frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 15 August 2023
DOI 10.3389/fimmu.2023.1209947

OPEN ACCESS

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RECEIVED 21 April 2023
ACCEPTED 31 July 2023
PUBLISHED 15 August 2023

CITATION
Cheng D, Ge K, Yao X, Wang B, Chen R, Zhao W, Fang C and Ji M (2023) Tumor-associated macrophages mediate resistance of EGFR-TKIs in non-small cell lung cancer: mechanisms and prospects. *Front. Immunol.* 14:1209947. doi: 10.3389/fimmu.2023.1209947

Tumor-associated macrophages mediate resistance of EGFR-TKIs in non-small cell lung cancer: mechanisms and prospects

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Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the first-line standard treatment for advanced non-small cell lung cancer (NSCLC) with EGFR mutation. However, resistance to EGFR-TKIs is inevitable. Currently, most studies on the mechanism of EGFR-TKIs resistance mainly focus on the spontaneous resistance phenotype of NSCLC cells. Studies have shown that the tumor microenvironment (TME) also mediates EGFR-TKIs resistance in NSCLC. Tumor-associated macrophages (TAMs), one of the central immune cells in the TME of NSCLC, play an essential role in mediating EGFR-TKIs resistance. This study aims to comprehensively review the current mechanisms underlying TAM-mediated resistance to EGFR-TKIs and discuss the potential efficacy of combining EGFR-TKIs with targeted TAMs therapy. Combining EGFR-TKIs with TAMs targeting may improve the prognosis of NSCLC with EGFR mutation to some extent.

KEYWORDS

NSCLC, EGFR-TKIs, resistance, tumor-associated macrophages, exosome

1 Introduction

1.1 Background

The epidermal growth factor receptor (EGFR) is one of the most frequently mutated driver oncogenes in non-small cell lung cancer (NSCLC), and EGFR mutation is found in approximately 50% of the Southeast Asian lung adenocarcinoma population (1). EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as first-generation EGFR-TKIs gefitinib or erlotinib have shown potent antitumor effects in advanced NSCLC patients with EGFR mutation (2). Osimertinib, a third-generation EGFR-TKI, has been approved as first-line therapy for advanced NSCLC patients with EGFR mutation due to its lower toxicity and stronger antitumor effects (3). However, resistance to EGFR-TKIs is inevitable, and disease progression occurs in most patients. The mechanisms of resistance to EGFR-TKIs are a current research focus in NSCLC. Several resistance mechanisms have been elucidated, including secondary mutations of EGFR, activation of bypass pathways, and histological

transformation (4). The development of fourth-generation EGFR-TKIs targeting the EGFR C797S mutation is underway (5). In recent years, the resistance of EGFR-TKIs mediated by tumor-associated macrophages (TAMs) has received broad attention (Table 1). Previous studies have demonstrated that high infiltration of TAMs is significantly associated with an unfavorable prognosis in NSCLC patients treated with EGFR-TKIs (6–9).

1.2 TAMs in NSCLC

The origin of TAMs in NSCLC is multifaceted, involving both tissue-resident macrophages (TRMs) and monocyte-derived macrophages (MDMs) (10). And TRMs can be classified into lung alveolar macrophages (LAMs) and interstitial macrophages (IMs) based on their anatomical locations. TRMs are present during embryonic development and can self-renew locally, independent of the hematopoietic system (11). They are crucial in coordinating tissue remodeling and maintaining tissue integrity (11). MDMs originate from the hematopoietic system, and many can be observed in inflammatory lesions (12). TAMs from different sources can promote the progression of NSCLC (13). TRMs mainly contribute to tumor generation, while MDMs primarily participate in tumor metastasis (13).

Macrophages can generally be classified into M1 and M2 types based on their polarization status (14, 15). M1-like macrophages secrete pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-12, and IL-23, to participate in antigen presentation and play a role in immune surveillance (16). And M2-like macrophages secrete inhibitory factors, such as IL-10 and transforming growth factor-β (TGF-β), and have weak antigen-presenting ability (16). TAMs mainly exhibit the M2-like macrophage phenotype (17) and are closely associated with resistance to anti-tumor drugs in various solid tumors, including NSCLC (6, 18–20). Additionally, TAMs exhibit both inter- and intra-tumor heterogeneity. High infiltration of TAMs has been linked to unfavorable prognosis in pancreatic cancer (21), bladder cancer (22), and malignant glioma (23). But in some instances, such as ovarian (24) and colorectal cancers (25), it is associated with a more favorable outcome. In the NSCLC investigation, a high TAMs infiltration level within tumor islets was associated with a favorable prognosis. In contrast, a high level of TAMs infiltration within tumor stroma was linked to unfavorable prognosis (26, 27). The heterogeneity of TAMs in NSCLC may be attributed to tumor hypoxia and the spatial distribution of TAMs within the tumor microenvironment (TME) (28).

