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Dynamic evolution process of tumor microenvironment in colorectal cancer metastasis

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Abstract: In the process of colorectal cancer metastasis, the tumor microenvironment interacts with primary tumors, secondary tumors, circulating tumor cells, and disseminated tumor cells. This article introduces its dynamic evolution process. The tumor microenvironment can not only exert its host defense mechanism to kill cancer cells, but also help cancer cells metastasize and spread through changes in the composition and structure of the microenvironment. Cancer cells complete their invasion, infiltration, circulation, extravasation, and seeding processes through phenotype transformation, secretion of cytokines, and cell dormancy.

Keywords: Tumor microenvironment; Colorectal cancer; Tumor metastasis; Premetastatic niches; Circulating tumor cells

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Metastatic recurrence of colorectal cancer (CRC) cells within a few years after initial treatment is a common and malignant phenomenon. High metastasis rates are a major reason for the high incidence of advanced CRC, low cure rates, and high mortality rates [1]. The tumor microenvironment represents a complex ecosystem that is closely associated with tumor metastasis, including tumor cells, immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, extracellular matrix (ECM), and other components [2]. This paper reviews the metastasis process of CRC, analyzing the interactions between the tumor microenvironment and primary tumors, secondary tumors, circulating tumor cells, and disseminated tumor cells. It aims to elucidate the mechanisms involved in different stages of CRC metastasis from the perspective of the tumor microenvironment.

1 Changes in the Local Microenvironment of Primary Tumors

1.1 Preparation for cancer cell invasion

Invasion is a complex, multi-step process involving the detachment of cancer cells from the primary tumor mass and their penetration into the surrounding stroma [3-4]. Phenotype switching is a necessary process during invasion when cancer cells are exposed to changing cellular and molecular components of the tumor microenvironment. Several studies have shown that CRC cells undergo epithelial-to-mesenchymal transition (EMT) during invasion, losing their epithelial phenotype and acquiring a mesenchymal phenotype [5]. During EMT, epithelial cells lose their cellular polarity and intercellular adhesion, gaining migratory and invasive properties characteristic of mesenchymal stem cells [6]. Cellular markers also change during EMT, in which the expression of epithelial markers such as E-calmodulin and keratins is absent, while the expression of mesenchymal markers such as vimentin, N-cadherin, and fibronectin is increased. Notably, the decrease of E-cadherin can lead to a decrease in cellular adhesion, enhancing the ability to invade and metastasize. The loss of E-cadherin is considered one of the most significant features of EMT [7]. Therefore, the EMT process facilitates the separation of adjacent cancer cells, enhancing their migratory, invasive, anti-apoptotic, and extracellular matrix-degrading capabilities, thus promoting cancer metastasis. Regulatory factors such as DDX21, circSKA3, and Slug are closely related to EMT in CRC. DDX21, a representative RNA-binding protein, is significantly upregulated in CRC tissues compared to adjacent normal tissues. The phase separation aggregates of DDX21 target and activate the *MCM5* gene, further activating the EMT signaling pathway and promoting liver and lung metastasis of CRC [8]. CircSKA3 is upregulated in CRC tissues but downregulated in serum samples and is retained in CRC cells through specific cellular motif elements. These motifs are also the sites of interaction between circSKA3 and the zinc finger transcription factor SLUG, which inhibits E-cadherin transcription and enhances EMT through E-box elements [9-10].

In addition to EMT, perineural invasion (PNI) has become an increasingly studied factor in tumor invasion processes such as CRC. PNI is a significant form of tumor cell invasion into the surrounding stroma and metastasis along the nerve sheath, defined as the presence of cancer cells in any layer of the nerve sheath or at least 33% of the nerve fiber circumference [11]. It has been shown that PNI is a marker of more aggressive tumor

phenotypes and poor prognosis in malignant tumors, with a 5-year overall survival rate of 72% for PNI-negative CRC and 25% for PNI-positive CRC [12]. PNI represents a clear pathway for cancer cell invasion and dissemination; however, the role of nerves in cancer progression remains relatively unknown. Some studies suggested that nerve infiltration into the tumor microenvironment was an active process [13]. Tumor-infiltrated nerve fibers can stimulate tumor growth and spread, while tumor cells can drive excessive nerve growth in interactions that promote tumor progression [11]. CRC liver metastasis is strongly associated with PNI due to the rich sympathetic nerve fibers that innervate the liver, which may originate from the same preganglionic source as those innervating the colon and rectum [14].

