中国临床研究 Chin J Clin Res, July 2025, Vol.38, No.7

**Cite as:** Chen GC, Cui L. Advances in the role and mechanisms of tumor microenvironment in colorectal cancer metastasis [J]. Chin J Clin Res, 2025, 38(7): 977-982.

**DOI:** 10.13429/j.cnki.cjcr.2025.07.001

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# Advances in the role and mechanisms of tumor microenvironment in colorectal cancer metastasis

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**Abstract:** Tumor microenvironment plays an important role in cancer progression and treatment resistance, and its complexity stems from the dynamic roles of multiple cell types (tumor-associated fibroblasts, mesenchymal stem cells, tumor-associated macrophages, and natural killer cells, etc.) and metabolic factors (lipid metabolites, reactive oxygen species, etc.). In this paper, the role of key components of the tumor microenvironment in colorectal cancer metastasis and the impact on treatment are systematically described, with a view to providing ideas and references for the treatment of colorectal cancer.

**Keywords:** Tumor microenvironment; Colorectal cancer; Mesenchymal stem cells; Fibroblasts; Macrophages; Natural killer cells; Lipid metabolites; Reactive oxygen species; Metastasis

**Fund program:** National Natural Science Foundation of China (82273022)

Colorectal cancer is a highly aggressive tumor with high incidence and mortality rates. Its development is the result of the combined effects of genetic susceptibility, dietary habits, lifestyle, and environmental factors [1]. Despite significant improvements in prognosis for early-stage patients through comprehensive treatments including surgery, chemotherapy, targeted therapy, and immunotherapy, metastasis remains one of the leading causes of treatment failure and death in colorectal cancer patients [2]. Studies have shown that more than half of colorectal cancer patients are diagnosed at advanced stages, with a five-year survival rate of less than 15% for those with metastasis [3]. Recently, the dynamic regulation of the tumor microenvironment has become a research hotspot. The tumor microenvironment is a dynamic ecosystem composed of cancer cells, stromal cells, immune cells, extracellular matrix (ECM), and secreted factors. Changes in its function and composition directly influence tumor growth, invasion, metastasis, and treatment responses [4]. The tumor microenvironment can form a "coevolution" relationship with tumor cells through mechanisms like metabolism, immune suppression, and signaling pathways, promoting cancer cell invasion, metastasis, and immune evasion [5]. Therefore, investigating the relationship between the tumor microenvironment and colorectal cancer metastasis is essential, not only for understanding the mechanisms of cancer cell metastasis but also for providing theoretical support for developing novel targeted therapies for the tumor microenvironment. This review aims to explore the role and mechanisms of the tumor microenvironment in colorectal cancer metastasis, providing references for the clinical treatment of colorectal cancer patients.

## 1 Stromal Cells

### *1.1 Tumor-associated Fibroblasts (CAFs)*

Fibroblasts are the most active cell types in the tumor microenvironment and are considered a key player in the tumor microenvironment. Fibroblasts can be divided into CAFs and myofibroblasts, with the role of CAFs in promoting tumor proliferation and metastasis reported in various malignancies including prostate

cancer, breast cancer, pancreatic cancer, and colorectal cancer. CAFs primarily consist of two subtypes: myofibroblasts and inflammatory fibroblasts. Myofibroblasts are mainly activated by the transforming growth factor (TGF)-β signaling pathway and secrete collagen and fibronectin, contributing to ECM remodeling; whereas inflammatory fibroblasts are driven by pro-inflammatory factors such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, and the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway, and secrete various pro-inflammatory cytokines and chemokines to promote tumor cell proliferation. Studies have shown that CAFs interact with tumor-associated immune cells and other immune components, enabling cancer cells to escape immune surveillance and playing a key role in immune suppression and enhancing tumor chemoresistance [6]. Furthermore, other studies have suggested that the fibrous collagen and other ECM components produced by CAFs can induce fibrosis around the tumor or form scar adhesions within tissues, making ECM remodeling stiff and hypoxic, thereby accelerating tumor progression and metastasis [7].

In studies on colorectal cancer metastasis, CAFs have been shown to act through mechanisms such as promoting angiogenesis, secreting various cytokines, and remodeling ECM. Hematogenous metastasis is considered a key factor contributing to the high metastasis rate and mortality of colorectal cancer. In the study by Peng *et al.* [8], CAFs were found to promote angiogenesis by secreting vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and other pro-angiogenic factors, inducing abnormal tumor vascular proliferation and providing a pathway for cancer cells to enter the bloodstream, thus promoting hematogenous metastasis in colorectal cancer. CAFs also excessively secrete ECM components like collagen and fibronectin, increasing ECM rigidity and hindering the infiltration of T cells, natural killer (NK) cells, and drugs into the tumor core, thereby supporting cancer cell colonization in metastatic target organs.

During liver metastasis, CAFs drive immune evasion through multiple mechanisms, providing a “immune privilege” environment for cancer cells. For example, TGF-β secreted by CAFs inhibits $CD8^+$ T cell proliferation and expression of cytotoxic molecules via the Smad pathway, while promoting the differentiation of regulatory T cells (Tregs), thus weakening the anti-tumor immune response [9]. Additionally, CAFs transfer immunosuppressive microRNAs (miRNAs) via exosomes to target organs, further preconditioning the liver microenvironment. miR-21 directly suppresses the expression of the tumor suppressor gene phosphatase and tensin homolog (PTEN), impairing the anti-tumor function of T cells, while miR-155 activates the STAT3 pathway to promote the immunosuppressive activity of myeloid-derived suppressor cells. These mechanisms collectively form an "immune desert" in the liver metastasis site, significantly reducing the efficacy of immune checkpoint inhibitors (ICIs) [10-11].

