光敏剂递送系统及肿瘤光动力治疗的研究进展

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摘要: 光动力治疗 (photodynamic therapy, PDT) 是一种新型肿瘤治疗手段, 用于皮肤癌、膀胱癌和前列腺癌等多种肿瘤的临床治疗。大多数光敏剂具有疏水性, 存在生物利用度低和肿瘤靶向性差等缺点。纳米递送系统可增加光敏剂的溶解性, 促进其在肿瘤部位的富集, 可通过制备联合其他抗肿瘤药物的多功能递送系统, 增强肿瘤协同治疗效果。需要提出的是, 光敏剂递送系统在解决光敏剂溶解性差和肿瘤靶向性不足等问题的同时, 还需要改善光敏剂在体内的药动学性质, 促进其在肿瘤部位快速富集和体内快速清除, 降低光敏剂的光毒性。本文总结了近年PDT在肿瘤治疗中的临床应用、光敏剂的发展、光敏剂递送系统以及和其他治疗方法的联合应用, 旨在为新型光敏剂递送系统的设计及其在肿瘤PDT的临床应用提供参考。

关键词: 纳米递送系统; 光敏剂; 光动力治疗; 临床应用; 联合治疗

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Recent progress in delivery systems for photosensitizers and anti-cancer photodynamic therapy

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Abstract: Photodynamic therapy (PDT) is a new modality for cancer therapy, which has been used in the clinical treatment for various tumors, such as skin cancer, bladder cancer and prostate cancer. Most photosensitizers have the disadvantages of hydrophobic, low bioavailability and the limited tumor targeting ability. The nanoscale delivery systems can improve the solubility of photosensitizers and enhance their accumulation at the tumor sites. The multifunctional nano-delivery systems are prepared in combination with other anti-tumor drugs to enhance the anti-tumor effect. In addition to addressing the issues of poor solubility and the insufficient tumor targeting ability, the nanoscale delivery systems need to improve the pharmacokinetic properties of photosensitizers, facilitating their rapid accumulation at the tumor sites and quick elimination *in vivo*, and reducing the skin phototoxicity. This review summarizes the recent clinical application of PDT of cancer, the development of photosensitizers, the delivery systems for photosensitizers and the combinatorial application with other therapeutic methods. The goal is to present an understanding of knowledge on the design of new types of photosensitizers and its clinical application in PDT of cancer.

Key words: nanoscale delivery system; photosensitizer; photodynamic therapy; clinical application; combinatorial therapy

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光动力治疗 (photodynamic therapy, PDT) 是一种新型的非侵入性肿瘤治疗方式, 和手术、放疗和化疗等传统肿瘤治疗方式相比, 具有创伤性小、选择性高和毒性低等特点, 广泛应用于治疗皮肤癌、食道癌和前列腺癌等多种肿瘤。PDT 的三要素是光敏剂、肿瘤部位氧气和合适的光源。PDT 通过富集在肿瘤部位的光敏剂, 在合适光源照射下, 依赖肿瘤部位的氧气产生具有细胞毒性的活性氧 (reactive oxygen species, ROS)。PDT 通过直接促使肿瘤细胞凋亡、坏死, 间接破坏肿瘤脉管系统, 阻断氧气和养料的供应, 也可诱发肿瘤部位炎性反应, 激活宿主免疫应答等发挥抗肿瘤作用[1,2]。PDT 不仅可以治疗皮肤癌类浅表性肿瘤, 由于激光光纤的应用, 对于肺癌、食道癌和膀胱癌等多种深部实体瘤也产生较好的治疗效果。光敏剂对肿瘤 PDT 治疗效果起关键作用, 但大多数光敏剂疏水性强, 生物利用度低, 肿瘤靶向性差, 给药后可能损伤正常组织, 限制其在肿瘤治疗中的应用。纳米递送系统可增加光敏剂溶解度、改善光敏剂稳定性和提高肿瘤靶向性, 同时纳米递送系统通过实现 PDT 与其他肿瘤治疗方法的联合, 提高肿瘤治疗效果。尽管传统纳米递送系统显著改善了光敏剂的体内递送效率, 但由于其在血液中长循环, 增加了光毒性风险。因此, 设计增加光敏剂在肿瘤部位富集且不改变光敏剂体内清除速率的递送系统愈发重要。本文主要对肿瘤 PDT 的临床应用、光敏剂的分类、光敏剂递送系统的研究进展以及 PDT 和其他肿瘤治疗方式的联合应用进行概述, 最后提出 PDT 的前景和展望, 希望为促进肿瘤 PDT 的发展提供参考。

1 PDT 在肿瘤治疗的临床应用

20 世纪初, 研究者用光敏剂和可见光治疗皮肤癌, 加拿大学者 Kennedy 于 1990 年报道 5-氨基酮戊酸 (5-aminolevulinic acid, 5-ALA) 介导的 PDT 治疗皮肤恶性肿瘤, 创立了 PDT 治疗皮肤癌的里程碑[3]。20 世纪五、六十年代, 血卟啉衍生物 (hematoporphyrin derivative, HpD) 的成功制备促进了 PDT 发展, 应用于荧光定位检测肿瘤和肿瘤 PDT[4]。同时, PDT 被成功推向皮肤癌、膀胱癌、肺癌、食道癌、胃癌和头颈部鳞状细胞癌等多种肿瘤的临床治疗[5]。其中, PDT 对头颈癌和皮肤癌等浅表性恶性肿瘤的治疗效果较为明显, 在乳腺癌、骨癌和肝癌等其他非浅表性恶性实体瘤的治疗中也有较好的发展前景[6]。

