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EDITORIAL

- 4300** Molecular mechanisms underlying roles of long non-coding RNA small nucleolar RNA host gene 16 in digestive system cancers
Yang TF, Li XR, Kong MW
- 4309** Navigating the complex landscape of crawling-type gastric adenocarcinomas: Insights and implications for clinical practice
Yu HB, Jia KF, Wang XF, Li BY, Xin Q
- 4315** Present and prospect of transarterial chemoembolization combined with tyrosine kinase inhibitor and PD-1 inhibitor for unresectable hepatocellular carcinoma
Zhang R, Liu YH, Li Y, Li NN, Li Z
- 4321** Unveiling the clinicopathological enigma of crawling-type gastric adenocarcinoma
Christodoulidis G, Agko SE, Kouliou MN, Koumarelas KE
- 4326** Practical hints for the diagnosis of mixed neuroendocrine-non-neuroendocrine neoplasms of the digestive system
Mattiolo P
- 4333** Endoscopic diagnosis and management of gallbladder carcinoma in minimally invasive era: New needs, new models
Deqing LC, Zhang JW, Yang J

REVIEW

- 4338** Advances in the diagnosis and treatment of MET-variant digestive tract tumors
Zhang C, Dong HK, Gao JM, Zeng QQ, Qiu JT, Wang JJ
- 4354** Effect of colorectal cancer stem cells on the development and metastasis of colorectal cancer
Deng RZ, Zheng X, Lu ZL, Yuan M, Meng QC, Wu T, Tian Y

MINIREVIEWS

- 4369** Current clinical trials on gastric cancer surgery in China
Zhang S, Hu RH, Cui XM, Song C, Jiang XH

ORIGINAL ARTICLE

Retrospective Study

- 4383** Pattern of colorectal surgery and long-term survival: 10-year experience from a single center
Zhu DX, Chen M, Xu DH, He GD, Xu PP, Lin Q, Ren L, Xu JM

- 4392** Drug-eluting beads chemoembolization combined with programmed cell death 1 inhibitor and lenvatinib for large hepatocellular carcinoma

Yang H, Qiu GP, Liu J, Yang TQ

- 4402** Effect of endoscopic submucosal dissection on gastrointestinal function and nutritional status in patients with early gastric cancer

Xu QD, Liu H, Zhang HW, Gao XM, Li YG, Wu ZY

- 4409** Comparison of clinical features of patients with or without severe gastrointestinal complications in aggressive gastrointestinal lymphomas

Liu XH, Chen G, Cao DD, Liu H, Ke XK, Hu YG, Tan W, Ke D, Xu XM

- 4424** Endoscopic and pathological features of neoplastic transformation of gastric hyperplastic polyps: Retrospective study of 4010 cases

Zhang DX, Niu ZY, Wang Y, Zu M, Wu YH, Shi YY, Zhang HJ, Zhang J, Ding SG

Basic Study

- 4436** BIRC3 induces the phosphoinositide 3-kinase-Akt pathway activation to promote trastuzumab resistance in human epidermal growth factor receptor 2-positive gastric cancer

Li SL, Wang PY, Jia YP, Zhang ZX, He HY, Chen PY, Liu X, Liu B, Lu L, Fu WH

- 4456** Impact and mechanism study of dioscin on biological characteristics of colorectal cancer cells

Cai XX, Huang ZF, Tu FY, Yu J

- 4468** Effects of invigorating-spleen and anticancer prescription on extracellular signal-regulated kinase/mitogen-activated protein kinase signaling pathway in colon cancer mice model

Wang W, Wang J, Ren XX, Yue HL, Li Z

SYSTEMATIC REVIEWS

- 4477** Prognostic value of neutrophil-to-lymphocyte ratio in gastric cancer patients undergoing neoadjuvant chemotherapy: A systematic review and meta-analysis

Wei ZH, Tuo M, Ye C, Wu XF, Wang HH, Ren WZ, Liu G, Xiang T

SCIENTOMETRICS

- 4489** Bibliometric analysis of olaparib and pancreatic cancer from 2009 to 2022: A global perspective

Feng X, Chai YH, Jiang KX, Jiang WB, Chen WC, Pan Y

CASE REPORT

- 4506** Pathologic complete response to conversion therapy in hepatocellular carcinoma using patient-derived organoids: A case report

