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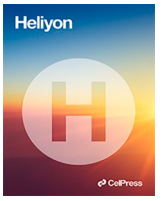

Review article

Tumor-associated macrophages affect the treatment of lung cancer

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ABSTRACT

As one of the most common malignant tumors in the world, lung cancer has limited benefits for patients despite its diverse treatment methods due to factors such as personalized medicine targeting histological type, immune checkpoint expression, and driver gene mutations. The high mortality rate of lung cancer is partly due to the immune-suppressive which limits the effectiveness of anti-cancer drugs and induces tumor cell resistance. The currently widely recognized TAM phenotypes include the anti-tumor M1 and pro-tumor M2 phenotypes. M2 macrophages promote the formation of an immune-suppressive microenvironment and hinder immune cell infiltration, thereby inhibiting activation of the anti-tumor immune system and aiding tumor cells in resisting treatment. Analyzing the relationship between different treatment methods and macrophages in the TME can help us better understand the impact of TAMs on lung cancer and confirm the feasibility of targeted TAM therapy. Targeting TAMs to reduce the M2/M1 ratio and reverse the immune-suppressive microenvironment can improve the clinical efficacy of conventional treatment methods and potentially open up more efficient combination treatment strategies, maximizing the benefit for lung cancer patients.

1. Introduction

According to the 2020 global statistics on cancer incidence and mortality, lung cancer accounted for 11.4 % of all cancer cases, making it the second most common malignancy after breast cancer. It remains the leading cause of cancer-related deaths in both males and females worldwide, accounting for 18 % of total cancer deaths [1]. Under normal circumstances, the human immune system is capable of effectively recognizing and eliminating malignant tumor cells. However, in long-term pathogenic factors and immune system abnormalities, the host's immune system surveillance may develop loopholes. These loopholes include upregulation of inhibitory immune checkpoints, expansion of local immune-suppressive microenvironments, and dysregulated T cell signaling that triggers functional abnormalities. In such an environment, tumor cells can increase unchecked [2].

Macrophages play a crucial role in the process of immune system surveillance. Macrophages are immune cells first discovered by

Abbreviations: Epithelial-mesenchymal transition, (EMT); Tumor microenvironment, (TME); Tumor-associated macrophages, (TAMs); Small cell lung cancer, (SCLC); Non-small cell lung cancer, (NSCLC); Colony-stimulating factor-1, (CSF-1); Toll-like receptor, (TLR); Vascular endothelial growth factor, (VEGF); Immune checkpoint inhibitors, (ICIs); Cytotoxic T lymphocytes, (CTLs); Radiation therapy, (RT); Signal regulatory protein alpha, (SIRP1α); Inducible nitric oxide synthase, (iNOS); Stimulator of interferon genes, (STING); Hydroxychloroquine, (HCQ); Dihydroartemisinin, (DHA); Chloroquine, (CQ).

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Professor Metchnikoff, with phagocytic cell function [3]. They play an important role in nonspecific and specific defense mechanisms. They are essential for the proper functioning of immune surveillance mechanisms. Macrophages possess the ability to detect and engulf abnormal or cancerous cells through a process called phagocytosis. They can also present antigens derived from these cells to other immune cells, thereby initiating an immune response against the tumor cells. Additionally, macrophages contribute to the regulation of the tumor microenvironment by releasing various cytokines and chemokines that can either promote or inhibit tumor growth. Overall, macrophages play a pivotal role in immune surveillance and the control of tumor development [2]. Macrophages produce a range of pro-inflammatory cytokines that can induce stem cell-like characteristics in tumor cells, promoting their growth and proliferation. Increasing evidence suggests that macrophages constitute a prominent immune cell population in lung cancer, playing critical roles at every stage of lung cancer progression. The tumor microenvironment (TME) has been shown to play a significant role in the pathogenesis of lung cancer. The TME is a heterogeneous collection consisting of extracellular matrix, fibroblasts, and perivascular cells, but most importantly, it is enriched with highly active immune cells. Macrophages in the TME are called tumor-associated macrophages (TAMs) [4]. TAMs can be activated by different factors to exhibit two phenotypes with vastly different effects: the M1 phenotype promotes inflammation and inhibits tumor growth, while the M2 phenotype is anti-inflammatory and suppresses immune function. They participate in physiological and pathological reactions by secreting relevant cytokines and chemokines [5].

The high plasticity of TAMs determines that macrophages will not stubbornly adhere to their original phenotypes. Upon disturbance, macrophages undergo phenotypic changes. Different tissue sites of the tumor can exhibit completely different TAM infiltration densities. Additionally, TAM infiltration density can change during the progression of malignant tumors, with a higher density of M2 phenotype macrophages, which promote tumor effects, often found in late-stage malignant tumors compared to M1 phenotype macrophages. Considering the functional characteristics of different macrophage phenotypes and their roles in tumor development, targeting the modulation of TAMs in the TME to deplete the immunosuppressive M2 phenotype or reprogram them into the M1 phenotype seems to be beneficial for cancer patients.

In recent years, with the maturity of immune therapy for cancer treatment, TAMs have received increasing attention as the main culprits involved in the formation of TME. Targeted therapy strategies aimed at specifically modulating macrophages within the TME have also gained prominence. This review primarily discusses the classification, polarization, and functions of TAMs, as well as their interplay with lung cancer therapeutic interventions. It aims to enhance our understanding of TAMs' impact on lung cancer and assess the feasibility of TAM-targeted therapies. By targeting TAMs to reduce the M2/M1 ratio and reverse the immunosuppressive microenvironment, this approach has the potential to improve the clinical efficacy of conventional therapies and may pave the way for more effective combination treatment strategies, ultimately maximizing the benefit for lung cancer patients.

2. The origin, classification and function of TAMs

Macrophages are immune cells derived from hematopoietic stem cells in the bone marrow. Before differentiating into macrophages within local tissues, they exist as circulating monocytes in the peripheral blood. Monocytes migrate to different tissues through circulation and then undergo development and differentiation into tissue-specific macrophages [6]. However, with the advancement of macrophage research, an increasing number of studies have revealed that macrophages do not solely originate from bone marrow hematopoietic stem cells, but also originate from the embryonic yolk sac. These specific macrophages are referred to as "resident" macrophages. Tissue "resident" macrophages include alveolar macrophages, epidermal Langerhans cells, brain microglia, liver Kupffer cells, and more [7].

The current understanding suggests that within the TME, immune cells are abundant, with TAMs typically being the most numerous. Initially, TAMs were believed to have a suppressive role in tumor development. However, with the advent of new technologies, analysis of mouse models and clinical lung cancer samples has uncovered the complex functions of TAMs. Initially, TAMs were simply considered as macrophages present in the TME, without further differentiation based on different phenotypes. To explore whether macrophages have diverse roles in cancer, researchers have discovered, through the construction of mouse models, that there are distinct phenotypes and functions exhibited by macrophages within the TME. They found that macrophages are capable of killing tumor cells through arginine metabolism, and further investigation revealed that macrophages eliminate tumor cells via the production of nitric oxide, which is a byproduct of arginine metabolism. Consequently, inducible nitric oxide synthase (iNOS) was discovered to play a role in activated macrophages. Building upon the Th1 and Th2 immune concepts, Mills et al. identified inherently different macrophages in various mouse models. This led to the development of a dichotomy of TAMs based on the relative balance of arginine metabolism: Th1 strains produce nitric oxide, while Th2 strains produce ornithine. The Th2 phenotype resembles observations seen during tissue repair, while the Th1 phenotype is characterized by iNOS expression and bactericidal activity [8,9].

