靶向CTC-血细胞相互作用的抗转移纳米递药系统研究进展

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摘要: 肿瘤转移是导致癌症患者死亡的主要原因, 其过程涉及循环肿瘤细胞 (circulating tumor cell, CTC) 与血液中多种细胞成分 (如血小板、中性粒细胞、巨噬细胞等) 的复杂相互作用。本文首先系统梳理了CTC与各类血细胞间的相互作用机制, 重点归纳了其在促进CTC存活、免疫逃逸及远处器官定植中的关键作用; 在此基础上, 聚焦纳米递送系统在靶向清除单个CTC、解离CTC同型簇、阻断CTC-血小板/中性粒细胞簇形成, 以及抑制中性粒细胞胞外诱捕网等方面的研究进展, 系统评述了配体介导靶向、细胞膜仿生递送及响应性释药等多种策略的应用; 最后, 对该类纳米递送系统在临床转化中所面临的挑战与未来发展方向进行了展望, 以期为抗转移治疗研究提供参考。

关键词: 循环肿瘤细胞; 纳米递药系统; 肿瘤转移; 血细胞互作; 仿生纳米药物

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Advances in nanotherapeutic platforms for targeting CTC-blood cell interactions

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Abstract: Metastasis is the leading cause of cancer deaths. It involves intricate interactions between circulating tumour cell (CTC) and blood components such as platelets, neutrophils and macrophages. This review first summarizes how CTC interact with these cells to promote their survival, immune evasion and seeding in distant organs. We then focus on recent advances in nanodelivery systems designed to counteract these processes — including the targeted elimination of single CTC, disruption of CTC homotypic clusters, blocking of CTC-platelet/neutrophil aggregates, and inhibition of neutrophil extracellular traps (NETs). Various strategies, such as ligand-mediated targeting, biomimetic cell membrane coating, and stimuli-responsive release, are critically discussed. Finally, we highlight key challenges and future directions for translating these systems into clinical anti-metastatic therapies.

Key words: circulating tumor cell; nanodrug delivery system; tumor metastasis; blood cell interaction; biomimetic nanomedicine

转移是癌症相关死亡的主要原因, 其过程复杂, 涉及肿瘤细胞从原发部位脱离、通过循环系统存活与扩散, 并在远处器官定植[1,2]。数十年来, 为对抗转移进展, 系统治疗手段不断丰富, 包括化疗、放疗、免疫治疗、基因治疗、光动力治疗及分子靶向治疗等[3,4]。然而, 这些疗法针对转移的临床疗效仍不尽如人意。这一局限主要归因于肿瘤异质性、免疫抑制性肿瘤微环境、低免疫原性、免疫耐受、全身毒性, 以及原发肿瘤脱落进

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入血液后与血细胞间复杂的相互作用[5-7]。因此, 转移的有效治疗仍是当前面临的重大挑战。

循环肿瘤细胞 (circulating tumor cell, CTC) 是多种癌症发生转移的前体细胞, 指原发肿瘤通过侵袭突破基底膜, 肿瘤细胞以单个CTC或CTC簇的形式脱落进入血液循环[8-10]。然而绝大多数CTC会因免疫监视、失巢凋亡、氧化应激、血流剪切力及缺氧/营养剥夺等微环境压力而发生大量凋亡, 导致其成功定植并形成转移灶的概率极低[11,12]。研究显示, 面对多种死亡威胁时, CTC簇比单个CTC具有更强的存活能力与转移潜能[6,13]。值得注意是的, 除了CTC与CTC形成同型簇外, CTC在循环过程中还可与多种血细胞 (如血小板、中性粒细胞、单核细胞/巨噬细胞、红细胞、淋巴细胞) 发生聚集形成异型簇, 也可与内皮细胞或癌症相关成纤维细胞等相互作用形成异型簇, 从而动态调控CTC的存活、增殖、侵袭及外渗等关键生物学行为[7,14,15] (图1)。基于此, 靶向干预CTC同型簇和CTC异型簇已成为抑制肿瘤转移的重要策略。

近年来, 纳米药物递送系统的发展为癌症精准治疗提供了新策略[16,17]。该系统通过工程化设计, 可在纳米颗粒 (nanoparticles, NPs) 表面整合抗体片段、适配体、多肽或细胞膜等靶向配体, 构建主动靶向界面[4,6]。此外, 为克服单一疗法的局限性, NPs还可被设计为多功能共递送平台, 实现多种药物的协同装载与联合治疗[18]。这些策略有望在肿瘤转移过程中高度异质且动态的扩散阶段, 靶向干预CTC及其与血细胞形成的团簇, 从而抑制血细胞介导的转移进程。值得关注的是, 目前已有多款抗肿瘤转移纳米药物获批临床应用或进入临床试验阶段[2] (表1)。这些进展共同表明, 纳米药物递送系统在抑制肿瘤转移方面具有广阔的应用前景。

Table 1 Nanomedicines approved for clinical use and in clinical trials for metastasis treatment. [a]The year indicates when the clinical study was initiated. [b]Discontinued because of manufacturing issues. HER2: Human epidermal growth factor receptor 2; KRAS: Kristen rat sarcoma viral oncogene homologue; N/A: Not available; NIR: Near-infrared; PEG: Polyethylene glycol; DOX: Doxorubicin; PSMA: Prostate-specific membrane antigen; siRNA: Small interfering RNA; STAT6: Signal transducer and activator of transcription 6

Translational stage	Product name	Composition	Indication	First approval	Explored for	Clinical trial (metastasis)[a]
Nanomedicines clinically approved for metastasis treatment	Doxil/Caelyx	PEGylated liposomal DOX	Multiple cancers, including metastatic breast cancer in patients at risk of heart problems	USA (1995), Europe (1996)	−	−
	DepoCyt(e)[b]	Liposomal cytarabine	Leptomeningeal metastasis	USA (1999), Europe (2001)	−	−
	Myocet	Liposomal DOX	Metastatic breast cancer (used with cyclophosphamide)	Europe/ Canada (2000)	−	−
	Abraxane	Albumin-bound paclitaxel	Metastatic breast cancer, metastatic adenocarcinoma of the pancreas	USA (2005), Europe (2008)	−	−
	Nanoxel	Micellar paclitaxel	Metastatic breast cancer, metastatic non-small-cell lung cancer, metastatic prostate cancer, metastatic epithelial ovarian cancer, metastatic gastric cancer	India (2006)	−	−
	Onivyde	Liposomal irinotecan	Metastatic adenocarcinoma of the pancreas	USA (2015), Europe (2016)	−	−
	Oncaspar	PEGylated *L*-asparaginase	Acute lymphoblastic leukaemia	USA (2006), Europe (2016)	−	−
	Vyxeos	Liposomal daunorubicin and cytarabine	Acute myeloid leukaemia	USA (2017), Europe (2018)	−	−

Continued

Translational stage	Product name	Composition	Indication	First approval	Explored for	Clinical trial (metastasis)[a]
Nanomedicines approved for clinical use against primary solid tumours or blood cancers and in clinical trials for metastasis treatment	DaunoXome	Liposomal daunorubicin	Kaposi sarcoma	USA (1996)	Metastatic breast cancer	NCT00004207, phase I, unknown status (2004)
	Lipusu	Liposomal paclitaxel	Non-small-cell lung cancer, breast cancer, ovarian cancer	China (2003)	Metastatic breast cancer, metastatic non-small-cell lung cancer, metastatic ovarian cancer	NCT02142790, phase IV, unknown status (2014); NCT02996214, phase IV, unknown status (2016); NCT04807166, phase II, active not recruiting (2021); NCT06102824, phase II, recruiting (2024)
	Genexol PM	Micellar paclitaxel	Breast cancer, pancreatic cancer non-small-cell lung cancer	South Korea (2007)	Metastatic pancreatic cancer, metastatic breast cancer, metastatic non-small-cell lung cancer	NCT00111904, phase II, completed (2005); NCT01169870, phase II, withdrawn (2007); NCT00882973, phase I, completed (2008); NCT00876486, phase III, completed (2008); NCT01770795, phase II, completed (2011); NCT01784120, phase II, unknown status (2011); NCT02064829, N/A, completed (2014); NCT02739633, phase II, unknown status (2016)
	Mepact	Liposomal mifamurtide	Osteogenic sarcoma	Europe (2009)	Metastatic osteosarcoma and metastatic liver cancer	NCT00631631, N/A, completed (2008); NCT02441309, phase II, terminated (2015); NCT03643133, phase II, active not recruiting (2018); NCT04062721, phase I, unknown status (2021)
	Marqibo	Liposomal vincristine sulfate	Acute lymphoblastic leukaemia	USA (2012)	Metastatic melanoma	NCT00145041, phase I, completed (2005); NCT00506142, phase II, completed (2007)
	Liporaxel	Lipid nanodroplets containing paclitaxel	Gastric cancer	South Korea (2016)	Metastatic gastric cancer, metastatic breast cancer	NCT02890511, phase I/II, completed (2010); NCT01839773, phase III, completed (2013); NCT03315364, phase II/III, active not recruiting (2017); NCT03326102, phase II, completed (2018); NCT04046016, phase I, completed (2018); NCT06326346, phase II, active not recruiting (2024)

