细胞膜包覆的纳米药物在肿瘤治疗中的研究进展

陈 宁[1], 韩丽飞[2], 胡浩霖[2*], 秦永林[3*]

(1. 东南大学医学院, 江苏 南京 210009; 2. 东南大学附属中大医院乳腺中心, 江苏 南京 210009;
3. 东南大学附属中大医院介入与血管外科, 江苏 南京 210009)

摘要: 传统的化疗手段缺乏肿瘤靶向性, 且会造成明显的全身毒副反应。纳米药物递送系统开启了癌症精准治疗的新篇章, 由于肿瘤内血管异常造成的增强渗透滞留效应, 纳米药物被动地靶向肿瘤组织。然而, 大多数纳米颗粒被单核吞噬系统迅速清除, 限制了其抗肿瘤疗效。近年来, 细胞膜纳米药物 (cell membrane-coated nanoparticles, CNPs) 在肿瘤治疗方面展现出广阔的应用潜力。CNPs是被细胞膜包裹的纳米药物颗粒, 不仅具有良好的生物相容性, 还能保留原细胞膜的生物特性: 红细胞膜CNPs能延长药物体内循环时间; 血小板膜CNPs、免疫细胞膜CNPs、干细胞膜CNPs均表现出趋向肿瘤的能力, 免疫细胞膜CNPs还能调节抗肿瘤免疫; 肿瘤细胞膜CNPs因其良好的同源靶向性得到广泛研究。本文概述了CNPs的构建过程, 分别介绍了基于各类细胞膜的CNPs在肿瘤治疗中的作用, 并讨论了其未来应用前景和挑战。

关键词: 细胞膜; 纳米材料; 药物递送系统; 肿瘤靶向; 肿瘤治疗

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Research progress of cell membrane-coated nanoparticles in tumor therapy

CHEN Ning[1], HAN Li-fei[2], HU Hao-lin[2*], QIN Yong-lin[3*]

(*1. School of Medical, Southeast University, Nanjing 210009, China; 2. Breast Center, Zhongda Hospital, Southeast University, Nanjing 210009, China; 3. Intervention and Vascular Surgery, Zhongda Hospital, Southeast University, Nanjing 210009, China*)

Abstract: Traditional chemotherapy methods lack tumor targeting and cause obvious systemic adverse reactions. The development of nano-drug particles delivery systems has ushered in a new chapter in precision tumor treatment. Due to the enhanced permeability and retention (EPR) effect caused by anomalous tumor blood vessels, nanoparticles can passively target tumor tissues. However, most nanoparticles are rapidly cleared by the mononuclear phagocytic system, limiting their anti-tumor efficacy. In recent years, cell membrane-coated nanoparticles (CNPs) have shown great potential for application in tumor therapy. CNPs are nano-drug particles wrapped by cell membranes, which can not only exhibit excellent biocompatibility, but also retain some of the biological characteristics of the original cell membrane. CNPs from erythrocyte can extend the blood circulation duration of drugs. CNPs from platelet, CNPs from immunocyte, and CNPs from stem cell all demonstrate a tumor-targeting capability, CNPs from immunocyte can also regulate anti-tumor immunity. CNPs from tumor cell have been extensively researched for their excellent homogenous targeting properties. In this review, we outline the construction process of CNPs, and introduce the roles of CNPs based on various cell membranes in tumor therapy,

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*通讯作者 Tel: 13815882715, E-mail: huhaolin1234@163.com;
Tel: 18061713626, E-mail: qinyl200801@139.com
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and discuss their future application prospects and challenges.

Key words: cell membrane; nanomaterial; drug delivery system; tumor targeting; tumor therapy

恶性肿瘤是21世纪威胁人类健康的重要公共卫生议题。据统计, 2022年新增癌症病例近2 000万例, 癌症死亡人数达970万例[1]。传统的癌症治疗方法包括放疗、手术和化疗等, 近年来一些新型疗法如基因治疗、免疫治疗、光动力治疗等不断发展, 丰富了癌症治疗的手段[2]。尽管如此, 化疗仍然是治疗中晚期癌症的主要方法[3]。大多数化疗药物通过静脉或口服给药, 肿瘤靶向性差, 药物利用率低, 可造成恶心呕吐、贫血、免疫抑制等一系列不良反应[4]。因此, 研究安全、高效、靶向的药物递送方式对于提高化疗疗效具有重要意义。

近年来, 纳米药物递送系统的发展开启了癌症精准治疗的新篇章[5,6]。多种纳米药物载体已被应用于肿瘤治疗, 包括脂质体、聚合物胶束、聚合物囊泡、水凝胶和无机纳米颗粒等[7,8]。由于肿瘤微环境中存在血管渗漏和淋巴引流不畅, 某些尺寸的纳米颗粒更容易渗透进入肿瘤组织并长时间停留, 即增强渗透滞留(enhanced permeability and retention, EPR)效应。EPR效应是纳米药物被动靶向肿瘤组织的有效基础[9,10], 然而肿瘤间质液压力较高、细胞外基质致密以及肿瘤相关巨噬细胞的脱靶摄取使得EPR效应表现不稳定, 严重影响纳米药物的临床转化和应用[11,12]。