Macrophages play a crucial role in maintaining homeostasis and mediating non-specific immunity. They possess various functions, including phagocytosis, antigen presentation, and immunomodulation. These cells exhibit high plasticity and dynamically respond to changes in the microenvironment to maintain tissue equilibrium [10]. Macrophages constitute a significant component of leukocytes infiltrating the TME. Referred to as TAMs, these macrophages participate in all stages of tumorigenesis, progression, and metastasis by secreting cytokines and growth factors [11].

The polarization of macrophages refers to the specific activation state of macrophages at a given point in time. Due to the remarkable flexibility of macrophages, they adapt their polarization state by integrating various signals from the surrounding environment. Currently, two well-recognized phenotypes exist: the M1 macrophage, which is classically activated by LPS, IFN-γ, and TNF-α, releases pro-inflammatory cytokines such as IL-12 and IL-23, displaying high expression of IL-12 and low expression of IL-10. Conversely, the M2 macrophages, which are alternatively activated by colony-stimulating factor-1 (CSF-1), IL-4, IL-13, IL-10, etc., exhibit high expression of IL-10 and low expression of IL-12 [12,13].

Immunohistochemical staining can be employed to identify TAMs during investigations into their distribution and function. For example, human M1 macrophages are labeled with CD68 on their surfaces, while M2 macrophages are labeled with CD163, CD206, CD204, and other markers. M1 TAMs contribute to inflammation promotion, immune stimulation, and inhibition of tumor progression, whereas M2 TAMs play a crucial role in anti-inflammation, immunosuppression, and promotion of tumor growth [10](Fig. 1). Toll-like receptor (TLR) ligands, such as LPS and IFN-γ, bind to TLRs on macrophages' surface, resulting in increased production of proinflammatory cytokines like TNF-α. This initiates a pro-inflammatory response and exhibits potent antitumor activity [14,15]. Conversely, type 2 cytokines like IL-4 and IL-13 induce an alternative activation phenotype and elicit an anti-inflammatory response via STAT6 activation pathways [16–18]. Additionally, IL-10 exerts a strong anti-inflammatory effect by activating the STAT3 through IL-10R [19,20].TAMs can promote the establishment of an immunosuppressive microenvironment, stimulate angiogenesis, and facilitate tumor invasion and metastasis by promoting tumor-related angiogenesis. Studies have shown that under hypoxia, transcription factor STAT3 activity is down-regulated to regulate TAM differentiation, inhibit anti-tumor immunity, and promote tumor progression and metastasis [21,22].

The above description presents a simplified binary classification of TAMs, but the dynamics of TAMs within the TME are undoubtedly complex and variable. Due to the high plasticity of macrophages, TAMs cannot be simply categorized as M1 and M2 phenotypes alone. Tumor cells within the TME can secrete specific cytokines to modulate TAMs, and the M1 and M2 phenotypes typically represent opposite ends of a spectrum. Many macrophages exist in between the M1 and M2 extremes and possess both pro-inflammatory and anti-inflammatory properties simultaneously [11]. In addition to M1 and M2, research has indicated that macrophage types also include CD169+ macrophages and TCR + macrophages. These macrophages are characterized by their distinct locations and have their unique characteristics and functions, highlighting the heterogeneity and plasticity of macrophage functionality [23]. While the dynamics of the TME and the interactions with macrophages are undoubtedly complex, macrophages can play both positive and negative roles under different inductions and TME states. However, data from animal models and analysis of clinical samples suggest that in the majority of cases, macrophages play a role in promoting tumor progression and metastasis [24].

Although macrophages exhibit heterogeneity and plasticity and cannot be summarized using a binary classification of phenotypes, in this review, we mainly described two functionally opposing macrophage phenotypes, M1 and M2(Fig. 2).

3. Polarization of TAMs

3.1. Macrophages in inflammatory response

In the TME, the conversion of M1 macrophages to M2 and vice versa can occur due to various factors, including cytokine secretion, hypoxia, and lactic acid production. This leads to the coexistence of these two phenotypes [25]. Cytokines play a significant role in macrophage polarization, with IFN-γinducing M1 polarization. Th2 cells secrete type 2 cytokines IL-4 and IL-13, which trigger the upregulation of arginase 1 through the STAT6 pathway. This, in turn, depletes arginine and competitively inhibits the effect of iNOS on

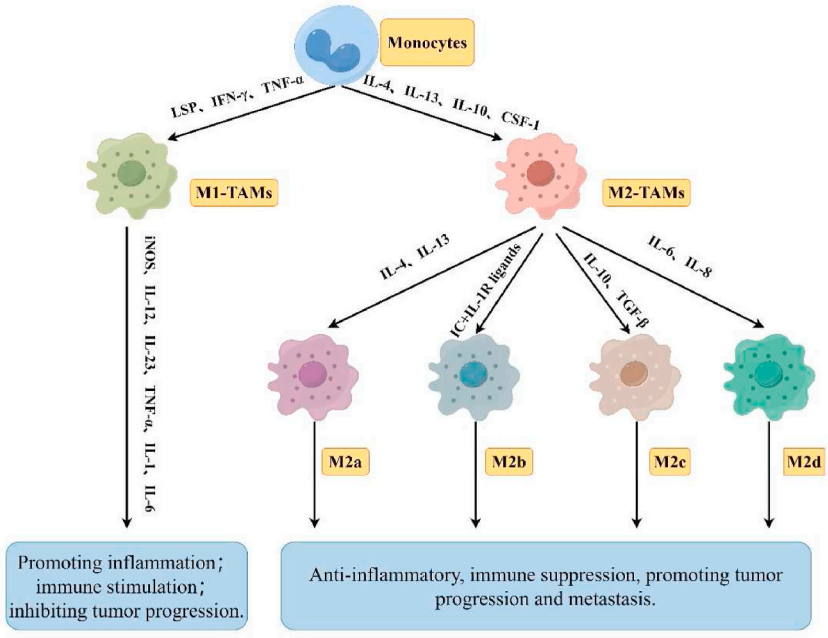

Fig. 1. Schematic illustration of tumor-associated macrophages (TAMs) polarization and primary functions in tumor tissue. Created with the graphical software Figdraw.