He YG, Wang Z, Li J, Xi W, Zhao CY, Huang XB, Zheng L

LETTER TO THE EDITOR

- 4514** Vascular endothelial growth factor pathway's influence on bevacizumab efficacy in metastatic colorectal cancer treatment
Qin Y, Ma FY, Zhang Z, Zhao CH, Huang B
- 4518** From biomarker discovery to combined therapies: Advancing hepatocellular carcinoma treatment strategies
Kong MW, Yu Y, Wan Y, Gao Y, Zhang CX
- 4522** Are preoperative inflammatory and nutritional markers important for the prognosis of patients with peritoneal metastasis of colorectal cancer?
Sforzin I, Borad M, Uson Junior PLS
- 4528** Elevated *ETV4* expression in cholangiocarcinoma is linked to poor prognosis and may guide targeted therapies
Okpete UE, Byeon H

ABOUT COVER

Editorial Board of *World Journal of Gastrointestinal Oncology*, Sezer Saglam, MD, Full Professor, Department of Medical Oncology, Demiroglu Istanbul Bilim University, Istanbul 34349, Türkiye. saglam@istanbul.edu.tr

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Effect of colorectal cancer stem cells on the development and metastasis of colorectal cancer

Run-Zhi Deng, Xin Zheng, Zhong-Lei Lu, Ming Yuan, Qi-Chang Meng, Tao Wu, Yu Tian

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Run-Zhi Deng, Xin Zheng, Zhong-Lei Lu, College of Biological Science and Engineering, Fuzhou University, Fuzhou 350108, Fujian Province, China

Ming Yuan, Department of Hepatobiliary Surgery, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong Province, China

Qi-Chang Meng, Department of General Surgery, Peking University First Hospital, Beijing 100034, China

Tao Wu, Department of General Surgery, West China Hospital of Sichuan University, Chengdu 610044, Sichuan Province, China

Yu Tian, Department of Thoracic Surgery, Yancheng No. 1 People's Hospital, Affiliated Hospital of Nanjing University Medical School, The First People's Hospital of Yancheng, Yancheng 224000, Jiangsu Province, China

Corresponding author: Yu Tian, Doctor, Department of Thoracic Surgery, Yancheng No. 1 People's Hospital, Affiliated Hospital of Nanjing University Medical School, The First People's Hospital of Yancheng, No. 166 Yulong Road, Yancheng 224000, Jiangsu Province, China. tianyujsyc@163.com

Abstract

The relevant mechanism of tumor-associated macrophages (TAMs) in the treatment of colorectal cancer patients with immune checkpoint inhibitors (ICIs) is discussed, and the application prospects of TAMs in reversing the treatment tolerance of ICIs are discussed to provide a reference for related studies. As a class of drugs widely used in clinical tumor immunotherapy, ICIs can act on regulatory molecules on cells that play an inhibitory role - immune checkpoints - and kill tumors in the form of an immune response by activating a variety of immune cells in the immune system. The sensitivity of patients with different types of colorectal cancer to ICI treatment varies greatly. The phenotype and function of TAMs in the colorectal cancer microenvironment are closely related to the efficacy of ICIs. ICIs can regulate the phenotypic function of TAMs, and TAMs can also affect the tolerance of colorectal cancer to ICI therapy. TAMs play an important role in ICI resistance, and making full use of this target as a therapeutic strategy is expected to improve the immunotherapy efficacy and prognosis of patients with colorectal cancer.

Key Words: Colorectal cancer; Colorectal cancer stem cells; Tumor metastasis; Tumor immune microenvironment; Review

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Core Tip: The role of colorectal cancer stem cells in the tumor immune microenvironment, the development and metastasis of colorectal cancer. This paper focuses on how colorectal cancer stem cells affect the tumor immune microenvironment through immune escape, immunosuppression and microenvironment remodeling, and analyzes their key functions in tumor progression and metastasis. In addition, this paper also summarizes potential therapeutic strategies for colorectal cancer stem cells, aiming to inhibit their cancer-promoting effects and provide new targets and ideas for the treatment of colorectal cancer.

