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结直肠癌转移机制及靶向药物相关研究进展

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摘　要

近年来，结直肠癌的发病率和死亡率不断上升，术后复发及转移是导致患者死亡的主要原因。肿瘤微环境通过各种机制参与转移性结直肠癌的发生、发展，因此，研究肿瘤微环境与结直肠癌远处转移的关系有助于寻找肿瘤治疗靶点。本文旨在综述结直肠癌转移机制的研究进展，并重点关注靶向药物在治疗结直肠癌转移中的应用。

关键词

结直肠癌，转移，肿瘤微环境，靶向治疗

Research Progress on Colorectal Cancer Metastasis Mechanisms and Targeted Therapy

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Abstract

In recent years, the incidence and mortality of colorectal cancer have been increasing, with postoperative recurrence and metastasis being the main causes of patient death. The tumor microenvironment is involved in the occurrence and development of metastatic colorectal cancer through various mechanisms. Therefore, studying the relationship between the tumor microenvironment and distant metastasis of colorectal cancer is helpful in identifying therapeutic targets for tumor treatment. This article aims to provide an overview of the research progress on the mechanisms of

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colorectal cancer metastasis, with a focus on the application of targeted therapy in the treatment of colorectal cancer metastasis.

Keywords

Colorectal Cancer, Metastasis, Tumor Microenvironment, Targeted Therapy

1. 引言

结直肠癌(colorectal cancer, CRC)已成为全球范围内第三大与癌症相关的致死原因[1]。在过去几十年间，在包括中国、日本和韩国在内的许多亚洲国家，结直肠癌的发病率和死亡率不断上升[2]。据报道，约 20%的 CRC 患者在就诊时已经发展成转移性疾病，而超过 30%的早期 CRC 患者最终会发生远处转移[3]。常见的转移部位包括肝脏(40%~50%)、肺部(10%~20%)、腹膜、卵巢、肾上腺、骨骼和脑部等[4]。近年来，因为化疗药物和靶向药物的进展，结直肠癌的死亡率每年下降约 2% [5]。转移性结直肠癌患者中位生存期显著延长，从过去的 3.6~6 个月，增加到最新研究显示的 24~28 个月[6] [7]。近年来，肿瘤微环境的研究成为热点领域，包括癌相关成纤维细胞(CAFs)、肿瘤相关巨噬细胞(TAMs)和循环肿瘤细胞(CTCs)等细胞参与了结直肠癌转移的机制，并为靶向治疗提供了可能性[8] [9] [10] [11]。深入研究结直肠癌转移机制，探索治疗新靶点对于那些出现远程转移的结直肠癌患者具有重要意义，因此本文将重点关注结直肠癌转移机制和靶向治疗的现状以及最新进展。

2. 结直肠癌转移机制

传统理论认为，癌细胞的致癌基因突变是引发癌症的主要原因。随后，周围未发生基因突变的细胞被招募并适应周围没有发生基因突变的细胞被吸引并适应，同时释放多种细胞间通信分子，包括细胞因子、趋化因子和泡状体，这导致肿瘤微环境(Tumor microenvironment, TME)的形成，并与癌细胞相互影响[12]。

TME 是癌症研究中的一个关键概念，包括肿瘤细胞、基质、基质细胞、细胞因子和其他组分[13]。结直肠癌微环境中癌相关成纤维细胞是最常见的基质细胞。CAFs 分泌的细胞因子，包括转化生长因子-β、白血病抑制因子等，均可以促进肿瘤侵袭和增殖[14] [15] [16]。这类细胞还可以通过重塑细胞外基质(ECM)促进肿瘤细胞转移，调节血管生成，影响肿瘤力学和药物透过性[17]。最近的一项研究表明，CAFs 分泌的白细胞介素-6 (IL-6)可以诱导癌细胞中的 JAK2/STAT3 信号通路，从而导致富亮氨酸 α-2 糖蛋白-1 (LRG1)的表达，而 LRG1 则使癌细胞具有更强的侵袭性并有能力转移到其他部位[18]。浸润的 CAF 在 TIME 中与其他免疫细胞相互作用，促进免疫抑制肿瘤微环境的形成，从而使癌细胞逃避免疫系统的监视[19]。

