智能响应型介孔二氧化硅抗肿瘤纳米递药系统的设计策略与研究应用

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摘要: 恶性肿瘤是危害人类健康的重大疾病, 由于其微环境复杂多变, 导致大多数抗肿瘤药物不能精准地到达病灶组织并可控释放。智能响应型纳米载体已成为抗肿瘤递药系统研究领域的热点。介孔二氧化硅作为一种优良的纳米材料, 具有无毒、稳定、孔容孔径可调及表面易于功能化修饰等优势, 凭借其对机体肿瘤微环境或生理变化的感知响应、实现递药系统在病灶组织定位释药或控制释药, 使其成为智能响应型递药系统的理想载体。本文基于介孔二氧化硅的智能响应型递药系统的设计策略及研究应用展开综述, 以期为抗肿瘤药物纳米制剂的研发提供参考。

关键词: 介孔二氧化硅; 智能递药系统; 刺激响应; 抗肿瘤; 靶向

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Application research and design strategy on smart responsive mesoporous silica anti-tumor nanodelivery systems

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Abstract: Malignant tumors are major diseases that endanger human health. Due to their complex and variable microenvironment, most anti-tumor drugs cannot precisely reach the focal tissue and be released in a controlled manner. Intelligent responsive nano carriers have become a hot spot in the field of anti-tumor drug delivery systems. As an excellent nano material, mesoporous silica has the advantages of non-toxic, stable, adjustable pore volume and pore diameter, and easy functional modification on the surface. By virtue of its perceptive response to the tumor microenvironment or physiological changes, it can achieve the targeted drug release or controlled drug release of the drug delivery system in the tissue, making it an ideal carrier for intelligent response drug delivery system. In this paper, we review the design strategies and current research status of smart responsive anti-tumor drug delivery systems based on mesoporous silica, in order to provide a reference for the development of anti-tumor drug nanoformulations.

Key words: mesoporous silica; intelligent drug delivery system; stimulus response; anti-tumor; targeted delivery

恶性肿瘤是威胁人类健康的重大疾病[1,2]。为实现肿瘤的精准治疗, 必须将有效剂量的抗癌药物递送到肿瘤部位。然而, 传统的化疗药物存在水溶性及靶向性差、生物利用度低、疗效欠佳等缺点[3]; 而且大多数的化疗药物选择性和靶向性差, 使其对正常组织存在严重的不良反应。因此, 如何实现药物在病灶组织定位释药或控制释药, 以便提高药效、降低药物的不良反应, 是癌症纳米医学亟待解决的关键科学问题。

近年来, 智能响应型纳米材料可实现对机体微环

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境或生理变化的感知响应而调控药物的精准释放, 已成为抗癌药物递送的热点领域[4-6]。介孔二氧化硅作为一种优良的纳米载体, 可增强肿瘤组织的渗透性和滞留性, 能在实体肿瘤中富集, 在癌症治疗方面具有很好的应用潜力[7]。自2001年首次作为药物递送载体以来, 介孔二氧化硅由于其良好的生物相容性、较高的载药率、尺寸大小可控及表面易修饰等特点, 在药物智能递送系统领域引起了广泛关注[8-11], 研究者基于内源性刺激响应或外源性刺激响应策略构建了多种智能响应型介孔二氧化硅纳米递送系统, 包括pH[12]、氧化还原[13,14]、酶[15,16]、光[17]、磁[18]、温度[19]、超声[20]等, 用于抗肿瘤药物的高效递送 (图1)。本文重点综述了智能响应型介孔二氧化硅抗肿瘤纳米递送系统设计策略及应用研究进展, 以期为抗肿瘤药物纳米制剂的研发提供参考。

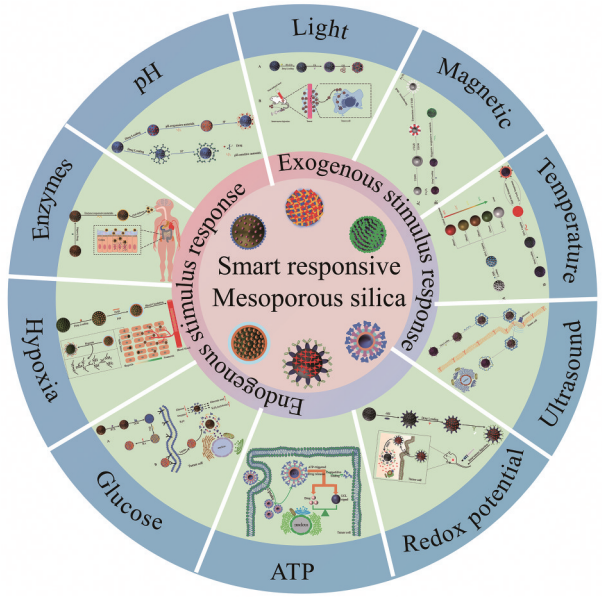

Figure 1　Classification of smart responsive mesoporous silica delivery system based on different response types

1　内源性刺激响应型介孔二氧化硅递药系统设计与研究应用

内源性刺激响应策略是基于疾病有关的病理代谢和生化过程的变化而设计的智能响应型药物递送系统[21]。正常和病理条件之间 (如肿瘤、炎症部位) 存在着生理和生化差异, 因此, 基于这些显著性的差异, 设计可精准响应其内部微环境微小变化的介孔二氧化硅纳米递药系统, 如不同的pH水平、氧化还原反应的电位及不同的酶分子和小分子物质的变化等。

1.1　pH响应型介孔二氧化硅递药系统

pH响应型介孔二氧化硅是研究最为广泛的内源性刺激响应设计类型, 特别是对于治疗肿瘤或炎症有关的疾病。研究表明, 与正常的组织 (pH = 7.23[22]) 相比, 肿瘤部位pH值通常为6.0～7.0[23], 而炎症部位的pH值为5.5[24]左右。因此, 根据病灶组织异常的pH, 并结合介孔二氧化硅的特点, 可设计生理病理pH信号敏感的智能响应型介孔二氧化硅递送系统。

pH响应型介孔二氧化硅的设计策略主要有两种 (图2A), 其一是先将药物装载于孔道中, 然后通过使用聚电解质、超分子纳米阀、pH敏感性聚合物、酸分解材料等在其表面进行修饰, 将药物封堵在孔道中[25]。在靶部位pH环境下, 介孔二氧化硅能够触发药物从孔道中缓慢释放, 从而对疾病实现精准、可控的治疗; 另一种是利用药物分子直接与介孔二氧化硅表面的基团生成pH敏感的化学键, 如硼酸酯键、亚胺键等, 当到达靶部位时, 由于pH值发生变化, 药物分子与介孔二氧化硅载体分离, 药物释放进入靶部位[26]。表1[27-43]列举了不同内源性刺激响应型介孔二氧化硅智能递药系统的研究应用实例。

