红细胞膜伪装的仿生纳米递送系统在疾病治疗中的应用

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摘要: 纳米递送系统在精准治疗领域具有良好的应用前景, 但纳米材料在制备过程中存在体内循环时间较短, 易被机体内免疫系统识别、清除等问题。近年来为解决这些问题, 由天然细胞膜介导的仿生纳米递送系统已成为研究热点。天然膜仿生递送系统使用机体内源性细胞膜对纳米载体表面进行包覆修饰, 巧妙地将天然生物膜“自体”性质和“人工”功能载体的优势相融合, 赋予其肿瘤靶向性、低免疫原性和血液长循环等特点。目前仿生纳米递送系统已用于治疗恶性肿瘤、心血管疾病、细菌感染等多种疾病。本文对天然细胞膜伪装的仿生纳米递送系统的发展状况与当前的研究热点进行分析, 综述了近年来红细胞膜伪装的仿生纳米递送系统在疾病治疗领域的最新研究进展, 重点探讨基于红细胞膜伪装的仿生纳米递送系统在改善药物递送方面的优势作用, 未来发展前景及局限性, 以期为该系统的深入研究与开发提供参考。

关键词: 红细胞膜; 仿生; 纳米递送系统; 肿瘤

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Biomimetic nanoparticle delivery systems b ased on red blood cell membranes for disease treatment

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Abstract: Nanoparticle delivery systems have good application prospects in the field of precision therapy, but the preparation process of nanomaterial has problems such as short *in vivo* circulation time, easy recognition, and clearance by the immune system in the body. In recent years, biomimetic nanoparticle delivery systems mediated by natural cell membranes have become a research hotspot to address these issues. The natural membrane biomimetic nanoparticle delivery system cleverly integrates the advantages of natural biofilm "autologous" and "artificial" functional carriers by using endogenous cell membranes to modify the surface of nanocarriers, endowing them with characteristics such as tumor targeting, low immunogenicity, and long blood circulation. Currently, biomimetic nanoparticle delivery systems have been used in the treatment of malignant tumors, cardiovascular diseases, bacterial infections, and other diseases. This paper analyzes the development status and current research hotspots of natural cell membrane camouflaged biomimetic nanoparticle delivery systems mainly reviews the latest research progress of red blood cell membrane camouflaged biomimetic nanoparticle delivery systems in the field of disease treatment in recent years. It focuses on exploring the advantages, future development prospects, and limitations of biomimetic nanoparticle delivery systems based on red blood cell membrane camouflage in improving drug delivery, to provide a reference for the in-depth research and development of this system.

Key words: red blood cell membrane; biomimetic; nanoparticle delivery system; tumor

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纳米载药系统因具备有效防止药物被人体快速清除和显著降低药物细胞毒性等优势, 在医药领域得到广泛关注和应用[1]。然而纳米材料作为外来物质也存在易被免疫系统识别和清除, 并难以进入靶器官等问题。亲水性聚合物常被用来修饰纳米载体表面以增加其生物相容性, 例如经聚乙二醇 (polyethylene glycol, PEG) 修饰过的纳米载药系统可以有效通过单核吞噬细胞, 而减少吞噬作用并实现全身长循环。但是经大量研究发现表明, PEG修饰的纳米载药系统在多次给药后会刺激免疫系统, 最终导致后续给药的纳米载药系统易被免疫系统识别和吞噬[2-5]。因此, 在人工合成纳米颗粒表面利用天然细胞膜伪装构成仿生纳米递送系统成为目前新型药物递送系统的研究热点。该仿生纳米递送系统不仅保留了常规纳米药物递送系统能够增加药物溶解性、改变药物体内分布、降低不良反应发生率等优势, 同时还具有天然细胞膜优异的生物相容性和低免疫原性, 可有效地避免被免疫系统识别及清除, 使纳米载体能够在体内长效循环从而提高治疗效果。此外, 该系统还可以减少递送过程中的药物渗漏, 提高治疗有效性的作用[6]。