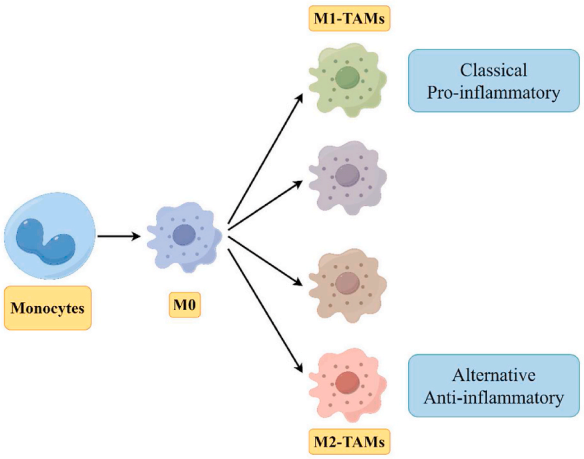

Fig. 2. The multifaceted classification of tumor-associated macrophages (TAMs) and the two extreme phenotypes of M1 and M2. Created with the graphical software Figdraw.

arginine, subsequently reducing the production of nitric oxide and driving M2 polarization [26,27]. Research has demonstrated a close connection between the occurrence and development of cancer and long-term chronic inflammatory stimulation [28,29]. During inflammation, LPS and IFN-γ drive macrophages towards M1 polarization, resulting in the secretion of elevated levels of pro-inflammatory cytokines such as TNF-α, IL-12, and IL-6. Prolonged exposure to these inflammatory mediators may lead to pathogenic effects. Over time, this sustained influence can eventually contribute to the development of cancer and other diseases [30]. The term "orderly inflammation" has been mentioned in the literature, referring to a regulatory mechanism that balances excessive inflammatory mediators with the inactivation mechanisms of corresponding mediators [31]. To prevent excessive inflammatory reactions, macrophages exert anti-inflammatory effects by regulating M1 apoptosis, transitioning to the M2 phenotype, and producing anti-inflammatory cytokines such as IL-10 [32].

3.2. Macrophages in TME

As mentioned earlier, macrophages exhibit high plasticity, allowing them to adapt to changes in the TME during cancer progression. In TME, the phenotypic ratio of M1 to M2 macrophages undergoes significant alterations. Initially, M1 macrophages dominate the early stages of solid tumor development, but their prominence shifts towards the M2 phenotype in the middle and late stages [33]. M1 macrophages exert antitumor activity by releasing iNOS and TNF-α, which can kill tumor cells. Notably, in a study on high-grade B-cell lymphoma, M1 macrophages demonstrated the ability to kill tumor cells through antibody-dependent cell-mediated cytotoxicity [34].

However, macrophages in TME can also contribute to tumor growth, invasion, and metastasis by promoting tumor angiogenesis and immunosuppression. M2 macrophages facilitate the formation of hyper-dense vascular networks by secreting angiogenic factors such as vascular endothelial growth factor (VEGF). These dense vascular networks ensure a continuous supply of oxygen and nutrients, promoting the expansion of tumor cells and the formation of solid tumors [35].

Moreover, the process of Epithelial-Mesenchymal Transition (EMT) plays a crucial role in tumor metastasis. EMT activation disrupts the cell-cell connections and degradation of the basement membrane of tumor endothelial cells. By undergoing this reversible cell transformation program, tumor cells acquire migratory abilities and stem cell-like properties. Epithelial cells express Major Histocompatibility Complex (MHC) proteins that aid in antigen recognition by cytotoxic T cells. However, activation of the EMT program reduces the expression of the MHCI class in mesenchymal cancer cells, hindering T-cell antigen presentation. Furthermore, EMT induction leads to the expression of programmed death ligand 1 (PD-L1), which, when combined with PD-1 on T cells, downregulates the anti-tumor activity of T cells. This immune escape by tumor cells is further facilitated by the recruitment of M2 macrophages by mesenchymal cells. M2 macrophages highly express IL-10, which promotes immunosuppression and evades immune surveillance [36]. In summary, EMT activation not only facilitates tumor metastasis but also contributes to immunosuppression [37].

4. TAMs and lung cancer

During tumorigenesis and development, most TAMs in the TME tend to exhibit the M2 phenotype. In a study on non-small cell lung cancer (NSCLC) conducted by Jackute et al. [38], it was found that a higher presence of M2 macrophages in tumor tissue, compared to M1 macrophages, as well as higher infiltration of M1 macrophages in tumor nests, were associated with longer overall survival in NSCLC patients. Conversely, tumor nests and stroma with high infiltration of M2 macrophages were associated with lower overall survival rates in NSCLC patients, with statistically significant differences observed in both cases. Additionally, poorly differentiated NSCLCs exhibited a higher total number of M2 macrophages compared to moderately and well-differentiated NSCLCs.

In an experimental study of NSCLC conducted by Cao et al. [39], the infiltration density of M2 macrophages was found to be positively correlated with the clinical stage of NSCLC. Furthermore, the group with a high infiltration density of M2 macrophages exhibited shorter overall survival compared to the group with a low infiltration density of M2 macrophages. During the progression from early-stage lung cancer to advanced lung cancer, tumor-associated macrophages tend to shift towards the M2 phenotype, and as the tumor advances, there is a tendency for M1-type macrophages to differentiate towards the M2 phenotype. Macrophages and myeloid dendritic cells can secrete IL-10, a potent immunosuppressive cytokine. Originally identified in Th2 cells, IL-10 production was later found to be induced in Th1 cells and Th17 cells as well. IL-10 inhibits the T-cell immune response and can contribute to immune evasion by promoting the conversion of T cells into regulatory T cells (Tregs), thereby antagonizing anti-tumor immune responses [40,41]. IL-34 functions as a ligand for the colony-stimulating factor-1 receptor (CSF-1R), assisting in the recruitment of macrophages and promotion of M2 macrophage polarization. High expressions of IL-34 in macrophages, CSF-1R, and advanced lung cancer show a significant correlation [42].

In patients with NSCLC, a significant correlation was observed between high expression of IL-10 in M2-type TAMs and advanced disease stage. This suggests that patients with advanced NSCLC exhibit higher levels of IL-10 expression in M2-type TAMs. Additionally, high IL-10 expression in TAMs is associated with poorly differentiated NSCLC [43]. A multivariate analysis in a separate study demonstrated a negative correlation between IL-10 expression levels and patient survival time [44]. Not only has this pattern been observed in NSCLC patients, but a study conducted staining analysis of macrophage markers in clinical samples of SCLC patients also revealed the infiltration of macrophages in SCLC tumors. Furthermore, the infiltration of macrophages was found to be positively correlated with the stage of SCLC [45]. These findings align with the earlier studies conducted by Cao et al. [39], which established a significant correlation between M2 macrophages and tumor clinical staging. Collectively, these results indicate that M2 TAMs are the predominant phenotype in patients with advanced NSCLC and that they play a role in tumor angiogenesis, invasion, metastasis, and suppression of anti-tumor immunity.

The predominance of M2 TAMs and the differentiation of anti-tumor M1 TAMs into M2 TAMs suppress the anti-tumor immune response during the progression of lung cancer to later stages. The regulation of macrophage polarization in the TME has become a focal point in macrophage-targeted therapy. Strategies such as inducing the reverse differentiation of the M2 phenotype into the M1 phenotype or blocking the differentiation of the M1 phenotype into the M2 phenotype have shown promise as effective targets for the treatment of lung cancer. However, the exact mechanisms for achieving this are not yet fully understood, and further research is needed to explore the role of epigenetics in this process, which is currently challenging.

