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REVIEW

# From silent partners to potential therapeutic targets: macrophages in colorectal cancer

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## Abstract

Cancer cells grow and survive in the tumor microenvironment, which is a complicated process. As a key part of how colorectal cancer (CRC) progresses, tumor-associated macrophages (TAMs) exhibit a double role. Through angiogenesis, this TAM can promote the growth of cancers. Although being able to modify and adjust immune cells is a great advantage, these cells can also exhibit anti-cancer properties including direct killing of cancer cells, presenting antigens, and aiding T cell-mediated responses. The delicate regulatory mechanisms between the immune system and tumors are composed of a complex network of pathways regulated by several factors including hypoxia, metabolic reprogramming, cytokine/chemokine signaling, and cell interactions. Decoding and figuring out these complex systems become significant in building targeted treatment programs. Targeting TAMs in CRC involves disrupting chemokine signaling or adhesion molecules, reprogramming them to an anti-tumor phenotype using TLR agonists, CD40 agonists, or metabolic modulation, and selectively removing TAM subsets that promote tumor growth. Multi-drug resistance, the absence of an accurate biomarker, and drug non-specificity are also major problems. Combining macrophage-targeted therapies with chemotherapy and immunotherapy may revolutionize treatment. Macrophage studies will advance with new technology and multi-omics methodologies to help us understand CRC and build specific and efficient treatments.

**Keywords** Tumor microenvironment · Tumor-associated macrophages · Colorectal cancer · Therapy

## Introduction

Colorectal cancer (CRC) is a type of cancer that begins in the colon or rectum and often starts from benign growths called polyps on the inner surface of the large intestine. Over the time, some of these polyps can go through neoplastic transformation and develop into cancer. CRC accounts for 10% of mortality worldwide which makes it the third most spread cause of death [1–3]. Researchers have identified four distinct molecular subtypes of CRC by examining gene expression patterns. These subtypes are referred to as consensus molecular subtypes (CMS 1–4). Different subtypes are associated with specific genes and biological pathways. These include the MSI immune subtype (CMS1), canonical subtype (CMS2), metabolic subtype (CMS3), and mesenchymal subtype (CMS4) [4]. Note that the MSI immune and metabolic groups typically relate to CRC on the right side of the colon. While conducting treatment, it is important to consider factors like the tumor's location (whether it's on the right or left side) and genetic changes (like mutations in RAS or RAF genes), among other factors [5, 6]. Treatment for CRC varies based on the stage of the disease and the unique characteristics of each patient. There are various treatment options available, such as surgery, chemotherapy, radiation therapy, or precision drugs [7, 8]. The European Screening Guidelines Working Group and European Council suggest establishing screening programs for early detection of CRC and surgical intervention to improve the survival rates of individuals aged 50–74 [6, 9, 10]. The progression of CRC is much more complex than the tumor cell characteristics

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themselves. However, the intricate surrounding environment also heavily influences the tumor [11]. It contains a diverse range of stromal cells, immune cells, and soluble substances. The constantly changing interactions of cancer cells with various components can influence their behavior and response to treatment [12, 13]. The gut microbiota significantly influences CRC development by modulating immune responses and metabolic processes [14]. Certain microbial communities produce metabolites that can either increase inflammation or alter gut barrier function, thus raising the risk of cancer [15–17].

Immune and stromal cells play a vital role in shaping the tumor microenvironment (TME) and are pivotal in the progression of CRC [18]. These cells, such as T cells and macrophages, exert varying effects on tumor development based on their activation status. They can either support the suppression of tumor growth or facilitate it by instigating inflammation. Moreover, stromal cells not only offer structural assistance to the tumor but also engage in intricate interactions that expedite tumor proliferation and impact the effectiveness of treatments. Researchers are currently studying macrophages and their role in the TME. The percentage and density of tumor-associated macrophages (TAMs) influence the prognosis and resistance to therapies in the context of treatment. TAMs primarily concentrate their efforts on two key functions: promoting immunosuppression and stimulating angiogenesis [19–21]. TAMs play a crucial role in the immune system by contaminating the body's tissues and creating a favorable environment for the proliferation of white blood cells (WBCs) in solid tumors. They have a significant impact on inflammation, which is closely linked to cancer, and they also play a crucial role in controlling the growth and advancement of cancer. Recent research findings have confirmed that TAMs may exhibit either pro-angiogenic or anti-tumorigenic properties, depending on the underlying mechanism [20, 22].

