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循环肿瘤细胞的微环境互作与时空节律调控及其精准干预策略

杜星　万方*
(内蒙古农业大学, 生命科学学院, 呼和浩特 010010)

摘要　循环肿瘤细胞(circulating tumor cells, CTCs)作为恶性肿瘤转移的核心媒介, 也是液体活检的重要靶标, 在肿瘤演变与临床诊疗中具有不可替代的科学价值。CTCs在血流中的生存与远端器官定植依赖于一系列高度协调的动态演变过程。该文系统探讨了CTCs的生物学基础, 阐明了上皮–间质转化(epithelial-mesenchymal transition, EMT)的动态平衡、表观遗传重编程、失巢凋亡抵抗(anoikis resistance, AR)及代谢重编程在维持CTC存活中的关键作用。最新研究发现, CTCs的释放与播散受到昼夜节律系统的严格调控。同时, CTC簇通过与血小板、免疫细胞等微环境组分形成异质性多细胞复合体, 极大增强了其免疫逃逸与远端靶器官定植能力。得益于微流控及单细胞多组学技术的迅猛发展, 研究人员通过高灵敏度检测体系实现了CTCs空间分子图谱的深度解析, 也为微小残留病灶(minimal residual disease, MRD)监测、靶向治疗与耐药动态监测提供了实时监控平台。未来针对CTCs的突破性诊疗方向将侧重于精准阻断AR通路、逆转异常甲基化、靶向干预膜蛋白及外泌体介导的器官趋向性转移关键靶点。整合多维度的液体活检数据, 将进一步推动临床标准化诊疗体系革新, 为实现癌症的精准防控提供有力支撑。

关键词　循环肿瘤细胞; 恶性肿瘤转移; 昼夜节律动力学; 免疫微环境; 单细胞多组学

Microenvironmental Remodeling and Circadian Regulation-Driven Evolution of Circulating Tumor Cells and Targeted Intervention Strategies

DU Xing, WAN Fang*
(*College of Life Sciences, Inner Mongolia Agricultural University, Hohhot 010010, China*)

Abstract　CTCs (circulating tumor cells) are central to cancer metastasis and serve as important targets for liquid biopsies, offering crucial insights into tumor evolution and clinical management. The survival of CTCs in the bloodstream and their subsequent spread across organs depend on highly coordinated, dynamic evolutionary processes. Here, this article systematically reviews the biological foundations of CTCs, highlighting the essential roles of EMT (epithelial-mesenchymal transition) plasticity, epigenetic reprogramming, AR (anoikis resistance), and metabolic rewiring in maintaining CTC viability. Recent studies suggest that CTC shedding and dissemination are tightly regulated by circadian rhythms. Additionally, CTCs often cluster with microenvironmental components, such as platelets and immune cells-to form heterotypic multicellular groups. These clusters greatly enhance immune

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*通信作者。Tel: 13404813212, E-mail: fwan@imau.edu.cn
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*Corresponding author. Tel: +86-13404813212, E-mail: fwan@imau.edu.cn

evasion and the efficiency of distant organ colonization. Thanks to rapid advances in microfluidics and single-cell multi-omics, high-sensitivity detection platforms now enable detailed analysis of spatial molecular landscapes. These technologies facilitate real-time monitoring of MRD (minimal residual disease), responses to targeted therapies, and the development of drug resistance. Future approaches targeting CTCs will likely focus on precisely disrupting AR pathways, reversing abnormal methylation, and inhibiting key metastatic drivers mediated by membrane proteins and exosomes. Integrating multidimensional liquid biopsy data offers the potential to drive a major shift in clinical protocols, ultimately enhancing precision oncology and improving cancer management.

Keywords circulating tumor cells; malignant tumor metastasis; rhythm dynamics; tumor microenvironment; single-cell multi-omics

循环肿瘤细胞(circulating tumor cells, CTCs)主要来自原发灶或继发性转移灶，经脱落后进入患者的外周血循环[1-3]。这些细胞构成了肿瘤向远端器官定植的病理基础。CTCs能够借助血液与淋巴管网络向全身播散，这也正是导致绝大多数实体瘤患者出现致死性转移的直接诱因[4]。作为液体活检的关键靶标，CTCs不仅携带了原发肿瘤的完整基因组与表观遗传信息，更通过其动态演变实时反映了肿瘤在治疗压力下的适应性轨迹。

CTCs进入血流后，通过上皮–间质转化(epithelial-mesenchymal transition, EMT)、表观及代谢重编程建立失巢凋亡抵抗(anoikis resistance, AR)，以克服剪切力与免疫清除等多重压力[5-6]。近期研究揭示，CTC脱落和播散受宿主昼夜节律严格驱动，提示临床干预需具有时间特异性[7]。在空间维度上，CTCs倾向于与血小板或中性粒细胞等微环境组分结合形成异质性细胞簇，进而通过物理屏障与免疫检查点激活介导免疫逃逸，显著促进其在远端靶器官的趋向性锚定与定植[8-10]。

基于上述科学背景，本文系统探讨CTCs在恶性转移中的核心生物学机制，深度剖析其在复杂微环境中的生存策略与昼夜节律动力学，并全面评估新型交叉检测技术在推动临床精准干预及标准化诊疗体系革新中的深远转化价值。

1 CTCs研究的演进脉络

1.1 萌芽探索期

CTCs的研究始于19世纪中叶，研究者首次在血液标本中鉴定出具有原发肿瘤形态特征的上皮细胞[11]。受当时分离与检测技术的限制，早期探索阶段进展较为缓慢。

20世纪后期，物理学与分子生物学交叉学科的快速发展，为CTCs的实质性研究奠定了基础。通过对肿瘤细胞脱落速率的定量分析，相关研究充分证实了CTCs在肿瘤转移过程中发挥核心桥梁作用。免疫学研究也进一步揭示，自然杀伤细胞(natural killer cell, NK)对CTCs具有显著清除效应[12]。逆转录–聚合酶链式反应(reverse transcription-polymerase chain reaction, RT-PCR)技术的引入显著提高了特定上皮标志物的检测灵敏度[13]。但此阶段依赖物理特性的富集策略存在显著的局限性。分离纯度低与假阳性率高是其面临的两大主要缺陷(图1A)。

20世纪末期至21世纪初期，生物技术与临床转化研究相继取得关键性突破。在此背景下，标准化且具备自动化功能的检测系统得以成功研发并获批应用。这一重要成就标志着相关技术迈入了新的发展阶段[14-15]。

