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Research Progress of Macrophage Polarization in the Treatment of Gastric Cancer

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Abstract: ***Gastric Carcinoma (GC) is one of the most common and lethal digestive tract malignancies worldwide, with clinical manifestations including abdominal pain, anorexia, weight loss and fatigue. Despite continuous advancements in diagnosis and treatment methods, the survival rate of patients remains unsatisfactory, and the complex pathogenesis has not been fully elucidated. In recent years, the role of macrophage polarization in tumorigenesis and development has received increasing attention. Studies have shown that macrophage polarization imbalance (particularly the transition from M1 type to M2 type) is closely related to the occurrence, progression and poor prognosis of gastric cancer. Targeting and regulating macrophage polarization, especially reversing the tumor-promoting M2 phenotype of Tumor-Associated Macrophages (TAMs), has become an emerging strategy for the treatment of gastric cancer. This article aims to systematically review the concept of macrophage polarization, its mechanism of action at different stages of the "inflammation-cancer" transformation of gastric cancer, and the research progress and challenges of targeted therapy strategies for gastric cancer based on the regulation of macrophage polarization.***

Keywords: Gastric cancer, Macrophage polarization, Tumor-associated macrophages (TAMs), Tumor microenvironment (TME), Targeted therapy, Immunotherapy.

1. Introduction

Gastric Carcinoma (GC) is the fifth most common malignant tumor worldwide and the third leading cause of cancer-related deaths. There were approximately 950,000 new cases and 680,000 deaths worldwide in 2024 [1]. China is a country with a high incidence of gastric cancer, accounting for about half of the global cases and deaths, with a male-to-female ratio of approximately (2.3-3.6): 1, and it is more prevalent among people aged 40-60. The occurrence of gastric cancer is the result of the long-term combined effects of multiple factors such as genetics, diet (high salt, pickled foods), environment (such as Helicobacter pylori infection). Helicobacter pylori (HP) infection is recognized as an important risk factor for gastric cancer, but the exact carcinogenic mechanism still needs to be further explored. Although progress has been made in the early diagnosis and drug treatment of gastric cancer, the prognosis for patients with advanced gastric cancer remains poor. Studies have shown that immune cells in the Tumor Microenvironment (TME), especially TAMs and their polarization states, play a key role in the occurrence, development, metastasis and drug resistance of gastric cancer [2]. Targeting and regulating TAMs polarization, particularly promoting their transition from immunosuppressive M2 type to anti-tumor M1 type, has emerged as a promising new direction for gastric cancer treatment.

2. The concept of Macrophage Polarization

Macrophages originate from blood monocytes and are important innate immune cells with functions such as phagocytosis and clearance of foreign substances, pathogens, immunomodulation, anti-inflammation, and promoting tissue repair. Macrophage polarization refers to the differentiation of macrophages into activated states with different functional phenotypes under the stimulation of different microenvironmental signals, which reflects their high heterogeneity and plasticity. The classical polarization states are mainly divided into pro-inflammatory M1 type and anti-inflammatory/pro-repair M2 type. The cytokines secreted by macrophages after polarization are crucial in the immune response, and their dysfunction or imbalance of M1/M2 can lead to a variety of diseases, including tumors [3].

2.1 M1-type Polarization

M1-type polarization is mainly caused by pathogen-associated molecular patterns (PAMPs), Such as bacterial lipopolysaccharide LPS) or Th1-type cytokines (such as IFN-γ, TNF-α) induce signaling pathways by activating Toll-like receptors (TLR), nuclear factor κB (NF-κB), and the STAT family (such as STAT1) [4]. M1-type macrophages highly express inducible nitric oxide synthase (iNOS) and secrete pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, IL-23, TNF-α and chemokines CXCL9, CXCL10, CXCL11. Its main functions include: potent bactericidal and pro-inflammatory (directly killing pathogens such as HP by generating reactive oxygen species (ROS) and reactive nitrogen species (RNS, such as nitric oxide NO) [5]; Secreted cytokines recruit and activate other immune cells such as neutrophils and Th1 cells, amplifying the inflammatory response); Enhanced antigen-presenting ability (high expression of MHC-class II molecules and co-stimulatory molecules CD80/CD86, effectively activating T-cell immune responses); Involved in "inflammation-cancer transformation" (in the context of gastric cancer) Excessive activation of M1-type macrophages and their secreted pro-inflammatory factors such as IL-1β, TNF-α, and IL-6 can cause persistent damage to the gastric mucosa (inhibiting mucin expression, disrupting tight junctions, promoting DNA damage/mutation), inducing intestinal metaplasia of the gastric epithelium such as activating CDX2 through STAT3, inhibiting gastric acid secretion and promoting HP colonization, Creating a microenvironment for gastric cancer occurrence.

