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光动力联合免疫检查点抑制剂治疗恶性肿瘤的研究进展

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摘 要:恶性肿瘤严重危害人体健康,光动力疗法是一种集创伤小、副作用低、时空可控性高等优点于一身的新兴疗法,被广泛应用于恶性肿瘤的临床治疗,但其只限于局部肿瘤的治疗,对于远处转移的肿瘤或无法精确定位的病灶,光动力疗法具有一定的局限性。免疫治疗尤其是免疫检查点抑制剂,使恶性肿瘤的治疗进入了一个全新的时代,然而免疫检查点在肿瘤细胞中的低表达水平及其对宿主免疫系统的激活不足构成主要障碍。光动力治疗可以激活机体的免疫功能,改善肿瘤微环境,这为光动力疗法与免疫疗法相结合提供了可能。而纳米粒子可以同时负载光敏剂和免疫检查点抑制剂,实现联合治疗效果,并提高药物的靶向性。本文对利用纳米技术将光动力与免疫检查点抑制剂相结合治疗恶性肿瘤的实验研究进行了综述,并对其在临床上的应用进行了展望。

关键词:光动力疗法;PD-1/PD-L1;CTLA-4;联合治疗;纳米载药粒子
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Research Progress of Photodynamic Combined Immune Checkpoint Inhibitors in the Treatment of Malignant Tumors

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Abstract: Malignant tumors are seriously harmful to human health. Photodynamic therapy is an emerging therapy with advantages of low trauma, low side effects and high spatiotemporal control. It has been widely used in the clinical treatment of malignant tumors, but it is limited to the treatment of local tumors. For distant metastatic tumours or lesions that cannot be precisely located, photodynamic therapy has certain limitations. Immunotherapy, especially immune checkpoint inhibitors, has brought the treatment of malignant tumors into a new era. However, the low expression level of immune checkpoint in tumor cells and its insufficient activation of the host immune system constitute major obstacles. Photodynamic therapy can activate the immune function of the body and improve the tumor microenvironment, which provides a possibility for the combination of photodynamic therapy and immunotherapy. Nanoparticles can simultaneously load photosensitizers and immune checkpoint inhibitors to achieve combined therapeutic effect and improve drug targeting. In this paper, the experimental research on the combination of photodynamic and immune checkpoint inhibitors using nanotechnology in the treatment of malignant tumors is reviewed. And its clinical application is prospected.

Key words: photodynamic therapy; PD-1/PD-L1; CTLA-4; combination therapy; nano drug-carrying particles

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0 引言

恶性肿瘤一直是危害人体健康和生命的“罪魁祸首”,其发病率[1]逐年上升,因此寻找高效的治疗方法成为人们孜孜不倦探索的动力。手术干预、放射治疗和化疗等传统治疗[2]的相对无效性促使人们对光动力疗法和免疫疗法等新兴疗法产生了兴趣。

光动力疗法(photodynamic therapy, PDT)[3-4]是一种临床上使用的微创治疗方法。因其具有靶向性好,对患者全身损伤小,安全高效等优点,在过去几十年中引起了极大的关注。在PDT中,积聚在肿瘤中的光敏剂(photosensitizers, PS)在氧气存在下被特定波长的光激活,产生活性氧(reactive oxygen species, ROS),主要是单线态氧$^1O_2$,其通过诱导细胞坏死或凋亡直接杀死肿瘤细胞[5-6],或通过破坏肿瘤血管系统和产生肿瘤特异性免疫间接杀死肿瘤细胞[7],但PDT只用于局部肿瘤治疗,对于远处转移的肿瘤或无法精确定位的病灶,PDT显得无能为力[8-9]。为了解决这些问题,研究人员开始探索将PDT与其他治疗方法联合应用的可能性,通过使用新的治疗方案来解决PDT的不足,扩大PDT的应用范围。

免疫疗法旨在增强机体的防御系统来消除肿瘤细胞[10],是癌症治疗领域的重大突破,尤其是免疫检查点抑制剂(immune checkpoint inhibitors, ICIs),作为一种有前景的癌症免疫疗法,近年来引起了人们的极大兴趣[11-13]。2018年,免疫检查点疗法获得诺贝尔生理或医学奖,更是将肿瘤免疫治疗的研究推向了高潮。因其相比于传统疗法具有毒副作用小,治疗广谱性和潜在的长期效果等优势,最近已成为晚期或转移性肿瘤的一种有前途的治疗方法[14]。这主要归因于免疫抑制系统可以被ICIs激活,然后重新识别和消除肿瘤细胞[15]。免疫检查点指的是具有免疫抑制作用的受体与配体对,肿瘤细胞与免疫细胞通过受体与配体的相互作用诱导免疫细胞停止杀伤肿瘤细胞,产生免疫逃避[16-17]。而ICIs主要通过抑制免疫检查点活性,阻断免疫检查点信号通路,激活机体的免疫应答。然而,ICIs也存在一些局限性,如免疫检查点在某种类型的肿瘤细胞中低表达及其对宿主免疫系统的激活不足[18]、治疗效果不稳定和治疗费用高昂等。为了解决这些问题,研究人员开始探索将ICIs与其他治疗方法联合应用的可能性。

PDT通过激活PS来破坏肿瘤细胞,经过不断地实验探索,越来越多的实验数据证明,PDT可以激活机体的免疫功能,这为癌症的联合治疗提供了更多的可能性[19-20]。高效PDT可以通过诱导急性炎症和增加肿瘤免疫原性,使肿瘤对免疫疗法敏感,免疫检查点抑制剂被应用于增强PDT介导的免疫应答,以改善PDT的抗肿瘤效果[21-23],从而扩展在恶性肿瘤中的应用。

1 光动力疗法

光动力疗法在肿瘤治疗中越来越受到关注,它利用PS与特定波长的光相互作用,以治疗目标组织,通常用于癌症以及其他一些疾病的治疗[24]。

1.1 光动力疗法的原理和优势

光动力疗法的三要素为光、光敏剂以及分子氧[25],其作用机理如图1所示,处于基态的PS在相应波长的激光照射下,跃迁至激发态;其中一部分激发态会辐射荧光释放能量返回基态,另一部分激发态会通过系间穿越转换为三重激发态,三重态的退激反应有两种,分别是PS将能量转移给细胞内的底物产生自由基(radicals, R)[26]以及将能量转移给分子氧产生$^1O_2$[27]。整个过程可用方程描述如下:

$$PS+h\nu \rightarrow {}^1PS^*,$$

$${}^1PS^* \rightarrow {}^3PS^*,$$

$${}^3PS^*+RH \rightarrow \text{radicals(Type I)},$$

$${}^3PS^*+{}^3O_2 \rightarrow PS+{}^1O_2\text{(Type II)}。$$

反应产生的$^1O_2$和R具有很强的氧化能力且反应活性高,很容易同细胞发生氧化反应,对细胞造成不可逆的损伤[28-29]。此外,PDT能够引起急性局部炎症,从而引起免疫反应[30-35],这为PDT与免疫的联合治疗提供了可能。

与传统治疗恶性肿瘤的方法(如化疗和放疗)相比,PDT具有以下优点[36-37]:(1)非侵入性[38]:PDT通常不需要开刀或内置医疗器械,这降低了治疗过程中感染的风险、缩短康复时

间并且减少不适感,使患者更容易接受。(2)局部治疗[39]:PDT可以精确瞄准疾病的目标区域,同时最大限度地减少对周围正常组织的影响,这有助于减少治疗引起的副作用和组织损伤。(3)选择性积累[40]:PDT通过选择合适的PS,可以实现PS在目标组织或细胞中的选择性积累,这意味着PDT可以更精确地作用于疾病组织,而不会过多影响健康组织。(4)多种用途:PDT可用于治疗多种疾病,不仅限于各种类型的癌症,还包括眼部疾病(如黄斑变性和青光眼)以及一些皮肤疾病(如疣和痤疮)[41-42]。这使得它成为多领域的治疗工具。(5)低毒性:PDT在临床上使用的PS可与内质网、线粒体、溶酶体或这些位点的组合的血浆或细胞膜结合。由于细胞核不是PS定位的主要部位,因此PDT比常规化疗或放疗具有更少的遗传毒性,且PS在未被激活的状态下通常是非毒性的,因此光动力治疗在治疗前不会对患者产生毒性影响[40,43-44]。(6)可重复性治疗:PDT可以进行多次治疗,而不会增加长期风险,这使得它在需要定期治疗或维持治疗的情况下非常有用,例如对于慢性疾病或癌症的复发性治疗。(7)潜在免疫刺激:PDT可以激活免疫系统的响应,促使免疫系统更好地识别和攻击肿瘤细胞[45-46]。这种免疫刺激效应有助于提高免疫治疗的效果,例如免疫检查点抑制剂的应用。(8)适用于多学科治疗:PDT可以与其他治疗方法,如手术、化疗、放疗和免疫疗法等结合使用,以提高治疗效果,这使得它成为多学科治疗团队中的有用工具[47-48]。

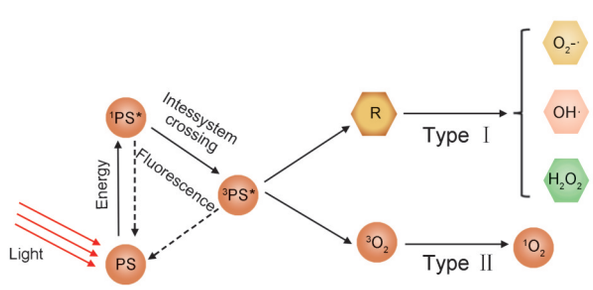

图1 光动力治疗反应机制[34]