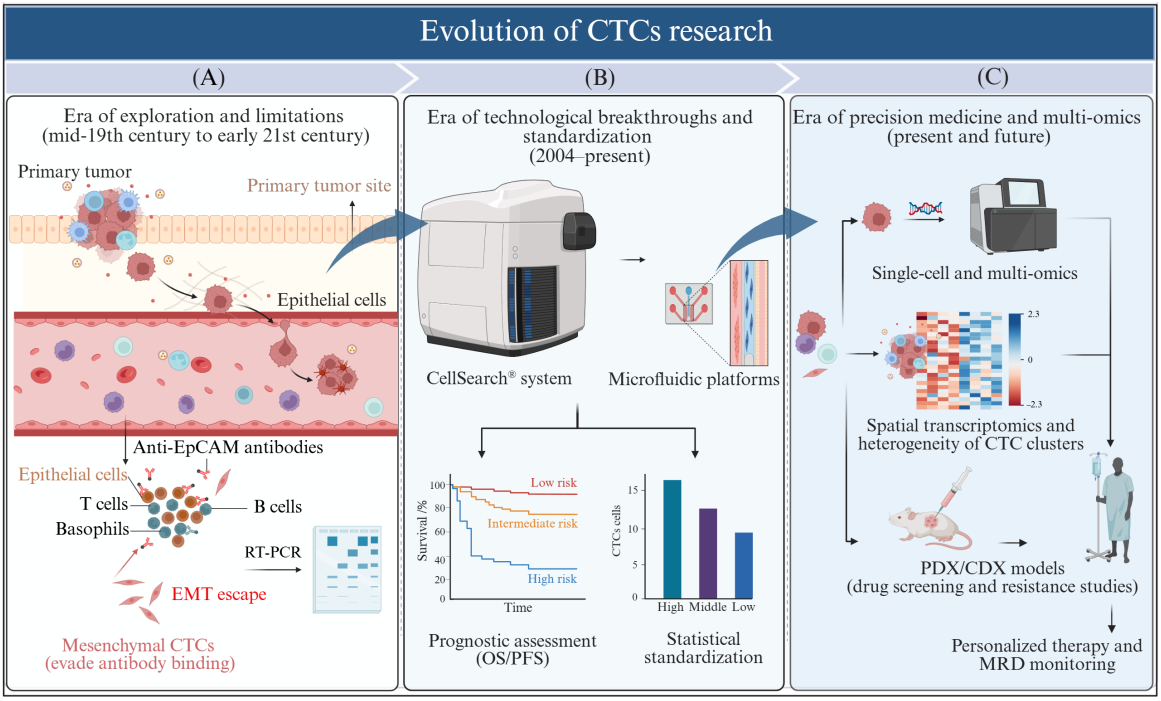
1.2 技术突破与创新平台

2004年，CellSearch®系统获得FDA批准，成为CTCs研究迈入新阶段的标志。这项免疫磁性富集技术靶向上皮细胞黏附分子，率先实现了CTCs的高重复性计数。大量临床研究表明，CTCs计数可作为转移性乳腺癌、前列腺癌与结直肠癌的独立预后指标，阳性细胞数阈值与更短的无进展及总生存期密切相关，有效推动了液体活检在肿瘤学领域的临床转化[15-18]。

早期检测手段极易漏检EMT细胞。为突破此技术瓶颈，以微流控芯片为代表的新型平台逐步得到应用(图1B)[19]。这些新技术解决了捕获效率低与纯度不足等问题，促使CTCs检测手段向多样化方向发展[20-21]。

1.3 精准医学与复杂机制

近年来，CTCs研究得益于微流控芯片与单细胞转录组测序(single-cell RNA sequencing, scRNA-seq)



A: 早期探索期——依赖RT-PCR和简单的EpCAM富集, 面临纯度低和假阳性率高的弊端; B: 技术突破期——以CellSearch®系统(FDA批准)和微流控平台为代表, 实现了CTCs的标准化计数及其在总生存期(OS)和无进展生存期(PFS)中的预后价值评估; C: 精准医疗与多组学期: 利用单细胞测序、空间转录组学、PDX/CDX模型, 并结合人工智能技术, 推动个性化治疗和微小残留病(MRD)的精准监测。

A: era of exploration and limitations: characterized by a reliance on RT-PCR and basic EpCAM enrichment, this stage was hampered by limitations such as low purity and high false-positive rates; B: era of technical breakthroughs and standardization: marked by the advent of the FDA-approved CellSearch® system and microfluidic platforms; achieved standardized CTCs enumeration and clinical validation of its prognostic value for OS (overall survival) and PFS (progression-free survival); C: era of precision medicine and multi-omics: leverages single-cell sequencing, spatial transcriptomics, and PDX/CDX models integrated with artificial intelligence; drives personalized therapeutic strategies and high-precision monitoring of MRD (minimal residual disease).

图1 循环肿瘤细胞(CTCs)研究的演进(本图由BioRender绘制)

Fig.1 Evolution of CTCs (circulating tumor cells) research (created by BioRender)

技术的进步, 已迈入单细胞组学阶段, 能够精准解析细胞簇的立体空间结构及细胞间信号传递, 从分子层面阐释肿瘤转移现象[8,22-26]。借助空间转录组学手段对比不同空间位置的转录图谱[27], 研究者可以直观解析细胞内的显著异质性, 并梳理出EMT与耐药性发展的分子轨迹, 为探究其内在机制奠定理论基础[28-31]。

细胞衍生异种移植(cell-derived xenograft, CDX)和患者来源肿瘤异种移植(patient-derived xenograft, PDX)模型的逐步发展, 确立了其在肿瘤功能学研究中的核心地位。研究者借助此类活体系统不仅验证了转移起始细胞驱动远端病灶形成及重塑肿瘤表型的内在能力, 还建立起了用于高通量药物筛选与动态评估耐药演变的平台[32-37]。

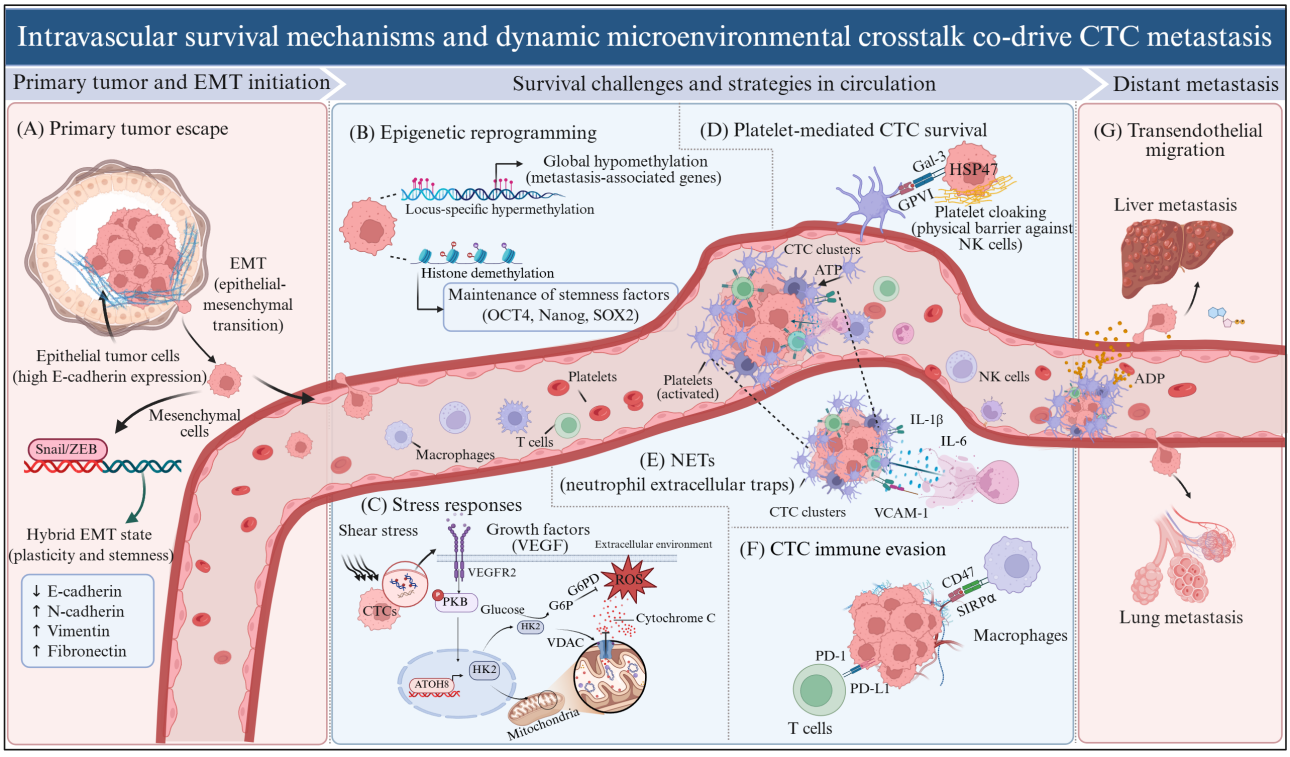
CTCs的研究正快速向多组学数据整合及临床转化应用方向发展。引入人工智能(artificial intelligence, AI)和机器学习(machine learning, ML)算法后, 细胞识别精确度及预后评估灵敏度得到显著提升[8,30-31,38-40]。这些技术的交叉应用更加清晰地描绘出CTCs的动态演变轨迹, 为微小残留病灶(minimal residual disease, MRD)的长期监测及个性化靶向治疗提供了理论基础(图1C)[2,33-37]。

