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乳腺癌肝转移机制的研究进展

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摘　要

乳腺癌是女性最常见的恶性肿瘤之一，远处转移仍然是其相关死亡的主要原因。骨、肺、肝和脑是乳腺癌转移的主要靶器官。其中肝脏作为高度血供、免疫耐受和代谢活跃的器官，是乳腺癌重要且预后不良的转移部位。乳腺癌肝转移是肿瘤细胞与肝脏微环境通过多阶段发展、多因素调控及多信号通路共同作用形成的复杂动态过程。进一步理解乳腺癌细胞与肝脏微环境在乳腺癌肝转移中的相互作用，对于指导未来临床治疗至关重要。本文系统综述了乳腺癌细胞与肝脏微环境对乳腺癌肝转移的贡献，可能对未来治疗策略和预防干预带来启示。

关键词

乳腺癌，肝转移，微环境，机制

Advances in the Mechanisms of Breast Cancer Liver Metastasis

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Abstract

Breast cancer is one of the most common malignancies among women, and distant metastasis remains the leading cause of cancer-related mortality. The bone, lung, liver, and brain are the principal target organs for metastatic spread. Among these, the liver—characterized by its rich vascularization, immune-tolerant milieu, and highly active metabolic environment—represents a critical site of metastasis associated with particularly poor prognosis. Breast cancer liver metastasis is a

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complex and dynamic process arising from the interplay between tumor cells and the hepatic microenvironment, involving multiple sequential stages, diverse regulatory factors, and intricate signaling pathways. A deeper understanding of the interactions between breast cancer cells and the liver microenvironment in BCLM is essential for informing future therapeutic strategies. This review systematically summarizes the contributions of both breast cancer cells and the hepatic microenvironment to the development of BCLM, with the aim of providing insights into potential avenues for therapeutic intervention and preventive strategies.

Keywords

Breast Cancer, Liver Metastasis, Microenvironment, Mechanisms

1. 引言

乳腺癌为全球女性恶性肿瘤发病率最高的疾病[1] [2]，其发病率和死亡率逐年上升，发病群体逐渐年轻化。远处转移是导致乳腺癌相关死亡的主要原因，骨、肺、肝脏及脑为常见转移器官[3]。肝脏虽不是乳腺癌最常见的转移部位，但与其他部位的转移相比，肝转移是导致乳腺癌患者总体生存期下降的独立危险因素[4]。乳腺癌肝转移(breast cancer liver metastasis, BCLM)患者预后不佳，其 5 年总生存率仅为 8.5% [5]。

肿瘤转移是一个多步骤参与的复杂过程。早在 19 世纪末，Stephen Paget 便提出“种子与土壤”假说，强调肿瘤转移并非随机事件，而是肿瘤细胞“种子”与特定器官微环境“土壤”之间相互适配的结果[6]。在此基础上，“转移前微环境”理论强调了原发肿瘤可通过分泌细胞因子、外泌体等方式，在远处器官中提前塑造有利于肿瘤细胞定植的微环境[7]。Semenza 将乳腺癌血管转移的过程分为以下步骤：入血、循环、边缘化、出血和定植[8]。这些理论为理解乳腺癌器官特异性转移提供了重要框架，也为 BCLM 的机制研究奠定了理论基础。研究发现，肝脏微环境在 BCLM 中发挥着重要作用[9] [10]。深入了解肝脏微环境在转移性乳腺癌细胞肝脏定植中的作用机制，对于开发有效的 BCLM 治疗方法至关重要。因此，本综述将讨论乳腺癌肝转移的分子机制，以指导未来临床治疗工作。

2. 乳腺癌肝转移的过程

2.1. 原发肿瘤细胞的侵袭与血行播散

上皮间质转化(epithelial-mesenchymal transition, EMT)是上皮源性恶性肿瘤细胞获得迁移和侵袭能力的重要机制[11]。既往研究表明 EMT 在乳腺癌肝转移过程中起到了不可或缺的作用。在此过程中，乳腺癌细胞下调 E-钙黏蛋白(E-cadherin)等上皮标志物，同时上调 N-钙黏蛋白(N-cadherin)、波形蛋白等间质相关蛋白，从而降低细胞间黏附并增强迁移与侵袭能力[12] [13]。近来研究进一步发现[14] [15]，EMT 并非全或无的二元过程，而是一个具有中间或部分 EMT 状态的可塑性动态过程。因此，肿瘤细胞可兼具上皮和间质特征，这种可塑性使其既能有效迁移，又保留了定植后恢复上皮表型的能力。EMT 过程受 Slug，Snail，ZEB1，ZEB2 和 Twist 相关转录因子的调控，并受到上游信号通路、microRNA 及表观遗传改变的共同影响。

