修饰的载PTX光交联pH敏感生物可降解PEG-P(TMBPEC-*co*-AC)胶束，具有较长的体内循环时间，可富集到SMMC-7721肝癌细胞，并有效抑制肝癌细胞的生长. 组织学分析结果证实，该靶向胶束比Taxol能更高效地杀死肿瘤细胞，同时减少对肝和肾的损伤. 透明质酸(HA)能与乳腺癌细胞(MDA-MB-231, MCF-7)和结肠癌细胞(HCT-116)表面过量表达的CD44和RHAMM受体结合，被广泛地用于抗癌药物的靶向释放. 本课题组[111]用硫辛酸接枝的HA制备了可逆交联的聚合物纳米载体，并将其用于乳腺癌的靶向治疗. 结果发现，该纳米粒在体内可长时间循环，高效富集到CD44阳性乳腺癌细胞并被癌细胞内吞，还原敏感解交联可实现药物在肿瘤细胞内快速释放，完全抑制肿瘤生长.

RGD短肽可以选择性地与细胞表面的整连蛋白受体结合，因此被广泛地用于肿瘤的靶向治疗和诊断. Gao课题组[112]将环状RGD(cRGD)引入PEG-PCL胶束表面，可极大地促进载药胶束内吞到肿瘤新生血管内皮细胞. 本课题组[113]设计合成了纳米金棒为核的PEG-PCL胶束(AuNR-M)，其在生理条件下非常稳定，药物很少泄漏；但在808 nm低强度近红外光(NIR, 0.2 W/cm^2)辐照下，由于光热效应使PCL链段熔融从而触发DOX药物的快速释放，有效杀死MCF-7/ADR耐药性肿瘤细胞. 以小鼠脑胶质瘤为模型，我们进一步研究了cRGD修饰的AuNR-M纳米胶束的体内肿瘤靶向和治疗效果，发现该复合纳米粒具有长血液循环时间，可富集到U87MG肿瘤，通过NIR辐照可实现药物快速释放，高效抑制肿瘤生长(图3)[114]. 张强课题组[115]制备了RGD短肽修饰的PEG-PLA胶束，该胶束通过物理包裹考布他汀及化学键合DOX，依次杀死肿瘤处的血管内皮细胞和肿瘤细胞. 用接种了B-16的老鼠模型研究证实了该胶束具有很好的靶向作用，能严重破坏肿瘤的血管系统，并极大地抑制肿瘤生长. 蒋锡群课题组[116]报道了iRGD功能化的聚(*N*-乙烯吡咯烷酮)-PCL胶束能促进胶束在肿瘤组织处的穿透能力和富集量. Langer课题组[15]将载有多西紫杉醇、*S*,*S*-2-[3-[5-氨基-1-羧基戊基]-脲基]-戊二酸(ACUPA)靶向分子修饰的PEG-PDLLA/PEG-PLGA胶束注射到接种有前列腺肿瘤的小鼠体内，与注射同量自由药相比，12 h后在肿瘤处的药物富集量更多，对肿瘤生长的抑制时间更长. 临床I期试验初步结果表明，ACUPA功能化的纳米药物(BIND-014)在低于临床多西紫杉醇的用量情况下，也能有效地抑制患者前列腺肿瘤的生长.

5 结论与展望

生物可降解聚合物纳米载体具有良好的生物相容性、较长的体内循环时间、可通过被动或主动靶向富集到肿瘤组织、在体内可降解为无毒产物等优点，被广泛用于制备纳米抗癌药物. 同时，随着对肿瘤病理学更深入的理解，我们进一步认识到聚合物纳米药物用于肿瘤治疗的众多关键挑战，包括纳米药物在体内循环过程中的稳定性、肿瘤组织渗透能力、肿瘤细胞的内吞及肿瘤细胞内的药物释放等. 近年来，人们研发了各种新型多功能可降解聚合物纳米载体，显著提高了纳米药物的肿瘤靶向和药物释放性能，增强了肿瘤治疗效果，同时进一步降低了抗癌药物的毒副作用.