2 CTCs生存的生物学基础

CTCs脱离原发灶并进入循环血液后, 必须适应严苛的血流微环境以维持存活, 最终在远端靶器官形成转移灶。这一过程涵盖了极为复杂的分子机制与生存策略(图2)。

2.1 EMT的动态平衡

上皮–间质转化是肿瘤细胞获得侵袭能力并进入血液循环成为CTCs的核心启动程序。在Snail家族锌指转录因子(snail family transcriptional repressor,



A: 原发肿瘤逃逸与EMT起始。原发肿瘤细胞通过EMT脱落进入血液。在此过程中, Snail/ZEB表达上调, 导致E-钙黏蛋白表达水平降低, 而N-钙黏蛋白、波形蛋白和纤连蛋白等间质标志物表达水平升高, 形成具有可塑性和干性的混合EMT状态。B: 表观遗传重编程。CTCs发生转移相关基因的全基因组低甲基化和位点特异性高甲基化, 并通过组蛋白去甲基化维持OCT4、Nanog和SOX2等干性因子的表达。C: 应激(失巢凋亡抵抗机制)。面对血液剪切应力, CTCs通过激活VEGFR2/PKB通路以及增强糖酵解来调控线粒体功能和活性氧(ROS)水平, 从而抵抗失巢凋亡。D: 血小板介导CTC存活。CTCs表面Gal-3通过与GPVI结合或通过HSP47分泌胶原形成“血小板伪装”, 为CTCs提供抵抗自然杀伤(NK)细胞的物理屏障。E: 中性粒细胞胞外诱捕网。中性粒细胞释放的胞外诱捕网(NETs)以及相关因子(如VCAM-1、IL-1β、IL-6)可促进CTC簇的形成和存活。F: CTC免疫逃逸。CTCs和CTC簇通过上调PD-L1和CD47表达, 分别与T细胞的PD-1和巨噬细胞的SIRPα结合, 从而逃避免疫监视。G: 远端转移。存活的CTCs最终发生跨内皮迁移, 导致肝脏、肺部等远端器官的肿瘤定植。

A: primary tumor escape and EMT initiation. Primary tumor cells detach and enter the bloodstream through EMT. This process is characterized by the upregulation of Snail/ZEB, leading to decreased E-cadherin and increased mesenchymal markers such as N-cadherin, vimentin, and fibronectin, resulting in a hybrid EMT state with high plasticity and stemness. B: epigenetic reprogramming. CTCs undergo genome-wide hypomethylation and site-specific hypermethylation of metastasis-related genes. They also maintain the expression of stemness factors (OCT4, Nanog, SOX2) via histone demethylation. C: stress (anoikis resistance mechanisms). In response to fluid shear stress, CTCs resist anoikis by activating the VEGFR2/PKB pathway and enhancing glycolysis to regulate mitochondrial function and ROS (reactive oxygen species) levels. D: platelet-mediated CTC survival. Gal-3 on the CTCS surface binds to GPVI, or facilitates collagen secretion via HSP47, to form a “platelet cloak”, which serves as a physical barrier protecting CTCs from NK (natural killer cell) mediated clearance. E: NETs (neutrophil extracellular traps). NETs released by neutrophils, along with associated factors (e.g., VCAM-1, IL-1β, IL-6), facilitate the formation and survival of CTC clusters. F: CTC immune escape. CTCs and CTC clusters evade immune surveillance by upregulating PD-L1 and CD47, which interact with PD-1 on T cells and SIRPα on macrophages, respectively. G: distant metastasis. Surviving CTCs eventually undergo transendothelial migration, leading to metastatic colonization in distant organs such as the liver and lungs.

图2　血管内生存机制和动态微环境串扰共同驱动CTC转移(本图由BioRender绘制)

Fig.2　Intravascular survival mechanisms and dynamic microenvironmental crosstalk co-drive CTC metastasis (created by BioRender)

Snail)和锌指E盒结合同源框蛋白(zinc finger E-box binding homeobox, ZEB)等转录因子的诱导调控下, 肿瘤细胞下调E-钙黏蛋白(E-cadherin, CDH1)上皮标志物, 同时上调N-钙黏蛋白(N-cadherin, CDH2)、纤连蛋白(fibronectin, FN)和波形蛋白(vimentin, VIM)间充质标志物, 为CTCs提供了一定程度的伪基质支撑, 缓冲流体剪切力对细胞膜的直接冲击(图2A)[41-44]。

当CTCs抵达远端毛细血管后, CTCs需经历逆向的EMT转化, 从而恢复增殖能力并完成远端定植[45-47]。该转化机制不仅驱动CTCs的转移级联反应, 而且介导治疗压力下的演化, 与肿瘤恶性进展及临床耐药密切相关[8,48]。转化过程伴随的表观遗传修饰可激活促迁移、抗凋亡相关基因, 且染色质重塑在维持

上皮表型及耐药方面发挥着协同作用[49]。

2.2 表观遗传学的深度调控

CTCs具备类似胚胎干细胞的低甲基化图谱, 能够特异性降低转录因子结合位点的甲基化水平: 八聚体结合转录因子4(octamer-binding transcription factor 4, OCT4)、Nanog和SRY-box转录因子2(SRY-box transcription factor 2, SOX2)结合位点的低甲基化状态, 赋予了细胞簇更强的自我更新能力与转移优势, 这也是患者临床预后不良的重要原因(图2B)[50]。逆转异常甲基化状态已在临床干预方向中得到应用[29]。例如, 应用特定的离子泵抑制剂可有效重塑CTCs的表观遗传特征, 进而阻断肿瘤的全身性播散[50]。

除DNA甲基化外, 组蛋白修饰也是决定细胞生存状态的关键。组蛋白去甲基化酶的异常上调可通过擦除甲基化标记和重塑染色质空间构象, 在转录层面维持细胞的干性特征[51]。同时, 多种甲基转移酶和去甲基化酶的协同作用不仅精准调控基因表达网络, 还能协助肿瘤细胞逃避宿主免疫系统的监视[52]。

2.3 机械力受体介导的代谢重编程

在正常生理状态下, 上皮细胞一旦脱离细胞外基质(extracellular matrix, ECM)的锚定, 便会触发失巢凋亡。CTCs存活的首要前提是克服隔离胁迫并阻断凋亡信号通路, 从而获得AR。

机械应力不仅是生存筛选压力, 更是促肿瘤转移信号。血流剪切力能够直接触发血管内皮生长因子受体2(vascular endothelial growth factor receptor 2, VEGFR2)及下游蛋白激酶B(protein kinase B, PKB)通路的活化, 从而诱导AR。例如, 在结直肠癌等模型中, 剪切应力刺激可导致CTCs分泌血管内皮生长因子(vascular endothelial growth factor, VEGF), 进而以自分泌的方式激活VEGFR2以及PKB级联信号。此过程进一步上调机械敏感转录因子无调性bHLH转录因子8(atonal bHLH transcription factor 8, ATOH8)的表达。ATOH8在CTCs中发挥着代谢重编程的核心作用, 其通过转录调控激活己糖激酶(hexokinase, HK)促进糖酵解(图2C)[53]。同时HK也与线粒体膜的电压依赖性阴离子通道(voltage-dependent anion channel, VDAC)结合, 阻碍细胞色素C从线粒体释放, 抑制线粒体介导的细胞凋亡。在缺乏基底膜附着的环境中, 这些代偿性机制共同维持细胞内部的生存信号, 显著提升CTCs的抗AR能力(图2C)[54-56]。