Continued

Translational stage	Product name	Composition	Indication	First approval	Explored for	Clinical trial (metastasis)[a]
	Hensify	Hafnium oxide nanoparticles	Locally advanced soft-tissue sarcoma	Europe (2019)	Metastatic liver cancer, metastatic cervix cancer, metastatic kidney cancer, metastatic melanoma, metastatic breast cancer, metastatic non-small-cell lung cancer, metastatic bladder cancer, metastatic head and neck squamous cell cancer	NCT02721056, phase I/II, terminated (2016); NCT03589339, phase I, recruiting (2019); NCT04862455, phase II, recruiting (2021); NCT05039632, phase I/II, recruiting (2023)
Nanomedicines in clinical trials for metastasis treatment	Radiolabelled Cornell dots	RGD-targeted silica nanoparticles radiolabelled with ^{124}I or ^{89}Zr (in addition to NIR fluorophore)	−	−	Imaging of various cancers, including metastatic brain tumours	NCT01266096, active not recruiting (2011); NCT03465618, phase I, active not recruiting (2018)
	BIND-014	PSMA-targeted polymeric nanoparticle loaded with docetaxel	−	−	Treatment of metastatic castration-resistant prostate cancer	NCT01300533, phase I, completed (2011); NCT01812746, phase II, completed (2013)
	MM-302	HER2-targeted liposome loaded with DOX	−	−	Treatment of advanced HER2$^+$ metastatic breast cancer	NCT01304797, phase I, unknown status (2011); NCT02213744, phase II/III, terminated (2014)
	^{64}Cu-MM-302	HER2-targeted liposome radiolabelled with ^{64}Cu and loaded with DOX	−	−	Treatment and imaging of advanced HER2$^+$ cancer with brain metastases	NCT01304797, phase I, unknown status (2011); NCT02735798, phase I, withdrawn (2016)
	AuroShell	Nanoparticle made of silica core and gold shell	−	−	Thermal ablation of different types of cancer	NCT01679470, terminated (2012)
	ThermoDox	Thermosensitive liposome loaded with DOX	−	−	Treatment of localized unresectable recurrent and metastatic breast, pancreas, bone and liver cancer	NCT00093444, phase I, completed (2004); NCT00441376, phase I, completed (2007); NCT00826085, phase I/II, completed (2013); NCT01464593, phase II, terminated (2012); NCT01640847, phase II, withdrawn (2012); NCT02181075, phase I, completed (2014); NCT03749850, phase I, unknown status (2021); NCT04791228, phase II, recruiting (2021); NCT04852367, phase I, withdrawn (2021)
	Cornell dots	RGD-targeted silica nanoparticle labelled with NIR fluorophore	−	−	Imaging of head and neck melanoma, including nodal metastases	NCT02106598, phase I/II, active not recruiting (2014)

Continued

Translational stage	Product name	Composition	Indication	First approval	Explored for	Clinical trial (metastasis)[a]
	FixVac (BNT111, BNT112, BNT113 and BNT116)	Liposome loaded with different RNAs	–	–	Cancer vaccine	NCT02410733, phase I, completed (2015); NCT04382898, phase I/II, terminated (2019); NCT04526899, phase II, active not recruiting (2021); NCT04534205, phase II, recruiting (2021); NCT05557591, phase II, recruiting (2023)
	CriPec	Polymeric micelles loaded with docetaxel	–	–	Treatment of metastatic solid tumours	NCT02442531, phase I, completed (2015)
	AGulX	Polysiloxane core matrix bound to gadolinium chelate	–	–	Radiosensitizer (+MRI) against various cancers (primarily glioblastoma and brain metastases)	NCT02820454, phase I, completed (2016); NCT04094077, phase II, terminated (2020); NCT03818386, phase II, active not recruiting (2019); NCT04899908, phase II, recruiting (2021)
	iNeST (RO7198457/ BNT122)	Lipid nanoparticles loaded with mRNA	–	–	Cancer vaccine	NCT03289962, phase I, active not recruiting (2017); NCT03815058, phase II, active not recruiting (2019)
	V940 (mRNA-4157)	Lipid nanoparticles loaded with mRNA	–	–	Cancer vaccine	NCT03313778, phase I, recruiting (2017); NCT03897881, phase II, recruiting (2019); NCT05933577, phase III, recruiting (2023)
	Talidox	PEGylated liposomal DOX	–	–	Advanced solid tumours	NCT03387917, phase I, recruiting (2018)
	iExosomes	Exosomes loaded with siRNA targeting KRAS mutation	–	–	Treatment of metastatic pancreatic cancer	NCT03608631, phase I, active, not recruiting (2021)
	ONM-100	pH-sensitive micelle encapsulating a fluorophore	–	–	Intraoperative fluorescence imaging	NCT04950166, phase II, completed (2021)
	exoASO-STAT6	Exosomes targeting STAT6 for immunotherapy	–	–	Treatment of advanced and metastatic cancers	NCT05375604, phase I, terminated (2022)
	THE001	Thermosensitive liposome loaded with DOX	–	–	Treatment of advanced and metastatic soft tissue sarcoma	NCT05858710, phase I, recruiting (2023)

尽管在肿瘤发生早期清除或抑制CTC转移并非首要任务, 且晚期疗效受限, 但针对CTC的靶向清除或转移干预在特定临床场景中仍具重要价值, 尤其在不可切除的晚期肿瘤治疗及转移复发预防方面。为此, 本文系统综述了基于纳米材料的药物递送系统在干预CTC与血细胞相互作用方面的进展, 重点介绍旨在阻断CTC-血小板簇、CTC-中性粒细胞簇形成, 促进CTC同质簇解离, 破坏中性粒细胞胞外诱捕网(neutrophil extracellular traps, NETs)及直接杀伤CTC的纳米策略, 并对该类纳米药物面临的挑战与未来发展方向进行展望。