Based on the pro-tumor characteristics of CAFs, various anti-CAFs therapies have been developed. The first class of anti-CAFs drugs includes inhibitors targeting VEGF, VEGF receptors (VEGFR), hepatocyte growth factor (HGF)/mesenchymal-epithelial transition factor (MET), which block multiple signaling pathways to inhibit CAF activation, thus improving tumor proliferation and angiogenesis. The second class targets CAF products, including inhibitors of matrix metalloproteinases, nestin C, tissue plasminogen activators, and serine proteases, which block angiogenesis and tumor development in colorectal cancer, enhancing chemotherapy efficacy. Additionally, the combination of ICIs with anti-TGF-β therapy has gained significant attention. This combination not only reverses CAF-mediated immune evasion but also enhances immune cell infiltration and efficacy by softening the tumor stroma. Therefore, targeting CAFs and their products may provide a new strategy for the prevention and treatment of colorectal cancer metastasis. The mechanism of CAFs was shown in **Tab.1.**

### *1.2 Mesenchymal Stem Cells (MSCs)*

MSCs are pluripotent stem cells primarily found in the bone marrow stroma, possessing the ability for self-renewal and the potential to differentiate into various cell types. MSCs have the capacity to actively migrate to sites of injury or specific pathological areas (such as tumors). This tropism enables them to migrate towards primary and metastatic tumor sites, becoming key stromal cells in the tumor microenvironment [12]. Numerous studies have shown that the tumor microenvironment varies across different cancers, with differences in cell types and ECM composition. Therefore, the role of MSCs in the tumor microenvironment also exhibits duality [13-14]. On one hand, MSCs can transform into tumor-associated MSCs (TAMSCs) upon interaction with various cells and factors within the local tumor microenvironment. This transformation influences tumor growth and metastasis by enhancing tumor invasiveness and migration, as well as inhibiting cancer cell apoptosis. On the other hand, MSCs can exert anti-tumor effects by enhancing immune responses, inhibiting angiogenesis, and regulating signal transduction pathways.

In colorectal cancer, the pro-tumor and anti-tumor roles of MSCs are particularly complex. For example, MSCs promote colorectal cancer development through activation of the AMP-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR)-mediated nuclear factor-κB (NF-κB) signaling pathway; MSCs enhance the migration and invasion abilities of colorectal cancer cells through IL-6/JAK2/STAT3 signaling [15-16]. MSCs can also induce epithelial-mesenchymal transition (EMT) in cancer cells through the secretion of growth factors such as TGF-β and HGF, activating Wnt/β-catenin signaling pathways, thereby enhancing invasiveness and metastatic potential. Conversely, MSCs can suppress colorectal

cancer progression. For instance, Eiro *et al.* [17] found that MSCs could migrate to colon tissue and induce Treg cell differentiation via Smad2, thereby inhibiting the development of colitis-associated colorectal cancer. MSCs can also inhibit the growth of colorectal cancer by regulating immune components within the colorectal tumor microenvironment [18]. The impact of MSCs on the occurrence and progression of colorectal cancer is both positive and negative. This complex mechanism underlines the promising therapeutic potential of MSC-based treatments. The specific homing ability of MSCs makes them an ideal carrier for anti-tumor drugs, accurately migrating to tumor sites and releasing the drug. This can enhance treatment safety and improve the targeted efficacy of anti-cancer agents. Moreover, combining MSCs with chemotherapy drugs may help ameliorate renal dysfunction and tissue damage caused by chemotherapy due to their tissue repair capacity. These studies indicate that there is a complex relationship between MSCs and colorectal cancer metastasis. MSCs have enormous therapeutic potential in the treatment of colorectal cancer; however, the design of treatment strategies requires caution to minimize the potential adverse effects of MSC-based therapies. The mechanisms of MSCs are summarized in Table 1.

## 2 Immune Cells

### *2.1 Tumor-Associated Macrophages (TAMs)*

TAMs are the most abundant immune population in the tumor microenvironment. Upon induction, they can differentiate into two phenotypes: inflammatory macrophages and immunosuppressive or anti-inflammatory macrophages. Inflammatory macrophages have high antigen-presenting capabilities and play roles in immune activation and tumor cytotoxicity, whereas immunosuppressive or anti-inflammatory macrophages contribute to immune suppression and promote tumor differentiation and metastasis. Although the classification of TAMs into anti-tumor inflammatory macrophages and pro-tumor immunosuppressive or anti-inflammatory macrophages is widely used in research, TAMs typically exhibit a range of phenotypic features that continuously adapt to signals in the tumor microenvironment. Therefore, TAM polarization should be regarded as a dynamic phenotypic lineage.

TAMs are closely related to the pathogenesis of colorectal cancer, and as the tumor progresses, the proportion of inflammatory and immunosuppressive or anti-inflammatory cells in the microenvironment changes accordingly [19]. In colorectal cancer, the polarization of TAMs gradually shifts towards immunosuppressive or anti-inflammatory states. The increased proportion of these cells is closely associated with immune suppression, vascular remodeling, and metastasis in colorectal cancer [20]. In recent years, with the development of single-cell sequencing technology, TAMs in colorectal cancer have been further subdivided into different subtypes, with vascularization-promoting TAMs and phagocytic/antigen-presenting TAMs being the two major subtypes. Vascularization-promoting TAMs are typically located in hypoxic and necrotic tumor areas, displaying pro-tumor characteristics. They are enriched in tumor angiogenesis, ECM receptor interactions, and tumor vasculature-related pathways, promoting tumor angiogenesis and metastasis, and are considered to be associated with poor prognosis in colorectal cancer patients [21]. Phagocytic/antigen-presenting TAMs possess antigen-presenting and phagocytic functions, enriching in complement activation and antigen processing pathways. These cells may exert anti-tumor effects by activating adaptive immune responses [22]. Nicotinamide phosphoribosyltransferase (NAMPT) is a critical target in vascularization-promoting TAMs. NAMPT inhibitors induce $NAD^+$ depletion by inhibiting $NAD^+$ biosynthesis, leading to ATP exhaustion and programmed cell death. However, inhibiting $NAD^+$ pathways also causes side effects such as fatigue, nausea, and electrolyte imbalances. CD40 agonists represent a therapeutic approach targeting phagocytic/antigen-presenting TAMs. They can activate specific classical type 1 dendritic cells and expand T helper 1-like cells and $CD8^+$ memory T cells, enhancing immune responses against tumors. However, CD40 agonists often require combination with other treatments, increasing the complexity and potential side effects of therapy. Therefore, targeting TAMs in colorectal cancer therapy still faces multiple challenges. Modulating TAM function or inhibiting their immunosuppressive or anti-inflammatory polarization is crucial for improving treatment outcomes and suppressing tumor metastasis, providing more therapeutic options for patients **(See Figure 1)**. The mechanisms of TAMs are shown in **Table 1**.