Chang等[27]设计了一种特异性靶向肿瘤部位的pH响应型介孔二氧化硅递药系统。首先制备了羧基功能化的介孔二氧化硅纳米粒 (MSN-COOH), 并负载模型药物多柔比星 (doxorubicin, DOX), 将聚乙烯亚胺 (polyethyleneimine, PEI) 与茴香酰胺 (anisamide, AA) 作为封孔剂嫁接在介孔硅表面。该递药系统通过AA介导内吞作用从而特异性识别肿瘤细胞, 当到达细胞溶酶体的酸性环境时 (pH = 4.5～5.0), PEI质子化导致药物在靶细胞器中稳定释放。Chen等[28]构建了一种主动靶向缓控释多功能pH响应型介孔二氧化硅, 实现对肿瘤的靶向性及药物的缓控释, 通过对介孔二氧化硅进行氨基化, 利用透明质酸 (hyaluronic acid, HA) 与介孔二氧化硅表面氨基形成酸不稳定的腙键, 将模型药物DOX封装在孔道中。该系统在正常生理 (pH = 7.2) 条件下表现出良好的稳定性, 而在肿瘤部位低pH条件下 (pH = 6.5) 触发药物释放。利用介孔二氧化硅表面修饰的HA靶向癌细胞上的CD44受体, 介导内吞作用增强癌细胞对介孔二氧化硅纳米粒的摄取。当介孔二氧化硅纳米粒进入弱酸性环境的肿瘤细胞时, HA与介孔二氧化硅形成的腙键发生水解, 药物在肿瘤部位释放。此外, Narayan等[29]以壳聚糖-葡萄糖醛酸 (chitosan glucuronic acid, CHS-GCA) 偶联物修饰负载氟尿嘧啶 (5-fluorouracil, 5-FU) 的介孔二氧化硅, 其中葡萄糖醛酸作为靶向配体, 壳聚糖作为pH敏感性聚合物, 使介孔二氧化硅纳米粒能靶向肿瘤细胞, 实现pH刺激响应性释药。

1.2　氧化还原响应型介孔二氧化硅递药系统

氧化还原响应型介孔二氧化硅靶向递药系统是一

Table 1 Overview of research on endogenous stimulus-responsive mesoporous silica smart-responsive drug delivery systems

Stimulus	Responsive linker	Model drug	Blocking cap	Advantage	Ref.
pH	Polyethyleneimine (PEI)	Doxorubicin (DOX)	PEI, anisamide (AA)	Targeted drug release through endocytosis mediated by fenpropathrin thereby specifically identifying tumor cells	[27]
	Hydrazine bond	DOX	Hyaluronic acid (HA)	Targeting CD44 receptor in cancer cells, mediating endocytosis, pH response triggers drug release	[28]
	Chitosan (CS)	Fluorouracil (5-FU)	Chitosan-glucuronide coupling (CHS-GCA)	Glucuronide-based targeting of colon cancer cells for pH-responsive smart drug release	[29]
Redox potential	-S-S-	DOX	DNA aptamer (AS1411); small interfering RNAs (siRNAs)	Targeting breast cancer cells, enhancing cancer cells uptake rate, glutathione (GSH) triggers smart drug release	[30]
	-Se-Se-	DOX	Bovine serum albumin	The introduction of selenium bonds not only enables redox-responsive real-time monitoring of drug delivery, but also reduces the toxicity to normal cells	[31]
	-S-S-	DOX	Carbonic anhydrase IX anti (A-CAIX Ab)	Targeting tumor sites to induce apoptosis of cancer cells for GSH-triggered smart drug release	[32]
	-S-S-	6-Mercaptopurine (6-MP)	Oligosaccharide hyaluronate (oHA)	A targeted drug delivery system that covalently links a biologically active drug and a targeting ligand to the inside and outside of mesoporous silica to construct a stimulus-responsive targeting drug delivery system	[33]
Enzymes	Azo bonds	DOX	CS	Intelligent drug release in response to colonic enzyme specificity, laying the foundation for colonic site-specific drug delivery studies	[34]
	Collagen	Cisplatin	Collagen	Self-driven targeting of lung cancer cells for drug release reduces the toxic side effects of traditional chemotherapy drugs	[35]
	HA	DOX	HA; triphenylphosphine (TPP)	Multi-stage targeting of cancer cells and intelligent mitochondrial drug release to effectively kill cancer cells	[36]
Hypoxia	Nitroimidazole (NI)	DOX	4-Nitroimidazole-*β*-cyclodextrin (NI-CD)	The drug delivery system can selectively deliver drugs to hypoxic tumor cells, and is an effective hypoxia-targeted cancer therapy drug delivery system	[37]
	Azobenzene	DOX	Azobenzene; F68	A hypoxia-responsive silica with an azobenzene polymer as a movable gate, which will expand the unique trigger of silica in the field of medicine and biomedicine due to the application of low oxygen concentration in many pathological conditions	[38]
	β-Cyclodextrin (*β*-CD, SNAC); 4-(phenylazo) benzoic acid (4-PA, SNA)	DOX	4-PA	The hypoxia-responsive mesoporous silica nanoparticles have good biocompatibility and low toxicity, and are potential drug delivery systems for treating diseases with hypoxia characteristics	[39]
Glucose	HA	Glucose oxidase; paclitaxel (PTX)	Polylysine; HA	Novel anti-tumor smart responsive delivery system combining starvation therapy with chemotherapy	[40]
ATP	Mucin-1 (MUC1); ATP aptamer (FA)	DOX	MUC1; FA	A mesoporous silica nanoparticle-based dual receptor-targeted tumor smart responsive drug delivery system	[41]
	FA	DOX	FA, AS1411 adaptor (TA)	Tumor cell-specific recognition and internalization of an ATP-smart responsive nanocarrier for real-time monitoring of drug delivery	[42]
	Zinc dipyridamole (TDPA-Zn^{2+})	DOX	TDPA-Zn^{2+}; peptide polymers	Real-time monitoring of drug release by monitoring the change of luminescence resonance energy transfer (LRET) signal during drug release	[43]