The macrophages, which are part of the various cellular components in the TME, play a significant role in the early stages and subsequent progression of CRC. Macrophages are extremely versatile cells that play a crucial role in fighting infections during the early stages of the immune response. They can also adapt and perform different functions as the immune system develops. One of their primary functions is to maintain tissue balance and reduce inflammation [23–25]. However, TME plays an important role in impairing the function of macrophages, leading to the development of a pro-tumorigenic phenotype that promotes cancer progression. The role of TAMs in promoting and inhibiting CRC highlights the complex relationships between the immune system and tumors. This highlights the importance of considering the TME in studies on cancer progression [25–27].

## Macrophages as silent partners in colorectal cancer progression

### Tumor-associated macrophages in colorectal cancer

Tumor cells and other stromal components release chemokines and growth factors into the microenvironment, which attract macrophages to the tumor site. The chemokine CCL2, also known as monocyte chemoattractant protein-1 (MCP-1), plays a crucial role in attracting monocytes to the tumor site, where they transform into macrophages [28, 29]. The CSF-1 signaling pathway, consisting of CSF-1R and its ligand CSF-1, plays an essential role in regulating the processes that bring in, activate, and polarize macrophages in CRC [30–32]. After they migrate to the tumor area, macrophages move toward the function switching, which occurs due to the microenvironmental phenomenon and complex intercellular signaling. Multiple factors that are connected to the oxygen and glucose levels, as well as the difference in the central cellular metabolism among the tumor cells, contribute to the release of M2 macrophages' pro-tumor characteristics. One can know the state by its characteristics, which include specific markers such as CD163, CD206, and Arginase-1 [33–36]. Unlike M1/M2 model making a compartment for a complex division of macrophages, these cells show interesting diversity of the macrophage characteristics in the TME. TAMs can display various phenotypes, ranging from pro-inflammatory and anti-tumor (as in the case of M1 macrophages) to immunosuppressive, pro-tumor properties (like in M2 macrophages) [30, 37]. The diversity of tumors is influenced by various factors, such as tumor stage, genetic characteristics, and the complex interaction between tumor cells, stromal cells, and immune components [38, 39].

### Pro-tumorigenic roles of TAMs

TAMs perform an essential role in facilitating angiogenesis, the process of creating new blood vessels. This process is critical for promoting the growth and spread of tumors. They release several pro-angiogenic substances, including vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), and matrix metalloproteinases (MMPs), which promote the growth, movement, and creation of blood vessel cells [40–42]. Furthermore, TAMs have the ability to directly interact with endothelial cells and impact their function through the production of cytokines, growth factors, and enzymes that alter the extracellular matrix [43].

TAMs boost the invasive and metastatic capabilities of CRC carcinoma cells through distinct approaches. The organisms generate several proteolytic enzymes, such as

MMPs, cathepsins, and serine proteases, which break down the extracellular matrix and contribute to the invasion of tumor cells [44, 45]. TAMs also release substances that trigger the epithelial-to-mesenchymal transition (EMT) in cancer cells. This biological process is linked to greater invasiveness, stem cell-like properties, and the ability to establish metastases [46, 47]. Additionally, TAMs may speed up the process of tumor cells entering the bloodstream and support the formation of pre-metastatic environments in distant locations, hence promoting metastasis [48–50].

TAMs have an essential effect on the composition of the immune system within the TME. They can suppress the immune response against tumors by releasing immunosuppressive cytokines, such as IL-10 and TGF-β, and attracting regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which further weaken the anti-tumor immune response [38, 51, 52]. In addition, TAMs may hinder the cytotoxic activities of natural killer (NK) cells and T cells by expressing inhibitory ligands, such as PD-L1, and generating reactive oxygen species (ROS) and nitric oxide (NO) [33].

TAMs also have a critical role in preserving the population of cancer stem cells (CSCs), which are accountable for the beginning, promotion, and resistance to the treatment of tumors. CSCs are stimulated to preserve their capacity to self-renew and retain their stem cell properties by triggering the release of multiple molecules such as IL-6, EGF, and Wnt ligands [53, 54]. In addition, TAMs can control the CSC environment by influencing the composition of the extracellular matrix and establishing a favorable milieu that promotes CSC survival and growth [55] (Fig. 1).