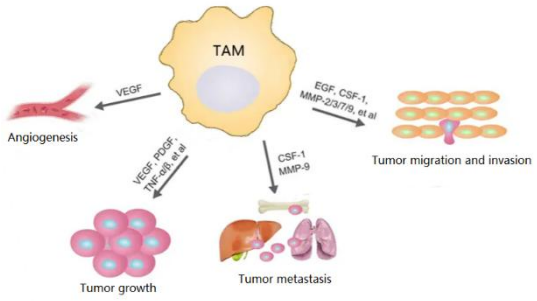


**Fig.1** TAMs mechanism diagram

### *2.2 NK Cells*

In the tumor microenvironment, cancer cells and immune cells compete for limited metabolic resources. However, both cancer cells and immune cells possess significant adaptive capabilities, enabling them to overcome adverse conditions by interacting and remodeling metabolic pathways. They utilize various available metabolic nutrients, and this reprogramming results in immune cell dysfunction, thereby driving tumor

progression and immune evasion [23]. Reports indicate that acquired immune cells dominate the tumor microenvironment, while the proportion of innate immune cells in tumor tissues is significantly reduced, suggesting a need for further investigation into the role of innate immune cells in the development and metastasis of malignant tumors [24]. NK cells are core members of the innate immune system and are an important component of anti-tumor responses. The anti-tumor effect of NK cells depends on the balance between their activating and inhibitory receptors. The activating receptors of NK cells mainly include NKG2D, natural cytotoxicity receptors, and the immunoglobulin-like receptor family. Upon activation, NK cells release pro-inflammatory cytokines [such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), etc.] and lytic granules (such as perforin and granzymes), ultimately leading to the lysis of tumor cells [25-26]. Some retrospective analyses showed that low NK cell infiltration and/or impaired NK cell function were associated with recurrence and poor overall survival in colorectal cancer patients following treatment [27-28]. Dysregulation of the innate immune system allows colorectal cancer to escape NK cell surveillance, thereby significantly increasing the metastatic and invasive potential of cancer cells. As Greenlee *et al.* [29] found, overexpression of human leukocyte antigen-E (HLA-E) inhibits NK cell activation through high-affinity interactions with the NKG2A receptor, preventing NK cells from recognizing and attacking tumor cells. Soluble MHC class I chain-related molecules (MIC) A and B, shed from transformed cells in the tumor microenvironment, continuously expose NK cells to these soluble MICA and MICB, reducing their cytotoxicity. This process involves downregulation of NKG2D receptor expression and ultimately promotes tumor cell proliferation and metastasis [30]. TGF-β1 and IL-10 can suppress NK cell secretion of IFN-γ, TNF-α, and other cytokines, weakening their immune surveillance function and hindering NK cell-mediated cytotoxicity against colorectal cancer cells. This promotes immune evasion and facilitates tumor growth and metastasis [31]. Thus, targeting immune cells within the tumor microenvironment to restore their immune surveillance function and improve tumor immune evasion characteristics may be a highly promising therapeutic strategy. The mechanisms of NK cells are shown in **Table 1.**

## 3 Metabolic Factors

### *3.1 Lipid Metabolites*

Fatty acids are an essential component of lipid molecules, and metabolic abnormalities in fatty acids can lead to disruptions in physiological functions, being closely related to the initiation and progression of various cancers. Studies have shown that tumor tissues with strong invasive ability often contain more mutant genes related to fatty acid synthesis and metabolism. Tumor cells adapt to their rapid proliferation demands by altering fatty acid synthesis and oxidation pathways. This includes activation of key enzymes in fatty acid synthesis, such as fatty acid synthase (FASN), and enhanced fatty acid oxidation [32]. Hypoxia, a common feature of solid tumors, promotes cancer development. Recent studies suggest that hypoxic stress induces a reprogramming of fatty acid metabolism, significantly upregulating FASN. Tumor cells are unable to balance lipid and protein synthesis, leading to sustained fatty acid supply for tumor metabolism, thereby facilitating the progression of malignant tumors towards chemotherapy resistance and invasive phenotypes [33-34]. The tumor microenvironment in colorectal cancer is rich in adipose tissue and cells, which interact with tumor cells during the progression of the disease. This interaction alters the biological characteristics of various lipid factors and receptors in the tumor microenvironment, resulting in abnormal expression. Huang *et al.* [35] found that as a key enzyme in fatty acid synthesis, FASN is significantly expressed in colorectal cancer, converting excess carbohydrates into fatty acids. Saturated fatty acids in these fatty acids can be converted into monounsaturated fatty acids by stearoyl-CoA desaturase 1, thus promoting colorectal cancer metastasis. Studies have also found that the PI3K/AKT/mTOR signaling pathway can promote lipogenesis, cell growth, and liver metastasis by regulating fatty acid synthesis-related enzymes. miR-20 activates the Wnt/β-catenin signaling pathway and upregulates fatty acid synthesis, promoting the proliferation and migration of metabolic colorectal cancer cells. Lipids not only serve as energy sources but also play an important role in signal transduction [36]. Tumor cells synthesize cholesterol and phospholipids to maintain the structural and functional integrity of their cell membranes, aiding their adaptation to the tumor microenvironment. Free fatty acids in the tumor microenvironment regulate glycolysis and oxidative phosphorylation, driving the polarization of immune-suppressive or anti-inflammatory macrophages. Therefore, fatty acids and fatty acid metabolism-related enzymes are closely related to tumor metastasis. In-depth research on fatty acid metabolism mechanisms could lead to innovative therapeutic approaches. The mechanisms of lipid metabolites are shown in **Table 1**.