目前, 随着天然细胞膜仿生技术的发展, 血细胞膜、免疫细胞膜、干细胞膜、肿瘤细胞膜等多种机体内源性细胞膜已成功用于构建仿生纳米递送系统且效果较好。天然细胞膜仿生纳米给药系统的组成如图1所示。由于细胞膜表面复杂的抗原特性, 使不同类型的细胞膜能够赋予该系统多种功能, 从而实现多样化的体内生物学行为。例如, 白细胞膜包被的纳米载体具有炎症靶向性, 对肿瘤细胞有免疫应答响应, 能够靶向循环肿瘤细胞; NK细胞膜包被的纳米载体可获得肿瘤靶向性及诱导巨噬细胞向M1型极化从而产生抗肿瘤免疫力; 肿瘤细胞膜包被的纳米载体具有同源靶向性及免疫逃逸功能, 增强药物在肿瘤组织的聚集, 实现对肿瘤的精准治疗等[7-9]。其中, 红细胞膜 (red blood cell membrane, RBCM) 是首个成功用于包裹纳米载体的天然生物膜, 研究结果显示该系统兼具纳米载体的高载药能力和红细胞的长循环性能, 开启了使用天然生物膜提高纳米载体生物相容性的新思路[2,10]。

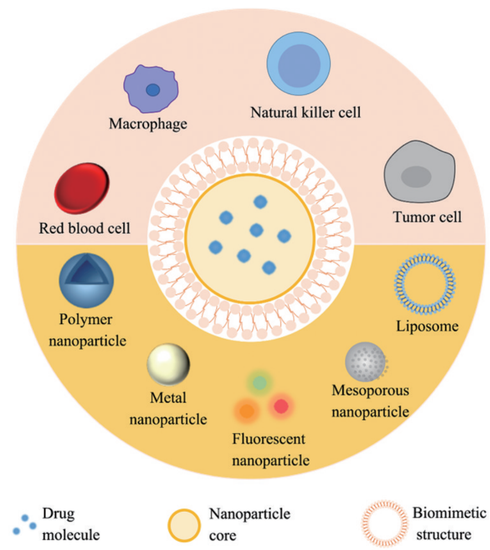

Figure 1 Composition of natural cell membrane bionic nanodelivery system

红细胞是血液中含量最丰富、循环寿命最长的细胞成分, 其在体内的循环时间长达100～120天, 能发挥运输和免疫功能, 具有悬浮稳定性、吸水性、可塑变形性等特性[11]。它可通过膜上表达的CD47蛋白对免疫细胞发出“不要吃我”的信号从而逃避网状内皮系统的清除, 因此红细胞膜具有良好的内在生物相容性和非免疫原性, 可用于延长纳米颗粒的循环时间[12]。并且由于成熟红细胞内容物少, 容易实现膜分离, 红细胞膜被视为一种理想的膜修饰材料。红细胞膜生物仿生纳米给药系统的应用如图2所示。

目前, 制备红细胞膜包被纳米载体的方法可以归纳总结为3个关键步骤: 膜提取、内核纳米载体制备和膜与纳米载体融合。成熟红细胞没有细胞核, 因此可以直接从全血样本中分离提取得到细胞膜。内核纳米

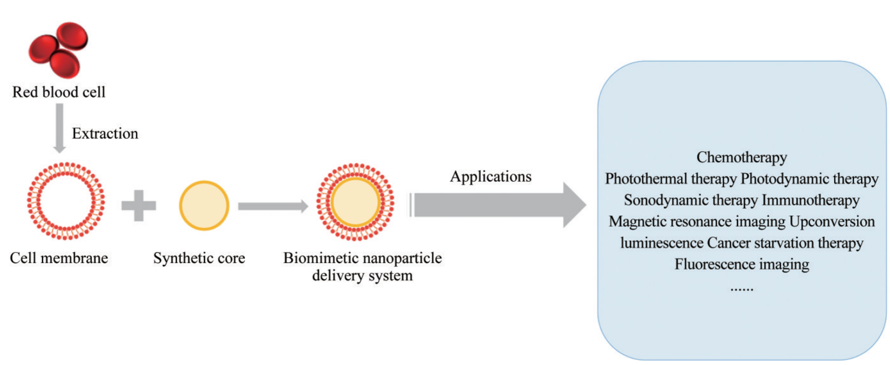

Figure 2 Construction and application of biomimetic nanodelivery system for erythrocyte membrane

载体的制备通常需要使用几种材料, 如聚乳酸–羟基乙酸共聚物酸、聚乳酸和聚己内酯等FDA批准的聚合物, 无机聚合物 (黑磷等), 以及金等金属[13]。在此基础上, 通过薄膜挤压法、超声融合法和电穿孔法等方法将红细胞膜和内核纳米载体结合。薄膜挤压技术通过挤压装置与纳米级聚碳酸酯多孔膜多次挤压, 利用机械力实现纳米材料与细胞膜的融合。尽管该方法操作简便, 但不适合大规模生产。超声波融合法是将二者共孵育后, 使用超声波促进包覆过程, 然而这种方法制备出的载体颗粒一致性较差。微流控电穿孔法将载体各组分在Y形通道中完全混合, 通过电穿孔制备出性质稳定、包覆率高的纳米载体[14]。