2.2 M2-type Polarization

M2-type polarization is mainly triggered by signals such as Th2-type cytokines (IL-4, IL-13), immunomodulatory factors (IL-10, TGF-β), glucocorticoids, or vitamin D3 through activation of STAT6 (IL-4R/IL-13R pathway), STAT3 (IL-10R pathway), or SMAD (TG) Pathways such as the F-β pathway are induced. M2-type macrophages highly express arginase-1 (Arg-1), mannose receptor (CD206), scavenger receptor (CD163) and secrete IL-10, TGF-β. Its main functions include: anti-inflammatory and tissue repair (inhibiting excessive inflammatory response, promoting angiogenesis, matrix remodeling and wound healing); Immunosuppressive and tumor-promoting (secreting IL-10, TGF-β to inhibit T cell function; Expression of immune checkpoint molecules such as PD-L1/PD-L2 induces T cell exhaustion; Secreting chemokines such as CCL17 and CCL22 to recruit immunosuppressive cells such as Tregs and MDSCs to jointly shape the immunosuppressive TME; Promoting tumor progression (M2-type TAMs are the main subgroup of gastric cancer TME by secreting angiogenic factor (VEGF, FGF, PDGF), matrix metalloproteinase (MMPs), growth factor (EGF, HGF), and epithelial-mesenchymal transition (EMT) factor (TGF-β), Promote tumor angiogenesis, invasion, and metastasis [6]. The increase in density was significantly associated with larger tumor volume of gastric cancer, diffuse type (Lauren classification), low differentiation, deep invasion, lymph node metastasis, advanced TNM stage, and poor prognosis. A reduced M1/M2 ratio (M2 dominant) is an independent poor prognostic factor for gastric cancer [7]. M2 subtypes can be further subdivided into M2a, M2b, M2c, and M2d subtypes, which are involved in different pathological processes [8]. Notably, M2 type macrophages can undergo reprogramming to M1 type under specific stimuli such as IFN-γ, TLR ligands [9].

3. The Role of Macrophage Polarization in the "inflammation-cancer" Transformation of Gastric Cancer

Gastric cancer follows the evolution pattern of "chronic non-atrophic gastritis → chronic atrophic gastritis → intestinal metaplasia → dysplasia → gastric cancer". During this process, the polarization state of macrophages shows dynamic changes:

3.1 Early Stage of Canceration (chronic gastritis → atrophic gastritis)

At this stage, endoscopic superficial erosion or small ulcer-like depressions of the mucosa (depth not exceeding the submucosa) can be seen, covered with white moss or with petechiae on the surface, with irregular margins, worm-eroded, nodular protrusions or breaks. At this stage, macrophage polarization is mainly M1 type. The key mechanism lies in pathogen (HP) -related molecules (such as LPS) and pro-inflammatory factors (such as IFN-γ, TNF-α) activating NF-κB and STAT1 signaling pathways [10]. M1-type macrophages have a dual role: on the one hand, they clear the pathogen (HP) by generating ROS/RNS for oxidative killing, secreting pro-inflammatory factors (IL-8, IL-12) to recruit neutrophils for synergistic killing, and releasing lysosomal enzymes (such as pepsin B/D) to degrade the outer membrane proteins of HP [11]. On the other hand, mediating glandular destruction and atrophy: ROS/RNS storms cause gastric mucosal epithelial DNA damage (such as the generation of 8-OHdG); Pro-inflammatory factors such as IL-1β inhibit the expression of gastric mucin MUC5AC, exposing the epithelium directly to damaging factors; TNF-α disrupts tight junction proteins (occludin/claudin-4) and increases carcinogenic penetration; IL-6 activates the STAT3 pathway to induce CDX2 transcription factor, promoting the transformation of gastric epithelium into intestinal form (intestinal metaplasia). These factors work together to disrupt the gastric mucosal barrier and promote "inflammation-cancer transformation".