The gut microbiota can also influence the systemic immunity by modulating the behavior and polarization of TAMs in TME [56]. Certain microbial metabolites, including short-chain fatty acids, have the potential to enhance anti-tumor immunity by promoting M1 macrophage polarization and inhibiting M2 polarization, the latter being linked to tumor

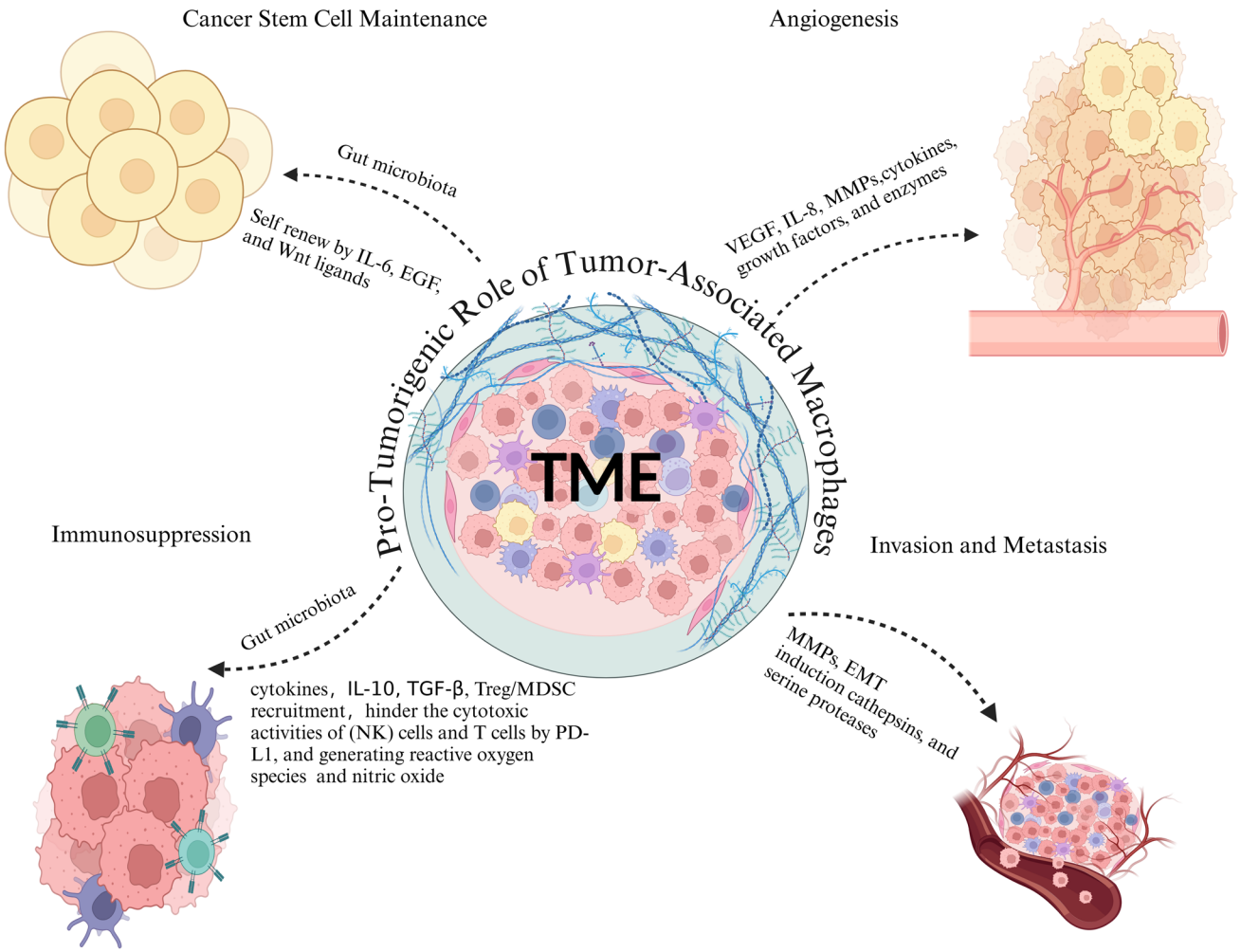


**Fig. 1** Pro-tumorigenic role of tumor-associated macrophages

progression [57]. Dysbiosis in gut flora can alter immune responses, potentially creating an environment that promotes cancer development. Comprehending this relationship may facilitate the development of novel cancer therapies aimed at the gut microbiome [58–60].