目前的主流研究方向是通过表面修饰来调节纳米粒的体内命运。传统表面改性的标准技术是聚乙二醇(polyethylene glycol, PEG)涂层, 可以抑制纳米颗粒非特异性聚集并减少调理素的吸附, 从而延长纳米药物体内血液循环时间[13]。然而, 在许多实验动物和人体中都发现了抗PEG抗体, 包括未接受过PEG化药物治疗的个体[14]。据报道, 72%的当代人血清样本中发现了抗PEG抗体, 其中18%为IgG, 25%为IgM, 30%为IgG和IgM[15]。这可能是由于暴露于环境中的PEG添加剂所致, 例如化妆品、加工食品和非处方药品[16]。抗PEG抗体与PEG化纳米药物结合后易导致补体激活, 引起体内过敏和清除加速[17,18]。

仿生的细胞膜纳米药物(cell membrane-coated nanoparticles, CNPs)弥补了上述缺陷。CNPs是利用天然细胞膜包裹的纳米药物颗粒, 实现纳米药物的表面改性[19]。Hu等[20]率先提取小鼠红细胞膜用以包裹聚乳酸–羟基乙酸(poly lactic-co-glycolic acid, PLGA)纳米颗粒(RBC-PLGA), 体内实验结果显示, RBC-PLGA的血浆半衰期较PEG-PLGA增加了150% (72 h), 证明了细胞膜涂层用于纳米颗粒表面改性较PEG表现出优势。CNPs具有良好的生物相容性和稳定性, 能显著延长纳米颗粒的血液循环时间。此外, CNPs能够保留原细胞膜的生物特性, 赋予纳米颗粒相应的生物功能, 除EPR效应外, 能通过膜表面的生物分子实现主动靶向[21], 在癌症治疗方面具有广阔前景。

1　细胞膜纳米药物的构建

CNPs是由细胞膜涂层、纳米药物载体和有效药物载荷组成(图1A)。制备过程常包括以下3个步骤: 细胞膜的提取、纳米药物的制备和CNPs的组装[22]。提取细胞膜的方法主要取决于细胞是否有细胞核。无核细胞可以用低渗法[23]或反复冻融法[24]将细胞裂解, 然后通过离心将细胞膜碎片分离出来。对于有核细胞, 除了低渗处理外, 还需要通过超声、均质等机械作用进一步破坏细胞结构, 再通过高速差速离心将细胞膜从含有细胞核和细胞器的混合物中分离出来[25,26]。

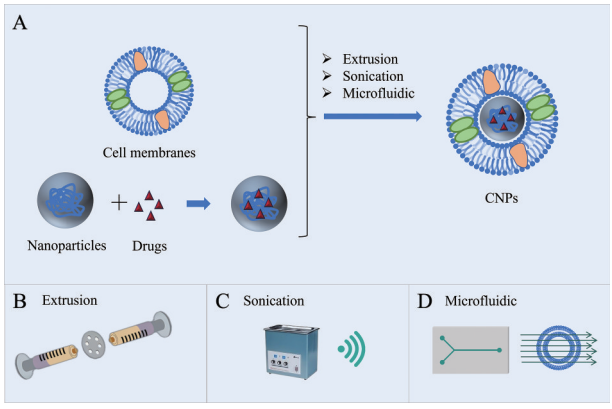


Figure 1　Composition and construction of CNPs. A: Fabrication of CNPs; B: Extrusion; C: Sonication; D: Microfluidic. CNPs: Cell membrane-coated nanoparticles

用细胞膜包覆纳米颗粒核心的方法有多种, 例如: 机械挤出、超声处理、微流控技术等。机械挤出法是将细胞膜囊泡和纳米颗粒核心通过聚碳酸酯膜反复挤出(图1B), 难以大规模制备[27]; 超声处理法是将细胞膜与纳米颗粒核心共孵育后利用超声波能量将组件组装成核壳结构(图1C), 与机械挤出法相比材料损失较少, 但是该方法可能会对纳米颗粒核心的结构造成一定的破坏[28]; 微流控技术是利用2个电极之间的电脉冲促进纳米颗粒核心进入细胞膜囊泡(图1D), 能获得包覆率更高、性质更均一的载药颗粒[29]。

2 CNPs在肿瘤治疗中的作用

将CNPs应用于肿瘤治疗已成为当前研究热点，不同类型的细胞膜涂层具有不同的功能[30]。本文选取目前研究较多的红细胞膜、血小板膜、免疫细胞膜、干细胞膜、肿瘤细胞膜及混合细胞膜进行阐述 (表1[20,31-56])。

2.1 红细胞膜 红细胞是体内含量最丰富的血细胞，寿命长达120天。由于红细胞缺乏细胞核和大多数细胞器，红细胞膜的提取程序比有核细胞更简单。此外，红细胞表面的整合素相关蛋白即CD47可与抑制性受体信号调节蛋白α (SIRPα) 连接，导致巨噬细胞对表达CD47细胞的吞噬作用减弱，从而减少免疫消除[57]。因此，利用红细胞膜包覆药物能明显降低其免疫原性、延长其体内循环时间。Su等[31]用红细胞膜包覆负载紫杉醇 (paclitaxel, PTX) 的聚合物核心 (RBC-NPs)，其血液循环时间明显延长，消除半衰期为32.8 h，比NPs组高5.8倍，并观察到该RBC-NPs能通过EPR效应在肿瘤组织中蓄积。