3.2 Transition Period (intestinal metaplasia → dysplasia)

This stage is characterized endoscopically by pale yellow or grayish-white patchy lesions on the mucosa, with fine granular or micronodular changes on the surface, uneven base with erosion or nodular hyperplasia, irregular margin with dike protrusion, and significant congestion and abnormal microvascular morphology. During this period, the immune microenvironment presents a coexistence of M1/M2 type macrophages, with a significant reduction in the proportion of M1 type, and the polarization phenotype shifts to M2 dominant [12]. The key pathways driving this shift include: 1. TGF-β/SMAD pathway: TGF-β secreted by damaged epithelial cells and fibroblasts activates SMAD signaling, inhibits the expression of M1 markers (such as iNOS), and induces the expression of M2 markers (such as Arg1). 2. IL-4/IL-13/JAK-STAT6 pathway: IL-4 and IL-13 secreted by Th2 cells activate JAK-STAT6 signaling and upregulate the expression of M2 characteristic genes (such as Arg1, Fizz1, Ym1/2, Mrc1), endowing macrophages with anti-inflammatory and tissue repair functions [8]. 3. Hypoxia /HIF-1α pathway: The hypoxia microenvironment upregulates hypoxia-inducible factor-1 α (HIF-1α), enhances the glycolytic ability of macrophages, and maintains their pro-repair M2 phenotype.

3.3 Cancerous Phase (intraepithelial neoplasia → invasive carcinoma)

At this stage, endoscopically, the mucosal color is often grayish-white, pale or dark red, with extensive superficial erosion, microulcers or scattered petechiae visible on the surface. If an ulcer is formed, the margin is a "dam-like" bulge, the texture is hard, brittle and prone to bleeding, the mucosa is stiff and inelastic, the folds are interrupted or clubbed, and the boundary is indistinct. At this stage, M2-type tumor-associated macrophages (TAMs) are significantly enriched and functionally dominant in the tumor microenvironment (TME). M2-type TAMs drive tumor progression through multiple mechanisms:

3.3.1 Mediating immunosuppression

Secreting immunosuppressive factors IL-10, TGF-β, arginase-1 (Arg-1), inducing T cell exhaustion; Expressing immune checkpoint molecules PD-L1/PD-L2, inducing apoptosis of T cells by binding to PD-1 [13]; Secrete chemokines such as CCL17 and CCL22, recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs),

and strengthen the immunosuppressive microenvironment.

3.3.2 Promote angiogenesis

Paracrine vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and matrix metalloproteinases (MMPs) promote endothelial cell proliferation, migration, and lumen formation, induce abnormal tumor neovascularization, and provide nutrients and oxygen for tumors [14]. Secrete tumor-derived Angiopoietin-1 further stabilizes neovascularization.

3.3.3 Drive tumor proliferation, invasion and metastasis

Secreting TGF-β, epidermal growth factor (EGF), etc. Induce epithelial-mesenchymal transition (EMT) in tumor cells, enhancing migration and invasion ability [15]; Secrete MMPs and cathepsin to degrade the basement membrane and extracellular matrix (ECM), opening up pathways for tumor cell invasion and metastasis; Secrete specific chemokines (such as CCL2, CCL18, CCL22) to mediate the metastasis and colonization of gastric cancer cells to the peritoneum, liver and other sites.

3.3.4 Mediating therapeutic resistance

Chemotherapy/immunotherapy resistance: Secretion of IL-10 and TGF-β activates pro-survival signaling pathways such as PI3K/Akt and NF-κB within tumor cells, enhancing resistance to chemotherapy drugs such as 5-fluorouracil and cisplatin, as well as PD-1/PD-L1 inhibitors. Secretion of hepatocyte growth factor (HGF) activates the MET pathway in tumor cells, leading to escape from targeted therapies such as EGFR inhibitors.

Radiotherapy resistance: Eliminate apoptotic cell debris produced by radiotherapy, reduce the release of pro-inflammatory mediators such as high mobility group protein B1 (HMGB1), and weaken the anti-tumor immune activation induced by radiotherapy.

Specific targeted resistance: Such as HER2-positive gastric cancer cells secreting microbubbles carrying glutaminase 1 (GLS1) through the CDC42-dependent pathway, reprogramming glutamine metabolism in macrophages, promoting their polarization to M2 and enhancing angiogenic function, leading to resistance to trastuzumab.

4. The Core Strategy of Gastric Cancer Treatment

Targeting macrophage polarization is to inhibit macrophage polarization to pro-tumor M2 type or reprogram them to anti-tumor M1 type, mainly targeting key signaling pathways that regulate the positive feedback loop between GC cells and TAMs (such as CXCL8/CXCR1/2, JAK/STAT1, IL-10, NF-κB).