## Anti-tumorigenic roles of macrophages

Numerous studies have widely recognized the anti-tumor function of macrophages. Even though TAMs generally promote tumor growth, they can also activate the body's immune response against tumors in early stages and in certain microenvironmental conditions.

Macrophages, being a key component of the body's defense system, exhibit an incredible capacity to recognize and eliminate specific tumor cells using various pathways that ultimately result in cell death [61]. It is well established that these lymphocytes play a crucial role in cancer immunotherapy by being able to internalize tumor-specific antigens and stress-marked molecules, leading to the elimination of the tumor [62, 63]. The macrophage, moreover, can produce ROS, NO and cytotoxic cytokines such as tumor necrosis factor-alpha (TNF-α) that can be dangerous for cancer cells [64, 65]. Although the macrophage is the cornerstone in linking innate and acquired immune responses, its function is mainly limited to a presentation of the tumor-associated antigens and a possible source of danger signaling to the T cells [66]. The process of extracellular delivery of antigens and their presentation to host MHC class I molecules using cross-presentation is possible for the macrophages that are present outside the body [67]. The specific purification procedure initiates the assigned cytotoxic CD8+ T lymphocytes [68–70]. Moreover, the role of macrophages includes the help of T helper cells, by transferring antigens to MHC class II molecules and giving the co-stimulatory signals [71] (Supplementary Fig. S1).

The complicated relationship between the TME and the host immune system influences the phenotype and function of macrophages, which play complex and context-dependent roles in cancer. These roles include their ability to perform anti-tumor actions [40, 72].

## Factors influencing macrophage phenotype and function

The combination of several factors, such as hypoxia, metabolic reprogramming, cytokine and chemokine signaling, and interaction with other immune cells, as well as specific macrophage phenotypes remains intricate to explore [43, 73]. Hypoxia is a condition that quickly forms around a solid tumor for the lack of blood flow. This lack of oxygen affects exosome release and chemokine expression, changing macrophage behavior. Both of these changes significantly impact the recipient cells [73]. The HIF-1α transcription factor which becomes stable subsequently stimulates the transference of macrophages to the pro-tumorigenic phenotype similar to the M2 macrophages [74–77]. Prostaglandin E2 (PGE2) activates anti-inflammatory M2 and inhibits M2 marker gene expression to change macrophage phenotypes. Alterations in mitochondrial function, specifically the collapse of mitochondrial membrane potential, affect these macrophages' transcriptional regulation of voltage-regulated genes [78–80].

Moreover, the metabolic changes, for example, the elevation of glycolysis as well as changes in lipid metabolism, which are induced in TME, also influence the activation and phenotype of macrophages [81].

The cytokine and chemokine environment that determine macrophage phenotypes and functions in the microenvironment. Cytokines, like IL-4, and IL-13, either act to provoke alternative macrophage activation or drive the development of M2-like phenotype. Yet, interferon-gamma (IFN- γ) producing classical activation process shows the tendency to transform M1-like phenotype [82, 83]. Moreover, chemokines, for example, CCL2 and CCL5 can engage positive or negative responses in macrophages that are consistent with different M1/M2 phenotypes [84, 85].

Communication with immune cells of different types, such as T cells, natural-killer cells and cancer-associated fibroblasts (CAFs), can determine macrophage polarization and function in the cancer-unique microenvironment [86, 87]. The intricate interaction between various types of M-RIDs indicates the dynamic nature of these cells which further suggests that focusing on specific pathways and seasonal environment signals is required to regulate the activity of M-RIDs in cancer treatment [88] (Table 1).

## Targeting macrophages: potential therapeutic strategies

Regarding the crucial role of macrophages in facilitating the progression of CRC, directing efforts toward these cells or adjusting their characteristics and functions gives a hopeful treatment strategy. Different approaches have been examined to specifically target macrophages in CRC [21]. These approaches involve inhibiting the recruitment and infiltration of macrophages, reprogramming their characteristics, or selectively removing macrophage populations that promote tumor growth [12, 88, 89] (Table 2).

## Inhibiting macrophage recruitment and infiltration

### Focused targeting chemokine signaling pathways

The research on restraining the number of TAM is one possible prevention measure in the progress of cancer. An effective approach would entail blocking the recruitment and checkmate the movement of macrophages into the TME. Numerous drugs have developed that do spend on the precise moment when key chemokine regulating routes very powerfully affect macrophage aggregation.