TABLE 1 Mechanisms of TAMs mediated resistance to EGFR-TKIs.

Mechanisms	References
Activating bypass pathways	
AKT/mTOR pathway	34
AKT, ERK1/2 and STAT3 pathways	17, 59
LncRNA-MSTRG.292666.16/miR-6836-5p/MAPK8IP3 pathway	35
NF-κB/RELB pathway	36
Suppressing T cells	
NOS and PD-L1 pathways	91
M2-like polarization	
Lipid metabolism pathways	103
STAT3/IL-4 pathway	107
LncRNA SOX2-OT/miR-627-3p/Smads pathway	114
Modulating tumor cell phenotypes	
Stabilizing tumor cell phenotype	115
Promoting the EMT	129, 130

TAM, tumor-associated macrophage; mTOR, mammalian target of rapamycin; RELB, v-rel reticuloendotheliosis viral oncogene homolog B; NOS: nitric oxide synthase; PD-L1, programmed cell death 1 ligand 1; LncRNA SOX2-OT, long non-coding RNA SOX2 overlapping transcript; EMT, epithelial-mesenchymal transition.

1.3 Effects of EGFR-TKIs on TAMs

Jia et al. (29) investigated the impact of EGFR-TKIs on the TME in NSCLC from a dynamic perspective. During early-stage treatment, EGFR-TKIs can increase the infiltration of $CD8^+$T cells and dendritic cells (DC) in TME while inhibiting the infiltration of $Foxp3^+$ regulatory T cells (Tregs) and M2-like polarization of TAMs (29). However, with the continuation of treatment, the immune-activated TME gradually dissipated while the proportion of immunosuppressive cells, myeloid-derived suppressor cells (MDSCs), progressively increased (29). Notably, there was a significant increase in $CD86^+$ macrophage expression driven by EGFR during the initial phase of EGFR-TKIs treatment, which exhibited robust antigen presentation capabilities (29). However, the gradual accumulation of M2-like TAMs, MDSCs, and Tregs during treatment hindered the antitumor immune effects of DC and T cells (29–31).

1.4 Aims

This study aims to comprehensively review the current mechanisms underlying TAM-mediated resistance to EGFR-TKIs and discuss the potential efficacy of combining EGFR-TKIs with targeted TAMs therapy (Figure 1). Combining EGFR-TKIs with TAMs targeting may improve the prognosis of NSCLC with EGFR mutation to some extent.