肿瘤相关巨噬细胞也是构成 TME 的重要的细胞类型。它们可以通过分泌细胞因子和趋化因子，协调炎症机制，调节原发肿瘤的生长、免疫应答、血管形成、细胞外基质重塑、血管侵犯和转移部位毛细血管外渗等[20] [21] [22] [23]。TAMs 释放多种细胞因子，包括血管内皮生长因子(VEGF)，白细胞介素-1 (IL-1)，白细胞介素-8 (IL-8)，肿瘤坏死因子-α (TNF-α)和基质金属蛋白酶(MMPs)，它们在 CRC 的血管形

成过程中以时空方式协同调节基质重塑和血管形成[23]。其中，MMPs 还可以通过破坏细胞-细胞黏附和细胞外基质来促进癌细胞转移[24] [25]。

上皮－间充质转化(EMT)是指细胞失去其上皮细胞特性(如极性和黏附性)并获得间充质细胞特性(如运动性)的过程[26] [27]。在结直肠癌中，EMT 在肿瘤进展、转移和耐药性方面扮演着重要角色。此外，具有上皮可塑性的细胞可能会成为癌干细胞(CSCs)，这类细胞对转移性肿瘤的再生和种植起着至关重要的推动作用[28]。

当原发部位的肿瘤细胞脱落并进入循环系统或淋巴系统时，它们被称为循环肿瘤细胞[29]。CTCs 在循环中面临许多生存挑战，包括免疫攻击、剪切力和细胞凋亡[30]。然而，血液中存在许多其他类型的细胞(如肿瘤相关中性粒细胞和血小板)，它们可以帮助 CTCs 存活和转移。最新证据[31]表明，肿瘤相关中性粒细胞(tumor-associated neutrophils, TANs)与癌症的不良预后有关，它可以通过释放多种细胞因子促进原发部位和转移部位的血管生成及肿瘤细胞扩散。此外，研究发现血小板在肿瘤转移中也发挥着不可或缺的作用。肿瘤细胞能够诱导血小板聚集和激活，激活后的血小板通过 GPIIb-IIIa-纤维蛋白原桥和上调的 P-选择素附着在 CTCs 表面，血小板黏附在 CTCs 表面形成物理屏障，可保护 CTCs 免受血流剪切力的物理损伤，更重要的是，这种血小板的黏附可以阻碍 NK 细胞的识别，帮助 CTCs 实现免疫逃逸[32]。那些在血液微环境中艰苦生存下来的 CTCs 将进入转移部位，进行存活和大量增殖，最后进展为转移癌。

在结直肠癌转移过程中，肝脏转移是最常见的。肝脏内部存在许多由肝窦内皮细胞(LSECs)和库普弗细胞(KCs)组成的肝血窦，其结构呈孔状，有助于循环肿瘤细胞的被动外流[33]。CTCs 进入血窦中，诱导 LSECs 和 KCs 中的促炎级联反应，促进它们向促肿瘤表型极化[34]。当 CTCs 初次接触到 KCs 时，会刺激其释放 TNF-α，该细胞因子与 LSECs 上的相应受体肿瘤坏死因子受体 1 结合，进而促进了内皮细胞上血管黏附受体 E-选择素、血管细胞黏附分子-1 和细胞间黏附分子-1 的内皮表达[35] [36]。这些受体与 CTCs 上对应的配体结合，促使肿瘤细胞穿过内皮层并进行迁移，从而成功地转移到肝实质中，发展为转移癌[34]。

3. 结直肠癌靶向治疗研究新进展

靶向药物治疗是一种通过抑制肿瘤细胞及其生长微环境的特定靶点，来抑制肿瘤的生长和增殖的治疗方式。相比传统治疗方法，靶向治疗更加特异，对正常组织细胞的不良反应更少[37]。接下来，我们将深入探讨目前结直肠癌靶向治疗研究的最新进展。