1　CTC与血细胞相互作用

进入循环系统后, CTC通过与各类血细胞直接接触或借助分泌因子介导的间接互作, 共同增强其存活

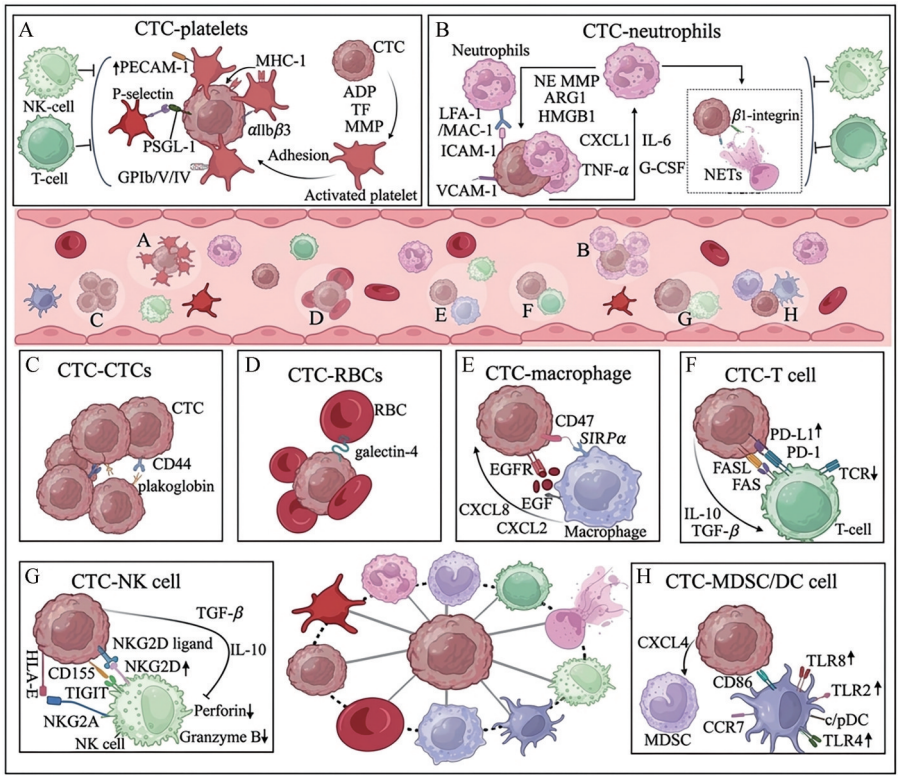


Figure 1 Key molecular mechanisms underlying CTC-blood cell interactions. A: CTC-derived ADP activates platelets, leading to upregulation of P-selectin, GPIb/V/IX and integrin *α*IIb*β*3, which mediate direct adhesion to CTC. This interaction not only protects CTC from hemodynamic shear forces but also facilitates immune evasion *via* transfer of MHC-I molecules to CTC; B: Neutrophils bind CTC through ICAM-1 on CTC and LFA-1/MAC-1 on neutrophils, forming CTC-neutrophil clusters that promote transendothelial migration and extravasation. CTC-secreted cytokines such as TNF-*α* induce the release of NETs, which further engage CTC *via* *β*1-integrin; C: CTC form homotypic clusters through plakoglobin and CD44, substantially enhancing their metastatic potential; D: CTC interact with red blood cells *via* galectin-4; E: Macrophages engage CTC through the CD47-SIRP*α* axis and signals involving EGFR, CXCL8 and CXCL2, thereby suppressing phagocytic clearance; F: T cells interact with CTC *via* PD-1/PD-L1, FAS/FASL, and IL-10/TGF-*β* pathways, contributing to an immunosuppressive microenvironment; G: CTC suppress NK cell activity by releasing TGF-*β* and IL-10, and by downregulating NKG2D ligands, thereby evading NK cell-mediated cytotoxicity; H: In cancer patients with elevated CTC counts, cDC upregulate TLR2, TLR4, TLR8 and CCR7, while pDC show increased CD86 expression. MDSC interact with CTC through enhanced Nodal signalling and subsequent ROS generation, activating the Notch pathway in CTC. CTC: Circulating tumor cells; ADP: Adenosine diphosphate; TF: Tissue factor; MMP: Matrix metalloproteinase; MHC-I: Major histocompatibility complex class I; PECAM-1: Platelet endothelial cell adhesion molecule-1; PSGL-1: P-selectin glycoprotein ligand-1; GPIb/V/IX: Glycoprotein Ib/V/IX; NKG2D: Natural killer group 2, member D; VCAM-1: Vascular cell adhesion molecule-1; NE: Neutrophil elastase; ARG1: Arginase 1; HMGB1: High mobility group box 1; ICAM-1: Intercellular adhesion molecule-1; LFA-1: Lymphocyte function-associated antigen-1; TNF-*α*: Tumor necrosis factor-*α*; IL-6: Interleukin-6; IL-10: Interleukin-10; G-CSF: Granulocyte colony-stimulating factor; SIRP*α*: Signal regulatory protein *α*; EGFR: Epidermal growth factor receptor; EGF: Epidermal growth factor; NETs: Neutrophil extracellular traps; CXCL1/2/4/8: C-X-C motif chemokine ligand 1/2/4/8; PD-1: Programmed cell death protein-1; PD-L1: Programmed death ligand-1; FAS/FASL: Fas cell surface death receptor/Fas ligand; TCR: T cell receptor; TGF-*β*: Transforming growth factor-*β*; NKG2A: Natural killer group 2 member A; HLA-E: Human leukocyte antigen-E; CD47: Cluster of differentiation 47; TLR2/4/8: Toll-like receptor 2/4/8; CCR7: C-C chemokine receptor type 7; CD40: Cluster of differentiation 40; CD86: Cluster of differentiation 86; RBCs: Red blood cells; MDSC: Myeloid-derived suppressor cell; DC: Dendritic cell; NK: Natural killer cell; cDC: Conventional dendritic cell; pDC: Plasmacytoid dendritic cell

能力、免疫逃逸与外渗潜能[7,19] (图1)。因此, 系统解析CTC-血细胞相互作用的分子机制, 对于研发靶向该过程的抗转移药物具有关键意义。

1.1 CTC-血小板

肿瘤细胞可通过多种途径诱导血小板活化与聚集, 主要包括直接接触、释放二磷酸腺苷 (adenosine diphosphate, ADP) 等可溶性激动剂、分泌含组织因子 (tissue factor, TF) 的细胞外囊泡, 以及经由基质金属蛋白酶 (matrix metalloproteinase, MMP) 相关通路调控或循环先天免疫细胞介导的间接作用[20-23]。活化后的血

小板高表达P-选择素与整合素等黏附蛋白, 并具备分泌细胞因子及参与免疫调节的功能, 从而在肿瘤进展中发挥多重作用[24,25]。

CTC与活化血小板的相互作用, 是其实现转移性黏附、迁移及免疫逃逸的关键。一方面, CTC表面P-选择素糖蛋白配体-1 (P-selectin glycoprotein ligand-1, PSGL-1) 与血小板P-选择素结合介导初始黏附与滚动, 进而激活血小板整合素 (如αIIbβ3), 通过高亲和力结合纤维蛋白原促进微血栓形成, 为CTC提供力学保护并增强血管壁锚定, 利于外渗[21,26,27]。滚动过程中, 血小板进一步活化并上调血小板内皮细胞黏附分子-1 (platelet endothelial cell adhesion molecule-1, PECAM-1), 与整合素协同作用延缓CTC移动并扩大内皮间隙, 协助其穿越血管屏障[24]。另一方面, 血小板通过物理“披覆”遮蔽CTC表面抗原, 并将自身主要组织相容性复合体I类分子 (major histocompatibility complex class I, MHC-I) 转移至CTC, 使其被自然杀伤细胞 (natural killer cell, NK) 误认为“自身”而逃逸清除[28]。此外, TF依赖的血小板和纤维蛋白原包被也被发现与NK细胞逃逸有关[29]。另外, 血小板诱导CTC释放可溶性自然杀伤细胞2族成员D (natural killer group 2, member D, NKG2D) 配体, 从而干扰免疫系统对肿瘤细胞的识别, 并同时抑制NK细胞的脱颗粒过程及其炎症性细胞因子的生成[30] (图1A)。

此外, 活化血小板通过旁分泌机制释放多种可溶性因子, 协同调控肿瘤转移过程。一方面, 其释放血小板源性生长因子 (platelet-derived growth factor, PDGF) 抑制NK细胞的细胞毒活性[31,32], 而转化生长因子-β (transforming growth factor-beta, TGF-β) 则抑制NK细胞表面分化簇226 (cluster of differentiation 226, CD226) 及分化簇96 (cluster of differentiation 96, CD96) 及其相关配体在CTC上的表面表达, 从而进一步强化其对NK细胞的抑制效应[30]。另一方面, 血小板分泌的腺苷酸核苷酸通过激活内皮细胞P2Y2受体 ($P2Y_2$ purinergic receptor) 松弛细胞间连接, 促进CTC外渗[33]; 释放的CXCL5 (C-X-C motif chemokine ligand 5, CXCL5)、CXCL7等趋化因子则募集粒细胞与单核细胞[34], 这可能增加CTC形成团簇的机会。同时, 血小板通过储存并释放血管内皮生长因子 (vascular endothelial growth factor, VEGF)、碱性成纤维细胞生长因子 (basic fibroblast growth factor, bFGF) 等促血管生成因子及内皮抑素等抑制性因子, 动态调节新生血管形成[35,36]; 此外, 血小板来源的细胞外囊泡 (platelet-derived extracellular vesicle, PEV) 亦可诱导血管生成, 为转移灶的定植与生长提供支持[37]。

1.2　CTC-中性粒细胞

CTC与中性粒细胞的相互作用通过多重机制共同促进肿瘤转移 (图1B)。一方面, CTC表面表达的细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1)/血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1)、分化簇47 (cluster of differentiation 47, CD47)、基质金属蛋白酶-9 (matrix metalloproteinase-9, MMP-9) 及CD44变构体 (CD44 variant, CD44v) 等配体, 可直接与中性粒细胞表面的整合素、信号调节蛋白α (signal regulatory protein α, SIRPα)、中性粒细胞明胶酶相关脂质运载蛋白 (neutrophil gelatinase-associated lipocalin, NGAL) 及选择素等受体结合, 以及借助微触手 (microtentacles, McTNs) 形成物理连接并聚集成簇, 从而显著增强CTC的存活、增殖及转移潜能[6,38,39]。另一方面, CTC分泌的粒细胞集落刺激因子 (granulocyte colony-stimulating factor, G-CSF)、白细胞介素-6 (interleukin-6, IL-6)、C-X-C基序趋化因子配体1 (C-X-C motif chemokine ligand 1, CXCL1)、白细胞介素-8 (interleukin-8, IL-8)、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、白细胞介素-1β (interleukin-1β, IL-1β) 及载脂蛋白E (apolipoprotein E, APOE) 等细胞因子可调控中性粒细胞的表型与活化, 进而发挥促肿瘤效应[40]; 中性粒细胞亦通过分泌IL-8、G-CSF、TGF-β、IL-6、VEGF等因子反向调节CTC行为[39] (图1B)。