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INTRODUCTION

Colorectal cancer is one of the most common types of cancer worldwide, accounting for approximately 10% of all new cancers and 8.5% of all cancer deaths[1-5]. The incidence of colorectal cancer tends to increase with age, with patients under the age of 40 accounting for 2%-8% of all colorectal cancer patients[6-10]. At present, the treatment of colorectal cancer is mainly based on the combination of surgical treatment, radiotherapy and chemotherapy[11-14]. The vast majority of early-stage patients can be cured by surgery, but only a small proportion of patients with metastatic colorectal cancer can be cured by surgery, and the 5-year survival rate is very low[15-20]. The recurrence of colorectal cancer occurs mostly in the form of metastasis, which is mainly caused by residual tumor cells that spread to distant organs before surgery[21-26]. However, current systemic therapy (systemic chemotherapy) does not eliminate latent residual tumor cells and has no therapeutic effect on the growth of metastases, providing patients with a survival advantage of only a few months[27-30]. Metastasis occurs when cancer spreads to distant organs and forms metastases, mainly involving the liver and lungs, in patients with colorectal cancer. To metastasize, cancer cells need to invade surrounding tissue, survive in circulation, colonize distant organs, and eventually regain their ability to grow, but metastasis is an inefficient process, and most cancer cells lose their ability to grow during metastasis[31-35]. Since 2016, scholars have gradually discovered related factors affecting colorectal cancer metastasis: Tumor regeneration in distant organs is closely related to the acquisition of stem cell-like phenotypes by cancer cells. Metastatic tumor stem cells have a variety of phenotypes and biological behaviors, and tumors mainly rely on interactions with the microenvironment to migrate, survive in circulation, and regenerate in distant organs[36-38]. This article reviews the effects of colorectal cancer stem cells and the microenvironment on colorectal cancer metastasis.

OVERVIEW OF COLORECTAL CANCER

Normal colon epithelial cells are constantly renewed, and the crypt cells at the base of the colon mucosal glands are rapidly proliferating and differentiating intestinal stem cells, which can maintain the steady regeneration of epithelial cells[39-44]. Signaling pathways regulating intestinal stem cell renewal and proliferation, including the Wnt, epidermal growth factor receptor/mitogen-activated protein kinase and Notch signaling pathways, have been continuously identified, and the transforming growth factor (TGF)- β signaling pathway induces cell cycle arrest[45-48]. The high proliferation state of intestinal stem cells increases the possibility of mutation in the DNA replication stage, and environmental factors such as lifestyle, diet and microorganisms also have a great influence on the transformation of epithelial cells. In patients with colorectal cancer, the most common genetic change is inactivation of the tumor suppressor gene *APC*, which activates the Wnt signaling pathway to maintain a continuous stem cell proliferation state in the initial stage of tumor development, resulting in benign epithelial cell proliferation, namely, adenoma[49-52]. Genetic experiments conducted in mouse models confirmed the hypothesis that mutations in the *APC* gene in intestinal stem cells are the origin of intestinal polyps[53-55]. However, a small percentage of primitive accumulations become aggressive through other mutations, which are mainly mediated by three signaling pathways: (1) The mitogen-activated protein kinase pathway. By activating mutations in the *KRAS*, *BRAF*, or *PIK3CA* genes, cancer cells acquire the ability to undergo autonomous mitosis and proliferate; (2) The p53 pathway is activated and inactivated by mutated p53 proteins, resulting in genomic instability; and (3) TGF- β pathway. Commonly, *TGFBR2*, *SMAD4*, *SMAD2*, or *SMAD3* are functionally deficient and inactivated, thus preventing the inhibitory effect of high TGF- β levels in the tumor microenvironment[56-60]. The acquisition of these mutations is a slow process. Due to chromosome instability and defects in the DNA mismatch repair system, tumors often accumulate hundreds or even thousands of genetic variants, some of which cause new biological behaviors in

cancer cells and increase their aggressiveness; moreover, some of the effects of these mutations are still unknown, and these factors work together to make the treatment of colorectal cancer difficult[61-66].

As noted above, mutations that promote the development of colorectal cancer affect signaling pathways that regulate the behavior of intestinal stem cells, allowing cancer cells to divide and grow autonomously, which is unregulated by intestinal stem cell signaling[67-70]. It has been hypothesized that mutations acquired in the mitogen-activated protein kinase pathway, p53 pathway, and TGF- β pathway promote the growth of tumor cells in unfavorable environments[71-74]. Although these mutations promote tumor development, metastasis is still uncommon, suggesting that other factors are involved in limiting tumor spread[75-77]. Most colorectal cancers are aggressive at diagnosis, which gives shed cancer cells a chance to enter the circulatory system for months or longer, and when disseminated colorectal cancer cells enter the portal circulation, they are transported to the hepatic sinuses within minutes and into the liver parenchyma when the blood vessels open[78-80]. In the case of lung metastasis, colorectal cancer cells first enter the systemic circulation and then infiltrate the lung parenchyma, while the ability of colorectal cancer cells to infiltrate other organs (the brain) is unknown[81-84]. Studies have shown that the limiting factor in tumor metastasis is the ability of circulating tumor cells to colonize distant organs[85-89]. Most tumor cells that survive in the circulatory system and infiltrate distant organs die for reasons that are unclear and may be related to the recognition and killing of tumor cells by the innate and adaptive immune systems, while tumor cells that survive and adapt to the new environment can metastasize[90-94]. However, not all cancer cells that successfully spread to distant locations can proliferate in a new environment, and they often remain dormant in distant organs for months to years before regaining their ability to proliferate.