在制备完成后, 通常需要进行理化性质的表征, 常用的方法包括扫描电子显微镜 (scanning electron microscope, SEM)、透射电子显微镜 (transmission electron microscope, TEM) 和动态光散射 (dynamic light scattering, DLS) 分析, 这些技术可以研究和比较其形态、尺寸和表面电荷。同时, 还需要通过十二烷基硫酸钠–聚丙烯酰胺凝胶电泳 (sodium dodecyl sulfate polyacrylamide gel electrophoresis, SDS-Page) 和蛋白免疫印迹 (Western blot) 等生化方法来检测特定膜蛋白标志物, 以验证其功能[13]。

本文探究了基于天然细胞膜伪装的仿生纳米递送系统的发展进程, 了解该领域发展前沿及目前的研究热点。总结了近几年基于红细胞膜伪装的仿生纳米递送系统 (RBCM-NPs) 在疾病治疗中的应用, 重点探讨基于红细胞膜伪装的仿生纳米递送系统在改善药物递送方面的重要作用, 未来发展前景及局限性, 以期为该系统的深入研究与开发提供参考。

1 RBCM-NPs在疾病治疗中的应用

1.1 恶性肿瘤 目前, 红细胞膜仿生技术已与药物治疗[15]、光热治疗[16]、免疫治疗[17]等多种治疗方法联合使用, 构建出多种具有不同功能的新型仿生纳米递送系统, 表1[2,15-65]总结了RBCM-NPs在恶性肿瘤中的应用。

Table 1 Application of RBCM-NPs in tumor therapy. CT: Chemotherapy; PTX: Paclitaxel; DOX: Doxorubicin; Tel: Telmisartan; Cur: Curcumin; 5-FU: 5- Fluorouracil; OM: Obatoclax mesylate; GEF: Gefitinib; ICA: Icariin; UA: Ursolic acid; RSV: Resveratrol; PTT: Photothermal therapy; SPN: Semiconducting conjugated polymer nanoparticles; HNP: Human black hair-derived nanoparticles; SDT: Sonodynamic therapy; GET: Gene therapy; EPI: Epirubicin; ICG: Indocyanine green; GA: Gambogic acid; IND: Indomethacin; PDT: Photodynamic therapy; CQP: Chloroquine phosphate; IMT: Immunotherapy; CDT: Chemodynamic therapy; HCPT: 10-Hydroxycamptothecin; CST: Cancer starvation therapy; IIT: Ion interference therapy; RT: Radio therapy

Therapy	Application	RBCM-NPs	Therapeutic agent	Function	Ref.
CT	Breast cancer	iRGD-RM-(DOX/MSNs)	DOX	High drug content, targeted delivery	[2]
		PTX-NP-EM	PTX	High drug content, long circulation	[15]
		RBC-4T1@DOX/CS-NPs	DOX	Targeted delivery	[18]
		ECM/Tel	Tel	High drug content, long circulation, targeted delivery	[19]
	Liver cancer	GACS-Cur@RBCm	Cur	Enhance immune escape ability, targeted delivery	[20]
		PDC@RBC-NPs	DOX	Enhance immune escape ability, long circulation	[21]
		5-FU-C-NPs-NEs	5-FU	Long circulation	[22]
	Lung cancer	RBCm-OM/PLGA	OM	Enhance immune escape ability, long circulation	[23]
		R-RBC@GEF-NPs	GEF	Enhance immune escape ability, targeted delivery, targeting imaging	[24]
		iRINP	ICA	Enhance immune escape ability, increasessolubility	[25]
		REMAIN	MiR-126-3p	Enhance immune escape ability, long circulation	[26]
		UMNP	UA	Enhance immune escape ability, targeted delivery, increases solubility	[27]
	Colorectal cancer	RSV-NPs@RBCm	RSV	Enhance immune escape ability, enhanced tumor tissue penetration	[28]
		PLGA/SK (+) @RBCm and PLGA/SK (−) @RBCm	Shikonin	Long circulation, enhanced tumor tissue penetration	[29]
	Ervical cancer	DOX@ZIF-8@eM-cRGD	DOX	Long circulation, enhanced tumor tissue penetration	[30]
PTT	Breast cancer	SPN@RBCM	SPN	Enhance immune escape ability, long circulation	[16]
	Liver cancer	HNP@RBCM-cRGD	HNP	Long circulation, targeted delivery	[31]
		RHAuNCs-miRNA	miRNA	Long circulation, sustained-release	[32]
		CuS@RBCs		Long circulation, enhanced tumor accumulation	[33]
	Lung cancer	DRBCM-BNF		Enhance immune escape ability, CT imaging	[34]
		Cyp-MNC@RBCs	Cyp	Enhanced tumor accumulation	[35]
SDT	Breast cancer	RBC-mTNPs@AQ4N	AQ4N	Enhance immune escape ability	[36]
GET	Ervical cancer	CM-PQDs/DNA		Sustained-release effect	[37]
CT/PTT	Breast cancer	DOX@IRP@RBC NPs	DOX, IR780	Enhance immune escape ability, long circulation	[38]