CCL2 inhibitors are drugs that are made to interfere with the function of the chemokine CCL2 (C-C motif chemokine ligand-2). CCL now has the property that it interacts with monocytes and encourages these monocytes to move to the tumor site where they then become macrophages. Various experimentations both preclinical and clinical have shown the drug that exclusively inhibits CCL2 or its receptor CCR2 work. Thrombus Carlumab, a kind of antibody that is focused on this CCL2 and CNTO888, a smelly which perpetuates the pathway of CCL2, have been studied in different types of cancer, such as CRC [90–92].

The signal transduction of the Colony-Stimulating Factor 1 receptor (CSF-1R) is pivotal for the survival growth and the polarization of the macrophage. PLX3397 and BZL945, two small molecule inhibitors of CSF-1R, have had favorable effects against cancers of the colon in preclinical models through the regulation of macrophages [93–95].

### Inhibiting the activity of adhesion molecules and integrins

Macrophages depend on particular adhesion molecules and integrins to move and penetrate the TME. Targeting these compounds has the potential to hinder the recruitment and functioning of macrophages. Antibodies that target integrins, specifically αvβ3 and α4β1, have demonstrated potential in preclinical investigations by suppressing the infiltration of macrophages and decreasing tumor growth and metastasis [96–98].

Researchers have investigated small molecule inhibitors that specifically target adhesion molecules and integrins, including RGD (Arg-Gly-Asp) peptides and disintegrants, as potential methods to disrupt the recruitment and function of macrophages [99] (Fig. 2).

### Transforming macrophages to exhibit tumor fighting abilities

The macrophages suggest that the conversion of these deadly cells into potential anti-cancer cells could be an efficient way of utilizing the anti-tumor immunity of macrophages. One stratagem entails synthesizing TLR agonist which is soluble factor that provides essential information about invading organisms and stimulate the macrophages in the mononuclear phagocyte system. Studies have shown that the drugs Resiquimod (an agonist of TLR7/8) and Maraviroc work well to fight tumors and boost the M1-like polarization [100–102]. Studies have been performed on TLR9 agonists, especially CpG ODN which has been usually found with other drugs that affect macrophage reprogramming and enhance the body's capacity to battle tumors [103–105].

Some therapies based on medications can attack the CD40 protein, which is the part of tumor necrosis factor receptor superfamily and is also present in different types of immune cells, for example, macrophages. CP-870,893 and APX005M have recently completed clinical trials as double agonistic anti-CD40 antibodies for solid tumors. These studies have demonstrated that the murine antibodies can have a high affinity for the CD47 surface receptor of TAMs which leads to their modification and ultimately improves the body's immunity against cancers [106–109]. Moreover,

**Table 1** Factors influencing macrophage phenotype and function

| Factors | Influence on macrophage phenotype and function | References |
|---|---|---|
| Hypoxia and metabolic reprogramming | Hypoxic circumstances and metabolic alterations in the TME can affect macrophage activation and phenotype, for example, enhanced glycolysis and modifications in lipid metabolism. | [73–77] |
| Cytokine and chemokine signaling | Cytokines such as IL-4 and IL-13 facilitate alternative macrophage activation (M2-like), whereas IFN-γ triggers classical activation (M1-like). Chemokines such as CCL2 and CCL5 can also affect macrophage phenotypes. | [83, 84] |
| Interactions with other immune cells | Associations involving T cells, natural-killer cells, and cancer-associated fibroblasts within the TME might influence macrophage polarization and activity. | [88, 89] |
| Tumor microenvironment complexity | The TME's complex interactions between macrophages and other immune cells show their dynamic character, requiring specialized pathways and external signals to regulate their activity in cancer treatment. | [43, 73, 88] |

TME; tumor microenvironment; IL-4; Interleukin-4, CCL2; chemokine ligand-2, IFN-γ; Interferon gamma

