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Tumor-Associated Macrophages as Treatment Target in Colorectal Cancer

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***Abstract*:** *Colorectal cancer (CRC) is one of the common malignant tumors in the digestive tract, and its treatment and prognosis are affected by many factors. Macrophages are cells that participate in innate immunity. Macrophages are cells that participate in innate immunity, maintain the body and resist the invasion of foreign pathogens, and play a supporting role in different organs and tissues. In the tumor microenvironment (TME), macrophages are called tumor-associated macrophages (TAMs), and they play an important role in tumor cell proliferation, metastasis, angiogenesis, and immunosuppression. In this article, we reviewed the interaction between TAMs and tumor cells, discussed the origin and polarization of TAMs, and described the role of TAMs in tumorigenesis and development, invasion and metastasis, and immunosuppression. Finally, we briefly summarized tumor treatment options targeting TAMs to provide new ideas for subsequent tumor research and treatment.*

Keywords: *Colorectal cancer, Tumor-associated macrophages, Tumor progression, Target treatmen*

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most lethal cancer [1]. According to the latest survey, the incidence of CRC in China has jumped to second place, and the mortality rate is fifth place [2]. The occurrence of cancer is complicated and involves not only the genetic changes of cells, but also the changes in their microenvironment and composition. A better understanding of the biological effects of tumor cells is essential for the development of new treatment methods [3-4]. Tumor Microenvironment (TME) is the environment in which tumor cells are located, composed of immune cells, fibroblasts, endothelial cells, and extracellular matrix [5]. Macrophages are an important component of TME, also known as Tumor-Associated Macrophages (TAMs), and their main functional phenotype is determined by the components in TME. Macrophages are widely distributed in human tissues and are part of the mononuclear phagocytic system. They play an important role in human innate immunity [6] and are also involved in tissue homeostasis, inflammation, etc [7]. This article discusses the source and differentiation of TAMs and expounds on the tumor-promoting function of TAMs. Finally, we briefly discussed the research progress of TAMs as therapeutic targets.

2. TAMs Origin and differentiation

Macrophages in TME are recruit by tumor-derived chemokines (CCL-2, CCL-7), chemokine ligand 12 (CXCL-12), etc, and differentiated into TAMs. After differentiation, TAMs produce corresponding cytokines, exosomes, and other factors that promote/inhibit tumor development [8]. Under the stimulation of different factors, macrophages can differentiate into two types-M1-like macrophages and M2-like macrophages, both of which play opposite roles. M1 macrophages are activated by bacterial cell wall components and interferon-gamma (IFN-γ), secreting a large number of inflammatory factors, and have a strong effect of killing microorganisms and tumor cells; M2 macrophages are composed of interleukin 4 (IL-4), IL -10 and play a role in anti-inflammatory, immunosuppressive and tissue repair [9-10]. Most of the TAMs in TME are M2 type [11], which is conducive to the occurrence and development of tumors.

3. Function of TAMs in CRC

TAMs have strong plasticity, can be polarized into different types under the influence of TME, and

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have two sides in tumor progression. Previously, researchers proposed that macrophages were activated to produce anti-tumor effects, and recent studies have shown that TAMs promote tumor progression by regulating tumor cell growth, angiogenesis, invasion and metastasis, and immunosuppression [12].

Table 1: Comparison of Macrophages with Two Different Activation Pathways

	M1-like macrophages (Classic activation pathway)	M2-like macrophages (Alternative activation method)
Inducing substance	Bacterial cell wall components, IFN-γ, tumor necrosis factor α (TNF-α), etc.	IL-4, IL-10, IL-13, tumor growth factor β (TGF-β), macrophage colony stimulating factor, etc.
Features	Produces inflammatory factors, NO	Up-regulation of mannose receptor expression, and high expression of scavenging molecules
Surface markers	CD68, CD11B	CD206, CD163, CD209
Effect	Kill microorganisms and tumor cells	Limit type I immune response, participate in tissue repair, wound healing

Edin et al [13] proved that both M1 and M2 macrophages exist in the early stage of tumor invasion, and the ratio of the two affects the prognosis—high infiltration of M1 macrophages is beneficial to the recovery of CRC patients, while M2 macrophages will promote The development of tumors aggravates the condition. In addition, many studies have shown that the infiltration density of CD68+ TAMs is positively correlated with the survival time of patients [14-16]. The possible mechanism is that the highly infiltrating CD68+ TAMs increase the expression of E-cadherin and hinder the epithelial-mesenchymal transition (Epithelial-Mesenchymal Transition, EMT), to prevent the transfer of CRC [17], but recent studies have reported the opposite conclusion [18]. The differences in the results obtained between the above studies may be caused by the lack of good standardization of the macrophage phenotype, tumor type, and detection and evaluation methods.