在此基础上，乳腺原发灶肿瘤细胞可突破基底膜并进入血管或淋巴管，形成循环肿瘤细胞(circulating

tumor cells, CTCs)。然而，在循环过程中，大多数 CTCs 因机械损伤、失巢凋亡、免疫清除及氧化应激等因素而被清除[16] [17]，只有少数循环肿瘤细胞能够在循环系统中存活并继续向远处器官播散。研究表明，CTCs 可与血小板结合形成细胞复合体，活化的血小板聚集并包裹肿瘤细胞起到保护屏障的作用，同时释放生长因子通过多种机制实现 CTCs 免疫逃逸促进癌症转移和进展[18]。此外，CTCs 常以细胞簇(clusters)的形式存在，CTC 簇的转移潜能显著高于单个 CTC [19]。这可能与细胞间黏附维持了特定的存活信号以及簇内细胞具有异质性有关。总体而言，EMT 驱动的表型可塑性及 CTCs 在循环中的生存策略共同决定了乳腺癌细胞远处播散的效率。

2.2. 肿瘤细胞的肝脏外渗与黏附

不同分子亚型的乳腺癌具有不同的器官转移倾向，其中 HER2 过表达型表现出较明显的肝脏“归巢”特性[4]。肝脏丰富的血流灌注及特有的肝窦结构为循环肿瘤细胞的滞留和外渗提供了有利条件。肿瘤细胞可通过肝窦内皮进入肝实质，进一步进入 Disse 间隙，直接与肝细胞接触[9] [20]。这一过程也依赖多种趋化因子及细胞黏附分子的协同作用。乳腺癌细胞表达多种趋化因子受体，C-X-C 趋化因子受体 4 (CXCR4)在肝转移中最为常见，其配体 CXCL12 及基质细胞衍生因子 1α (SDF-1α)在肝组织中高表达，提示 CXCL12/CXCR4 信号轴参与乳腺癌肝转移过程[21]。此外，肿瘤细胞通过整合素、选择素等黏附分子与肝窦内皮细胞发生作用，促进循环肿瘤细胞在肝窦内滞留，为后续血管外渗及定植创造条件。这些因素协同作用决定了乳腺癌细胞在肝脏的选择性归巢与外渗过程。

2.3. 早期定植与微转移形成

肿瘤细胞成功进入肝组织后，需进一步适应局部环境以实现长期存活与扩增。在此过程中，转移灶的生长模式对其进展具有重要影响。结直肠癌的肝转移模型研究证实，肿瘤肝内生长方式包括纤维型、膨胀型和替代型三种模式[22]。乳腺癌肝转移以替代型生长为主，该方式属于非血管生成型生长且可保留原有肝脏间质结构[23]。既往研究认为[24]，替代型生长模式在早期可能处于相对静止的休眠状态，而随着肿瘤进展，乳腺癌细胞逐渐获得促进生长的脉管系统，从而推动微转移灶的发展。

在转移灶形成过程中，肿瘤细胞表型的可塑性同样发挥重要作用。E-钙黏蛋白的丢失是 EMT 的重要标志，通常与肿瘤细胞侵袭能力增强相关[11]。然而有研究发现[25]，在乳腺癌肝转移过程中，E-钙黏蛋白高表达的肿瘤细胞反而更有利于转移灶的形成，这一现象与间质上皮转化(mesenchymal-epithelial transition, MET)有关，使肿瘤细胞在转移部位重新获得上皮特征，从而提高其在肝脏转移灶存活和增殖能力。此外，EMT 也与干细胞样特性的获得有关[26]。CD44 高表达的肿瘤细胞表现出更强的黏附能力、侵袭能力及抗凋亡能力[27]。CD44 高表达、CD24 低表达的乳腺癌细胞具有较强的干细胞特性[28]。乳腺癌患者血清中可检测到干细胞标志物 CD44，肝转移患者中 CD44v5 和 CD44v6 亚型表达更为常见[29]。