2 TAMs mediate EGFR-TKIs resistance by activating bypass pathways

2.1 Background

Activation of phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) signaling

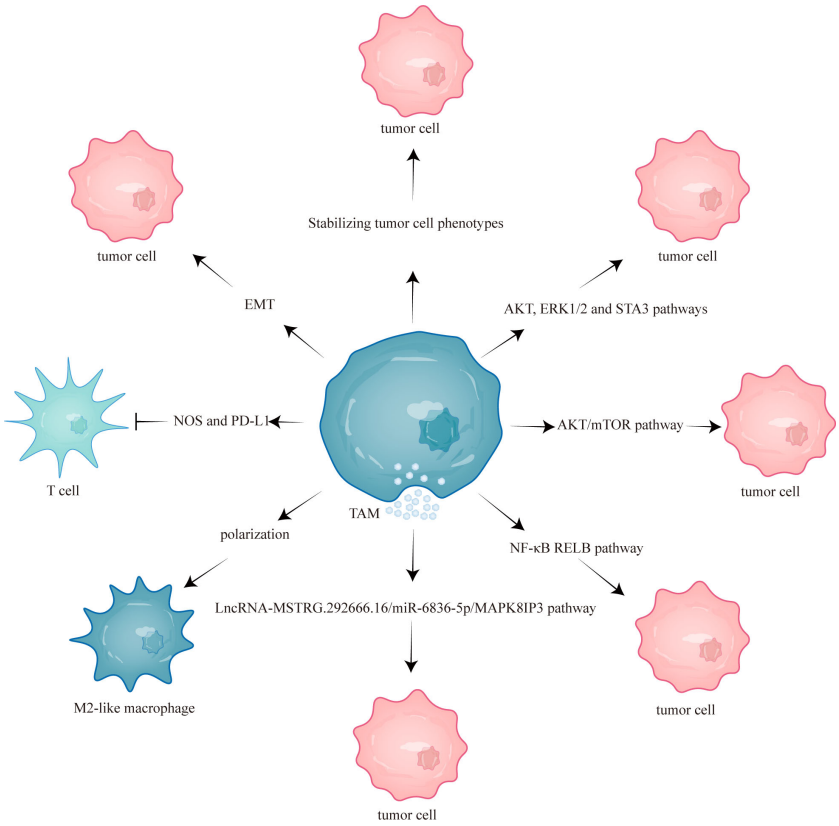

FIGURE 1
TAMs mediated EGFR-TKIs resistance through different mechanisms. TAM, tumor-associated macrophage; mTOR, mammalian target of rapamycin; NOS, nitric oxide synthase; EMT, epithelial-mesenchymal transition; RELB, v-rel reticuloendotheliosis viral oncogene homolog B; PD-L1, programmed cell death one ligand 1.

pathways compensates for the inhibition of EGFR signaling by EGFR-TKIs, promoting resistance of EGFR-TKIs (32). Yuan et al. (33) showed that TAMs can affect the biological behavior of lung adenocarcinoma cells by activating the PI3K/AKT pathway. This suggests that TAM-mediated EGFR-TKIs resistance may be closely related to the activation of bypass pathways. Furthermore, several studies have demonstrated that TAMs contribute to the resistance of EGFR-TKIs by activating bypass pathways, such as AKT/mammalian target of rapamycin (mTOR) pathway (34), AKT pathway (17), extracellular signal-related kinases 1 and 2 (ERK1/2) pathway (17), signal transducer and activator of transcription 3 (STAT3) pathway (17), LncRNA-MSTRG.292666.16/miR-6836-5p/MAPK8IP3 pathway (35) and atypical nuclear factor-κB (NF-κB)/v-rel reticuloendotheliosis viral oncogene homolog B (RELB) pathway (36).

2.2 AKT/mTOR pathway

EGFR-TKIs can increase the content of serum chemokine (C-C motif) ligand 2 (CCL2) (29), which plays an essential role in the process of EGFR-TKI resistance (8). CCL2 in the TME can recruit macrophages (37–39). Xiao et al. (34) showed that gefitinib resistance cell lines increased the release of CCL2 by decreasing the expression of β-catenin protein. Furthermore, tumor cells recruit more M2-like macrophages by releasing CCL2, and these macrophages promote gefitinib resistance by activating the AKT/mTOR pathway (34). As a serine/threonine kinase, mTOR has a catalytic domain similar to PI3K and is considered an atypical protein kinase in the PI3K-related kinase family (40). Through various mechanisms, including activation of growth factor receptor pathway, inhibition of autophagy, and influence on lipid metabolism pathway et al., mTOR could promote tumor development, metastasis, and drug resistance (41, 42). The rapamycin analogs, which inhibit mTOR, have been approved for treating renal cell carcinoma, while several other mTOR inhibitors are currently in development (40).

2.2.1 Prospects

Preclinical studies (43–50) have shown that mTOR inhibitors can improve the resistance of NSCLC to EGFR-TKIs. For example, Wang et al. (51) showed that the combination of ferumoxytol and CpG oligodeoxynucleotide 2395 could effectively suppress EGFR and its downstream AKT/mTOR signaling pathway, thereby enhancing the antitumor activity of macrophages in NSCLC with EGFR mutation. Qu et al. (52) employed a combination of MEK1/2 inhibitor AZD6244 and PI3K/mTOR inhibitor BEZ235 to improve gefitinib resistance in a xenograft model of NSCLC. However, Moran et al. (53) showed that afatinib, in combination with

mTOR inhibitor sirolimus, did not show the expected anti-tumor effect. The toxicity was not tolerable in NSCLC patients with EGFR-TKIs resistance. The intricate resistance mechanism of EGFR-TKIs may account for the limited antitumor efficacy. This implies the necessity of identifying NSCLC patients who are responsive to mTOR inhibitors. Notably, altering the administration mode of mTOR inhibitors to target the TME in NSCLC might alleviate the adverse effects of combination therapy. In conclusion, further exploration is warranted for the combination of mTOR inhibitors and EGFR-TKIs in EGFR-mutated NSCLC based on available evidence (54, 55).