4.1 Inhibition of the pro-M2 Polarization Signaling Pathway

4.1.1 CSF-1/CSF-1R axis blockade

Colony-stimulating factor-1 (CSF-1) and its receptor (CSF-1R) signals promote the recruitment, survival, and M2 polarization of TAMs [16]. Block the pathway using small molecule inhibitors (such as Pexidartinib/PLX3397, BLZ945, PLX7486) or monoclonal antibodies (such as Emactuzumab/ RG7155, Cabiralizumab/FPA008) Effective reduction of TAMs, inhibition of M2 polarization, enhancement of T-cell immunity in preclinical gastric cancer models. Clinical studies have shown its potential. For example, a Phase II study in combination with PD-1 inhibitors for gastric cancer showed an objective response rate (ORR) of 34%, significantly higher than 18% with PD-1 monotherapy.

4.1.2 CCL2/CCR2 axis blockade

CCL2 (MCP-1) mediates the recruitment of monocytes to the TME by binding to the CCR2 receptor, which then differentiates into tumor-promoting M2-type TAMs [17]. The application of CCR2 small molecule antagonists (such as PF-04136309, CCX872) or anti-CCL2 /CCR2 antibodies can inhibit monocyte infiltration, reduce TAMs density and reverse immunosuppression. In preclinical models of gastric cancer, it has shown effects of inhibiting tumor growth and improving prognosis. CCX872 also shows potential in clinical studies of other cancer types, such as pancreatic cancer (NCT02345408, NCT03778879).

4.1.3 Inhibition of the IL-4/IL-13/STAT6 pathway

IL-4 and IL-13 are classic M2 polarization factors that exert their effects by binding to IL-4Rα and activating STAT6 [18]. Targeting inhibition of this pathway (such as the application of IL-4Rα -blocking monoclonal antibody Dupilumab or STAT6-specific inhibitor AS1517499) can interfere with the M2 polarization signal of TAMs. Although direct research on gastric cancer is insufficient, preliminary results of AS1517499 in gastric cancer models suggest that it can inhibit M2-TAMs and enhance anti-tumor immunity.

4.1.4 Inhibition of IL-10/STAT3 pathway

IL-10 is a potent immunosuppressant that promotes M2 polarization and immunosuppressive function of macrophages by activating STAT3 [19]. The use of STAT3 inhibitors (such as WP1066, Napabucasin) or antibodies/ antagonists targeting IL-10/IL-10R can suppress the immunosuppressive activity of TAMs and may facilitate their transition to a pro-inflammatory phenotype. STAT3 inhibitors have shown efficacy in preclinical studies of a variety of tumors, including gastric cancer [20].

4.2 Reprogramming the TAMs Phenotype

4.2.1 CD40 agonists

CD40 is a member of the TNF receptor superfamily, and its agonists (such as Selicrelumab/RO7009789, APX005M) can activate antigen-presenting cells (including macrophages), induce their differentiation into M1-like phenotypes, enhance antigen-presenting ability and pro-inflammatory factor secretion, and activate T-cell responses [21]. It has shown potential in gastric cancer models and early clinical trials (often in combination with other immunotherapies), such as

Selicrelumab combined with chemotherapy achieving a disease control rate (DCR) of 58% in patients with advanced gastric cancer.

4.2.2 TLR receptor agonists

Targeting Toll-like receptors (such as TLR3, 4, 7/8, 9) can induce TAMs to polarize towards pro-inflammatory M1 phenotypes [22]. Synthetic agonists (such as TLR3 agonist Poly I:C, TLR4 agonist MPLA, TLR7/8 agonist Imiquimod, TLR9 agonist CpG ODN like SD-101) can prompt TAMs to secrete pro-inflammatory factors such as TNF-α, IL-12, IL-6, etc. It enhances its ability to phagocytize tumor cells and activates adaptive immunity. Often administered intratumoral or systemic, and in combination with other therapies. A phase II study of gastric cancer showed that the TLR9 agonist CpG ODN effectively promotes M1 polarization in TAMs by inducing IFN-α.

4.3 Combination Therapy Strategies

4.3.1 Combination of immune checkpoint inhibitors

(1) PD-1/PD-L1 inhibitors + M2-type TAM inhibitors

For example, PD-1/PD-L1 antibodies (like Pembrolizumab, Atezolizumab) relieve T-cell suppressive signaling, combined with CSF-1R inhibitors (such as Pexidartinib) reduce the number or function of immunosuppressive TAMs and remodel the TME [23]. Clinical trials of Pexidartinib in combination with Atezolizumab have been conducted in multiple solid tumors to explore synergistic effects.