种非常有效的智能递药策略, 其基本原理是基于肿瘤部位与正常组织之间还原物浓度的差异。研究表明, 肿瘤细胞中的谷胱甘肽 (glutathione, GSH) 等内源性还原剂是正常细胞的3倍。因此, 许多研究者基于肿瘤细胞中GSH等还原物差异, 依赖二硫键、二硒键等氧化还原敏感基团, 设计了各种氧化还原响应型介孔

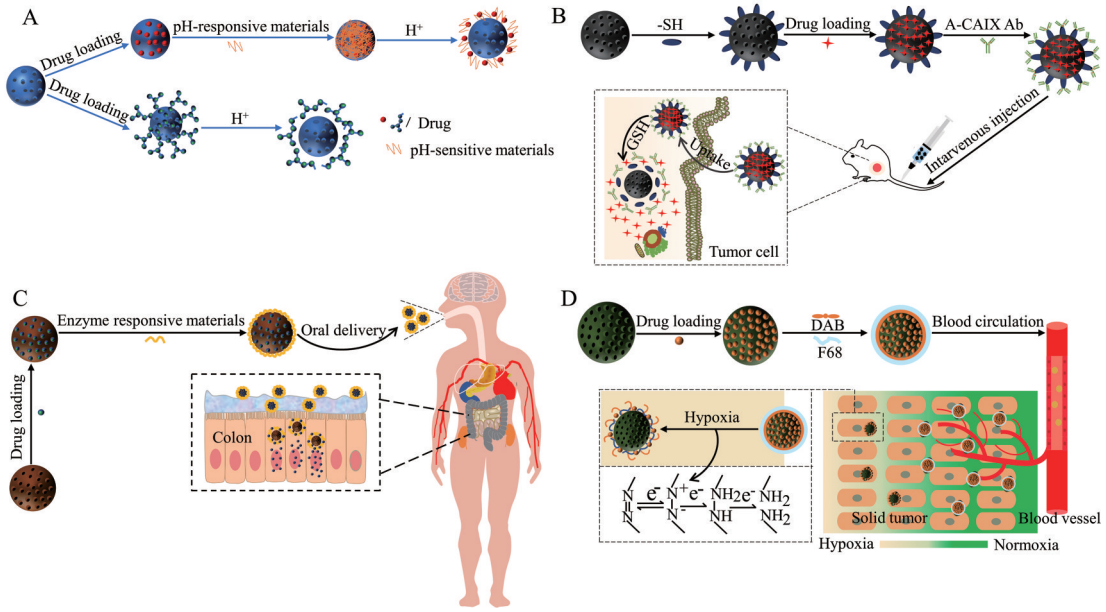

Figure 2　A: Design idea of pH-responsive mesoporous silica drug delivery system. B: Glutathione (GSH)-based redox-responsive mesoporous silica drug delivery system for tumor targeting. C: Enzyme-mediated release mechanism of smart-responsive mesoporous silica from colon cancer. D: Hypoxia-responsive mesoporous silica nanoparticle targeted tumor drug delivery system. A-CAIX Ab: Anti-carbonic anhydrase IX antibody; F68: Pluronic F68; DAB: 4,4′-Azodianiline

二氧化硅纳米递药系统 (图2B)。

基于二硫键的DNA适配体 (AS1411) 和小干扰RNA (siRNAs) 共修饰的负载DOX的氧化还原响应型介孔二氧化硅, 可实现对转移性乳腺癌的靶向智能响应性治疗[30]。该氧化还原响应型介孔二氧化硅递药系统, 由于AS1411对癌细胞表面过表达的膜蛋白具有高度的亲和力, 从而对乳腺癌细胞具有靶向作用, 并增强转移性乳腺癌细胞对介孔二氧化硅纳米粒的摄取。另外, siRNAs能抑制乳腺癌细胞中血管生成素的酪氨酸激酶受体TIE2的表达, 具有协同治疗转移性乳腺癌的作用。该系统在正常组织的GSH (2～20 μmol·L^{-1}) 环境中表现出良好的稳定性, 但在肿瘤细胞的微环境中, 高浓度的GSH (20 mmol·L^{-1}) 与二硫键发生氧化还原反应, 导致二硫键的断裂, 触发药物释放。

Yan等[31]将牛血清白蛋白或肌红蛋白门控上转化纳米粒, 并通过二硒键嵌入介孔二氧化硅纳米载体中, 成功构建了一种氧化还原刺激响应递药系统。在肿瘤细胞微环境中, 负载模型药物DOX的介孔二氧化硅纳米粒表面修饰的蛋白的构象转变及硒键的氧化裂解释放药物, 并通过药物释放伴随着荧光共振能量转移 (fluorescence resonance energy transfer, FRET) 信号的变化而实时地监控药物的释放。Chen等[32]设计了一种抗体靶向肿瘤氧化还原响应型介孔二氧化硅递药系统, 该设计同样是通过二硫键将肿瘤部位高度表达的碳酸酐酶IX (carbonic anhydrase IX, CAIX) 的抗体 (anti-carbonic anhydrase IX antibody, A-CAIX Ab) 嫁接到负载模型药物DOX的介孔二氧化硅表面。该系统不仅能通过GSH触发氧化还原响应智能释药, 而且对肿瘤细胞具有靶向作用。可见, MSNs-CAIX是一种很有前景的智能型靶向递送系统。Zhao等[33]通过二硫键将6-巯基嘌呤 (6-mercaptopurine, 6-MP) 与介孔硅偶联, 透明质酸寡糖 (hyaluronic acid oligosaccharide, oHA) 作为靶向配体修饰在介孔硅表面, 以提高介孔硅在生理条件下的稳定性和生物相容性。该研究通过将生物活性药物与靶向配体共价连接到介孔二氧化硅内外的新策略, 以构建氧化还原响应型的靶向药物递送系统。

1.3　酶响应型介孔二氧化硅递药系统

癌症发生发展过程中, 特定酶的过表达或失调, 成为实现酶介导的智能药物释放的触发器。近年来, 基于功能化的酶响应型介孔二氧化硅的研究引起了人们的广泛关注。Cai等[34]设计了一种具有结肠酶切割位点的功能化介孔二氧化硅, 能特异性响应结肠酶而释放药物 (图2C)。将可生物降解的天然多糖壳聚糖 (chitosan, CS) 通过偶氮键连接到介孔硅的表面作为封孔剂, 阻断药物过早地从孔道中释放出来。药物通过口服到达结肠部位时, 介孔硅与壳聚糖之间形成的偶氮键可被结肠部位酶切割, 介孔硅表面的孔道打开, 释放药物。因此, 该系统能实现药物在结肠部位智能响应型释药, 为结肠部位特异性递药的研究奠定了基础。Vaghasiya等[35]设计了一种由胶原蛋白包裹负载顺铂靶