此外, 中性粒细胞通过释放蛋白酶及形成NETs等途径重塑转移微环境。其所分泌的中性粒细胞弹性蛋白酶 (neutrophil elastase, NE)、组织蛋白酶G (cathepsin G, CG)、基质金属蛋白酶 (matrix metalloproteinases, MMPs) 及精氨酸酶1 (arginase 1, Arg1) 等可调控微环境因子活性并促进CTC外渗[6,41]。同时, NETs能够遮蔽CTC表面抗原, 协助其逃避免疫清除, 并借助所含蛋白酶与活性氧 (reactive oxygen species, ROS) 降解细胞外基质 (extracellular matrix, ECM)、增加血管通透性, 从而共同推动CTC的播散与定植[22,42]。

1.3　CTC-红细胞

CTC与红细胞的相互作用机制尚未完全阐明, 但其在肿瘤进展中的潜在作用日益受到关注。研究表明, 红细胞不仅可与免疫细胞互作并调节其功能[43], 还在接触癌细胞后发生细胞因子谱改变与免疫调节功能变化[44]。Pereira-Veiga等[43]发现转移性乳腺癌和肺癌患者的红细胞可诱导肿瘤细胞发生表型与功能改变, 包括黏附、迁移及侵袭能力增强, 并促进体内远端扩散。Helwa等[45]提出, 肿瘤细胞可能通过表达半乳糖凝集素-4 (galectin-4, Gal-4) 与红细胞结合。临床相关性研究显示, CTC短期培养体系中红细胞的存在提示

不良预后[46]; 同时发现癌症患者的红细胞蛋白谱较健康供体发生了显著改变[47]。近期, Richert等[48]通过成像流式细胞术在前列腺癌患者中首次观察到直接的红细胞-CTC相互作用, 检出率达9% (图1D)。

1.4 CTC-巨噬细胞

巨噬细胞作为源于髓系祖细胞的多功能免疫细胞, 在吞噬清除、免疫调节及抗原呈递等过程中发挥关键作用。相较于原发灶中已被充分研究的肿瘤细胞−巨噬细胞互作, 该领域仍需深入探索[49,50]。现有研究表明, CTC可能通过表面CD47与巨噬细胞SIRPα结合, 激活“别吃我”信号, 从而逃避免疫清除[51,52]。CD47/SIRPα轴作为髓系特异性免疫检查点, 不仅参与生理性免疫调节, 也被多种肿瘤利用以实现免疫逃逸[53]。另外, CTC表面富含由波形蛋白与微管蛋白支撑的微触手结构, 不仅能抵抗血流剪切力与失巢凋亡, 也促进其与巨噬细胞的聚集[54]。此外, 巨噬细胞通过分泌表皮生长因子 (epidermal growth factor, EGF)、CXCL8等促肿瘤因子, 进一步助力CTC转移[14] (图1E)。

研究显示, 小细胞肺癌来源的CTC可在体外诱导外周血单核细胞向肿瘤相关巨噬细胞 (tumor-associated macrophage, TAM) 样表型分化, 并促进几丁质酶3样蛋白1 (chitinase-3-like protein 1, CHI3L1)、MMP-9、VEGF等因子的分泌, 这些因子与肿瘤侵袭、血管生成及免疫抑制密切相关[55]。值得注意的是, 在癌症患者外周血中已检测到具有巨噬细胞表型的细胞[56], 提示巨噬细胞可能与CTC在循环系统中发生直接或间接相互作用, 但其具体功能与分子机制仍有待进一步阐明。

1.5 CTC-T细胞

CTC与不同T细胞亚群之间存在复杂的双向调控关系 (图1F)。一方面, CTC通过改变表面分子表达或分泌免疫调节分子, 实现对毒性T细胞 (尤其$CD8^+$效应T细胞) 的逃逸, 并诱导效应T细胞向抑制性/耗竭表型转化[57,58]; 另一方面, 分化簇8阳性T (cluster of differentiation 8 positive T, $CD8^+$ T) 细胞作为关键的免疫监视细胞, 可被CTC通过调控MHC-I表达及免疫检查点信号等方式逃逸杀伤[59,60]。值得注意的是, CTC还能够通过释放C-C基序趋化因子配体5 (C-C motif chemokine ligand 5, CCL5)、CCL22、CXCL9/10等趋化因子募集$CD4^+FOXP3^+$调节性T细胞 (regulatory T cell, Treg), 后者通过抑制$CD8^+$ T细胞增殖、削弱NK细胞及树突状细胞 (dendritic cell, DC) 的细胞毒性, 进而增强CTC的存活能力与转移潜能[61-63]。

1.6 CTC-自然杀伤细胞

自然杀伤细胞 (natural killer cell, NK) 是抗肿瘤免疫监视的关键效应细胞, 然而CTC可通过多途径抑制其功能 (图1G)。一方面, CTC通过与NK细胞表面免疫检查点分子相互作用, 直接抑制NK细胞活性[64,65]; 另一方面, CTC通过调控表面MHC-1表达, 与NK细胞抑制性受体 (如自然杀伤细胞2族成员A, natural killer group 2 member A, NKG2A) 或激活性受体 (如NKG2D) 结合, 进而干扰其识别与杀伤功能[66]。此外, CTC还可分泌TGF-β等抑制性因子, 诱导NK细胞向非细胞毒性状态转化, 并募集Treg、髓源性抑制细胞 (myeloid-derived suppressor cell, MDSC) 等进一步抑制NK细胞活[67,68]; CTC来源的一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 亦能损害NK细胞的代谢与增殖[69]。这些作用共同导致NK细胞数量减少与功能受损, 从而削弱机体对CTC的免疫清除能力, 促进肿瘤转移进程。

1.7 CTC-B细胞

近年研究逐步揭示了B细胞及其介导的抗体反应在癌症转移过程中的双重调控作用。B细胞在TME及转移灶中既可促进转移, 亦可发挥抗转移效应。一方面, B细胞能够增强肿瘤细胞的运动、侵袭能力, 促进血管及淋巴管生成, 并参与ECM的重塑, 从而驱动癌细胞的扩散[15]; 其还可通过诱发致病性免疫球蛋白反应及募集免疫抑制细胞, 协助转移定植[70]。另一方面, B细胞亦能通过增强抗原呈递、抑制癌细胞从原发灶播散及分泌识别性抗体等方式, 发挥抗转移作用[71]。值得注意的是, CTC亦可通过高表达CD40配体 (CD40 ligand, CD40L)、B细胞活化因子 (B-cell activating factor, BAFF) 等分子, 反向调控B细胞功能, 促进调节性B细胞扩增并抑制抗原呈递性B细胞的成熟, 从而形成双向交互的肿瘤免疫调控网络[72]。

1.8 CTC-髓源性抑制细胞

MDSC作为具有强免疫抑制功能的异质性髓系细胞, 通过分泌白细胞介素-10 (interleukin-10, IL-10)、TGF-β及介导精氨酸耗竭、产生ROS/活性氮 (reactive nitrogen species, RNS) 等途径, 显著抑制效应T细胞与NK细胞功能, 从而降低CTC被清除的几率, 间接促进其存活与外渗[73-75]。同时, MDSC还通过分泌VEGF等促血管因子及释放金属蛋白酶 (如MMP-9), 增强血管通透性与ECM重塑, 进一步促进CTC的黏附与跨内皮迁移, 并在肺等靶器官协助形成前转移微环境及细胞团滞留[76-78] (图1H)。

临床研究表明, 癌症患者循环中MDSC数量显著增多, 并与CTC水平呈正相关[79]。进一步研究证实, CTC可与MDSC在血液中形成CTC-MDSC细胞簇; 该簇不仅能诱导MDSC向促肿瘤表型分化, 还可通过ROS及Notch信号通路激活CTC的促生存机制[80]。类