Continued

Therapy	Application	RBCM-NPs	Therapeutic agent	Function	Ref.
		MoS_2-RBC-DOX	DOX	Enhance immune escape ability	[39]
		Fe-PDA-EPI@FA-RBCm	EPI	Targeted delivery	[40]
		MSNR@DOX&ICG@RBCM	DOX, ICG	Enhance immune escape ability	[41]
	Liver cancer	DIRNPs	DOX, ICG	Long circulation, targeted delivery	[42]
	Cervical cancer	WID@M-FA NPs	DOX, ICG	Long circulation	[43]
		RmGIB NPs	GA, ICG	Long circulation	[44]
		GID@RF NPs	DOX, ICG	Enhance immune escape ability, long circulation	[45]
		PCDI@M	Cs-6, IND	Targeted delivery	[46]
PTT/PDT	Breast cancer	Ce6@DiR-M NPs	Ce6, DiR	Long circulation	[47]
		cRGD-RBC@mTHPC/TAT-IR820		Long circulation, targeted delivery	[48]
		PMRCR NPs		Targeted delivery	[49]
	Cervical cancer	ZNPC-ICG@RBC	ZNPC, ICG	Enhance immune escape ability, long circulation, enhanced tumor accumulation	[50]
CT/PDT	Breast cancer	ARISP	ICG, Sal	Enhance immune escape ability, long circulation	[51]
	Lung cancer	HA＆RBCm-LCNPs	PTX, IR780	Long circulation, enhanced tumor accumulation	[52]
	Colorectal cancer	HNPOC	Oxa	Long circulation, targeted delivery	[53]
		PLGA/GCC@FR	CQP	Long circulation, targeted delivery	[54]
IMT/PTT	Breast cancer	RBCm/PAAV-SNO/IR1061+ 1-MT NPs	IR1061, 1-MT	Long circulation, controlled-release	[17]
		RDIR1048		Enhance immune escape ability, long circulation, targeted delivery	[55]
CDT/CT/PTT	Breast cancer	HCPT@Cu/ZIF@PDA	HCPT	Enhance immune escape ability, long circulation	[56]
		RM-Cu/P@DOX	DOX	Long circulation, targeted delivery	[57]
CDT/PTT	Liver cancer	FGIR		Long circulation	[58]
IMT/CT	Melanoma	RBC-NPs	Hgp	Long circulation	[59]
		lCUR-DOX@RBC NPs	DOX	Enhance immune escape ability, enhanced tumor accumulation	[60]
	Breast cancer	HR-UCAD	DOX	Enhance immune escape ability, targeted delivery	[61]
CST/PTT	Breast cancer	AMS+-Gox@TSL@[RBC-CC-TSL]M		Enhance immune escape ability	[62]
IIT/CDT/CST	Breast cancer	Cu-CaO2/GOx@FRs		Targeted delivery	[63]
PTT/RT	Lung cancer	RBCM-BNF		Improved biocompatibility	[64]
IMT/PDT	Melanoma	M@AP NPs	P2-PPh3, poly (I:C)	Enhanced tumor accumulation	[65]

红细胞膜与药物治疗结合能够提高药物溶解度、稳定性及生物相容性, 并具有长循环及免疫逃逸等优势, 对红细胞膜表面进行修饰还可以实现对肿瘤部位的靶向递送, 从而提高肿瘤部位的药物浓度达到增强疗效的目的。例如, Wang等[21]构建的PDC@RBC-NPs通过包裹RBCM提高了其在血清中的稳定性, 并延长了血液循环时间, PDC@RBC-NPs更多积累于肿瘤部位, 在增强治疗肝癌效率的同时还能够降低药物的心脏毒性。Liang等[26]构建了一种有效递送miRNA的纳米颗粒REMAIN, 具有循环时间长、生物相容性好及免疫逃逸等优势, 能有效避免miR-126-3p被核酸酶消化, 使其通过靶向ADAM9有效诱导癌细胞凋亡并抑制肿瘤的发展与恶化。白藜芦醇 (resveratrol, RSV) 可以有效抑制结肠癌细胞的生长, 但RSV具有水溶性差、生物利用度低等问题, Zhang等[28]构建一种有效递送的RSV的纳米颗粒RSV-NPs@RBCm, 改善其溶解度, 此外该纳米颗粒具有长循环及免疫逃逸功能。此外, 将其与肿瘤穿透肽iRGD联用可增强纳米颗粒的肿瘤穿透力, 进一步提高抗肿瘤活性。