Fig. 1 Mechanism of PDT[34]

1.2 影响光动力疗法的治疗效果的因素

PS[49]是一种能够吸收特定波长的光并转化为化学或热能的物质。在PDT中,PS在肿瘤组织中的选择性积累是关键因素,这可以通过改变PS的药物传递系统、选择特定的PS结构或利用肿瘤特异性标志物实现。PS在体内的积累通常通过血液供应和肿瘤的特殊生理和病理特征实现。

选择合适的光照射参数在PDT中非常重要,包括激光的波长、功率和能量。光照射的波长应与PS的吸收峰相匹配[50],以确保PS被激发从而产生毒性。光照射的时间、强度和方式也需要根据具体的治疗需求进行调节。由于肿瘤组织的厚度不同,不同波长的激光具有不同的组织穿透深度,因此不同功率的激光对不同厚度的肿瘤组织会产生不同效果,确保所使用的激光在功率不超过生物安全范围时具有足够的组织穿透深度也是至关重要的。

分子氧在PDT中同样扮演着关键的角色,在PDT的Ⅱ型反应机制中受到氧浓度的影响,在治疗过程中会消耗组织中的氧以产生$^1O_2$,随着治疗进行,组织中的氧含量会显著减少,若不能及时补足氧,$^1O_2$的产率将会下降,PDT的治疗效果就会降低[51]。

PDT的治疗效果还受到其他因素的影响,包括光路径、肿瘤大小和形状,以及PS浓度。在临床治疗中,需要考虑患者的个体差异以及上述因素,制定详细的治疗方案,以获得最佳治疗效果。

2 免疫检查点抑制剂

目前,研究较多的免疫检查点分子主要包括程序性细胞死亡1(programmed cell death1,PD-1)/程序性细胞调亡配体1(programmed cell death-ligand 1,PD-L1)、细胞毒性T淋巴细胞抗原-4(cytotoxic T lymphocyte-associated antigen-4,CTLA-4)和吲哚胺-2,3-二加氧酶(indoleamine2,3-dioxygenase,IDO)[52-53],见表1。针对这些免疫检查点的抑制剂已被证实是一种有效的免疫治疗手段,其机制在于阻断免疫检查点信号通路,重新激活对肿瘤的免疫反应,如图2所示。

2.1 PD-1/PD-L1抗体

PD-1和PD-L1被称为与免疫抵抗相关的重要免疫检查点分子[54]。PD-1/PD-L1是目前

表1 常见免疫检查点的表达细胞及其代表性抑制剂

Table 1 Expression cells of common immune checkpoints and their representative inhibitors

ICIs	表达细胞	代表性抑制剂	参考文献
程序性死亡受体1(PD-1)	T cells;B cells	Nivolumab; Pembrolizumab	[54]
程序性细胞死亡配体1(PD-L1)	Tumor cells	Avelumab; Durvalumab;Atezolizumab; Cemiplimab	[54]
细胞毒性T淋巴细胞相关蛋白-4(CTLA-4)	$CD4^+$, $CD8^+$ T cells; Tregs; DCs; NK; Tumor cells	Ipilimumab	[55]
吲哚胺-2,3-二加氧酶(IDO)	Tumor cells; DCs	NLG919; 1-MT; KHK2455; Indoximod; Epacadostat	[56-57]

研究最多的免疫检查点通路之一,PD-1/PD-L1通路是肿瘤免疫抑制的关键性驱动因素[59-60],其作用机制如图3所示。PD-L1在多种肿瘤细胞表面过表达,当与T细胞表面的PD-1结合时,它会抑制T细胞对肿瘤的攻击作用,导致T细胞无法有效发挥作用,使肿瘤逃避免疫系统的攻击。PD-1或PD-L1抗体可以阻断这一通路,恢复T细胞对肿瘤细胞的识别功能,并最终清除肿瘤细胞[60-61]。使用PD-L1或PD-1抗体抑制PD-L1和PD-1之间的相互作用,已显示出对晚期和转移性肿瘤具有令人鼓舞的治疗效果[62-64]。

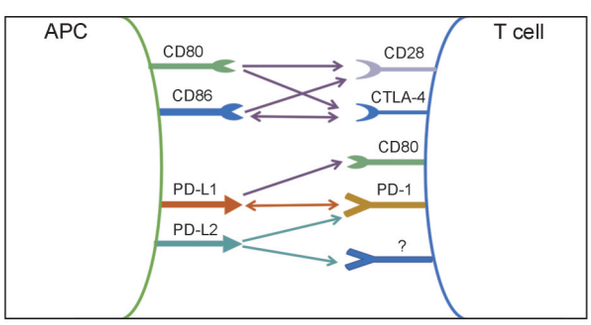

图2 免疫检查点信号通路[58]

Fig. 2 Immune checkpoint signaling pathways[58]

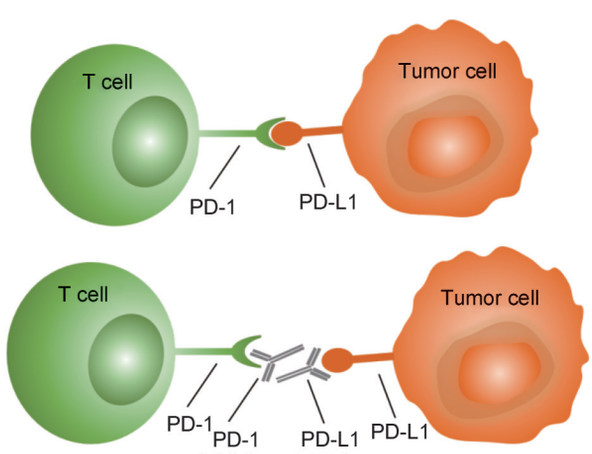

图3 PD-1 / PD-L1通路作用原理[65]

Fig. 3 Principle of PD-1 / PD-L1 pathways[65]

2.2 CTLA-4抗体

CTLA-4[55]是一种重要的免疫检查点分子,也称为CD152,不仅在自身免疫中起到重要的调节作用,同时也是肿瘤细胞逃逸免疫监视的一个关键因素,因此,CTLA-4已成为研究肿瘤免疫逃逸机制的热点。CTLA-4分子与PD-1一样,是CD28受体家族中的一种蛋白质,主要表达于$CD4^+$、$CD8^+$T细胞和调节性T细胞(regulatory T cells, Tregs)表面。CTLA-4及其共刺激同源物CD28共享内源性配体CD80(B7-1)和CD86(B7-2),B7为共刺激分子,当它与CD28结合时,促进T细胞活化。此外,B7-1还通过与CTLA-4结合抑制T细胞活性,从而调节免疫反应。CTLA-4对B7的亲和力优于CD28,导致T细胞活性被抑制,T细胞功能失调。且表达于Tregs表面的CTLA-4促进Tregs在肿瘤组织的浸润,抑制抗肿瘤免疫,CTLA-4抗体阻断CTLA-4通路后,肿瘤浸润的Tregs功能被钝化,从而增强瘤内免疫应答[66-68]。除了T细胞外,有证据表明,其他细胞类型,如树突状细胞(dendritic cell, DC)、自然杀伤细胞(nature killer cell,NK)、人单核细胞和肿瘤细胞也表达CTLA-4[69-71]。目前,已经批准上市的CTLA-4抗体主要有伊匹单抗(Ipilimumab)和曲美木单抗(Tremelimumab)用于治疗晚期黑色素瘤和肺癌等[72]。尽管CTLA-4抗体取得了一些不可否认的成功,但其疗效有限[73]。因此,设计一种治疗方案提高其疗效将是我们研究的方向。

2.3 小分子免疫抑制剂

在免疫检查点中,IDO是一个特殊的检查点,因为它的抑制剂是一些小分子药物[56-57]。虽处于药物分子结构创新阶段,但因其相对分子质量小,理化性质稳定,治疗成本低,患者负

担小等优势,在肿瘤治疗中很有发展前景。IDO在许多类型的实体瘤中高度表达,是一种免疫调节酶,催化色氨酸(tryptophan, Trp)向犬尿氨酸(kynurenine, Kyn)转化[74]。肿瘤微环境中Trp的匮乏和Kyn的积累可能会抑制T细胞的增殖,促进Tregs的生成和激活,形成免疫抑制微环境[75-76],而IDO抑制剂可以缓解免疫抑制肿瘤微环境并引发宿主免疫应答,在检查点阻断方面显示出有前景的应用。常见的IDO抑制剂有NLG919、1-MT和KHK2455等。

3 光动力联合免疫检查点抑制剂治疗肿瘤

PDT诱导的免疫主要是通过$CD8^+$T细胞进行的,其在根除肿瘤细胞中起着关键作用。然而,这种免疫反应有时并不足以抑制PDT后存活的剩余肿瘤细胞的生长[77]。此外,产生的抗肿瘤免疫反应可能会被肿瘤微环境中的各种免疫抑制因子所抵消。例如,骨髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)和Tregs会抑制效应T细胞的肿瘤杀伤作用,导致肿瘤复发[78]。为了增强PDT诱导的免疫反应,我们使用ICIs与PDT联合治疗肿瘤。目前,基于PDT和免疫联合的治疗方案已有相关报道,其中PDT与PD-L/PD-L1、CTLA-4抗体和小分子免疫药物等的联合应用实验结果表明,通过联合治疗可以有效提高机体免疫应答,增强抗肿瘤效果[79-80]。