### *3.2 Reactive Oxygen Species (ROS)*

ROS are a class of single-electron reduction products in the body, primarily composed of free radicals. ROS can regulate multiple signaling pathways, playing a key role in various cellular processes, including metabolism, differentiation, proliferation, and cell death. Studies show that low doses of ROS can stimulate cells and activate their signaling systems, while excessively high ROS levels damage biological macromolecules, such as DNA and proteins. This damage can either activate oncogenes or inactivate tumor suppressor genes, leading to disruptions in the cell cycle and promoting tumorigenesis and progression [37]. Therefore, ROS have become a hot topic in cancer prevention and treatment research.

Metabolic reprogramming in colorectal cancer is associated with mutations in both classic and non-classic Wnt/β-catenin signaling pathways, which may be regulated by ROS in the tumor microenvironment [38]. Furthermore, elevated ROS levels in the tumor microenvironment can alter many cellular functions and matrix components. Some studies indicate that ROS can promote tumor cell proliferation, migration, and invasion by activating and regulating NF-κB and PI3K/AKT signaling pathways in colorectal cancer metastasis. ROS can also influence the transcription factors regulating colorectal cancer metastasis, such as hypoxia-inducible factor-1α (HIF-1α) and STAT3, thereby participating in the regulation of apoptosis and mediating angiogenesis. Additionally, ROS can upregulate intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), enhancing the adhesion of colorectal cancer cells to mesothelial cells, promoting liver metastasis [39-42]. Understanding the molecular mechanisms of ROS in colorectal cancer treatment will aid in the integration of various precision therapeutic strategies. For example, inhibiting members of the $NAD^+$ oxidoreductase family or enhancing antioxidant defense systems can effectively control ROS levels, thereby reducing damage to healthy tissues and improving the efficacy of chemotherapy or radiotherapy. Additionally, the interaction between ROS-mediated signaling pathways and immune checkpoints provides a theoretical basis for combining ROS regulators with immune checkpoint inhibitors (ICIs), aiming for a "molecular-immune-therapy" integration to reduce damage to healthy tissues and enhance efficacy while minimizing side effects. The mechanisms of ROS are shown in **Table 1.**.

**Tab.1** Summary of key cells and mechanisms in the microenvironment of colorectal

| Type | Mechanism | Related Pathways/Factors | Clinical Application |
|---|---|---|---|
| **CAFs** | Promote angiogenesis, remodel ECM, inhibit immune response | TGF - β/Smad pathway, JAK/STAT3 pathway, exosomal miRNA | Anti - CAFs drugs, combined use of ICIs |
| **MSCs** | Have bidirectional effects of promoting and inhibiting tumors | IL - 6/JAK2/STAT3, Wnt/β - catenin, NF - KB pathway | Utilize the homing ability of MSCs for targeted drug delivery, combined with chemotherapy to relieve tissue injury |
| **TAMs** | Angiogenic promotion type promotes tumor angiogenesis and metastasis; M1 - like (with phagocytosis/antigen presentation function) exerts anti - tumor effect by activating adaptive immune response | VEGF/NAMPT pathway, complement activation pathway, antigen presentation pathway | NAMPT inhibitors inhibit NAD synthesis, CD40 agonists activate M1 - like TAMs |
| **NK cells** | Release inflammatory cytokines and cytotoxic granules, ultimately leading to tumor cell lysis | NKG2D receptor signal, TGF - β/Smad pathway, secrete IFN - γ and TNF - α | Block MHC I, MICB or NKG2A to restore NK cell function, combined immunotherapy (such as ICIs) |
| **Lipid Metabolites** | FASN promotes fatty acid synthesis, drives EMT and tumor metastasis; High - concentration ROS can inactivate tumor suppressor genes or oncogenes, disrupt the cell growth cycle, and promote tumor occurrence and development | FASN/FAO pathway, PI3K/AKT/mTOR, ROS/NF - KB pathway; ROS/Wnt/β - catenin pathway | FASN inhibitors; Inhibit members of the NADPH oxidase family or enhance the antioxidant defense system to improve treatment efficacy |
| **ROS** | High concentrations of ROS can inactivate tumor suppressor genes or oncogenes, disrupting the cell growth cycle and promoting tumor occurrence and development | ROS/NF - κB, ROS/Wnt/β - catenin pathways | Inhibit members of the NADPH oxidase family or enhance the antioxidant defense system to improve treatment efficacy |

## 4 Conclusion and Outlook

Invasion and metastasis are among the most important biological characteristics of malignant tumors, involving multiple contributing factors and closely related to the unique microenvironment surrounding tumor cells. Tumor cells alter the function of both cellular and non-cellular components through complex signaling networks, using non-cancerous cells for their benefit. The complex network formed by various components in the tumor microenvironment serves as a source of intercellular communication and promotes tumor survival and resistance through multiple pathways. Understanding how colorectal cancer cells interact with the tumor microenvironment can help researchers precisely design and develop therapeutic strategies to overcome immune evasion and resistance mechanisms in treatment

**Conflict of interest** None

## Reference

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**Submission Received: 2025-04-10 Revised: 2025-05-15**

·学术前沿·

# 肿瘤微环境在结直肠癌转移中的作用和机制

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**摘要：** 肿瘤微环境在恶性肿瘤进展和治疗耐药中有着重要作用，其复杂性源于多种细胞类型（肿瘤相关成纤维细胞、间充质干细胞、肿瘤相关巨噬细胞、自然杀伤细胞等）及代谢因子（脂质代谢物、活性氧等）的动态作用。本文系统阐述了肿瘤微环境中的关键组分在结直肠癌转移中的作用以及对治疗的影响，以期为结直肠癌的治疗提供思路和参考。