**Table 2** Therapeutic strategy of TAMs

| Therapeutic strategy | Description/examples | Challenges and considerations | References |
|---|---|---|---|
| Inhibiting Macrophage Recruitment and Infiltration | Blocking chemokine signaling pathways (e.g., CCL2 inhibitors, CSF-1R inhibitors)<br>Targeting adhesion molecules and integrins (e.g., αvβ3 and α4β1 integrin antibodies, RGD peptides) | Specificity to avoid affecting beneficial macrophage populations or other immune cells.<br>Tumor heterogeneity and potential resistance mechanisms. | [90–92] |
| Transforming Macrophages to Exhibit Anti-Tumor Functions | TLR agonists (e.g., resiquimod, CpG ODN).<br>CD40 agonists (e.g., CP-870,893, APX005M)<br>Modulating macrophage metabolism (e.g., 2-DG, 3-BP, metformin) | Complexity of macrophage phenotypes and dynamic responses to the TME.<br>Potential off-target effects and toxicities. | [99, 100, 103] |
| Direct Targeting of Tumor-Promoting Macrophages | Antibodies targeting CSF-1R (e.g., cabiralizumab) or CCR2.<br>Nanoparticle-based delivery of toxins (e.g., clodronate, bisphosphonates) | Improving specificity and reducing off-target effects. Overcoming tumor heterogeneity and resistance mechanisms | [117–119] |
| Combination with Other Therapeutic Modalities | Combining with chemotherapy, immunotherapy, radiotherapy or gut microbiota | Addressing tumor heterogeneity and resistance mechanisms. Improving preclinical models to better represent the human TME. Identifying reliable biomarkers for patient stratification and response prediction, enhancing the growth of beneficial microbiota. | [126–135, 143, 144, 160] |
| Monitoring and Overcoming Therapeutic Resistance | Understanding and overcoming resistance mechanisms (e.g., compensatory signaling pathways, myeloid cell infiltration) | Maintaining a balance between therapeutic efficacy and potential adverse effects.<br>Developing strategies to overcome resistance and sustain therapeutic responses | [146–149, 152] |

This table shows the various potential therapeutic strategies for targeting macrophages in colorectal cancer. CCL2; C-C chemokine ligand-2, CSF-1R; Colony-stimulating factor 1 receptor, αvβ3; Alpha-v beta-3, RGD peptides; Arginylglycylaspartic acid peptides, CpG ODN; CpG oligodeoxynucleotide, CD40; Cluster of differentiation 40, CCR2; C-C chemokine receptor type 2, TME; tumor microenvironment.