1.1 治疗皮肤恶性肿瘤

5-ALA 或氨基乙酰丙酸甲酯 (methyl aminolevutinate, MAL) 介导的局部 PDT 被广泛用于治疗包括基底细胞癌和皮肤鳞状细胞癌在内的浅表性非黑色素瘤皮肤癌或癌前病变。和手术相比, PDT 在治疗皮肤癌时, 具有复发率低、治疗时间短、安全性好、不易损伤容貌和不良反应较低等优点[7,8]。PDT 尤其适用于不能接受手术治疗、对局部治疗药物耐药和手术后复发等患者。5-ALA 的商业化产品 Levulan®被批准治疗光线性角化病和基底细胞癌, MAL 的商业化产品 Metvix® 被批准治疗光线性角化病和 Bowen 病[9]。光敏剂二氢卟吩 e6 (chlorin e6, Ce6) 的商业化试剂 Fotolon®被批准用于皮肤和黏膜恶性肿瘤的 PDT[10]。Zhang 等[11]将 5-ALA 介导的 PDT 作为不适合手术治疗的皮肤鳞状细胞癌患者的替代治疗, 在完成治疗的 29 名患者中, 5 名患者在经历 2～9 次治疗后, 肿瘤得到完全缓解, 并且在治疗后 18 个月内无复发, 剩余 24 名患者症状减轻, 生活质量得到改善。证实 PDT 可成为不可手术切除肿瘤的替代疗法, 成为改善患者预后的有效肿瘤治疗方式。

1.2 治疗肺癌

PDT 是一种微创性治疗方法, 可缩小无法手术切除的肺癌肿瘤体积, 减少肺切除体积, 可作为姑息性治疗方式, 改善患者呼吸功能, 改善患者预后, 对早期中央型肺癌也有较好治疗效果[12]。PDT 治疗肺癌时, 具有创伤性小、适应性好和可重复治疗等优势。HpD 的商品化试剂 Photofrin®被批准用于治疗非小细胞肺癌, 第二代光敏剂他拉泊芬钠的商品化试剂 Laserphyrin® 被批准用于肺癌治疗[13]。Kimura 等[14] 使用 Laserphyrin®对 12 名晚期肺癌患者进行 PDT, 治疗后患者的卡式功能状态评分 (100) 高于治疗前 (85)。治疗后所有患者的症状均改善, 6 例患者出现部分缓解, 治疗后两个月患者的肺活量明显提高。

1.3 治疗膀胱癌

PDT 已成功用于膀胱癌的临床治疗, 适用于卡介苗灌注难治性膀胱癌、常规治疗后复发性肿瘤和非浸润性膀胱癌的治疗, 有耐受性好和复发率低的优势[15]。Photofrin®是治疗膀胱癌的第一代光敏剂, 能缓解浅表性膀胱癌, 但存在长期光毒性和膀胱萎缩的治疗弊端[16]。5-ALA 常用于提高膀胱癌手术切除前的肿瘤细胞检测灵敏度, 有助于切除残留的肿瘤细胞。同时, 在手术过程中, 5-ALA 在光照下发生光化学反应, 有利于消融肿瘤并改善患者预后[17]。Bader 等[18]使用 5-ALA 的己酯衍生物 (hexaminolevulinate, HAL) 介导 PDT 作为膀胱癌的辅助治疗, 88.24% 患者实现肿瘤组织完全清除, 52.90% 患者在 6 个月内实现肿瘤组织清除。

1.4 治疗前列腺癌

常规手术、局部放疗和激素疗法等前列腺癌治疗手段存在术后尿失禁、性功能障碍和复发率高等问题[19]。PDT 是一种用于低风险前列腺癌的局部治疗措施, 可

选择性消融肿瘤并减少损伤。和其他局灶性治疗方式相比, PDT具有姑息性、可重复性、低毒性、更高安全性和减少不良反应等优势[20]。Photofrin®、替莫泊芬(m-THPC)的商品化试剂Foscan®、5-ALA和帕利泊芬的商品化试剂Tookad®等多种光敏剂被用于前列腺癌的临床PDT治疗。其中, Tookad®介导的血管靶向光动力疗法 (vascular-targeted photodynamic therapy, VTP)已被获准治疗低风险前列腺癌。该疗法靶向肿瘤血管, 导致血管收缩和血栓形成, 阻断脉管系统的营养物质供应, 使肿瘤对PDT诱导的损伤更加敏感, 具有选择性高和防止肿瘤复发的优势[21,22]。Noweski等[23]对68名前列腺癌患者进行VTP治疗, 75%患者总体实现了局灶性消融术的成功, 50%患者的前列腺叶中无肿瘤发生, 证实Tookad®介导的VTP是一种用于局部低风险前列腺癌的安全有效的治疗方式。

1.5 治疗头颈部肿瘤

手术和放疗是头颈部恶性肿瘤的主要治疗措施, 但治疗后存在疤痕明显、吞咽困难和黏膜炎等问题。PDT作为一种微创的治疗手段, 可用于治疗头颈部的癌前病变和恶性病变, 单独使用可治疗早期肿瘤, 也可结合其他治疗手段治疗晚期肿瘤[24]。Photofrin®、5-ALA、Ce6、他拉泊芬钠、m-THPC和ASP-1929 (Akalux®)等介导的PDT被用于头颈部肿瘤的临床研究。其中, m-THPC被批准用于头颈部鳞状细胞癌的早期治愈性和姑息性治疗, Akalux®被批准用于治疗不可手术切除的局部晚期和复发性头颈部鳞状细胞癌[25-27]。Jerjes等[28]对56名接受m-THPC介导的PDT的患者进行调研, 治疗后患者的生活质量均有所改善。Hosokawa等[29]对42例头颈部鳞状细胞癌患者进行Photofrin®介导的PDT, 患者的5年生存率为57.8%, 完全缓解率为69%, 有效率为97.6%, 且患者越早接受PDT治疗, 生存期越长。Cognetti等[30]对30名区域性复发性头颈部鳞状细胞癌患者实施RM-1929介导的PDT, 结果显示客观缓解率为26.7%, 完全缓解率为13.3%, 部分缓解率为30%, RM-1929介导的PDT为其他治疗方法失败的患者提供了新的治疗方案, 改善了头颈区域的功能和患者形象, 但参与研究的患者预后不良, 对治疗方案的反应率有限, 该疗法还需进一步研究。