**关键词：** 肿瘤微环境；结直肠癌；间充质干细胞；成纤维细胞；巨噬细胞；自然杀伤细胞；脂质代谢物；活性氧；转移
**中图分类号：** R735.3 **文献标识码：** A **文章编号：** 1674-8182(2025)07-0977-06

# Advances in the role and mechanisms of tumor microenvironment in colorectal cancer metastasis

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**Abstract:** Tumor microenvironment plays an important role in cancer progression and treatment resistance, and its complexity stems from the dynamic roles of multiple cell types (tumor-associated fibroblasts, mesenchymal stem cells, tumor-associated macrophages, and natural killer cells, etc.) and metabolic factors (lipid metabolites, reactive oxygen species, etc.). In this paper, the role of key components of the tumor microenvironment in colorectal cancer metastasis and the impact on treatment are systematically described, with a view to providing ideas and references for the treatment of colorectal cancer.

**Keywords:** Tumor microenvironment; Colorectal cancer; Mesenchymal stem cells; Fibroblasts; Macrophages; Natural killer cells; Lipid metabolites; Reactive oxygen species; Metastasis
**Fund program:** National Natural Science Foundation of China (82273022)

DOI:10.13429/j.cnki.cjcr.2025.07.001
**基金项目：** 国家自然科学基金(82273022)
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**出版日期：** 2025-07-20

QR code for English version

结直肠癌是一种高侵袭性的肿瘤，具有较高的发病率和死亡率，其发生发展是遗传易感性、饮食习惯、生活方式及环境因素等多因素协同作用的结果[1]。尽管以手术、化疗、靶向治疗和免疫治疗为核心的综合治疗手段可极大地改善早期患者的预后，但转移仍是结直肠癌患者治疗失败和死亡的主要原因之一[2]。据统计，半数以上的结直肠癌患者在确诊时已处于中晚期，而发生转移的结直肠癌患者5年生存率不足15%[3]。近年来，肿瘤微环境的动态调控作用逐渐成为研究热点。肿瘤微环境是一个由癌细胞、基质细胞、免疫细胞、细胞外基质（ECM）及分泌因子组成的动态生态系统，其功能和组成的变化直接影响肿瘤的生长、侵袭、转移以及对治疗的反应[4]。肿瘤微环境可通过代谢、免疫抑制及信号传导等机制，与肿瘤细胞形成“共进化”关系，促进癌细胞侵袭、转移及免疫逃逸[5]。可见，探讨肿瘤微环境与结直肠癌转移之间的关系十分必要，不仅有助于理解癌细胞转移的作用机制，还可为开发靶向肿瘤微环境的新型治疗策略提供理论依据。本文旨在针对肿瘤微环境在结直肠癌转移中的作用与机制作一综述，以期为结直肠癌患者的临床治疗提供参考。

## 1　基质细胞

1.1　*肿瘤相关成纤维细胞（CAFs）*　成纤维细胞是肿瘤微环境中最活跃的细胞类型，因此也被认为是肿瘤微环境中的关键角色。成纤维细胞可分为CAFs和肌成纤维细胞两种亚型，其中CAFs促进肿瘤增殖及转移的作用已在前列腺癌、乳腺癌、胰腺癌和结直肠癌等多种恶性肿瘤中报道。CAFs主要分为肌成纤维细胞型和炎症型两种亚型，肌成纤维细胞型主要由转化生长因子（TGF）-β信号通路诱导激活，可分泌胶原蛋白、纤连蛋白，帮助重塑ECM；而炎症型主要由白细胞介素（IL）-1、肿瘤坏死因子（TNF）-α等促炎因子及Janus激酶（JAK）/信号转导子和转录激活子3（STAT3）通路驱动，可分泌多种促炎细胞因子和趋化因子，促进肿瘤细胞增殖。研究显示，CAFs可与肿瘤相关免疫细胞及其他免疫成分相互作用，使癌细胞能够逃脱免疫监视，在形成免疫抑制、增强肿瘤化学抗性方面起着关键作用[6]。除此之外，也有研究指出，CAFs产生的纤维状胶原和其他ECM成分可引起肿瘤周围纤维化或在组织内形成瘢疤粘连，使基质重塑僵硬和缺氧，从而加速肿瘤进展和转移[7]。

在结直肠癌转移的相关研究中，CAFs通过促进血管生成、分泌多种细胞因子、重塑ECM等机制发挥作用。血源性转移被认为是导致结直肠癌高转移率及高死亡率发生的关键因素。有研究显示，CAFs被发现可通过分泌血管内皮生长因子（VEGF）、成纤维细胞生长因子（FGF）、血小板衍生生长因子（PDGF）等促血管生成因子，诱导肿瘤血管异常增生，为癌细胞进入血液循环提供通道，从而促使结直肠癌发生血源性转移[8]。CAFs还可过度分泌胶原蛋白、纤连蛋白等ECM成分，导致ECM刚性增加，阻碍T细胞、自然杀伤（NK）细胞及药物向肿瘤核心区的渗透，为癌细胞在转移靶器官中的定植提供支持。

在肝转移进程中，CAFs通过多重机制驱动免疫逃逸，为癌细胞提供“免疫豁免”环境。例如，CAFs分泌的TGF-β通过Smad通路抑制$CD8^+$ T细胞的增殖和细胞毒性分子的表达，同时促进调节性T细胞（Tregs）的分化，从而削弱抗肿瘤免疫应答[9]。此外，CAFs通过外泌体传递免疫抑制性微小RNA（microRNA，miR）至靶器官，进一步预处理肝脏微环境：miR-21可直接抑制肿瘤抑制基因磷酸酶和张力蛋白同源物的表达，削弱T细胞的抗肿瘤功能；而miR-155则通过激活STAT3通路促进髓系来源抑制细胞的免疫抑制活性，这些机制共同作用，使肝转移灶形成“免疫沙漠”状态，显著降低免疫检查点抑制剂（ICIs）的疗效[10-11]。