EFFECT OF COLORECTAL CANCER STEM CELLS ON COLORECTAL CANCER METASTASIS

Hierarchical structure of tumor cells: The concept of tumor stem cells

Tumors that first appear in the blood are a class of cells with self-renewal ability and unlimited differentiation potential[95-100]. Tumor stem cells differentiate into tumor cells with phenotypes different from those of the original cells in a suitable environment, thus leading to the formation of tumor metastases[101-106]. Some scholars have proposed that colorectal cancer is caused by groups of cells with different tumorigenic potentials, called tumor-initiating cells[107-109]. Studies have shown that tumor-initiating cells (also known as colorectal cancer stem cells), located at the top of the tumor cell hierarchy, can self-renew and have the potential to proliferate and differentiate over a long period of time, causing tumors when injected into mice[110-115]. The balance between stem cell pluripotency and cell differentiation in colorectal cancer relies on signaling pathways that regulate normal intestinal stem cells, many of which are supplied by tumor stromal cells, and the presence of other stroma-derived cytokines and growth factors at invasion sites further promotes the self-renewal of colorectal cancer stem cells[116-118]. Because colorectal cancer stem cells have the ability to self-renew and initiate tumors, they may represent (or give rise to) so-called metastatic stem cells, the cells of origin of metastasis. Studies have shown that only cells with long-term self-renewal capabilities are likely to metastasize[119-121].

Most colorectal cancers are a relatively disordered mix of stem cells and differentiated cells, and distant metastases form metastases with the same properties[122-128]. Although colorectal cancer stem cells present in tumor glands are tumorigenic when isolated and xenografted in mice, under natural conditions, they are only capable of metastasizing when they first undergo phenotypic changes that enable them to migrate and excrete, a process that occurs when cancer cells exchange substances with neighboring tissues and tumor stroma.

The metastasis of dormant and slowly proliferating tumor cells usually occurs

The incubation period of colorectal cancer cells is up to five years after the incubation period, which is the result of disseminated tumor cells remaining dormant[129-131]. Currently, the standard chemotherapy for removing these surviving tumor cells is standard chemotherapy, but chemotherapy causes limited damage to these surviving tumor cells because chemotherapy usually targets rapidly proliferating tumor cells, while dormant and slowly proliferating tumor cells are largely resistant to chemotherapy. Dormant tumor cells develop a special state of response to signals that induce cell death, thus protecting them from the immune system[132-136]. The latency of metastasis may be caused by two mechanisms: Population dormancy, that is, the equilibrium state of tumor cell proliferation and death, resulting in the non-expansion of micrometastases; this is a state in which cells are stationary or temporarily mitotic[137-140]. Understanding these mechanisms gives physicians the opportunity to cure patients by eliminating remaining lesions (or inhibiting their growth) before significant metastases occur. Although the origin, characterization, and regulation of the dormant cell population in colorectal cancer are unknown, these findings may provide directions for the study of the diversity of normal intestinal epithelial cells.

Genetic changes in tumor cells

Due to genomic instability, tumors acquire hundreds of genetic and epigenetic changes that give tumor cells a different phenotype, which can lead to clonal expansion, an evolutionary phenomenon that is the basis for tumors to adapt to different environments, colonize distant areas, and resist treatment[141-145]. Conceptually, phenotypic heterogeneity due to tumor cell grade and clonal diversity may have some correlation, with colorectal cancer stem cells representing clonally selected units that mutate in cells that are more differentiated but have a lower chance of being selected due to the population's shorter lifespan[146-148]. Although clonal diversity has been associated with treatment resistance and an enhanced ability to metastasize, genetic sequencing of primary colorectal cancer and metastases did not reveal specific genetic mutations associated with tumor spread, and similarities between primary tumors and metastases suggest that nongenetic factors may play a special role in this process (Figure 1).