红细胞膜药物递送系统靶向肿瘤的作用较弱，可以通过脂质插入的方法进一步修饰，促进红细胞膜包覆的纳米颗粒趋化至疾病部位[58]。Wang等[32]用叶酸 (folic acid, FA) 修饰红细胞膜，使其靶向过度表达FA受体的癌细胞系。该研究以多柔比星 (doxorubicin, DOX) 为模型药物，结果表明，与DOX组相比，用FA修饰的红细胞膜包覆药物可以大大延长体内药物循环时间并提高肿瘤组织中积累的药物浓度，从而增强化疗药物的抗肿瘤效果并降低药物相关毒性。

表面修饰还可以促进红细胞膜包覆的纳米颗粒穿过生理屏障。研究表明，将血管肽素-2修饰到红细胞膜表面可以通过克服生物屏障来增强化疗，该类纳米药物在三维肿瘤球模型和体内都具有优越的跨越生物屏障的能力[33]。将药物递送穿过血脑屏障也是研究热

Table 1 Various CNPs used in tumor therapy and their functions. MSC: Mesenchymal stem cell; MDSC: Myeloid-derived suppressor cell; NK cell: Natural killer cell; PTX: Paclitaxel; DOX: Doxorubicin; VCR: Vincristine; ICG: Indocyanine green; TRAIL: Tumor necrosis factor related apoptosis inducing ligand; CFZ: Carfilzomib; TPZ: Tirapazamine; CA4: Combretastatin A4; Apa: Apatinib; IL-2: Interleukin-2; Cur: Curcumin; PLGA: Poly lactic-co-glycolic acid; TPP: Triphenylphosphine; MOF: Metal organic framework; MSNs: Mesoporous silica nanoparticles; CTC: Circulating tumor cell

Cell membrane	Payload	Core nanoparticle	Function	Ref
Erythrocyte	/	PLGA	Good biocompatility; long circulation	[20]
	PTX	PCL	Good biocompatility; long circulation	[31]
Modified erythrocyte	DOX	/	Specific tumor-targeting	[32]
	DOX	/	Deep penetration	[33]
	VCR	SLNs	Specific tumor-targeting; deep penetration	[34]
	DACHPt, ICG	aBSA NCs	Specific tumor-targeting; deep penetration	[35]
Platelet	TRAIL	Si particles	Good biocompatility; efficacious CTC-targeting	[36]
	TRAIL, DOX	NV	Good biocompatility; efficacious CTC-targeting	[37]
	R848	PLA	Good biocompatility; effective tumor-targeting	[38]
	siRNA	MOF	Good stability; effective tumor-targeting	[39]
	TPZ, DMXAA	SiO_2 NPs (MSNs)	Targetting vascular disruption	[40]
	CA4, Apa	SiO_2 NPs (MSNs)	Targetting vascular disruption	[41]
Immunocyte				
T lymphocyte	PTX	PLGA	Effective tumor-targeting	[42]
MDSC	/	Fe_3O_4 NPs	Low immunogenicity; effective tumor-targeting	[43]
Macrophage	Emtansine	Liposome	Efficacious CTC-targeting	[44]
	TGF-β inhibitor, PD-1 antibody	Fe_3O_4 NPs	Long circulation; enhanced antitumor immunity	[45]
Neutrophil granulocyte	CFZ	PLGA	Efficacious CTC-targeting	[46]
	/	PLGA	Improved immune microenvironment; enhanced antitumor immunity	[47]
NK cell	TCPP	mPEG-PLGA	Effective tumor-targeting; enhanced antitumor immunity	[48]
Stem cell				
MSC	DOX	PLGA	Effective tumor-targeting	[49]
	DOX, siRNA	PDA	Good stability; effective tumor-targeting	[50]
Modified MSC	PTX	$HMnO_2$	Effective tumor-targeting; potential antitumor immunity	[51]
Tumor cell				
HepG2 cell	DOX	PLGA	Homologous tumor-targeting ability	[52]
TE10 cell	DOX, Cur	PLGA	Homologous tumor-targeting ability	[53]
4T1 cell	PTX, IL-2	PHF, PEI-DMMA	Homologous tumor-targeting ability	[54]
	R837	TPP-nMOF	Homologous tumor-targeting ability; promoted tumor-antigen presentation; activated antitumor immunity	[55]
AML cell	CpG-1826	PLGA	Promoted tumor-antigen presentation; activated antitumor immunity	[56]

点之一, Fu等[34]用T7肽和NGR肽修饰的红细胞膜包覆长春新碱 (vincristine, VCR) 纳米颗粒, 使其穿过体外的血脑屏障和血脑肿瘤屏障, 在小鼠脑神经胶质瘤中表现出较高的药物蓄积量, 显著提高了长春新碱抗神经胶质瘤的功效。