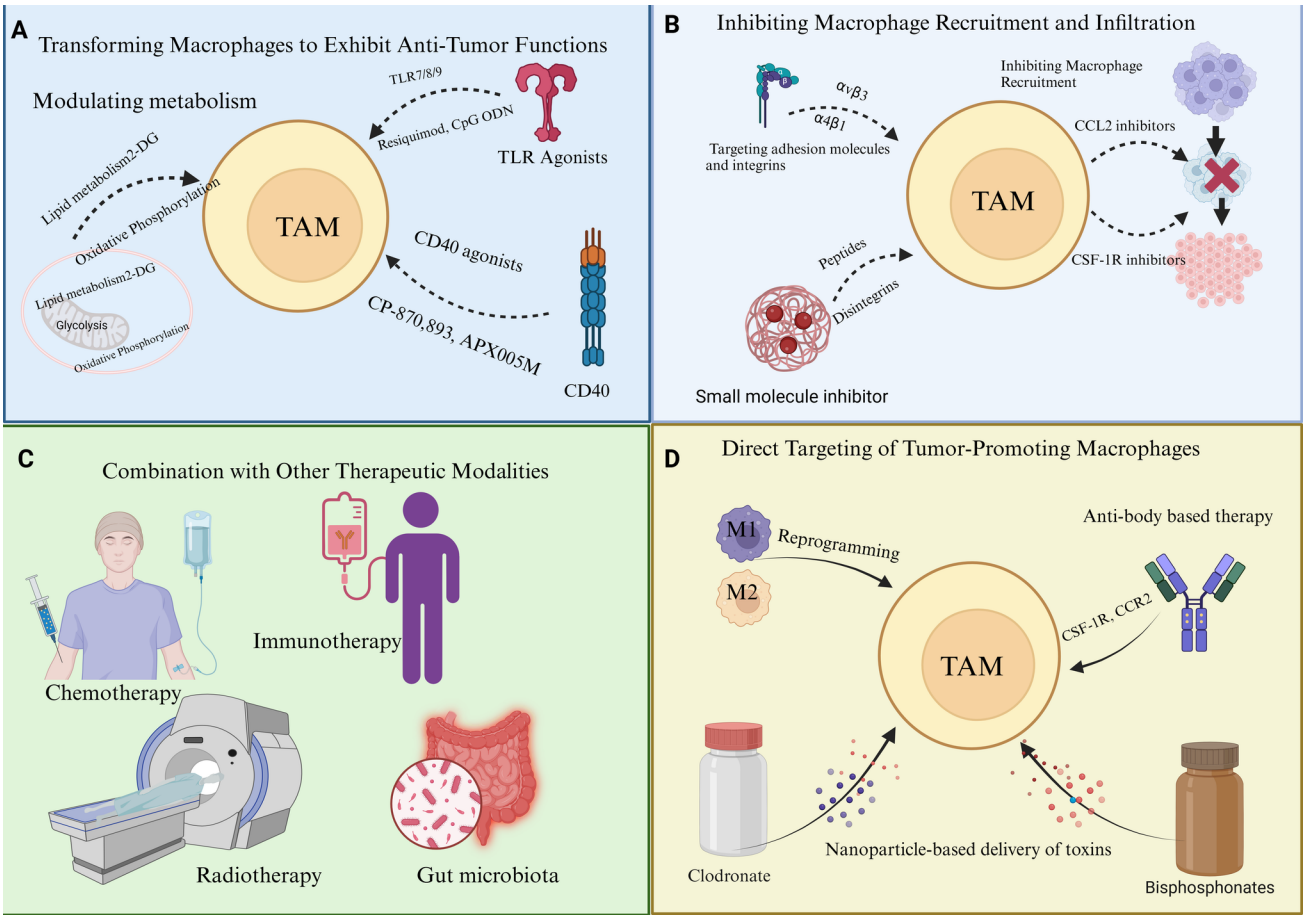


**Fig. 2** Targeting macrophages for potential therapeutic strategies; **A** transforming macrophages to exhibit anti-tumor functions; **B** inhibiting macrophage recruitment and infiltration; **C** combination with other therapeutic modalities; **D** direct targeting of tumor-promoting macrophages

genetic investigators have analyzed gene therapy strategies which implies vectors that express CD40 ligand (CD40L) to cause CD40 signaling and remodel macrophages [110, 111]. Also, modulating macrophage metabolism pathways, for example, glycolysis, oxidative phosphorylation, and lipid metabolism, through which they are turned into an anti-tumor stat has been demonstrated as being a useful approach. As examples, compounds consisting of 2-deoxyglucose (2-DG), 3-bromopyruvate (3-BP), agents inhibiting glycolytic enzymes and metformin and phenformin causing ATP production using oxidative phosphorylation were reported to be promising results [112, 113]. In addition, the inhibition of important enzymes involved in lipid metabolism, such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), has demonstrated potential in controlling the characteristics of macrophages and improving the body's ability to fight against tumors [114–116] (Fig. 2).

## Direct targeting of tumor-promoting macrophages

Reprogramming is designed to alter the functional behavior of the M1-like macrophages, whereas the other strategy intends to eliminate the M2-like pro-tumorigenic macrophage population within the microenvironment. Researchers have studied antibody-based therapies like cabiralizumab that are selectively targeted to CSF-1R antibodies to eradicate pro-tumorigenic macrophages and thus promote anti-tumor response. Successful effects demonstrated in both preclinical and clinical studies [117–119]. Besides, scientists pondered the ability to create antibodies which target CCR2 - a receptor for CCL2 - as a way to stop monocytes recruitment process. These monocytes can transform into pro-tumorigenic macrophages in the TME [120].

Nanoparticle-based delivery methods have become an increasingly useful toxin to destroy tumor-promoting macrophages while ensuring minimal damage to other cells. The preclinical testing of liposomal formulations with either clodronate or bisphosphonates that selectively target macrophages has been used to evaluate their efficacy. The

findings of these formulations indicate that they are effective in inhibiting the growth and spreading of tumors [121–123]. Besides, nanoparticles are also able to be modified by targeting molecules (antibodies or peptides) to deliver their therapeutic substances to pro-tumorigenic macrophages and bypass other macrophage populations [124–127] (Fig. 2).

## Integration of combination techniques with other therapeutic modalities

Directing therapeutic interventions toward macrophages in CRC holds considerable promise, although various obstacles need to be overcome to implement these approaches in clinical settings successfully. The heterogeneity and flexibility of macrophages are characterized by their varied phenotypes and roles, which can dynamically change in response to signals from the TME [21, 128]. The intricate nature of this situation presents difficulty in creating precise treatments that may efficiently regulate the actions of macrophages without any unexpected side effects [129].