光热治疗 (photothermal therapy, PTT) 采用近红外 (near infrared, NIR) 辐射, 通过热效应使癌细胞凋亡和坏死。Liang等[66]基于光热治疗原理构建了黑磷量子点 (black phosphorus quantum dot, BPQD)-RMNV纳米颗粒用以治疗乳腺癌。BPQD表面的膜结构可以使其免受氧气与光的影响, 在体内仍能保持理想的光热特性, 并发挥免疫规避作用促进BPQD的肿瘤积蓄, 从而获得良好的治疗效果。此外, Zhang等[31]以成人黑发为原料制备出一种具有PTT效应的天然纳米颗粒HNP, 并用RBCM和cRGD对其进行修饰获得HNP@RBCM-cRGD。该纳米颗粒具有优异的生物相容性、较长的体内循环时间及肿瘤靶向能力, 并可通过PTT效应特异性杀死肝癌细胞, 实现对肿瘤部位的高效精准治疗。

除此之外, 将药物治疗与光热治疗的结合能够发

挥协同作用从而增强治疗效果, 为癌症治疗提供了一种新的思路。Xiao等[46]构建了PCDI@M纳米颗粒, 表层RBC-HeLa混合细胞膜伪装使其具有长循环效应, 同源靶向能力和优异的生物相容性与安全性。此外, 共载的IND能够有效减少PTT引起的炎症反应, 降低肿瘤细胞对Cs-6的耐药性。Liu等[67]构建了HA@RBC@PB@CS-6 NPs纳米药物递送系统, 该系统在RBCM上修饰了能够与乳腺癌细胞表面CDAA受体特异性结合的透明质酸分子, 获得了肿瘤靶向能力, 可进一步提高PTT/化疗 (chemotherapy, CT) 效果及药物的生物安全性。

光动力疗法 (photodynamic therapy, PDT) 是一种结合光敏剂、光和氧分子, 通过光动力学反应治疗疾病的方法。Zhang等[52]开发了一种多功能纳米递送系统——HA&RBCm-LCNPs, 该系统同时负载紫杉醇 (paclitaxel, PTX) 与IR780发挥CT/PDT协同治疗作用。研究表明, RBCm-LCNPs在小鼠体内的平均滞留时间约为LCNPs的3倍, 免疫系统清除率也显著降低; HA&RBCm-LCNPs在肿瘤部位的释药量约为LCNPs的4倍, 也显著高于RBCm-LCNPs。并且苏木精−伊红染色结果显示LCNPs、RBCm-LCNPs均对小鼠各主要脏器组织有不同程度影响, 但HA&RBCm-LCNPs无明显影响, 证明该系统不仅能提高药物抗肿瘤疗效, 还具有良好的生物安全性。

鉴于PTT和PDT的治疗机制与特定细胞受体的表达无关, 光疗被认为是癌症治疗的理想方案, 但是, 单PTT在肿瘤组织内因温度空间分布不均, 不能完全消除肿瘤细胞, 单PDT在很大程度上依赖于氧气, 因此, 单光疗的治疗效果并不理想, 二者结合可以实现优势互补, 提高肿瘤治疗效率[47]。Liu等[68]为进一步提升$Cu_{2-x}Se$ NPs作为光疗剂对癌症的治疗效果, 在其表面包被RBCM构建出RBC@$Cu_{2-x}Se$ NPs。研究表明, 与$Cu_{2-x}Se$ NPs相比, RBC@$Cu_{2-x}Se$ NPs拥有更高的稳定性及良好的生物相容性, 能够有效减少巨噬细胞的摄取, 并且在血液中的循环时间是$Cu_{2-x}Se$ NPs的4.43倍, 其肿瘤积蓄能力更强, 有利于提升PTT/PDT协同治疗效率。Zhang等[47]开发的Ce6@DiR-M NPs纳米系统表现出良好的PDT/PTT协同治疗作用, 与Ce6@DiR NPs相比, Ce6@DiR-M NPs在血液中拥有较长循环时间并增强其高通透性和滞留效应 (enhanced permeability and retention effect, EPR), 有利于提升治疗效果。