3.1 光动力和免疫检查点抑制剂抗肿瘤的联合机制

PDT和ICIs是两种不同但可以联合使用的抗肿瘤治疗方法。PDT通过使用PS和激光光束破坏肿瘤组织,释放肿瘤抗原并增强肿瘤的免疫原性[81-83],PDT破坏肿瘤组织释放的抗原使其可以被T细胞更容易地识别,这为免疫系统提供了更多机会来识别和攻击肿瘤细胞。ICIs则可以进一步增强了免疫系统对肿瘤的反应,使其更有效地对抗肿瘤[84-85]。这种联合治疗还有助于建立长期的免疫记忆,确保免疫系统能够在需要时继续对抗肿瘤细胞。

2016年,Wang等[86]证明了PDT介导的癌症免疫治疗可以通过在肿瘤细胞中PD-L1基因敲除来增强。实验发现,在B16-F10黑色素瘤移植瘤模型中,PDT和PD-L1基因敲除联合使用与单独使用PDT相比,对肿瘤生长和远处转移的抑制作用明显增强。这一结果为PDT联合抗PD-LI抗体提高治疗肿瘤的疗效提供了理论依据。

3.2 光动力联合免疫检查点抑制剂疗法在抗肿瘤治疗中的应用

PDT和ICIs联合治疗是一种新兴的肿瘤治疗方法,它可以克服PDT和ICIs单独应用的局限性,提高治疗效果。然而,充分发挥联合治疗效果的前提是将PS和ICIs递送到肿瘤组织并在组织中富集,无论是PS还是ICIs,均需要提高其在肿瘤部位的局部浓度,因此可以通过设计合理高效的药物递送策略来提高抗肿瘤疗效。纳米粒子[87-88](nano-Particles, NPs)可以同时负载PS和ICIs,提高PDT和ICIs的靶向性,减少对正常细胞的损伤[89-90]。大量的NPs已被开发为用以提高疗效的药物递送载体[91],如包括胶束[92]、脂质体[93-94]、聚合物纳米颗粒[95-96]、量子点[97]、磁性纳米颗粒[98-99]、介孔二氧化硅纳米颗粒[100-101]、上转换纳米粒子[30]、金纳米粒子[102]和碳基纳米材料[103-104]等。

3.2.1 纳米粒子载药的优势

纳米粒子载药[105]是将药物封装在纳米颗粒内,以更有效地传递和释放药物到特定目标的方法。它备受关注并具有多项优势,包括:

(1)精确的药物递送:NPs可以精确地将药物递送到目标组织或细胞,最小化对健康组织的损伤,降低药物的副作用[106]。(2)提高药物的生物利用度[76]:某些药物易在体内代谢或排出,NPs延长药物在体内循环时间,提升生物利用度,减少用药频率。(3)改善溶解性:NPs将药物包裹可改善其溶解性,增加水溶性,提高输送效率[107]。(4)可控释药[107]:药物可持续、缓慢或根据需要释放,满足特定治疗需求。(5)增强药物稳定性[108-110]:NPs封装药物能增强其稳定性,避免在体内降解,提高疗效。(6)减轻免疫应答:NPs可以减少药物被免疫系统识别和清除的机会,延长药物在体内的存留时间[111-114]。(7)多功能性:NPs可通过表面修饰增加多功能性,如将靶向配体附加到纳米粒子上,能够更精确地识别和附着于特定目标[115]。

(8)降低用药剂量:由于药物的精确传递和释放,NPs通常可以在较低的用药剂量下实现相同或更好的治疗效果,减轻药物毒性和不良反应[116-117]。(9)适用于多种药物类型:NPs适用于多种类型的药物,包括小分子药物、生物大分子(如蛋白质和核酸药物)[118-119]等。

3.2.2 利用NPs提高PDT和ICIs联合治疗肿瘤疗效

随着肿瘤联合治疗的兴起和纳米粒子载药系统的快速发展,PDT与ICIs的联合应用在肿瘤治疗中显示出独特的优势和较大的潜力[80,120]。

2016年,Duan等[121]通过焦磷酸锌ZnP纳米粒子负载光敏剂焦脂质ZnP@pyro联合PD-L1抗体根除了原发性4T1乳腺肿瘤。2017年,Xu等[23]提出了一种基于上转换纳米颗粒(upconversion nanoparticles, UCNP)的PDT策略,联合CTLA-4抗体,在近红外(near-infrared, NIR)光照射下有效地治疗原发肿瘤,并抑制PDT难以治疗的远处肿瘤,并通过免疫记忆效应防止肿瘤复发。2019年,Lan等[27]报道了基于纳米金属有机框架nMOF由光敏剂Fe-TBP介导的PDT显著提高了PD-L1抗体治疗大肠癌的疗效,导致肿瘤消退>90%,实现协同治疗效果。同年,Song等[122]设计了一种合成嵌合肽PpIX-1-MT,整合了光敏剂原卟啉IX(Protoporphyrin IX, PpIX)和免疫检查点抑制剂1-甲基色氨酸(1-MT),该方法实现了PDT和ICIs的联合治疗,有效抑制了原发性和肺转移性肿瘤。

2019年,Huang等[123]设计了一种由PpIX和IDO抑制剂NLG919组成的双功能药物偶联物,实现原发性肿瘤和远处转移的抑制。Gao等[124]通过整合聚乙二醇(PEG)化的PS和NLG919,设计了前药囊泡(enzyme-activatable prodrug vesicle, EAPV),观察到EAPV介导的PDT可以增加干扰素γ(interferon-γ, IFN-γ)在肿瘤组织中的浸润,抑制肿瘤组织中Trp的降解,减少肿瘤内Tregs的浸润,与NLG919联合达到更佳的治疗效果。Xing等[125]通过含氟聚合物纳米颗粒,同时包封Ce6和NLG919,构建了一个多功能纳米平台,增加T细胞浸润,进一步抑制原发性和脓肿肿瘤的生长。Li等[126]选择Ce6、1-MT和PD-L1抗体作为药物,构建基于两亲性聚合物前药的纳米载药系统——aPD-L1@HC/PM NPs,可用于治疗肿瘤转移、复发和术后再生。Wang等[127]研究报告了使用纳米颗粒介导的PDT和磁热疗的组合来协同增强抗肿瘤免疫反应,与CTLA-4抗体结合时,能够显著根除原发性和深度转移性肿瘤。

2020年,Chen等[128]开发了一种微针(microneedle, MN)辅助平台,将光敏剂氯化锌酞菁(ZnPc)和CTLA-4抗体共递送,在减少副作用的同时产生协同治疗效果。徐继明[129]构建了靶向性载药纳米胶束NLG919@HA-Ce6,实现Ce6和NLG919在肿瘤部位有效蓄积,显著抑制了小鼠原位肿瘤的生长。

2021年,Liu等[130]将光敏染料BDP-I-N和PD-L1抗体封装在两亲性聚合物PS-g-PEG中,开发了BDP-I-N-a-PD-L1 NPs,实现了用于肿瘤治疗的联合效果,且疗效显著提高。Yuan等[131]报道了NPs负载光敏剂mTHPC——mTHPC@VeC/T-RGD NPs介导的PDT可以增强PD-L1抗体对结直肠癌(colorectal cancer, CRC)的抗肿瘤疗效,并研究了PDT在该联合治疗中增强PD-L1抗体治疗效果的潜在机制。Xiong等[132]制备了一种临床可用的多功能脂质体,该脂质体将二甲双胍(metformin, Met)和光敏剂吲哚菁绿ICG共载,用于治疗原发性和脓肿肿瘤,结果证实了PDT可以增加肿瘤组织中IFN-γ的浸润,上调肿瘤细胞膜上PD-L1的表达,抑制T细胞的免疫杀伤作用。Guo等[133]设计了一种新型光敏剂ZnTMPyP,借助核壳磁性纳米复合材料(magnetic nano composites, MNCs),实现了PDT诱导的适应性免疫应答,增加了肿瘤细胞、DCs和巨噬细胞中PD-L1的表达。

2022年,Yu等[51]用免疫佐剂CPG-ODN和ICG合成DNA光敏剂纳米球(intertwining DNA-photosensitizer nanosphere, iDP-NS),同时联合PD-L1抗体发挥抗肿瘤反应抑制4T1肿瘤术后的转移和复发。左月月[134]构建了包载ICG和NLG919的聚合物囊泡NIPS,结果表明,NIPS介导的光热-光动力联合多重免疫的治疗手段能够有效地抑制黑色素瘤发生肺转移,为临床上治疗黑色素瘤提供了研究基础。Tong

等[135]报道了一种环状RGD(cyclic RGD,cRGD)修饰的脂质体递送系统,其负载PD-L1抗体和光敏剂脱镁叶绿酸a(pheophorbide A,Pa),Pa介导的PDT靶向低PD-L1表达的4T1小鼠乳腺肿瘤细胞,提高了肿瘤细胞上PD-L1的表达,促进DCs的活化和成熟以及细胞毒性T淋巴细胞的浸润,增强抗肿瘤免疫反应。Wu等[136]通过将ICG封装到透明质酸缀合的脂质聚乙二醇中来制备肿瘤靶向纳米药物,PD-L1抗体在PDT后5 d给予,显著抑制局部肿瘤生长并抑制肿瘤转移。