1.6 治疗食道癌和胃癌

放疗和化疗是不可手术切除的局部晚期食管癌的主要治疗方案, 但仍存在肿瘤复发和耐药等问题, PDT常作为挽救性治疗手段, 用于放疗和化疗后复发性食道癌的局部治疗, 食道癌也是最早被批准的PDT临床适应症之一[31]。PDT治疗食道癌的缓解率相对较高, 疗效较好, 复发率较低, 常见的不良反应是皮肤光毒性和造成食管狭窄[32]。Photofrin®介导的PDT在美国和日本被批准用于治疗食道癌, 常用于阻塞性食道癌患者的姑息性局部治疗、巴雷特食管的根除性治疗和浅表食道癌病变的治疗。他拉泊芬钠介导的PDT在日本被批准用于放疗和化疗失败后无转移的浅表性食道鳞状细胞癌的局部治疗[33,34]。m-THPC仍处于早期食道癌局部治疗的临床研究阶段, 尚未被批准使用[35]。Liu等[36]对79例不符合手术治疗的早期食管癌患者进行PDT。其中, HpD介导的PDT, 治疗组的完全缓解率为6.4%, 部分缓解率为66.0%; 血卟啉注射液介导的PDT, 治疗组的完全缓解率为9.4%, 部分缓解率为59.4%。两种光敏剂对不同临床分期的食管癌治疗效果良好, 疗效相近, 不良反应较轻, 耐受性好, 是食道癌有效的姑息治疗手段。

PDT在日本被批准治疗由于黏膜下浸润和溃疡疤痕存在而无法进行常规内镜下切除治疗的早期胃癌, 是一种安全可靠的治疗方式[33]。Ma等[37]用血卟啉注射液介导的PDT治疗无法化疗和手术的晚期胃癌患者, 4次PDT后, 该患者连续两次病理检测未发现癌变组织, 肿瘤标记物逐渐恢复正常水平, PDT后该患者的卡式功能状态评分 (90) 高于治疗前 (80)。

1.7 治疗脑肿瘤

PDT对脑肿瘤的治疗研究主要集中在脑胶质瘤, 脑胶质瘤的标准治疗方式是手术后放疗或化疗, 但存在局部复发和生存率有限等问题, PDT可改善脑胶质瘤患者的预后, 提高PDT和荧光引导手术切除治疗后患者的生存率[38]。Photofrin®、m-THPC、维替泊芬的商品化试剂Visudyne®和5-ALA等多种光敏剂已用于脑胶质瘤的临床研究。其中, 欧盟已批准5-ALA介导的荧光影像引导切除术用于高级别脑胶质瘤, 可减少术后肿瘤残留, 延缓肿瘤复发[39, 40]。Li等[41]用光敏剂血卟啉注射液介导PDT治疗复发性脑胶质瘤, 手术后接受PDT治疗患者的卡式功能状态评分 (83.2) 显著高于术后未PDT组 (74.6), 复发率显著低于术后未PDT组。

1.8 治疗其他肿瘤

PDT除了被批准治疗上述肿瘤外, 在乳腺癌和胆管癌等肿瘤中也进行临床研究。PDT治疗乳腺癌的研究大多都停留在临床前阶段, 临床试验主要用于治疗乳腺癌引发的皮肤转移, 例如用具有高组织渗透性的维替泊芬的商业化试剂Visudyne®治疗乳腺癌的皮肤转移[42]。PDT为手术切除后胸壁复发性乳腺癌提供了一种新型的微创治疗方式, 具有不良反应小和可重复实施的优势, Morrison等[43]用低剂量的Photofrin®介导PDT, 对9名手术切除后胸腔复发的乳腺癌患者进行

PDT, 治疗响应率为67%, 治疗后, 治疗部位的溃烂发生率降低。

已有临床试验表明PDT治疗胆管癌有效, 可治疗不可手术切除的胆管癌, 亦可用于接受其他治疗后的胆管癌姑息治疗, 但照射通道狭窄、光毒性和肿瘤缺氧等问题限制其临床应用[44]。Moole等[45]回顾了经PDT后, 胆管癌患者的生存期 (413天) 显著延长, 高于对照组 (183 天)。Gonzalez-Carmona 等[46]用 Photofrin® 和 Foscan®介导的PDT对不可手术切除的胆管癌进行治疗, 34例PDT患者的中位生存期 (15个月) 长于单独化疗患者的中位生存期 (10个月)。

PDT可单独治疗肿瘤, 也可和其他治疗方式联合, 在恶性肿瘤治疗中发挥重要作用, 但PDT过程中常出现疼痛和肿胀等问题, 导致患者退出治疗, 应用受限。PDT对浅表性肿瘤的治疗效果较好, 但对深部实体瘤的治疗仍存在局限性, 需提高光敏剂在肿瘤部位的递送效率, 以提高肿瘤PDT的治疗效果和拓宽临床应用范围。另外, 由于体内残留光敏剂的长时间存在, 尤其是临床上应用最广泛的第一代光敏剂Photofrin®, 患者在接受PDT后需数日或数周避免阳光直射以减轻光毒性, 导致患者对PDT的接受度受限。

2 光敏剂

临床上光敏剂的选择取决于疾病种类和给药途径。理想的光敏剂应具有较高纯度、较好的稳定性、合适的疏水性、较好的安全性、较高的光化学反应性、良好的肿瘤靶向性、合适的半衰期以及从组织中快速消除等优势[47]。理想的肿瘤PDT需要快速增加光敏剂在肿瘤部位的富集, 增强治疗效果, 在治疗结束后能从体内快速清除, 不会长时间在体内循环以降低光毒性的发生[48]。随着PDT临床应用的推广, 光敏剂也得到了不断发展, 表1[13,49-55]总结了部分被批准临床使用的第一代和第二代光敏剂的主要结构和适应症。