5. Association of TAMs with lung cancer treatment

Based on the previous article, it is evident that remodeling the immunosuppressive TME by reprogramming or depleting M2 TAMs,

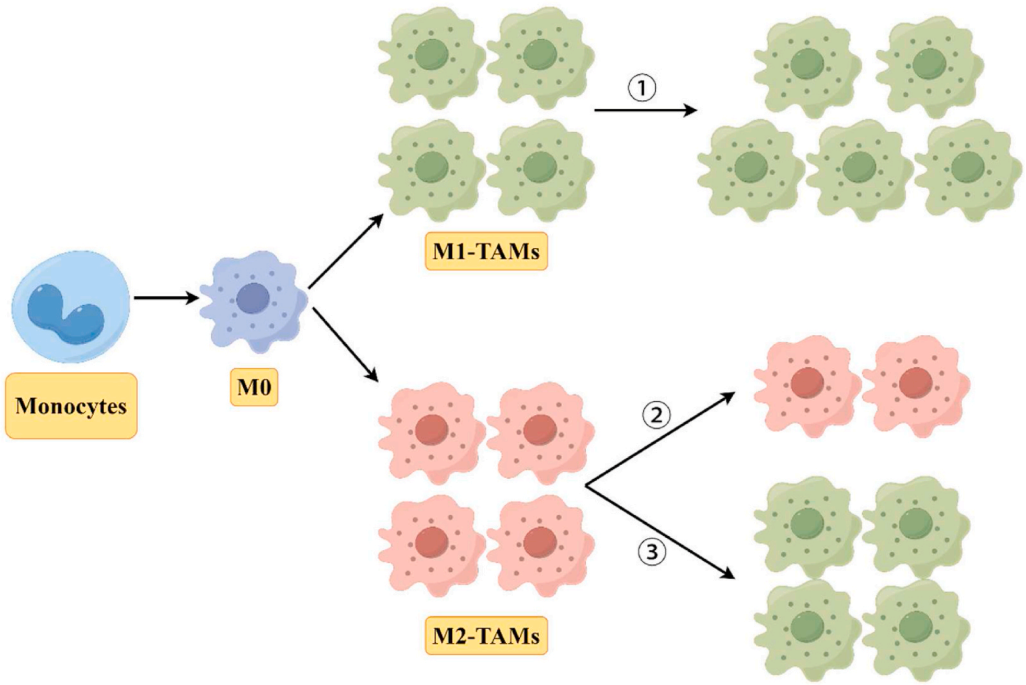

Fig. 3. The three main approaches for targeting tumor-associated macrophages (TAMs) include:① promoting the polarization of M1 macrophages to increase the number of M1-type macrophages; ②inhibiting the polarization of M2 macrophages to reduce the number of M2-type macrophages; ③reprogramming M2-type macrophages into M1-type macrophages. Created with the graphical software Figdraw.

and thereby reducing the M2/M1 ratio, can facilitate the re-infiltration of immune cytokines and enhance their anti-tumor effects, consequently impeding the progression of lung cancer. By conducting a detailed analysis of the intricate relationship between various treatments and TAMs, we establish a theoretical foundation for the targeted modulation of TAMs in combination with other therapeutic approaches for lung cancer treatment(Fig. 3).

5.1. Chemotherapy and TAMs

5.1.1. Neoadjuvant chemotherapy

Neoadjuvant chemotherapy offers surgical opportunities for patients who are eligible for surgical resection. As an adjunct to surgical treatment, preoperative neoadjuvant chemotherapy significantly contributes to improved survival outcomes for patients with operable NSCLC [46]. In a study evaluating the impact of neoadjuvant chemotherapy on the immune microenvironment of NSCLC patients, it was observed that patients receiving neoadjuvant chemotherapy exhibited a higher overall density of tumor-associated immune cells within the TME compared to those not undergoing neoadjuvant chemotherapy. These immune cell populations included $CD3^+$ T cells, $CD3^+CD4^+$ helper T cells, $CD3^+CD8^+$ cytotoxic T cells, and NK cells. The infiltration density of $CD68^+$ TAMs was also significantly higher in patients receiving neoadjuvant chemotherapy. Subsequent analysis of the overall patient survival time revealed that the densities of helper T cells and $CD68^+$ TAMs could serve as prognostic indicators, indicating that patients with high densities of these immune cells experienced longer survival times. Additionally, there was higher expression of PD-L1 in tumors of patients receiving neoadjuvant chemotherapy, suggesting that combining neoadjuvant chemotherapy with immunotherapy may offer better outcomes compared to monotherapy for NSCLC patients [47]. Zhao et al. conducted a phase II clinical trial supporting this notion, illustrating that neoadjuvant chemotherapy combined with immune checkpoint inhibitors (ICIs) can benefit patients with NSCLC. Patients receiving this combination therapy exhibited higher rates of major pathological remission and greater potential for successful surgical resection [48]. Ongoing studies are exploring the combination of neoadjuvant chemotherapy and immunotherapy in the current era of immunotherapy. Preliminary results indicate that neoadjuvant chemotherapy combined with Navulizumab yields significantly improved pathological complete remission rates and event-free survival compared to chemotherapy alone [49,50]. This may be attributed to chemotherapy drugs enhancing the number of anti-tumor macrophages and transforming the TME into an immune-stimulating microenvironment, thereby maximizing the anti-tumor effects of antineoplastic drugs and establishing favorable conditions for subsequent surgical resection.

However, another study involving a target population of NSCLC patients showed no notable difference in PD-L1 expression levels on tumor tissues before and after neoadjuvant chemotherapy. The density of $CD8^+$ T cells and LAMP + dendritic cells (DC-LAMP + cells) in tumor lesions was comparable between patients receiving and not receiving neoadjuvant chemotherapy, in contrast to previous studies. This discrepancy may be attributed to factors such as the combination of chemotherapeutic drugs, medical history, race, and lifestyle habits of the target population [51]. Moreover, a higher density of infiltrating $CD8^+$ T cells and DC-LAMP + cells, rather than $CD68^+$ TAMs, might serve as a prognostic indicator for favorable outcomes in this particular patient group. The role of TAMs in NSCLC patients has yet to be fully defined, and before this study, the prognostic value of $CD68^+$ TAMs in NSCLC patients receiving neoadjuvant chemotherapy had rarely been reported [51,52].

5.1.2. Adjuvant chemotherapy

As immunotherapeutic regimens have become established in the standardized treatment of lung cancer, many researchers believe that PD-L1 expression levels on tumor cells can predict the response to immunotherapy and the survival benefits of NSCLC. However, a clear marker for response to chemotherapy has not yet been identified. Previous studies have shown that there is no significant difference in PD-L1 expression levels and the survival benefits of early NSCLC patients, making it challenging to predict the clinical benefits of adjuvant chemotherapy in these patients [53]. Nevertheless, an increasing number of studies have indicated that PD-L1 expression on immune cells, such as TAMs, can also serve as a predictor of treatment response. PD-L1 transmits negative signals to macrophages and induces them to acquire immunosuppressive phenotypes. Patients with high PD-L1 expression in macrophages have shown prolonged overall survival following treatment with anti-PD-L1 antibodies [54–56]. Recent studies have found that there are no significant differences in the counts of $CD68^+$ TAMs, CD163+ TAMs, helper T lymphocytes, killer T lymphocytes, B lymphocytes, and NK cells between NSCLC patients receiving adjuvant chemotherapy and those without it. However, patients with high PD-L1 expression on TAMs and/or tumor cells experience significantly greater survival benefits after adjuvant chemotherapy compared to those without high PD-L1 expression. Furthermore, patients with high PD-L1 expression levels benefit from adjuvant chemotherapy regardless of their myeloid/lymphatic lineage ratio status. In patients with high ratio status, the benefit from adjuvant chemotherapy is even more pronounced, particularly for patients with only TAMs or high PD-L1 expression on TAMs and tumor cells [57].