3 CTC簇的组分异质性及其微环境互作机制

血液中绝大多数CTCs呈单细胞游离状态, 仅极少数聚集成多细胞簇。CTCs在血液循环中除了经历单细胞层面的重构外, 还会通过相互黏附形成CTC簇。这种多细胞聚集模式赋予了肿瘤细胞更强的机械抗性, 使其能够有效抵御血流剪切力带来的物理损伤[57]。

在流经管径狭小的毛细血管床时, 此类团簇展现出极强的形态适应性。它们能够发生可逆的构象重排, 自发延展为单行链状结构以穿过空间受限的机械屏障。完成穿越后, 这些细胞会在血管内迅速重新组装, 恢复为最初的三维团簇形态[58]。

3.1 CTC簇的强转移潜能

CTC簇并非主要由血管内随机聚集形成, 而多由原发灶克隆细胞共同脱落形成。在转移过程中, 其CTC簇比例会发生系统性变化[57,59]。CTC簇的转移能力远强于单细胞CTC, 是单个CTC的20~100倍[60]。CTC簇内细胞常呈现干性相关特征, 在治疗压力下更易进入相对静止状态并形成耐药表型[50,57,60-61]。

在分子层面, CTCs可通过白细胞分化抗原44(cluster of differentiation 44, CD44)、细胞间黏附分子1(intercellular adhesion molecule 1, ICAM1)、丛状蛋白B2(plexin-B2, PLXNB2)及整合素相关蛋白增强肿瘤细胞间黏附作用[8,60-62]。

3.2 CTC簇异质性微环境

CTC簇可与血小板、中性粒细胞及髓系细胞形成异质簇, 提高CTCs在血流中存活和器官转移率[8,58,63]。

3.2.1 *血小板介导CTCs存活与促转移生态位构建* 血小板能够在血液循环中包裹CTC簇[64-68]。这种保护和促进作用依赖于血小板与肿瘤细胞表面的特定配体结合。肿瘤细胞表达的半乳糖凝集素-3(galectin-3, Gal-3)与血小板糖蛋白VI(platelet glycoprotein VI, GPVI)发生靶向结合[69]。热休克蛋白47(heat shock protein 47, HSP47)介导的胶原分泌过程也能显著增强两者间黏附强度(图2D)[66]。这些互作不仅赋予CTC簇更强的存活优势, 也为在远端靶器官血管内皮上的特异性锚定提供支持[22,66,69]。

在微血管内完成初始滞留后, 血小板作为局部微环境调控的信号源, 直接推动肿瘤细胞的跨内皮迁移。一方面, 血小板通过旁分泌途径释放多种可

溶性因子, 诱导CTCs发生EMT转化[65]。另一方面, 受肿瘤细胞激活的血小板会释放二磷酸腺苷(adenosine diphosphate, ADP)等活性介质(图2G)。这些物质直接作用于血管内皮细胞, 导致内皮屏障减弱和血管通透性上升, 为肿瘤细胞的外渗定植扫除障碍[65,68,70]。

3.2.2 中性粒细胞介导的CTCs保护与外渗机制 除了血小板外, 中性粒细胞也是CTC簇的重要成分。CTC-中性粒细胞簇在乳腺癌患者中频繁出现, 与更差的预后相关[63]。中性粒细胞通过血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)与CTCs结合, 并分泌白介素-6(interleukin-6, IL-6)和白介素-1β(interleukin-1β, IL-1β)等细胞因子, 促进CTCs的细胞周期进程和增强其转移潜能。此外, 中性粒细胞胞外诱捕网(NETs)能够捕获CTCs, 保护其免受剪切力损伤, 促进其在血管壁的阻滞和外渗(图2E)[71]。

3.2.3 CTCs单细胞层面的基础免疫逃逸机制 在单细胞水平上, CTCs通过多种机制逃逸免疫监视。

一是白细胞分化抗原47(cluster of differentiation 47, CD47)介导的巨噬细胞逃逸机制。CD47在CTCs表面高表达, CD47与巨噬细胞表面的信号调节蛋白α(signal regulatory proteins α, SIRPα)结合抑制吞噬作用(图2F)[72]。此种机制, 类似于造血干细胞迁移过程中通过CD47上调实现免疫抑制效应[73]。研究表明, 在肝脏等富含巨噬细胞的器官中CD47的表达水平与CTCs的转移潜能呈正相关。应用抗CD47抗体可显著降低转移率, 凸显了该通路在免疫逃逸中的重要作用[74]。

二是CTCs通过程序性死亡受体配体1(programmed death-ligand 1, PD-L1)的表达实现免疫抑制。临床结果显示, 转移性乳腺癌患者的外周血CTCs中普遍存在该分子的表达(图2F)[75]。scRNA-seq分析发现, 具有EMT特征的CTCs更易伴随PD-1/PD-L1通路激活和T细胞耗竭, 说明CTCs能够主动重塑外周免疫微环境, 从而抑制T细胞的增殖与细胞杀伤能力[76]。

三是其他免疫检查点分子的表达, 如淋巴细胞活化基因-3(lymphocyte-activation gene 3, LAG-3)、T细胞免疫球蛋白黏蛋白结构域分子3(T-cell immunoglobulin and mucin domain 3, Tim-3)、细胞毒性T淋巴细胞相关蛋白4(cytotoxic T-lymphocyte-associated protein 4, CTLA-4)等。这些分子的表达促使CTCs诱导T细胞的功能障碍, 形成促抑制性反馈环路[77]。

4 CTC转移的昼夜节律调控机制与医学干预策略

长期以来, 学者普遍认为CTCs脱落是肿瘤生长过程中的随机事件。然而近年研究发现, 这一过程具有时间生物学特征。

4.1 挑战传统认知: 睡眠驱动的CTC转移爆发

在乳腺癌患者及小鼠模型中发现, CTC脱落入血过程受到生物钟的严格调控。人类在夜间睡眠时以及小鼠在白昼休息时均会出现CTCs数量的峰值, 而活跃期采集的血液标本中CTCs数量则会大幅下降[78]。

静息期释放入血的CTCs在生物学特性上表现出更高的侵袭性。其增殖及有丝分裂相关的基因呈高表达(图3A), 从而赋予细胞更强的远端器官转移能力。这种时间维度的差异充分说明CTCs渗入血液的特定时机以及其后续的转移定植能力均受到昼夜节律的同步驱动[78]。