似现象亦在胰腺导管腺癌模型中得到验证[81], 提示靶向CTC-MDSC簇的形成与功能可能为抑制肿瘤远处转移提供新的干预策略。

1.9　CTC-树突状细胞

作为专职抗原呈递细胞, DC的功能可被CTC劫持, 从而协助建立免疫耐受[82]。CTC与DC直接接触可下调DC表面MHC-II及共刺激分子的表达, 削弱其激活肿瘤特异性T细胞的能力[83]。此外, CTC-DC簇中黏附分子 (ICAM-1、VCAM-1) 表达上调, 有利于CTC在血管壁的滞留与外渗[38]。单细胞RNA测序 (single-cell RNA sequencing, scRNA-seq) 进一步显示, 受CTC驯化的DC呈现耐受性表型, 特征为程序性死亡配体1 (programmed death ligand 1, PD-L1)、吲哚胺2,3-双加氧酶1 (indoleamine 2,3-dioxygenase 1, IDO1) 与IL-10高表达, 并能通过募集Treg促进转移前微环境的形成[84,85] (图1H)。

临床研究提示, CTC可驱动DC表型与功能向促炎方向异常分化, 并与不良预后相关。在炎性乳腺癌队列中, 21例 (32.3%) CTC ≥ 5的患者总生存期 (overall survival, OS) 显著劣于CTC < 5的患者 (P = 0.045)[86]。该群体DC在Toll样受体 (Toll-like receptor, TLR) 激活后表现出TNF-α与白细胞介素-12 (interleukin-12, IL-12) 分泌异常, 且共刺激分子 (如CCR7、CD86) 表达上调, 提示炎性微环境可能通过改变DC功能进而影响患者生存[86]。

2　阻断CTC-血细胞相互作用的纳米递药系统

尽管靶向CTC及其与血小板、中性粒细胞等形成的细胞簇, 以及相关的NETs, 是抑制肿瘤转移的潜在策略, 但其临床应用仍面临诸多挑战。CTC的异质性、稀有性及NETs的复杂性, 限制了传统疗法在疗效与特异性上的提升。纳米医学凭借其精准递送与高效调控的优势, 为克服上述瓶颈提供了新途径。本文重点综述了近年来靶向纳米平台的研发进展, 包括用于直接清除CTC、解离CTC同型簇、阻断CTC-血小板/中性粒细胞簇的形成及抑制NETs生成的多种纳米策略见表2[87-106]。

Table 2　Representative nanomedicine strategies targeting CTC-blood cell interactions. TRAIL: TNF-related apoptosis-inducing ligand; dTNP: Dual-targeting nanoparticle; EpCAM: Epithelial cell adhesion molecule; uPtD NPs: Ultrasmall Pt (II) dots nanoparticles; ITGA5: Integrin alpha 5; TNBC: Triple-negative breast cancer; Rg3-Lp/DTX: Rg3-modified liposome loading docetaxel; GLUT1: Glucose transporter 1; CD44v6: CD44 variant 6; TCSN: Targeted core-satellite nanomedicine; NM-NP-CFZ: Neutrophil-mimicking nanoparticle loading carfilzomib; PLGA: Poly (lactic-*co*-glycolic acid); Dox-MPK@MDL: Doxorubicin-loaded pH-sensitive prodrug incorporated into macrophage membrane and liposome coated DNA dendrimer; EMPCs: Exosome-like membrane-coated sequential-bioactivating prodrug nanoplatform complexes; ROS: Reactive oxygen species; PTX: Paclitaxel; CuB: Cucurbitacin B; CPDD: Cancer membrane-coated digoxin and doxorubicin co-encapsulated PLGA nanoparticles; DIG: Digoxin; GSNO@BMS: NO donor-modified GOx@the hydrophobic drug BMS-202; NO: Nitric oxide; GV-Lipo/SF/DT: GV-lipo/sorafenib/digitoxin; hQNM-PLGA: hQ-MMAE2-loaded neutrophil membrane-camouflaged PLGA nanoparticles; MMAE2: Monomethyl auristatin E; Au-PB@mPDA: Gold-plasmonic blackbody@mesoporous polydopamine; mP-NP-DNase/PTX: Modified poly-lysine-based nanoparticles co-delivering deoxyribonuclease I and paclitaxel prodrug; MMP-9: Matrix metalloproteinase-9; GSH: Glutathione

Strategy category	Nanosystem	Core components & design	Function	Ref.
Targeting single CTC	E-selectin/TRAIL liposome	Liposome co-decorated with E-selectin and TRAIL	E-selectin mediates targeted adhesion; membrane-anchored TRAIL induces apoptosis in CTC	[87]
	dTNP	Paclitaxel-loaded nanoparticle conjugated with K237 peptide and Ep23 aptamer	Simultaneously targets tumor vasculature and CTC *via* EpCAM, providing synergistic inhibition of primary tumor and metastasis	[88]
	uPtD NPs	Ultrasmall platinum (II) dot nanoparticles modified with anti-ITGA5 antibody	Targets ITGA5 on TNBC cells, induces DNA damage and cell cycle arrest in stem-like cells within CTC clusters	[89]
	Rg3-Lp/DTX	Docetaxel-loaded liposome functionalized with ginsenoside Rg3	Rg3 mediates active targeting *via* GLUT1 on CTC, combining chemotherapy with metastasis microenvironment modulation	[90]
	CD44v6-targeting micelles	CD44v6-targeted polymeric micelles loaded with niclosamide	Specifically binds CD44v6, accumulates at colorectal cancer stem cell sites, and clears CTC	[91]
	TCSN	EpCAM antibody-conjugated thermo-photosensitive magnetic core-satellite nanodrug	Magnetic enrichment combined with antibody targeting enables efficient CTC capture and subsequent photothermal/photodynamic inactivation	[92]

Continued

Strategy category	Nanosystem	Core components & design	Function	Ref.
	Platelet membrane-coated system	Hollow mesoporous silica nanoparticles co-loaded with sorafenib and anti-PD-L1, coated with platelet membrane	Utilizes platelet membrane to target CTC-platelet clusters, enabling synergistic targeted therapy and immune checkpoint blockade	[93]
	NM-NP-CFZ	PLGA nanoparticles loaded with CFZ and coated with inflamed neutrophil membrane	Inherits neutrophil membrane proteins for targeting; CFZ induces apoptosis and inhibits proliferation of CTC	[94]
	DOX-MPK@MDL	Macrophage membrane-coated, cell-mimetic nanoparticles with a pH-sensitive DOX prodrug	Macrophage membrane targets lung metastatic sites; pH-responsive drug release directly clears CTC	[95]
	EMPCs	Exosome membrane-engineered nanoparticles co-loaded with a ROS-sensitive PTX prodrug and CuB	Exosome membrane confers targeting; CuB inhibits the FAK/MMP pathway and triggers ROS-activated prodrug cascades	[96]
	Hybrid membrane-coated magnetic NPs	Magnetic nanoparticles loaded with indocyanine green and coated with a hybrid membrane	Combines tumor-homing specificity and "self" recognition, enabling efficient magnetic capture and photothermal inactivation of CTC	[97]
Dissociating CTC homotypic clusters	CPDD	Tumor cell membrane-camouflaged PLGA nanoparticles co-loaded with DIG and DOX	Homologous targeting; DIG inhibits Na^+/K^+-ATPase to dissociate clusters, synergizing with DOX for anti-metastasis	[98]
Blocking CTC-platelet clusters	GSNO@BMS	Self-assembled nanozyme from glucose oxidase-NO donor conjugate and BMS-202	Depletes glucose to inhibit platelet activation; releases NO to disrupt adhesion; combines with immune checkpoint blockade	[99]
	P-Lipo (nanoplateletsomes)	Biomimetic nanoparticles formed by fusion of platelet membrane and lipid membrane	Acts as a decoy to competitively bind CTC, blocking their interaction with natural platelets and subsequent extravasation	[100]
Disrupting CTC-neutrophil clusters	GV-Lipo/SF/DT	Multifunctional liposomes co-loaded with SF, DT, and anti-VCAM-1 mAb	SF eliminates primary tumor ("root"); DT dissociates clusters; anti-VCAM-1 mAb blocks cluster formation ("seed")	[101]
	hQNM-PLGA	Hypoxia-responsive neutrophil membrane-camouflaged PLGA nanoparticles loaded with prodrug MMAE2	Competitively inhibits cluster formation; hypoxia-triggered drug release enables targeted therapy	[102]
	aNEM NPs	Activated neutrophil membrane-coated nanoparticles	Serves as nanodecoys to block adhesion between neutrophils, CTC, and vascular endothelium	[103]
Inhibiting CTC-NETs	DNase I-coated NPs	Nanoparticles surface-coated with DNase I	Enzymatically degrades the DNA backbone of NETs, releasing trapped CTC and inhibiting metastasis	[104]
	Au-PB@mPDA	Photo-responsive gold-polydopamine core-shell platform loaded with DNase I	NIR-II light triggers localized DNase I release to degrade NETs in the tumor microenvironment	[105]
	mP-NP-DNase/PTX	Dual-functional system with MMP-9-responsive DNase I release and GSH-triggered paclitaxel delivery	Degrades NETs and delivers chemotherapy synergistically, enhancing tumor cell uptake and inhibiting primary/metastatic growth	[106]

