Tumor-Associated Macrophages (TAMs)

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Tumor-associated macrophages (TAMs) are a major component of the immune cells of the TME. They play a prominent role by secreting cytokines and chemokines and coordinating with inflammatory mechanisms to promote tumor development, invasion, metastasis, immunosuppression, angiogenesis, and drug tolerance. Different subtypes of TAMs have different functions, which can be dynamically changed in response to various signals from cancer cells or the TME.

Keywords: colorectal cancer ; tumor microenvironment (TME) ; macrophage ; polarization ; therapy ; prognosis

1. Introduction

Colorectal cancer, whose abnormal cells grow in the colon or the rectum of the large intestine, is the third most common malignant tumor worldwide. The global incidence of colorectal cancer (CRC) has increased in recent years. According to the global cancer statistics for 2020 released by the International Agency for Research on Cancer (IARC), there were approximately 1.9 million new cases of CRC and 940,000 cancer deaths worldwide in 2020; its global mortality rate ranks second [1]. Some Asian countries, such as Japan and Malaysia, also have high CRC incidence. In China, the incidence of CRC has risen to become the fourth most common malignancy with the fifth highest mortality rate [2], making CRC a major public health issue.

The main risk factors of CRC are increasing age and genetic, lifestyle, and environmental factors. Genetic and epigenetic alterations inside the cell—such as the activation of oncogenes and proliferative signals from the abnormal microenvironment surrounding the cell—play the intrinsic role, while lifestyle or environmental factors such as obesity, inadequate exercise, tobacco or alcohol use, and processed meat consumption constitute the exogenous causes of CRC, interacting synergistically with the endogenous factors to promote CRC occurrence and development [3][4].

Over the past two decades, increasing evidence has shown that the tumor microenvironment (TME) plays an equally significant role in tumor initiation, progression, and metastasis as the genetic and epigenetic changes in cancer cells. The components of the tumor microenvironment include all of the nonmalignant stroma cells inside the tumor other than the tumor cells, including fibroblasts, endothelial cells, immune cells, and platelets [5][6]. Paget proposed the “seed and soil” theory in 1889 and conducted an in-depth analysis of the molecular characteristics of “seeds” (cancer cells) [7][8][9][10][11]. By studying the “soil” formed by cancer cells and host immune cells, scientists found that immune cells usually bind to cancer cells and obtain specific biological phenotypes via interactions with them. As a result, the TME is a unique environment which develops alongside tumor progression. It is now widely recognized that neglection of the complex changes in tumor microenvironment during tumor development is one important reason for the failure of current targeted therapies against tumor cells. Therefore, new therapeutic strategies targeting the component cells of the TME can be combined with traditional treatments to benefit CRC patients in individual medicine.

Tumor-associated macrophages (TAMs) are a major component of the immune cells of the TME. They play a prominent role by secreting cytokines and chemokines and coordinating with inflammatory mechanisms to promote tumor development, invasion, metastasis, immunosuppression, angiogenesis, and drug tolerance [12][13][14][15][16][17][18][19]. Different subtypes of TAMs have different functions, which can be dynamically changed in response to various signals from cancer cells or the TME. Studies have shown that TAMs are associated with poor prognosis in most solid tumors; however, their role is slightly more complicated in CRC, in which reeducating the polarization of TAMs may facilitate tumor immunotherapy [17][20][21][22][23][24]. The current review focuses on the phenotypic polarization of TAMs in CRC, the underlying functional mechanisms, and how these mechanisms can be used as potential targets for the treatment and prognosis of CRC.

2. The Functional Mechanism of TAMs in CRC

In the TME, TAMs and tumor cells promote tumor cell proliferation through the secretion of cytokines. In vitro studies confirmed that colon cancer cells upregulated the expression of RGC-32 in macrophages by secreting TGF-β1, and RGC-32 promoted the migration of macrophages and further accelerated the proliferation of colon cancer cells [25]. Yu, X. et al. reported that overexpression of C-X-C-motif receptor 4 (CXCR4) in the intestinal epithelial mucosa can promote epithelial–mesenchymal transition (EMT) and macrophage infiltration in colonic tissue, leading to colitis-associated tumorigenesis and progression [26]. Tacconi, C. et al. found that TAMs expressed VEGFR3, inhibited antitumor immunity, and promoted primary colorectal cancer growth through the VEGFC/VEGFR3 axis [27]. Furthermore, by coculturing TAMs and CT26 colon cancer cells in vitro, it was found that the oxidative stress regulated by TAMs can affect the proliferation of colon cancer cells. TAMs can maintain the level of reactive oxygen species (ROS) by regulating the activity of NADPH oxidase, thereby maintaining the redox state of the TME and promoting tumor cell proliferation [28].