2.1 第一代光敏剂

第一代光敏剂的主要成分是HpD。HpD的商业化产品Photofrin®被批准用于治疗膀胱癌和食管癌等肿瘤。但是由于第一代光敏剂化学纯度低、合成复杂、吸收波长较短、组织渗透性差、半衰期较长、在皮肤中非特异性富集和存在光毒性等问题, 导致其临床应用受限[56]。

2.2 第二代光敏剂

第二代光敏剂主要包括卟啉、二氢卟吩、酞氰、花青素和姜黄素等, 具有化学纯度更高、吸收波长更长、组织渗透性更强和摩尔吸光系数更高等优势, 提高了其介导的肿瘤PDT效果[57]。但大多数第二代光敏剂疏水性强, 静脉给药受限, 易在生理环境中发生聚集, 造成ROS产生效率降低。同时, 光敏剂肿瘤靶向性差, 在体内的非特异性富集, 给药后患者需长时间避光[58]。

2.3 第三代光敏剂

第三代光敏剂克服了第二代光敏剂疏水性强和肿瘤靶向性差的不足。第三代光敏剂的设计思路主要有两种。一是将光敏剂和具有肿瘤靶向性的抗体、多肽和糖类等物质连接, 可实现主动靶向递送, 增加光敏剂在肿瘤细胞中的富集。二是把第二代光敏剂通过物理包埋或共价连接的方式包载于脂质体、胶束或纳米颗粒等递送系统, 基于“高渗透性和滞留效应”(enhanced permeability and retention effect, EPR), 通过被动靶向递送增加药物在肿瘤中的富集 (详见下文)[59,60]。图1展示了代表性的光敏剂递送系统。

抗体-光敏剂偶联策略已在临床上成功应用。可光活化的酞氰衍生物IRDye700DX (IR700) 和具有肿瘤靶向性的抗体偶联, 抗体可特异性与表达特定抗原的肿瘤细胞结合, 通过近红外光敏剂在光照射下促进细胞膜损伤和破裂, 杀死肿瘤细胞, 并减少对邻近正常组织的非选择性损伤[61]。用可靶向表皮生长因子受体的西妥昔单抗和IR700偶联制备得到ASP-1929 (Akalux®), 于2020年9月在日本被批准用于治疗复发性头颈部鳞状细胞癌[62,63]。目前, 抗体-光敏剂偶联策略主要用全长抗体和光敏剂进行偶联, 但全长抗体分子量比较大, 肿瘤渗透性较弱, 肿瘤治疗效果有限[64]。更重要的是, 抗体分子在体内的循环半衰期较长, 导致光敏剂的体内清除时间延长, 增加光毒性风险, 可能损伤皮肤和眼睛等正常组织[65]。表2[65-68]总结了临床前研究中通过偶联肿瘤靶向抗体策略制备的第三代光敏剂。

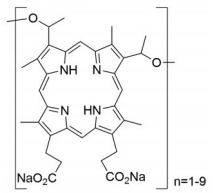
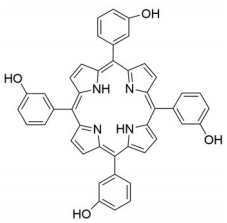
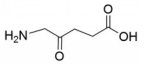
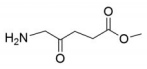
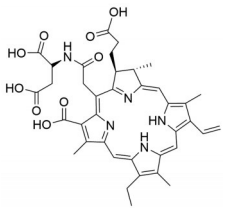
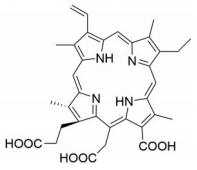
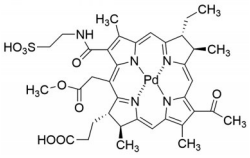
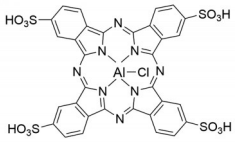
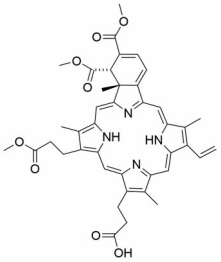
3 载光敏剂纳米递送系统

纳米递送系统可增强疏水性光敏剂的溶解性, 减少光敏剂在正常组织的非特异性富集, 用具有肿瘤靶向性的基团和配体对其进行修饰, 可增强光敏剂在肿瘤部位的特异性富集[69]。常见载光敏剂的纳米递送系统分为有机纳米递送系统和无机纳米递送系统, 包括脂质体、聚合物胶束、聚合物纳米粒、纳米凝胶、上转换纳米粒、碳纳米粒和量子点等在内的纳米递送系统[70,71]。同时, 可将其设计成具有内部肿瘤环境响应 (pH响应、酶响应和氧化还原响应等) 和外部刺激响应 (超声响应和磁响应等) 的功能性纳米递送系统, 控制光敏剂在肿瘤部位精确释放, 实现智能化给药[69,72]。表3[73-97]总结了常见光敏剂纳米递送系统的优势和应用。

3.1 有机纳米递送系统

3.1.1 脂质体 脂质体是一种理想的光敏剂递送系统, 可提高药物稳定性, 改善光敏剂的药动学性质, 增

Table 1 The approved photosensitizers and their application in clinical practice[13,49-55]

Photosensitizer	Structure	Trade name	Application
Hematoporphyrin derivative (HpD)		Photofrin®	Lung cancer, bladder cancer, cervical cancer
Meta-tetrahydroxyphenyl chlorine (m-THPC, temoporfin)		Foscan®	Head and neck cancer
5-Aminolevulinic acid (5-ALA)		Levulan®	Actinic keratoses, basal cell carcinoma, head and neck cancer
Methyl aminolevutinate (MAL)		Metvix®	Actinic keratoses, basal cell carcinoma
Mono-*L*-aspartyl chlorine e6 (NPe6)		Aptocine®/ Laserphyrin®	Lung cancer, recurrent subcutaneous tumors
Chlorin e6-polyvinylpyrrolidone polymer complex (Ce6-PVP)		Fotolon®	Skin and mucous membranes cancer
Padeliporfin		Tookad®	Prostate cancer
Aluminum phthalocyanine tetrasulfonate (AlPcS4)		Photosens®	Age-related macular degeneration, prostate cancer
Benzoporphyrin derivative monoacid ring A (BPD-MA, verteporfin)		Visudyne®	Age-related macular degeneration, non-melanoma skin cancer