根据CAFs的促肿瘤特性，目前已开发多种抗CAFs疗法，如以VEGF、VEGF受体（VEGFR）、肝细胞生长因子（HGF）/间质表皮转化因子（MET）等的抑制剂为代表的第一类抗CAFs药物，可阻断多种信号通路抑制CAFs的激活，从而改善肿瘤增殖、血管生成；第二类抗CAFs药物主要针对CAFs的产物，包括基质金属蛋白酶、巢蛋白C、组织蛋白酶和丝氨酸蛋白酶等的抑制剂，可阻断结直肠癌血管生成和肿瘤发展，从而提高化疗的有效性；此外，联合使用ICIs与抗TGF-β治疗也受到了许多关注，这种联合疗法不仅能逆转CAFs介导的免疫逃逸，还能通过软化肿瘤基质增强免疫细胞的浸润和疗效。可见，靶向CAFs及其产物治疗可能为结直肠癌转移的防治提供新策略。CAFs机制见表1。

1.2　*间充质干细胞（MSCs）*　MSCs是一种主要存在于骨髓基质中的多能干细胞，具有自我更新能力和分化为多种细胞类型的潜能。MSCs具有主动迁移到体内损伤或特定病理部位（如肿瘤）的能力，这种趋向性可使其向肿瘤原发灶和转移灶迁移，成为肿瘤微环境中关键基质细胞之一[12]。大量研究显示，不同癌症的肿瘤微环境存在差异，细胞类型和ECM的组成均有区别，因此MSCs在肿瘤微环境中的作用也

表现出两面性[13-14]。一方面，MSCs在与局部肿瘤微环境中的各种细胞和因子作用后，可转化为肿瘤相关MSCs，通过增强肿瘤侵袭和迁移能力、抑制癌细胞凋亡等方式影响肿瘤生长和转移；另一方面，MSCs也可通过增强免疫反应、抑制血管生成、调控信号转导等发挥抑瘤作用。

在结直肠癌中，MSCs的促瘤与抑瘤作用尤为复杂。如MSCs可通过激活腺苷酸活化蛋白激酶（AMPK）/哺乳动物雷帕霉素靶蛋白（mTOR）介导的核因子-κB（NF-κB）信号通路促进结直肠癌的发展；通过IL-6/JAK2/STAT3信号转导MSCs可增强结直肠癌细胞的迁移和侵袭能力[15-16]。MSCs还可通过分泌TGF-β、HGF等生长因子，激活Wnt/β-catenin等信号通路，诱导癌细胞发生上皮间质转化（EMT），增强其侵袭性和转移能力。MSCs也可抑制结直肠癌进展，如Eiro等[17]发现MSCs可以迁移到结肠组织并通过Smad2诱导Treg细胞分化，从而抑制结肠炎相关结直肠癌的发展；MSCs可以通过调节结直肠肿瘤微环境中的免疫成分来抑制结直肠癌的生长[18]。MSCs对结直肠癌的发生及进展既有积极影响也有消极影响，这种复杂的作用机制使基于MSCs的治疗方法显示出了良好的应用前景。MSCs的特异性归巢能力使其可以作为抗肿瘤药物的载体，准确迁移到肿瘤部位并释放药物，可增加治疗的安全性，提高抗癌药物的靶向疗效。除此之外，还可将MSCs与化疗药物相结合，利用其组织修复能力改善化疗药物引起的肾功能不全和组织损伤。以上研究提示，MSCs与结直肠癌转移之间存在着复杂的关系，MSCs在治疗结直肠癌方面具有巨大潜力，但其治疗策略的设计需谨慎，以降低MSCs治疗可能带来的不良影响。MSCs机制见表1。

## 2 免疫细胞

2.1 *肿瘤相关巨噬细胞（TAMs）* TAMs是肿瘤微环境中最丰富的免疫群体，其经过诱导可分化为炎性巨噬细胞和免疫抑制或抗炎巨噬细胞两种表型，其中炎性巨噬细胞具有高抗原呈递能力，可发挥免疫促进、肿瘤杀伤作用，而免疫抑制或抗炎巨噬细胞则具有免疫抑制和促进肿瘤分化、转移的作用。尽管这种抗肿瘤炎性巨噬细胞、促肿瘤免疫抑制或抗炎巨噬细胞分类方式在TAMs的研究中被广泛应用，但TAMs通常表现出一系列表型特征，会根据肿瘤微环境中的信号不断调整，因此应将TAMs的极化视为一种动态的表型谱系。

TAMs与结直肠癌的发病机制密切相关，随着肿瘤进展，微环境中TAMs的炎性细胞及免疫抑制或抗炎细胞占比会随之发生改变[19]。在结直肠癌中，TAMs的极化状态会逐渐向免疫抑制或抗炎倾斜，其比例增加与结直肠癌的免疫抑制、血管重塑及转移密切相关[20]。近年来，随着单细胞测序技术的发展，结直肠癌中的TAMs被进一步细分为不同的亚型，血管生成促进型TAMs和吞噬/抗原呈递型TAMs是两种最主要的亚型。血管生成促进型TAMs通常位于缺氧和坏死的肿瘤区域，表现出促肿瘤特性，在肿瘤血管生成、ECM受体相互作用和肿瘤血管相关通路中富集，能够促进肿瘤的血管生成和转移，被认为与结直肠癌患者的不良预后相关[21]。吞噬/抗原呈递型TAMs具有抗原呈递和细胞吞噬功能，在补体激活和抗原处理相关通路中富集，可能通过激活适应性免疫应答发挥抗肿瘤作用[22]。烟酰胺磷酸化转移酶（NAMPT）是血管生成促进型TAMs的重要靶点，NAMPT抑制剂可通过抑制烟酰胺腺嘌呤二核苷酸（$NAD^+$）生物合成诱导$NAD^+$消耗，随后导致三磷酸腺苷耗竭，诱导程序性细胞死亡，但抑制$NAD^+$途径也会引起疲劳、恶心、电解质紊乱等一系列副作用。CD40激动剂是一种针对吞噬/抗原呈递型TAMs的疗法，可以激活特异性经典1型树突状细胞并扩增辅助性T细胞1样细胞和$CD8^+$记忆T细胞，从而增强针对肿瘤的免疫反应，但CD40激动剂通常需要与其他治疗手段联合使用，这增加了治疗的复杂性和潜在的副作用。可见，在结直肠癌的治疗中，针对TAMs的治疗方案仍面临多种挑战，调节TAMs功能或抑制TAMs的免疫抑制或抗炎极化对改善治疗效果和抑制肿瘤转移方面具有重要意义，可为患者提供更多的治疗选择。见图1。TAMs机制见表1。