除了化疗以外, 基于红细胞膜的CNPs也被应用于肿瘤的光热治疗。Liu等[35]将光敏剂吲哚菁绿 (indocyanine green, ICG) 封装于阴离子牛血清白蛋白纳米簇 (aBSA NCs) 中, 然后将铂类药物DACHPt与之结合得到DACHPt@ICG@aBSA NCs。最后, 将DACHPt@ICG@aBSA NCs进一步用红细胞膜包覆, 并通过脂质插入的方式引入肿瘤靶向肽cRGD得到R-RBC@BPtI。R-RBC@BPtI显示出良好的稳定性和高包封率, 且能促进肿瘤靶向摄取。在近红外激光刺激下, R-RBC@BPtI通过单线态氧和光热效应破坏红细胞膜, 引发有效的药物释放, 实现铂类药物和活性氧在肿瘤部位的深度渗透和聚集。该研究为肿瘤的化疗–光疗联合提供了一种新型仿生纳米平台策略。

2.2　血小板膜　血小板是骨髓巨核细胞胞质裂解脱落下来的细胞碎片, 可通过活化、聚集、黏附等反应参与凝血过程, 在止血、维持血管完整性等生理过程, 以及血栓形成、动脉粥样硬化等病理过程中发挥关键作用[59]。此外, 血小板还参与肿瘤转移过程, 是肿瘤转移微环境中的重要成员。一方面, 肿瘤细胞能通过诱导血小板活化和聚集来调节血小板功能; 另一方面, 血小板能够通过激活内皮细胞功能和募集免疫细胞来促进肿瘤细胞的播散[60]。因此, 基于血小板膜的CNPs或可成为肿瘤治疗中的一种新策略。

血小板能够识别循环肿瘤细胞 (circulating tumor cells, CTCs) 表达的血小板组织因子III/CD142, 进而通过GPIIb-IIIa-纤维蛋白原桥和P-选择蛋白附着在CTCs的表面[61]。因此可将血小板膜纳米药物用于靶向CTCs[36]。Hu等[37]设计了一种装载肿瘤坏死因子相关凋亡诱导配体 (tumor necrosis factor related apoptosis inducing ligand, TRAIL) 和DOX的血小板膜涂层的核壳纳米药物递送系统 (TRAIL-DOX-PM-NV), 利用血小板膜上过表达的P-选择素特异性地结合癌细胞表面上调的CD44受体实现主动靶向肿瘤部位的抗癌药物递送。在裸鼠乳腺癌肺转移模型中, 与TRAIL-DOX-NV相比, 用TRAIL-DOX-PM-NV治疗的小鼠肺中转移性癌结节的数量明显减少, 这表明TRAIL-DOX-PM-NV可有效消除血液中的CTCs。

由于良好的肿瘤靶向性, 血小板膜纳米药物在免疫治疗、基因治疗等方面也具有良好的表现。Bahmani等[38]利用血小板膜包被的纳米颗粒局部递送Toll样受体激动剂R848 (PNP-R848), 并用肿瘤内给药的方式评价其疗效。结果显示, 血小板膜能促进PNP-R848与肿瘤微环境中各种细胞相互作用, 提高R848在肿瘤部位和周围淋巴组织的生物利用度。在小鼠结直肠腺癌模型中, 观察到PNP-R848能促进引流淋巴结内抗原呈递细胞 (antigen-presenting cells, APC) 的强烈活化并增加免疫浸润。此外, Zhuang等[39]利用血小板膜靶向递送小干扰RNA (siRNA) 来沉默肿瘤相关基因。该纳米粒子 (P-MOF-siRNA) 的多孔金属有机骨架结构 (metal organic framework, MOF) 及血小板膜涂层能有效减少内源性核糖核酸酶对siRNA的降解, 并表现出一定的肿瘤靶向, P-MOF-siRNA处理可使目标基因的mRNA水平降低约80%。在小鼠乳腺癌模型中, 未经治疗的小鼠的中位生存期为50天, 而P-MOF-siRNA治疗将该值延长至92天。

血管破裂的过程往往伴随着血小板募集, 将肿瘤血管破坏剂用血小板膜伪装可提高药物递送效率。利用血管破坏和血小板模拟生物趋化之间的相互反馈, Zhang等[40]用血小板膜包被负载缺氧激活前药替拉帕明 (tirapazamine, TPZ) 和血管破坏剂DMXAA的介孔二氧化硅纳米粒子 (mesoporous silica nanoparticles, MSNs), 进入肿瘤后, 该纳米治疗剂可以破坏局部血管以抑制肿瘤, 并且表现出类似血小板的出血趋化功能被持续招募。依靠这种积极的相互反馈, 该纳米粒子能够通过多重生物效应协同发挥抗肿瘤作用。Li等[41]构建了以血小板膜为涂层的MSNs, 共装载肿瘤血管破坏剂考布他汀A4 (combretastatin A4, CA4) 和抗血管生成剂阿帕替尼 (apatinib, Apa)。该纳米粒子通过血小板膜表面对受损血管部位的靶向黏附在肿瘤组织中积累, 在动物实体瘤模型中发挥血管破坏功能和抗血管生成功能, 表现出有效的抗肿瘤效应。