这些研究显示光动力疗法与免疫检查点抑制剂联合具有良好的协同作用,光动力疗法在杀伤局部肿瘤的同时能有效激活机体的免疫应答,进而抑制肿瘤转移和复发。现将目前光动力与免疫检查点抑制剂联合治疗的研究汇总如表2所示。

4 结语

近年来,越来越多的研究论文讨论了光动力疗法与免疫检查点抑制剂的联合治疗在恶性肿瘤治疗中的潜力。这一联合治疗不仅在体外和体内都能克服光动力疗法的局限性,而且显著提高了免疫治疗的效果,可以同时抑制原发性和远处肿瘤的生长。因此,未来的癌症治疗方向之一是开发高效且安全的光动力疗法与免疫治疗的协同疗法。目前,研究人员主要通过纳米载药粒子来实现光动力疗法和ICIs的联合应用。然而,还需要更多的研究来确定这种治疗组合的扩展和优化方式,深入研究光动力疗法和ICIs联合治疗的机制,以寻找更加有效的联合治疗方案。这将有助于在临床前研究和进一步的临床试验中实现最佳的治疗效果,为恶性肿瘤的治疗提供更多选择和希望。

总之,光动力疗法与免疫检查点抑制剂的联合治疗为恶性肿瘤治疗提供了新的可能性。目前的研究为这种联合治疗方法应用于临床奠定了坚实的理论基础,为医生提供了更多治疗选择,同时也为癌症患者提供了更多的治疗希望。

表2 PDT联合ICIs治疗肿瘤

Table 2 PDT combined with ICIs to treat tumor

ICIs	光敏剂	肿瘤	载体	参考文献
aPD-L1	pyrolipid	4T1/TUBO breast cancer	NPs(ZnP@pyro)	[121]
aPD-L1	Fe-TBP	CT26 colon cancer	nMOFs	[27]
aPD-L1	Ce6	B16F10 melanoma	aPD-Ll@HC/PM	[126]
aPD-L1	BDP-I-N	MC38 colon cancer	BDP-I-N-a-PD-L1 NPs	[130]
aPD-L1	ICG	4T1 breast cancer	iDP-NS	[51]
aPD-L1	ICG	MB49 Bladder carcinoma; CT26 colon cancer	liposome	[132]
aPD-L1	mTHPC	CT26 colon cancer	VeC/T-RGD NPs	[131]
aPD-L1	ZnTMPyP	4T1 breast cancer	MNCs	[133]
aPD-L1	Pa	4T1 breast cancer; B16F10 melanoma; Lewis lung carcinoma; CT26 colon cancer	DPPC and DSPE-mPEG2000 micelles	[135]
aPD-L1	ICG	4T1 breast cancer	Polymer DSPE-PEG-HA	[136]
aCTLA-4	ZnPc	4T1 breast cancer	ZnPc/aCTLA4@Ac-DEX NPs	[128]
aCTLA-4	Ce6	CT26 colon cancer	UCNP-Ce6-R837-	[23]
aCTLA-4	Ce6	4T1 breast cancer	M-MONs@Ce6	[127]
NLG919	PpIX	4T1 breast cancer	Liposomes	[123]
NLG919	PPa	4T1 breast cancer; CT26 colon cancer	EAPVs	[124]
NLG919	Ce6	4T1 breast cancer	NLG919@HA-Ce6	[129]
NLG919	Ce6	4T1 breast cancer	PF-PEG@Ce6 NPs	[125]
NLG919	ICG	B16F10 melanoma	NIPS	[134]
1MT	PpIX	CT26 colon cancer	PpIX-1MT NPs	[122]

参考文献:

[1] MILLER K D, NOGUEIRA L, MARIOTTO A B, *et al*. Cancer Treatment and Survivorship Statistics, 2019[J]. *CA Cancer J Clin*, 2019, **69**(5): 363−385. DOI: 10.3322/caac.21565.

[2] ESPOSITO M, GANESAN S, KANG Y B. Emerging Strategies for Treating Metastasis[J]. *Nat Cancer*, 2021, **2**(3): 258−270. DOI: 10.1038/s43018-021-00181-0.

[3] BENOV L. Photodynamic Therapy: Current Status and Future Directions[J]. *Med Princ Pract*, 2015, **24**(Suppl 1): 14−28. DOI: 10.1159/000362416.

[4] NAIDOO C, KRUGER C A, ABRAHAMSE H. Photodynamic Therapy for Metastatic Melanoma Treatment: A Review[J]. *Technol Cancer Res Treat*, 2018, **17**: 1533033818791795. DOI: 10.1177/1533033818791795.

[5] LI X S, ZHENG B D, PENG X H, *et al*. Phthalocyanines as Medicinal Photosensitizers: Developments in the last Five Years[J]. *Coord Chem Rev*, 2019, **379**: 147−160. DOI: 10.1016/j.ccr.2017.08.003.

[6] KESSEL D. Photodynamic Therapy: A Brief History[J]. *J Clin Med*, 2019, **8**(10): E1581. DOI: 10.3390/jcm8101581.

[7] GAO M, FAN F, LI D D, *et al*. Tumor Acidity-activatable TAT Targeted Nanomedicine for Enlarged Fluorescence/Magnetic Resonance Imaging-guided Photodynamic Therapy[J]. *Biomaterials*, 2017, **133**: 165−175. DOI: 10.1016/j.biomaterials.2017.04.013.

[8] WANG Q, XIA B, XU J Z, *et al*. Biocompatible Small Organic Molecule Phototheranostics for NIR-II Fluorescence/Photoacoustic Imaging and Simultaneous Photodynamic/Photothermal Combination Therapy[J]. *Mater Chem Front*, 2019, **3**(4): 650−655. DOI: 10.1039/c9qm00036d.

[9] JIANG N, AHMED R, RIFAT A A, *et al*. Functionalized Flexible Soft Polymer Optical Fibers for Laser Photomedicine[J]. *Adv Opt Mater*, 2018, **6**(3): 1701118. DOI: 10.1002/adom.201701118.

[10] ANZENGRUBER F, AVCI P, DE FREITAS L F, *et al*. T-cell Mediated Anti-tumor Immunity After Photodynamic Therapy: Why Does It Not Always Work and How Can We Improve It?[J]. *Photochem Photobiol Sci*, 2015, **14**(8): 1492−1509. DOI: 10.1039/c4pp00455h.

[11] FAN Q, CHEN Z P, WANG C, *et al*. Toward Biomaterials for Enhancing Immune Checkpoint Blockade Therapy[J]. *Adv Funct Materials*, 2018, **28**(37): 1802540. DOI: 10.1002/adfm.201802540.

[12] PARDOLL D M. The Blockade of Immune Checkpoints in Cancer Immunotherapy[J]. *Nat Rev Cancer*, 2012, **12**(4): 252−264. DOI: 10.1038/nrc3239.

[13] DENG H, ZHANG Z P. The Application of Nanotechnology in Immune Checkpoint Blockade for Cancer Treatment[J]. *J Control Release*, 2018, **290**: 28−45. DOI: 10.1016/j.jconrel.2018.09.026.

[14] FESNAK A D, JUNE C H, LEVINE B L. Engineered T Cells: The Promise and Challenges of Cancer Immunotherapy[J]. *Nat Rev Cancer*, 2016, **16**(9): 566−581. DOI: 10.1038/nrc.2016.97.

[15] JAKOBSEN M K, GJERSTORFF M F. CAR T-cell Cancer Therapy Targeting Surface Cancer/Testis Antigens[J]. *Front Immunol*, 2020, **11**: 1568−1574. DOI: 10.3389/fimmu.2020.01568.

[16] 王梓慈, 吴砂, 王薇. 免疫检查点PD-1/PD-L1阻断疗法与妇科恶性肿瘤[J]. 中国免疫学杂志, 2020, **36**(12): 1512−1515. DOI: 10.3969/j.issn.1000-484X.2020.12.022.
WANG Z C, WU S, WANG W. Immunotherapy of PD-1/PD-L1 Immune Checkpoint Inhibitors with Gynecologi-cal Malignancies[J]. *Chin J Immunol*, 2020, **36**(12): 1512−1515. DOI: 10.3969/j. issn. 1000-484X.2020.12.022.

[17] PHUENGKHAM H, REN L, SHIN I W, *et al*. Nanoengineered Immune Niches for Reprogramming the Immunosuppressive Tumor Microenvironment and Enhancing Cancer Immunotherapy[J]. *Adv Mater*, 2019, **31**(34): e1803322. DOI: 10.1002/adma.201803322.

[18] GALLUZZI L, HUMEAU J, BUQUÉ A, *et al*. Immunostimulation with Chemotherapy in the Era of Immune Checkpoint Inhibitors[J]. *Nat Rev Clin Oncol*, 2020, **17**(12): 725−741. DOI: 10.1038/s41571-020-0413-z.

[19] DONOHOE C, SENGE M O, ARNAUT L G, *et al*. Cell Death in Photodynamic Therapy: From Oxidative Stress to Anti-tumor Immunity[J]. *Biochim Biophys Acta Rev Cancer*, 2019, **1872**(2): 188308. DOI: 10.1016/j.bbcan.2019.07.003.