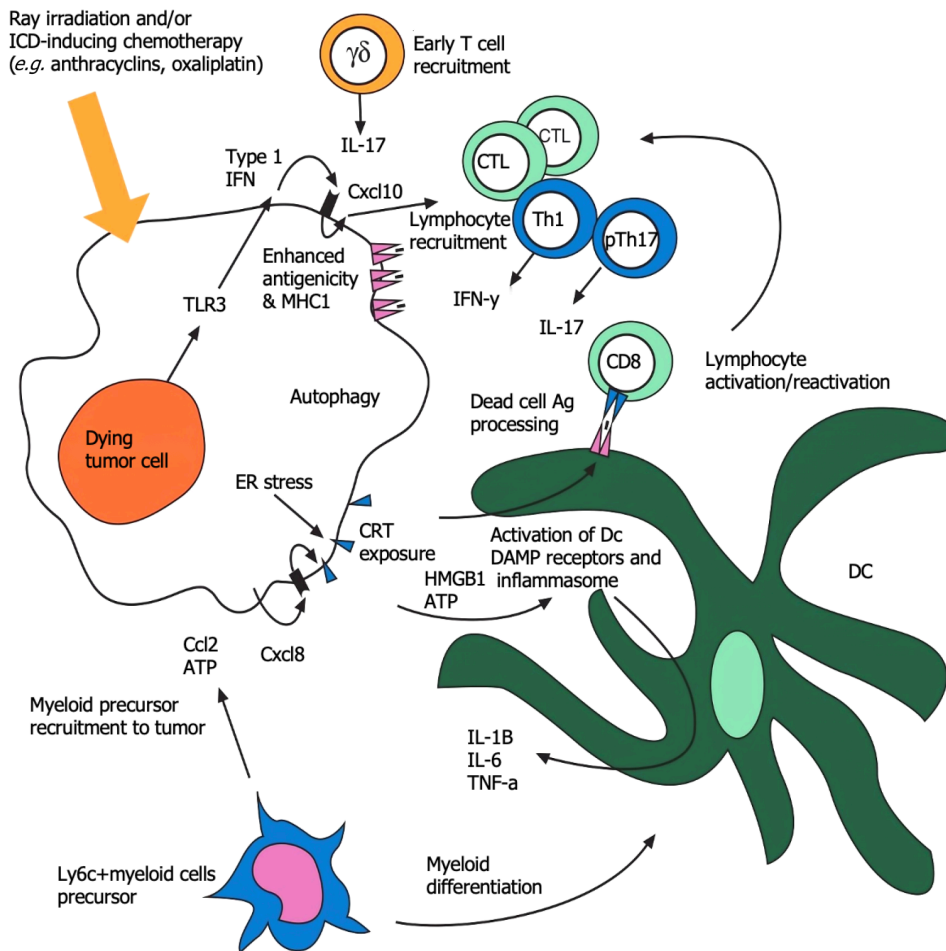


Figure 1 Immunogenic chemotherapy and radiotherapy to restore the tumor microenvironment. ICD: International Classification of Diseases; IL: Interleukin; IFN: Tumor necrosis factor; CXCL: Chemokine (C-X-C motif) ligand; TLR3: Toll-like receptor 3; MHC1: Major histocompatibility complex class I; ER: Endoplasmic reticulum; CRT: Calreticulin; CCL: Chemokine (C-C motif) ligand; HMGB1: High mobility group box; DC: Dendritic cell; DAMP: Damage-associated molecular pattern; TNF: Tumor necrosis factor.

EFFECT OF THE MICROENVIRONMENT ON COLORECTAL CANCER METASTASIS

Colorectal cancer epithelial mesenchymal heterogeneity brings new ideas to the diagnosis and treatment of colorectal cancer patients, and intratumoral heterogeneity also includes many other cell types that penetrate the tumor, collectively known as the stroma or tumor microenvironment[149-151]. The function of the stroma is related to all steps of cancer progression and metastasis. During the process of cancer progression, cancer cells exchange substances with the stroma and develop together[152-154]. Conceptually, transformed cancer cells strongly change the properties and composition of the matrix, and these changes form a suitable microenvironment for cancer cell growth, providing protection for cancer cells[155]. Therefore, an increasing number of studies have focused on the characteristics of specific stromal cell populations related to tumor malignancy and metastatic colonization (Figure 2).

Cancer-associated fibroblasts in the microenvironment

Cancer-associated fibroblasts are a group of highly homologous activated fibroblasts with special phenotypes in the tumor stroma that can be isolated from different parts of the tumor. Cancer-associated fibroblasts differ from normal fibroblasts in that they activate the myofibroblast phenotype and promote the expression of alpha smooth muscle actin, fibroblast-specific protein-4, and fibroblast-activating protein, which are specific markers for the recognition of cancer-associated fibroblasts[156-158]. Cancer-associated fibroblasts provide a range of cytokines to colorectal cancer cells that promote cancer cell survival and tumor development[159-162]. In addition, gene expression signatures obtained from cancer-associated fibroblasts may be associated with poor prognosis in patients with colorectal cancer[163-165]. Therefore, cancer-associated fibroblasts are an important cell population in the tumor microenvironment that provides a suitable environment for cancer progression (Figure 3).