向肺癌细胞的自驱动介孔二氧化硅递药系统。在正常细胞中, 胶原蛋白包裹的介孔硅能有效阻止药物释放; 而在癌细胞中, 过表达的基质金属蛋白酶-2 (matrix metalloproteinase-2, MMP-2) 与胶原蛋白反应触发药物释放。

线粒体在调节细胞代谢和细胞凋亡中发挥重要作用, 已成为癌症治疗研究的热门靶点。将药物递送到癌细胞的线粒体中, 线粒体中特定的酶, 如透明质酸酶 (hyaluronidase, HAase) 等, 可作为触发药物释放的智能开关, 从而提高治疗效果[36]。Naz 等[36]设计了一种基于介孔二氧化硅的酶响应型级联靶向抗癌药物递送系统, 能精准靶向癌细胞及线粒体。该系统主要由介孔二氧化硅、三苯基膦 (triphenylphosphine, TPP)、HA 构成, 其中 HA 作为封孔剂和靶向剂, 能与癌细胞表面过表达的 CD44 受体特异性结合, 提高癌细胞对纳米粒的摄取率。处于癌细胞的酸性微环境中, HA 易被 HAase 降解, 暴露出来的 TPP 修饰的介孔二氧化硅纳米粒能靶向线粒体释放药物, 从而有效杀死癌细胞。因此, 这种能实现级联靶向递药的酶响应型介孔二氧化硅在癌症治疗方面展现出了巨大潜力。

1.4 低氧响应型介孔二氧化硅递药系统

肿瘤内部常因细胞快速增殖导致耗氧量增加而呈低氧状态[37]。肿瘤组织微环境中独特的缺氧特征, 使其成为智能响应型递药系统抗肿瘤的新靶点。通过利用低氧敏感的化学基团构建缺氧响应型介孔二氧化硅智能药物递送系统, 可实现对肿瘤细胞的靶向药物递送与治疗。

Khatoon 等[37]报道了一种负载模型药物 DOX 的 4-硝基咪唑-β-环糊精 (4-nitroimidazole-β-cyclodextrin, NI-CD) 复合物包裹的低氧响应型靶向肿瘤介孔二氧化硅递药系统。介孔二氧化硅载体表面修饰的硝基咪唑 (nitroimidazole, NI) 作为肿瘤细胞缺氧环境中的触发器, 在缺氧的肿瘤细胞中, 硝基咪唑疏水部分还原为亲水诱导复合物裂解释放药物。该递药系统能将药物选择性地递送到缺氧的肿瘤细胞中, 是一种有效的缺氧靶向药物递送系统。Yan 等[38]设计了以偶氮苯聚合物作为响应阀门, 盐酸 DOX 作为模型药物, 并修饰两亲性的 Pluronic F68 以提高稳定性与分散性的低氧响应型介孔二氧化硅递药系统 (图 2D)。利用偶氮苯在肿瘤低氧环境中易得到电子还原为苯胺, 使介孔二氧化硅孔道打开释放药物。低氧响应型介孔二氧化硅递药系统的设计丰富了刺激响应介孔硅二氧化硅纳米载体家族, 可实现对缺氧环境中的各种疾病的诊断与治疗。此外, Jang 等[39]制备了一种由 4-(苯唑)-苯甲酸 [4-(phenylazo) benzoic acid, 4-PA, SNA] 和 β-环糊精 (β-cyclodextrin, β-CD, SNAC) 包裹的负载模型药物 DOX 的低氧响应型介孔二氧化硅递药系统。4-PA 与 β-CD 通过主客体相互作用阻断介孔二氧化硅纳米粒的孔道, 在肿瘤细胞的缺氧条件下, 4-PA 的偶氮基团被细胞中的硝基还原酶 (nitroreductases, NTRs) 与还原型辅酶 II (nicotinamide adenine dinucleotide phosphate, NADPH) 裂解, 导致与 4-PA 结合的 β-CD 分离释放药物。该低氧响应型介孔二氧化硅纳米粒具有良好的生物相容性、低毒性等优势, 是治疗具有缺氧特征性疾病的潜在药物递送系统。

1.5 小分子物质响应型介孔二氧化硅递药系统

1.5.1 葡萄糖响应型介孔二氧化硅 近年来, 癌症饥饿疗法在癌症治疗中得到广泛的研究。研究发现, 癌细胞的生长速度远大于正常细胞的原因是其能量的来源不同。正常细胞所需能量主要通过氧化磷酸化途径产生, 而肿瘤细胞主要通过糖酵解途径。增殖期的癌细胞需要比正常细胞摄取更多的葡萄糖, 用于产生更多能量。因此, 通过阻断葡萄糖供应或提高癌细胞营养物质的消耗, 可用于癌症饥饿治疗。

葡萄糖氧化酶 (glucose oxidase, GOx) 作为葡萄糖的生物传感器, 可将葡萄糖氧化为葡萄糖酸和过氧化氢。过氧化氢在细胞生长、免疫反应和衰老的各种生理过程中发挥着积极作用。研究发现, 内源性过氧化氢的积累可能导致正常细胞的恶性转化, 但也会导致癌细胞死亡[40]。因此, 将 GOx 应用于肿瘤治疗不仅会触发细胞内葡萄糖的消耗, 导致能量供应中断, 同时还能提高内源性过氧化氢水平, 导致瘤内细胞毒性。Du 等[40]将 GOx 与抗癌药物紫杉醇 (paclitaxel, PTX) 负载于介孔二氧化硅中, 并在其表面修饰聚赖氨酸及 HA, 降低细胞毒性、提高生物相容性。该多功能介孔二氧化硅纳米粒 (MSNs-GOx/PLL/HA) 通过 HA 介导内吞作用, 在肿瘤细胞内触发 GOx 与 PTX 共同释放, GOx 可将葡萄糖转化为过氧化氢, 导致瘤内细胞毒性增加, 具有与 PTX 协同抗肿瘤作用 (图 3)。