此外，缺氧诱导因子(hypoxia-inducible factor, HIF)调控的相关基因也被认为与乳腺癌的肝脏趋向性密切相关。HIF 能够诱导多种下游分子的表达，包括赖氨酰氧化酶(lysyloxidase, LOX)、骨桥蛋白(osteopontin, OPN)、转录因子 TWIST 以及血管内皮生长因子(vascular endothelial growth factor, VEGF)等。同时，炎症反应也参与介导乳腺癌细胞在肝脏内的定植过程[30]。

3. 肝转移前微环境的形成

在乳腺癌肝转移过程中，原发肿瘤通过分泌多种细胞因子及生长因子诱导肝脏在 CTCs 到达之前发生一系列积极的改变，形成利于癌细胞定植的转移前微环境(premetastatic niche, PMN) [7]。这一概念最早于 2005 年由 Kaplan 等首次提出。BCLM 转移前微环境的形成涉及多种因素的复杂相互作用，包括原发肿瘤驱动的远程调控、免疫抑制及炎症反应等多种机制的协同作用，为后续 CTCs 的归巢与定植奠定基础。

乳腺原发肿瘤可通过释放多种因子对肝脏进行远程调控，从而在 CTCs 到达之前诱导 PMN 的形成。VEGF 参与肿瘤新生血管形成[31]，可特异性结合高亲和力的血管内皮生长因子受体(vascular endothelial growth factor receptors, VEGFRs)，主要分布在肿瘤血管的内皮表面。原发肿瘤可分泌多种因子使表达 VEGFR1 的骨髓来源造血干细胞迁移到肝脏，并在 CTCs 到达之前帮助形成富含纤维连接蛋白的微环境，有助于 CTCs 在肝组织中停留。该研究进一步发现从小鼠骨髓中去除表达 VEGFR1 的细胞可以显著抑制 PMN 的形成，进而抑制转移[32]。对 VEGFR 激酶加以抑制，可明显减少肝转移灶的形成，同时延缓原发性乳腺癌的生长进程[33]。

此外，肿瘤来源的外泌体在 PMN 形成中的作用至关重要[34]。外泌体是一类由细胞分泌的直径介于 30 至 100 nm 的细胞外囊泡，可携带 DNA、RNA、蛋白质和脂质等多种生物活性分子，经血液循环到达远处器官，并借助其特有的整合素表达谱介导器官趋向性。在 BCLM 转移前微环境的构建中，外泌体聚集于肝组织中并被肝脏固有细胞摄取。研究发现，外泌体所携带的整合素 $\alpha v\beta 5$ 能够特异性结合肝脏库普弗细胞并参与转移前微环境的构建[35]。

在免疫监视机制作用下，肿瘤发生发展的任一环节都可能受到抑制。在 PMN 的构建过程中，多种细胞参与其中，通过抑制抗肿瘤免疫应答共同推动肿瘤实现免疫逃逸，其中涉及调节性 T 细胞、髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)、肿瘤相关巨噬细胞等[36]。原发肿瘤释放的信号可诱导 MDSCs 在肝脏中聚集，从而抑制 T 细胞增殖并抑制自然杀伤(natural killer, NK)细胞的细胞毒性，这种有利的免疫抑制微环境能够促进 CTCs 在肝脏的转移性定植[37]。

慢性炎症也参与了 BCLM 转移前微环境的形成。肿瘤坏死因子-α (TNF-α)诱导肝窦内皮细胞表达 E-选择素，从而增强循环细胞在肝窦内的滞留能力[38]。中性粒细胞具有表型异质性[39]。其中，未成熟低密度中性粒细胞(immature low-density neutrophils, iLDNs)可促进肝转移[40]，而成熟的高密度中性粒细胞则可抑制肝转移的形成。此外，这类细胞还可通过中性粒细胞胞外诱捕网(neutrophil extracellular traps, NETs)发挥促进乳腺癌肝转移功能[41] [42]，肝脏转移前微环境中 NETs 可通过癌细胞表面特异性 NET-DNA 受体 CCDC25 吸引 CTCs 并促进乳腺癌肝转移[43]。葡萄糖缺乏时，iLDNs 可通过分解谷氨酸和脯氨酸以维持线粒体代谢，保障 NETs 的持续进行，进而促进肝转移灶的生成[40]。多项临床研究表明中性粒细胞与淋巴细胞比率(neutrophil-lymphocyte ratio, NLR)升高与乳腺癌患者预后不良相关。中性粒细胞可通过不同的机制促进癌症进展和转移。其可通过抑制 $CD8^+$ T 细胞的活化[44]，或在癌细胞外渗阶段削弱 NK 细胞功能[45]从而建立免疫抑制微环境。