4.2 激素调节轴与转移潜能

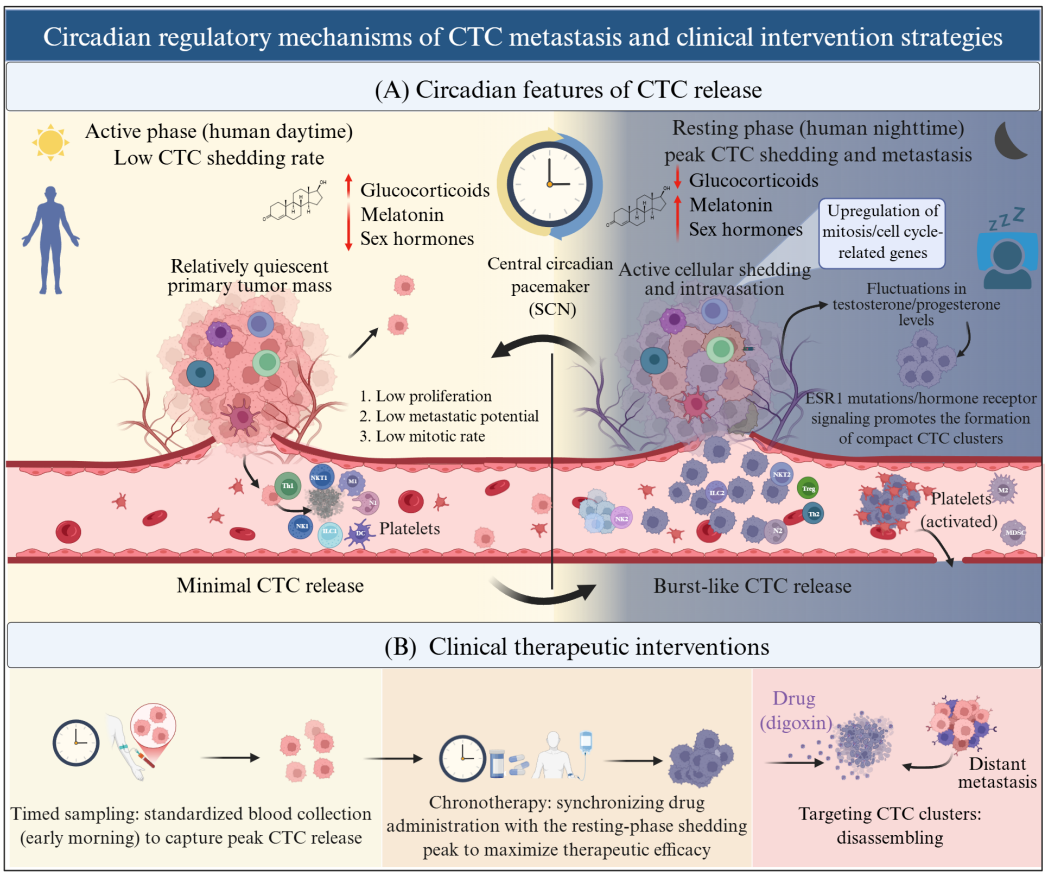
动物实验与临床观察发现, 休息期是CTC释放入血的核心窗口期。该现象与糖皮质激素、褪黑素及性激素等昼夜节律相关激素的动态波动密切相关(图3A)。这表明宿主生物钟与内分泌系统在整体水平上共同影响CTC播散及侵袭能力[37,78-79]。

激素信号能够进一步重塑CTCs的转移特征。在人类表皮生长因子受体2(human epidermal growth factor receptor 2, HER2)驱动的乳腺癌发生初期, 孕酮信号即诱导癌细胞发生血管外渗并形成早期播散[80]。临床数据表明, 易发生骨转移的患者CTCs普遍存在雄激素受体通路的异常激活[81]。在雌激素受体(estrogen receptor, ER)阳性转移性乳腺癌中, 雌激素受体1(estrogen receptor 1, ESR1)突变会重编程细胞间的黏附特性, 增强其在血液中的转移能力[82]。

4.3 时间控制采样与给药

CTCs的昼夜节律特征表明, 临床诊疗需引入时间维度。随机采样易错过细胞释放高峰而低估病情, 规范采血时间可显著提升检出率[78-79]。此外, 地高辛等药物已被发现能有效解离细胞团簇[50,83]。

在治疗方面, 将地高辛联合节律调节与实时监



A: CTC释放的昼夜节律特征。在活跃期, 较高水平的糖皮质激素、较低水平的褪黑素和性激素使原发肿瘤团处于相对静止状态, 表现为低增殖、低转移潜能和低有丝分裂, CTC脱落率极低。在休息期, 受昼夜节律中枢及睾酮/孕酮水平波动调控, 有丝分裂和细胞周期相关基因上调, 导致CTCs爆发性释放。B: 针对CTCs的精准临床干预策略。

A: circadian characteristics of CTC release. During the active phase, elevated glucocorticoid levels, paired with diminished concentrations of melatonin and sex hormones, maintain primary tumor masses in a relatively quiescent state. This phase is characterized by low proliferative activity, reduced metastatic potential, and minimal mitosis, resulting in negligible CTC shedding. Conversely, during the resting phase, modulated by the central circadian pacemaker and fluctuations in testosterone and progesterone levels, the upregulation of mitosis- and cell cycle-related genes triggers an episodic, “burst-like” release of CTCs. B: precision clinical intervention strategies for CTCs.

图3 CTC转移的昼夜节律调控机制与医学干预策略(本图由BioRender绘制)

Fig.3 Circadian regulatory mechanism of CTC metastasis and medical intervention strategies (created by BioRender)

控, 依据人体生物钟优化给药时点(图3B), 既可在细胞转移期实施精准杀伤, 也能通过阻断信号通路抑制病灶细胞脱落。既往研究已证实, 抗肿瘤药物效应存在时间依赖性[78]。

5 基础研究及其临床应用突破口

目前CTCs研究已融入精准诊疗框架, 但临床转化仍受制于多重技术与理论壁垒。未来研究需要在以下几个方向寻求突破。

5.1 突破口一: 打破休眠与抗凋亡的关键节点

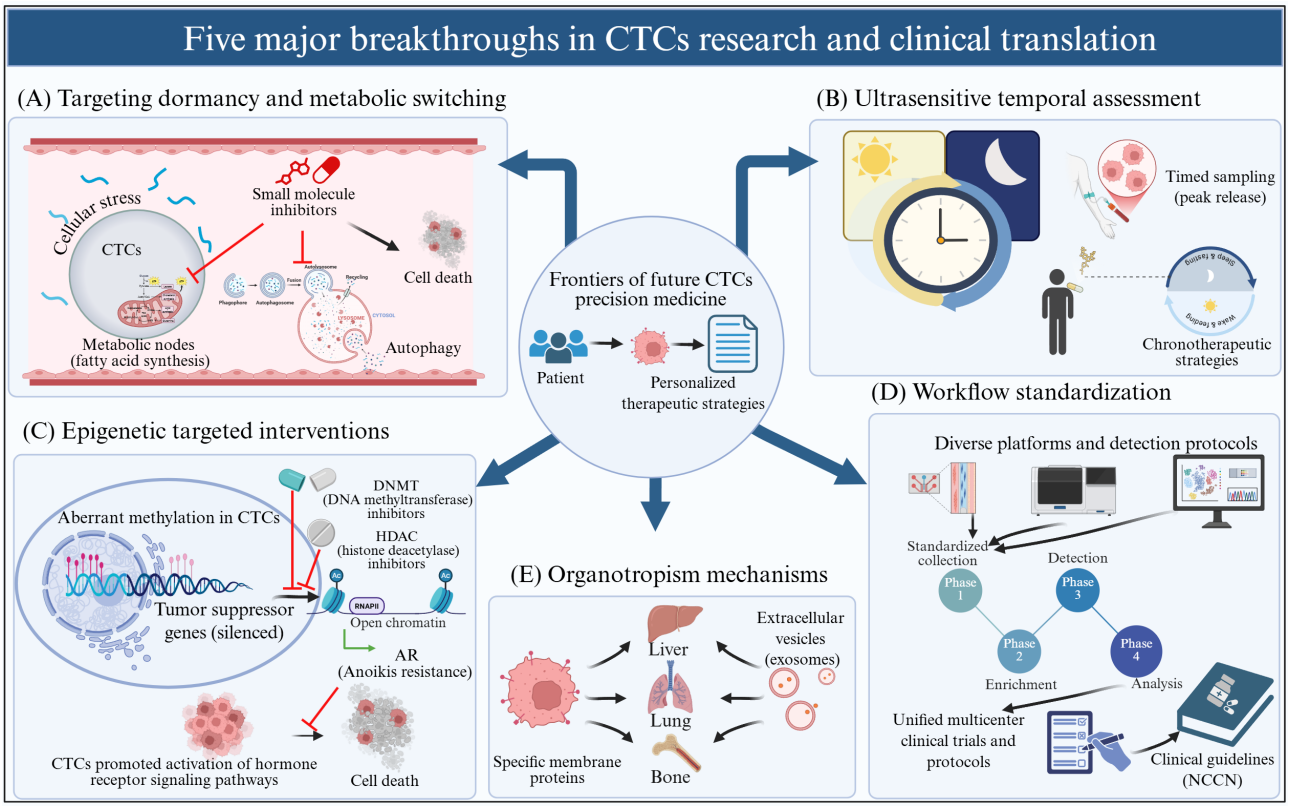
CTCs在极端隔离环境下的存活与长期休眠机制仍有待阐明。未来研究应挖掘其在隔离胁迫下的关键代谢节点。在其脱落入血初期, 可通过特异性小分子药物靶向阻断AR通路、磷酸戊糖和脂肪酸合成代谢通路、自噬信号通路中的关键上游靶点(图4A)[84]。