尽管多功能生物可降解聚合物纳米药物载体在

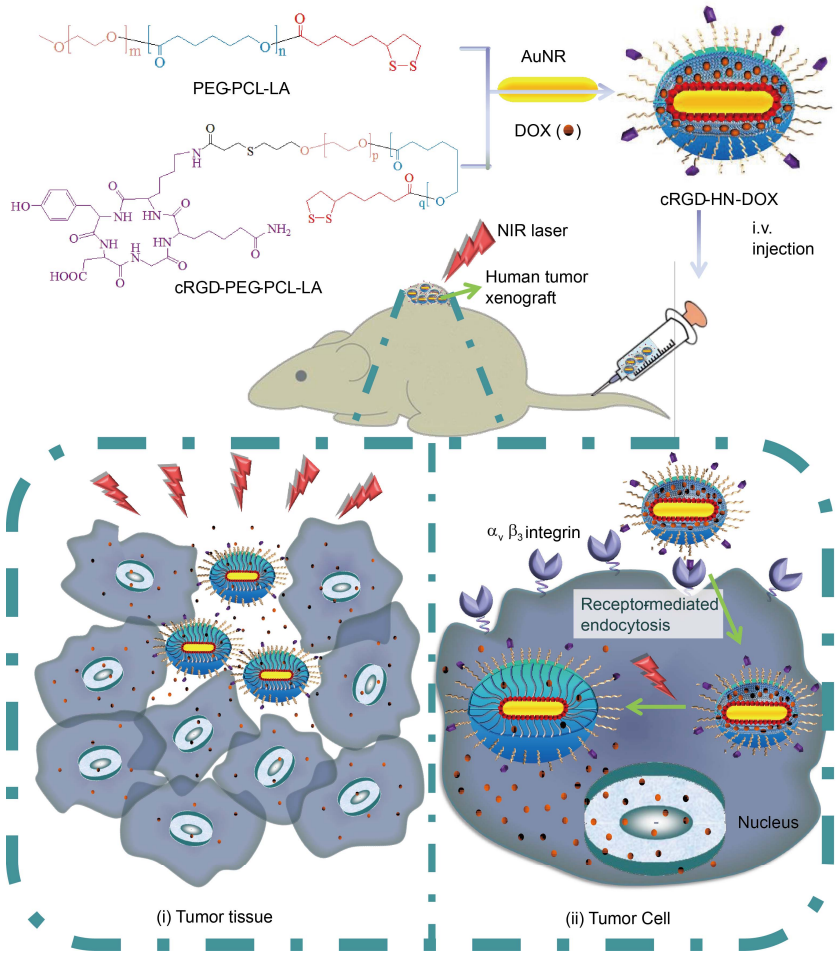

图 3 (网络版彩色)cRGD 修饰的 NIR 响应 AuNR/PEG-PCL 复合纳米胶束[114]

Figure 3 (Color online) Illustration of cRGD-directed and NIR-responsive AuNR/PEG-PCL hybrid nanoparticles (cRGD-HNs) for targeted delivery of DOX to human glioblastoma xenograft in mice[114]

肿瘤靶向治疗中展现了光明的前景，但距离临床应用还比较遥远，有许多问题需要解决. 首先，多功能聚合物纳米载体通常基于新材料，且制备过程比较繁琐，现有研究侧重提高纳米药物的抗癌药效，忽略了纳米药物在安全性、药物代谢动力学、制备重现性、储存稳定性等方面的考虑和研究，难以通过食品药品管理部门的批准并最终进入临床试验. 其次，在纳米药物表面修饰上合适的生物靶向分子，原理上可以增强纳米药物的肿瘤富集及肿瘤细胞内吞，实现肿瘤主动靶向治疗；然而生物靶向分子(如多肽或抗体)的引入可能改变纳米药物的物理化学性能，增强非特异性吸附，影响纳米药物的血液循环时间，进一步降低纳米药物的肿瘤渗透能力等. 此外，许多靶向分子的特异性并不强，且靶向效果与纳米粒的尺寸、稳定性、靶向分子表面密度等息息相关. 近年来，国内外研究组在“主动靶向”纳米药物上开展了越来越多的研究，但是综合考虑不同影响因素的系统研究比较缺乏. 再次，纳米药物研究主要集中在实体瘤的靶向和治疗，然而肿瘤治疗最大的临床挑战是耐药肿瘤、转移性肿瘤及肿瘤干细胞等的靶向治疗. 最后，临床癌症治疗常通过2个甚或多个抗癌药物联合治疗方式，达到协同治疗效果，而纳米药物研究基本上还是以单一药物治疗为主. 聚合物纳米载体可同时包载2个或多个抗癌药物，并同时释放到肿瘤细胞内，可望实现肿瘤的靶向协同治疗. 毫无疑问，肿瘤靶向治疗将是未来肿瘤治疗的主要方式，而生物可降解纳米载体是实现肿瘤靶向治疗最具潜力的系统之一. 我们相信多功能聚合物纳米药物经缜密设计、精确制备和系统研发将陆续进入临床，并在肿瘤靶向治疗中发挥重要作用.