2.2 *NK细胞* 在肿瘤微环境中，癌细胞与免疫细胞需要争夺有限的代谢资源，然而，癌细胞和免疫细胞都具有显著的适应能力，能够通过相互作用和重塑代谢途径来克服不利条件，并利用不同可用的代谢营养物质，这种重编程会导致免疫细胞功能缺陷，从而驱动了肿瘤进展和免疫逃逸[23]。据报道，在肿瘤微环境中，获得性免疫细胞占主导地位，而先天免疫细胞在肿瘤组织中的比例显著降低，提示需要深入研究先天免疫细胞在恶性肿瘤发展和转移中的作用[24]。NK细胞是先天免疫细胞中的核心成员，也是抗肿瘤反应的重要组成部分。NK细胞的抗肿瘤效应取决于其表面激活受体与抑制受体比例。NK细胞的激活受

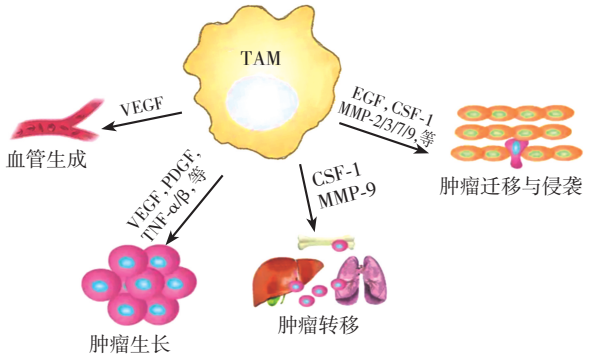


**图 1**　TAMs 机制图

**Fig.1**　TAMs mechanism diagram

体主要包括自然杀伤细胞家族 2 成员 D(NKG2D)、自然细胞毒性受体以及杀伤细胞免疫球蛋白样受体家族，当 NK 细胞被激活时，会释放具有炎症作用的细胞因子[干扰素-γ(IFN-γ)、TNF-α等]以及含裂解性颗粒(穿孔素、颗粒酶等)，最终导致肿瘤细胞的裂解[25-26]。一些回顾性分析显示，NK 细胞浸润程度低和(或)NK 细胞功能受损与结直肠癌患者治疗后复发及总生存率低有关[27-28]。先天免疫系统的功能紊乱会导致结直肠癌逃避 NK 细胞的监视，从而显著提升癌细胞的转移性和侵袭性。研究发现，过表达的人类白细胞抗原 E 可通过与 NKG2A 受体的高亲和力相互作用，抑制 NK 细胞的激活，使其无法识别并攻击肿瘤细胞[29]。肿瘤微环境中存在由转化细胞脱落的可溶性 MHC Ⅰ类链相关分子(MIC)A 和 MICB，NK 细胞持续暴露于这些可溶性 MICA、MICB 会降低其细胞毒性，并通过下调 NKG2D 受体的表达，最终促进肿瘤细胞增殖和转移[30]。TGF-β1 及 IL-10 可抑制 NK 细胞分泌 IFN-γ、TNF-α等细胞因子，削弱了 NK 细胞的免疫监视功能，使 NK 细胞无法很好发挥对结直肠癌细胞的杀伤作用，从而促进肿瘤的免疫逃逸，有利于肿瘤的生长和转移[31]。可见，通过靶向肿瘤微环境中的免疫细胞，恢复其免疫监视功能，从而改善肿瘤免疫逃逸特性可能是一种非常有前景的治疗方法。NK 细胞机制见表 1。

## 3　代谢因子

3.1　*脂质代谢物*　脂肪酸是脂质分子的重要组成部分，其代谢异常会导致生物体的生理功能紊乱，被发现与多种癌症的发生发展密切相关。研究显示，侵袭能力强的肿瘤组织中往往存在更多的有关脂肪酸合成及代谢相关的突变基因，肿瘤细胞通过改变脂肪酸合成和氧化途径来适应其快速增殖的需求，这包括对脂肪酸合成的关键酶如脂肪酸合成酶(FASN)的激活以及脂肪酸氧化的增强[32]。低氧是实体瘤的常见特征之一，能够促进癌症的发展。近年来一些研究表明，低氧损伤会诱导脂肪酸代谢的重编程，使 FASN 显著上调，肿瘤细胞无法平衡脂质和蛋白质的合成，导致脂肪酸持续向肿瘤代谢提供燃料，更利于恶性肿瘤向化疗耐药和侵袭性表型进展[33-34]。结直肠癌的肿瘤微环境中富含脂肪组织和细胞，在肿瘤发展过程中，与肿瘤细胞相互作用，使得肿瘤微环境中多种脂肪因子及受体生物学特性发生改变，出现异常表达。Huang 等[35]在结直肠癌的研究中发现，作为脂肪酸合成的关键酶，FASN 在结直肠癌中显著表达，可将多余的碳水化合物转化为脂肪酸，而脂肪酸中的饱和脂肪酸可通过硬脂酰辅酶 A 去饱和酶 1 转化为单不饱和脂肪酸，从而促进结直肠癌转移。也有研究发现，磷脂酰肌醇 3 激酶(PI3K)/蛋白激酶 B(AKT)/mTOR 信号通路可通过调节脂肪酸合成相关酶促进脂肪生成、细胞生长和肝转移；miR-20 激活 Wnt/β-catenin 信号通路并上调脂肪酸合成，可促进代谢性结直肠癌细胞的增殖和迁移。脂质不仅是能量来源，还在信号转导中发挥重要作用[36]。肿瘤细胞通过合成胆固醇和磷脂维持细胞膜的结构和功能完整性，帮助其适应肿瘤微环境；肿瘤微环境中的游离脂肪酸通过调控糖酵解和氧化磷酸化，推动免疫抑制或抗炎巨噬细胞的极化。可见，脂肪酸及脂肪酸代谢相关酶与肿瘤转移密切相关，对脂肪酸代谢机制的深入研究有助于治疗方法的创新。脂质代谢物机制见表 1。

