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Research Progress of Phagocytosis in CRC Therapy

Xinyu Zhang, Na Lu*
State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Carcinogenesis and Intervention, Department of Physiology, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing 211198, Jiangsu, China.

**Author to whom correspondence should be addressed.*

Abstract: In recent years, immunotherapy has demonstrated substantial clinical efficacy in the treatment of colorectal cancer (CRC). However, due to factors such as high heterogeneity and drug resistance of CRC, the incidence and mortality of this disease continue to increase annually. Phagocytosis is involved in the regulation of the immune system and plays a crucial role in the development of CRC. Studies have demonstrated that the combination of phagocytosis-related genes with immunotherapeutic regimens exhibits great potential for cancer treatment. Therefore, exploring the mechanism of action and research progress of phagocytosis in CRC provides new insights for developing novel therapeutic strategies and improving the prognosis of CRC patients. This review will summarize the process of phagocytosis, the current status of CRC immunotherapy, and the research progress of phagocytosis-related checkpoints in CRC, aiming to provide assistance for the clinical treatment of CRC.

Keywords: Colorectal cancer; Macrophage; Phagocytosis

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1. Introduction

Accumulating evidence indicates that the activation characteristics of immune cells within the CRC microenvironment can better predict therapeutic efficacy and survival prognosis for patients, highlighting the importance of the tumor immune microenvironment in CRC progression[1]. Tumor-associated macrophages are among the most abundantly infiltrating immune cells within the CRC microenvironment[2], exhibiting high plasticity and functional diversity[3]. Upon specific stimulation, macrophages can be activated to exert anti-tumor effects by enhancing their phagocytosis of tumor cells. Therefore, a comprehensive and in-depth exploration of the mechanisms underlying macrophage phagocytosis in CRC, along with the identification of reliable prognostic biomarkers, holds profound clinical significance for reducing CRC mortality.

2. Functional Characteristics of Tumor-Associated Macrophages

2.1. Pro-tumoral Effects of Tumor-Associated Macrophages

Tumor-associated macrophages (TAMs) promote tumor proliferation by modulating reactive oxygen species (ROS) and

secreting cytokines like IL-1β, IL-6, and TNF-α[4]. They also drive tumor migration, epithelial-mesenchymal transition (EMT), and invasion via matrix metalloproteinases (e.g., MMP-9), while stimulating angiogenesis through VEGF-α secretion[5]. Furthermore, a complex bidirectional crosstalk exists between TAMs and tumor cells. CRC cells release exosomal miRNAs via the CXCL12/CXCR4 axis to induce pro-tumoral TAM activation (via the PTEN/PI3K/AKT pathway), which in turn enhances EMT and angiogenesis[6]. Additionally, TAM-derived IL-6 promotes tumor EMT (via the JAK2/STAT3/miR-506-3p/FoxQ1 axis), while tumor-secreted CCL2 recruits more TAMs. This creates a vicious positive feedback loop that continuously amplifies tumor progression[7].

2.2. Anti-tumoral Effects of Tumor-Associated Macrophages

Tumor-associated macrophages exert a dual role in cancer: while they can secrete factors to promote tumor progression, they also possess the ability to inhibit tumor growth[7]. The primary anti-tumor mechanism of TAMs is antibody-dependent cellular phagocytosis (ADCP)[8]. During monoclonal antibody therapy, macrophage Fc receptors bind to the antibody's Fc domain, activating downstream immunoreceptor tyrosine-based activation motifs (ITAMs) to trigger tumor cell phagocytosis[9]. However, complex tumor-macrophage interactions and phagocytic checkpoint molecules often suppress this effector function by providing direct inhibitory signals[10]. Consequently, blocking these phagocytic checkpoints has emerged as a vital strategy for reactivating the anti-tumor phagocytic capacity of TAMs.

3. Macrophage Phagocytosis and Its Aberrant Regulation in CRC

3.1. Target Recognition Stage

Macrophage phagocytosis initiates with target recognition, driven by "find-me" signals (e.g., lysophosphatidylcholine, sphingosine-1-phosphate, nucleotides, and Fractalkine/CX3CL1) that guide macrophage chemotaxis[11]. In CRC, chemotherapeutics like oxaliplatin can induce immunogenic cell death, releasing ATP to significantly enhance macrophage recruitment into the tumor microenvironment[12,13]. Upon arrival, macrophages utilize surface receptors (e.g., TIM-4 and LRP-1) to recognize target cell signals (such as phosphatidylserine and calreticulin), thereby initiating the phagocytic program[14,15]. However, CRC cells frequently evade this recognition stage and induce immune tolerance by downregulating surface calreticulin exposure or overexpressing anti-phagocytic signals like CD47 and CD24.