[20] GOMES-DA-SILVA L C, ZHAO L W, BEZU L, *et al*. Photodynamic Therapy with Redaporfin Targets the Endoplasmic Reticulum and Golgi Apparatus[J]. *EMBO J*, 2018, **37**(13): e98354. DOI: 10.15252/embj.201798354.

[21] HE C B, DUAN X P, GUO N N, *et al*. Core-shell Nanoscale Coordination Polymers Combine Chemotherapy and Photodynamic Therapy to Potentiate Checkpoint Blockade Cancer Immunotherapy[J]. *Nat Commun*, 2016, **7**: 12499. DOI: 10.1038/ncomms12499.

[22] YANG G B, XU L G, CHAO Y, *et al*. Hollow MnO_2 as a Tumor-microenvironment-responsive Biodegradable Nano-platform for Combination Therapy Favoring Antitumor Immune Responses[J]. *Nat Commun*, 2017, **8**(1): 902. DOI: 10.1038/s41467-017-01050-0.

[23] XU J, XU L G, WANG C Y, *et al*. Near-infrared-

triggered Photodynamic Therapy with Multitasking Upconversion Nanoparticles in Combination with Checkpoint Blockade for Immunotherapy of Colorectal Cancer[J]. *ACS Nano*, 2017, **11**(5): 4463−4474. DOI: 10.1021/acsnano.7b00715.

[24] LAN M H, ZHAO S J, LIU W M, *et al*. Photosensitizers for Photodynamic Therapy[J]. *Adv Healthc Mater*, 2019, **8**(13): e1900132. DOI: 10.1002/adhm.201900132.

[25] WEIJER R, BROEKGAARDEN M, KOS M, *et al*. Enhancing Photodynamic Therapy of Refractory Solid Cancers: Combining Second-generation Photosensitizers with Multi-targeted Liposomal Delivery[J]. *J Photochem Photobiol C Photochem Rev*, 2015, **23**: 103−131. DOI: 10.1016/j.jphotochemrev.2015.05.002.

[26] HAN R C, ZHAO M, WANG Z W, *et al*. Super-efficient *in Vivo* Two-photon Photodynamic Therapy with a Gold Nanocluster as a Type I Photosensitizer[J]. *ACS Nano*, 2020, **14**(8): 9532−9544. DOI: 10.1021/acsnano.9b05169.

[27] LAN G X, NI K Y, VERONEAU S S, *et al*. Titanium-based Nanoscale Metal-organic Framework for Type I Photodynamic Therapy[J]. *J Am Chem Soc*, 2019, **141**(10): 4204−4208. DOI: 10.1021/jacs.8b13804.

[28] KAST R E, MICHAEL A P, SARDI I, *et al*. A New Treatment Opportunity for DIPG and Diffuse Midline Gliomas: 5-ALA Augmented Irradiation, the 5aai Regimen[J]. *Brain Sci*, 2020, **10**(1): 51-58. DOI: 10.3390/brainsci10010051.

[29] HAMBLIN M R. Photodynamic Therapy for Cancer: What's Past is Prologue[J]. *Photochem Photobiol*, 2020, **96**(3): 506−516. DOI: 10.1111/php.13190.

[30] YANG D, LEI S X, PAN K R, *et al*. Application of Photodynamic Therapy in Immune-related Diseases[J]. *Photodiagnosis Photodyn Ther*, 2021, **34**: 102318. DOI: 10.1016/j.pdpdt.2021.102318.

[31] KEPP O, MARABELLE A, ZITVOGEL L, *et al*. Oncolysis without Viruses: Inducing Systemic Anticancer Immune Responses with Local Therapies[J]. *Nat Rev Clin Oncol*, 2020, **17**: 49−64. DOI: 10.1038/s41571-019-0272-7.

[32] MOKOENA D R, GEORGE B P, ABRAHAMSE H. Photodynamic Therapy Induced Cell Death Mechanisms in Breast Cancer[J]. *Int J Mol Sci*, 2021, **22**(19): 10506. DOI: 10.3390/ijms221910506.

[33] MENG Z Q, ZHOU X F, XU J, *et al*. Light-triggered in Situ Gelation to Enable Robust Photodynamic-immunotherapy by Repeated Stimulations[J]. *Adv Mater*, 2019, **31**(24): e1900927. DOI: 10.1002/adma.201900927.

[34] SUN Y X, ZHAO D Y, WANG G, *et al*. Recent Progress of Hypoxia-modulated Multifunctional Nanomedicines to Enhance Photodynamic Therapy: Opportunities, Challenges, and Future Development[J]. *Acta Pharm Sin B*, 2020, **10**(8): 1382−1396. DOI: 10.1016/j.apsb.2020.01.004.

[35] CHILAKAMARTHI U, GIRIBABU L. Photodynamic Therapy: Past, Present and Future[J]. *Chem Rec*, 2017, **17**(8): 775−802. DOI: 10.1002/tcr.201600121.

[36] WANG Y M, FENG W, CHANG M Q, *et al*. Engineering 2D Multifunctional Ultrathin Bismuthene for Multiple Photonic Nanomedicine[J]. *Adv Funct Mater*, 2021, **31**(6): 2005093. DOI: 10.1002/adfm.202005093.

[37] MA S H, WANG L, LIU Z, *et al*. "one Stone, Two Birds": Engineering 2-D Ultrathin Heterostructure Nanosheet BiNS@$NaLnF_4$ for Dual-modal Computed Tomography/Magnetic Resonance Imaging Guided, Photonic Synergetic Theranostics[J]. *Nanoscale*, 2021, **13**(1): 185−194. DOI: 10.1039/D0NR07590F.

[38] FAN W P, HUANG P, CHEN X Y. Overcoming the Achilles' Heel of Photodynamic Therapy[J]. *Chem Soc Rev*, 2016, **45**(23): 6488−6519. DOI: 10.1039/c6cs00616g.

[39] 王国安, 吴宏成. 光动力治疗在呼吸道肿瘤中的临床应用[J]. 现代实用医学, 2020, **32**(1): 7−8. DOI: 10.3969/j.issn.1671-0800.2020.01.003.
WANG G A, WU H C. Clinical Application of Photodynamic Therapy in Respiratory Tract Tumors[J]. *Mod Pract Med*, 2020, **32**(1): 7−8. DOI: 10.3969/j.issn.1671-0800.2020.01.003.

[40] KWIATKOWSKI S, KNAP B, PRZYSTUPSKI D, *et al*. Photodynamic Therapy - Mechanisms, Photosensitizers and Combinations[J]. *Biomed Pharmacother*, 2018, **106**: 1098−1107. DOI: 10.1016/j.biopha.2018.07.049.

[41] SANKEY E W, GRABOWSKI M M, SRINIVASAN E S, *et al*. Time to Steroid Independence after Laser Interstitial Thermal Therapy Vs Medical Management for Treatment of Biopsy-proven Radiation Necrosis Secondary to Stereotactic Radiosurgery for Brain Metastasis[J]. *Neurosurgery*, 2022, **90**(6): 684−690. DOI: 10.1227/neu.0000000000001922.

[42] BENZAQUEN M, FONGUE J, PAULY V, *et al*. Laser-assisted Hyaluronic Acid Delivery by Fractional Carbon Dioxide Laser in Facial Skin Remodeling: a Prospective Randomized Split-face Study in France[J]. *Lasers Surg Med*, 2021, **53**(9): 1166−1172. DOI: 10.1002/lsm.23403.

[43] HOU X Y, TAO Y K, PANG Y Y, *et al*. Nanoparticle-based Photothermal and Photodynamic Immunotherapy

for Tumor Treatment[J]. *Int J Cancer*, 2018, **143**(12): 3050−3060. DOI: 10.1002/ijc.31717.

[44] ZHANG D, FENG F, LI Q L, *et al*. Nanopurpurin-based Photodynamic Therapy Destructs Extracellular Matrix Against Intractable Tumor Metastasis[J]. *Biomaterials*, 2018, **173**: 22−33. DOI: 10.1016/j. biomaterials.2018.04.045.

[45] FALK-MAHAPATRA R, GOLLNICK S O. Photodynamic Therapy and Immunity: An Update[J]. *Photochem Photobiol*, 2020, **96**(3): 550−559. DOI: 10.1111/php.13253.

[46] CRAMER G M, MOON E K, CENGEL K A, *et al*. Photodynamic Therapy and Immune Checkpoint Blockade [J]. *Photochem Photobiol*, 2020, **96**(5): 954−961. DOI: 10.1111/php.13300.

[47] CHEN W S, OUYANG J, LIU H, *et al*. Black Phosphorus Nanosheet-based Drug Delivery System for Synergistic Photodynamic/Photothermal/Chemotherapy of Cancer[J]. *Adv Mater*, 2017, **29**(5): 1603864. DOI: 10.1002/adma.201603864.

[48] CHU C C, REN E, ZHANG Y M, *et al*. Zinc(II)-dipicolylamine Coordination Nanotheranostics: Toward Synergistic Nanomedicine by Combined Photo/Gene Therapy[J]. *Angew Chem Int Ed Engl*, 2019, **58**(1): 269−272. DOI: 10.1002/anie.201812482.

[49] ZHOU Z J, ZHANG L, ZHANG Z R, *et al*. Advances in Photosensitizer-related Design for Photodynamic Therapy[J]. *Asian J Pharm Sci*, 2021, **16**(6): 668−686. DOI: 10.1016/j.ajps.2020.12.003.