加肿瘤部位的富集, 可构建环境响应性的功能性脂质体, 实现光敏剂在肿瘤部位按需、可控和可触发递送, 提供PDT和其他肿瘤治疗方法的联合平台, 增强抗肿瘤效果[98]。目前, 已有多种基于脂质体递送系统开发的光敏剂产品商业化。维替泊芬的商业化脂质体制剂Visudyne®改善了光敏剂容易聚集的问题, 提高了光敏剂的组织穿透能力和肿瘤选择性[99]。m-THPC是一种临床使用的高效光敏剂, 但由于其高疏水性和高亲脂性, 生物利用度低, 肿瘤富集不足和皮肤光毒性的缺点, 限制其应用。目前使用无水乙醇和丙二醇制备的

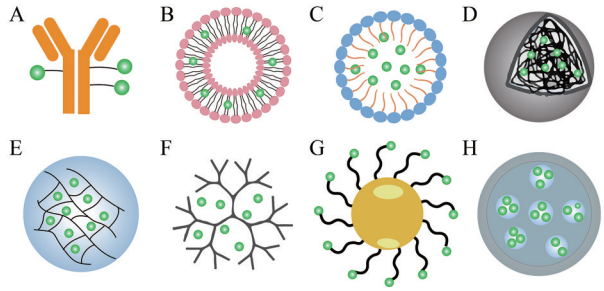


Figure 1 Schematic illustration of various delivery systems for photosensitizers. (A) antibody-photosensitizer conjugates, (B) liposomes, (C) polymeric micelles, (D) polymeric nanoparticles, (E) nanogels, (F) dendrimers, (G) gold nanoparticles, and (H) mesoporous silica nanoparticles

市售制剂Foscan®仍会造成给药部位疼痛和水肿等问题, 同时注射后容易在眼睛和皮肤中蓄积长达6周, 给患者带来极大的不便[100]。商业化的m-THPC脂质体制剂Foslip®和Fospeg®, 生物相容性好, 与游离药物相比, 提高了生物利用度, 改善了药代动力学性质, 减少了m-THPC的全身不良反应, 并增强了光敏剂在肿瘤部位的特异性富集[101, 102]。

3.1.2 聚合物胶束 聚合物胶束由两亲性嵌段共聚物构成, 具有疏水性内核和亲水性外壳, 生物相容性好和生物可降解, 可作为疏水性药物的良好载体。聚合物胶束可改善疏水性光敏剂的体内过程, 增加其在肿瘤部位的富集, 可同时装载光敏剂和化疗药物, 实现PDT与化疗联合抗肿瘤[103]。但聚合物胶束静脉给药后和血液成分相互作用或被血液稀释造成结构不稳定, 导致光敏剂迅速释放, 影响光敏剂在肿瘤部位的富集[104]。Ma等[105]用叶酸修饰聚乙二醇-b-聚天冬氨酸(PEG-b-PAsp)并连接西达本胺后得到嵌段共聚物, 与疏水性光敏剂焦脱镁叶绿酸-a自组装形成聚合物胶束, 通过叶酸增加光敏剂在肿瘤部位的富集, 并在肿瘤酸性微环境中响应性释放, 提高PDT肿瘤治疗效果。

3.1.3 聚合物纳米粒 聚合物纳米颗粒由海藻酸钠、白蛋白和壳聚糖等天然高分子或聚丙烯酰胺、聚乙烯吡咯烷酮和聚乳酸-羟基乙酸等聚合物构成。聚合物纳米颗粒具有生物相容性好、可生物降解、易于表面修饰和稳定性良好等优势, 可改善疏水性光敏剂的溶解度, 增加其在肿瘤部位的富集[106]。但聚合物纳米颗粒可能与体内生物分子相互作用, 导致其原始尺寸和表面性质改变, 最终影响纳米颗粒的体内生物分布和肿瘤对其的摄取[107]。针对四苯基卟啉(tetraphenyl porphyrin, TPP)水溶性差和聚集淬灭的特点, Zhang等[108]先将TPP和具有ROS响应的Linker连接, 形成TPP交联聚合物, 再以两亲性材料mPEG-PLA为载体构建聚合物纳米颗粒(poly(TPP)NPs), 该递药系统对TPP有较高的载药量, 同时避免聚集淬灭效应, 增加TPP在肿瘤部位的富集并提高体内抗肿瘤效果。

3.1.4 纳米凝胶 纳米凝胶是通过化学交联或物理自组装形成的具有三维网状结构的纳米递送系统, 可装载亲水性和疏水性药物的。纳米凝胶递送光敏剂可提高光敏剂的水溶性, 实现光敏剂的触发性释放和肿瘤微环境响应性释放, 减少对正常组织的损伤。纳米凝胶还可通过调整尺寸、形状和表面修饰等措施增加光敏剂在肿瘤部位的富集, 提高肿瘤靶向性[77,109]。Cho等[110]将岩藻多糖和光敏剂Ce6通过二硫键连接, 自组装形成具有较好生物相容性的纳米凝胶递药系统CFN-gel。该纳米凝胶通过岩藻多糖主动靶向肿瘤新生血管内皮细胞或肿瘤细胞上过表达的P-选择素, 增加Ce6在肿瘤部位的富集。但该纳米凝胶显著延长光敏剂在血液中的循环时间, 和游离药物相比, 给药后24 h在全身仍有明显的荧光信号。