1.5.2 ATP 响应型介孔二氧化硅递药系统 三磷酸腺苷 (adenosine triphosphate, ATP) 是一种多功能核苷酸, 通过打破磷酸酐键, 为生物过程提供能量。研究表明, ATP 水平的上调与许多病理过程相关, 如在癌变组织及肿瘤的生长过程中 ATP 水平显著上调, 使其成为区分癌细胞和正常细胞的重要标志[41]。因此, 研究者设计了多种 ATP 响应型药物递送系统, 通过特异性识别 ATP 或与 ATP 适配体竞争性结合实现智能响应释药。

Bagheri 等[41]通过在羧基功能化介孔硅的表面修饰两种类型的适配体 MUC1 (mucin-1) 和 ATP 适配体,

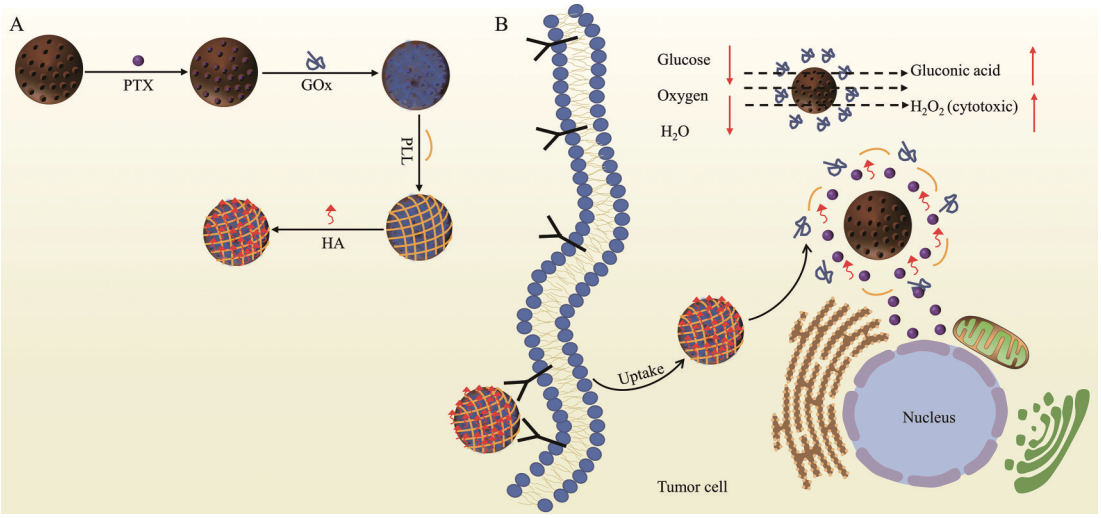

Figure 3　Schematic illustration of MSNs-GOx/PLL/HA nanoparticles synergistically targeting tumor starvation therapy. A: The preparation processes of MSNs-GOx/PLL/HA nanoparticles; B: The cellular process containing the CD44-mediated cellular internalization, degradation of HA by HAase together with the exposure of PLL at HAase-rich tumor milieu, endosomal or lysosomal escape, cytoplasmic release of GOx and PTX and the intracellular reaction of GOx with glucose. GOx: Glucose oxidase; MSNs: Mesoporous silica nanocarriers; PLL: Poly (*L*-lysine); HA: Hyaluronic acid; HAase: Hyaluronidase; PTX: Paclitaxel

利用 MUC1 和 ATP 适配体 (ATP1、ATP2) 在介孔硅表面形成 Y 型 DNA 结构, 从而实现对肿瘤的靶向智能响应递药。其中, MUC1 适配体识别 MUC1 受体, ATP 适配体与癌细胞中高水平的 ATP 相互作用, 导致纳米粒内化到癌细胞释放药物。Zheng 等[42]利用石墨烯量子点 (graphene quantum dots, GQDs), 将 ATP 适配体覆盖在荧光介孔硅的表面, 成功制备了一种用于细胞内药物传递与实时监测药物递送的 ATP 智能响应纳米载体。细胞外 ATP 水平较胞内低, 介孔二氧化硅的孔道处于关闭状态; 一旦被肿瘤细胞特异性识别并内化后, 胞内高水平的 ATP 将使 ATP 适配体的构象发生改变, 导致 GQDs 从纳米载体上脱落而释放药物; 同时介孔硅的荧光随着 GQDs 的脱落而打开, 从而实时监测药物从孔道中释放。另外, Lai 等[43]也开发了一种用于实时监测药物释放的 ATP 响应型递药系统。该系统是通过上转化纳米粒 UCNPs 为核, 多肽聚合物包裹的介孔硅为壳组装的核壳结构, 将药物负载在介孔硅的孔道中, 并使用锌二吡胺类化合物 (zinc-dipicolylamine analogue, TDPA-Zn^{2+}) 进行功能化。由于 ATP 对 TDPA-Zn^{2+} 具有较高的亲和力, 介孔硅表面结合多肽被竞争性置换下来; 通过药物释放伴随着发光共振能量转移 (luminescence resonance energy transfer, LRET) 信号的变化而实时地监控药物的释放。

2　外源性刺激响应介孔二氧化硅递药设计与研究应用

外源性刺激响应型介孔二氧化硅是指能对外部施加的刺激作出敏感的响应, 并能持续释放药物。通常利用外部物理因素作为诱导因子, 通过人为改变施加刺激的部位及时间, 从而实现药物在病变部位精准释放, 降低药物的不良反应[44]。

2.1　光响应型介孔二氧化硅递药系统

光响应型药物递送系统常用于复杂的受控药物的释放, 以减少传统化疗对正常组织的不良反应并提高对疾病的治疗效果[45-47]。通常, 某些特定波长的紫外线 (ultraviolet, UV)、可见光 (visible light, Vis) 及近红外光 (near infrared, NIR) 可作为外源性刺激触发药物释放[48], 其机制主要是依赖于光敏性纳米载体的构象转变实现对药物的缓控释放。基于介孔硅的结构特性, 利用光敏性材料作为“开关”, 实现对病变组织精准、可控的靶向释放。表 2[49-60]列举了近年来外源性刺激响应型介孔二氧化硅递药系统的设计与研究应用概况。

Tang 等[49]基于氧化石墨烯及靶向肿瘤适配体 (Cy5.5-AS1411), 设计了一种具有双“开关”的新型靶向光响应型介孔二氧化硅递药系统。通过 Cy5.5-AS1411 特异性靶向肿瘤细胞使 Cy5.5 荧光恢复, 氧化石墨烯将光能转化为热能, 使氧化石墨烯膨胀导致药物释放。这种新型的“开关”式的光响应型智能介孔二氧化硅递药系统在靶向给药、可控式药物释放方面具有广阔的应用前景。此外, 研究者基于偶氮苯与 α-环糊精设计了一种组装在介孔二氧化硅表面的光响应型纳米阀控制药物从介孔硅孔道中释放[50]。当偶氮苯受到紫外照射时, 将从稳定的反式构型转变为不稳定的顺式构型从而导致药物释放; 当紫外照射关闭时, 偶氮苯能可逆