Among all the stromal cells in the tumor microenvironment, CAFs are the most abundant and closely related to cancer progression. CAFs regulate the biological properties of tumor cells and other stromal cells through cell-to-cell communication, releasing numerous regulatory factors, synthesizing, and remodeling the ECM, thus affecting cancer development and progression [15]. Franzè *et al.* [16] demonstrated that IL-34 could induce normal fibroblasts to acquire a CAF-like phenotype in CRC, and IL-34 knockout in CAFs reduced their tumorigenic properties. The most distinctive feature of CAFs is their high capacity for ECM synthesis and remodeling during the fibrotic response. Activated fibroblasts produce large amounts of various types of collagens, hyaluronic acid, fibronectin, and laminin, which constitute the ECM and basal membrane [15]. ECM remodeling leads to tissue mechanical stiffening and stromal fibrosis, increasing tension in the surrounding tissue of the tumor. CAFs exert pulling forces through this remodeling property, promoting cancer cell invasion through the tumor microenvironment and generating physical tracks in the ECM, facilitating collective invasion of cancer cells [17-18].

1.2 Preparation for cancer cell intravasation

Cancer cell intravasation refers to the process by which cancer cells cross the endothelial layer to enter the circulation. The integrity of the vascular system within tumors is often compromised, with potential damage to the vascular basement membrane and endothelial barrier, leading to increased vascular leakage and facilitating cancer cell intravasation [19]. Tumor-associated macrophages play a critical role in cancer cell intravasation. Macrophages can be classified into two phenotypes based on their functions and cytokine profiles: the pro-inflammatory M1 type and the anti-inflammatory M2 type [20]. In tumor-associated diseases, M1 macrophages exhibit anti-tumor effects and inhibit tumor growth, while M2 macrophages display pro-tumor effects and promote the formation of new blood vessels in tumors [21]. During intravasation, tumor-associated macrophages localize to the perivascular niche and induce angiogenesis by modulating matrix metalloproteinase (MMPs), serine proteases, and tissue proteases, degrading the basement membrane, and secreting pro-angiogenic factors, cytokines, and chemokines, including vascular endothelial growth factor (VEGF), chemokine (C-X-C motif) ligand (CXCL)8, MMP7, MMP9, and MMP12. This promotes the formation of the tumor vascular network. For instance, the VEGF-A signaling pathway induced by M2 macrophages leads to a transient increase in vascular permeability, aiding cancer cells in breaching the vascular barrier and promoting cancer cell infiltration. Removal of VEGF-A from macrophages can inhibit the phosphorylation of tumor VEGFR2, thereby restoring normal vascular development [22]. During CRC progression, M2 polarization of tumor-associated macrophages is regulated through various pathways. Runt-related transcription factor 1 (RUNX1) can promote the secretion of C-C motif ligand 2 (CCL2) and activate the Hedgehog signaling pathway to recruit macrophages and induce their polarization to M2, thereby promoting tumor angiogenesis and malignant behavior of cancer cells [23]. Microbes promote the formation of intra-tumoral lactate, which induces polarization of macrophages to the M2 phenotype through lactylation modification of macrophage RIG-Ilys852, regulating CRC liver metastasis [24]. Exosomal miR-1246 plays a critical role in the reprogramming of CRC-associated macrophages, driving tumor-associated macrophages to polarize towards a tumor-supportive (M2) phenotype, thereby impairing the infiltration and function of $CD8^+$ T cells [25].

CAFs play a crucial role in remodeling the basement membrane and extracellular matrix, and they also impact the infiltration process of CRC cells. CAFs isolated from CRC not only invade the basement membrane through matrix metalloproteinases, but also exert mechanical contraction forces on the basement membrane through pulling and stretching. Thus, in addition to proteolysis, the mechanical forces exerted by CAFs represent another mechanism by which CAFs facilitate cancer cell infiltration [26]. CAFs located proximally to tumors can collaborate with tumor-associated macrophages to complete the infiltration process. CAFs secrete CXCL12 chemokine, attracting tumor-associated macrophages and accompanying cancer cells to the perivascular region, where infiltration of cancer cells is promoted [27].