2.1 靶向杀伤单个CTC

该策略的核心在于靶向识别CTC表面特征性蛋白, 如E-选择素、上皮细胞黏附分子 (epithelial cell adhesion molecule, EpCAM)、葡萄糖转运蛋白1 (glucose transporter 1, GLUT1)、CD44变构体6 (CD44 variant 6, CD44v6)、整合素*α*5 (integrin *α*5, ITGA5)、人表皮生长因子受体2 (human epidermal growth factor receptor 2, HER2)、雌激素受体 (estrogen receptor, ER)及叶酸受体 (folate receptor, FR) 等, 并据此设计两大类纳米药物以实现精准杀伤: 一是通过配体修饰实现主动靶向的递药系统, 负载紫杉醇 (paclitaxel, PTX)、多西他赛 (docetaxel, DTX) 等化疗药、肿瘤坏死因子相关凋亡诱导配体 (tumor necrosis factor-related apoptosis-inducing ligand, TRAIL) 促凋亡蛋白、超小型铂 (II) 点 [ultrasmall platinum (II) dot] DNA损伤剂或氯硝柳胺等, 直接诱导CTC凋亡或周期阻滞; 二是基于细胞膜仿生策略的纳米粒, 包覆血小板、中性粒细胞、巨噬细胞、外泌体或杂交细胞膜, 共载索拉非尼 (sorafenib, SO/SF) 与抗PD-L1抗体、卡非佐米 (carfilzomib, CFZ)、多柔比星前药 [doxorubicin (DOX) prodrug]、葫芦素B

或吲哚菁绿 (indocyanine green, ICG) 等, 通过免疫调控、化疗或光热/光动力效应协同清除CTC。上述系统借助配体识别、磁捕获或仿生黏附机制, 实现对CTC的高效捕获与杀伤, 为阻断肿瘤转移提供了精准干预手段[87-92,107-110]。

2.1.1　配体介导的靶向纳米药物　CTC表面糖基化配体可在血流剪切力下与内皮细胞E-选择素发生特异性黏附, 为靶向递药提供了理论依据[111]。Ortiz-Otero等[87]构建了E-选择素与TRAIL共修饰的脂质体, 在前列腺癌 (prostate cancer, PC) 模型中可清除患者血样中 > 75%的CTC, 其疗效显著优于可溶性TRAIL, 表明膜锚定递送对增强凋亡诱导具有关键作用。除E-选择素外, EpCAM是另一经典CTC靶点。研究表明, EpCAM特异性RNA适配体Ep23兼具高亲和力结合与促进受体内吞的双重功能[112,113]。基于此, Yao等[88]将靶向肿瘤血管的K237肽与Ep23适配体共价偶联至载PTX NPs, 构建了双靶向纳米平台 (dual-targeting nanoplatform, dTNP), 该平台在4T1肺转移模型中能有效拦截CTC并抑制转移定植, 实现对原发瘤与CTC的协同抑制[114]。此外, ITGA5在三阴性乳腺癌 (triple negative breast cancer, TNBC) 高侵袭性细胞及肺转移灶中高表达[115]。Li等[89]构建了经抗ITGA5抗体修饰、负载超小型铂 (II) 点的纳米递药系统 [ultrasmall Pt (II) dot nanoparticles, uPtD NPs], 该系统能特异性诱导CTC簇中干细胞样细胞的DNA损伤与周期阻滞, 最终抑制肺转移进程。

除黏附分子外, CTC表面过度表达的代谢相关蛋白及干细胞标志物亦可作为靶向切入点。GLUT1在多种CTC上高表达, 人参皂苷Rg3作为一种两亲性化合物, 其结构包含亲水性糖基和类胆固醇疏水性甾体骨架, 对肿瘤细胞表面高表达的GLUT1具有特异性结合能力[90,116]。Xia等[90]构建了Rg3功能化脂质体 (Rg3-Lp/DTX) 用于共递送DTX, 该系统通过Rg3介导的GLUT1识别主动靶向CTC, 同时发挥化疗杀伤与转移微环境调控作用。另一方面, CD44变异体CD44v6特异性表达于恶性细胞, 与肿瘤转移及不良预后密切相关[117,118]。Andrade等[91]开发了CD44v6靶向的聚合物胶束, 负载氯硝柳胺后能在结直肠癌干细胞部位有效蓄积, 并在体内展现出显著的CTC清除能力。

为克服单一疗法局限, Chiang等[92]设计了可靶向的光敏−磁性核卫星纳米药物 (targeted photosensitive and magnetic core-satellite nanomedicine, TCSN), 其结构包含用于磁场富集CTC的磁性核及负载光热/光动力治疗剂的金纳米笼。通过偶联抗EpCAM抗体, TCSN对CTC的结合亲和力提升3.7倍, 微流实验证实其能实现对4T1细胞的高效磁捕获与后续光灭活。

2.1.2　仿生递送纳米药物　仿生纳米药物通过包覆天然细胞膜, 继承其表面分子与生物识别功能, 在CTC靶向与清除中展现出独特优势。根据膜来源与设计策略, 主要可分为单膜仿生系统与混合膜仿生系统两类。

血小板膜 (platelet membrane, PM) 包被的纳米粒在肿瘤治疗中展现出重要潜力, 其不仅可作为高效药物载体, 还能保留膜表面关键蛋白与分子识别特性。PM高表达的P-选择素能与肿瘤细胞表面CD44受体结合, 从而实现精准靶向并提升递药效率[93,119-121]。例如, Da等[93]将SO与抗PD-L1抗体共载于中空介孔二氧化硅纳米粒 (hollow mesoporous silica nanoparticles, HMSNs), 并包覆PM, 构建了可靶向CTC-血小板簇的仿生系统 (aPD-L1-PM-SO@HMSNs), 通过协同靶向递送抗肿瘤药物与免疫检查点抑制剂有效清除CTC。此外, 炎症活化的中性粒细胞膜 (neutrophil membrane, NM) 亦被用于包覆载有蛋白酶体制剂CFZ的聚乳酸−羟基乙酸共聚物 [poly (latic-*co*-glycolic acid), PLGA] 纳米粒 (carfilzomib-loaded NM-NPs, NM-NP-CFZ), 该系统通过膜表面整合素等黏附蛋白识别CTC并靶向转移前微环境, 凭借CFZ诱导凋亡与抑制增殖的双重机制清除CTC, 阻断肿瘤远处播散[94]。针对肺转移治疗, 巨噬细胞膜 (macrophage membrane, MM) 因其表面表达的α4整合素可与肿瘤细胞上调的VCAM-1特异性结合, 具有良好的肺转移灶靶向潜力[122,123]。基于此, Li等[95]设计了一种智能细胞样纳米前药系统 (intelligent cell-like nano-prodrug, DOX-MPK@MDL)。该体系以DNA四面体树枝状聚合物为刚性骨架, 负载pH敏感型DOX-MPK前药 (其中DOX作为双链DNA嵌入剂), 通过层级自组装依次包覆脂质体和MM, 形成具有仿生结构的NPs。该系统可主动靶向乳腺癌肺转移灶, 在病理微环境中响应释放DOX, 从而有效清除CTC并抑制肺转移进程。

外泌体是一类直径约50～150 nm的细胞外囊泡, 可由肿瘤细胞、免疫细胞、干细胞及内皮细胞等多种细胞分泌[124]。其膜表面富含CD44、CD47等特异性黏附分子, 赋予其良好的靶向识别能力[125]。基于此, Wang等[96]开发了外泌体膜修饰的纳米药物 (exosome-like sequential-bioactivating prodrug nanoplatform, EMPCs), 该体系能通过高亲和力相互作用特异性捕获并清除CTC。EMPCs设计整合了ROS敏感的紫杉醇−油酸前药 (paclitaxel-linoleic acid conjugates, PTX-S-LA) 与葫芦素B (cucurbitacin B, CuB) 两种组分: 进入肿瘤细胞后, 释放的CuB可下调FAK/MMP信号通路以抑制转移, 同时升高细胞内氧化水平, 进而触发ROS敏感的

前药级联活化, 协同发挥抗转移作用。体外和体内实验表明, EMPCs具有长循环、选择性靶向及良好肿瘤穿透能力, 可通过清除CTC并调控FAK/MMP通路有效抑制肿瘤转移。