Table 2 Overview of studies on mesoporous silica exogenous stimulus-responsive drug delivery systems

Stimulus	Responsive linker	Model drug	Blocking cap	Advantage	Ref.
Light	Graphene oxide	DOX	Graphene oxide	Photoresponsive targeted cancer therapy with important applications in controlled drug release, targeted drug delivery, and chemotherapy	[49]
	Azobenzene	DOX	Azobenzene; α-cyclodextrin	Targeted delivery of anti-cancer drugs based on external light stimulation responsive nanovalves	[50]
	Graphene oxide	Antimicrobial peptide PA-C1b	Graphene oxide; folic acid	This drug delivery system provides both protection against antimicrobial peptides and intelligent tumor-targeted drug release	[51]
Magnetic	Paramagnetic iron oxide	DOX	Thermosensitive polymers (NIPAM, NHMA, MBA)	Synergistic effect between intracellular heat therapy and chemotherapy triggered by alternating magnetic fields to significantly inhibit tumor growth	[52]
	Triiron tetraoxide	Camptothecin	Iron (III) tetraoxide; 2,3-dimercaptosuccinic acid	High cellular uptake rate for precise delivery of drugs to cancer cells for various biomedical applications	[53]
	Triiron tetraoxide	DOX	Polyethylene glycol; folic acid	Smart drug release through specific binding to FA receptors overexpressed on cancer cells for specific targeting of tumors	[54]
Temperature	*N*-Isopropylacrylamide polymer (PNIPAM)	DOX	PNIPAM	High temperature sensitivity and biocompatibility of the system, prolonging its retention time in the blood	[55]
	DNA single strand	DOX	DNA single strand	A novel temperature-responsive nanocarrier with reversible DNA valves	[56]
	Thermosensitive polymer PNIPAM-*b*-glycine	Imatinib mesylate	Thermosensitive polymer PNIPAM-*b*-glycine	Significantly inhibits the growth of leukemic cancer cells by targeting them through a temperature-responsive mediated drug delivery system	[57]
Ultrasound	Polyethylene glycol (PEG)	DOX	PEG	A novel intelligent graded ultrasound-responsive mesoporous silica that facilitates cancer cell uptake and thus enhances anticancer effects	[58]
	Sodium alginate (SA)	Rhodamine (RhB)	Cross-linking of sodium alginate with calcium chloride	Reversible ultrasound responsive smart drug release and good biocompatibility, providing an effective method for remote ultrasound stimulation responsive smart drug release mode	[59]
	Perfluoropentane	DOX	Lipids	This smart responsive drug delivery system offers high drug loading and cellular uptake rates	[60]

地转变为反式构型, 阻止药物释放。该系统是一种基于外部光刺激响应型的纳米阀, 实现对抗癌药物的靶向释放。抗菌肽PA-C1b具有较强的抗癌活性, 且无明显溶血现象, 是治疗癌症的潜在药物。然而, 多肽类药物在体内易被蛋白酶降解, 生物利用度低。Dong等[51]开发了一种靶向肿瘤的光响应型抗菌肽递送系统, 将磺基氰胺标记的抗菌肽PA-C1b载入氧化石墨烯包裹的介孔二氧化硅纳米粒中, 并将具有靶向作用的叶酸偶联到介孔二氧化硅表面 (图4A)。该递药系统对抗菌肽具有保护作用, 同时又能靶向肿瘤智能释药。

2.2 磁响应型介孔二氧化硅递药系统

磁响应型介孔二氧化硅递药系统是在外部磁场的刺激下, 将载药的磁性介孔二氧化硅纳米粒有效递送到病变部位, 并通过交变磁场产生的热量控制药物的释放。其中, 磁性介孔二氧化硅复合材料因其优良的性能, 引起了研究者的广泛兴趣。在外部磁场驱动下, 磁性介孔二氧化硅纳米粒能精准到达肿瘤部位释放药物。磁响应型介孔二氧化硅的设计思路主要有两种 (图4B), 一是以磁性纳米材料为核, 介孔硅为壳, 形成核壳结构; 另一种是将磁性纳米材料直接修饰在介孔硅的表面。目前, 基于这两种设计思路的磁响应型介孔硅均已开展了广泛研究。

Guisasola等[52]提出了一种在外部磁场的作用下介孔二氧化硅介导体内肿瘤治疗的创新方法。该方法是通过将顺磁性氧化铁纳米粒作为核嵌入表面涂有热敏性聚合物的介孔二氧化硅内构成核壳结构。氧化铁磁性纳米粒在交变磁场 (alternating magnetic field, AMF) 作用下, 导致局部温度升高, 引发介孔硅表面聚合物构象转变, 触发药物释放。Chen等[53]将2,3-二巯基琥珀酸功能化的四氧化三铁纳米粒直接修饰在氨基化的介孔二氧化硅表面, 构建一种新型磁响应型介孔二氧化硅递送系统。在没有磁场的情况下, 药物几乎无法从孔道中释放出来; 当受到外部可控磁场时, 即可打开介孔二氧化硅的孔道, 释放药物。Wu等[54]设计了一种以磁性材料为核, 介孔二氧化硅为壳的磁性纳米粒, 并利用具有生物相容性的聚乙二醇及对癌细胞具有靶向性的叶酸对其表面进行功能化, 实现特异性靶向肿瘤智能释药。将水溶性差的抗癌药物多西紫杉醇载入该磁