3.2. Phagosome Formation Stage

Upon receptor activation, small GTPases such as Rac1, Cdc42, and ARF6 are activated[16,17], driving the Arp2/3 complex-mediated reorganization of the actin cytoskeleton. This process propels the cell membrane to form pseudopodia that engulf the target cells[18,19]. In CRC cells, the binding of highly expressed CD47 to macrophage SIRPα leads to the phosphorylation of the receptor's intracellular immunoreceptor tyrosine-based inhibitory motifs and the recruitment of SHP-1/2 phosphatases. These phosphatases subsequently dephosphorylate actin-regulatory proteins, thereby preventing cytoskeletal rearrangement and phagosome formation[8]. This molecular mechanism inhibits the extension of pseudopodia and the closure of the phagocytic cup, serving as a critical structural basis for CRC cells to evade phagocytosis.

3.3. Phagosome Maturation and Degradation Stage

Following its formation, the phagosome must fuse with a lysosome to clear the engulfed target via acidification and enzymatic degradation[20]. Studies indicate that the accumulation of lactate within the CRC microenvironment can act as a key signaling molecule. It drives the metabolic reprogramming of macrophages and their polarization toward a pro-tumoral phenotype via the HIF-1α axis, thereby suppressing their normal anti-tumor phagocytosis and degradation functions[21]. Furthermore, anti-inflammatory mediators (such as TGF-β and IL-10) produced during the degradation phase may induce the immunosuppressive polarization of macrophages. This, in turn, promotes the growth and metastasis of CRC, establishing a vicious cycle.

4. Phagocytic Checkpoints and Their Clinical Significance in CRC

4.1. CD47-SIRPα

CD47, a transmembrane glycoprotein widely overexpressed on cancer cells, serves as a critical inhibitory signal. By binding to macrophage SIRPα, it inhibits phagocytosis, facilitates tumor immune evasion, and maintains cancer stemness and immune resistance[22,23]. In CRC, elevated CD47 expression strongly correlates with advanced tumor stage, metastasis, and poor prognosis, establishing it as a valuable diagnostic biomarker[24].Therapeutically, blocking the CD47-SIRPα axis reactivates TAM phagocytosis and impedes tumor growth[25]. Novel targeted strategies have shown significant promise; for instance, the fusion protein SIRPα D1-Fc enhances tumor cell autophagy via the Akt/mTOR/ROS pathway[26], while QPCTL inhibition disrupts CD47-SIRPα binding to further augment macrophage-mediated tumor clearance[27].

4.2. PD-1-PD-L1

Beyond its well-established role in T cells, the PD-1/PD-L1 axis critically regulates the phagocytosis of tumor-associated macrophages[28]. PD-1+ TAMs exhibit a significantly reduced phagocytic capacity against cancer cells[29]. Consequently, PD-1/PD-L1 blockade enhances macrophage-mediated phagocytosis, diminishes tumor growth, and prolongs survival in a macrophage-dependent manner[29]. Because immune checkpoint inhibitors block inhibitory interactions in both T cells and macrophages, combination strategies offer significant therapeutic potential. For instance, CD47/PD-1 bispecific antibodies demonstrate synergistic anti-tumor efficacy[30]. Furthermore, reprogramming TAMs toward an anti-tumor phenotype transcriptionally upregulates PD-L1 via STAT3, which limits the efficacy of monotherapies. Therefore, combining macrophage reprogramming with PD-1/PD-L1 blockade effectively overcomes these compensatory deficiencies, representing a promising novel strategy for cancer therapy[31].

4.3. MHC-I-LILRB1

MHC-I bridges innate and adaptive immunity, but the MHC-I-LILRB1 signaling axis facilitates tumor immune evasion[32]. Specifically, tumor-expressed MHC-I binds to the LILRB1 receptor on macrophages, directly inhibiting macrophage-mediated phagocytosis[33,34]. Although general MHC-I downregulation correlates with poor prognosis[35], blocking the MHC-I/LILRB1 interaction significantly enhances the phagocytosis of CRC cells both in vitro and in vivo. Furthermore, HLA-G, a tolerogenic non-classical MHC-I molecule secreted into the tumor microenvironment, suppresses immune activation and has been targeted by monoclonal antibodies in CRC treatments[36,37]. Given its high expression on CRC cells, targeting MHC-I to reactivate macrophage phagocytosis represents a promising novel strategy for immunotherapy.