2.3 AKT, ERK1/2 and STAT3 pathways

Exosomes are extracellular vesicles ranging in size from 30 to 150nm, capable of transporting nucleic acids or proteins derived from maternal cells and facilitating intercellular communication (56). Exosomes play a crucial role in the pathogenesis, progression, and metastasis of tumors (57). Yuan et al. (17) investigated the contribution of TAM-derived exosomes to EGFR-TKI resistance and demonstrated that these exosomes could impede the antitumor efficacy of gefitinib. Further protein expression analysis confirmed that TAMs-derived exosomes mediated EGFR-TKIs resistance by activating AKT, ERK1/2, and STAT3 signaling pathways (17). On the other hand, previous studies have shown that epiregulin (EREG), as a ligand for EGFR, can promote the progression of NSCLC (58). EREG-enriched macrophages induce gefitinib and erlotinib resistance by inducing AKT phosphorylation in a human epidermal growth factor receptor 2 (HER-2)-dependent manner (59).

2.3.1 Prospects

The abnormal activation of the AKT pathway is closely related to the resistance of EGFR-TKIs in NSCLC (60, 61). Several studies (62–67) have shown that inhibition of the AKT pathway can improve the resistance of EGFR-TKIs in NSCLC. For example, Lai et al. (68) demonstrated that Polyphyllin I can reverse osimertinib resistance by regulating the PI3K/AKT pathway in NSCLC. Wang et al. (69) showed that combination therapy with gefitinib and miR-30a-5p could overcome acquired resistance to EGFR-TKIs by regulating the PI3K/AKT pathway in NSCLC. However, Clément-Duchêne et al. (70) showed no improvement in progression-free survival (PFS) and overall survival (OS) for EGFR-mutated NSCLC treated with enzastaurin (an oral AKT inhibitor) combined with erlotinib compared to erlotinib alone in a phase II study. This finding contradicts previous preclinical studies and warrants further investigation to identify the subset of NSCLC patients who may benefit from AKT inhibitors. Additionally, TAM-induced AKT phosphorylation is closely associated with HER-2 (59), suggesting that the use of HER-2 inhibitors may improve resistance to EGFR-TKIs in NSCLC (71, 72). Consistent with this hypothesis, Peng et al. (73) have developed a trastuzumab-modified, mannosylated liposome system that effectively targets M2-type TAMs and HER-2 positive NSCLC cells to overcome EGFR-TKIs resistance mediated by the EGFR T790M mutation. Importantly, HER-2 and HER-3 belong to the HER family and have highly similar structures and biological functions (74). Vicencio et al. (75) demonstrated that osimertinib combined with HER-3 antibody therapy could enhance the antitumor effect in NSCLC. Therefore, in addition to directly inhibiting the AKT pathway, combining HER2 or HER3 inhibitors may be a therapeutic strategy for improving the efficacy of EGFR-TKIs.

2.4 LncRNA-MSTRG.292666.16/miR-6836-5p/MAPK8IP3 pathway

Non-coding RNAs (ncRNAs), including circular RNA (circRNA), long ncRNA (lncRNA), and microRNA (miRNA) et al., play an essential role in the initiation and progression of cancer (76). Deng et al. (77) analyzed the serum exosomal-lncRNAs of osimertinib resistant patients and found that the knock of lncRNA MSTRG.292666.16 can improve the osimertinib resistance in NSCLC cells. Furthermore, Wan et al. (35) showed that TAM-derived exosomes promote osimertinib resistance by activating MSTRG.292666.16/miR-6836-5p/1MAPK8IP3 signaling pathway in NSCLC.

2.4.1 Prospects

TAM-derived exosomes play a crucial role in mediating resistance to EGFR-TKIs. Unfortunately, there is a lack of effective methods to target these exosomes. Further investigation is warranted to refrain from the biogenesis of TAM-derived exosomes or impede the binding of exosomes to tumor cells.

2.5 NF-κB/RELB pathway

In pathological conditions like cancer, myeloid cells may transform myeloid-derived suppressor cells (MDSCs), contributing to tumor metastasis and conferring resistance to anti-cancer drugs (78). MDSCs play a crucial role in promoting immunosuppression and inducing the generation of regulatory T cells within the TME (79). Feng et al. (36) suggested that $S100A9^{+}$ MDSC (a subset of monocytic MDSC) derived macrophages induce gefitinib resistance *via* NF-κB/RELB pathway.