除此之外, Zhu等[69]构建的ZGAM纳米颗粒同时负载葡萄糖氧化酶 (glucose oxidase, GOx) 与金纳米棒 (gold nanorods, AuNRs) , 具有优异的肿瘤靶向能力和生物相容性, 不仅可以通过释放GOx有效催化葡萄糖氧化来抑制肿瘤生长, 还能够抑制热休克蛋白的表达以增强PTT效应, 显示出良好的饥饿疗法/PTT协同治疗效果。Dai等[65]开发的M@AP纳米颗粒不仅对肿瘤有直接抑制作用, 还能够激活抗肿瘤免疫反应, 对肿瘤转移有良好治疗效果, 为预防肿瘤复发和转移提供潜在治疗策略。

1.2　细菌感染　细菌感染是威胁人类健康甚至生命安全的临床常见病, 抗生素的出现使细菌感染获得了有效治疗途径[70]。然而, 长期使用抗生素会导致细菌耐药性不断增强从而降低抗生素疗效, 增加治疗难度[71]。因此开发新的有效治疗策略、尽可能降低耐药性成为临床治疗的迫切需求[72,73]。RBCM涂层纳米颗粒吸收毒素, 缓解临床症状, 但并没有将细菌杀死或摧毁。将毒素吸收并且杀死细菌可能是有效治疗细菌感染的一种手段。耐甲氧西林金黄色葡萄球菌 (methicillin-resistant *Staphylococcus aureus*, MRSA) 作为引起软组织感染、肺炎、菌血症和其他致命疾病的主要耐药病原体, 万古霉素 (vancomycin, Van) 是众所周知的对抗MRSA感染的最后一道防线, 但其治疗效果却逐年下降[74]。Chen等[75]报道了仿生可回收纳米颗粒RBC@Fe_3O_4可以作为抗菌剂。除了毒素吸收活性外, 该纳米颗粒还通过近红外光照射下的光热效应表现出破坏细菌的能力。协作治疗对MRSA感染伤口的小鼠产生了极好的治疗效果。RBC@Fe_3O_4纳米颗粒可以以简单的方式回收, 而不会影响杀菌效果。RBCM-NPs在对抗生物膜方面也显示出潜力。Ran等[76]制备的RBCM-NW-G仿生纳米系统也对细菌感染表现出良好的治疗效果。该系统以AuAg纳米颗粒为载体递送庆大霉素, 使用聚多巴胺 (polydopamine, PDA) 涂层包被AuAg来提高药物负载率, 通过RBCM伪装延长其血液循环时间并有效聚集于感染部位, 在PTT效应、Ag+及抗生素的协同作用下获得高效抗菌性能并延缓了抗生素耐药性的发生。

PDT已成为一种前景广阔的治疗策略, Zhuge等[77]设计了一种孔隙形成毒素 (pore-forming toxins, PFTs) 响应型生物仿生纳米气泡, 通过在红细胞膜内共同封装全氟碳纳米乳液和光敏剂构建仿生纳米气泡。多种细菌的PFTs可被纳米气泡所吸收。吸收毒素后, 纳米气泡表面形成的孔隙可使溶解在纳米乳液中的氧气与光敏剂一起加速释放, 从而增强光导透射和杀菌效果。除此之外, 高生物相容性和可降解的明胶纳米颗粒可以作为包封抗菌剂微环境响应性释放的最佳药物递送载体。RBCM-NPs在细菌感染中的具体应用归纳于表2[75-83]中。

1.3　在其他疾病方面的研究　神经系统疾病是全球

Table 2 Application of RBCM-NPs in the treatment of bacterial infection. PMB: Polymyxin B; DAPT: Daptomycin; AM: Antibiotics amikacin

RBCM-NPs	Application	Core material	Function	Ref.
RBC@Fe_3O_4	Anti-bacterial infection	Fe_3O_4, RBCM	Adsorption of bacterial toxins	[75]
RBCM-NW-G	Anti-bacterial infection	AuAg-G, PDA, RBCM	Drug delivery	[76]
RBC(IR780)-PFC(O2)	Anti-bacterial infection	PFC, IR780, RBCM	Neutralization of pore-forming toxins	[77]
P-RL	Anti-*Escherichia coli* infection	Lip, RBCM, PMB	Neutralize internal and external toxins	[78]
RPTR-701Ns	Methicillin-resistant *Staphylococcus aureus* infection	PTR-701Ns, RBCM	Neutralization of exotoxins	[79]
RBCDVL	Methicillin-resistant *Staphylococcus aureus* infection	VAN, Lip, DAPT, RBCM	Targeted delivery	[80]
RM-PL	Broad-spectrum detoxification	PL, RBCM	Neutralization of pore-forming toxins	[81]
PEM-ARM	Prevention of Plasmodium infection	Lip-ARM, RBCM, CLIPPKF	Blockade of CDP-Cho mediated Phosphatidylcholine synthesis	[82]
AB@LRM NPs	Anti-*Pseudomonas aeruginosa* infection	BPQD, AM, RBCM	Targeted delivery	[83]