5.1.2.1. Chemotherapy. Chemotherapeutic drugs can enhance the immune response by affecting immune cells in the TME. Furthermore, these drugs can induce the accumulation of mononuclear macrophages at the tumor site and alter the macrophage phenotype, resulting in immunosuppression. After effective chemotherapy, it has been observed that numerous M2 phenotype TAMs gather around the tumor lesions, particularly in the vicinity of tumor vessels. These M2 phenotype macrophages release VEGF and other substances, promoting the development of an extensive vascular system that aids in tumor revascularization [35]. M2 phenotype macrophages additionally secrete immunosuppressive cytokines, such as IL-10, creating an immunosuppressive microenvironment that hinders tumor cell apoptosis. These M2 TAMs also suppress the expression of cytotoxic T lymphocytes (CTLs), thereby diminishing the effectiveness of chemotherapy. This chemotherapy resistance persists during the stage of tumor recurrence, indicating a correlation

between the accumulation of M2 TAMs as the predominant phenotype at the tumor site after chemotherapy, and the development of chemoresistance [58–60].

Tumor cell resistance to chemotherapy is a major challenge in effective tumor treatment. One key contributor to this resistance is the aggregation and polarization of M2 TAMs, which are markers of enhanced chemotherapy resistance [61–63]. IL-34 is a ligand of the CSF-1R and is known to stimulate the viability, growth, differentiation, and proliferation of monocytes and macrophages [64]. In lung cancer, IL-34 production by cancer cells induces M2 polarization of macrophages, leading to immune inhibition and promoting chemotherapy resistance. Additionally, the production of IL-34 by lung cancer cells recruits monocytes and macrophages, which promotes M2 polarization and increases the proportion of immunosuppressive macrophages. Consequently, lung cancer cells become more resistant to chemotherapy, hampering its efficacy [65]. Targeting CSF-1R and inhibiting the aggregation of M2 TAMs, in combination with chemotherapy, has been found to slow down tumor progression, and metastasis, and improve survival time in mouse models [60,65]. This approach aims to avoid drug resistance in tumor cells and inhibit tumor recurrence by targeting tumor-associated macrophages.

CSF-1R is a protein tyrosine kinase receptor that plays a crucial role in macrophage recruitment and differentiation towards a pro-tumor M2 phenotype. Pharmacological blockade of CSF-1R reduces M2 TAMs, but it alone does not yield clinically relevant tumor suppression results. However, combining CSF-1R antagonists with conventional anti-tumor therapies may inhibit tumor progression [66]. CSF-1R antagonists help rebalance the macrophage populations in the tumor microenvironment, reducing the density of tumor-promoting macrophages and shifting the macrophage balance towards a less tumorigenic state. Moreover, combining CSF-1R antagonists with cisplatin, a chemotherapeutic drug, has shown promising results in reducing tumor burden and increasing the ratio of M1/M2 TAMs in lung tumor tissue [67,68]. Such targeted depletion of immunosuppressive M2 TAMs can overcome chemotherapy resistance and inhibit tumor growth. Additionally, the COX-2 inhibitor nimesulide has been shown to deplete immunosuppressive macrophages and impede the growth of non-small cell lung tumors when combined with cisplatin, by inhibiting the secretion of monocyte chemotactic protein and prostaglandin E2 [69,70]. Certain drugs with immunomodulatory properties, when used alone, may not improve antitumor effects but can enhance the effectiveness of other treatments. For example, some drugs can enhance the antitumor activity of oxaliplatin by upregulating antitumor macrophage activity in NSCLC [71].

Chloroquine (CQ), commonly used for malaria treatment, has been found to enhance the antitumor effect of chemotherapeutic drugs by inhibiting lysosomes. It can also reprogram TAMs to the M1 phenotype, thus improving the immunosuppressive microenvironment. However, the potential side effects of CQ should be considered [72–74]. Hydroxychloroquine (HCQ), a hydroxylated compound of chloroquine, can raise the lysosomal pH in lung cancer cells, inactivating P-glycoprotein, which causes drug resistance by trapping antitumor drugs in lysosomes or pumping them out of cells. HCQ can also promote the release of trapped chemotherapeutic drugs in lysosomes, thus improving the efficacy of chemotherapy. Additionally, HCQ can reprogram M2 TAMs to the M1 phenotype, enhancing anti-tumor immune function and promoting infiltration of cytotoxic T lymphocytes, thereby activating cellular immunity. HCQ shows potential as a safer adjuvant for anti-lung cancer chemotherapy [75,76].

Chemotherapy is a crucial treatment for lung cancer, but resistance often develops, leading to disease progression. The development of chemoresistance involves complex biological and molecular mechanisms, including the expression of programmed cell death suppressor genes, activation of tumor stem cells, reduction of chemotherapeutic targets, and alteration of the tumor microenvironment, among others [77–80]. Chemotherapeutic drugs can increase the infiltration density of TAMs and other immune cells, wherein the accumulation and polarization of immunosuppressive macrophages promote tumor progression and recurrence. However, combining chemotherapy with specific drugs can reverse the immunosuppressive microenvironment, enhance the antitumor effect of chemotherapy, and overcome chemoresistance [81–84].

5.2. Radiotherapy and TAMs

Radiation therapy (RT) is a treatment method that directly uses radiation to kill tumor cells and is still one of the most important methods for treating NSCLC. As the use of RT becomes more widespread in clinical practice, its immunomodulatory effects are gradually being recognized [85]. Radiation can activate the immune system by killing tumor cells and releasing antigenically active substances that upregulate MCH-1 molecules. Through this mechanism, it can also overcome tumor cells' resistance to anti-PD-1 ICIs [86]. Combining RT with other drugs can enhance the antitumor efficacy of RT. For example, anti-angiogenic drugs can improve the effectiveness of RT by normalizing blood vessels and inducing changes in TAMs that favor an anti-tumor immune response. The combination of anti-angiogenic drugs with RT can inhibit the infiltration of M2 TAMs and promote an anti-tumor immune response [87]. RT combined with anti-angiogenic drugs and immunotherapy can increase lymphocyte infiltration and reverse the immunosuppressive state of the TME. In lung cancer mice, combining RT with other drugs can optimize the anti-tumor effects of RT [88].

However, it is known that the clinical effectiveness of RT in lung cancer patients is limited due to tumor resistance to radiation and the need for increased radiation doses. One important factor contributing to this limitation is the immunosuppressive microenvironment in which immunosuppressive cells help tumor cells resist radiation [89,90]. Redeployment of TAMs from M2 to M1 phenotype and upregulation of cytotoxic T cell activity by ICIs and other immunosuppressive factor inhibitors can enhance the immune effects of RT and synergistically improve its antitumor effects. This holds the promise of reducing the required RT doses to minimize systemic toxicities [91,92]. Another technique called RadScopal involves using high-dose RT for primary tumors and low-dose RT for secondary tumors. Combining RadScopal therapy with ICIs can extend the survival time of mice with highly metastatic lung adenocarcinomas by resetting the TME [93]. Unlike conventional radiotherapy, molecularly targeted radiotherapy can significantly inhibit the growth of lung cancer in mice by targeting cancer-associated fibroblasts and altering the M1/M2 ratio. When combined with immunosuppressive agents, molecularly targeted radiotherapy can even induce lung tumor regression [94,95].