正如前文所述，血管生成在支持癌细胞的生长、存活和转移扩散中起着至关重要的作用。该过程通过调节血管生成的相关因子(包括血管内皮生长因子、血小板源性生长因子和成纤维细胞生长因子等)及其受体之间的相互作用来调节[38]。贝伐珠单抗是一种靶向调节血管内皮生长因子的人源化免疫球蛋白 G 单克隆抗体(mAb)，其作用机制包括抑制肿瘤血管生成，以及通过暂时将肿瘤血管网络正常化来增强化疗药物的传递[39]。在过去 20 年间，多项III期临床试验进一步证实，将贝伐珠单抗与氟尿嘧啶单药化疗联合应用可显著延长无进展生存期[40] [41]。虽然还有其他针对血管生成的药物可用于结直肠癌转移的二线和后续治疗，比如阿柏西普、雷莫芦单抗，但由于其高昂的成本和毒性，它们的使用并不像贝伐珠单抗那样广泛[42]。

表皮生长因子受体(EGFR/ErbB1)属于酪氨酸激酶受体(ErBb)家族，其细胞外结构域与相应配体结合后被磷酸化，从而激活内皮细胞增殖和血管生成的信号通路[43]。西妥昔单抗是一种嵌合型免疫球蛋白 G-1 单抗，可以靶向结合 EGFR 胞外结构域，竞争性抑制其他配体与 EGFR 结合，从而阻断下游信号转导通路发挥抗肿瘤功能[44]。相比之下，帕尼单抗是一种全人源化抗体，不会像西妥昔单抗那样引起抗体依赖性细胞介导的细胞毒作用，并且对 EGFR 具有更高的亲和力[45]。

人表皮生长因子受体 2 (HER2)，也称为 ErbB-2，是一种编码在染色体 17q12 上的蛋白酪氨酸激酶受体。HER2 与 EGFR 的作用方式类似，因为它们共享许多下游通路，如 RAS/RAF/MEK 和 PI3K/AKT，并通过信号通路调控细胞增殖[46]。研究揭示，在 HER2 扩增的情况下，EGFR 抑制可能得到补偿[47]。这导致 HER2 阳性肿瘤通常对 EGFR 靶向药产生抗药性，使患者预后变得更加恶劣。所以联合使用 HER2 和 EGFR 靶向药可以抑制肿瘤细胞增殖，并产生比单一药物更强的效果[48]。拉帕替尼是一种小分子酪氨酸激酶抑制剂，可以双重结合 EGFR 和 HER2 的胞内结构域，因此可能成为 HER2 阳性 mCRC 靶向治疗药物[49]。对于晚期 CRC 患者(III~IV 期)，HER2 阳性被证实为独立的预后危险因素[50]。目前临床常用免疫组化或 FISH 来判断 HER2 扩增情况并预测 EGFR 靶向治疗的抗肿瘤能力。

在转移性结直肠癌病例中，约有 8%至 12%的患者存在 BRAF 突变，其中 V600E 突变最为常见[51]。然而，单一应用 BRAF 抑制剂对 BRAF 突变型 mCRC 表现出耐药性[52]。临床前实验表明，BRAF 抑制剂可能导致EGFR过度激活，而抗EGFR治疗则可能使先前耐药的细胞系对BRAF抑制剂产生敏感性[53]。Kopetz S 等人[54]的随机研究证实，在加入 BRAF 抑制剂维莫非尼(vemurafenib)的基础上，联合使用西妥昔单抗和伊立替康可以延长 BRAF 突变型患者的生存期。

成纤维细胞活化蛋白(FAP)是一种丝氨酸蛋白酶，在 CAFs 表面高度表达[55]。由于其在调节成纤维细胞分化和增殖方面的作用，FAP 被认为是一个具有重要研究价值的治疗靶点。在结肠癌小鼠模型中，研究人员通过皮下注射针对肿瘤基质抗原FAP的基因疫苗，成功引发了T细胞介导的抗癌免疫反应[56]。此外，针对 FAP 的单克隆抗体已经进行了小型 I 期和 II 期临床试验，并取得了良好的结果[57]。

4. 展望

自 20 世纪 80 年代初以来，随着对结直肠癌发病机制的深入研究以及治疗新靶点的发现，结直肠癌患者尤其是难治性患者在应用针对特定靶点设计的相应药物后生存期显著延长。新的靶向药物有助于临床医生为每位结直肠癌患者提供更加个性化的治疗方案。虽然治愈仍然不常见，但靶向治疗可以改变CRC的治疗前景。这提示我们，结直肠癌发生、发展及转移的相关机制研究始终是至关重要的。根据这些发病机制，研制并验证敏感和特异性的靶向药物仍然是一个非常活跃的研究领域。

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