The TME is mainly composed of stromal cells and immune cells such as macrophages, T lymphocytes, natural killer (NK) cells, dendritic cells (DC), neutrophils, and myeloid-derived suppressor cells (MDSCs) [5][29][30]. As the main component of the TME, the initial mechanism of TAMs is to recruit and activate T cells and NK cells by presenting tumor antigens, producing chemokines and cytokines, inhibiting the immune microenvironment of colon cancer, and exerting an immunosuppressive effect [31]. The release of chemokines mediated by TAMs, such as CCL2, CCL3, CCL4, CCL5, and CCL20, further contributes to Treg cell recruitment into the TME, and TAMs suppress the antitumor effects of T cells and NK cells [12][32][33].

TAMs highly express the ligands PD-1 and CTLA-4 (along with PDL1, B7-H1, and other ligands); suppress the cytotoxic function of T cells, NKT cells, and NK cells; and further reduce the body's ability to kill colon cancer cells [34]. Peritoneal macrophages secrete IL-17, which enhances G-MDSCs accumulation, increases the proportion of Th17 cells, and ultimately promotes CAC development [35]. Furthermore, mutant p53 regulates macrophages through exosomes miR-1246 to increase the activity of TGF-β and promote the anti-inflammatory immunosuppression of macrophages [36].

Metabolism regulates the differentiation, mobilization, phenotypic polarization, and function of macrophages. The metabolic pathways are significantly different among heterogeneous macrophages. In cancer, the macrophage metabolism reprogramming induced by cytokines and other mediators from tumor cells and the TME involves changes in metabolism-related enzymes, metabolites, and metabolic pathways [37][38][39].

3. Potential Applications of TAMs in Therapy of CRC

Given the significance of TAMs in CRC—as discussed in the previous section: TAMs facilitate tumor proliferation, invasion, migration, and angiogenesis; suppress antitumor immunity; regulate metabolism; and interact with the microbiota—there has been growing interest in new strategies that target TAMs in CRC treatments. Although preclinical studies have obtained some promising evidence that supports a combination of these approaches with traditional methods such as chemotherapy or radiation therapy, new therapeutic approaches targeting TAMs should be carefully evaluated for efficacy and safety in clinical trials.

Blocking the infiltration of mononuclear cells in tumor-related inflammatory tissues is a promising strategy for the treatment of primary tumors. Chanmee, T. et al. confirmed that colon cancer TAMs induce an enhanced expression of the transcription factors HIF-1, CXCL-12, and CXCR4 in the hypoxic TME environment. Targeting the HIF-1/CXCR4 pathway blocks the accumulation of TAMs [12]. Furthermore, NT157 represents a new class of anticancer drugs that targets both the IGF-1 receptor (IGF-1R) and the STAT3 oncogenic signaling pathway, exerting an inhibitory effect on tumor cells. Studies have shown that NT157 inhibits the expression of tumorigenic cytokines, chemokines, and growth factors, such as IL-6, IL-11 and IL-23, CCL2, CCL5, CXCL7, CXCL5, intercellular adhesion molecule-1 (ICAM1), and TGF-β, thereby inhibiting TAMs in the TME [40]. Mantovani et al. found that TAMs derived from monocytes in colon cancer have the ability to differentiate. Thus, a combination therapy that blocks differentiation is urgently needed to effectively target these cells. TNF-γ can induce monocyte or macrophage recruitment to the TME of colon cancer and inhibit their differentiation into TAMs in vivo [41].

The plasticity of macrophages allows researchers to re-educate TAMs. Since TAMs mainly exhibit the M2 phenotype and promote angiogenesis and immunosuppression [42][43], TAMs can be re-educated by inducing polarization from the M2 to the M1 phenotype. For instance, Georgoudaki, A.M. et al. investigated the effect of immune checkpoint therapy by inhibiting the expression of macrophage receptor with collagenous structure (MARCO) by TAMs, which repolarized TAMs to the M1 type in a mouse MC38 colon cancer model and induced antitumor activity [44]. As a small-molecule immunotherapy, tasquinimod reduces the immunosuppressive potential of the TME by altering the number and frequency

of tumor-infiltrating myeloid cells [45]. Olsson, A. et al. found that tasquinimod targets early-stage tumor-infiltrating myeloid cells and induces phenotype switching from the proangiogenic and immunosuppressive M2-like phenotype to the proinflammatory M1-like phenotype, which alters the TME to promote immunomodulation, prevent angiogenesis, and inhibit metastasis [46].

As evolutionarily conserved tumor suppressors, T2 RNases can inhibit tumor growth in vivo by balancing the M1/M2 macrophage ratio in tumors and recruiting adaptive antitumor CD8 + T cells [47]. Furthermore, Halama, N. and his colleagues also confirmed that inhibiting CCR5 can repolarize the phenotype of TAMs from M2 to M1 by regulating the STAT3/SOCS3 signaling pathway in TAMs, thereby exerting antitumor effects in a phase I clinical trial of patients with CRC liver metastases [48].