范围内致残的主要原因, 严重影响患者生活质量, 并且近年来其发病率、致残率、死亡率一直保持上升趋势[84]。研究神经系统疾病的发病机制, 寻找高效、安全的治疗方法是目前脑科学研究的热点与方向[85]。其中, 血脑屏障 (blood brain barrier, BBB) 是中枢神经系统 (central nervous dystem, CNS) 的一个基本特征, BBB限制了绝大多数化学物质进入CNS, 将有毒化学物质从CNS中隔离开来, 以保证CNS的正常功能, 因此BBB是将药物输送到大脑的最大障碍[86]。功能肽TGNYKALHPHN (TGN) 能够利用内吞作用介导的机制穿过BBB, 在提高脑运输效率方面具有巨大潜力, Gu等[87]开发了一种使用TGN肽作为配体通过BBB的脑靶向药物递送系统, 该递送系统在体外和体内实验均证实TGN-RBC-NPs具有穿越BBB的能力并表现出卓越的大脑靶向效应。Liu等[88]利用RBCM封装碳量子点 (carbon quantum dots, CQD) 和PDA的载体, 而产生纳米复合材料PDA-CQD/RBC。该纳米复合材料与近红外相结合用于阿尔兹海默病 (Alzheimer's disease, AD) 治疗。纳米粒子表面修饰红细胞膜使其具有免疫逃逸能力, 纳米粒子有效减轻氧化应激损伤, 防止β-淀粉样蛋白 (β-amyloid, Aβ) 聚集。除此之外近红外激光照射诱导局部加热可以瓦解形成的Aβ纤维并增强血脑屏障的通透性。该制剂超越了单靶点治疗的局限性, 在减缓疾病进展的同时提高了治疗效果。Liu等[89]建的RVG29-RBCm/Cur-NCs具有良好的缓释效果与生物相容性, 能够有效逆转帕金森小鼠的行为缺陷, 其表层修饰的RVG29-RBCm不仅延长了循环寿命还能够将药物直接递送至脑内, 克服了血脑屏障, 提高了药物的生物利用率, 是帕金森及其他神经退行性疾病治疗的有效潜在策略。

心血管疾病是全球范围内死亡的主要原因, 也是主要致残原因之一, 靶向性较差、生物利用度低、毒副作用等是心血管疾病诊疗过程中亟待解决的主要难题[90-92]。Zhao等[93]建立的T-RBC-DTC NPs具有良好的生物相容性, 其表面修饰的CREKA肽具有血浆纤维蛋白靶向功能, 能够有效促进纳米颗粒在血栓部位聚集。体内研究表明, 与DTC NPs (血栓形成度约80.3%) 相比, T-RBC-DTC NPs (血栓形成程约14.9%) 抗血栓效率显著提升, 未来可能适用于治疗动脉血栓、肺栓塞等多种与血栓相关的疾病。除此之外, RBCM-NPs在其他疾病中的应用见表3[87-89,93-109]。

总之, 红细胞膜伪装的仿生纳米递送系统在药物递送中发挥了重要作用。红细胞膜的磷脂双分子层结构不仅能够有效保护药物免受外界环境的干扰, 提高药物的稳定性, 还因与生物结构的高度一致性, 展现出良好的生物相容性; 此外, 红细胞膜包被能够掩盖纳米颗粒的非自然特征, 避免被免疫系统识别和清除, 在血液中长时间稳定存在, 延长药物的血液循环时间; 通过修饰红细胞膜或结合特定的靶向分子, RBCM-NPs可以实现对特定细胞或组织的精准靶向递送, 减少药物的全身分布和不良反应。RBCM-NPs在药物递送方面的这些优势, 使其在肿瘤治疗、细菌感染等多个领域展现出广阔的应用前景。