Stromal environment

The stromal environment surrounding tumor cells has a growing network of blood vessels that provide nutrients and oxygen for tumor cell growth[166-168]. Growth factors secreted by tumor cells stimulate the proliferation and differentiation of endothelial cells, thus promoting the formation of blood vessels, while tumor-related angiogenesis leads to

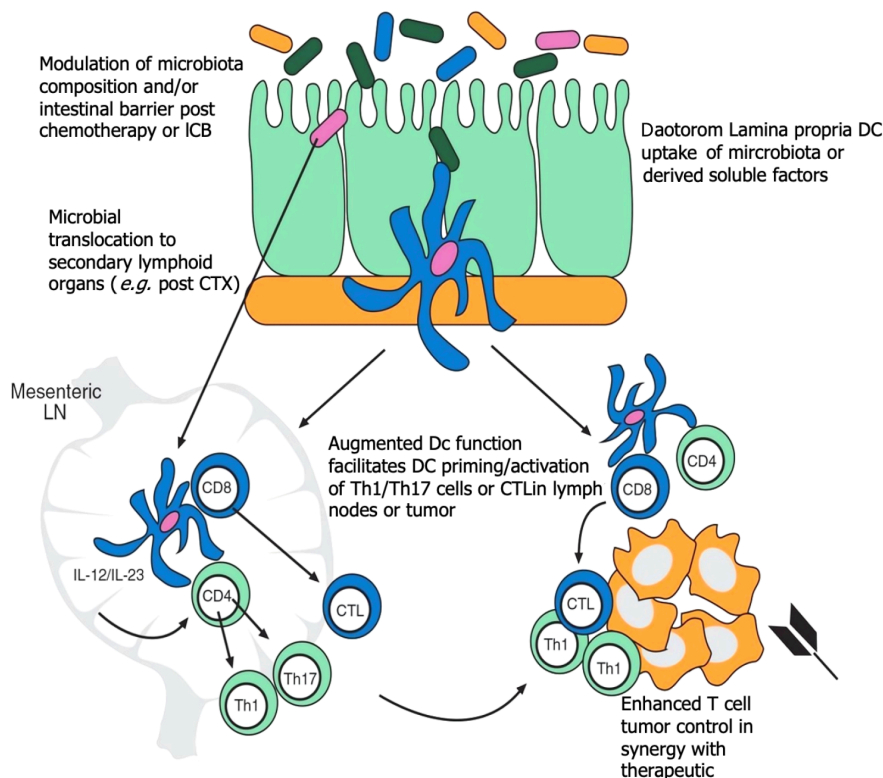


Figure 2 The microbiota can augment dendritic cell function and thus contribute to anticancer immunity. ICB: Immune checkpoint blockade; CTX: Cyclophosphamide; LN: Lymph node; IL: Interleukin; Th: T helper cell; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell.