(2) PD-1/PD-L1 inhibitors + TAMs reprogramming agonists

Such as PD-1 antibody Pembrolizumab in combination with TLR9 agonist SD-101. Agonists induce TAMs to shift from M2 to M1. Clinical studies showed that the combination therapy had an objective response rate (ORR) of up to 44%, significantly better than Pembrolizumab monotherapy (ORR 24%).

4.3.2 Chemotherapy-synergistic

1) M2 inhibitors + chemotherapy

CSF-1R inhibitors (such as Pexidartinib) weaken TAMs mediated immunosuppression in combination with standard chemotherapy drugs (such as Cisplatin) directly kill tumor cells and improve the immune microenvironment.

2) Signaling pathway inhibitors + chemotherapy

STAT3 inhibitors (such as Napabucasin) target survival-promoting and immunosuppressive signaling nodes, combined with chemotherapy drugs (such as Paclitaxel), aim to enhance the effect of chemotherapy.

3) Immune agonists + chemotherapy (inducing immunogenic cell death, ICD)

TLR agonists (such as CpG ODN) or CD40 agonists activate innate immune/antigen-presenting cells (APCs) in combination with chemotherapy drugs that induce ICD to release tumor antigens (such as Oxaliplatin). This strategy takes advantage of chemotherapy-releasing antigens and the strong activation of APCs (including DCS and some TAMs) by immune agonists, significantly enhancing their antigen-presenting ability and co-stimulatory signaling, thereby more effectively initiating T-cell anti-tumor immune responses and generating strong synergies.

4.3.3 Radiotherapy combination

In addition to directly killing tumor cells, local radiotherapy induces the release of factors such as CCL2, recruiting monocytes to differentiate into tumor-promoting M2-type TAMs at the tumor site, a process that may weaken the effect of radiotherapy or even promote metastasis [3]. Therefore, radiotherapy combined with CSF-1R inhibitors or CCR2 antagonists aims to block radiotherapy-induced TAMs recruitment and enhancement of the immunosuppressive microenvironment, and may suppress distant metastasis (abscopal effect).

4.3.4 Nanotechnology enhances drug targeting and efficacy

Nanocarriers (such as supramolecular nanoparticles DSN, nanocomplexes) have unique advantages in improving drug targeting, solubility, stability, and tumor tissue enrichment [24]. Strategies include targeted delivery and combined inhibition (e.g., DSN loaded with dual-kinase inhibitors that can simultaneously target and inhibit the CSF1R and MAPK signaling pathways, which can efficiently and persistently vertically suppress key tumor-promoting signals and significantly enhance the repolarization efficiency of M2-type TAMs to the anti-tumor M1 phenotype); Remodeling the tumor microenvironment like designing nanoplatforms that can co-deliver multiple therapeutic agents (such as the natural active molecule baicalin, tumor antigens, immunostimulants) to M2-like TAMs, which can not only effectively induce the reversal of M2 to M1 phenotype, but also actively reshape the immunosuppressive TME, relieve immunosuppression and promote tumor clearance).

4.3.5 Targeted therapy of Traditional Chinese medicine

Traditional Chinese medicine has unique value in preventing tumorigenesis, reducing the toxicity of radiotherapy and chemotherapy, enhancing efficacy, and reducing recurrence and metastasis, and its anti-cancer mechanism is closely related to regulating macrophage polarization. A variety of traditional Chinese medicine components and compound prescriptions regulate polarization by influencing different signaling pathways: Promoting M1 polarization/inhibiting M2 polarization: Single drug component: Baicalin (activating the JAK2-STAT1 pathway to promote M1); Atractylodes II (reduces p-PI3K to promote M1) [25]; Dendrophenol (inhibits M2 polarization); Polygonatum (inhibits AMPK/PDH pathway, inhibits M2 polarization and ATP production); Sinomenine (inhibits STAT6/C/EBPβ phosphorylation and IL-6, inhibits M2 polarization) [26]; Curcumin (inhibits the TLR4-MAPK/NF-κB pathway, inhibits overactivation of M1) [27]. Compound preparation: Linggui Zhugan Decoction drug-containing serum (promotes M2 polarization, reduces inflammation) [28]; Spleen-strengthening, stasis-resolving

and Detoxifying Formula (regulating the PKA/NLRP3 pathway, inhibiting pyroptosis of macrophages, reducing infiltration) [29]. TCM offers a multi-target intervention strategy for the prevention and treatment of gastric cancer, but its specific mechanism of action, active ingredients and clinical efficacy need to be studied in depth.