3.2 无机纳米递送系统

无机纳米递送系统可改善光敏剂的靶向递送效率, 控制药物释放, 具有稳定性好、易于尺寸调节和表面修饰等特点, 可设计成具有环境响应性的功能性递送系统[111]。常见用于光敏剂递送的无机纳米递送系统包括金属纳米粒、碳纳米材料、介孔硅纳米粒、上转换纳米粒和磁性纳米粒等[112,113]。但无机纳米递送系统存在生物相容性差和体内降解慢等问题(表3)[114]。

Table 2 The antibody-photosensitizer conjugates for the delivery of photosensitizers in preclinical study and their application

Antibody-photosensitizer conjugate	Property	Application
B7-H3-Ce6[65]	To increase water solubility, enhance cell uptake efficiency, promote photodynamic therapy (PDT) efficiency, and enhance the blood circulation time and tumor accumulation	Non-small cell lung cancer
TMPC[66]	To enhance the accumulation of Ce6 in tumors with longer retention time	Human epidermal growth factor receptor 2 (HER2) over expressed breast cancer
CMPC[67]	To enhance the affinity to cancer cells expressing epidermal growth factor receptor (EGFR), induce the synergistic antitumor response, enhance the solubility and fluorescence of Ce6	EGFR positive pancreatic cancer
Pyro-Linker-Z_{HER2}[68]	Highly specific accumulation	HER2-highly expressed NCI-N87 tumors

Table 3 Nano-delivery systems for photosensitizers and their application

Nanoparticles	Material	Photosensitizer	Property	Application for PDT
Natural polymeric nanoparticles[73,74]	Chitosan	Ce6	Good biocompatibility and biodegradability, nontoxicity, low immunogenicity	To improve the biocompatibility and phototoxicity, enhance the cellular uptake of Ce6 in A549 cells
Synthetic polymer nanoparticles[75,76]	Poly (lactic-co-glycolic acid), PLGA	Pheophorbide A	To protect the loaded drug from hydrolysis and degradation, with excellent loading efficiency, controlled and sustained release of drug, efficient bioavailability	To overcome the limitation related to the high hydrophobicity and the lack of the target specificity of pheophorbide A, enhance the phototoxicity and accumulation of pheophorbide A in CaSki tumor model
Nanogel[77-80]	PDA-PEG and PDA-PEG-AEME	Pheophorbide A	To achieve localized delivery and on-demand release of photosensitizers, with high biocompatibility	To activate the photosensitizers in tumor tissue, enhance the long circulation time and PDT efficiency in head and neck squamous cell carcinoma tumor model
Cell membrane biomimetic modified nanoparticles (CMBMNPs)[81,82]	Cancer cell membranes	Protoporphyrin IX (PpIX)	To enhance the circulation durations and selective accumulation within the tumor, with highly homotypic targeting toward cancerous cells	To enhance the accumulation of PpIX at 4T1 tumor site and the tumor cellular internalization, with high biocompatibility and long circulation time
Gold nanoparticles[83-85]	Polypeptide-modified gold nanoclusters (GNCs)	Ce6	To enhance the accumulation of photosensitizers, increase the production of ROS, with high chemical inertness, easily tunable optical properties, large extinction coefficients, facile surface modifications, localized surface plasmon resonance (LSPR)	To enhance the cellular internalization of Ce6 in A549 cells, with excellent tumor targeting ability, long blood circulation time, inhibit the growth of A549 tumor in mice
Carbon-based nanoparticles[86,87]	Single wall carbon nanotubes (SWCNT)	Verteporfin	Versatile surface modifications and chemical functionalization, low or non-toxicity, good biocompatibility	The verteporfin-loaded SWCNTs functionalized with amine for PDT
Quantum dots (QDs)[88,89]	Manganese-doped carbon quantum dots (Mn-CQDs)	Ce6	High emission quantum yield and photo-stability, good biocompatibility, easy surface-functionalization	To exhibit lower toxicity, improve biocompatibility, selectively target and detect cancer cells, exert PDT effects
Magnetic nanoparticles[90-92]	Ce-doped-γ-Fe_2O_3 maghemite nanoparticles (MNPs)	m-THPC	Superparamagnetic and biocompatible	Stable in aqueous suspensions, to enhance the cellular internalization and PDT efficiency of m-THPC in MDA-MB231 cells, direct the nanocomposites to the targeted sites, enhance the PDT efficiency in the breast cancer
Silica nanoparticles[93,94]	Folic acid (FA)-decorated silica nanoparticles	Ce6	Huge specific surface area, controllable pore size and morphology, functionalized modification, satisfying biocompatibility and biodegradability	Stable in physiological solution, highly taken up by the MDA-MB-231 cells, higher MDA-MB-231 cell-killing effect than free Ce6
Upconversion nanoparticles (UCNPs)[95-97]	NaGdF4 UCNPs	Ce6	To improve tissue penetration depth, with high photochemical stability, free of auto-fluorescence background	To enhance the PDT efficacy in 4T1 tumor bearing mice, enhance the penetration and retention effect, with good biocompatibility

3.2.1 金纳米颗粒 金纳米颗粒具有化学惰性、易于合成和易于表面修饰等优势, 是光敏剂的理想载体, 可将光敏剂共价连接在金纳颗粒表面, 也可负载于金纳米颗粒的中空结构中, 可通过纳米结构的“EPR”效应和其表面易于被抗体和蛋白等功能性分子修饰的特点, 增加光敏剂在肿瘤组织中的选择性富集[112]。金纳米颗粒的生物相容性较低, 可用多糖、脂质或合成聚合物等进行涂层以提高生物相容性[115]。Haimov 等[116]将疏水性光敏剂 m-THPC 和金纳米颗粒偶联得到递药系统 AuNP-mTHPC, 具有较好的溶解度和稳定的胶体特性, 与同剂量的光敏剂相比, 显著提高了对肿瘤细胞的杀伤能力, 增加了肿瘤细胞对 m-THPC 的摄取能力。