2 Formation of Premetastatic Niches Prior to Secondary Tumor

The impact of developing tumors on the host extends beyond the local tumor microenvironment. Through paracrine effects, primary tumors trigger a series of events that create a favorable microenvironment for cancer cells in distant organs before metastatic spread occurs. The primary tumor prepares a distant site, well beyond the tumor boundaries, for the arrival of disseminated cancer cells, known as the premetastatic niche.

The specific mechanisms of premetastatic niche formation in CRC are not fully understood. Some studies

suggested that in CRC liver metastasis, the hypoxic microenvironment in primary CRC lesions promoted the release of exosomes, selectively initiating the formation of premetastatic niches in the liver. Kupffer cells (KCs) in the liver can phagocytose exosomes containing high levels of miR-135a-5p from the blood circulation. Exosomal miR-135a-5p activates the LATS2-YAP-MMP7 axis to promote CRC liver metastasis, and CD30-TRAF2-p65-mediated immune suppression also contributes to this process [28]. Other studies suggested that TGF-β1-rich extracellular vesicles derived from CRC cells induced the formation of premetastatic niches in the liver. TGF-β1 is a key factor in the formation of liver premetastatic niches and is closely related to the occurrence and prognosis of liver metastasis. Specifically, extracellular vesicles released by CRC cells induce hepatic stellate cells (HSCs) to transform into CAFs, thereby remodeling the liver premetastatic niche. Extracellular vesicles also activate HSCs to secrete the CXCL12, further recruiting myeloid-derived suppressor cells, leading to liver immune suppression and enabling the immune escape of disseminated cancer cells [29]. Research found that CRC patients with fatty liver are more prone to liver metastasis. The potential mechanism was closely related to the premetastatic niche. Fatty liver upregulates Rab27a expression, promoting hepatocytes to produce hepatocyte-derived extracellular vesicles. These vesicles enhance CRC liver metastasis progression by promoting carcinogenic Yes-associated protein signaling and immune-suppressive microenvironments [30].

3 Circulating Tumor Cells and the Tumor Microenvironment

3.1 Microenvironment attacks and circulating tumor cell evasion

After intravasation, tumor cells enter the bloodstream or lymphatic circulation and become circulating tumor cells (CTCs). These cells face a range of damages and challenges from the foreign microenvironment during circulation. Factors such as cell detachment-induced apoptosis, high shear stress in the blood circulation, and immune-mediated attacks collectively contribute to the death of most CTCs [31-33]. The small fraction of CTCs that survived the cycle avoided destruction through multiple mechanisms. Laminar shear stress (LSS) upregulates ATOH8 protein expression in CTCs of CRC through the VEGF-VEGFR2-AKT signaling pathway, promoting hexokinase 2 (HK2) transcriptional activity and mediating CTC survival [34]. Platelets are also key promoters of CTCs survival. Their mechanisms include enhancing CTCs adhesion and aggregation, forming a “platelet shield” around CTCs that protects them from physical stress and destructive forces from NK cells, cytotoxic T cells, dendritic cells, and other immune surveillance [35]. Recent studies also found elevated platelet counts and Erbin protein expression in platelets in patients with metastatic CRC, and Erbin gene knockout in platelets can inhibit CRC lung metastasis in mice, providing a new avenue for metastatic treatment [36].

3.2 Extravasation of CTCs

The next step for the small portion of CTCs that survived the cycle is extravasation into secondary organs, which is partly determined by the organotropism inherent to each primary cancer type. The classic theory is Paget's "seed and soil" hypothesis proposed in the 1880s [37]. This metastatic propensity is highly specific. CRC patients primarily metastasize to lymph nodes, liver, and lungs, with some cases spreading to bones and ovaries [38]. The organotropism of CRC metastasis is influenced by multiple mechanisms. Comprehensive analysis of epithelial cells showed that subpopulations of stem-like cells expressing high levels of protein tyrosine phosphatase receptor type O and ASCL2 transcription factors exhibited different preferences for liver or ovarian metastasis. Cells expressing high δ-like ligand 4 and MAF bZIP transcription factor A were enriched in primary CRC and ovarian metastases, suggesting a possible link to ovarian metastasis. P3 cells, which have similar expression patterns to cholangiocytes, were primarily found in primary CRC and liver metastases, indicating they maight be major contributors to liver-specific metastasis [39].