2.3　免疫细胞膜　免疫细胞是人体防御系统的重要组成部分, 它们的主要作用包括: 清除死亡细胞和体内代谢废物、产生抗体和细胞因子以调节免疫反应、识别和杀灭外来病原体和肿瘤细胞等等。免疫细胞参与肿瘤进展, 同时肿瘤细胞产生各种细胞因子和趋化因子有募集免疫细胞的作用, 使免疫细胞具有靶向肿瘤的能力[62]。某些免疫细胞如T细胞、巨噬细胞、中性粒细胞和树突状细胞的细胞膜已被广泛用于制造仿生纳米颗粒[63]。一方面, 免疫细胞膜可利用自我识别机制来减少吞噬细胞的摄取; 另一方面, 其天然表面配体可选择性地与疾病部位的受体结合[64]。基于免疫细胞膜的CNPs能够有效地输送药物, 在肿瘤的治疗中表现出一定的优势[65]。

利用免疫细胞表面的黏附分子可以靶向肿瘤组

织递送抗癌药物。Zhang等[42]构建了T淋巴细胞膜包裹的PLGA纳米粒 (T-lymphocyte membrane-coated nanoparticles, TNPs) 并负载PTX, 免疫荧光结果显示, TNPs在肿瘤部位的积累比PLGA纳米颗粒更具特异性。该研究还发现用低剂量的X射线照射肿瘤部位可增强肿瘤血管上细胞间黏附分子1的表达, 使更多的TNPs积聚以产生更好的抗肿瘤效果。另一个例子是髓系抑制细胞 (myeloid-derived suppressor cell, MDSC), 该类细胞对肿瘤具有高亲和力。Yu等[43]将MDSC的膜涂覆到氧化铁磁性纳米粒子上 (MNP@MDSC), 结果显示, MNP@MDSC在肿瘤部位的积累量比MNP@RBC和MNP更多, 有效的肿瘤靶向性可进一步促进巨噬细胞的激活和$CD8^+$ T淋巴细胞的浸润, 加强抗肿瘤免疫。

免疫细胞膜药物递送系统还具有一定的抗肿瘤转移能力。在乳腺癌肺转移模型中, 巨噬细胞可以通过自身表面的$\alpha4\beta1$整合素与癌细胞表面的血管细胞黏附分子-1相互作用, 主动与转移性癌细胞结合[66]。因此, Cao等[44]制备了用巨噬细胞膜包覆的美坦新脂质体 (macrophage membrane-coated emtansine liposome, MEL), 多模态成像结果显示, 美坦新脂质体很少到达肺转移部位, 而MEL的红色荧光信号大量与肺转移结节的生物发光信号相结合, 表明MEL对肺转移具有特异性和有效的靶向性。用抗体阻断MEL中$\alpha4\beta1$整合素后, 荧光信号几乎不与生物发光信号共定位, 表明MEL对肺转移的靶向性可能是由$\alpha4\beta1$整合素介导的。此外, 活化的中性粒细胞与CTCs通过粒细胞集落刺激因子介导的途径被募集到肿瘤转移前微环境[67], 二者在肿瘤转移的多个步骤中相互作用[68]。因此, Kang等[46]开发了一种保留中性粒细胞膜相关蛋白的生物结合特性的纳米颗粒 (NM-NPs), NM-NPs在体外与4T1乳腺癌细胞的结合率较裸NPs更高, 利用体内流式细胞术观察到了NM-NPs可以更有效地捕获CTCs。负载第二代蛋白酶体抑制剂卡非佐米 (carfilzomib, CFZ) 后进行细胞毒性实验, 结果显示, NM-NPs-CFZ组早期凋亡的4T1细胞比例 (23.0 ± 3.2)%显著高于NPs-CFZ组 (1.88 ± 0.30)%和游离CFZ组 (1.58 ± 0.27)%。在小鼠乳腺癌肺转移模型中, 接受NM-NPs-CFZ治疗的小鼠肺部转移沉积物的含量最少。上述研究表明, 基于免疫细胞膜的CNPs为防治肿瘤转移提供了新的研究思路。

免疫CNPs在肿瘤免疫治疗中具有天然优势。该类CNPs可通过模仿免疫细胞与肿瘤的相互作用来提高抗癌免疫力。Deng等[48]使用自然杀伤 (natural killer, NK) 细胞膜包覆载有光敏剂TCPP的mPEG-PLGA纳米颗粒 (NK-NPs), 对NK细胞膜进行蛋白质组学分析, 发现NK-NPs的NK细胞膜涂层能够靶向肿瘤组织并可诱导促炎性M1巨噬细胞极化的以产生抗肿瘤效应。此外, 可将外源性蛋白添加到免疫细胞膜上用于肿瘤免疫治疗。Zhang等[45]将PD-1抗体锚定于小鼠巨噬细胞膜表面, 并用超声法使TGF-β抑制剂装载于膜内, 将修饰的巨噬细胞膜涂覆到Fe_3O_4磁芯上。该纳米颗粒可以长时间循环, 并通过PD-1抗体与肿瘤基质细胞中高表达的PD-1受体结合来靶向肿瘤。PD-1抗体和TGF-β抑制剂能够使$CD4^+$ T细胞和$CD8^+$ T细胞的比例增加并诱导M1巨噬细胞的极化, 从而改善肿瘤微环境的免疫原性。某些免疫细胞还具有中和细胞因子和趋化因子的能力, 能够逆转肿瘤微环境中的免疫抑制。Li等[47]的研究表明, 中性粒细胞−NPs能够在体内中和粒细胞−巨噬细胞集落刺激因子和趋化因子配体2, 抑制了MDSC的生成、扩增和肿瘤向性迁移, 而MDSC原本会建立免疫抑制性肿瘤微环境。在皮下携带B16F10肿瘤的小鼠中, 该中性粒细胞−NPs可抑制MDSC的迁移, 促进T淋巴细胞的活化, 并增强免疫检查点阻断法的抗癌功效。