The IL-4/IL-13-activated STAT6 signaling pathway induces the polarization of M2-type macrophages. M2 TAMs secrete immunosuppressive cytokines such as IL-10 and TGF-β, which promote lung cancer progression [17,18,96]. TGF-β is considered a potent suppressor of antitumor immunity. RT upregulates TGF-β to activate multiple signaling pathways that induce tumor drug resistance [97]. A recent study found that RT activates STAT6-related signaling pathways to promote the polarization and aggregation of M2 macrophages at lung tumor sites. By blocking the STAT6 signaling pathway, the number of M2 TAMs can be reduced and reprogrammed to the M1 phenotype to enhance the sensitivity of NSCLC to RT. Additionally, blocking STAT6 can also reduce the level of TGF-β and enhance the anti-tumor effect. Combining STAT6 inhibitors with RT can slow down the growth of primary tumors and distant metastatic tumors in NSCLC [98].

In summary, while RT is effective in impeding tumor progression by directly killing tumor cells or indirectly enhancing anti-tumor immunity, the highly infiltrative TME with M2 TAMs often leads to RT resistance. Combining RT with other therapeutic drugs can reverse M2 polarization and help create an immunostimulatory microenvironment to enhance the anti-tumor effect of RT.

5.3. Immunotherapy and TAMs

From the end of the last century to the beginning of this century, the discovery of immune checkpoint programmed cell death factor 1 and its ligand in mice revealed their role in causing immune escape of tumor cells by suppressing the anti-tumor activity of T cells. Subsequent research on the mechanism led to the emergence of ICIs, marking a new era in tumor immunotherapy. ICIs work by blocking the PD-1 and PD-L1 signaling pathways, restoring the immune response of T cells against tumor cells. Currently, anti-tumor immunotherapy has been applied to various malignant tumors including non-small cell lung cancer, renal cell carcinoma, melanoma, breast cancer, and more [99–101].

After years of research, it is now widely accepted that macrophages in the TME play a complex role in immunotherapy. The formation of an immunosuppressive microenvironment in tumors poses a significant challenge to the effectiveness of tumor immunotherapy [102,103]. Macrophages in the TME contribute to immune evasion by expressing cell surface receptor proteins like PD-1 and secreting immunosuppressive cytokines such as arginase 1 and IL-10. These factors directly inhibit the activity of NK cells and CTLs [104–106]. Additionally, macrophages indirectly enhance the activity of Tregs and suppress T cell anti-tumor activity [107–109]. Immunosuppressive TAMs hinder the ability of ICIs to kill tumor cells. Targeting TAMs to reshape the immunosuppressive microenvironment can enhance the effectiveness of immunotherapeutic drugs [110,111]. Axl, a member of the receptor tyrosine kinase receptor family, plays a role in promoting tumor growth and invasion in NSCLC by regulating TAM polarization. Anti-Axl monoclonal antibodies induce apoptosis of NSCLC tumor cells by inhibiting the secretion of immunosuppressive cytokines by TAMs [112,113]. Recent studies have shown that anti-Axl antibodies can deplete M2 TAMs, promote the repolarization of M2 macrophages, and inhibit the activation of the EMT program, thus avoiding immune tolerance. This leads to the reversal of the immunosuppressive microenvironment and the anti-tumor effect in lung cancer [114].

Unlike the conventional immune checkpoints PD-1, PD-L1, and CTLA-4, the stimulator of interferon genes (STING) regulates innate antitumor immunity, and STING activators stimulate relevant signaling pathways to drive polarization of antitumor TAMs and mediate antitumor immunity [115,116]. Previous studies on STING have demonstrated its ability to repolarize M2 TAMs to the M1 phenotype in mouse NSCLC models [117]. Recent studies have shown that high expression of macrophage STING in small cell lung cancer (SCLC) patients leads to increased infiltration of immune cells such as $CD68^+$ TAMs, MHC II, and $CD8^+$ T cells. High STING expression and immune cell infiltration are associated with prolonged survival in SCLC patients. Furthermore, STING activators can trigger anti-tumor adaptive immunity by reprogramming pro-tumor M2 macrophages into an anti-tumor phenotype [118,119].

An immunostimulatory microenvironment can enhance the anti-tumor effect of ICIs. Retrospective analysis of three studies on solid tumors treated with Tislelizumab has shown that patients with high levels of pro-inflammatory TAMs and cytotoxic T cells have longer survival times. Macrophages promote tumor cell apoptosis by activating helper T cells, and $CD8^+$ T cells activate INF γ-related signaling pathways to promote the polarization of M1 macrophages. The high abundance of these two cell types in the TME enhances the anti-tumor activity of Tislelizumab [120].

On the contrary, a TME with high infiltration of immunosuppressive macrophages affects the sensitivity of NSCLC tumor cells to ICIs. Infiltration of M1 phenotype macrophages is positively correlated with immunotherapy response, while M2 phenotype macrophages are associated with immunotherapy drug resistance. The spatial distribution of TAMs is also related to the survival and prognosis of NSCLC [121,122]. It is increasingly believed that ICIs can induce TME remodeling in NSCLC patients and that the high infiltration of M2-type TAMs in the TME hampers the response of tumor cells to antitumor drugs. The development of a pro-tumor microenvironment leads to tumor cell tolerance to immunotherapeutic agents [123–125]. As mentioned earlier, cytokines released by tumor cells can modulate TAMs and induce chemoresistance. Tumor cells also secrete key immunosuppressive molecules that recruit pro-tumor macrophages, suppressing the effectiveness of immunotherapeutic drugs. Targeting these immunosuppressive molecules with inhibitors can counteract suppression and inhibit tumor progression [65,126].

In the past decade, the CD47-SIRP1α signaling axis has been implicated in maintaining the homeostasis of red blood cells, platelets, and hematopoietic stem cells. However, since CD47 is expressed in both healthy cells and cancer cells, its expression in cancer cells can inhibit tumor cell killing mediated by myeloid cells. CD47 binds to the signal regulatory protein alpha (SIRP1α) receptor on bone marrow cells, transmitting a “don’t eat me” signal, similar to the inhibitory effect of the PD-1-PD-L1 immune checkpoint on T cell activity. SIRP1α is expressed in all bone marrow cell types, including macrophages, and the CD47-SIRP1α signaling axis can regulate the role of macrophages in tumor control [127]. Due to the remarkable efficacy of immune checkpoint inhibitors, particularly the blockade of CTLA-4 or PD-1, in lung cancer, there has been exciting anti-tumor activity observed, leading to the evaluation of other immune checkpoints [128]. Blocking the CD47-SIRP1α signaling axis can enhance phagocytosis and anti-tumor activity of myeloid

cells, especially macrophages. Anti-SIRP1α antibodies promote macrophage engulfment and killing of tumor cells by inhibiting the interaction between CD47 and SIRP1α. Furthermore, these antibodies have shown relatively minimal toxicity [129]. A study conducted in a mouse model of SCLC demonstrated that CD47 blockade antibodies can induce phagocytosis of SCLC cells by human macrophages. To further validate the inhibitory effect of CD47 blockade antibodies on SCLC tumor growth in vivo, the SCLC mouse model was treated with CD47 blockade antibodies or control agents. While all mice in the control group succumbed to the disease, most mice in the experimental group exhibited only small tumors and showed no further progression over time. This further supports the potential of CD47 blockade as an effective therapeutic approach for SCLC patients. Additionally, CD47 blockade agents can convert TAMs into an anti-tumor M1 phenotype. However, it is yet to be fully clarified whether specific polarizing stimuli can enhance macrophage response to CD47 blockade therapy. Targeting the CD47-SIRP1α signaling axis with macrophage-directed therapy for lung cancer holds great promise. The synergistic effects of CD47 blockade therapy with other therapeutic antibodies can also be realized [45]. However, the impact of such drugs on other immune cells and hematopoietic cells requires further investigation, and their associated toxicities need to be assessed. There are a number of current techniques such as machine learning and scRNA-seq that should also be looked at for applications in tumor-associated macrophages [130–132]. More research on the underlying mechanisms and clinical trials are required to further confirm these findings.