5.2 突破口二: 表观遗传靶向干预

临床研究表明, DNA甲基转移酶与组蛋白去乙酰化酶抑制剂能够逆转CTCs的异常甲基化状态[85]。研发特异性靶向药物已成为当前的重点研究方向。该策略有望通过恢复抑癌基因表达, 进而克服AR抑制相关激素受体活性, 有效清除血液内的CTCs(图4B)。

5.3 突破口三: 超高灵敏度时间评估

CTC释放具有明显的昼夜节律特征。未来临床试验和诊断流程应严格控制采样时间, 甚至开发基



推动CTCs研究走向临床精准医疗的五大关键突破方向。A: 靶向CTCs的小分子抑制剂, 抑制脂肪酸合成和细胞自噬机制以打破其休眠状态; B: 结合生物钟规律实施高灵敏度的时间维度采样与疗法; C: 开发DNMT、HDAC抑制剂等表观遗传药物以逆转抑癌基因沉默及克服失巢凋亡抵抗; D: 推进从样本收集、富集、检测到分析的标准化多中心流程并纳入临床指南(如NCCN); E: 深入解析由细胞特异性膜蛋白及外泌体(EVs)介导的肿瘤器官向性转移机制。

Five key breakthrough directions for advancing CTCs research toward clinical precision medicine. A: small-molecule inhibitors targeting CTCs, developing inhibitors to target CTCs specifically, focusing on the suppression of fatty acid synthesis and autophagy mechanisms to disrupt their dormant state. B: circadian-integrated temporal diagnostics and chronotherapy. Leveraging circadian rhythms to implement high-sensitivity temporal sampling and precision chronotherapeutic strategies. C: epigenetic therapeutics for resistance circumvention. Advancing epigenetic agents, such as DNMT and HDAC inhibitors, to reverse the silencing of tumor suppressor genes and overcome resistance to anoikis. D: standardization and clinical integration: establishing standardized, multicenter protocols—encompassing sample collection, enrichment, detection, and analysis—for formal inclusion in clinical practice guidelines (e.g., NCCN). E: mechanistic insights into organotropic metastasis. Elucidating the mechanisms of organ-specific metastasis mediated by cell-specific membrane proteins and EVs (extracellular vesicles).

图4　CTCs研究与临床转化的五大突破方向(本图由BioRender绘制)

Fig.4　Five key breakthrough directions in CTCs research and clinical translation (created by BioRender)

于昼夜节律的精准给药策略, 以最大化治疗效果(图4C)[78]。

5.4　突破口四: 标准化流程

CTCs技术的临床普及受制于检测平台繁多且结果难以整合。未来亟需开展大规模多中心随机对照试验, 确立涵盖采集、富集、检测及分析的全流程规范。这是推动该技术通过监管审批并最终纳入各癌种NCCN临床指南的必经之路(图4D)[38-39,86-87]。

5.5　突破口五: 揭示CTCs的器官趋向性机制

未来应探究CTCs表面膜蛋白调控器官特异性定植的机制, 以及外泌体先抵达远端器官并构建免疫抑制微环境的具体发生过程。此类研究有望为阻断特定器官转移提供全新靶点[88](图4E)。

6　结语与展望

CTCs作为肿瘤转移的核心媒介, 为液体活检提供高维度的在体病灶信息。研究者可通过单细胞多组学深度解析, 揭示其表型可塑性与异质性簇集行为。这种生物学特性赋予了CTCs在早期诊断、MRD监测以及耐药性分析等方面的重要临床评估价值。

在基础研究方面, 急需攻克CTC休眠与凋亡逃逸机制。阐明它们应对血液微环境代谢压力的生存策略, 通过靶向干预手段, 逆转异常的DNA甲基化等表观遗传学修饰, 有望从根本上阻断其转移并削

弱其在血液循环中的存活优势。明确肿瘤源性外泌体在器官特异性定植及靶器官微环境重塑中的作用, 同样是阻遏转移级联反应的重要研究方向。

在临床转化方面, 引入时间生物学理念有助于优化液体活检体系。根据机体昼夜时序特征制定个体化的采样与靶向给药方案, 能够有效提升整体治疗效果。结合AI与ML技术, 推动技术纳入临床指南, 从而指导个体化医疗的实施。

CTCs作为原发灶与转移灶间的实体纽带, 其分子解析和功能研究正持续深化我们对肿瘤生物学、液体活检及精准治疗理念的理解。随着技术体系日趋完善, CTCs必将在预后判断、疗效监测及转移预警中发挥重要的标志物作用, 为攻克癌症提供全新思路。

参考文献 (References)

[1] DAI C S, MISHRA A, EDD J, et al. Circulating tumor cells: blood-based detection, molecular biology, and clinical applications [J]. Cancer Cell, 2025, 43(8): 1399-422.

[2] DENG Z, WU S, WANG Y, et al. Circulating tumor cell isolation for cancer diagnosis and prognosis [J]. EBioMedicine, 2022, 83: 104237.

[3] ESLAMI-S Z, CORTÉS-HERNÁNDEZ L E, THOMAS F, et al. Functional analysis of circulating tumour cells: the KEY to understand the biology of the metastatic cascade [J]. Br J Cancer, 2022, 127: 800-10.

[4] PEREIRA-VEIGA T, SCHNEEGANS S, PANTEL K, et al. Circulating tumor cell-blood cell crosstalk: biology and clinical relevance [J]. Cell Rep, 2022, 40(9): 111298.

[5] HU G, LI H, SU R, et al. Unravelling the complexity of cancer premetastatic niche-mechanistic insights and clinical therapies [J]. Pharmacol Ther, 2026, 280: 108994.

[6] DUGGINA N, MOHAN S, SHARIF S H, et al. Metabolic and epigenetic reprogramming in circulating tumor cells: advances in liquid biopsy and cancer management [J]. Clin Chim Acta, 2026, 580: 120738.

[7] LIN A, FANG X, ZHANG P, et al. Temporal dynamics in cancer immunotherapy: the interplay between circadian rhythms, tumor microenvironment, and immune checkpoint blockade [J]. J Natl Cancer Cent, 2026, 6(1): 98-115.

[8] SCHUSTER E, DASHZEVEG N K, TONG F, et al. Computational ranking identifies plexin-B2 in circulating tumor cell clustering with monocytes in breast cancer metastasis [J]. Nat Commun, 2025, 16(1): 7649.

[9] GVOZDENOVIC A, ACETO N. A growing entourage for heterotypic circulating tumor cell clusters [J]. Trends Cancer, 2025, 11(12): 1137-8.

[10] ZHANG J, HUANG X, MA L, et al. Micro-organ chip deciphers tumor-derived G-CSF as remote commander of lung pre-metastatic niche via VEGFA-KDR cascade [J]. Adv Sci, 2026, 13(7): e18584.

[11] BARDIA A, HABER D A. Solidifying liquid biopsies: can circulating tumor cell monitoring guide treatment selection in breast cancer [J]? J Clin Oncol, 2014, 32(31): 3470-1.

[12] HANNA N. Role of natural killer cells in control of cancer metastasis [J]. Cancer Metastasis Rev, 1982, 1(1): 45-64.

[13] SEIDEN M V, KANTOFF P W, KRITHIVAS K, et al. Detection of circulating tumor cells in men with localized prostate cancer [J]. J Clin Oncol, 1994, 12(12): 2634-9.

[14] JOOSSE S A, GORGES T M, PANTEL K. Biology, detection, and clinical implications of circulating tumor cells [J]. EMBO Mol Med, 2015, 7: 1-11.