Numerous tactics designed to reprogram or deplete macrophages lack specificity, which means they may have an impact on macrophage populations that are beneficial or other types of immune cells. Enhancing the precision of targeting by creating new substances, such as antibodies or nanoparticles that strongly bind to pro-tumorigenic macrophages, is essential for reducing unintended effects and toxicities [130, 131]. Tumor heterogeneity refers to the presence of varied genetic and molecular characteristics in CRC. This variability can be observed among different patients as well as within the same tumor. The presence of heterogeneity among cells might cause varying reactions to medicines that target macrophages. Additionally, the growth of tumors can give rise to subclones that are resistant to treatment [132–134].

Combining macrophage-targeted therapies with other treatment modalities, such as chemotherapy, immunotherapy, and radiotherapy, may be necessary to achieve the best therapeutic results and overcome resistance mechanisms in the TME [21, 135, 136].

A common limitation of preclinical models is that they cannot faithfully recreate the complexity of the human TME, so there is a risk that the results of the research might not be successfully transferred to clinical applications [137]. The advancement is needed to increase the strength and clinical translation of the models, for instance, patient-derived xenografts and organoids [138]. The progress may improve the accuracy of preclinical studies [139, 140]. Finding reliable biomarkers to categorize patients and predict their responses to drugs targeting macrophages is crucial. It is critical for the development of personalized treatment programs. By utilizing various multi-omics techniques, such as transcriptomics, proteomics, and metabolomics, a comprehensive understanding of the role of macrophages in disease progression can be obtained [141, 142].

Combining the modulation of gut microbiota with targeting TAMs can also offer a promising therapeutic strategy for CRC [59]. This approach aims to enhance beneficial microbial populations, thereby boosting immune responses, reducing inflammation, and concurrently reshaping TAMs toward an anti-tumor phenotype. The synergistic effects of these actions may result in enhanced treatment efficacy and improved patient outcomes [17, 56, 143]. Gut microbiota combination with other strategies such as chemotherapy and immunotherapy also play an important role for CRC therapy [144].

## Monitoring and overcoming therapeutic resistance

Considering the critical roles of macrophages in maintaining a steady homeostatic balance and generating adequate immune responses, it is paramount to closely watch the impact of this therapy that is tailored to target macrophages on the overall functioning of the immune system as well as any negative effects that may be produced [145, 146]. Moreover, it is essential to understand and overcome the factors of the treatment resistance including the compensatory signaling pathways or the infiltration of the myeloid cell populations, to ensure the lasting effects [147–149].

Research currently focused on the creation of drugs which could specifically act on macrophages, the utilization of different ways for the delivery of these chemicals, and the elucidation of the molecular mechanisms that govern the communications between the macrophages and the tumors [136, 150, 151].

Macrophages possess a remarkable capability to penetrate and accumulate within solid tumors, making them extremely attractive for precise drug administration. Methods that involve the incorporation of therapeutic agents into macrophages or the application of nanoparticles derived from macrophages have the potential to improve drug delivery to the tumor location and reduce the impact on the rest of the body [136, 152, 153].

Recent studies highlight the vital role of metabolic reprogramming and epigenetic regulation in influencing macrophage phenotype and function in the TME. Exploring essential metabolic pathways or epigenetic regulators may offer innovative approaches to influencing macrophage behavior and bolstering anti-tumor responses [21, 154–158].

The development of gene editing technologies and cellular engineering approaches has opened the way for exploring the potential of macrophages in cancer treatment. Engineered macrophages can express therapeutic payloads, including cytokines, antibodies, or enzymes [159–161]. They can also be programmed to target specific antigens

or receptors found in tumor cells. These specially designed macrophages can be powerful agents against tumors or transport drugs directly to their targets [162–164].

## Conclusion

Macrophages are essential to CRC progression and growth. Through strategically adjusting their characteristics using specific treatments and different strategies, there is potential for overcoming resistance and enhancing results. Advancements in predictive biomarkers and macrophage-based treatments have the potential to greatly improve the management of CRC and enhance patient survival rates. More research is required in the field of TAMs to explore their role in progression and its implication as CRC therapy.

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## Declarations

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