4.4. CD24-Siglec-10

CD24 is a heat-stable antigen expressed on innate immune cells[38]. Acting as a “don’t eat me” signal on tumor cells, its binding to the inhibitory receptor sialic acid-binding Ig-like lectin 10 (Siglec-10) on various immune cells can inhibit phagocytosis by phagocytes within the innate immune system[39]. Evidence has demonstrated that CD24 expression is significantly higher in CRC tissues than in adjacent non-tumor tissues, and is positively correlated with the degree of tumor differentiation, lymph node metastasis, and TNM stage, making it a potential biomarker for poor prognosis in CRC[40]. Furthermore, genetic ablation and therapeutic blockade of CD24 or Siglec-10, as well as blocking the CD24-Siglec-10 interaction with monoclonal antibodies, can significantly enhance macrophage-mediated phagocytosis in all CD24-expressing human tumors[40,41]. Therefore, CD24 represents a promising target for cancer immunotherapy.

5. Phagocytosis-Enhancing Strategies for the Treatment of CRC

5.1. Combination Treatment Strategies

To overcome the limited efficacy of phagocytosis checkpoint monotherapies, combination strategies leverage synergistic anti-tumor mechanisms. Pharmacologically, co-administering magrolimab with cetuximab pairs CD47 blockade with

cetuximab-mediated ADCP, demonstrating a favorable safety profile and preliminary efficacy in advanced KRAS wild-type CRC[21]. Additionally, in combination with radiotherapy—which induces immunogenic cell death (ICD) but compensatorily upregulates SIRPα on myeloid cells—SIRP-α blockers can reverse this immunosuppressive feedback. By reducing myeloid-derived suppressor cell (MDSC) recruitment and enhancing CD8+ T cell infiltration, this combined approach successfully converts immunologically "cold" tumors into "hot" ones[42].

5.2. Bispecific Antibodies

To overcome the red blood cell (RBC) toxicity and poor solid tumor targeting of traditional CD47 blockers, innovative bispecific antibodies (BsAbs, e.g., anti-CD47/PD-L1) utilize an asymmetrical design. By pairing a low-affinity CD47 arm with a high-affinity tumor-targeting arm, these BsAbs leverage bivalent avidity to selectively accumulate on tumor cells co-expressing both antigens. This effectively circumvents the RBC antigen sink effect, significantly improving their safety profile[43]. Mechanistically, this dual blockade of the CD47-SIRPα and PD-1/PD-L1 axes bridges innate and adaptive immunity. It directly relieves macrophage inhibition to enhance antibody-dependent cellular phagocytosis, and crucially, promotes post-phagocytic antigen cross-presentation to activate tumor-specific CD8+ T cells[44]. Ultimately, this synergistic, high-efficacy, and low-toxicity approach offers a precise pathway to convert immunologically cold tumors into hot ones.

5.3. Engineered Macrophage Therapy

Addressing the bottlenecks faced by CAR-T therapy in solid tumors—namely, limited infiltration and susceptibility to microenvironmental suppression—engineered macrophages (CAR-M) have established a novel strategy centered on phagocytosis and antigen presentation. Researchers have utilized the chimeric adenoviral vector Ad5f35 to overcome the technical barriers associated with the difficult transduction of primary macrophages, successfully constructing HER2-targeted CAR-Ms. Through the CD3ζ intracellular domain, these engineered cells drive the reorganization of the actin cytoskeleton, enabling the specific phagocytosis of tumor cells. Even within an immunosuppressive microenvironment, they can maintain an anti-tumoral phenotype and activate adaptive T-cell responses via antigen cross-presentation mechanisms[45]. By effectively bridging innate and adaptive immunity[46,47], CAR-Ms hold promise as a next-generation precision treatment strategy to overcome the heterogeneity and drug resistance of CRC.

6. Conclusions and perspectives

As a critical component of the immune response, macrophage phagocytosis is essential for maintaining tissue homeostasis and driving anti-tumor immunity; however, tumor cells often upregulate anti-phagocytic molecules to evade clearance and promote progression. Achieving an optimal anti-tumor response requires carefully navigating the complex network of promoting and inhibitory signals that regulate phagocytosis. As research into CRC deepens, future clinical and translational efforts should focus on integrating phagocytosis-related checkpoints with existing modalities—such as immunotherapy, chemotherapy, and radiotherapy—to develop personalized combination regimens. Simultaneously, elucidating the heterogeneity of tumor-associated macrophages and the regulatory mechanisms of the tumor microenvironment (TME) to develop tumor-specific targeted drugs will ultimately drive CRC treatment toward greater precision and improve patient prognosis.

Disclosure statement

The author declares no conflict of interest.

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