2.4 干细胞膜 干细胞是一类具有无限的或永生的自我更新能力的细胞, 能够产生至少一种类型的、高度分化的子代细胞。其中, 间充质干细胞 (mesenchymal stem cell, MSC) 已经表现出对肿瘤微环境的趋向性[69]。肿瘤细胞和肿瘤相关基质细胞可产生多种趋化因子, 包括血小板衍生的生长因子、基质细胞衍生因子-1和血管内皮生长因子等, 这些因子可吸引MSC迁移[70]。被MSC膜伪装的纳米粒子能够靶向迁移至肿瘤部位, 同时MSC膜表面蛋白的免疫伪装性提高了纳米粒子的生物相容性。

MSC可从各种人体组织中分离出来, 骨髓是临床上最广泛认可的MSC来源, 但骨髓采集的侵入性程序限制了骨髓MSC的应用。脐带血通常被当作医疗废物丢弃, 是MSC的理想的来源[71]。Yang等[49]利用脐带来源MSC膜包覆载DOX的PLGA纳米颗粒 (PM-NP-DOX) 用于肿瘤靶向化疗药物的递送, 以脂质体包覆的纳米颗粒 (Lipo-NP-DOX) 为对照, 体内实验结果表明, 尾静脉注射20 h后肿瘤中的PM-NP-DOX的荧光强度比Lipo-NP-DOX高出约2倍, 表明PM-NP-DOX除了具有EPR效应相关的被动靶向作用外, 还表现出主动靶向肿瘤的特性。同时, Lipo-NP-DOX和PM-NP-DOX的抑瘤率分别为32.8%和78.2%, 表明PM-NP-DOX能通过有效的肿瘤靶向药物递送来抑制肿瘤的快速生长。研究首次证明了脐带MSC膜在功能化合成纳米材料方面的潜力。

此外, 基因治疗、免疫治疗等与化疗相结合也是实

体肿瘤研究的热点之一。Mu等[50]开发了MSC膜包裹PDA纳米粒子作为一种有效的肿瘤靶向递送平台(PDA-DOX/siRNA@SCM NPs), 其负载的DOX和PD-L1 siRNA用于前列腺癌骨转移的化学免疫治疗。制备的PDA-DOX/siRNA@SCM NPs在体内和体外表现出显著的稳定性和肿瘤靶向能力, MSC膜不仅降低了DOX的毒性, 而且提高了PD-L1 siRNA基因沉默的效率, 对前列腺癌骨转移产生更好的协同治疗效果。

通过脂质插入的方式也能对MSC膜进行修饰。Xie等[51]用MSC膜包裹空心二氧化锰 ($HMnO_2$) 纳米粒子并用TAT肽修饰, 负载化疗药物PTX, 构建了高性能的核靶向药物递送系统 ($HMnO_2$-MSC-TAT@PTX), 用于非小细胞肺癌的系统治疗。研究发现, 完整的MSC膜表面蛋白赋予$HMnO_2$-MSC-TAT@PTX肿瘤归巢特性, 而TAT肽促进了核定位, 因此, $HMnO_2$-MSC-TAT@PTX在体外和体内均能有效靶向A549肿瘤细胞。此外, $HMnO_2$-MSC-TAT@PTX在血清和肿瘤中还诱导了高水平的干扰素-β、肿瘤坏死因子-α和白介素6, 这表明其在抗肿瘤免疫中或可发挥作用。

2.5　肿瘤细胞膜　肿瘤细胞在体外有较强的增殖能力, 能够通过体外多重培养大量收集, 是细胞膜药物载体的重要来源[72]。肿瘤细胞膜表面携带着肿瘤转移、侵袭等各阶段细胞黏附分子, 如钙黏蛋白、整合素、选择素和免疫球蛋白等[73]。因此, 经肿瘤细胞膜包裹的纳米粒子具有免疫逃逸的能力和良好的同源靶向性[74], 在肿瘤治疗领域得到了广泛的研究。