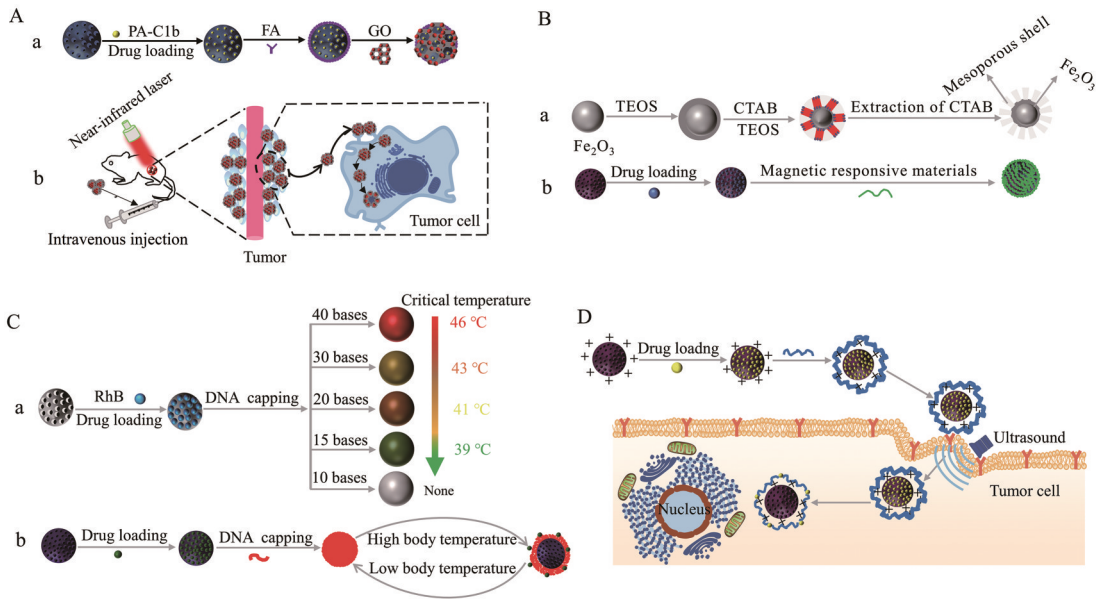

Figure 4　A: Design of near-infrared light-responsive mesoporous silica nanoparticles *in vivo* targeted tumor drug delivery system. a: The preparation processes of MSN@Cy7-PA-C1b@FA-GO nanoparticles; b: MSN@Cy7-PA-C1b@FA-GO targets tumors *in vivo*. B: Design concept of magnetically responsive mesoporous silica drug delivery system. a: The synthetic route of core-shell mesoporous silica; b: Preparation of magnetically responsive mesoporous silica nanoparticles. C: Design strategy for DNA valve-mediated temperature reversible smart responsive mesoporous silica drug delivery system. a: Scheme of different critical temperature for different DNA valves; b: Temperature-responsive DNA-gated nanocarriers for controlled release. D: Design of ultrasonic-responsive mesoporous silica delivery system

性纳米粒中, 在外部磁场的作用下递送到肿瘤部位, 与癌细胞上过表达的FA受体特异性结合, 增强癌细胞的摄取。

2.3　温度响应型介孔二氧化硅递药系统

通常, 温度不仅可作为某些疾病的内源性刺激响应, 如肿瘤、炎症等引起的局部组织温度升高4或5 ℃; 另一方面, 通过其他外源性刺激引起的温度变化也可用于构建智能响应型递送系统。温度响应型介孔二氧化硅递药系统主要是通过在介孔硅的表面修饰温敏性材料, 依据周围温度的变化控制药物的释放。

N-异丙基丙烯酰胺聚合物 (*N*-isopropylacrylamide polymer, PNIPAM) 是较为常见的的温敏性聚合物。Singh等[55]报道了通过将PNIPAM嫁接在*N*-(3-氨基丙基) 甲基丙烯酰胺修饰的介孔硅表面作为控制药物释放的开关, 构建了一种温度响应型递药系统。Yu等[56]提出了一种简单有效的温度响应型介孔二氧化硅递药系统, 将药物负载于介孔硅的孔道中, 并在其表面涂上温度可逆的DNA单链作为控制药物释放的阀门; 通过改变单链DNA核苷酸的长度从而改变纳米载体的临界释放温度 (图4C)。当体温处于正常情况时 (37 ℃), 阀门处于关闭的状态; 体温异常升高时 (T > 37 ℃), 介孔硅的阀门打开, 药物释放。直到体温恢复到正常后, 介孔硅的DNA阀门又重新关闭。因此, 成功开发出了一种基于介孔二氧化硅的具有可逆DNA阀门的新型温度响应型纳米载体。Amgoth等[57]将热敏性聚合物PNIPAM-*b*-甘氨酸嫁接在负载抗癌药物甲磺酸伊马替尼的介孔硅表面作为药物的保护层, 对白血病癌细胞具有明显抑制作用。

2.4　超声响应型介孔二氧化硅递药系统

超声被认为是纳米药物递送系统中最有前途的外源性刺激响应之一, 具有对组织穿透能力强、频率可控等特点。一般来说, 超声刺激响应主要是通过热效应或声控效应来控制纳米载体药物的释放。热效应是通过连续不断的超声波在体内转化为热能, 从而破坏修饰在介孔硅表面的材料, 导致药物释放; 而声控效应是在持续超声波作用下破坏介孔硅表面形成的机械稳定性的化学键, 导致介孔硅表面修饰的材料塌陷释放药物。

研究报道了一种新型的超声响应递送系统, 介孔二氧化硅作为载体, 超声敏感性聚合物p (MEO_2MA-*co*-THPMA) 作为封孔剂。在超声的作用下, 聚合物结构发生转变, 介孔硅的孔道打开药物释放。Paris等[58]开发了一种新型的智能分级超声响应的介孔二氧化硅, 在靶向肿瘤的过程中具有不同的表面特征。通过聚乙二醇包裹带正电荷的介孔硅, 在高频超声波的作用下, 介孔硅表面的聚乙二醇脱落, 暴露出带正电荷的

介孔硅将有利于癌细胞的摄取, 从而增强抗癌作用(图4D)。

Li等[59]利用海藻酸钠 (sodium alginate, SA) 修饰介孔硅, 并引入氯化钙与其发生交联作用, 设计出了一种可逆的超声响应型介孔二氧化硅递药系统。在超声刺激作用下, 聚合物与介孔硅表面形成的化学键被破坏, 导致药物快速释放; 当超声关闭时, 化学键重新连接在一起, 介孔硅的孔道关闭。这些具有良好的超声响应特性的药物递送系统, 在药物智能递送应用中具有重要的意义。Amin等[60]设计了一种以DOX为模型药物, 全氟戊烷为超声响应材料, 脂质包裹介孔硅的超声响应型递药系统。脂质涂层能够有效防止药物过早的释放, 并增强癌细胞的摄取, 超声作用产生的机械效应及热效应诱导全氟戊烷转化为气态形式, 促使脂质层的破裂释放药物。