2.5.1 Prospects

The oncogenic role of NF-κB has been reported (80). Notably, NF-κB can facilitate the epithelial-mesenchymal transition (EMT) of tumor cells, which may constitute one of the potential mechanisms by which TAMs mediate resistance to EGFR-TKIs (80). Targeting NF-κB has been reported to improve EGFR-TKIs resistance potentially. For example, Yeo et al. (81) improved acquired resistance to EGFR-TKIs by inhibiting NF-κB and activation-induced cytidine deaminase (AICDA) in NSCLC. Liu et al. (82) reported that Liver X receptor ligands could induce apoptosis in EGFR-TKIs resistant cells by inhibiting the AKT-NF-κB pathway in NSCLC. On the other hand, RELB can upregulate the expression of programmed cell death one ligand 1 (PD-L1) and facilitate immune evasion in prostate cancer (83). Previous studies

(84) have shown that PD-L1 expression is also increased in NSCLC patients after developing resistance to EGFR-TKIs, and RELB may up-regulate PD-L1 expression following EGFR-TKIs resistance in NSCLC. Up-regulation of PD-L1 promotes an immunosuppressive TME, which may also be one potential mechanism for EGFR-TKI resistance (84). Therefore, RELB may be a potential target for improving EGFR-TKIs resistance in NSCLC.

3 TAMs mediate EGFR-TKIs resistance by suppressing T cells

3.1 Background

The EGFR signal can reduce chemokine (C-X-C motif) ligand 10 (CXCL10) and CCL5 by reducing interferon regulatory factor-1 (85). EGFR-TKIs can induce an interferon response in NSCLC, and the efficacy of EGFR-TKIs is influenced by immune activation (86). Previous studies (87–89) have shown that macrophages can promote chemotherapy resistance by inhibiting T-cell-mediated responses. Similarly, TAMs mediate T cell inhibition in the TME (90), which causes resistance to EGFR-TKIs related to TAMs (91).

3.2 TAMs inhibit T cells by expressing inducible nitric oxide synthase and PD-L1

Stimulator of interferon genes (STING) regulates the human immune system (92). Lin et al. (91) demonstrated that the enrichment of TAMs impedes T cell activation in NSCLC patients treated with osimertinib. The immunosuppressive TME attenuates the efficacy of EGFR-TKIs in anti-tumor therapy (91). Reprogramming macrophages with STING agonist, MSA-2, can restore T cell activation and reverse osimertinib resistance (91). This implies that the combination of EGFR-TKIs and STING agonists can potentiate the antitumor effects of EGFR-TKIs. In addition, Lin et al. (91) demonstrated that TAMs may mediate T-cell inhibition by up-regulating the expression of inducible nitric oxide (NO) synthase and PD-L1. Studies have shown that NO can promote cisplatin resistance in NSCLC and inhibit T cell proliferation (93, 94). Upregulation of PD-L1 expression in TAMs can increase immunosuppression and tumor aggressiveness in NSCLC (95, 96). These mechanisms provide targets for reactivating T cells in TME. However, Lin et al. (91) did not rule out the possibility that other cells may also be involved in anti-tumor immunity when stimulated by STING agonists, such as dendritic cells and endothelial cells (97, 98).

3.3 Prospects

Further deliberation is warranted on strategies to enhance T cell infiltration in the TME of NSCLC. Immune checkpoint inhibitors (ICIs) can potentially induce M1 polarization of TAMs and reactivate T cells within the TME (99). Theoretically, the combination therapy of ICIs and EGFR-TKIs may enhance the efficacy of EGFR-TKIs in NSCLC. However, the combination of ICIs and EGFR-TKIs has been found to result in intolerable toxicity during clinical trials (100). Strategies to enhance T cell infiltration in the TME of NSCLC, such as reprogramming TAMs or reducing their infiltration, should be developed for clinical implementation.

4 TAMs mediate EGFR-TKIs resistance through M2-like polarization of macrophage

4.1 Lipid metabolism pathways

Lipid metabolism is closely related to TAMs polarization (101). Chen et al. (102) showed that overexpression of sterol regulatory element-binding protein 1 (SREBP1) can mediate osimertinib resistance. Furthermore, Liang et al. (103) analyzed the role of 9 genes related to lipid metabolism in osimertinib resistance. They found that T-cell lymphoma invasion and metastasis 2 (TIAM2) can induce TAMs M2-like polarization mediated osimertinib resistance through PI3K/AKT/mTOR signaling pathway (Figure 2).

4.1.1 Prospects

Targeting lipid metabolic pathways to cause repolarization of TAMs is a feasible approach to improve resistance to EGFR-TKIs. Jin et al. (104) found that simvastatin can mediate TAMs repolarization by targeting cholesterol metabolism. Yin et al. (105) developed a dual-targeting liposomal system for the codelivery of simvastatin/gefitinib to treat NSCLC with brain metastases. Dual-targeting liposomal system with modification of anti-PD-L1 nanobody and transferrin receptor-binding peptide T12 can enter the blood-brain barrier to reverse EGFR T790M mutation-mediated resistance *via* TAMs repolarization (105).