DOX是临床上常用的化疗药物, Xu等[52]用HepG2肝癌细胞膜包覆装载DOX的PLGA纳米粒子 (CCM-NPs-DOX), 与NPs-DOX相比, CCM-NPs-DOX明显提高了HepG2肝癌细胞对DOX的内吞作用, 在体外和体内实验中表现出满意的抗肿瘤疗效。在另一项研究中, Gao等[53]开发了一种同源肿瘤细胞膜 (TE10细胞膜)修饰的CNPs用于克服食管癌的多药耐药性。其中, 纳米颗粒核心由共载DOX和姜黄素 (curcumin, Cur) 的PLGA纳米颗粒 (NPs) 组成。通过高剂量诱导建立DOX耐药食管癌细胞模型TE10/DOX。结果表明, 该纳米药物可直接靶向TE10细胞、TE10/DOX细胞或TE10/DOX移植瘤, 在体外、体内实验中均表现出良好的肿瘤靶向性和抑瘤效果, 且具有较高的生物安全性。PTX也被探索与CCM-NPs相结合, Shang等[54]设计了一种肿瘤细胞膜包覆的pH响应型纳米凝胶 (NG@M), 共同递送化疗药物PTX和免疫治疗剂白细胞介素2 (interleukin-2, IL-2), 用于三阴性乳腺癌的联合治疗。NG@M在同源肿瘤中的蓄积量是用异源肿瘤细胞膜包被的4.59倍。此外, NG@M具有良好的稳定性和生物相容性, 能响应酸性肿瘤微环境实现药物控释, 快速释放的PTX和IL-2能促进树突状细胞的成熟, 迅速激活原位抗肿瘤免疫反应。在4T1乳腺癌小鼠肺转移模型中, NG@M通过联合化学免疫治疗高效地在肺部实现了肿瘤转移抑制, 并延长了中位生存期 (39天)。

近年来, 肿瘤免疫治疗的策略不断丰富, 除了免疫检查点阻断疗法、细胞因子疗法、工程化嵌合抗原受体T细胞 (chimeric antigen receptor T-cell, CAR-T) 疗法等以外, 肿瘤疫苗也是研究热点之一[75]。肿瘤疫苗可以通过将肿瘤相关抗原或肿瘤特异性抗原与免疫佐剂一起递送到APC中来激活肿瘤特异性免疫反应, 引发强大的抗肿瘤免疫力[76]。为了提高肿瘤疫苗的疗效, 同时尽量减少其对正常组织的不良反应, 各类仿生纳米疫苗递送系统也在被研究中[77]。肿瘤细胞膜表面富含大量潜在的肿瘤抗原, 可以诱发针对广泛肿瘤抗原的抗肿瘤免疫反应[78]。Luo等[56]开发了急性髓系白血病 (acute myeloid leukemia, AML) 细胞膜包被的纳米疫苗AMCNPs, 其PLGA纳米核心内包装了免疫刺激佐剂CpG-1826。体外实验结果表明, 该AMCNPs可被APCs有效获得, 增加共刺激信号表达, 并促进AML相关抗原呈递。在AML模型小鼠中, AMCNPs疫苗治疗组的存活率 (85%) 高于对照全细胞裂解液疫苗治疗组 (60%), 且AMCNPs疫苗能明显延长荷瘤小鼠的中位生存期 (4.4周)。Johnson等[55]设计用乳腺癌4T1细胞膜包覆三苯基膦 (triphenylphosphine, TPP) 修饰的纳米金属有机骨架 (metal organic framework, MOF) 来递送Toll样受体激动剂R837。体外实验结果显示, 该纳米粒子被同源肿瘤细胞内化后能有效地靶向线粒体, 在超声暴露的条件下诱导免疫原性细胞死亡 (immunogenic cell death, ICD), 从而促进肿瘤抗原呈递, 同时通过递送Toll样受体激动剂R837促进树突状细胞成熟。在体内, 该纳米粒子能与细胞毒性T淋巴相关抗原4抗体 (抗CTLA-4) 协同作用, 以逆转免疫抑制性肿瘤微环境 (tumor micro-environment, TME), 从而抑制肿瘤转移灶的进展并促进抗肿瘤免疫记忆的形成。

2.6　混合细胞膜　将多种细胞膜整合为杂化细胞膜可以结合各类细胞膜的特性并优化其功能, 为CNPs的构建提供更加灵活的设计思路 (表2[79-81])。

Dehaini等[79]尝试将混合血小板膜和红细胞膜用于包覆PLGA纳米颗粒 (RBC-P@NPs), 将红色荧光标记的红细胞膜与用绿色荧光的血小板膜充分混合后涂覆到PLGA上, 在共聚焦显微镜下可以观察到荧光信号的明显共定位, 并且蛋白质分析结果显示RBC-P@NPs可以同时呈现红细胞和血小板的特异性标志物。该研究体现了杂化细胞膜纳米粒子的应用潜力。

Table 2 CNPs from hybrid cells and their functions

Cell membrane	Payload	Core nanoparticle	Function	Ref.
Erythrocyte + platelet	−	PLGA	Long circulation; efficacious CTC-targeting	[79]
Erythrocyte + tumor cell	BLZ-945	DH	Good biocompatility; homologous tumor-targeting	[80]
Dendritic cell + tumor cell	CpG-ODN	PLGA	Activated antitumor immunity; homologous tumor-targeting	[81]