参考文献

1 Peer D, Karp J M, Hong S, et al. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol, 2007, 2: 751–760

2 Davis M E, Chen Z, Shin D M. Nanoparticle therapeutics: An emerging treatment modality for cancer. Nat Rev Drug Discov, 2008, 7: 771–782

3 Deng C, Jiang Y, Cheng R, et al. Biodegradable polymeric micelles for targeted and controlled anticancer drug delivery: Promises, progress and prospects. Nano Today, 2012, 7: 467–480

4 Torchilin V P. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nat Rev Drug Discov, 2014, 13: 813–827

5 Egusquiaguirre P S, Igartua M, Hernandez R M, et al. Nanoparticle delivery systems for cancer therapy: Advances in clinical and preclinical research. Clin Transl Oncol, 2012, 14: 83–93

6 Kim T Y, Kim D W, Chung J Y, et al. Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. Clin Cancer Res, 2004, 10: 3708–3716

7 Matsumura Y, Hamaguchi T, Ura T, et al. Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. Br J Cancer, 2004, 91: 1775–1781

8 Kato K, Chin K, Yoshikawa T, et al. Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer. Invest New Drugs, 2012, 30: 1621–1627

9 Hamaguchi T, Doi T, Eguchi-Nakajima T, et al. Phase I study of NK012, a novel SN-38-incorporating micellar nanoparticle, in adult patients with solid tumors. Clin Cancer Res, 2010, 16: 5058–5066

10 Plummer R, Wilson R H, Calvert H, et al. A Phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours. Br J Cancer, 2011, 104: 593–598

11 Yamamoto Y, Hyodo I, Takigahira M, et al. Effect of combined treatment with the epirubicin-incorporating micelles (NC-6300) and 1,2-diaminocyclohexane platinum(II)-incorporating micelles (NC-4016) on a human gastric cancer model. Int J Cancer, 2014, 135: 214–223

12 Harada M, Bobe I, Saito H, et al. Improved anti-tumor activity of stabilized anthracycline polymeric micelle formulation, NC-6300. Cancer Sci, 2011, 102: 192–199

13 Takahashi A, Yamamoto Y, Yasunaga M, et al. NC-6300, an epirubicin-incorporating micelle, extends the antitumor effect and reduces the cardiotoxicity of epirubicin. Cancer Sci, 2013, 104: 920–925

14 Hrkach J, von Hoff D, Ali M M, et al. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. Sci Transl Med, 2012, 4: 128–139

15 Cabral H, Kataoka K. Progress of drug-loaded polymeric micelles into clinical studies. J Control Release, 2014, 190: 465–476

16 Jain R K, Stylianopoulos T. Delivering nanomedicine to solid tumors. Nat Rev Clin Oncol, 2010, 7: 653–664

17 Lammers T, Kiessling F, Hennink W E, et al. Drug targeting to tumors: Principles, pitfalls and (pre-) clinical progress. J Control Release, 2012, 161: 175–187

18 Bae Y H, Yin H. Stability issues of polymeric micelles. J Control Release, 2008, 131: 2–4

19 Read E S, Armes S P. Recent advances in shell cross-linked micelles. Chem Commun, 2007, (29): 3021–3035

20 Bae Y, Kataoka K. Intelligent polymeric micelles from functional poly(ethylene glycol)-poly(amino acid) block copolymers. Adv Drug Deliver Rev, 2009, 61: 768–784

21 Holback H, Yeo Y. Intratumoral drug delivery with nanoparticulate carriers. Pharm Res, 2011, 28: 1819–1830

22 Gullotti E, Yeo Y. Extracellularly activated nanocarriers: A new paradigm of tumor targeted drug delivery. Mol Pharm, 2009, 6: 1041–1051

23 Oerlemans C, Bult W, Bos M, et al. Polymeric micelles in anticancer therapy: Targeting, imaging and triggered release. Pharm Res, 2010, 27: 2569–2589

24 Lammers T, Subr V, Ulbrich K, et al. Polymeric nanomedicines for image-guided drug delivery and tumor-targeted combination therapy. Nano Today, 2010, 5: 197–212

25 Rijcken C J, Snel C J, Schiffelers R M, et al. Hydrolysable core-crosslinked thermosensitive polymeric micelles: Synthesis, characterisation and *in vivo* studies. Biomaterials, 2007, 28: 5581–5593