For extravasation itself, tumor cells must first adhere and attach to the endothelial cell lumen, a process facilitated by the cell adhesion molecules and their ligands, integrins, and extracellular matrix components expressed by both tumor cells and endothelial cells [40]. Platelets and neutrophils may continue to move with CTCs, further enhancing tumor cell adhesion to the vascular system [41-42]. Platelet adhesion to the endothelial wall is crucial for metastatic disease progression. Platelets can increase the adhesion levels between cancer cells and endothelial cells, and antiplatelet drugs may reduce adhesion between colorectal cancer cells and endothelial cells, potentially reducing metastatic spread [43]. CRC-derived IL-8 can recruit neutrophils to the liver, forming neutrophil extracellular traps (NETs). NETs capture disseminated tumor cells, allowing CTCs to colonize the liver and stimulating the secretion of IL-8 by CRC cells in metastases, which in turn recruits more neutrophils, creating a feedback loop that promotes colorectal cancer cell migration and invasion [44]. After adhesion, CTCs subsequently traverse endothelial cell junctions and enter the organ parenchyma. This typically requires active proteolysis and degradation of cell adhesion molecules, including junctional adhesion molecules and cadherins [45-46]. In CRC research, the elevated expression of type I collagen receptor tyrosine kinase in samples from stage T4, lymph node metastasis, and peritoneal metastasis patients suggested that DDR2 expression levels might be a potential therapeutic target for CRC metastasis [47].

4 Disseminated Tumor Cells and Tumor Microenvironment

After infiltration into the secondary site, tumor cells complete metastatic seeding, becoming disseminated tumor cells (DTCs) and facing a new set of challenges from the foreign tissue environment, and the vast majority of tumor cells are again killed by host defense mechanisms [48]. The few DTCs that survive to be implanted in the new organ may initially enter a dormant state to protect them from recognition and killing by the immune system, these cells stop proliferating in the dormant state and survive in a quiescent state for several years, DTCs can lead to metastasis and recurrence of the cancer after the dormant period [49]. It has been shown that colorectal cancer cells that metastasize to the liver do not immediately form lesions visible to the naked eye. Instead, these cells enter a dormant phase in the liver and become resistant to therapeutic interferences. In studying the factors affecting tumor dormancy, it was found that low levels of FBX8 expression were associated with lower overall survival in patients with CRC, and that FBX8 upregulated a number of markers associated with tumor cell dormancy, as well as downregulating genetic markers associated with dormancy activation in tumor cells. Based on these findings, FBX8 may be involved in CRC dormancy at liver metastasis sites, which provides a potential target for the treatment of dormant CRC liver metastatic cells and a new theory for the prevention and treatment of tumor metastasis [50].

In summary, the complex dynamic process of CRC metastasis needs to be considered holistically in terms of both tumor cell intrinsic factors and tumor microenvironment extrinsic factors in understanding the process. The complexity of the metastatic process of colorectal cancer also suggests that the anticancer effect of drugs with a single target may be limited, and it is necessary to explore the whole process of tumor invasion, endocytosis, circulation, exocytosis, and seeding, to develop drugs targeting a variety of targets in response to the many influencing factors of the dynamic process of cancer metastasis, and to search for individualized therapeutic approaches targeting the tumor microenvironment, which has become a difficult and hot spot of the current research on CRC metastasis.

Conflict of interest None

Reference

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·研究进展·

肿瘤微环境在结直肠癌转移中的动态演变过程

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摘要：在结直肠癌转移过程中，肿瘤微环境与原发肿瘤、继发肿瘤、循环肿瘤细胞、播散性肿瘤细胞之间相互作用，本文介绍了其动态演变过程。肿瘤微环境既可以发挥其宿主防御机制杀灭肿瘤细胞，又会通过微环境的成分及结构的改变帮助肿瘤细胞转移扩散。肿瘤细胞则通过表型转换、分泌细胞因子、细胞休眠等方式完成其侵袭、内渗、循环、外渗及播种过程。