Angiogenesis is a process in which cancer interacts with stromal cells and is a prerequisite for tumor metastasis. Studies have shown that the number of TAMs in CRC is positively correlated with vascular density [19]. TAMs secretes epidermal Growth Factor (EGF), endothelial Growth Factor (VEGF), Transforming Growth Factor -β (TGF-β), and Thymidine Phosphorylase. TP) and other angiogenic factors to promote angiogenesis; It can also produce Matrix metalloproteinase (MMP) and tissue protein to degrade the basement membrane and promote angiogenesis. Under hypoxia, TAMs aggregates at hypoxia sites and promote VEGF secretion and angiogenesis through the expression of hypoxia-inducible factor α (HIF1-α)[20]. TAMs can also increase the expression of angiogenic proteins in TME by regulating the activity of NADPH oxidase [21]. In addition, TAMs can promote angiogenesis together with related factors secreted by cancer cells.

Cancer metastasis accounts for 90% of all cancer-related deaths, and previous studies have shown that TAMs are involved in cancer metastasis. A large number of TAMs can be found in the sites with a high incidence of EMT, where tumor cells are more prone to metastasis and invasion. TAMs activates the JAK/STAT3 pathway through il-6 production, and the activated STAT3 transcriptional inhibition of tumor suppressor Mir-506-3p leads to increased expression of FoxQ1, induces the occurrence of EMT, and accelerates the migration and invasion of CRC cells[22]. Secondly, macrophages can also up-regulate the expression of MMP-2 and MMP-9, hydrolyze extracellular matrix proteins, not only promote tumor microvascular formation but also induce and accelerate the EMT process, creating conditions for tumor invasion and metastasis[23-24]. In vitro experiments have shown that macrophages can increase the migration ability of CRC cells, and the possible mechanism is that M2 macrophages can promote EMT through activation of the NF-κB pathway, and accelerate the invasion and metastasis of CRC cells [25]. TGF-β generated by TAMs activates Smad signaling pathway and regulates Snail transcription, induces EMT in colon cancer cells, and promotes metastasis of colon cancer [26]. M2 macrophages produce exosomes to transport highly expressed Mir-21-5p and Mir-155-5p to colon cancer cells, down-regulate the expression of BRG1 and promote the metastasis of CRC cells [27].

Macrophages are one of the main components of infiltrating cells in TME and play an important role in immune surveillance. The innate immune system with macrophages as the main component and the adaptive immune system with T cells as the component is coordinated with each other. It plays an important role in preventing tumor progression. When TAMs are tumor-promoting, they will inhibit the proliferation of T cells, destroy the function of T cells, and lead to the failure of the adaptive immune system [28-29]. At the same time, under the influence of tumor secretion factors, the related factors secreted by TAMs (such as IL-10, TGF-β, etc.) can also change the composition of immune cells in TME, and establish a tumor-promoting effect by recruiting more immunosuppressive cells. The growth environment accelerates tumor progression [30]. In addition, TAMs also cooperate with other immune cells to inhibit the anti-tumor response. Myeloid-derived suppressor cells and Treg cells are the main

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cells that mediate immunosuppression in the tumor microenvironment. TAMs produce a variety of chemokines (CCL17, CCL2, etc.) to recruit these cells to the tumor site and further increase the number of immunosuppressive cells [31].

4. Macrophages and CRC therapy

Many studies have shown that TAMs play a central role in all aspects of tumor progression [32-33], the anti-tumor mechanism based on TAMs offers a variety of potential treatment strategies, also provides new thinking for clinical cancer treatment. So far, the method of targeted regulation of TAMs function has achieved good results in experimental studies and clinical trials. In addition, targeting TAMs treated with traditional treatment also showed a powerful synergy, the combination of both also has brought the new direction for tumor treatment.