3 多重响应型介孔二氧化硅设计与应用

近年来, 多重刺激响应型递药系统成为介孔二氧化硅智能递药系统研究的新方向[61]。虽然单一刺激响应型介孔二氧化硅递药系统已展现出独特的癌症治疗优势, 但单一刺激响应型的递送系统还是存在响应灵敏度低、响应速度迟缓等问题。因此, 通过设计两种或多种不同刺激响应的递药系统, 将内源性与外源性相结合, 以提高智能响应型药物递送系统的响应灵敏度, 使药物在靶组织或细胞精准释放。

Porrang等[62]研究报道了基于温敏性材料*N*-异丙基丙烯酰胺聚合物(*N*-isopropylacrylamide polymer, NIPAAm) 与pH响应性材料聚丙烯酸 (polyacrylic acid, PAA) 共修饰的介孔二氧化硅, 成功构建了温度和pH双刺激响应型的介孔二氧化硅智能递送系统。由于肿瘤组织温度较正常组织高 (T > 37 ℃), 以及处于微酸性环境 (pH < 7.4), 负载模型药物DOX的介孔硅能靶向肿瘤部位并实现双重刺激响应, 从而提高介孔硅智能递药系统的灵敏度。Cui等[63]利用二硫键在介孔硅表面嫁接经叶酸 (folic acid, FA) 修饰的γ-苄基-*L*-谷氨酸聚合物 (γ-benzyl-*L*-glutamic acid polymer, PBLG), 使其具有肿瘤特异性识别及GSH和温度双重刺激响应。其中, FA能靶向癌细胞, PBLG可因癌变组织中GSH浓度增加而发生解离及在高温条件下发生构象的转变, 实现智能响应释放药物。

Ding等[64]提出了一种新型的pH和ROS双重响应型的介孔二氧化硅递药系统, 该系统是通过静电相互作用将羧甲基甲壳素 (carboxymethyl chitin, CMCH) 包裹的可被ROS响应裂解的硫缩酮 (thioketal, TK) 键合在中空介孔二氧化硅纳米粒表面, 并进一步使用葡萄糖调节蛋白结合肽 (glucose regulatory protein, GRP-78P) 进行表面修饰, 用于靶向递送DOX和α-生育酚琥珀酸酯 (alpha-tocopheryl succinate, α-TOS) 到达肿瘤部位。pH与ROS双刺激触发药物在肿瘤细胞中释放, 提高抗肿瘤疗效及降低不良反应。该系统作为可生物降解以及生物相容性的抗肿瘤化疗药物的载体, 已显示出巨大的潜力。

Lei等[65]利用聚多巴胺 (polydopamine, PDA) 具有pH、氧化还原及近红外吸收等特性, 通过二硫键将PDA修饰在介孔硅表面, 成功地设计出一种三重响应型的生物相容性介孔二氧化硅递药系统。该递药系统不仅在弱酸性和高GSH浓度的条件下表现出刺激响应性释药, 同时由于PDA的近红外吸收较强, 具有良好的光热转化效率, 对近红外光也同样具有刺激性响应。因此, 聚多巴胺修饰的介孔硅可作为一种新型的化疗和光热联合治疗的多响应型智能药物递送系统。

4 智能响应型介孔二氧化硅抗肿瘤递药系统存在的问题与思考

4.1 智能响应型介孔二氧化硅递药系统体内靶向敏感性与可控性有待深入研究

尽管智能响应型介孔二氧化硅递药系统在肿瘤治疗方面已展现出可行性与有效性, 但智能响应型介孔二氧化硅的研究仍处于初级阶段, 仍面临着靶向敏感性与可控性差、递送效率低的挑战, 在实现药物定时、定量、定位的选择性递送方面仍需深入探析[66]。肿瘤病理微环境复杂多变, 且存在多种刺激响应信号, 使单一刺激性响应系统难以准确、快速地在靶部位释放高浓度的药物, 通过设计多种生理信号刺激响应型介孔二氧化硅递送系统, 可进一步改善其靶向精准性与可控性。此外, 不同类型的肿瘤、不同肿瘤的生长过程及不同个体的肿瘤微环境也存在较大差异, 甚至某些正常细胞也具有肿瘤细胞微环境相似的特征, 导致环境响应性介孔二氧化硅递药系统靶向敏感性降低。如何提高介孔二氧化硅载体的智能响应性递药, 控制药物在到达靶部位前零释放, 使其到达靶部位时, 根据靶部位的生理环境或病理条件智能高效释放是治疗肿瘤的重大挑战[67]。因此, 设计各种内源性与外源性智能响应型介孔二氧化硅靶向递药系统时, 通过提高其选择性、灵敏度、可控性及稳定性, 使介孔二氧化硅递送系统朝着更精准化递药的方向发展。

4.2 智能响应型介孔二氧化硅递药系统的体内毒性研究不足

尽管介孔二氧化硅已得到快速发展, 但其生物学效应及安全性仍存在众多不足, 如介孔二氧化硅粒径的大小、形貌、给药剂量、给药途径等产生的毒性及其

潜在的基因毒性研究不透彻[3]。各种不同材料修饰的智能响应型介孔二氧化硅递药后在体内的药物分布及载体的细胞毒性等问题也仍需深入研究[68]。介孔二氧化硅作为外源物质, 体内可诱导免疫反应, 而且介孔二氧化硅体内的降解和排泄速度相对较慢, 存在体内蓄积安全性等问题。因此, 通过设计新型有机杂化介孔二氧化硅, 可提高其生物可降解性和生物安全性[69,70]。相信随着介孔二氧化硅的优化设计及其体内毒性研究的不断深入和细化, 基于介孔二氧化硅的纳米制剂研究能真正迈向临床。

5　展望

目前, 如何根据生理特性及利用内源性、外源性刺激设计合适的智能响应型药物递送系统来控制药物在病灶部位释放, 已成为药剂学近十年来研究的热点。介孔二氧化硅具有良好的生物相容性、孔径易调节、粒径可控及表面易修饰等特性, 成为设计智能响应型递送系统研究的良好的载体材料。根据不同的内源性或外源性刺激条件, 可设计具有不同性质的响应型介孔二氧化硅递送系统, 依据载体材料对机体微环境或生理变化的感知响应、实现递药系统在病灶组织定位释药或控制释药, 为肿瘤等复杂疾病的治疗提供了非常有效的方法。然而由于载体材料及各种修饰材料生物安全性等问题, 使得智能响应型递送系统在临床转化时存在巨大挑战。通过对介孔二氧化硅智能响应型递药系统载体合成、修饰的优化以提高其响应灵敏度和生物安全性, 将对智能响应型介孔二氧化硅递药系统的临床转化应用具有重要意义。

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