26 Iijima M, Nagasaki Y, Okada T, et al. Core-polymerized reactive micelles from heterotelechelic amphiphilic block copolymers. Macromolecules, 1999, 32: 1140–1146

27 Shuai X T, Merdan T, Schaper A K, et al. Core-cross-linked polymeric micelles as paclitaxel carriers. Bioconjugate Chem, 2004, 15: 441–448

28 Ding J, Zhuang X, Xiao C, et al. Preparation of photo-cross-linked pH-responsive polypeptide nanogels as potential carriers for controlled drug delivery. J Mater Chem, 2011, 21: 11383–11391

29 Yan L, Yang L, He H, et al. Photo-cross-linked mPEG-poly(gamma-cinnamyl-*L*-glutamate) micelles as stable drug carriers. Polym Chem, 2012, 3: 1300–1307

30 Rodriguez-Hernandez J, Babin J, Zappone B, et al. Preparation of shell cross-linked nano-objects from hybrid-peptide block copolymers. Biomacromolecules, 2005, 6: 2213–2220

31 Xiong J, Meng F, Wang C, et al. Folate-conjugated crosslinked biodegradable micelles for receptor-mediated delivery of paclitaxel. J Mater Chem, 2011, 21: 5786–5794

32 Yang R, Meng F, Ma S, et al. Galactose-decorated cross-linked biodegradable poly(ethylene glycol)-*b*-poly(epsilon-caprolactone) block copolymer micelles for enhanced hepatoma-targeting delivery of paclitaxel. Biomacromolecules, 2011, 12: 3047–3055

33 Jiang Y, Chen J, Deng C, et al. Click hydrogels, microgels and nanogels: Emerging platforms for drug delivery and tissue engineering. Biomaterials, 2014, 35: 4969–4985

34 Chen W, Zheng M, Meng F, et al. *In situ* forming reduction-sensitive degradable nanogels for facile loading and triggered intracellular release of proteins. Biomacromolecules, 2013, 14: 1214–1222

35 Kang N, Perron M E, Prud'homme R E, et al. Stereocomplex block copolymer micelles: Core-shell nanostructures with enhanced stability. Nano Lett, 2005, 5: 315–319

36 Carstens M G, Bevernage J J L, van Nostrum C F, et al. Small oligomeric micelles based on end group modified mPEG-oligocaprolactone with monodisperse hydrophobic blocks. Macromolecules, 2007, 40: 116–122

37 Meng F, Cheng R, Deng C, et al. Intracellular drug release nanosystems. Mater Today, 2012, 15: 436–442

38 Ge Z, Liu S. Functional block copolymer assemblies responsive to tumor and intracellular microenvironments for site-specific drug delivery and enhanced imaging performance. Chem Soc Rev, 2013, 42: 7289–7325

39 Meng F, Zhong Y, Cheng R, et al. pH-sensitive polymeric nanoparticles for tumor-targeting doxorubicin delivery: Concept and recent advances. Nanomedicine, 2014, 9: 487–499

40 Bae Y, Fukushima S, Harada A, et al. Design of environment-sensitive supramolecular assemblies for intracellular drug delivery: Polymeric micelles that are responsive to intracellular pH change. Angew Chem Int Ed, 2003, 42: 4640–4643

41 Bae Y, Nishiyama N, Kataoka K. *In vivo* antitumor activity of the folate-conjugated pH-sensitive polymeric micelle selectively releasing adriamycin in the intracellular acidic compartments. Bioconjugate Chem, 2007, 18: 1131–1139

42 Bae Y, Nishiyama N, Fukushima S, et al. Preparation and biological characterization of polymeric micelle drug carriers with intracellular pH-triggered drug release property: Tumor permeability, controlled subcellular drug distribution, and enhanced *in vivo* antitumor efficacy. Bioconjugate Chem, 2005, 16: 122–130

43 Zhan F, Chen W, Wang Z, et al. Acid-activatable prodrug nanogels for efficient intracellular doxorubicin release. Biomacromolecules, 2011, 12: 3612–3620

44 Zhou L, Cheng R, Tao H, et al. Endosomal pH-activatable poly(ethylene oxide)-graft-doxorubicin prodrugs: Synthesis, drug release, and biodistribution in tumor-bearing mice. Biomacromolecules, 2011, 12: 1460–1467

45 Gu Y, Zhong Y, Meng F, et al. Acetal-linked paclitaxel prodrug micellar nanoparticles as a versatile and potent platform for cancer therapy. Biomacromolecules, 2013, 14: 2772–2780