4.1. Targeting macrophage recruitment

Preventing macrophages from recruiting to TME to reduce its tumour-promoting effect is one of the current TAMs based therapeutic strategies. CCL2/CCR2 is the main molecular axis that supplements the number of TAMs. Blocking the CCL2/CCR2 axis can significantly reduce the number of TAMs, thereby inhibiting tumor growth and spread [34-35]. Studies have found that inhibition of CCL2 can block the recruitment of TAMs in TME and slow tumor progression and metastasis [36-37]. The other is to inhibit CCL2 secretion by inactivating the ubiquitin-like pathway, thus reducing monocyte infiltration in TME[38]. An increase in TAMs may improve patient survival. Currently, there are mainly two CCL2/ CCR2-based therapies: one is CCL2 blocking antibody, and the other is CCR2 small molecule inhibitor[39]. Carlumab (CCL2-blocking antibody) has a good inhibitory effect on malignant tumors[40]. A study of pancreatic malignancies showed that the CCR2 inhibitor PF-04136309 combined with FOLFIRINOX was effective, safe, and well tolerated[41]. It is worth noting that long-term CCL2/CCR2 suppressor therapy may lead to the enhancement of other chemokine production pathways, resulting in an increase in the number of TAMs in TME[42], while the sudden interruption of CCL2/CCR2 blocking therapy may accelerate tumor progression[43].

The CSF-1/CSF-1R signaling pathway is another critical control point for macrophage recruitment, polarization, and survival. It will lead to the lack of the most rapid depletion of macrophage in mice. At present, the ligand for CSF-1 antibody has been developed and related research is ongoing[44]. Monoclonal antibody (RG7155) reduced the number of F4/80+ TAMs and increased the ratio of CD8+/CD4+ T cells by inhibiting CSF-1R[45]. In melanoma, small molecule PLX3397 (CSF-1R inhibitor) inhibits the accumulation of TAMs, and in combination with extra-terminal inhibitors can enhance the efficacy of tumor therapy[46].

In recent years, studies have found that traditional Chinese medicine can also improve the immune function of patients by regulating TAMs, thus achieving the anti-tumor effect. Rhubarb can inhibit the liver metastasis of CRC by reducing the number of polarized M2 macrophages[47]. Tengatin can reduce the expression of CXCL2, reduce the infiltration of TAMs, reshape TME, reduce the expression of IL-10 and other factors, and prevent macrophages from becoming m2-type macrophages[48].

In addition to blocking the recruitment of macrophages to TME, it can also induce the apoptosis of TAMs and reduce the number of TAMs. Bisphosphonates, a key enzyme in cholesterol synthesis and protein acylation, can be absorbed by TAMs and play an anti-tumor role by interfering with various functions of TAMs[49]. Tribetedine is an antitumor drug, which has certain effects on TME components in addition to targeting cells. Trabectidin induces TAMs apoptosis through TNF-related apoptosis-inducing ligand-mediated mechanism, reduces the number of TAMs, and inhibits tumor growth[50].

4.2. Targeting the polarization of macrophages

Although numerous studies and clinical trials have shown that elimination of TAMs is an effective tumor therapy, current approaches do not eliminate all macrophages; Second, TME contains anti-inflammatory and tumor-killing macrophages, and removing all of them would put the body at unknown risk. Macrophages are highly plastic cells. In different environments, different molecules and other substances can stimulate macrophages and polarize different phenotypes of macrophages. Therefore, repolarization of anti-inflammatory TAMs into tumor-killing macrophages to exert an anti-tumor effect will lead to more effective tumor therapy.