4.2 STAT3/IL-4 pathway

Chen et al. (106) found that T790M-cis-L792F mutation is one of the mechanisms of osimertinib resistance. And Sun et al. (107) found that the expression and secretion of IL-4 increased in T790M-cis-L792F mutant cells, promoting the M2-like polarization of TAMs. Furthermore, Sun et al. (107) demonstrated that TAMs M2-like polarization is one of the downstream mediators of the STAT3/IL-4 signaling pathway, and blocking STAT3 with SH-4-54 and IL-4 with dupilumab can reverse osimertinib resistance to some extent.

4.2.1 Prospects

Targeting STAT3 could be a promising strategy for overcoming resistance to EGFR-TKIs (108). Park et al. (109) showed that the root extract of Scutellaria baicalensis can induce apoptosis in EGFR-TKIs resistant NSCLC by inhibiting STAT3. Shu et al. (110) reversed afatinib resistance in NSCLC by knocking down lncRNA BLACAT1

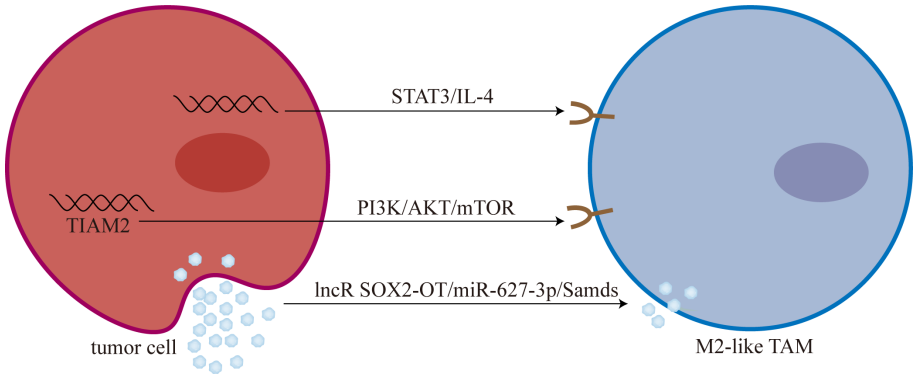

FIGURE 2
Tumor cells promoted M2-like polarization of TAMs. M2-like TAM: M2-like tumor-associated macrophage; mTOR, mammalian target of rapamycin; lncR SOX2-OT, long non-coding RNA SOX2 overlapping transcript; Smads, drosophila mothers against decapentaplegic proteins.

by regulating STAT3 signaling. In addition, it has been previously reported that aberrant activation of STAT3 can promote M2-like polarization of macrophages (111). Lu et al. (111) showed that gefitinib combined with STAT3 inhibitor and anti-CD47 monoclonal antibody could reprogram TAMs and ameliorate acquired resistance to gefitinib in NSCLC. Small molecule inhibitors targeting STAT3 have shown preliminary antitumor effects (112, 113). Further investigation into STAT3 and IL-4 as potential targets is warranted to overcome resistance to EGFR-TKIs.

4.3 LncRNA SOX2-OT/miR-627-3p/Smads pathway

Recently, Zhou et al. (114) found that long non-coding RNA SOX2 overlapping transcript (lncRNA SOX2-OT) is highly expressed in exosomes derived from NSCLC cells. Subsequently, exosomal lncRNA SOX2-OT can promote M2-like polarization of TAMs and promote EGFR-TKIs resistance (114). Mechanistically, lncRNA SOX2-OT promotes M2-like polarization of TAMs by increasing the expression of drosophila mothers against decapentaplegic proteins (Smads) through sponging miR-627-3p (114).

4.3.1 Prospects

lncRNA SOX2-OT/miR-627-3p/Smads axis represents a promising target for reprogramming TAMs. However, there still needs to be more feasible approaches to target this pathway.

5 TAMs mediate EGFR-TKIs resistance by modulating tumor cell phenotypes

5.1 Stabilizing tumor cell phenotypes

Zhao et al. (115) treated NSCLC cells with gefitinib and subsequently co-cultured them with macrophages to mimic the behavior of migrating macrophages. Migrating macrophages contributed to gefitinib resistance by stabilizing tumor cell phenotypes before macrophage polarization. Additionally, Zhao and colleagues (115) postulated that the upregulation of vimentin mediated by TGF-β might also account for the accelerated acquisition of gefitinib resistance in NSCLC cells.