此外, 通过融合不同来源的细胞膜, 可集成多种靶向功能并减少非特异性吸附[97,126,127]。Sun等[97]构建了由人乳腺癌细胞膜 (tumor cell membranes, TMs) 与白细胞膜 (white blood cell membranes, WMs) 组成的杂交膜 (hybrid membrane, HM), 用以包覆负载ICG的磁性纳米粒。该设计同时继承TMs的靶向特异性和WMs的“自我”识别功能, 在提升CTC捕获效率与纯度的基础上, 进一步结合光热/光动力效应实现捕获后的原位灭活, 形成了“捕获−清除”一体化的协同策略。

2.2 靶向解离CTC同型簇

CTC在血液与淋巴系统中可以单细胞或细胞簇形式存在, 其中CTC簇的转移潜能可达单细胞的23～50倍, 因此抑制CTC簇的形成与循环已成为抗肿瘤转移的关键靶点[128]。Na^+/K^+-ATP酶抑制剂可通过升高细胞内Ca^{2+}水平破坏细胞间连接, 促使CTC簇解离, 从而抑制转移进程[129]。基于此, Li等[98]开发了肿瘤细胞膜修饰的共载地高辛 (digoxin/digitoxin, DIG/DT) 与DOX PLGA纳米粒 (cancer membrane-coated DIG and DOX co-encapsulated PLGA nanoparticles, CPDD)。该纳米系统利用同源肿瘤细胞膜实现精准靶向, 可同时作用于原位肿瘤细胞与CTC簇。所负载的DIG通过抑制Na^+/K^+-ATP酶活性诱导细胞内Ca^{2+}积聚, 促使CTC簇解离, 同时诱导线粒体介导的肿瘤细胞凋亡, 并抑制上皮−间质转化 (epithelial-mesenchymal transition, EMT) 过程, 从而阻断乳腺癌细胞的迁移与侵袭。实验结果表明, CPDD在体内外模型中不仅能有效抑制CTC簇的形成与循环, 还可精准杀伤原位肿瘤, 展现出显著的抗肿瘤及抗转移效果。

2.3 阻断CTC-血小板簇

在循环系统中, 血小板通过捕获CTC、增强其黏附并促进血管外渗, 显著加速肿瘤转移进程。因此, 靶向抑制肿瘤细胞诱导的血小板聚集 (tumor cell-induced platelet aggregation, TCIPA) 及阻断CTC-血小板簇的形成, 已成为干预血小板介导转移的重要策略。

血小板活化依赖能量代谢, 抑制其代谢可有效削弱聚集功能。Hu等[99]构建了由一氧化氮 (nitric oxide, NO) 供体修饰的葡萄糖氧化酶与免疫检查点抑制剂BMS-202自组装而成的纳米酶系统 (GSNO@BMS)。该系统可特异性耗竭TME中葡萄糖, 从而抑制血小板能量代谢与活化, 减少CTC-血小板微聚集体形成; 同时原位释放的NO可破坏血小板对CTC的黏附保护, 并协同BMS-202阻断PD-1/PD-L1通路, 激活T细胞免疫, 实现多机制协同清除CTC。

利用PM或仿生结构竞争性结合CTC, 可阻断其与天然血小板的相互作用。Zhang等[100]开发了一种由PM与脂质膜融合而成的“纳米血小板体”(P-Lipo), 该仿生结构可竞争性结合CTC, 阻断其与天然血小板的相互作用。研究表明, P-Lipo能作为纳米诱饵高效捕获CTC, 干扰其在血管内皮处的滞留、外渗及EMT进程。在小鼠乳腺肿瘤转移模型中, P-Lipo通过上述竞争性结合降低CTC在血液中的存活率, 并进一步通过抑制炎症反应、阻断CTC逃逸, 有效遏制转移瘤的生长。

2.4 阻断CTC-中性粒细胞簇

CTC-中性粒细胞簇通过保护CTC免受免疫清除, 已成为肿瘤转移进程的关键驱动因素。基于中性粒细胞向炎症部位的天然趋向性, 目前已有3类纳米治疗策略通过靶向干预该簇团形成而展现抗转移潜力。

Mu等[101]开发了一种“根源与种子”多点协同纳米系统 (GV-Lipo/SF/DT), 可同时靶向原发肿瘤与CTC。该纳米装置通过将SF和DT共载于脂质体, 并在其表面同时修饰抗磷脂酰肌醇蛋白聚糖3 (glypican-3, GPC3) 单克隆抗体与抗VCAM1单克隆抗体制备而成。该系统利用SF清除原发肿瘤, 从源头上减少CTC释放; 同时借助对GPC3与VCAM1的识别增强CTC捕获, 并利用DT解离CTC簇, 借助抗VCAM1单克隆抗体阻断CTC-中性粒细胞簇形成, 进而通过SF杀伤CTC。在H22及原位肝癌模型中, 该系统显著提升CTC清除率、抑制转移并增强抗肿瘤疗效。Huang等[102]设计了一种靶向原发肿瘤与中性粒细胞-CTC簇的多位点攻击纳米药物, 用于增强癌症治疗与转移抑制。首先, 将缺氧响应性醌修饰的一甲基澳瑞他汀E (monomethyl auristatin E, MMAE) 二聚体前药 (hQ-MMAE2) 包载于PLGA纳米粒中。进一步, 将NM包覆于PLGA纳米粒表面 (hQNM-PLGA), 赋予其中性粒细胞的生物学特性, 如肿瘤归巢能力及对CTC的黏附能力。经静脉注射后, hQNM-PLGA纳米粒可借助中性粒细胞的天然功能被募集至炎性肿瘤部位, 从而增强其稳定性与肿瘤蓄积, 并最大限度减少MMAE在体循环中的泄漏。在晚期乳腺癌的严重缺氧微环境下, hQ-MMAE2可发生降解, 促进MMAE释放, 从而实现显著的抗肿瘤疗效。此外, hQNM-PLGA纳米粒能够有效与中性粒细胞竞争性结合CTC, 从而阻断中性粒细胞-CTC簇的形成, 进一步抑制肿瘤转移。这种多位点攻击、高载药量的仿生纳米药物为肿瘤转移抑制与癌症治疗提供了新策略。Zeng等[103]则研制了活

化NM包被的纳米粒子 (aNEM NPs), 将其作为纳米诱饵以阻断中性粒细胞介导的转移进程。aNEM NPs可干扰中性粒细胞向原发灶及转移前微环境的募集, 抑制其与血管内皮及CTC的黏附, 并在体内外破坏CTC-中性粒细胞簇的形成。在4T1移植瘤模型中, 该系统显著降低多器官转移发生率。

总之, 靶向CTC-中性粒细胞簇的纳米策略通过竞争性结合中性粒细胞、阻断簇团形成、协同杀伤CTC等多重机制, 在抑制肿瘤转移方面展现出良好的应用前景。随着仿生递送、微环境响应及多功能协同技术的不断深入, 此类干预策略有望为肿瘤转移防治提供新的临床转化方向。

2.5　阻断CTC-NETs

为阻断NETs介导的CTC免疫逃逸与转移促进作用, 新兴纳米策略聚焦于NETs的抑制或降解[22]。Park等[104]率先采用脱氧核糖核酸酶I (deoxyribonuclease I, DNase I) 包被的纳米粒酶解NETs的DNA骨架, 在乳腺癌小鼠模型中成功解离被捕获的CTC, 并使肺转移降低62%; 研究同时证实DNase I在体外可通过破坏NETs结构抑制乳腺癌细胞迁移。

Yin等[106]构建了兼具MMP-9响应性DNase I释放与谷胱甘肽触发PTX递送的双功能纳米系统 (mP-NP-DNase/PTX), 在TNBC模型中实现84%的NETs降解效率, 并通过Tat肽介导使肿瘤细胞内吞效率提高3.2倍, 最终协同抑制原发瘤生长 (降低58%) 与远处转移 (抑制73%)。

Chen等[105]进一步构建了一种以具有宽谱光活性的等离激元金黑体 (plasmonic gold blackbody, AuPB) 为核心、介孔聚多巴胺 (mesoporous polydopamine, mPDA) 为外壳的纳米平台, 可实现DNase I的高效负载及光控释放。在第二近红外 (second near-infrared, NIR-II) 光照射下, 按需释放的DNase I可有效破坏“NETs介导的物理屏障”, 从而增强活体小鼠中免疫效应细胞与肿瘤细胞的接触, 增敏原发性结直肠癌 (colorectal cancer, CRC) 的免疫检查点治疗。值得注意的是, 该AuPB@mPDA载体经系统给药后可在CRC最频发的转移器官肝脏中富集, 并通过光控药物释放消除NETs介导的CTC捕获, 进而抑制转移定植。该研究为免疫介导的肿瘤消退与转移抑制提供了具有临床转化潜力的新策略。