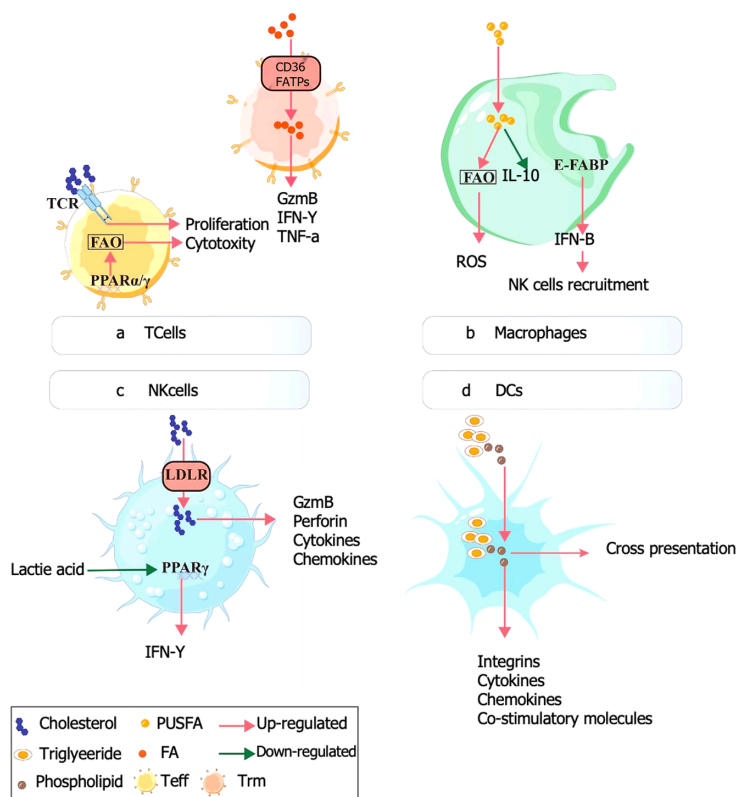


Figure 3 Lipid metabolism in the antitumor immune response. FATPs: Fatty acid transport proteins; TCR: T cell receptor; FAO: Fatty acid oxidation; IFN: Interferon; TNF: Tumor necrosis factor; IL: Interleukin; E-FABP: Epidermal fatty acid binding protein; NK: Natural killer; ROS: Reactive oxygen species; LDLR: Low-density lipoprotein receptor; PPAR: Peroxisome proliferator-activated receptor; PUSFA: Polyunsaturated fatty acids; FA: Fatty acid.