46 Chen W, Meng F, Li F, et al. pH-responsive biodegradable micelles based on acid-labile polycarbonate hydrophobe: Synthesis and triggered drug release. Biomacromolecules, 2009, 10: 1727–1735

47 Steinhilber D, Witting M, Zhang X, et al. Surfactant free preparation of biodegradable dendritic polyglycerol nanogels by inverse nanoprecipitation for encapsulation and release of pharmaceutical biomacromolecules. J Control Release, 2013, 169: 289–295

48 Yang B, Lv Y, Zhu J Y, et al. A pH-responsive drug nanovehicle constructed by reversible attachment of cholesterol to PEGylated poly(*L*-lysine) via catechol-boronic acid ester formation. Acta Biomater, 2014, 10: 3686–3695

49 Li L, Bai Z, Levkin P A. Boronate-dextran: An acid-responsive biodegradable polymer for drug delivery. Biomaterials, 2013, 34: 8504–8510

50 Aguirre-Chagala Y E, Santos J L, Huang Y, et al. Phenylboronic acid-installed polycarbonate for pH-dependent release of diol-containing molecules. ACS Macro Lett, 2014, 3: 1249–1253

51 Meng F, Zhong Z. Polymersomes spanning from nano- to microscales: Advanced vehicles for controlled drug delivery and robust vesicles for virus and cell mimicking. J Phys Chem Lett, 2011, 2: 1533–1539

52 Lee J S, Feijen J. Polymersomes for drug delivery: Design, formation and characterization. J Control Release, 2012, 161: 473–483

53 Meng F, Zhong Z, Feijen J. Stimuli-responsive polymersomes for programmed drug delivery. Biomacromolecules, 2009, 10: 197–209