[50] OZOG D M, RKEIN A M, FABI S G, *et al*. Photodynamic Therapy: a Clinical Consensus Guide[J]. *Dermatol Surg*, 2016, **42**(7): 804−827. DOI: 10.1097/DSS.0000000000000800.

[51] YU G H, DONG F, GE W S, *et al*. Self-assembled Nanospheres Mediate Phototherapy and Deliver CpG Oligodeoxynucleotides to Enhance Cancer Immunotherapy of Breast Cancer and Melanoma[J]. *Nano Today*, 2022, **44**: 101498. DOI: 10.1016/j.nantod.2022.101498.

[52] LIANG B H, HU X M, DING Y H, *et al*. Tumor-derived Exosomes in the PD-1/PD-L1 Axis: Significant Regulators as Well as Promising Clinical Targets[J]. *J Cell Physiol*, 2021, **236**(6): 4138−4151. DOI: 10.1002/jcp.30197.

[53] PISIBON C, OUERTANI A, BERTOLOTTO C, *et al*. Immune Checkpoints in Cancers: From Signaling to the Clinic[J]. *Cancers*, 2021, **13**(18): 4573−4595. DOI: 10.3390/cancers13184573.

[54] ZAPPASODI R, MERGHOUB T, WOLCHOK J D. Emerging Concepts for Immune Checkpoint Blockade-based Combination Therapies[J]. *Cancer Cell*, 2018, **33**(4): 581−598. DOI: 10.1016/j.ccell.2018.03.005.

[55] KENNEDY A, WATERS E, ROWSHANRAVAN B, *et al*. Differences in CD80 and CD86 Transendocytosis Reveal CD86 as a Key Target for CTLA-4 Immune Regulation[J]. *Nat Immunol*, 2022, **23**(9): 1365−1378. DOI: 10.1038/s41590-022-01289-w.

[56] LU J Q, LIU X S, LIAO Y P, *et al*. Breast Cancer Chemo-immunotherapy through Liposomal Delivery of an Immunogenic Cell Death Stimulus Plus Interference in the IDO-1 Pathway[J]. *ACS Nano*, 2018, **12**(11): 11041−11061. DOI: 10.1021/acsnano.8b05189.

[57] GAO A, HU X L, SAEED M, *et al*. Overview of Recent Advances in Liposomal Nanoparticle-based Cancer Immunotherapy[J]. *Acta Pharmacol Sin*, 2019, **40**(9): 1129−1137. DOI: 10.1038/s41401-019-0281-1.

[58] TOPALIAN S L, DRAKE C G, PARDOLL D M. Immune Checkpoint Blockade: A Common Denominator Approach to Cancer Therapy[J]. *Cancer Cell*, 2015, **27**(4): 450−461. DOI: 10.1016/j.ccell.2015.03.001.

[59] WU X M, GU Z K, CHEN Y, *et al*. Application of PD-1 Blockade in Cancer Immunotherapy[J]. *Comput Struct Biotechnol J*, 2019, **17**: 661−674. DOI: 10.1016/j.csbj.2019.03.006.

[60] OHAEGBULAM K C, ASSAL A, LAZAR-MOLNAR E, *et al*. Human Cancer Immunotherapy with Antibodies to the PD-1 and PD-L1 Pathway[J]. *Trends Mol Med*, 2015, **21**(1): 24−33. DOI: 10.1016/j. molmed.2014.10.009.

[61] SUNSHINE J, TAUBE J M. PD-1/PD-L1 Inhibitors[J]. *Curr Opin Pharmacol*, 2015, **23**: 32−38. DOI: 10.1016/j.coph.2015.05.011.

[62] HELMINK B A, GAUDREAU P O, WARGO J A. Immune Checkpoint Blockade across the Cancer Care Continuum[J]. *Immunity*, 2018, **48**(6): 1077−1080. DOI: 10.1016/j.immuni.2018.06.003.

[63] GAO L Q, ZHANG C R, GAO D, *et al*. Enhanced Antitumor Efficacy through a Combination of Integrin Avβ6-targeted Photodynamic Therapy and Immune Checkpoint Inhibition[J]. *Theranostics*, 2016, **6**(5): 627−637. DOI: 10.7150/thno.14792.

[64] HU Z W. The Future of Immune Checkpoint Blockade Immunotherapy: Towards Personalized Therapy or towards Combination Therapy[J]. *J Thorac Dis*, 2017, **9**(11): 4226−4229. DOI: 10.21037/jtd.2017.10.31.

[65] 李倩. 基于聚合物前药的光动力: 免疫联合治疗纳米制剂的抗肿瘤研究[D]. 济南: 山东大学, 2020.

LI Q. Anti-tumor Study of Nano-preparation of Photodynamic-immunotherapy Based on Polymer Prodrug[D]. Jinan: Shandong University, 2020.

[66] SAHA D, MARTUZA R L, RABKIN S D. Macrophage Polarization Contributes to Glioblastoma Eradication by Combination Immunovirotherapy and Immune Checkpoint Blockade[J]. *Cancer Cell*, 2017, **32**(2): 253−267. DOI: 10.1016/j.ccell.2017.07.006.

[67] ZHAO Y L, LEE C K, LIN C H, *et al*. PD-L1: CD80 *Cis*-heterodimer Triggers the Co-stimulatory Receptor CD28 while Repressing the Inhibitory PD-1 and CTLA-4 Pathways[J]. *Immunity*, 2019, **51**(6): 1059−1073. DOI: 10.1016/j.immuni.2019.11.003.

[68] GUO Q Y, HUANG F, GONCALVES C, *et al*. Translation of Cancer Immunotherapy from the Bench to the Bedside[J]. *Adv Cancer Res*, 2019, **143**: 1−62. DOI: 10.1016/bs.acr.2019.03.001.

[69] OYEWOLE-SAID D, KONDURI V, VAZQUEZ-PEREZ J, *et al*. Beyond T-cells: Functional Characterization of CTLA-4 Expression in Immune and Non-immune Cell Types[J]. *Front Immunol*, 2020, **11**: 608024. DOI: 10.3389/fimmu.2020.608024.

[70] ZHANG H J, DUTTA P, LIU J G, *et al*. Tumour Cell-intrinsic CTLA4 Regulates PD-L1 Expression in Non-small Cell Lung Cancer[J]. *J Cell Mol Med*, 2019, **23**(1): 535−542. DOI: 10.1111/jcmm.13956.

[71] GHORBANINEZHAD F, MASOUMI J, BAKHSHIVAND M, *et al*. CTLA-4 Silencing in Dendritic Cells Loaded with Colorectal Cancer Cell Lysate Improves Autologous T Cell Responses *in Vitro*[J]. *Front Immunol*, 2022, **13**: 931316. DOI: 10.3389/fimmu.2022.931316.

[72] LAX B M, PALMERI J R, LUTZ E A, *et al*. Both Intratumoral Regulatory T Cell Depletion and CTLA-4 Antagonism are Required for Maximum Efficacy of Anti-CTLA-4 Antibodies[J]. *Proc Natl Acad Sci USA*, 2023, **120**(31): e2300895120. DOI: 10.1073/pnas.2300895120.

[73] YOFE I, LANDSBERGER T, YALIN A, *et al*. Anti-CTLA-4 Antibodies Drive Myeloid Activation and Reprogram the Tumor Microenvironment through FcγR Engagement and Type I Interferon Signaling[J]. *Nat Cancer*, 2022, **3**(11): 1336−1350. DOI: 10.1038/s43018-022-00447-1.

[74] OPITZ C A, LITZENBURGER U M, OPITZ U, *et al*. The Indoleamine-2, 3-dioxygenase (IDO) Inhibitor 1-methyl-D-tryptophan Upregulates IDO1 in Human Cancer Cells[J]. *PLoS One*, 2011, **6**(5): e19823. DOI: 10.1371/journal.pone.0019823.

[75] AWUAH S G, ZHENG Y R, BRUNO P M, *et al*. A Pt (IV) Pro-drug Preferentially Targets Indoleamine-2, 3-dioxygenase, Providing Enhanced Ovarian Cancer Immuno-chemotherapy[J]. *J Am Chem Soc*, 2015, **137**(47): 14854−14857. DOI: 10.1021/jacs.5b10182.

[76] CHEN Y C, XIA R, HUANG Y X, *et al*. An Immunostimulatory Dual-functional Nanocarrier that Improves Cancer Immunochemotherapy[J]. *Nat Commun*, 2016, **7**: 13443. DOI: 10.1038/ncomms13443.

[77] KLEINOVINK J W, FRANSEN M F, LÖWIK C W, *et al*. Photodynamic-immune Checkpoint Therapy Eradicates Local and Distant Tumors by $CD8^+$ T Cells[J]. *Cancer Immunol Res*, 2017, **5**(10): 832−838. DOI: 10.1158/2326-6066.CIR-17-0055.

[78] LUCKY S S, SOO K C, ZHANG Y. Nanoparticles in Photodynamic Therapy[J]. *Chem Rev*, 2015, **115**(4): 1990−2042. DOI: 10.1021/cr5004198.

[79] YU X H, GAO D, GAO L Q, *et al*. Inhibiting Metastasis and Preventing Tumor Relapse by Triggering Host Immunity with Tumor-targeted Photodynamic Therapy Using Photosensitizer-loaded Functional Nanographenes [J]. *ACS Nano*, 2017, **11**(10): 10147−10158. DOI: 10.1021/acsnano.7b04736.