2 展望与挑战

未来RBCM-NPs的研究方向将是推动这一领域进一步发展的关键。首先, 由于红细胞膜本身不具备靶向能力, 红细胞膜表面改性技术将成为未来研究的重要方向。通过化学修饰或与其他类型细胞膜进行杂交等都可提高膜的功能性, 以增强其靶向性和细胞摄取能力; 其次, 纳米载体的设计与优化同样至关重要。结合多种功能的纳米载体, 将有助于实现联合治疗策略, 从而提高治疗效果。此外, 为实现从学术研究向临床应用的转化, 长期安全性评估也是不可忽视的研究内容。评估红细胞膜伪装纳米递送系统的药代动力学

Table 3 Application of RBCM-NPs in the treatment of other diseases. PBNP: Prussian blue nanoparticles. RAPA: Rapamycin; UK: Urokinase; LFP: Lipid-specific fluorophore

Application	RBCM-NPs	Therapeutic agent	Function	Ref.
Alzheimer's disease	TGN-RBC-NPs-Cur	Cur	Overcoming the blood-brain barrier, targeted delivery	[87]
	PDA-CQD/RBC		Overcoming the blood-brain barrier, enhance immune escape ability, targeted delivery	[88]
	RVG/TPP-RSV NPs	RSV	Overcoming the blood-brain barrier, targeted delivery	[94]
	T807/TPP-RBC-NP	Cur	Overcoming the blood-brain barrier, targeted delivery	[95]
	Cu_XO@EM-K	Cu_XO	Enhance immune escape ability, long circulation, targeted delivery	[96]
	AFPS/CTAB@RBC	H_2S	Enhance drug stability	[97]
	TR-ZRA		Overcoming the blood-brain barrier	[98]
	CQD-Ce-RBC		Overcoming the blood-brain barrier, enhance immune escape ability	[99]
	PB/RBC	PBNP	Overcoming the blood-brain barrier	[100]
Parkinson's disease	RVG29-RBCm/Cur-NCs	Cur	Overcoming the blood-brain barrier, long circulation, targeted delivery	[89]
	RBCM/UCMG		Overcoming the blood-brain barrier, enhance immune escape ability, targeted delivery	[101]
Traumatic brain injury	C3/SS31-RBCNLCs	Ola	Targeted delivery	[102]
Autism spectrum disorder	SCM@RAPA	RAPA	Overcoming the blood-brain barrier	[103]
Thrombus	T-RBC-DTC NPs	Tirofiban	Long circulation, targeted delivery	[93]
	PM/RM@PLGA@P/R	Rg1	Enhance immune escape ability, targeted delivery	[104]
	RGD-RBCM@PPUNPs	UK	Enhance immune escape ability	[105]
	USIO/UK@EM	UK	Extended half-life	[106]
Atherosclerosis	RBC/LFP@PMMP	Prednisolone, LFP	Long circulation	[107]
	RBC@P-LVTNPs		Enhance immune escape ability	[108]
	CXCR2 [RBC-P] NPs	CXCR2	Long circulation	[109]

特性和潜在毒性, 将为临床应用提供重要的安全性数据。最后, 跨学科的合作将是推动红细胞膜伪装纳米递送系统临床转化的关键。结合多个领域的知识, 可以更全面地解决当前面临的挑战, 加速学术研究向临床运用的转换。

RBCM-NPs虽然在结构和功能上具有独特优势, 但目前还是存在一些问题, 一方面是制备与表征过程中仍有诸多问题亟待改进。首先, 制备路线繁琐, 需要耗费大量细胞, 这导致重现性较差难以实现批量化制备; 其次, 表征方法有限, 主要通过粒径与电位检测、形态观察来判断膜包被是否成功, 通过蛋白质印迹分析验证膜表面蛋白的完整性, 但这些方法均无法验证包被后细胞膜是否被部分破坏。另一方面从学术研究向临床应用转化的过程中, 也面临诸多挑战。主要问题包括: 红细胞个体差异性和血型抗原差异导致异体输血问题, 自体来源血液虽具个性化治疗潜力, 但在临床推广上存在困难; 细胞储存环境要求高, 缺乏统一标准; 给药途径、细胞来源、给药标准化等方面存在异质性, 难以建立统一质量管理标准; 采集、转移和处理过程中存在污染风险, 但现有的灭菌技术可能会破坏膜上重要蛋白, 损伤红细胞数量; 最后临床转化阶段也需要大量资金支持。

综上, 虽然RBCM-NPs在实现实验室到临床过程中仍存在诸多问题, 但其独特优势和应用潜力不可忽视, 随着研究的不断深入及技术手段的改进升级, RBCM-NPs有望成为临床恶性肿瘤、细菌感染等多种疾病治疗的有力手段。

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