关键词：肿瘤微环境；结直肠癌；肿瘤转移；转移前生态位；循环肿瘤细胞
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Dynamic evolution process of tumor microenvironment in colorectal cancer metastasis

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Abstract: In the process of colorectal cancer metastasis, the tumor microenvironment interacts with primary tumors, secondary tumors, circulating tumor cells, and disseminated tumor cells. This article introduces its dynamic evolution process. The tumor microenvironment can not only exert its host defense mechanism to kill cancer cells, but also help cancer cells metastasize and spread through changes in the composition and structure of the microenvironment. Cancer cells complete their invasion, infiltration, circulation, extravasation, and seeding processes through phenotype transformation, secretion of cytokines, and cell dormancy.

Keywords: Tumor microenvironment; Colorectal cancer; Tumor metastasis; Premetastatic niches; Circulating tumor cells
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结直肠癌患者在初次治疗后数年内经常出现转移性肿瘤细胞的恶性再生。高转移率是结直肠癌晚期患者多、治愈率低、病死率高的主要原因[1]。肿瘤微环境代表着复杂的生态系统，与肿瘤转移密切相关，其中包括肿瘤细胞、免疫细胞、肿瘤相关成纤维细胞(CAFs)、内皮细胞、细胞外基质等[2]。本文通过梳理结直肠癌转移的发生过程，分析肿瘤微环境与原发肿瘤、继发肿瘤、循环肿瘤细胞、播散性肿瘤细胞的相互作用，从肿瘤微环境方面对结直肠癌转移发生的不同阶段中涉及的机制进行阐述。

1　原发肿瘤局部微环境的变化

1.1　*肿瘤细胞侵袭准备*　侵袭是一个复杂的、多步骤的过程，包括肿瘤细胞彼此分离，从原发肿瘤块移开，并侵入周围的基质[3-4]。在侵袭过程中，肿瘤细胞暴露于不断变化的肿瘤微环境细胞和分子成分中，表型转换是一个必要的过程。一些研究已经发现结直肠肿瘤细胞在侵袭过程中会通过特定程序失去上皮表型，获得间质表型，这个过程称为上皮-间充质转化(EMT)[5]。EMT 期间，上皮细胞失去其细胞极性和细胞间黏附，获得迁移和侵袭特性以获得间充质干细胞表型[6]。细胞标志物也在 EMT 过程中发生了变化，其中上皮标志物如 E-钙黏蛋白、角蛋白等表达缺失，而波形蛋白、N-钙黏蛋白、纤维连接蛋白等间质标志物表达增加，其中 E-钙黏蛋白水平的下降可以导致细胞的黏附力降低，使细胞获得易于侵袭和转移的特性，是 EMT 最显著的特征[7]。因此肿瘤细胞的 EMT

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过程有利于邻近的肿瘤细胞分离,增强肿瘤细胞迁移、侵袭、抗凋亡和降解细胞外基质的能力,促使肿瘤转移。一些调控因子如 DDX21、circSKA3、Slug 等与结直肠癌 EMT 过程密切相关。DDX21 是一种有代表性的 RNA 结合蛋白,DDX21 在结直肠癌组织中的表达水平显著高于癌旁正常组织,DDX21 的相分离凝集物靶向并激活 *MCM5* 基因,进一步激活 EMT 信号通路,促进结直肠癌的肝转移与肺转移[8];circSKA3 在结直肠癌组织中表达上调,而在血清样本中表达下调,并通过特定的细胞 motif 元件保留在结直肠肿瘤细胞中。motif 元件还是 circSKA3 与锌指转录因子 SLUG 相互作用的位点,可通过 E-box元件抑制 E-钙黏蛋白转录并增强 EMT[9-10]。