5.4. Targeted TAMs

With a comprehensive understanding of the role of TAMs in lung cancer progression and their contribution to drug resistance in various treatments, TAMs emerge as potential targets for lung cancer treatment. Strategies to target TAMs encompass the following aspects: 1. Inhibiting the accumulation of TAMs at the tumor site; 2. Depleting tumor-promoting macrophages; 3. Augmenting the population of anti-tumor macrophages; 4. They are reprogramming tumor-associated macrophages to adopt an anti-tumor phenotype.

5.5. CSF-1and CSF-1R inhibitors

CSF-1 plays a crucial role in the proliferation, differentiation, and maintenance of monocytes and macrophages. It regulates the growth, differentiation, and proliferation of these immune cells. Tumor cells recruit macrophages by secreting the macrophage recruitment factor CSF-1 [133–135]. Activating the CSF-1 and CSF-1R signaling pathways promotes the production and proliferation of macrophage precursors, facilitating their recruitment to tumor sites [136]. In mouse tumor models, the use of anti–CSF–1R monoclonal antibodies or other small molecular inhibitors to block the CSF-1 and CSF-1R signaling pathways has been shown to hinder tumor progression. This approach can regulate TAMs or alter the immunosuppressive state of the TME [137–139]. In a study investigating the therapeutic effects of monoclonal antibodies targeting the CSF-1 receptor in solid tumors, the Gomez-Roca team found that antagonizing CSF-1R specifically reduced the number of M2 TAMs. Gene expression profile analysis revealed a down-regulation of genes predominantly expressed in M2 TAMs, such as CSF-1R and CD163. Consequently, it is reasonable to speculate that depleting the immunosuppressive macrophage phenotype via therapeutic interventions targeting macrophages can facilitate the formation of an immune-stimulated TME [66]. Targeting CSF-1R to block its signaling pathway depletes TAMs and reprograms M2 TAMs, leading to the prevention of immunosuppression and restoration of anti-tumor immune surveillance [140].

Small-molecule inhibitors that antagonize CSF-1R can hinder the recruitment of immunosuppressive TAMs and exhibit pro-tumor activity. Anti–CSF–1R drugs help remodel the TME and enhance immune function in lung cancer [141]. Targeting TAMs enables the regulation of TAM recruitment, polarization, and activity. Depleting immunosuppressive macrophages can reverse the poor state of immune cell infiltration. TME remodeling driven by CSF-1R antagonists can improve the clinical efficacy of immunotherapy. The combination of targeted TAMs and immunotherapy drugs can enhance the infiltration density of cytotoxic T cells in advanced NSCLC tumors, potentially benefiting NSCLC patients clinically [142]. Currently, CSF-1R-targeted drugs are being developed in combination with other clinical agents for the treatment of advanced solid tumors. These combinations include an anti–CSF–1R antibody (elotuzumab) in combination with a CD40 agonist (selicrelumab) [143], an anti–CSF–1R antibody (elotuzumab) in combination with the chemotherapy drug paclitaxe [66], and a CSF-1R small molecule inhibitor (LY3022855) in combination with an anti-PD-L1 antibody (durvalumab) [144]. NSCLC patients have exhibited good tolerability to combination drugs, but the anti-tumor clinical benefits have been limited. Although CSF-1R-targeted drugs can deplete TAMs, the subsequent accumulation of other tumor-associated cells may hinder the clinical benefit for tumor patients. A recent study discovered an interaction between tumor-associated neutrophils and macrophages, forming a positive feedback pathway in which neutrophils aggregate and recruit TAMs after targeted macrophage drug therapy. This interaction has resulted in a limited clinical response to therapy [125].

5.6. Targeted marco

Reprogramming anti-inflammatory TAMs into pro-inflammatory TAMs is a therapeutic strategy for targeting macrophages. Marco, a scavenger receptor belonging to the scavenger receptor family, is expressed on macrophages and is associated with pro-tumor and anti-inflammatory macrophage subtypes [145,146]. Analysis of tumor tissues from NSCLC patients has demonstrated a positive correlation between Marco expression and immunosuppressive TAMs, consistent with previous findings. This suggests that Marco could serve as a new immunotherapy target for macrophages in NSCLC patients [146]. In another study involving NSCLC patients, anti-Marco antibodies targeting human Marco were developed to reprogram immunosuppressive TAMs into immunostimulatory TAMs. By targeting macrophages and inhibiting regulatory T cell activation while preserving cytotoxic T cell activity, these antibodies reshape the TME in lung cancer patients and enhance the effectiveness of anticancer therapies [147].

5.6.1. Targeted TLR

The TLR was initially identified as a crucial protein involved in the organism's innate immunity. It plays a role in anti-tumor immune surveillance by recognizing certain endogenous ligands, such as LPS and IFN-γ. TLR agonists stimulate antigen-presenting cells to secrete cytokines like IL-6 and IL-12, promoting the generation and differentiation of cytotoxic T cells [148]. Initial clinical studies investigating the combination of TLR9 agonists and platinum-containing dual-agent chemotherapy in advanced NSCLC showed promising clinical outcomes [149,150]. However, a subsequent phase III trial revealed that this drug combination failed to improve overall survival or progression-free survival [151]. Similarly, limited clinical benefits were observed in two gynecologic oncology trials involving TLR agonists. Nevertheless, the role of TLR agonists in immune activation within the TME should not be disregarded [152, 153]. Furthermore, studies have demonstrated that the combination of TLR agonists and interferon can reprogram macrophages in a mouse lung cancer model. In synergy, they induce M1-like macrophages with anti-tumor properties to eliminate tumor cells. This suggests that TLR agonists combined with interferon could be a promising avenue for tumor immunotherapy, although further clinical trials are necessary to validate these findings [154,155].