[15] ALLARD W J, MATERA J, MILLER M C, et al. Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases [J]. Clin Cancer Res, 2004, 10(20): 6897-904.

[16] DE BONO J S, SCHER H I, MONTGOMERY B, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer [J]. Clin Cancer Res, 2008, 14(19): 6302-9.

[17] CRISTOFANILLI M, HAYES D F, BUDD G T, et al. Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer [J]. J Clin Oncol, 2005, 23(7): 1420-30.

[18] COHEN S J, PUNT C J A, IANNOTTI N, et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer [J]. J Clin Oncol, 2008, 26(19): 3213-21.

[19] KONIGSBERG R, OBERMAYR E, BISES G, et al. Detection of EpCAM positive and negative circulating tumor cells in metastatic breast cancer patients [J]. Acta Oncol, 2011, 50(5): 700-10.

[20] NAGRATH S, SEQUIST L V, MAHESWARAN S, et al. Isolation of rare circulating tumour cells in cancer patients by microchip technology [J]. Nature, 2007, 450(7173): 1235-9.

[21] OZKUMUR E, SHAH A M, CICILIANO J C, et al. Inertial focusing for tumor antigen-dependent and -independent sorting of rare circulating tumor cells [J]. Sci Transl Med, 2013, 5(179): 179ra47.

[22] ZHANG H, JIAO J, LONG Y, et al. Targeting capture and eradicate circulating tumor cells by activated platelet derived vehicle for inhibiting triple-negative breast cancer metastasis [J]. Mater Today Bio, 2025, 31: 101597.

[23] VAN KESSEL E, WOERDMAN N, PLUIM D, et al. Added prognostic value of circulating tumor cell numbers in CSF of patients with leptomeningeal metastasis from epithelial tumors [J]. Eur J Cancer, 2025, 220: 115377.

[24] GUO S, HUANG J, LI G, et al. The role of extracellular vesicles in circulating tumor cell-mediated distant metastasis [J]. Mol Cancer, 2023, 22(1): 193.

[25] GUO H, VUILLE J A, WITTNER B S, et al. DNA hypomethylation silences antitumor immune genes in early prostate cancer and CTCs [J]. Cell, 2023, 186(13): 2765-82.

[26] ABBOSH C, HODGSON D, DOHERTY G J, et al. Implementing circulating tumor DNA as a prognostic biomarker in resectable non-small cell lung cancer [J]. Trends Cancer, 2024, 10(7): 643-54.

[27] ABBOSH C, HODGSON D, DOHERTY G J, et al. Implementing circulating tumor DNA as a prognostic biomarker in resectable

non-small cell lung cancer [J]. Trends Cancer, 2024, 10(7): 643-54.

[28] DING H, YUAN M, YANG Y, et al. Identifying key circulating tumor DNA parameters for predicting clinical outcomes in metastatic non-squamous non-small cell lung cancer after first-line chemoimmunotherapy [J]. Nat Commun, 2024, 15(1): 6862.

[29] GU X, WEI S, LÜ X. Circulating tumor cells: from new biological insights to clinical practice [J]. Signal Transduct Target Ther, 2024, 9(1): 226.

[30] HEEKE S, GAY C M, ESTECIO M R, et al. Tumor- and circulating-free DNA methylation identifies clinically relevant small cell lung cancer subtypes [J]. Cancer Cell, 2024, 42(2): 225-37.

[31] KE H, KAO S, VAN ZANDWIJK N, et al. Circulating tumor cell detection may offer earlier diagnosis in patients suspected of asbestos-related lung cancer [J]. Lung Cancer, 2024, 192: 107829.

[32] KLUSA D, LOHAUS F, FRANKEN A, et al. Dynamics of CXCR4 positive circulating tumor cells in prostate cancer patients during radiotherapy [J]. Int J Cancer, 2023, 152(12): 2639-54.

[33] LAWRENCE R, WATTERS M, DAVIES C R, et al. Circulating tumour cells for early detection of clinically relevant cancer [J]. Nat Rev Clin Oncol, 2023, 20(7): 487-500.

[34] LIU X, SONG J, ZHANG H, et al. Immune checkpoint HLA-E:CD94-NKG2A mediates evasion of circulating tumor cells from NK cell surveillance [J]. Cancer Cell, 2023, 41(2): 272-87.

[35] RING A, NGUYEN-STRÄULI B D, WICKI A, et al. Biology, vulnerabilities and clinical applications of circulating tumour cells [J]. Nat Rev Cancer, 2023, 23(2): 95-111.

[36] STOECKLEIN N H, FLUEGEN G, GUGLIELMI R, et al. Ultra-sensitive CTC-based liquid biopsy for pancreatic cancer enabled by large blood volume analysis [J]. Mol Cancer, 2023, 22(1): 181.

[37] DAUVILLIERS Y, THOMAS F, ALIX-PANABIÈRES C. Dissemination of circulating tumor cells at night: role of sleep or circadian rhythm [J]? Genome Biol, 2022, 23(1): 214.

[38] ADAR L, SHACHAR E, LASKOV I, et al. Tailoring treatment for advanced and/or recurrent ovarian cancer using the response of circulating tumor cells to therapy: a retrospective analysis [J]. Int J Gynecol Cancer, 2025: 102767.

[39] CIAVOLELLA G, GRANET J, GOETZ J G, et al. Deciphering circulating tumor cells binding in a microfluidic system thanks to a parameterized mathematical model [J]. J Theor Biol, 2025, 600: 112029.

[40] LI S, YUAN T, YUAN J, et al. Opportunities and challenges of using circulating tumor DNA to predict lung cancer immunotherapy efficacy [J]. J Cancer Res Clin Oncol, 2024, 150(11): 501.

[41] TING D T, WITTNER B S, LIGORIO M, et al. Single-cell RNA sequencing identifies extracellular matrix gene expression by pancreatic circulating tumor cells [J]. Cell Rep, 2014, 8(6): 1905-18.

[42] KALLURI R, WEINBERG R A. The basics of epithelial-mesenchymal transition [J]. J Clin Invest, 2009, 119(6): 1420-8.

[43] LAMOUILLE S, XU J, DERYNCK R. Molecular mechanisms of epithelial-mesenchymal transition [J]. Nat Rev Mol Cell Biol, 2014, 15(3): 178-96.

[44] NOWAK E, BEDNAREK I. Aspects of the epigenetic regulation of EMT related to cancer metastasis [J]. Cells, 2021, 10(12): 3435.

[45] TERMINI R, ŽIHALA D, TERPOS E, et al. Circulating tumor and immune cells for minimally invasive risk stratification of smoldering multiple myeloma [J]. Clin Cancer Res, 2022, 28(21): 4771-81.

[46] WANG X, SHI X, LU H, et al. Succinylation inhibits the enzymatic hydrolysis of the extracellular matrix protein fibrillin 1 and promotes gastric cancer progression [J]. Adv Sci, 2022, 9(27): 2200546.

[47] WANKHEDE D C, GROVER S, HOFMAN P. Circulating tumor cells as a predictive biomarker in resectable lung cancer: a systematic review and meta-analysis [J]. Cancers, 2022, 14(24): 1662.

[48] HEIDRICH I, DEITERT B, WERNER S, et al. Liquid biopsy for monitoring of tumor dormancy and early detection of disease recurrence in solid tumors [J]. Cancer Metastasis Rev, 2023, 42: 161-82.

[49] WOO H J, KIM S H, KANG H J, et al. Continuous centrifugal microfluidics (CCM) isolates heterogeneous circulating tumor cells via full automation [J]. Theranostics, 2022, 12(8): 3676-89.

[50] GKOUNTELA S, CASTRO-GINER F, SZCZERBA M B, et al. Circulating tumor cell clustering shapes DNA methylation to enable metastasis seeding [J]. Cell, 2019, 176(1/2): 98-112.