除了 EMT,周围神经浸润(PNI)也是结直肠癌等肿瘤侵袭过程中的重要因素。PNI 是肿瘤细胞浸润周围的基质并沿神经鞘转移的一种重要形式,是指肿瘤细胞出现在神经鞘的任何层或周围至少 33% 的神经纤维周长[11]。有研究表明 PNI 是恶性肿瘤中更具侵袭性的肿瘤表型和预后不良的标志物,在结直肠癌中 PNI 阴性肿瘤的 5 年总生存率为 72%,PNI 阳性肿瘤的 5 年总生存率为 25%[12]。然而神经在肿瘤进展中的作用相对未知,有研究表明,神经渗透入肿瘤微环境是一个主动过程[13]。被肿瘤浸润的神经纤维可以刺激肿瘤的生长和扩散,而肿瘤细胞也可以在促进肿瘤进展的交互作用中驱动神经过度生长[11]。结直肠癌肝转移就与 PNI 之间有强关联关系,因为支配肝脏的交感神经纤维十分丰富且可能与支配结肠和直肠的交感神经属于同一个节前起源[14]。

在肿瘤微环境的所有基质细胞中,CAFs 是最丰富的,并与肿瘤的进展密切相关。CAFs 通过细胞与细胞的通讯以调节肿瘤细胞和其他基质细胞的生物学特性,释放大量的调节因子,合成和重构细胞外基质,从而影响肿瘤的发生和发展[15]。Franzè 等[16]证明在结直肠癌中白细胞介素(IL)-34 可以诱导正常成纤维细胞获得与 CAFs 相似的细胞表型,而 CAFs 中 IL-34 的敲除降低了其致瘤特性。CAFs 的特征是它们在促纤维增生反应期间具有高细胞外基质合成和重塑能力,在结缔组织形成过程中,活化的成纤维细胞大量合成构成细胞外基质和基底膜的各种类型的胶原蛋白、透明质酸、纤连蛋白和层黏连蛋白[15]。细胞外基质的重塑会导致组织的机械硬化和基质细胞纤维化,间质硬化后肿瘤周围组织张力增加,CAFs 就是通过这种重塑特性来施加拉力,促使肿瘤细胞通过肿瘤微环境侵袭并在细胞外基质中产生物理轨迹,帮助肿瘤细胞出现群体侵袭[17-18]。

1.2　*肿瘤细胞内渗准备*　肿瘤细胞内渗是指肿瘤细胞穿越内皮层进入循环,肿瘤中血管系统的完整性经常受损,血管基底膜和内皮屏障可能被破坏,从而增加血管渗漏,促进肿瘤细胞的内渗[19]。肿瘤相关巨噬细胞在肿瘤细胞内渗中发挥着重要的作用,巨噬细胞可依据其功能和生成的细胞因子不同而分为两种细胞表型,分为具有促炎作用的 M1 型与具有抑炎作用的 M2 型[20]。M1 型巨噬细胞表现为具有抗肿瘤效应,对肿瘤的生长起到抑制作用。M2 型巨噬细胞表现为促肿瘤效应,对肿瘤新生血管的形成起到促进作用[21]。在内渗过程中,肿瘤相关巨噬细胞定位于血管周围生态位,通过调节基质金属蛋白酶(MMP)、丝氨酸蛋白酶和组织蛋白酶,诱导血管生成,降解基底膜,并分泌促血管生成因子、细胞因子和趋化因子,包括血管内皮生长因子(VEGF)、趋化因子配体(CXCL)8、MMP7、MMP9 和 MMP12,促进肿瘤血管网络的形成。如 M2 型巨噬细胞诱导的 VEGF-A 信号通路会导致血管通透性的短暂增加,促进肿瘤细胞内渗,从巨噬细胞中去除 VEGF-A 可抑制肿瘤 VEGFR2 的磷酸化水平,促进血管发育恢复正常[22]。结直肠癌发展过程中,肿瘤相关巨噬细胞的 M2 极化受到多种途径的调控,Runt 相关转录因子 1(RUNX1)能够通过促进 CCL2 的分泌和激活 Hedgehog 信号通路,招募巨噬细胞并诱导其向 M2 型极化,从而促进肿瘤血管生成和肿瘤细胞的恶性行为[23];微生物促进瘤内乳酸形成,通过对巨噬细胞RIG-I^{lys852}乳酸化修饰诱导其极化为 M2,调控结直肠癌肝转移[24];外泌体 miR-1246 在结直肠癌相关巨噬细胞的重编程中发挥关键作用,外泌体 miR-1246 能够驱动肿瘤相关巨噬细胞向肿瘤支持型(M2 型)极化,从而破坏 CD8$^+$T 细胞的浸润和功能[25]。