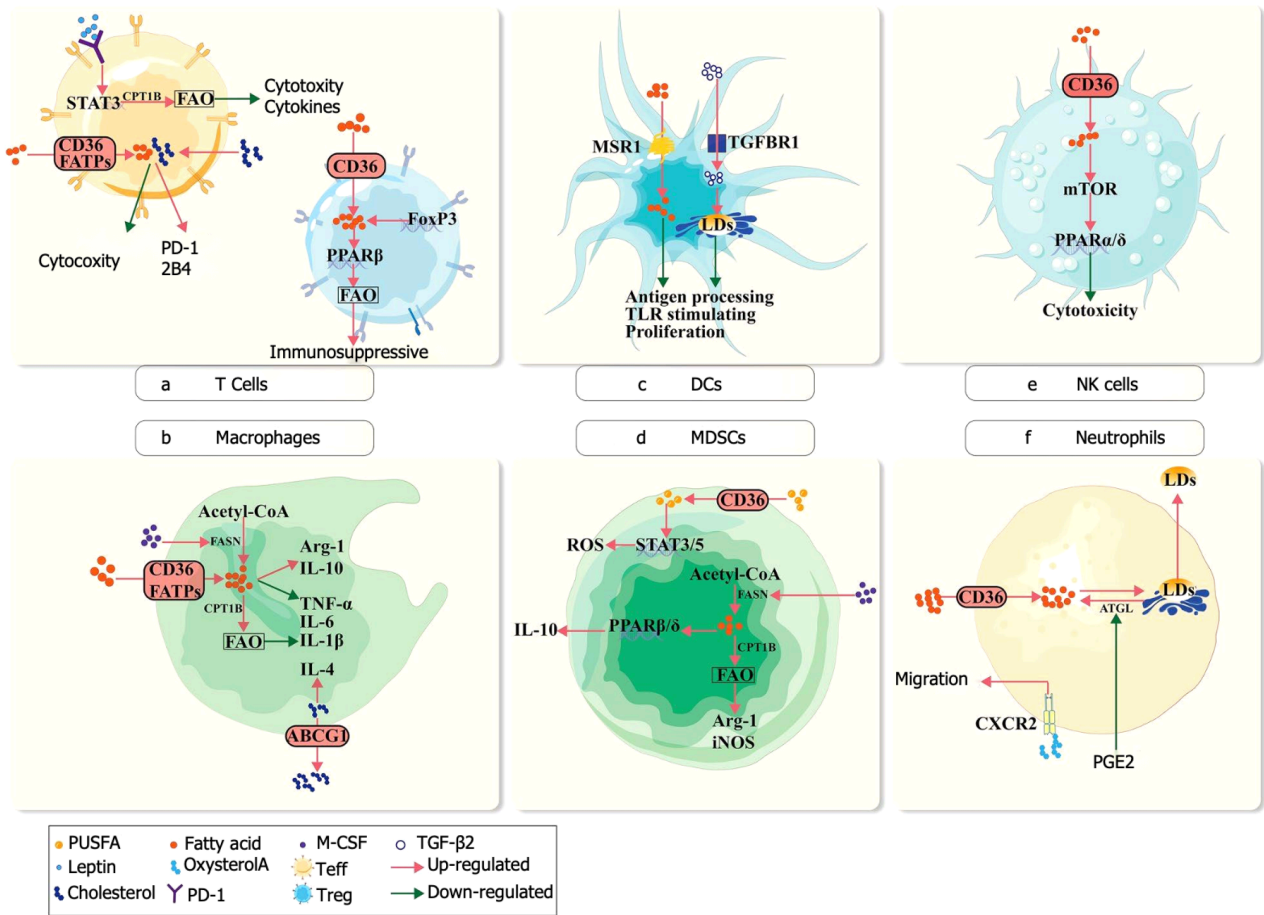


Figure 4 Lipid metabolism in protumor immune responses. STAT3: Signal transducer and activator of transcription 3; CPT1B: Carnitine palmitoyltransferase 1B; FAO: Fatty acid oxidation; PD-1: Programmed cell death protein 1; PPAR: Peroxisome proliferator-activated receptor; MSR1: Macrophage scavenger receptor 1; TGFBR1: Transforming growth factor beta receptor 1; TLR: Toll-like receptor; mTOR: Mechanistic target of rapamycin; DC: Dendritic cell; MDSC: Myeloid-derived suppressor cell; NK: Natural killer; FFA2: Fatty acid transport protein; Arg: Arginine; IL: Interleukin; TNF: Tumor necrosis factor; ABCE1: ATP-binding cassette sub-family G member 1; ROS: Reactive oxygen species; iNOS: Inducible nitric oxide synthase; CXCR2: C-X-C chemokine receptor; ATGL: Adipose triglyceride lipase; PGE2: Prostaglandin E2; PUSFA: Polyunsaturated fatty acids; M-CSF: Macrophage colony-stimulating factor; TGF: Transforming growth factor; Treg: Regulatory T cell.

vascular abnormalities, which often manifest as network disorders, excessive branching, reduced coverage and leakage of surrounding cells[169-171]. Vascular abnormalities are associated with metastasis and poor prognosis in patients with colorectal cancer. Vascular endothelial growth factor (VEGF) is a key regulator of the proliferation of most human tumor endothelial cells and can induce the activation of mitogen-activated protein kinase/extracellular signal-regulating kinase signaling pathways[172]. VEGF expression in tumors is associated with the invasion of cancer cells, increased vascular density and metastasis[173-176]. The combination of bevacizumab, monoclonal antibodies against VEGF, and angiogenesis inhibitors with chemotherapy has been shown to improve survival in patients with stage IV colorectal cancer (Figure 4).

SA100A6 protein

SA100A6 is a calcium-ion binding protein and a member of the SA100 protein family[177-183]. At present, the SA100A4 protein family is known to indirectly promote tumor cell metastasis through the tumor microenvironment, and SA100A4 can promote monocyte polarization to the M2 type, thus promoting tumor metastasis. Studies have shown that SA100A6 can promote the progression and metastasis of colorectal cancer, but the underlying mechanism is not yet clear[184-190].

Interleukin-33

Interleukins are cytokines whose molecular structure and biological function are largely clear, and they play important regulatory roles[191-195]. It plays multiple roles in the activation and proliferation of immune cells and the regulation of the immune response[196-200]. Interleukin-33 is a cytokine secreted by endothelial and epithelial cells that can activate the mitogen-activated protein kinase signaling pathway and plays an important role in tumor angiogenesis in colorectal cancer[200-204]. Recent studies have shown that interleukin-33 plays a regulatory role in the occurrence, development and metastasis of tumors, and its abnormal expression may be related to the clinical characteristics of patients with tumors[205-209]. Interleukin-33 secreted by tumor cells significantly increases the generation of new blood vessels by increasing the proliferation, migration and differentiation of endothelial cells into blood vessels, thus increasing the

metastasis and spread of colorectal cancer cells to the liver[210-212]. Blocking the signaling pathway mediated by interleukin-33 can inhibit angiogenesis and reduce the occurrence of tumors[213-215].

CONCLUSION

The effects of colorectal cancer stem cells and tumor microenvironment regulation on the progression and metastasis of colorectal cancer, as well as the formulation, optimization and application of treatments, are highly important. The theory of colorectal cancer stem cells explains why colorectal cancer is difficult to cure. Although the ability of colorectal cancer stem cells to cure colorectal cancer can be eradicated from the root, research on the use of these cells is still in its infancy, and further research is needed to determine the optimal treatment for colorectal cancer. The tumor microenvironment is closely related to the aggressiveness of the tumor, so the study of the tumor microenvironment is highly important for the prevention and treatment of tumor metastasis. Tumor heterogeneity plays a role in the generation and maintenance of drug resistance and metastasis ability of colorectal cancer stem cells, especially colonized metastasis supported by the tumor microenvironment. Treatments that target colorectal cancer stem cells and the microenvironment can prevent distant metastases in early-stage colorectal cancer patients who are at risk for distant metastases. In the future, targeted therapy targeting colorectal cancer stem cells and the microenvironment of cancer cells combined with radical surgery and systemic chemotherapy may provide a new direction for the treatment of colorectal cancer patients.

FOOTNOTES

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