4. TAMs and Prognosis in CRC

The role of TAMs seems to be complicated in regard to colon cancer progression, as they are reported to perform both tumor-suppressive and tumor-promoting activities [49]. Some studies have shown that TAMs are associated with better CRC patient prognosis, while others have associated TAMs with poor prognosis. A summary of the related literature is shown in **Table 1**.

Table 1. Literature reports on the associations between TAMs and the prognosis of CRC patients.

Study Result	Expression in TAMs	Sample Size (Case)	Reference
Benign prognosis			
High-density $CD68^+$ TAM subtypes in CRC tissues were significantly associated with good 5-year overall survival (OS) rates	**High-density $CD68^+$**	**6115**	[50]
The ratio of $CD68^+$ macrophages to colon cancer cells is associated with improved survival in colon cancer patients	**High $CD68^+$/colon cancer cells ratio**	**205**	[51]
Adjuvant chemotherapy significantly improved recurrence-free survival (RFS) and OS for patients with high $CD206^+/CD68^+$ ratio of TAMs	**High $CD206^+/CD68^+$ ratio**	**835**	[52]
Both $CD68^+$- and VEGF-expressing TAMs were predictive of improved survival rates in stage II and stage III colon cancer patients	**$CD68^+$ and VEGF**	**131**	[53]
High infiltration of M1 macrophages is correlated with better prognosis in CRC in a stage-dependent manner	**High $M1^+$**	**485**	[54]
Poor prognosis			
Infiltration of TAMs $CD68^+/iNOS^-$ in the tumor stroma is a negative prognostic factor	**$CD68^+/iNOS^-$**	**89**	[55]
An increased ratio of $CD163^+/CD68^+$ in the tumor invasive front (TF) was positively correlated with shorter CRC RFS and OS times	**High $CD163^+/CD68^+$**	**81**	[56]
An increase in the proportion of M2/M1 type TAMs was positively correlated with an increase in liver metastases in patients with colorectal cancer	**High M2/M1 ratio**	**120**	[57]
A decrease in the number of infiltrating $CD68^+$ TAMs in the tumor stroma was associated with longer RFS and OS times in advanced CRC patients receiving bevacizumab combined with chemotherapy	**High $CD68^+$**	**123**	[58]
The combination of $FSP\text{-}1^+$ CAFs and $CD163^+$ M2 TAMs was associated with poor survival rates more significantly than when these markers were studied alone	**$FSP\text{-}1^+$ CAFs and $CD163^+$ M2 TAMs**	**289**	[59]

Some studies have shown that CD68 + TAMs are mostly distributed in CRC tumor stroma, mainly along the front edge of the invasion, and CD68 + TAMs infiltrated into this site can improve the prognosis of CRC patients [50][51][60][61]. Feng, Q. et al. recruited two independent cohorts of consecutively enrolled patients at one medical center with pathological stage II colon cancer after radical resection. In both cohorts, adjuvant chemotherapy significantly prolonged the recurrence-free survival (RFS) and overall survival (OS) rate of patients with a high CD206/CD68 ratio. This suggests that the CD206/CD68 ratio is probably a better biomarker for prognosis and prediction of stage II colon cancer after adjuvant chemotherapy [52]. However, TAM infiltration alone was not highly significant in prognostic analysis, while the presence of

both CD68- and VEGF-expressing TAMs was predictive of better survival rates in stage II and stage III colon cancer patients [53]. In addition, Najbauer, J. et al. found that high M1 macrophage infiltration is correlated with a better prognostic situation in CRC patients in a stage-dependent manner [54].

Nevertheless, different types and locations of TAMs have different prognostic significance for CRC patients. Infiltration of CD68 + TAMs and M2 TAMs is associated with poor CRC prognosis [62][63][64]. Infiltration of CD68 + /iNOS − TAMs in the tumor stroma is a negative prognostic factor [55]. An increased CD163 + /CD68 + ratio in the tumor invasive front (TF) was positively correlated with shorter RFS and OS rates in CRC [56]. In addition, an increase in the proportion of M2/M1 type TAMs was positively correlated with liver metastases in patients with colorectal cancer [57]. In a retrospective study of 123 patients with advanced CRC who were treated with bevacizumab combined with chemotherapy, the RFS and OS rates of CRC patients with low tumor interstitial CD68 + TAMs were significantly higher. This suggests that an increase in the number of CD68 + TAMs infiltrating the tumor stroma may reduce the efficacy of bevacizumab combined with chemotherapy in patients with advanced CRC [58]. In addition, Herrera, M. et al. demonstrated that the combination of FSP-1 + CAFs (cancer-associated fibroblasts) and CD163 + M2 TAMs was associated with poor survival rates more significantly than when these markers were studied alone [59].

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