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CD40 is a receptor of the TNF superfamily, widely expressed on the surface of antigen-presenting cells and tumor cells, and can act as a stimulant of the immune system. Studies have shown that anti-CD40 antibody stimulates the anti-tumor effect of TAMs by promoting the secretion of NO and TNF-α in mouse melanoma[51]. CD40 pathway "educates" TAMs to become fatal in human pancreatic ductal adenocarcinoma[52]. The use of CSF1R blockers depletes TAMs and reduces the anti-tumor activity of CD8+ T cells, while the use of an agonist CD40 antibody encodes TAMs as an anti-tumor phenotype[53]. In addition, CD40 antibody and CSF1R increased the number of pro-inflammatory macrophages when combined with drugs[54]. Although CD40 has a good therapeutic effect, it is also accompanied by serious adverse reactions, such as cytokine release syndrome and hepatotoxicity, which limits the clinical use of the drug. The researchers hope that improving the structure and injection of CD40 antibody methods to reduce the occurrence of adverse events, enhances the ability to kill tumors[55].

CD47 is a membrane protein widely expressed in normal and cancer cells. When it binds to the SIRPα expressed by macrophages, it sends a 'don't eat me' signal to avoid phagocytosis by macrophages[56]. Thus, the tumor-killing effect of TAMs can be restored and enhanced by interfering with the CD47-SIRP α axis. Studies have shown that targeting CD47-SiRP α can induce antibody-dependent cell phagocytosis, resulting in the main type of mouse macrophages being M1 macrophages[57]. In the study of glioblastoma, we found that CD47 monoclonal antibody can transform the macrophage phenotype into M1 subtype in vivo and enhance its killing effect on tumors[58]. In addition, the use of CD47 blocking antibodies can significantly increase the phagocytosis of macrophages in liver cancer and increase the infiltration of pro-inflammatory macrophages into tumor tissues[59].

Toll-like receptor (TLR) plays an important role in activating nonspecific immunity. It is the bridge between non-specific immunity and specific immunity. It is mainly expressed on the surface of antigen-presenting cells, fibroblasts, and epithelial cells. TLR7 and TLR9 were mainly expressed on the surface of macrophages and plasma cells. TLR, stimulated by viruses, bacteria, and other substances, can induce macrophages to become pro-inflammatory cells and play the role of phagocytosis[60]. In the treatment of CRC, it was found that TLR7/8 agonist could induce the differentiation of bone-derived inhibitory cells into killing macrophages and improve the efficacy of oxaliplatin, providing a new direction of drug selection for CRC drug resistance[61]. The TLR9 agonist IMO-2125 induced macrophages to kill tumors in mouse models, achieving the therapeutic purpose[62]. In addition, studies have shown that cationic polymers used in clinical cancer therapy can activate and repolarize TAMs through the TLR4 signaling pathway, thus playing a role in killing tumors[63]. The combination of TLR and other drugs can improve the efficacy of tumors. TLR7/8 agonist MEDI9197 in combination with PD-1 blocking antibody can polarize TAMs into tumor-killing TAMs and activate NK cells, thus exerting better efficacy[64]. TLR7 agonist 1V270 and PD-1 were used to treat squamous cell carcinoma of the head and neck. It was observed that 1V270 induced an increase in the ratio of M1/M2 TAMs and improved the effect of PD-1[65].

The plasticity of macrophages makes them a target for inhibiting tumor progression. By changing the polarization of macrophages, macrophages can play an anti-tumor role.To make macrophages play a better role in TME and understand the activation state of TAMs, it is necessary to conduct more in-depth studies on the special markers on the surface of macrophages to distinguish the different functions and activation methods of anti-tumor and tumor-promoting TAMs.

5. Future perspective

TAMs are commonly found in the stroma of many solid tumors and play an important role in patient prognosis, angiogenesis, tumor cell metastasis, and immune escape. At present, TAMs have a good prospect as a therapeutic target, but the therapeutic methods targeting TAMs cannot completely kill tumor cells, and in some cases, it has the disadvantage of high drug toxicity. Secondly, the communication between tumor cells and TAMs is carried out through multiple signal axes, and the targeting relying only on a single signal axis is ineffective. Therefore, it is necessary to further understand the ability of TME to promote macrophage polarization and the factors that lead to macrophage polarization, to provide new ideas for the development of new therapeutic methods. At the same time, combined with genomics, proteomics, and metabolomics analysis, we will gain a more detailed understanding of the networks that regulate TAMs function and discover new therapeutic targets from them. In addition, future studies need to further determine the types and numbers of TAM subsets in different tumors, different stages, and different tissue types, to further improve the existing therapeutic methods targeting TAM.

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