3.2　*活性氧(ROS)*　ROS 是体内一类单电子还原产物，主要成分是自由基。ROS 可调节多种信号通路，在代谢、分化、增殖和细胞死亡在内的众多细胞过程中发挥关键作用。研究显示，低剂量 ROS 能刺激细胞，其信号传递系统被激活，而当 ROS 浓度过高时，则会对 DNA、蛋白质等生物大分子造成损伤，进而使癌基因或使抑癌基因失活，导致细胞生长周期紊乱，促进肿瘤发生发展[37]。因此，近年来 ROS 逐渐成为肿瘤防治研究领域的热点。结直肠癌的代谢重编程与经典和非经典 Wnt/β-catenin 信号通路的突变状态有关，而这可能是受到了肿瘤微环境中 ROS 的调节[38]。除此之外，肿瘤微环境中的 ROS 水平提升还会改变许多细胞功能活性和基质成分，一些研究指出，ROS 在结直肠癌转移中既可通过激活和调控 NF-κB 和 PI3K/AKT 信号通路促进肿瘤细胞的增殖、迁移及侵袭，也可通过影响调控结直肠癌转移的转录因子(如缺氧诱导因子-1α、STAT3)，

参与调节癌细胞凋亡和介导血管新生，还可通过上调细胞间黏附分子-1、血管细胞黏附分子-1，增强结直肠癌细胞与间皮细胞的黏附，促进肝转移[39-42]。理解ROS在结直肠癌治疗中的分子机制，将有助于整合多种精准治疗策略，例如，通过抑制还原型$NAD^+$磷酸氧化酶家族成员或增强抗氧化防御系统，可以有效控制ROS水平，从而减少对健康组织的损伤并提高化疗药物或放疗的疗效。此外，ROS介导的信号通路与免疫检查点之间的相互作用为联合使用ROS调控剂与ICIs提供了理论依据，有望实现“分子-免疫-治疗”一体化，以减少对患者健康组织的损伤，从而提高疗效并减少副作用。ROS机制见表1。

**表1** 结直肠癌微环境中的关键细胞及机制总结

**Tab.1** Summary of key cells and mechanisms in the microenvironment of colorectal cancer

| 类型 | 机制 | 相关通路/因子 | 临床应用 |
|---|---|---|---|
| CAFs | 促进血管生成、重塑ECM、抑制免疫应答 | TGF-β/Smad通路、JAK/STAT3通路、外泌体miRNA | 抗CAFs药物、联合使用ICIs |
| MSCs | 具有促瘤和抑瘤的双向作用 | IL-6/JAK2/STAT3、Wnt/β-catenin、NF-κB通路 | 利用MSCs的归巢能力靶向递送药物、与化疗联用缓解组织损伤 |
| TAMs | 血管生成促进型促进肿瘤的血管生成和转移；吞噬/抗原呈递型通过激活适应性免疫应答发挥抗肿瘤作用 | VEGF/NAMPT通路、补体激活通路、抗原呈递通路 | NAMPT抑制剂抑制$NAD^+$合成、CD40激动剂激活抗原呈递型TAMs |
| NK细胞 | 释放具有炎症作用的细胞因子以及含裂解性颗粒，最终导致肿瘤细胞的裂解 | NKG2D受体信号、TGF-β/Smad通路、分泌IFN-γ及TNF-α | 阻断MICA、MICB或NKG2A受体恢复NK细胞功能、联合免疫治疗（如ICIs） |
| 脂质代谢物 | FASN促进脂肪酸合成，驱动EMT和肝转移 | FASN/FAO通路、PI3K/AKT/mTOR、ROS/NF-κB通路 | FASN抑制剂 |
| ROS | 高浓度ROS可使癌基因或使抑癌基因失活，导致细胞生长周期紊乱，促进肿瘤发生发展。 | ROS/NF-κB、ROS/Wnt/β-catenin通路 | 抑制还原型$NAD^+$磷酸氧化酶家族成员或增强抗氧化防御系统，可提高治疗疗效 |

## 4 结语与展望

侵袭和转移是恶性肿瘤最重要的生物学特征，涉及多种因素的共同参与，与肿瘤细胞周围独特的微环境密切相关。肿瘤细胞通过复杂的信号网络，改变细胞和非细胞成分的功能，从而利用非癌细胞为自身服务。肿瘤微环境中各种成分组成的复杂网络是细胞间通讯的来源，可通过多种途径促进自身生存和耐药。理解结直肠癌细胞如何与肿瘤微环境相互作用，可以帮助研究人员精准设计和开发治疗策略，改善治疗过程中的免疫逃逸及耐药机制。

**利益冲突** 无

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**收稿日期**:2025-04-10 **修回日期**:2025-05-15 **编辑**:王国品