[51] MUSELLA M, GUARRACINO A, MANDUCA N, et al. Type I IFNs promote cancer cell stemness by triggering the epigenetic regulator KDM1B [J]. Nat Immunol, 2022, 23: 1379-92.

[52] SHEN D D, PANG J R, BI Y P, et al. LSD1 deletion decreases exosomal PD-L1 and restores T-cell response in gastric cancer [J]. Mol Cancer, 2022, 21(1): 75.

[53] HUANG Q, LI S W, HU X, et al. Shear stress activates ATOH8 via autocrine VEGF promoting glycolysis dependent-survival of colorectal cancer cells in the circulation [J]. J Exp Clin Cancer Res, 2020, 39(1): 25.

[54] OSMANI N, FOLLAIN G, GARCÍA LEÓN M J, et al. Metastatic tumor cells exploit their adhesion repertoire to counteract shear forces during intravascular arrest [J]. Cell Rep, 2019, 28(10): 2491-500.

[55] SHIBUE T, BROOKS M W, INAN M F, et al. The outgrowth of micrometastases is enabled by the formation of filopodium-like protrusions [J]. Cancer Discov, 2012, 2(8): 706-21.

[56] SHIBUE T, BROOKS M W, WEINBERG R A. An integrin-linked machinery of cytoskeletal regulation that enables experimental tumor initiation and metastatic colonization [J]. Cancer Cell, 2013, 24(4): 481-98.

[57] ACETO N, BARDIA A, MIYAMOTO D T, et al. Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis [J]. Cell, 2014, 158(5): 1110-22.

[58] AU S H, STOREY B D, MOORE J C, et al. Clusters of circulating tumor cells traverse capillary-sized vessels [J]. Proc Natl Acad Sci USA, 2016, 113(18): 4947-52.

[59] CHEUNG K J, PADMANABAN V, SILVESTRI V L, et al. Polyclonal breast cancer metastases arise from collective dissemination of keratin 14-expressing tumor cell clusters [J]. Proc Natl Acad Sci USA, 2016, 113(7): E854-63.

[60] DASHZEVEG N K, JIA Y, ZHANG Y, et al. Dynamic glycoprotein hyposialylation promotes chemotherapy evasion and metastatic seeding of quiescent circulating tumor cell clusters in breast cancer [J]. Cancer Discov, 2023, 13(9): 2050-71.

[61] TAFTAF R, LIU X, SINGH S, et al. ICAM1 initiates CTC cluster formation and trans-endothelial migration in lung metastasis of breast cancer [J]. Nat Commun, 2021, 12(1): 4867.

[62] RODRIGUES P, VANHARANTA S. Circulating tumor cells: come together, right now, over metastasis [J]. Cancer Discov, 2019, 9(1): 22-4.

[63] SZCZERBA M B, CASTRO-GINER F, VETTER M, et al. Neutrophils escort circulating tumour cells to enable cell cycle progression [J]. Nature, 2019, 566(7745): 553-7.

[64] LABELLE M, BEGUM S, HYNES R O. Platelets guide the formation of early metastatic niches [J]. Proc Natl Acad Sci USA, 2014, 111(30): E3053-61.

[65] XU X, YOUSEF G M, NI H. Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents [J]. Blood, 2018, 131(16): 1777-89.

[66] XIONG G, CHEN J, ZHANG G, et al. Hsp47 promotes cancer metastasis by enhancing collagen-dependent cancer cell-platelet interaction [J]. Proc Natl Acad Sci USA, 2020, 117(7): 3748-58.

[67] LABELLE M, HYNES R O. The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination [J]. Cancer Discov, 2012, 2(12): 1091-9.

[68] GAY L J, FELDING-HABERMANN B. Contribution of platelets to tumour metastasis [J]. Nat Rev Cancer, 2011, 11(2): 123-34.

[69] MAMMADOVA-BACH E, GIL-PULIDO J, SARUKHANYAN E, et al. Platelet glycoprotein VI promotes metastasis through interaction with cancer cell-derived galectin-3 [J]. Blood, 2020, 135(14): 1146-60.

[70] SCHUMACHER D, STRILIC B, SIVARAJ K K, et al. Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor [J]. Cancer Cell, 2013, 24(1): 130-7.

[71] PARK J, WYSOCKI R W, AMOOZGAR Z, et al. Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps [J]. Sci Transl Med, 2016, 8(361): 361ra138.

[72] PAPADAKI M, KOUTSOPOULOS A, TSOULFAS P G, et al. Clinical relevance of immune checkpoints on circulating tumor cells in breast cancer [J]. Cancers, 2020, 12(2): 376.

[73] JAISWAL S, JAMIESON C H M, PANG W W, et al. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis [J]. Cell, 2009, 138(2): 271-85.

[74] BACCELLI I, STENZINGER A, VOGEL V, et al. Co-expression of MET and CD47 is a novel prognosticator for survival of luminal-type breast cancer patients [J]. Oncotarget, 2014, 5(18): 8147-60.

[75] MAZEL M, JACOT W, PANTEL K, et al. Frequent expression of PD-L1 on circulating breast cancer cells [J]. Mol Oncol, 2015, 9(9): 1773-82.

[76] BRECHBUHL H M, PAUL K, GILLEN A E, et al. Analysis of circulating breast cancer cell heterogeneity and interactions with peripheral blood mononuclear cells [J]. Mol Carcinog, 2020, 59(10): 1129-39.

[77] WANG X, JAIMES M, GU H, et al. Cell by cell immuno-and cancer marker profiling of non-small cell lung cancer tissue: checkpoint marker expression on $CD103^{+}$, $CD4^{+}$ T-cells predicts circulating tumor cells [J]. Transl Oncol, 2021, 14(1): 100953.

[78] DIAMANTOPOULOU Z, CASTRO-GINER F, SCHWAB F D, et al. The metastatic spread of breast cancer accelerates during sleep [J]. Nature, 2022, 607: 156-62.

[79] CORTÉS-HERNÁNDEZ L E, ESLAMI-S Z, DUJON A M, et al. Do malignant cells sleep at night [J]? Genome Biol, 2020, 21(1): 276.

[80] HOSSEINI H, OBRADOVIĆ M M S, HOFFMANN M, et al. Early dissemination seeds metastasis in breast cancer [J]. Nature, 2016, 540(7634): 552-8.

[81] ACETO N, BARDIA A, WITTNER B S, et al. AR expression in breast cancer CTCs associates with bone metastases [J]. Mol Cancer Res, 2018, 16(4): 720-7.

[82] LI Z, WU Y, YATES M E, et al. Hotspot ESR1 mutations are multimodal and contextual modulators of breast cancer metastasis [J]. Cancer Res, 2022, 82(7): 1321-39.

[83] KURZEDER C, NGUYEN-STRÄULI B D, KROL I, et al. Digoxin for reduction of circulating tumor cell cluster size in metastatic breast cancer: a proof-of-concept trial [J]. Nat Med, 2025, 31(4): 1120-4.

[84] HONG X, ROH W, SULLIVAN R J, et al. The lipogenic regulator SREBP2 induces transferrin in circulating melanoma cells and suppresses ferroptosis [J]. Cancer Discov, 2021, 11(3): 678-95.

[85] TSAI H C, LI H, VAN NESTE L, et al. Transient low doses of DNA-demethylating agents exert durable antitumor effects on hematological and epithelial tumor cells [J]. Cancer Cell, 2012, 21(3): 430-46.

[86] PANTEL K, ALIX-PANABIÈRES C. Functional studies on viable circulating tumor cells [J]. Clin Chem, 2016, 62(2): 328-34.

[87] PANTEL K, SPEICHER M R. The biology of circulating tumor cells [J]. Oncogene, 2016, 35(10): 1216-24.

[88] MARQUETTE C H, BOUTROS J, BENZAQUEN J, et al. Circulating tumour cells as a potential biomarker for lung cancer screening: a prospective cohort study [J]. Lancet Respir Med, 2020, 8(7): 709-16.