[80] HAO Y, CHUNG C K, GU Z L, *et al*. Combinatorial Therapeutic Approaches of Photodynamic Therapy and Immune Checkpoint Blockade for Colon Cancer Treatment[J]. *Mol Biomed*, 2022, **3**(1): 26. DOI: 10.1186/s43556-022-00086-z.

[81] MAEDING N, VERWANGER T, KRAMMER B. Boosting Tumor-specific Immunity Using PDT[J]. *Cancers*, 2016, **8**(10): 91. DOI: 10.3390/cancers8100091.

[82] ANDRADE L M, MARTINS E M N, VERSIANI A F, *et al*. The Physicochemical and Biological Characterization of a 24-month-stored Nano Complex Based on Gold Nanoparticles Conjugated with Cetuximab Demonstrated Long-term Stability, EGFR Affinity and Cancer Cell Death Due to Apoptosis[J]. *Mater Sci Eng C Mater Biol Appl*, 2020, **107**: 110203. DOI: 10.1016/j.msec.2019.110203.

[83] SHAFIRSTEIN G, BATTOO A, HARRIS K, *et al*. Photodynamic Therapy of Non-small Cell Lung Cancer. Narrative Review and Future Directions[J]. *Ann Am Thorac Soc*, 2016, **13**(2): 265−275. DOI: 10.1513/annalsats.201509-650fr.

[84] HWANG H S, SHIN H, HAN J, *et al*. Combination of Photodynamic Therapy (PDT) and Anti-tumor Immunity in Cancer Therapy[J]. *J Pharm Investig*, 2018, **48**(2): 143−151. DOI: 10.1007/s40005-017-0377-x.

[85] LU K D, HE C B, GUO N N, *et al*. Chlorin-based Nanoscale Metal-organic Framework Systemically Rejects Colorectal Cancers via Synergistic Photodynamic Therapy and Checkpoint Blockade Immunotherapy[J]. *J Am Chem Soc*, 2016, **138**(38): 12502−12510. DOI: 10.1021/jacs.6b06663.

[86] WANG D G, WANG T T, LIU J P, *et al*. Acid-activatable Versatile Micelleplexes for PD-L1 Blockade-enhanced Cancer Photodynamic Immunotherapy[J]. *Nano Lett*, 2016, **16**(9): 5503−5513. DOI: 10.1021/acs.nanolett.6b01994.

[87] BAO R, WANG Y P, LAI J H, *et al*. Enhancing Anti-PD-1/PD-L1 Immune Checkpoint Inhibitory Cancer Therapy by CD276-targeted Photodynamic Ablation of Tumor Cells and Tumor Vasculature[J]. *Mol Pharm*, 2019, **16**(1): 339−348. DOI: 10.1021/acs. molpharmaceut.8b00997.

[88] XU J J, YU S, WANG X D, *et al*. High Affinity of Chlorin E6 to Immunoglobulin G for Intraoperative Fluorescence Image-guided Cancer Photodynamic and Checkpoint Blockade Therapy[J]. *ACS Nano*, 2019, **13**(9): 10242−10260. DOI: 10.1021/acsnano.9b03466.

[89] RIERA-DOMINGO C, AUDIGÉ A, GRANJA S, *et al*. Immunity, Hypoxia, and Metabolism-the Ménage à Trois of Cancer: Implications for Immunotherapy[J]. *Physiol Rev*, 2020, **100**(1): 1−102. DOI: 10.1152/physrev.00018.2019.

[90] LIU Y L, PAN Y X, CAO W, *et al*. A Tumor Microenvironment Responsive Biodegradable $CaCO_3$/MnO_2-Based Nanoplatform for the Enhanced Photodynamic Therapy and Improved PD-L1 Immunotherapy[J]. *Theranostics*, 2019, **9**(23): 6867−6884. DOI: 10.7150/thno.37586.

[91] CHENG H W, FAN X S, YE E Y, *et al*. Dual Tumor Microenvironment Remodeling by Glucose-contained Radical Copolymer for MRI-guided Photoimmunotherapy[J]. *Adv Mater*, 2022, **34**(25): e2107674. DOI: 10.1002/adma.202107674.

[92] TORCHILIN V P. Micellar Nanocarriers: Pharmaceutical Perspectives[J]. *Pharm Res*, 2007, **24**(1): 1−16. DOI: 10.1007/s11095-006-9132-0.

[93] SONG X J, XU J, LIANG C, *et al*. Self-supplied Tumor Oxygenation through Separated Liposomal Delivery of H_2O_2 and Catalase for Enhanced Radio-immunotherapy of Cancer[J]. *Nano Lett*, 2018, **18**(10): 6360−6368. DOI: 10.1021/acs.nanolett.8b02720.

[94] HAIDER M, ABDIN S M, KAMAL L, *et al*. Nanostructured Lipid Carriers for Delivery of Chemotherapeutics: a Review[J]. *Pharmaceutics*, 2020, **12**(3): 288. DOI: 10.3390/pharmaceutics12030288.

[95] ZHAO X H, CHEN X Y, YUK H, *et al*. Soft Materials by Design: Unconventional Polymer Networks Give Extreme Properties[J]. *Chem Rev*, 2021, **121**(8): 4309−4372. DOI: 10.1021/acs.chemrev.0c01088.

[96] 赵宇, 曹琬晴, 刘阳. 聚合物纳米药物载体的研究进展[J]. 高等学校化学学报, 2020, **41**(5): 909−923. DOI: 10.7503/cjcu20190646.
ZHAO Y, CAO W Q, LIU Y. Recent Advances in Polymeric Nano-sized Carrier Systems[J]. *Chem J Chin Univ*, 2020, **41**(5): 909−923. DOI: 10.7503/cjcu20190646.

[97] WU R, FENG Z, ZHANG J J, *et al*. Quantum Dots for Electrochemical Cytosensing[J]. *Trac Trends Anal Chem*, 2022, **148**: 116531. DOI: 10.1016/j.trac.2022.116531.

[98] WU K, SU D Q, LIU J M, *et al*. Magnetic Nanoparticles in Nanomedicine: A Review of Recent Advances [J]. *Nanotechnology*, 2019, **30**(50): 502003. DOI: 10.1088/1361-6528/ab4241.

[99] 陶灿. 磁性纳米载药体系的构建与抗肿瘤活性研究[D]. 广州: 广东药科大学, 2021. DOI: 10.27690/d.cnki.ggdyk.2021.000260.
TAO C. Construction of Magnetic Nanometer Drug Delivery System and Research of Antitumor Activity[D]. Guangzhou: Guangdong Pharmaceutical University, 2021.DOI: 10.27690/d.cnki.ggdyk.2021.000260.

[100] CHEN W, GLACKIN C A, HORWITZ M A, *et al*. Nanomachines and other Caps on Mesoporous Silica Nanoparticles for Drug Delivery[J]. *Acc Chem Res*, 2019, **52**(6): 1531−1542. DOI: 10.1021/acs. accounts.9b00116.

[101] 杨惠舒, 李乐, 刘馨遥, 等. 介孔二氧化硅纳米颗粒作为药物载体的研究现状[J]. 材料导报, 2022, **36**(S1): 56−61.
YANG H S, LI L, LIU X Y, *et al*. Research Status of Mesoporous Silica Nanoparticles as Drug Carriers[J]. *Mater Rep*, 2022, **36**(S1): 56−61.

[102] DREADEN E C, ALKILANY A M, HUANG X H, *et al*. The Golden Age: Gold Nanoparticles for Biomedicine[J]. *Chem Soc Rev*, 2012, **41**(7): 2740−2779. DOI: 10.1039/c1cs15237h.

[103] PANWAR N, SOEHARTONO A M, CHAN K K, *et al*. Nanocarbons for Biology and Medicine: Sensing, Imaging, and Drug Delivery[J]. *Chem Rev*, 2019, **119**(16): 9559−9656. DOI: 10.1021/acs.chemrev.9b00099.

[104] 张鑫. 碳基纳米多功能材料的制备及生物医药应用[D]. 西安: 西北大学, 2019.
ZHANG X. The Preparation of Carbon Based Nano

Materials with Multifunction and Their Applications in Biomedical Field[D]. Xi'an: Northwest University, 2019.

[105] LI Y M, YE Z F, YANG H Y, *et al*. Tailoring Combinatorial Lipid Nanoparticles for Intracellular Delivery of Nucleic Acids, Proteins, and Drugs[J]. *Acta Pharm Sin B*, 2022, **12**(6): 2624−2639. DOI: 10.1016/j.apsb.2022.04.013.

[106] OROOJALIAN F, BEYGI M, BARADARAN B, *et al*. Immune Cell Membrane-coated Biomimetic Nanoparticles for Targeted Cancer Therapy[J]. *Small*, 2021, **17**(12): e2006484. DOI: 10.1002/smll.202006484.

[107] GOYAL R, MACRI L K, KAPLAN H M, *et al*. Nanoparticles and Nanofibers for Topical Drug Delivery[J]. *J Control Release*, 2016, **240**: 77−92. DOI: 10.1016/j.jconrel.2015.10.049.