54 Li M H, Keller P. Stimuli-responsive polymer vesicles. Soft Matter, 2009, 5: 927–937

55 Feng A, Yuan J. Smart nanocontainers: Progress on novel stimuli-responsive polymer vesicles. Macromol Rapid Commun, 2014, 35: 767–779
56 Chen W, Meng F, Cheng R, et al. pH-sensitive degradable polymersomes for triggered release of anticancer drugs: A comparative study with micelles. J Control Release, 2010, 142: 40–46
57 Yin H, Kang H C, Huh K M, et al. Biocompatible, pH-sensitive AB(2) miktoarm polymer-based polymersomes: Preparation, characterization, and acidic pH-activated nanostructural transformation. J Mater Chem, 2012, 22: 19168–19178
58 Choucair A, Soo P L, Eisenberg A. Active loading and tunable release of doxorubicin from block copolymer vesicles. Langmuir, 2005, 21: 9308–9313
59 Li S, Meng F, Wang Z, et al. Biodegradable polymersomes with an ionizable membrane: Facile preparation, superior protein loading, and endosomal pH-responsive protein release. Eur J Pharm Biopharm, 2012, 82: 103–111
60 Gubernator J. Active methods of drug loading into liposomes: Recent strategies for stable drug entrapment and increased *in vivo* activity. Expert Opin Drug Deliv, 2011, 8: 565–580
61 Sanson C, Schatz C, Le Meins J F, et al. A simple method to achieve high doxorubicin loading in biodegradable polymersomes. J Control Release, 2010, 147: 428–435
62 Liu G, Ma S, Li S, et al. The highly efficient delivery of exogenous proteins into cells mediated by biodegradable chimaeric polymersomes. Biomaterials, 2010, 31: 7575–7585
63 Du Y, Chen W, Zheng M, et al. pH-sensitive degradable chimaeric polymersomes for the intracellular release of doxorubicin hydrochloride. Biomaterials, 2012, 33: 7291–7299
64 Meng F, Hennink W E, Zhong Z. Reduction-sensitive polymers and bioconjugates for biomedical applications. Biomaterials, 2009, 30: 2180–2198
65 Cheng R, Feng F, Meng F, et al. Glutathione-responsive nano-vehicles as a promising platform for targeted intracellular drug and gene delivery. J Control Release, 2011, 152: 2–12
66 Sun H, Meng F, Cheng R, et al. Reduction-responsive polymeric micelles and vesicles for triggered intracellular drug release. Antioxid Redox Signal, 2014, 21: 755–767
67 Sun H, Guo B, Cheng R, et al. Biodegradable micelles with sheddable poly(ethylene glycol) shells for triggered intracellular release of doxorubicin. Biomaterials, 2009, 30: 6358–6366
68 Sun H, Guo B, Li X, et al. Shell-sheddable micelles based on dextran-SS-poly(epsilon-caprolactone) diblock copolymer for efficient intracellular release of doxorubicin. Biomacromolecules, 2010, 11: 848–854
69 Tang L Y, Wang Y C, Li Y, et al. Shell-detachable micelles based on disulfide-linked block copolymer as potential carrier for intracellular drug delivery. Bioconjugate Chem, 2009, 20: 1095–1099
70 Wang Y C, Wang F, Sun T M, et al. Redox-responsive nanoparticles from the single disulfide bond-bridged block copolymer as drug carriers for overcoming multidrug resistance in cancer cells. Bioconjugate Chem, 2011, 22: 1939–1945
71 Wen H Y, Dong H Q, Xie W J, et al. Rapidly disassembling nanomicelles with disulfide-linked PEG shells for glutathione-mediated intracellular drug delivery. Chem Commun, 2011, 47: 3550–3552
72 Li J, Huo M, Wang J, et al. Redox-sensitive micelles self-assembled from amphiphilic hyaluronic acid-deoxycholic acid conjugates for targeted intracellular delivery of paclitaxel. Biomaterials, 2012, 33: 2310–2320
73 Wang W, Sun H, Meng F, et al. Precise control of intracellular drug release and anti-tumor activity of biodegradable micellar drugs via reduction-sensitive shell-shedding. Soft Matter, 2012, 8: 3949–3956
74 Sun Y, Yan X, Yuan T, et al. Disassemblable micelles based on reduction-degradable amphiphilic graft copolymers for intracellular delivery of doxorubicin. Biomaterials, 2010, 31: 7124–7131
75 Liu J, Huang W, Pang Y, et al. Molecular self-assembly of a homopolymer: An alternative to fabricate drug-delivery platforms for cancer therapy. Angew Chem Int Ed, 2011, 50: 9162–9166
76 Sun P, Zhou D, Gan Z. Novel reduction-sensitive micelles for triggered intracellular drug release. J Control Release, 2011, 155: 96–103
77 Wang X, Sun H, Meng F, et al. Galactose-decorated reduction-sensitive degradable chimaeric polymersomes as a multifunctional nanocarrier to efficiently chaperone apoptotic proteins into hepatoma cells. Biomacromolecules, 2013, 14: 2873–2882
78 Cheng R, Meng F, Deng C, et al. Dual and multi-stimuli responsive polymeric nanoparticles for programmed site-specific drug delivery. Biomaterials, 2013, 34: 3647–3657
79 Chen W, Zhong P, Meng F, et al. Redox and pH-responsive degradable micelles for dually activated intracellular anticancer drug release. J Control Release, 2013, 169: 171–179
80 Wei C, Guo J, Wang C. Dual stimuli-responsive polymeric micelles exhibiting “AND” logic gate for controlled release of adriamycin. Macromol Rapid Commun, 2011, 32: 451–455