CAFs 是重塑基底膜和细胞外基质的关键角色,CAFs 也作用于结直肠肿瘤细胞内渗的过程中。结肠癌患者中分离出的 CAFs 不仅可以依赖 MMP 的方式侵入基底膜,还可通过拉扯、拉伸等方式施加机械收缩力在基底膜产生间隙。因此,除了蛋白水解之外,CAFs 施加的机械力代表了 CAFs 促使肿瘤细胞内渗的另一种机制[26]。位于肿瘤近端的 CAFs 还可与肿瘤相关巨噬细胞合作完成内渗过程,CAFs 分泌 CXCL12,将肿瘤相关巨噬细胞和伴随的肿瘤细胞吸引到血管周围区域,在那里促进肿瘤细胞发生内渗[27]。

2　继发肿瘤转移前生态位的形成

发展中的肿瘤对宿主的影响并不局限于局部肿瘤微环境,通过旁分泌效应,原发肿瘤触发一系列事件,在转移扩散发生之前,它们在远处器官中产生有利于肿瘤细胞的微环境。原发肿瘤为未来播散性肿瘤细胞的到来提前准备的远超肿瘤边界的远距离部位,称为转移前生态位。

关于结直肠癌转移前生态位的具体作用机制尚不清楚,有研究认为在结直肠癌肝转移中,原发性结直肠癌病变中的缺氧微环境促进了外泌体的释放,选择性在肝脏中启动了转移前生态位的形成。定居于肝内的巨噬细胞 Kupffer 细胞可以从血液循环中吞噬含有高表达 miR-135a-5p 的外泌体进入肝脏,外泌体 miR-135a-5p 启动 LATS2-YAP-MMP7 轴以促进结直肠癌肝转移的发生,CD30-TRAF2-p65 介导的免疫抑制信号也促成了这一过程[28]。也有研究认为结直肠癌来源的富含转化生长因子(TGF)-β1 的细胞外囊泡能够诱导肝脏转移前生态位的的形成[29]。具体而言,结直肠肿瘤细胞释放的细胞外囊泡通过诱导肝星状细胞(HSCs)转化为 CAFs,从而重塑肝脏转移前生态位。细胞外囊泡还通过激活 HSCs 分泌 CXCL12,进一步招募髓系抑制细胞,从而形成免疫抑制,导致播散性肿瘤细胞的免疫逃逸[29]。有研究发现患有脂肪肝的

结直肠癌患者更易发生结直肠癌肝转移,其潜在机理也与转移前生态位密切相关,脂肪肝上调 Rab27a 表达,促进肝细胞产生肝细胞源性细胞外囊泡,通过促进致癌的 Yes 相关蛋白信号传导和免疫抑制微环境,促进了结直肠癌肝转移的进展[30]。

3　循环肿瘤细胞与肿瘤微环境

3.1　*微环境攻击与循环肿瘤细胞逃避攻击*　肿瘤细胞内渗后会进入血液循环或淋巴循环变成循环肿瘤细胞,它们会在循环过程中面对外来微环境中一系列不同的损害和挑战。由细胞分离引起的失巢凋亡[31]、血液循环中的高剪切力和免疫介导的攻击[32-33],共同导致大多数 CTCs 的死亡。经历循环后生存下来的小部分循环肿瘤细胞通过多种机制避免被破坏。层流剪切应力(LSS)通过触发的 VEGF-VEGFR2-AKT 信号通路,上调 ATOH8 蛋白在结直肠癌循环肿瘤细胞中的表达,从而促进己糖激酶(HK2)转录活性介导循环肿瘤细胞的存活[34]。血小板也是循环肿瘤细胞存活的关键促进因子,其机制包括增强循环肿瘤细胞的黏附和聚集,在循环肿瘤细胞周围形成“血小板保护罩”,可以保护它们免受物理压力和自然杀伤(NK)细胞、细胞毒性 T 细胞、树突状细胞和其他细胞免疫监视的破坏性力量[35]。最新研究也表明结直肠癌转移患者血小板数量显著增加,同时转移患者血小板中 Erbin 蛋白表达量高,血小板中的 *Erbin* 基因敲除可抑制小鼠结直肠癌肺转移,这为转移治疗提供了新的途径[36]。