4. 肿瘤细胞对肝脏微环境的适应

在此过程中，肿瘤细胞并非被动适应，而是通过主动调控多种分子及信号通路，逐步利用并重塑肝脏微环境，从而建立有利于其生存与增殖的转移生态位。乳腺癌细胞到达肝脏后，其能否形成转移灶，取决于其对肝脏微环境的适应能力。成功的转移性生长依赖于肿瘤细胞与肝组织驻留细胞及招募免疫细胞之间的动态相互作用，以及肿瘤细胞对局部免疫、代谢及基质环境的持续适应。

当乳腺肿瘤细胞进入肝脏微循环时，它们首先会遇到肝窦内皮细胞。肝窦内皮细胞有大量窗孔，细胞间连接松散且缺乏内皮外基膜[46]。乳腺癌细胞通过钙黏蛋白-2 (claudin-2)直接与下方的细胞外基质(extracellular matrix, ECM)成分(如纤连蛋白和 IV 型胶原)相互作用，而 claudin-2 通过上调乳腺癌细胞表面 $\alpha 2\beta 1$ 和 $\alpha 5\beta 1$ 整合素复合物的表达来增强细胞间黏附作用，并促进乳腺癌肝转移性定植[47]。乳腺癌细胞会伸出细胞突起穿过肝窦内皮细胞，并与肝细胞直接接触[20]。与基质黏附类似，乳腺癌细胞与肝细胞的相互作用也由 claudin-2 促进，但这并不依赖于整合素复合物[48]。乳腺肿瘤细胞与肝细胞的相互作用可能通过 MET 来促进转移性生长[26]。研究表明，肝细胞可以直接诱导邻近乳腺癌细胞中 E-cadherin

的重新表达，从而驱动其恢复上皮表型，增强了细胞间的黏附性[25]。

库普弗细胞作为肝血窦中定居的肝巨噬细胞，通常作为抵御进入门静脉或动脉循环的颗粒物、病原体和异常细胞的第一道防线[49]。肝脏转移性定植早期，库普弗细胞主要表现出抗肿瘤作用，这可能通过分泌粒细胞－巨噬细胞集落刺激因子(granulocyte macrophage colony stimulating factor, GM-CSF)、干扰素γ (interferonγ, IFN-γ)等炎症因子募集 NK 细胞，协同促进库普弗细胞的抗肿瘤作用[50]。有研究表明库普弗细胞的抗肿瘤特性仅限于肝脏转移性定植的早期阶段[51]。在有关结直肠癌的研究中[52]-[54]，在 CTCs 外渗后，库普弗细胞可以产生细胞因子和生长因子，包括白介素-6、VEGF 和肝细胞生长因子，以及基质金属蛋白酶 MMP-9 和 MMP-14 等，从而促进肝转移进程。然而，在 BCLM 中是否具有这些双重作用还有待进一步研究。近期一项研究揭示了乳腺癌细胞可通过分泌蛋白 DMBT1 诱导 CD62L + 的库普弗细胞形成，而 CD62L + 库普弗细胞分泌趋化因子 CCL8 招募并激活中性粒细胞，促进 NETs 的形成和肝转移[55]。

在肝脏中，肝巨噬细胞除了库普弗细胞还有单核细胞来源的巨噬细胞(monocyte-derived macrophages, Mo-Macs) [56]。这些巨噬细胞通常发挥促肿瘤作用，它们会激活转移部位，促进肿瘤细胞的血管外渗、存活和持续生长。巨噬细胞可以诱导新生血管生成和基质重塑，同时还具有免疫抑制作用，从而促进乳腺癌的进展和转移[57] [58]。已有研究表明，乳腺癌细胞的 EMT 受肝转移微环境中 M2 型巨噬细胞的调控[59]。

癌症相关成纤维细胞(cancer-associated fibroblasts, CAFs)也是构成肿瘤微环境的重要部分，其来源具有异质性。肝星状细胞(hepatic stellate cells, HSCs)被认为是肝脏中 CAFs 的重要来源之一[60]。肿瘤细胞诱导 HSCs 活化，而活化的 HSCs 反过来通过增强肿瘤细胞的黏附、侵袭、存活和增殖刺激肿瘤生长[61]。活化的 HSCs 可以通过介导赖 LOX 表达增强重塑 ECM，从而促进乳腺癌细胞的转移性定植[62]。肝内松弛素(relaxin, RLN)是一种存在于肝组织中的抗纤维化肽，它可以抑制活化 HSCs 的活性并促进肝纤维化的消退。相关研究通过纳米颗粒递送编码 RLN 的质粒 DNA，这些纳米颗粒优先靶向转移性乳腺癌细胞和活化的 HSCs，从而逆转基质微环境，使其不利于已形成的肝转移灶生长[63]。同时，活化的 HSCs 可以获得类似平滑肌细胞的功能，并诱导肝窦内皮细胞和内皮细胞转移灶内形成毛细血管芽，从而启动肿瘤血管生成[64]。