3.2.2 二氧化硅纳米颗粒 二氧化硅纳米颗粒具有蜂窝状有序的多孔结构、较高的比表面积、易于表面修饰、较高的稳定性和尺寸可调等优势, 可有效保护荷载药物、控制药物释放和增加药物在肿瘤部位的累积, 对光敏剂有较高的负载能力, 可增加其在肿瘤部位的富集[117]。将光敏剂物理吸附于二氧化硅的网状结构中, 会导致光敏剂过早从载体中释放出来, 降低治疗效率并产生不良反应, 而将光敏剂共价连接在纳米颗粒的内部可克服上述缺点[118]。Clemente 等[119]用介孔二氧化硅偶联疏水性光敏剂维替泊芬, 提高光敏剂的生物利

用度, 其介导的PDT减少肿瘤淋巴管生成从而抑制肿瘤生长。Peng等[120]将疏水性光敏剂酚菁稳定负载于分散性和稳定性良好的中空二氧化硅纳米粒 (HSNs)的空腔内, 该载药系统实现PDT和光热治疗, 显著提高肿瘤治疗效果。

3.3 其他纳米递送系统

尽管传统的光敏剂纳米递送系统和抗体-光敏剂偶联策略增加了光敏剂的肿瘤富集, 但仍存在一定的局限性。通过物理包埋或化学连接将光敏剂装载于纳米递送系统, 光敏剂跟随纳米粒在血液中长循环, 造成治疗窗口距给药时间点较长, 光敏剂在血液中的消除半衰期延长, 增加对皮肤、眼睛等正常组织的光毒性[121-123]。抗体-光敏剂偶联策略中光敏剂在血液中的循环时间受偶联抗体半衰期的影响, 同样存在光毒性风险。因此, 提高肿瘤靶向性同时不显著降低光敏剂的体内清除速率, 是光敏剂递送系统设计面临的挑战。

Xu等[124]提出光敏剂的“抗体搭乘”递送策略, 将Ce6和免疫球蛋白G (immunoglobulin G, IgG)通过天然存在的高亲力制备纳米复合物Chloringlobulin, 能显著增加Ce6在肿瘤部位的富集, 实现了Ce6在肿瘤部位高浓度和短时间富集, 为PDT提供足够的光照治疗时间窗。另外, 该纳米复合物不改变Ce6在血液中的消除半衰期, 其体内清除速率不受IgG影响。与传统纳米递送系统相比, 这种“快上快下”的“搭便车”光敏剂递送系统, 能够满足光敏剂在肿瘤部位快速富集和从体内快速清除的递送需求。同时, 该策略也为PDT和免疫检查点阻断疗法提供联合递送平台, 联合治疗后显著延长脑胶质瘤和结肠癌荷瘤小鼠的生存时间。Lin等[125]基于“抗体搭乘”策略构建了载脱镁叶绿酸A的纳米递药系统IgG:PhA NPs, 实现了脱镁叶绿酸A在给药后短时间内增加肿瘤部位富集和从体内快速清除的递送目的 (图2), 并采用荧光活体显微成像技术可视化了脱镁叶绿酸A从血管内转运到肿瘤实质的过程和脱镁叶绿酸A和IgG的体内解离过程。

4 载光敏剂纳米递送系统联合其他肿瘤治疗方法

载光敏剂纳米递送系统的发展促进了PDT和其他肿瘤治疗方式的联合, 实现协同增强肿瘤治疗效果。PDT常与化疗、放疗、免疫疗法和光热疗法等肿瘤治疗方法进行联合。

4.1 联合化疗

单一化疗在治疗过程中存在非特异性药物积累、生物利用度低和多药耐药性等问题, 造成严重的全身性不良反应和肿瘤复发[126]。PDT可增加肿瘤细胞对化疗药物的敏感性, 减少化疗药物的使用剂量, 降低不良反应[127]。化疗和PDT联合可增强免疫原性细胞死

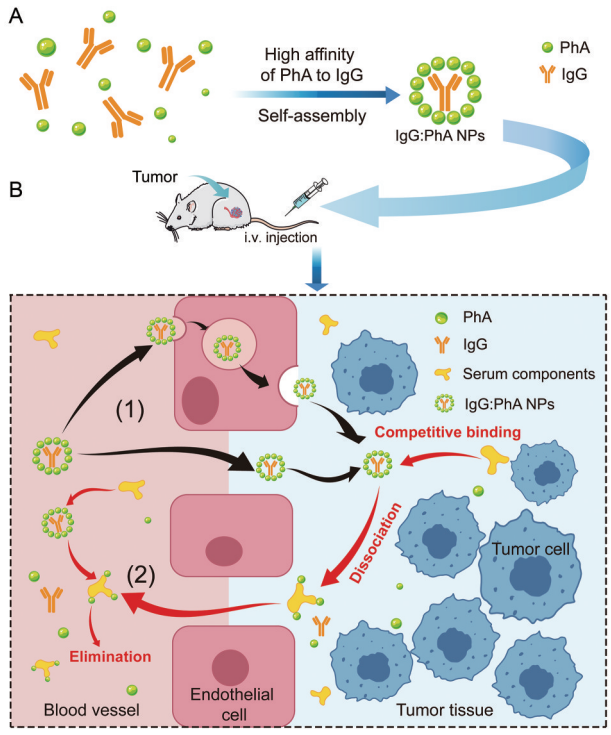


Figure 2 The schematic illustration of IgG:PhA NPs prepared by the "IgG-hitchhiking" strategy through the naturally high affinity of PhA to IgG. IgG:PhA NPs increase the accumulation of PhA at tumor sites and do not change the clearance rate of PhA in the blood owing to the competitive binding of serum components[125]. (Reprinted with permission from reference[125], Copyright 2023 Elsevier®). PhA: Pheophorbide A; IgG: Immunoglobulin G