5.1.1 Prospects

Reducing the recruitment of TAMs or depleting the TAMs in the TME of NSCLC may be a potential approach to improve EGFR-TKIs resistance. CCL2-chemokine (C-C motif) receptor 2 (CCR2) signaling and the colony-stimulating factor 1(CSF1)-CSF1 receptor (CSF1-CSF1R) axis are potential therapeutic targets (116, 117). For example, previous studies (118) have shown that CSF1R inhibitors can deplete M2 macrophages in the TME. Sidorov et al. (119) demonstrated that the combination therapy of erlotinib and MLN0128 (an mTOR inhibitor) effectively reduces the infiltration of immunosuppressive chemokines, such as CCL2 and periostin, as well as TAMs in the TME of glioblastoma, leading to a significant improvement in survival outcomes for glioblastoma mice. Schmall et al. (120) demonstrated that inhibiting the recruitment of TAMs and promoting their M1-like polarization through CCR2 inhibition can effectively inhibit lung cancer progression. In addition, targeting surface receptors such as CD52, scavenger receptor-A, folic acid receptor-β, and CD206 represents potential approaches for depleting TAMs (121). Future research endeavors should investigate the clinical applications of these protocols in NSCLC.

5.2 Promoting the EMT

EMT, the process of epithelial-to-mesenchymal transition, plays a crucial role in physiological processes such as wound healing, development, and stem cell behavior (122). However, it is closely associated with tumorigenesis, tumor progression, and drug resistance under pathological conditions (123). Importantly, EMT is one of the mechanisms of acquired resistance to EGFR-TKIs (124). Approaches to overcome EGFR-TKI resistance in NSCLC by reversing EMT are currently under investigation, including the targeting of CD70, cyclin-dependent kinase 7 (CDK7), lipid metabolism pathways, and

fibroblast growth factor receptor 1 (FGFR1) (125–128). Several studies (129, 130) have revealed that TAMs can promote the EMT of tumor cells. Bonde et al. (129) showed that TAMs promote tumor EMT through TGF-β signaling and activation of the β-catenin pathway in NSCLC. And Shen et al. (130) demonstrated that inhibition of TAMs can reverse tumor EMT in NSCLC.

5.2.1 Prospects

Further investigation is warranted to target TAMs to reverse EMT in EGFR-TKI-resistant cells. Reprogramming TAMs to reduce the secretion of pro-EMT signals, such as TGF-β, may represent a promising strategy. Consistent with this hypothesis, Jin et al. (104) showed that targeting lipid metabolism could improve EMT-related drug resistance by reprogramming TAMs in NSCLC.

6 Discussion

Resistance to EGFR-TKIs remains a global challenge, and exploring new methods to enhance the efficacy of EGFR-TKIs is imperative in NSCLC. This review summarizes the multiple mechanisms of TAM-mediated EGFR-TKIs resistance in NSCLC, including activation of bypass pathways, inhibition of T cell activity, M2-like polarization, and regulation of tumor cell phenotypes. Several pertinent issues warrant discussion.

Inhibiting the TAMs-related bypass pathway may be a potential approach to improving resistance to EGFR-TKIs in NSCLC (Table 2). The significance of the mTOR-related pathway in enhancing resistance to EGFR-TKIs warrants reiteration. Previous studies (131) have shown that high expression of mTOR correlates with a diminished therapeutic response to erlotinib in NSCLC. TAMs can induce resistance to EGFR-TKIs by activating the AKT/mTOR signaling pathway directly (34). Additionally, mTOR-related pathways may mediate EMT-related EGFR-TKIs resistance (132). Zhang et al. (133) demonstrated that MTI-31, an inhibitor of mTORC1/2, effectively impedes the progression and EMT of NSCLC while simultaneously enhancing antitumor immunity. Significantly, the PI3K/AKT/mTOR signaling pathway can also facilitate M2-like polarization of TAMs to promote EGFR-TKIs resistance (103). Based on this existing evidence, combination therapy involving mTOR inhibitors and EGFR-TKIs may improve resistance to EGFR-TKIs by blocking multiple resistance signals. However, current clinical trials have demonstrated that the combination therapy does not yield a superior clinical response compared to EGFR-TKIs monotherapy, and its toxicity profile is challenging to manage (53). Further experimentation is warranted to elucidate this phenomenon in the future. On the other hand, targeting STAT3 may represent a promising strategy to enhance the efficacy of EGFR-TKIs by overcoming TAM-mediated resistance. TAMs-derived exosomes can mediate EGFR-TKIs resistance by activating STAT3 signaling pathway (17). Moreover, STAT3 also plays a crucial role in promoting the M2-like polarization of TAMs (111). Combining STAT3 inhibitors with EGFR-TKIs inhibits drug resistance mediated by exosomes derived from TAMs and reprograms TAMs. Previous studies (134–136) have shown the potential of STAT3 inhibitors in combination with EGFR-TKIs for anti-tumor therapy. W2014-S, a novel STAT3 inhibitor, can significantly enhance the anti-tumor effect of EGFR-TKIs in TKI-resistant NSCLC (137). Wang et al. (138) demonstrated that the STAT3 inhibitor BBI608 could potentiate the anti-tumor efficacy of EGFR-TKIs by modulating the ROR1/ABCB1/P53 signaling pathway.