81 Hu X, Li H, Luo S, et al. Thiol and pH dual-responsive dynamic covalent shell cross-linked micelles for triggered release of chemotherapeutic drugs. Polym Chem, 2013, 4: 695–706
82 Chen W, Achazi K, Schade B, et al. Charge-conversional and reduction-sensitive poly(vinyl alcohol) nanogels for enhanced cell uptake and efficient intracellular doxorubicin release. J Control Release, 2015, 205: 15–24
83 Zhang J, Wu L, Meng F, et al. pH and reduction dual-bioresponsive polymersomes for efficient intracellular protein delivery. Langmuir, 2012, 28: 2056–2065
84 Du J Z, Du X J, Mao C Q, et al. Tailor-made dual pH-sensitive polymer-doxorubicin nanoparticles for efficient anticancer drug delivery. J Am Chem Soc, 2011, 133: 17560–17563
85 Qiao Z Y, Zhang R, Du F S, et al. Multi-responsive nanogels containing motifs of ortho ester, oligo(ethylene glycol) and disulfide linkage as carriers of hydrophobic anti-cancer drugs. J Control Release, 2011, 152: 57–66
86 Cajot S, Lautram N, Passirani C, et al. Design of reversibly core cross-linked micelles sensitive to reductive environment. J Control Release, 2011, 152: 30–36
87 Pan Y J, Chen Y Y, Wang D R, et al. Redox/pH dual stimuli-responsive biodegradable nanohydrogels with varying responses to dithiothreitol and glutathione for controlled drug release. Biomaterials, 2012, 33: 6570–6579
88 Xing T, Lai B, Ye X, et al. Disulfide core cross-linked PEGylated polypeptide nanogel prepared by a one-step ring opening copolymerization of *N*-carboxyanhydrides for drug delivery. Macromol Biosci, 2011, 11: 962–969
89 Ding J, Shi F, Xiao C, et al. One-step preparation of reduction-responsive poly(ethylene glycol)-poly (amino acid)s nanogels as efficient intracellular drug delivery platforms. Polym Chem, 2011, 2: 2857–2864
90 Xu H, Meng F, Zhong Z. Reversibly crosslinked temperature-responsive nano-sized polymersomes: Synthesis and triggered drug release. J Mater Chem, 2009, 19: 4183–4190
91 Cheng R, Meng F, Ma S, et al. Reduction and temperature dual-responsive crosslinked polymersomes for targeted intracellular protein delivery. J Mater Chem, 2011, 21: 19013–19020
92 Sun J, Chen X, Lu T, et al. Formation of reversible shell cross-linked micelles from the biodegradable amphiphilic diblock copolymer poly(*L*-cysteine)-block-poly(*L*-lactide). Langmuir, 2008, 24: 10099–10106
93 Wang Y C, Li Y, Sun T M, et al. Core-shell-corona micelle stabilized by reversible cross-linkage for intracellular drug delivery. Macromol Rapid Commun, 2010, 31: 1201–1206
94 Yan L, Wu W, Zhao W, et al. Reduction-sensitive core-cross-linked mPEG-poly(ester-carbonate) micelles for glutathione-triggered intracellular drug release. Polym Chem, 2012, 3: 2403–2412
95 Dai J, Lin S, Cheng D, et al. Interlayer-crosslinked micelle with partially hydrated core showing reduction and pH dual sensitivity for pinpointed intracellular drug release. Angew Chem Int Ed, 2011, 50: 9404–9408
96 Li Y, Xiao K, Luo J, et al. Well-defined, reversible disulfide cross-linked micelles for on-demand paclitaxel delivery. Biomaterials, 2011, 32: 6633–6645
97 Ryu J H, Chacko R T, Jiwpanich S, et al. Self-cross-linked polymer nanogels: A versatile nanoscopic drug delivery platform. J Am Chem Soc, 2010, 132: 17227–17235
98 Sun H, Meng F, Cheng R, et al. Reduction and pH dual-bioresponsive crosslinked polymersomes for efficient intracellular delivery of proteins and potent induction of cancer cell apoptosis. Acta Biomater, 2014, 10: 2159–2168
99 Xu Y, Meng F, Cheng R, et al. Reduction-sensitive reversibly crosslinked biodegradable micelles for triggered release of doxorubicin. Macromol Biosci, 2009, 9: 1254–1261
100 Li Y L, Zhu L, Liu Z, et al. Reversibly stabilized multifunctional dextran nanoparticles efficiently deliver doxorubicin into the nuclei of cancer cells. Angew Chem Int Ed, 2009, 48: 9914–9918
101 Wei R, Cheng L, Zheng M, et al. Reduction-responsive disassemblable core-cross-linked micelles based on poly(ethylene glycol)-*b*-poly(*N*-2-hydroxypropyl methacrylamide)-lipoic acid conjugates for triggered intracellular anticancer drug release. Biomacromolecules, 2012, 13: 2429–2438
102 Wu L, Zou Y, Deng C, et al. Intracellular release of doxorubicin from core-crosslinked polypeptide micelles triggered by both pH and reduction conditions. Biomaterials, 2013, 34: 5262–5272
103 Yu S, Ding J, He C, et al. Disulfide cross-linked polyurethane micelles as a reduction-triggered drug delivery system for cancer therapy. Adv Healthcare Mater, 2014, 3: 752–760
104 Lee S J, Min K H, Lee H J, et al. Ketal cross-linked poly(ethylene glycol)-poly(amino acid)s copolymer micelles for efficient intracellular delivery of doxorubicin. Biomacromolecules, 2011, 12: 1224–1233
105 Wu Y, Chen W, Meng F, et al. Core-crosslinked pH-sensitive degradable micelles: A promising approach to resolve the extracellular stability versus intracellular drug release dilemma. J Control Release, 2012, 164: 338–345