亡, 增强细胞毒性T淋巴细胞浸润, 增强联合抗肿瘤效果[128]。通过有机或无机纳米递送系统递送化疗药物和光敏剂, 可提高疏水性药物的溶解度, 最大限度提高两种药物的生物利用度, 减少对正常组织的损害[129]。Tang等[130]设计了一种具有pH响应性的磁靶向联合递药系统Fe_3O_4@mSiO_2(DOX)@HSA(Ce6), 可共递送化疗药物多柔比星 (DOX)和光敏剂Ce6, 实现PDT和化疗的联合。该纳米递送系统在生理环境下有较好的稳定性, 在肿瘤低pH环境下缓释, 具有较好的生物相容性, 其介导的联合治疗组显著抑制脑胶质瘤的生长。

4.2 联合放疗

由于激发光的穿透能力有限, 对深部实体瘤的PDT效果不佳。相较而言, 放疗的较高组织穿透性在深部组织中能激活光敏剂, PDT和放疗联合可克服PDT的治疗深度限制, 并减少放疗对正常组织的辐射损伤, 产生更有效的肿瘤治疗效果, 纳米技术的发展为两者的联合提供了可行性平台[131,132]。Hou等[133]开发了尺寸可变且具有ROS响应性的纳米递送系统 (BGBC), 用生物相容性较高的牛血清白蛋白 (BSA)作

为载体, 同时将放疗敏化剂钆 (Gd) 和光敏剂Ce6递送至肿瘤组织深部。该递药系统实现放疗和PDT联合, 不仅提高了光敏剂在肿瘤部位的富集, 减少治疗过程中对非肿瘤组织的损伤, 还增强了肿瘤细胞对X射线的敏感性, 在4T1荷瘤小鼠中取得显著的联合抑瘤效果。

4.3 联合免疫疗法

近些年, 肿瘤的免疫治疗虽然取得了重要的临床进展, 但是仍存在肿瘤组织的异质性高、抗原呈递能力不足和免疫相关不良反应等问题。PDT可启动肿瘤细胞的免疫原性死亡, 促进肿瘤相关抗原释放和树突状细胞的成熟, 提高抗原呈递能力, 增加细胞毒性T淋巴细胞的浸润, 增强抗肿瘤免疫应答[134,135]。PDT和免疫疗法的联合对原发性肿瘤和转移性肿瘤均有较好的治疗效果。目前关注较多的是PDT和免疫检查点阻断疗法的联合应用, 免疫检查点阻断疗法可逆转免疫细胞和肿瘤细胞之间的负调节信号, 增强光动力的抗肿瘤免疫应答[136]。Tong等[137]制备了一种精氨酸−甘氨酸−天冬氨酸环肽 (cyclic arginine-glycine-aspartic acid, cRGD) 修饰的主动靶向脂质体递药系统cRGD-PaNPs, 改善了疏水性光敏剂脱镁叶绿酸A的溶解性, 并通过cRGD主动靶向4T1乳腺癌肿瘤细胞过表达的整合素 $\alpha_v\beta_3$, 增加光敏剂在肿瘤部位的富集。cRGD-PaNPs介导的PDT提高了程序性死亡受体配体-1 (programmed cell death ligand-1, PD-L1) 低表达的4T1乳腺癌对抗PD-L1抗体 (αPD-L1) 的治疗响应率, 联合αPD-L1可增强抗肿瘤免疫应答和治疗效果, 延长4T1荷瘤小鼠的中位生存期。

4.4 联合光热疗法

光热疗法将光能转换为热能, 对肿瘤组织和细胞造成热损伤和热消融, 但治疗过程中需要较高的激光功率才能达到显著的抑瘤效果[138]。亚致死剂量的光热疗法无法彻底杀死肿瘤细胞治愈肿瘤, 常导致肿瘤转移和复发。光热疗法和PDT联合可提高实体瘤治疗效果[138,139]。Yang等[140]制备了光热治疗联合PDT的纳米递送平台MSNR@MoS_2-HSA/Ce6, 以生物相容性好的介孔二氧化硅纳米棒作载体, 用高光热转换效率的MoS_2作光热剂, 用人血清白蛋白 (HSA) 修饰以提高生物利用度并降低毒性, 最后通过化学偶联加入疏水性光敏剂Ce6, 可增加Ce6在肿瘤部位的富集。该递药系统可实现光热治疗和PDT的联合, 实现荧光影像指导治疗, 显著提高对4T1肿瘤的抑瘤效果。

5 总结与展望

PDT通过特定光源激发光敏剂, 在肿瘤组织产生ROS, 通过直接杀死肿瘤细胞、破坏血管和激发机体免疫应答产生强大的抗肿瘤效果。PDT已广泛应用于多种恶性肿瘤的临床治疗, 如皮肤恶性肿瘤、食管癌、膀胱癌和前列腺癌等。光敏剂也随之快速发展, 基于抗体−光敏剂偶联策略设计的第三代光敏剂和脂质体光敏剂递送系统也有产品上市。光敏剂的研发需要重点关注光敏剂溶解性差、肿瘤靶向性差和较长半衰期等问题。载光敏剂的纳米递送系统可改善光敏剂溶解性差和肿瘤靶向性不足的缺点, 为实现高效的肿瘤PDT提供新递送策略。同时, 纳米递送系统的应用可实现PDT和其他治疗方法的联合应用, 发挥抗肿瘤协同疗效。

需要指出的是, 尽管纳米递送系统改善了疏水性光敏剂的肿瘤部位富集, 但目前研究和报道的大多数光敏剂纳米递送系统因其自身的体内长循环性质, 导致光敏剂的体内清除时间被延长, 增加了光毒性风险, 延长了患者的避光时间, 降低了用药的顺应性。这对光敏剂的纳米递送系统的设计和研发提出了新要求, 即设计能增加光敏剂在肿瘤部位富集和体内快速清除的纳米递送系统, 使其同时兼具高效和安全性是未来研究的方向。另外, 对于深部肿瘤的PDT, 需要利用光敏剂的荧光性质, 并借助于荧光内窥镜等手段, 实施荧光影像指导的PDT, 提高治疗的精准性[141]。因此, 光敏剂需要发挥对微小肿瘤病灶的光动力诊断功能, 实现光动力诊疗一体化。这对于光敏剂递送系统的精准性提出了更高的要求。

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