综上所述, 基于DNase I的NETs靶向纳米策略通过降解NETs结构、阻断CTC捕获、改善免疫微环境等多重机制, 在抑制肿瘤转移方面展现出广阔前景。随着响应性递送、多功能协同及精准靶向技术的不断发展, 此类策略有望为肿瘤转移干预提供新的临床转化路径。

2.6　纳米药物的临床研究与应用

尽管转移性肿瘤的治疗面临诸多挑战, 纳米药物凭借其独特的药代动力学特征与靶向递送优势, 已在临床抗转移治疗中展现出重要价值。截至目前, 全球已有8款纳米药物获批用于转移性肿瘤的治疗[2] (表1)。其中, 聚乙二醇化脂质体多柔比星 (Doxil/Caelyx) 作为首个获批的肿瘤纳米药物, 广泛用于转移性乳腺癌等恶性肿瘤的治疗[130]; 白蛋白结合型紫杉醇 (Abraxane) 则获批用于转移性乳腺癌、胰腺癌及非小细胞肺癌等[131,132]。此外, 脂质体伊立替康 (Onivyde)、脂质体阿糖胞苷 (DepoCyt) 及紫杉醇胶束 (Nanoxel、Genexol PM) 等制剂也相继获批用于不同转移性肿瘤的治疗[133]。值得注意的是, 上述纳米药物的临床应用多源于其在晚期肿瘤治疗中的疗效与安全性优势, 而非针对转移过程的特异性设计。然而, 临床研究数据显示, 这些制剂可通过延长循环时间、增强肿瘤蓄积及降低系统毒性, 显著改善转移性肿瘤患者的治疗获益[134,135]。

近年来, 随着对肿瘤转移级联过程认知的深入, 越来越多的新型纳米药物进入临床研究阶段, 其设计策略已超越传统被动靶向范畴, 向主动靶向、刺激响应性释放及免疫联合治疗等方向拓展 (表1)。例如, 靶向前列腺特异性膜抗原 (prostate-specific membrane antigen, PSMA) 的BIND-014纳米粒已完成治疗转移性去势抵抗性前列腺癌的II期临床研究[136]; 靶向HER2的MM-302脂质体曾进入治疗HER2阳性转移性乳腺癌的II/III期临床[137]; 温敏脂质体 (lyso-thermosensitive liposomal doxorubicin, LTLD) 联合射频消融治疗肝转移瘤的临床研究显示, 其可在局部热疗触发下实现药物可控释放[138,139]。值得关注的是, 以脂质纳米颗粒递送的mRNA疫苗已进入针对多种转移性实体瘤的临床研究阶段, 通过表达肿瘤新抗原激活特异性免疫应答[140,141]。此外, 兼具影像诊断与治疗功能的诊疗一体化纳米药物, 如放射性标记的Cornell点及pH敏感型ONM-100荧光成像探针, 为转移灶的精准定位与手术导航提供了新工具[142,143]。上述研究进展表明, 纳米药物在转移性肿瘤治疗领域的临床转化正逐步从传统的化疗增敏向免疫调控、基因治疗及多模态联合干预的方向演进, 为改善转移性肿瘤患者预后开辟了新路径。

3　展望与挑战

CTC的远端定植并非孤立事件, 而是其与血液中多种细胞成分 (如血小板、中性粒细胞、巨噬细胞、淋巴细胞等) 发生复杂动态互作的结果[14,15]。这些相互

作用通过提供物理庇护、介导免疫逃逸、协助血管黏附与外渗, 以及塑造转移前微环境等多种机制, 共同构成了支撑肿瘤血行转移的关键生物学基础。针对这一过程, 纳米医学提供了多层次的干预策略: 通过功能化配体或仿生膜涂层主动靶向并清除单个CTC; 利用离子通道调节剂等解离高转移潜能的CTC同型簇; 以及通过抑制血小板活化、竞争性结合中性粒细胞或降解NETs等方式, 阻断CTC-血细胞异型簇的形成与功能。这些策略充分展现了纳米平台在时空精准递送与多机制协同治疗方面的独特优势。

然而, 该领域在迈向临床转化过程中仍面临多重挑战 (表3)[87-110,126,127]。首要挑战源于靶点本身的复杂性。CTC及其簇的分子表型具有高度异质性, 且其与血细胞的相互作用网络动态多变, 这对纳米药物的广谱识别能力和适应性能提出了极高要求。其次, 作用机制的认知仍需深化。目前对CTC与特定血细胞 (如红细胞、B细胞) 相互作用的详细分子机制了解尚不充分, 这限制了对作用环节的精准干预。第三, 纳米系统的生物相容性与可控性问题突出。仿生纳米药物面临细胞膜来源、量产标准化、活性保持及潜在风险 (如免疫原性、促血栓性) 等挑战; 而合成纳米载体在集成多重功能时, 其体内稳定性、药代动力学行为及长期安全性需系统评估。最后, 临床转化模型与疗效验证存在鸿沟。多数研究基于小鼠模型, 其循环系统与免疫环境与人体存在差异, 难以完全模拟人体内CTC的生存与互作状态; 针对循环中稀有CTC的清除效率, 也需在更接近临床的模型中予以验证。

未来应在以下几方面重点突破: 一是深化互作机制研究。综合利用多组学技术与活体成像, 系统阐明不同CTC-血细胞互作在转移全过程中的关键分子事件与信号通路, 为发现新靶点提供理论基础。二是推动纳米技术升级。开发更智能的仿生与合成材料, 提高其对动态靶点的识别能力及在复杂血流环境下的性能; 利用微流控、自动化等技术优化制备工艺, 提升批次间一致性。三是探索联合治疗新范式。将纳米介导的CTC靶向清除与全身性免疫治疗、放疗或靶向治疗深度结合, 实现原发灶控制与转移预防的协同。四是构建更具预测性的转化模型。积极利用人源化小鼠模型、患者来源类器官及肿瘤芯片等先进平台, 在更贴近人体生理的环境中评估纳米策略的有效性与安全性。

总之, 靶向CTC-血细胞相互作用的纳米策略为干预肿瘤转移提供了具有前景的新途径。尽管在机制认知、技术转化与临床评估方面仍存在诸多挑战, 但随着跨学科融合的深入与纳米技术的持续创新, 这类精准可控的治疗工具有望为未来遏制癌症转移、改善患者预后开辟新的道路。

Table 3 Strengths and limitations of nanomedicine targeting CTC-blood cell interactions. HCC: H22 hepatocellular carcinoma

Strategy category	Strength	Limitation	Experimental model	Ref.
Targeting single CTC	Active recognition and clearance *via* specific ligands (antibodies, aptamers) or biomimetic membranes	Heterogeneity and loss of target antigens on CTC; binding efficiency under high shear stress in blood flow; scalable production and standardization of biomimetic membranes	Patient blood samples (prostate cancer); 4T1 mammary tumor model; colorectal cancer stem cell model; TNBC lung metastasis model	[87-97, 107-110, 126,127]
Dissociating CTC homotypic clusters	Disrupting intercellular junctions by modulating key targets (e.g., Na^+/K^+-ATPase), reducing metastatic potential of clusters	Potential off-target effects on normal cell functions; ensuring sufficient drug accumulation at the site of CTC clusters	Orthotopic mammary tumor model; lymph node metastasis model; experimental CTC cluster metastasis model	[98]
Blocking CTC-platelet clusters	Inhibiting platelet activation or using nanodecoys to competitively bind CTC, thereby blocking physical protection and immune evasion	Risk of interfering with normal hemostasis; potential pro-thrombotic risk associated with platelet membrane-based materials	4T1 mammary tumor model	[99,100]
Disrupting CTC-neutrophil clusters/NETs	Destabilizing clusters or degrading NETs to remove CTC protection and enhance immune surveillance	Possible impairment of neutrophil-mediated host defense; need for precise spatiotemporal control of NETs inhibition to avoid excessive inflammation	HCC model; 4T1 mammary tumor model; colorectal cancer liver metastasis model; A549 subcutaneous xenograft model; postoperative breast cancer recurrence model	[101-106]
Integrated multifunctional platforms	Combining chemotherapy, immunotherapy, and physical therapy for synergistic anti-metastatic efficacy	Complexity in design, synthesis, and quality control; challenges in balancing efficacy and safety due to intricate pharmacokinetics of multicomponent systems	Microfluidic chip model	[92]

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