[108] CHUNG C K, FRANSEN M F, VAN DER MAADEN K, *et al*. Thermosensitive Hydrogels as Sustained Drug Delivery System for CTLA-4 Checkpoint Blocking Antibodies[J]. *J Control Release*, 2020, **323**: 1−11. DOI: 10.1016/j.jconrel.2020.03.050.

[109] NIKPOOR A R, TAVAKKOL-AFSHARI J, SADRI K, *et al*. Improved Tumor Accumulation and Therapeutic Efficacy of CTLA-4-blocking Antibody Using Liposome-encapsulated Antibody: In Vitro and in Vivo Studies[J]. *Nanomedicine*, 2017, **13**(8): 2671−2682. DOI: 10.1016/j.nano.2017.08.010.

[110] LUK B T, ZHANG L F. Cell Membrane-camouflaged Nanoparticles for Drug Delivery[J]. *J Control Release*, 2015, **220**(Pt B): 600−607. DOI: 10.1016/j.jconrel.2015.07.019.

[111] LUO L J, IQBAL M Z, LIU C, *et al*. Engineered Nano-immunopotentiators Efficiently Promote Cancer Immunotherapy for Inhibiting and Preventing Lung Metastasis of Melanoma[J]. *Biomaterials*, 2019, **223**: 119464. DOI: 10.1016/j.biomaterials.2019.119464.

[112] YANG W J, ZHU G Z, WANG S, *et al*. In Situ Dendritic Cell Vaccine for Effective Cancer Immunotherapy[J]. *ACS Nano*, 2019, **13**(3): 3083−3094. DOI: 10.1021/acsnano.8b08346.

[113] WANG M, SONG J, ZHOU F F, *et al*. NIR-triggered Phototherapy and Immunotherapy *via* an Antigen-capturing Nanoplatform for Metastatic Cancer Treatment[J]. *Adv Sci*, 2019, **6**(10): 1802157. DOI: 10.1002/advs.201802157.

[114] MING J, ZHANG J J, SHI Y R, *et al*. A Trustworthy CpG Nanoplatform for Highly Safe and Efficient Cancer Photothermal Combined Immunotherapy[J]. *Nanoscale*, 2020, **12**(6): 3916−3930. DOI: 10.1039/c9nr09402d.

[115] HONG E J, CHOI D G, SHIM M S. Targeted and Effective Photodynamic Therapy for Cancer Using Functionalized Nanomaterials[J]. *Acta Pharm Sin B*, 2016, **6**(4): 297−307. DOI: 10.1016/j.apsb.2016.01.007.

[116] LIU J Y, PENG Q. Protein-gold Nanoparticle Interactions and Their Possible Impact on Biomedical Applications[J]. *Acta Biomater*, 2017, **55**: 13−27. DOI: 10.1016/j.actbio.2017.03.055.

[117] YOUNIS M R, HE G, QU J L, *et al*. Inorganic Nanomaterials with Intrinsic Singlet Oxygen Generation for Photodynamic Therapy[J]. *Adv Sci*, 2021, **8**(21): e2102587. DOI: 10.1002/advs.202102587.

[118] ZHENG Y L, LI Z Y, CHEN H J, *et al*. Nanoparticle-based Drug Delivery Systems for Controllable Photodynamic Cancer Therapy[J]. *Eur J Pharm Sci*, 2020, **144**: 105213. DOI: 10.1016/j.ejps.2020.105213.

[119] CRYER A M, THORLEY A J. Nanotechnology in the Diagnosis and Treatment of Lung Cancer[J]. *Pharmacol Ther*, 2019, **198**: 189−205. DOI: 10.1016/j.pharmthera.2019.02.010.

[120] DUAN X P, CHAN C, LIN W B. Nanoparticle-mediated Immunogenic Cell Death Enables and Potentiates Cancer Immunotherapy[J]. *Angew Chem Int Ed Engl*, 2019, **58**(3): 670−680. DOI: 10.1002/anie.201804882.

[121] DUAN X P, CHAN C, GUO N N, *et al*. Photodynamic Therapy Mediated by Nontoxic Core-shell Nanoparticles Synergizes with Immune Checkpoint Blockade to Elicit Antitumor Immunity and Antimetastatic Effect on Breast Cancer[J]. *J Am Chem Soc*, 2016, **138**(51): 16686−16695. DOI: 10.1021/jacs.6b09538.

[122] SONG W, KUANG J, LI C X, *et al*. Enhanced Immunotherapy Based on Photodynamic Therapy for both Primary and Lung Metastasis Tumor Eradication[J]. *ACS Nano*, 2018, **12**(2): 1978−1989. DOI: 10.1021/acsnano.7b09112.

[123] HUANG Z Q, WEI G F, ZENG Z S, *et al*. Enhanced Cancer Therapy through Synergetic Photodynamic/Immune Checkpoint Blockade Mediated by a Liposomal Conjugate Comprised of Porphyrin and IDO Inhibitor[J]. *Theranostics*, 2019, **9**(19): 5542−5557. DOI: 10.7150/thno.35343.

[124] GAO A, CHEN B F, GAO J, *et al*. Sheddable Prodrug Vesicles Combating Adaptive Immune Resistance for Improved Photodynamic Immunotherapy of Cancer [J]. *Nano Lett*, 2020, **20**(1): 353−362. DOI: 10.1021/acs.nanolett.9b04012.

[125] XING L, GONG J H, WANG Y, *et al*. Hypoxia Alleviation-triggered Enhanced Photodynamic Therapy in Combination with IDO Inhibitor for Preferable Cancer Therapy[J]. *Biomaterials*, 2019, **206**: 170−182. DOI: 10.1016/j.biomaterials.2019.03.027.

[126] LI Q, ZHANG D, ZHANG J, *et al*. A Three-in-one Immunotherapy Nanoweapon via Cascade-amplifying Cancer-immunity Cycle Against Tumor Metastasis, Relapse, and Postsurgical Regrowth[J]. *Nano Lett*, 2019, **19**(9): 6647−6657. DOI: 10.1021/acs.nanolett.9b02923.

[127] WANG Z, ZHANG F, SHAO D, *et al*. Janus Nanobullets Combine Photodynamic Therapy and Magnetic Hyperthermia to Potentiate Synergetic Anti-metastatic Immunotherapy[J]. *Adv Sci*, 2019, **6**(22): 1901690. DOI: 10.1002/advs.201901690.

[128] CHEN S X, MA M, XUE F F, *et al*. Construction of Microneedle-assisted Co-delivery Platform and Its Combining Photodynamic/Immunotherapy[J]. *J Control Release*, 2020, **324**: 218−227. DOI: 10.1016/j.jconrel.2020.05.006.

[129] 徐继明 . 用于光动力/免疫联合抗肿瘤的透明质酸载药纳米胶束研究[D]. 成都: 电子科技大学, 2020.
XU J M. Study on Hyaluronic Acid Drug-loaded Nano-micelles for Photodynamic/Immune Combined Anti-tumor[D]. Chengdu: University of Electronic Science and Technology of China, 2020.

[130] LIU Q, TIAN J W, TIAN Y, *et al*. Near-infrared-II Nanoparticles for Cancer Imaging of Immune Checkpoint Programmed Death-ligand 1 and Photodynamic/Immune Therapy[J]. *ACS Nano*, 2021, **15**(1): 515−525. DOI: 10.1021/acsnano.0c05317.

[131] YUAN Z T, FAN G H, WU H L, *et al*. Photodynamic Therapy Synergizes with PD-L1 Checkpoint Blockade for Immunotherapy of CRC by Multifunctional Nanoparticles[J]. *Mol Ther*, 2021, **29**(10): 2931−2948. DOI: 10.1016/j.ymthe.2021.05.017.

[132] XIONG W, QI L, JIANG N, *et al*. Metformin Liposome-mediated PD-L1 Downregulation for Amplifying the Photodynamic Immunotherapy Efficacy [J]. *ACS Appl Mater Interfaces*, 2021, **13**(7): 8026−8041. DOI: 10.1021/acsami.0c21743.

[133] GUO J C, AN Q, GUO M Y, *et al*. Oxygen-independent Free Radical Generation Mediated by Core-shell Magnetic Nanocomposites Synergizes with Immune Checkpoint Blockade for Effective Primary and Metastatic Tumor Treatment[J]. *Nano Today*, 2021, **36**: 101024. DOI: 10.1016/j.nantod.2020.101024.

[134] 左月月 . 可在体组装个性化疫苗的纳米载体用于黑色素瘤的光热-光动力联合免疫治疗[D]. 北京: 北京协和医学院, 2022. DOI: 10.27648/d.cnki.gzxhu.2022.000375.
ZUO Y Y. In Vivo Self-assembled Personalized Tumor Vaccine for Effective Photothermal-photodynamic Therapy Combined with Immunotherapy Against Melanoma[D]. Beijing: Peking Union Medical College, 2022.

[135] TONG Q L, XU J J, WU A H, *et al*. Pheophorbide A-mediated Photodynamic Therapy Potentiates Checkpoint Blockade Therapy of Tumor with Low PD-L1 Expression[J]. *Pharmaceutics*, 2022, **14**(11): 2513. DOI: 10.3390/pharmaceutics14112513.

[136] WU Q H, CHEN Y, LI Q, *et al*. Time Rules the Efficacy of Immune Checkpoint Inhibitors in Photodynamic Therapy[J]. *Adv Sci*, 2022, **9**(21): e2200999. DOI: 10.1002/advs.202200999.