3.2　*循环肿瘤细胞外渗*　通过循环存活的小部分循环肿瘤细胞,下一步骤是外渗到继发器官,这在一定程度上是由每一种原发癌症的潜在器官趋向性决定的,经典代表学说是 Paget 在 19 世纪 80 年代首次提出的“种子和土壤”假说[37]。这种转移倾向性可以是高度典型的,结直肠癌主要扩散到淋巴结、肝脏和肺部,也有一部分可以扩散到骨骼和卵巢[38]。结直肠癌转移的器官倾向性受多种机制的影响,上皮细胞的综合分析显示,具有高蛋白酪氨酸磷酸酶受体 O 型和 ASCL2 转录因子表达的干细胞样细胞群中不同的亚群显示出不同的肝脏或卵巢转移偏好;具有高 δ 样配体 4 和 MAF bZIP 转录因子 A 表达的细胞群在原发性结直肠癌和卵巢转移灶富集,因此可能与卵巢转移相关;与胆管细胞具有相似表达模式的 P3 细胞主要在原发性结直肠癌和肝脏转移灶中发现,其可能是特异性转移至肝脏的主要诱因[39]。

对于外渗本身,肿瘤细胞必须首先滞留并附着在内皮细胞的管腔上,这一步骤是由肿瘤细胞和内皮细胞表达的细胞黏附分子及其配体、整合素和细胞外基质成分促进的[40]。血小板和中性粒细胞可仍与循环肿瘤细胞一起移动,进一步增强肿瘤细胞对脉管系统的黏附[41]。血小板黏附在内皮壁是转移性疾病进展的关键,血小板可以增加肿瘤细胞与内皮细胞的黏附水平,抗血小板药物可以降低结直肠肿瘤细胞和内皮细胞之间的黏附,具有减少转移扩散的潜在作用[42]。结直肠癌来源的 IL-8 可以招募中性粒细胞到达肝脏内并形成中性粒细胞陷阱(NETs),NETs 捕获播散的肿瘤细胞使循环肿瘤细胞在肝内定植并刺激转移灶中的结直肠肿瘤细胞 IL-8 分泌,从而招募更多的中性粒细胞,形成闭环,促进结直肠肿瘤细胞迁移和侵袭能力[43]。黏附后,循环肿瘤细胞接着穿过内皮细胞连接处,进入器官实质部。这通常需要活性蛋白水解及降解细胞黏附分子,包括连接黏附分子,钙黏蛋白等[44]。在结直肠癌研究中,Ⅰ型胶原蛋白受体酪氨酸激酶在 T4 期、淋巴结转移及腹膜转移患者样本中表达水平升高,表明盘状结构域受体 2(DDR2)的表达水平可能是结直肠腹膜转移的一个潜在治疗靶点[45]。

4　播散性肿瘤细胞与肿瘤微环境

在渗入继发部位后,肿瘤细胞完成转移性播种,成为播散性肿瘤细胞并面临着来自外来组织环境的一系列新的挑战,并且绝大多数肿瘤细胞会再次被宿主防御机制杀死[46]。少数存活下来种植在新器官的播散性肿瘤细胞最初可进入休眠状态,以保护它们免受免疫系统的识别和杀伤,这些细胞在休眠状态下会停止增殖,并在静止状态下存活数年,播散的肿瘤细胞在休眠期后会导致肿瘤的复发和转移[47]。有研究表明结直肠肿瘤细胞转移到肝脏后,不会立即形成肉眼可见的病变。相反,这些细胞进入肝脏的休眠期,并对治疗干扰产生抵抗力,在研究影响肿瘤休眠的因素时发现低水平的 FBX8 表达与结直肠癌患者的总生存期较低有关,FBX8 可以上调一些与肿瘤细胞休眠相关的标志物,同时还下调与肿瘤细胞休眠激活相关的遗传标记[48]。

综上所述,结直肠癌转移过程的复杂性提示单一靶点的药物抗肿瘤作用可能有限,要探索肿瘤侵袭、内渗、循环、外渗及播种全过程,针对肿瘤转移动态过程的众多影响因素来研发针对各种靶点的药物,寻找针对肿瘤微环境的个体化治疗方法,成为当前结直肠癌转移的研究难点和热点。

利益冲突　无

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