近年来, 杂化细胞膜纳米粒子的技术被不断丰富。Wang等[80]制备了一种红细胞膜−肿瘤细胞膜混合涂层的pH响应性葡聚糖共聚物胶束 (DH@ECm), 用于靶向递送集落刺激因子1受体 (colony stimulating factor 1 receptor, CSF-1R) 抑制剂BLZ-945。CSF-1R是维持肿瘤相关巨噬细胞 (tumor associated macrophages, TAM) 功能的信号之一, BLZ-945是一种高选择性CSF-1R抑制剂, 可以减少TAM的数量并促进$CD8^+$ T细胞的浸润。制备的DH@ECm具有适宜的粒径、良好的免疫伪装性和有效的肿瘤靶向性。在肿瘤酸性微环境中, DH@ECm具有pH响应特性, 可通过葡聚糖-CD206受体特异性相互作用促进TAM对DH@ECm的识别和摄取 (约为游离药物的3.9倍)。在体内的研究中, DH@ECm被证明提高$CD8^+$ T细胞的浸润, 逆转肿瘤免疫微环境, 产生有效的肿瘤免疫治疗 (抑瘤率: 64.5%)。Zhang等[81]制备了一种基于杂化细胞膜的纳米肿瘤疫苗 (FCM-NPs), 将树突状细胞膜和卵巢癌细胞膜混合涂覆在负载免疫佐剂CpG-ODN的PLGA纳米颗粒上。该FCM-NPs能够促进树突状细胞的成熟, 上调共刺激分子CD80/CD86的表达, 促进树突状细胞的淋巴结归巢。此外, 呈递该FCM-NPs兼具肿瘤细胞的免疫原性和树突状细胞的抗原能力, 可刺激幼稚T淋巴细胞产生大量肿瘤特异性的细胞毒性$CD8^+$ T淋巴细胞, 在体内外实验中均表现出较强的免疫激活作用, 为开发治疗卵巢癌的肿瘤疫苗提供了一种新思路。

3 展望与挑战

CNPs已成为癌症治疗的新型策略, 细胞膜涂层可以减少单核吞噬系统对纳米药物的吞噬, 降低其免疫原性, 促进其在肿瘤部位的富集[82]。此外, 细胞膜赋予纳米颗粒相应的生物功能, 红细胞膜纳米颗粒能明显降低药物的免疫原性、延长其体内循环时间, 通过表面修饰能进一步增强其肿瘤靶向性和穿过生理屏障的能力; 血小板膜纳米颗粒具有一定的靶向肿瘤组织和靶向循环肿瘤细胞的能力, 并能被肿瘤血管破坏所募集; 免疫细胞膜纳米颗粒可靶向肿瘤组织和循环肿瘤细胞, 并保留一定的免疫调节功能从而改善抗癌免疫力; 干细胞膜纳米颗粒也表现出对肿瘤微环境的趋向性和肿瘤靶向性; 肿瘤细胞膜纳米颗粒具有良好的同源靶向性, 且富含大量潜在的肿瘤抗原, 或可成为肿瘤疫苗的开发的新策略。将多种细胞膜整合为杂化细胞膜, 为CNPs的构建提供了更加灵活的设计思路。

然而, CNPs具有各自的限制与不足 (表3), 在实现临床应用方面仍面临一系列挑战。对于红细胞膜而言, 不同血型的红细胞膜是否会造成凝血反应还需要进一步的研究; 对于血小板膜、免疫细胞膜、干细胞膜而言, 必须大量培养细胞以获得足够的含量进行膜提取, 难以满足癌症治疗的要求, 血小板的致血栓风险、免疫反应的难以预测以及干细胞获取中的伦理问题进一步限制了其应用; 对于肿瘤细胞膜而言, 如果未完全去除亲代肿瘤细胞的遗传物质, 可能会导致肿瘤再发与扩散。因此, 有必要建立提取、纯化细胞膜的标准方案, 从而提高细胞膜涂层制备方法的可重现性[83]。为了保留膜蛋白的活性, 避免微生物的污染, CNPs的制备和存储需要低温和无菌, 对生产环境、制造设备、运输条件提出了较高的要求[84]。此外, 本综述中报道的研究主要在小鼠模型中测试, 而人类的体内反应更为复杂, 需要识别出具有真正特定功能的蛋白质, 应预先考察细胞膜成分和细胞内信号传导的变化, 以评估其在人体中的免疫原性。

在当前研究的基础上, 可以深入开展以下几个方

Table 3 Advantages and limitations of CNPs

Source cell	Advantage	Limitation	Ref.
Erythrocyte	Good biocompatility; long circulation; abundant sources	Passive tumor-targeting; interference from blood-types	[20,31-35]
Platelet	Good biocompatility; tumor and CTCs targeting; targeting vascular disruption	Difficulty in increasing production; risk of thrombosis	[36-41]
Immunocyte	Good biocompatility; tumor and CTCs targeting; improved immune microenvironment; enhanced antitumor immunity	Difficulty in increasing production; unpredictable immune response	[42-48]
Stem cell	Good biocompatility; effective tumor-targeting; potential antitumor immunity	Difficulty in increasing production; ethical issues	[49-51]
Tumor cell	Good biocompatility; homologous tumor-targeting ability; promoted tumor-antigen presentation; good proliferation ability *in vitro*	Risk of carcinogenicity; ethical issues	[52-56]

面的研究: 优化细胞膜的提取和纯化技术, 规范CNPs的制备方法和质量控制过程, 引入微流控技术以提高批次间一致性和减少制备过程的蛋白损失[85]; 完善CNPs的生物学基础研究, 阐明膜表面功能蛋白的具体作用及分子机制, 以实现纳米药物的精准改性; 发展新型细胞膜涂层并将其与多种肿瘤治疗手段 (如化疗、光热治疗、基因治疗等) 联合应用。随着生命科学技术的进步, 将会出现更多的创新研究来促进CNPs的性能优化和临床转化, 为肿瘤治疗提供新的思路。

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