106 Li Y, Xiao W, Xiao K, et al. Well-defined, reversible boronate crosslinked nanocarriers for targeted drug delivery in response to acidic pH values and cis-diols. Angew Chem Int Ed, 2012, 51: 2864–2869
107 Zhong Y, Meng F, Deng C, et al. Ligand-directed active tumor-targeting polymeric nanoparticles for cancer chemotherapy. Biomacromolecules, 2014, 15: 1955–1969
108 Zhong Y, Yang W, Sun H, et al. Ligand-directed reduction-sensitive shell-sheddable biodegradable micelles actively deliver doxorubicin into the nuclei of target cancer cells. Biomacromolecules, 2013, 14: 3723–3730
109 Chen W, Zou Y, Meng F, et al. Glyco-nanoparticles with sheddable saccharide shells: A unique and potent platform for hepatoma-targeting delivery of anticancer drugs. Biomacromolecules, 2014, 15: 900–907
110 Zou Y, Song Y, Yang W, et al. Galactose-installed photo-crosslinked pH-sensitive degradable micelles for active targeting chemotherapy of hepatocellular carcinoma in mice. J Control Release, 2014, 193: 154–161
111 Zhong Y, Zhang J, Cheng R, et al. Reversibly crosslinked hyaluronic acid nanoparticles for active targeting and intelligent delivery of doxorubicin to drug resistant CD44+ human breast tumor xenografts. J Control Release, 2015, 205: 144–154
112 Nasongkla N, Shuai X, Ai H, et al. cRGD-functionalized polymer micelles for targeted doxorubicin delivery. Angew Chem Int Ed, 2004, 43: 6323–6327
113 Zhong Y, Wang C, Cheng L, et al. Gold nanorod-cored biodegradable micelles as a robust and remotely controllable doxorubicin release system for potent inhibition of drug-sensitive and -resistant cancer cells. Biomacromolecules, 2013, 14: 2411–2419
114 Zhong Y, Wang C, Cheng R, et al. cRGD-directed, NIR-responsive and robust AuNR/PEG-PCL hybrid nanoparticles for targeted chemotherapy of glioblastoma *in vivo*. J Control Release, 2014, 195: 63–71
115 Wang Y, Yang T, Wang X, et al. Materializing sequential killing of tumor vasculature and tumor cells via targeted polymeric micelle system. J Control Release, 2011, 149: 299–306
116 Zhu Z, Xie C, Liu Q, et al. The effect of hydrophilic chain length and iRGD on drug delivery from poly(epsilon-caprolactone)-poly(*N*-vinylpyrrolidone) nanoparticles. Biomaterials, 2011, 32: 9525–9535

Multifunctional biodegradable polymeric nanocarriers: Design, synthesis, and applications in targeted tumor therapy

DENG Chao[1,2], MENG FengHua[1,2], CHENG Ru[1,2] & ZHONG ZhiYuan[1,2]

[1]*Biomedical Polymers Laboratory, Soochow University, Suzhou 215123, China;*
[2]*College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China*

Biodegradable polymeric nanocarriers have emerged as one of the most promising platforms for targeted tumor therapy owing to their excellent biocompatibility, prolonged circulation time, enhanced accumulation in tumors, and *in vivo* biodegradability. Remarkably, several anticancer nanomedicines based on biodegradable polymeric nanocarriers showed clear advantages, including decreased side effects and improved drug tolerance, and have advanced to clinical practices or clinical trials. However, the therapeutic outcomes are far from optimal, owing to poor *in vivo* stability, low tumor targetability, inefficient cellular uptake, and slow intracellular drug release, etc. Thus, the development of new strategies to improve the therapeutic efficiency of polymeric nanomedicines is of great interest. This review highlights the recent developments made by our group and others in multifunctional biodegradable polymeric nanocarriers for safe and efficient cancer chemotherapy. In particular, we will present the following four polymeric nanoscale systems: (i) chemically or physically crosslinked biodegradable polymeric nanocarriers that display markedly improved stability and tumor targetability while prohibiting drug leakage; (ii) bio-responsive, biodegradable polymeric nanocarriers that enhance tumor cell uptake via reversal of the stealth effect in response to the tumor microenvironment or rapidly and efficiently releasing drugs into the tumor tissue and/or inside the tumor cells; (iii) stimuli-responsive crosslinked biodegradable polymeric nanocarriers that elegantly address the extracellular stability and intracellular drug release dilemma; and (iv) tumor-targeted biodegradable polymeric nanocarriers that enhance drug retention in the tumor and facilitate tumor cell uptake of nanomedicines. Finally, the pros and cons of current multifunctional polymeric nanosystems are discussed. We are convinced that, with rationale design, precision preparation, and systemic research and development, various multifunctional polymeric nanoparticulate drugs will soon advance to clinical settings and play an indispensable role in targeted cancer therapy.

nanocarrier, anticancer drug, controlled drug release, targeted delivery, tumor therapy

doi: 10.1360/N972015-00141