肝细胞在肝转移中的作用尚不完全清楚。肝细胞可分泌胰岛素样生长因子-1 (Insulin-like Growth Factor-1, IGF-1)和肝细胞生长因子样蛋白(hepatocyte growth factor-like protein, HGFL)等多种生长因子，这些因子可促进肝转移[65]。有研究表明阻断转移性肿瘤细胞中的 IGF-1 信号传导可以抑制结肠癌和肺癌细胞的实验性肝转移[66] [67]。据报道，乳腺癌中 RON 受体过表达，HGFL 可激活 RON，增强肿瘤的生长、迁移和侵袭[68]。

5. 乳腺癌肝转移的预后因素

在转移性乳腺癌患者中，HER-2 阳性乳腺癌患者肝转移的风险相对较高，三阴型乳腺癌次之；相比之下，HR 阳性/HER2 阴性乳腺癌患者的肝转移发生率最低[69]。同时，该研究发现 HR 阳性/HER2 阳性乳腺癌患者的中位生存期最长，达 36.0 个月，而三阴型乳腺癌患者的中位生存期最短[69]。另有研究发现，乳腺癌肝转移病灶多为多发，局限于单叶且病灶体积较小；经多因素分析证实，肝转移灶直径 ＞2.5 cm 与手术切缘阳性是 BCLM 肝切除术后总生存的独立危险因素[70]。有研究根据转移灶的数量和形态，BCLM 分为五类形态：寡转移(≤3 个边界清晰的肝脏转移灶)、非融合性转移(≥4 个非融合性肝脏转移灶)、融合性转移(肝脏转移灶呈融合性结节状)、浸润性肝转移(弥漫性浸润性转移，累及双侧肝叶)和假性肝硬化(肝脏弥漫性结节状轮廓，伴广泛肝转移)，该研究表明影像学检查中显示的融合性或浸润性肿瘤生长与

不良预后相关[71]。

6. 乳腺癌肝转移的系统治疗

目前，乳腺癌肝转移的治疗主要依赖于系统性药物治疗[72]。两项 III 期临床试验表明，多柔比星单药治疗较紫杉醇单药治疗可显著延长中位无进展生存期(7.5 个月 vs. 3.9 个月，$P < 0.001$)，但两组在中位总生存期上未观察到统计学显著差异(18.5 个月 vs. 15.6 个月，$P = 0.380$) [73]。此外，多柔比星联合紫杉醇或多柔比星联合环磷酰胺方案均能带来生存获益，中位总生存期分别为 20.6 个月和 20.5 个月[74]。对于既往接受过蒽环类和紫杉类药物治疗的患者，可考虑使用卡培他滨、长春瑞滨或含铂类的化疗方案[72]。一项针对乳腺癌肝转移的 II 期研究评估了奥沙利铂联合卡培他滨的疗效，结果显示中位无进展生存期为 7.9 个月，中位总生存期为 19.2 个月[75]。此外，射频消融和肝切除术也能延长乳腺癌肝转移患者的生存期。据报道，射频消融可使部分患者的中位无进展生存期达到 12.0 个月，中位总生存期最长可达 60.0 个月[76]。一项系统性综述显示，接受肝切除术的孤立性肝转移患者，其中位无进展生存期为 17.0 个月，中位总生存期范围为 29.5 至 116.0 个月。即使存在肝外转移，肝切除术仍能为患者带来获益，中位无进展生存期在 10.0 至 36.0 个月之间，中位总生存期在 32.0 至 58.0 个月之间[77]。

7. 小结与展望

乳腺癌肝转移是一个由肿瘤细胞内在特性与肝脏微环境共同驱动的过程。各个环节机制既相对独立，又相互交织、彼此影响。乳腺癌肝转移患者预后较差、生存期较短，深入阐明其转移相关分子机制与肝脏微环境特征，可为临床诊疗提供新的思路与方向，为后续开发预防和治疗 BCLM 的新方法奠定基础。

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