5.6.1.1. Dihydroartemisinin. Dihydroartemisinin (DHA) belongs to a class of anti-malarial drugs extensively used in clinical practice. The potential anticancer activity of DHA has garnered significant interest. It has been found that DHA can enhance the cytotoxicity of T cells, induce apoptosis in tumor cells, and promote immune function by inducing endoplasmic reticulum stress [156,157]. While the exact mechanism by which DHA modulates the TME to enhance anti-tumor immunity remains unclear, it has been observed that DHA triggers the repolarization of M2 phenotype macrophages via the mTOR signaling pathway in experimental models of lung cancer in mice [158,159]. Additionally, miRNAs delivered through targeted means can activate the mTOR signaling pathway to reprogram TAMs into an anti-tumor phenotype [160]. Furthermore, DHA-induced iron death has been found to demonstrate cytotoxicity against tumor cells. In TAMs, DHA-driven iron death leads to DNA damage and activates downstream signals, such as NF-κB, to reprogram macrophages that promote tumor growth [161,162]. The DNA damage response plays a pivotal role in recruiting and activating immune cells by upregulating the expression of immunostimulatory signals. While the DNA damage response contributes to maintaining the microenvironment and organismal homeostasis, it has been suggested that it might also play a role in tumorigenesis and progression [163]. Recent studies have shown that DHA triggers cellular iron death, resulting in the production of reactive oxygen species, which in turn induces endoplasmic reticulum stress and DNA damage. DNA damage leads to an increased release of HMGB1 and HSP90, located in the nucleus, thereby increasing immunogenicity while destroying tumor cells. This suggests that herbal medicine may present a novel approach to modulating the TME in terms of anti-tumor immunity [164–166].

5.7. Anti-angiogenic drugs

Vascular disruptors have shown promise in impeding tumor progression by targeting the abundant blood vessels within tumor lesions. Preclinical experiments using vascular disruptors in a mouse model of lung cancer demonstrated their ability to induce repolarization of M2-like TAMs and stimulate the secretion of various immunostimulatory cytokines. This, in turn, enhances the anti-tumor immune response mediated by cytotoxic T cells [117,167]. Currently approved anti-angiogenic drugs for NSCLC patients include bevacizumab and apatinib. A preclinical study revealed that apatinib can inhibit the accumulation of immunosuppressive TAMs and improve TME, suggesting a potential treatment strategy for NSCLC by combining apatinib with ICIs [168]. Analysis of NSCLC patients receiving camrelizumab in combination with apatinib demonstrated promising antitumor efficacy. A phase II clinical trial investigating the combination of camrelizumab and apatinib for neoadjuvant NSCLC reported encouraging results in terms of overall response rate, pCR, operability, and maneuverability. However, data on PFS and other outcomes are not yet available [169, 170]. Furthermore, the combination of anti-angiogenic agents and RT has shown synergistic effects in promoting tumor vascular normalization and reprogramming of M2 TAMs [87,88]. Thus, drugs targeting angiogenesis not only contribute to the reconstruction of the TME but also have the potential to become novel and effective combination therapies with immunotherapeutic agents.

5.8. Targeted therapy

Targeted therapeutics have emerged as the first-line treatment for NSCLC patients with genetically detected driver-sensitive mutations, including common driver mutations such as EGFR, ALK, and ROS1. Previous studies have revealed a correlation between the response to EGFR-TKIs and the number of TAMs in patients with advanced NSCLC [171]. Preclinical experiments conducted on mouse models demonstrated that anlotinib can reduce the M2/M1 ratio and enhance immune cell infiltration, thereby activating the anti-tumor innate immunity through increased infiltration of antigen-presenting cells and NK cells [172]. Similarly, in another study using an experimental mouse model, oral gefitinib was found to inhibit the polarization of M2-like TAMs by blocking the IL-13/STAT6 signaling pathway. Although it did not significantly inhibit lung cancer tumor growth, it showed a significant hindrance to lung metastasis [173]. These findings suggest that EGFR-TKIs can potentially optimize the TME in NSCLC patients. However, the high M2/M1 ratio in the TME poses a limitation on the maximum benefit from EGFR-TKIs, as it promotes tumor cell tolerance to targeted drugs. The interaction between targeted drugs and macrophages within the TME is complex and can influence sustained benefits for patients through the coordination of an immunostimulatory microenvironment and targeted therapies [174–176].

6. Conclusion

Lung cancer, the second most common malignant tumor in the world, poses a significant challenge due to its high incidence and mortality rates. Overcoming lung cancer has been a longstanding focus of research, and traditional treatments such as surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy have been employed. Personalized medication tailored to each patient's condition has shown promise in improving treatment outcomes. However, despite years of advancement, these treatments can only offer limited effectiveness in helping lung cancer patients. We have discovered that the immunosuppressive nature of the TME greatly restricts the ability of lung cancer patients to benefit from conventional therapies.

This paper explores the origin of TAMs and the functional differences among macrophage phenotypes. We have identified that M2-like TAMs play a crucial role not only in the development and progression of lung cancer by promoting tumor angiogenesis, facilitating tumor cell migration, and creating an immunosuppressive microenvironment but also in impeding the efficacy of anticancer therapies. Targeting TAMs shows promise as an anti-tumor strategy by inhibiting TAM aggregation, depleting M2 macrophages, increasing M1 macrophages, and reprogramming the M2 phenotype towards an anti-tumor M1 phenotype. Existing studies have demonstrated the exciting anti-tumor potential of targeted TAM therapy, making it a promising candidate for synergistic combinations with conventional lung cancer treatments. However, due to the involvement of complex epigenetic mechanisms, further preclinical experiments and subsequent clinical trials are needed to understand the underlying mechanisms fully.

The macrophage-centric therapeutic approach holds great promise by targeting the tumor-promoting activity of TAMs and promoting their anti-tumor functionality. However, as previously mentioned, macrophages are heterogeneous and plastic immune cells. This study only discusses the two extreme phenotypes, M1 and M2, while in the complex tumor microenvironment, macrophage phenotypes are undoubtedly complex and variable. For certain macrophage phenotypes, their specific functions are still unknown, and there hasn't even been a classification for them, let alone a discussing the targeted induction of these macrophages to exert anti-tumor effects. Furthermore, due to the unique biological characteristics of SCLC, research in this area is limited; hence, the majority of this article focuses primarily on discussing non-small cell lung cancer.

There are currently several challenges in the development of targeted drugs for TAMs, such as developing drugs that specifically target the tumor-promoting phenotypes of macrophages. These drugs aim to induce polarization of tumor-promoting macrophages towards an anti-tumor phenotype or selectively reduce the population of tumor-promoting macrophages. However, if the drugs inhibit both tumor-promoting and anti-tumor macrophages simultaneously, it may render them ineffective or even have adverse effects. In the previous sections, we described the primary treatment approaches for lung cancer that involve modulating anti-tumor functions, as well as promising strategies targeting macrophages for anti-tumor effects. These results are encouraging, but the specific mechanisms are not fully understood. Given this context, even if drug development is successful, the high level of uncertainty poses potentially irreversible consequences in clinical trials. Therefore, further exploration of the underlying mechanisms is necessary to assess whether manipulating macrophages affects other immune cells and disrupts normal physiological processes.

In addition, targeted drugs for TAMs seem to have synergistic effects with other anti-lung cancer drugs. However, further research is needed to determine the specific interactions and the direction of influence between these drugs. I believe that with ongoing research, our understanding of the role of TAMs in lung cancer treatment will continue to advance.

Ethics approval and consent to participate

Not applicable.

Data availability

Not applicable. No data was used for the research described in the article.

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CRediT authorship contribution statement

Zhuchen Yu: Writing – review & editing, Writing – original draft, Data curation. **Juntao Zou:** Writing – review & editing, Supervision, Conceptualization. **Fei Xu:** Supervision, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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