5. Prospects and Challenges

5.1 Future Outlook

5.1.1 Optimize combination strategies

Explore the best combinations of TAMs targeted therapy with immune checkpoint blockade, chemotherapy, radiotherapy, targeted therapy, and different mechanism of action immunomodulators (such as other agonists/inhibitors, cell therapy) in order to generate synergistic effects and overcome drug resistance.

5.1.2 Precision medicine and biomarkers

Discover specific biomarkers (such as TAMs surface markers, specific gene/protein expression profiles, circulating factors, radiomics features) that can predict TAMs polarization status, function, treatment response, and prognosis for patient stratification and individualized treatment decisions.

5.1.3 Artificial Intelligence and multi-omics Integration

Applying artificial intelligence (AI) and machine learning techniques to integrate multi-dimensional data such as genomics, transcriptomics, proteomics, metabolomics, microbiome, and radiomics to construct models for predicting TAMs polarization dynamics, TME status, and treatment response to guide precise intervention.

5.1.4 Novel Targets and drug development

Continuously delve into the TAMs polarization regulatory network, identify new key targets and signaling pathways, and develop more selective and potent drugs (such as bispecific antibodies, PROTAC degraders).

5.2 Existing Challenges

5.2.1 Tumor and TME heterogeneity

The high heterogeneity (intratumoral/intratumoral) of gastric cancer and the spatiotemporal dynamics of TAMs polarization state increase the complexity and difficulty of targeted therapy.

5.2.2 Drug Delivery and targeting Efficiency

How to deliver drugs efficiently and specifically to specific TAMs subpopulations within the TME and overcome immunosuppressive barriers remains a technical bottleneck.

5.2.3 Preclinical model limitations

Existing models (cell lines, mouse models) have difficulty fully simulating the complexity of human gastric cancer TME and the interaction between TAMs and the host immune system. Optimizing organoid co-culture models, humanized mouse models, etc. is crucial for improving the predictability of clinical translation.

5.2.4 Safety considerations

Systemic regulation of macrophage function may affect systemic immune homeostasis, and potential side effects (such as excessive inflammation, autoimmune responses, tissue damage) need to be closely monitored.

5.2.5 Depth and standardization of mechanisms in Traditional Chinese medicine

Traditional Chinese medicine has complex components, and its specific molecular mechanisms for regulating macrophage polarization, active ingredients, optimal doses, and standardized preparations require more in-depth basic and clinical research for verification.

6. Conclusion

Macrophage polarization is a core immune event in the occurrence and development of gastric cancer. During the progression from chronic inflammation to gastric cancer, the state of macrophage polarization shows a dynamic change from M1 dominance to M1/M2 coexistence, and eventually to M2-type TAMs. M2-type TAMs are a key driver of gastric cancer progression by mediating immunosuppression, promoting angiogenesis, driving tumor invasion and metastasis, and inducing therapy resistance. Targeting and regulating macrophage polarization, particularly by suppressing pro-M2 signaling or inducing repolarization to anti-tumor M1 type, offers a promising new strategy for gastric cancer treatment. The current research has involved blocking key pathways (CSF-1R, CCL2/CCR2, IL-4R/STAT6, IL-10/STAT3), using immunoagonists (CD40, TLR), developing nanodelivery systems, and tapping into the treasure trove of traditional Chinese medicine, and has shown potential in preclinical and early clinical studies. Combination therapy strategies (especially in combination with immune checkpoint inhibitors, chemotherapy, and radiotherapy) are expected to overcome the limitations of monotherapy and improve efficacy. However, issues such as tumor heterogeneity, drug delivery efficiency, limitations of preclinical models, and the depth of mechanisms of traditional Chinese medicine remain current challenges. Future research needs to focus on developing more precise and efficient targeting strategies, exploring reliable biomarkers, using AI to integrate multi-omics data to guide individualized treatment, and clarifying the mechanisms of action of traditional Chinese medicine. A deeper understanding of the mechanism of macrophage polarization in gastric cancer not only enriches the theory of gastric cancer pathogenesis but also lays a solid foundation for the development of new and effective prevention and treatment strategies.

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