TABLE 2 Strategies for improving resistance to EGFR-TKIs by targeting TAMs.

Strategies	Up/Down	Targets	References
Dictamnine	Down	PI3K/AKT/mTOR and MAPK pathways	43
Torin2	Down	AKT/mTOR pathway	44
Temsirolimus	Down	mTOR	45
BEZ235	Down	PI3K/mTOR pathway	46, 49, 52
Active fraction (HS7) from Taiwanofungus camphoratus	Down	AKT-mTOR, ERK and STAT3 pathways	47
Everolimus	Down	mTOR	45,48, 55
Ku-0063794	Down	mTOR	50
Ferumoxytol and CpG oligodeoxynucleotide 2395	Down	EGFR and AKT/mTOR pathways	51
T0901317 and GW3965	Down	AKT	62
Bufalin	Down	MET/PI3K/AKT Pathway	63
Chloroquine	Down	AKT	64
Norcantharidin	Down	MET/PI3K/AKT Pathway	65
MiR-30a-5p	Down	PI3K/AKT Pathway	66, 69
BMS-708163	Down	PI3K/AKT Pathway	67
Polyphyllin I	Down	PI3K/AKT Pathway	68

(Continued)

TABLE 2 Continued

Strategies	Up/Down	Targets	References
anti-HER-3 antibody	Down	HER-3 and PI3K/AKT Pathway	71
anti-HER-3 antibody	Up	STING	75
HECrossMAb	Down	PI3K/AKT Pathway	72
Gefitinib and Vorinostat	Up	M1-like polarization of TAMs	73
Cosuppression of NF-κB and AICDA	Down	NF-κB and AICDA	81
Liver X receptors agonist	Down	AKT and NF-κB	82
STING agonist MSA-2	Up	M1-like polarization of TAMs	91
Simvastatin	Up	M1-like polarization of TAMs	104, 105
The Root Extract of Scutellaria baicalensis	Down	STAT3	109
Knockdown of lncRNA BLACAT1	Down	STAT3	110
STAT3 inhibitor and an anti-CD47 monoclonal antibody	Up	M1-like polarization of TAMs	111
Simvastatin	Down	EMT	104
MTI-31	Down	EMT	133
W2014-S	Down	STAT3	137
BBI608	Down	STAT3	138

EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; TAMs, tumor-associated macrophages; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-related kinases; STAT3, signal transducer and activator of transcription 3; MET, mesenchymal to epithelial transition factor; HER-3, human epidermal growth factor receptor 3; STING: Stimulator of interferon genes; NF-κB, nuclear factor-κB; AICDA, activation-induced cytidine deaminase; EMT, epithelial-mesenchymal transition.

Reprogramming TAMs is a crucial strategy for improving the resistance to EGFR-TKIs in NSCLC. It is worth mentioning that reprogramming TAMs can enhance the efficacy of EGFR-TKIs through a variety of mechanisms, including inhibition of TAM-related drug resistance pathway (34), reactivation of T cells in the TME (91), and reversal of EMT of tumor cells (104). STING (91), lipid metabolic pathways (101), mTOR (34), Smads (114), IL-4 (107), and STAT3 (111) have been reported as targets for reprogramming TAMs in NSCLC. In addition, other strategies for reprogramming TAMs are currently under investigation, which may offer insights into improving resistance to EGFR-TKIs in NSCLC. Parayath et al. (139) reprogrammed TAMs by intraperitoneal injection of Hyaluronic Acid-Based Nanoparticles Encapsulating MicroRNA-125b in NSCLC. Sarode et al. (140) reprogrammed TAMs by targeting the β-catenin/FOSL2/ARID5A signaling pathway in lung cancer. Future research should investigate innovative approaches to reprogramming TAMs in NSCLC with EGFR mutation.

Finally, reducing the number of TAMs in the TME of EGFR-mutant NSCLC, either by inhibiting TAM recruitment or depleting TAMs, may represent a promising strategy to overcome resistance to EGFR-TKIs. The clinical applicability of these methods warrants further investigation (116, 117).

7 Conclusions

TAMs mediate EGFR-TKIs resistance in NSCLC through various mechanisms, including activation of bypass pathways, inhibition of T cell activity, M2-like polarization, and regulation of tumor cell phenotypes. In the future, developing therapeutic regimens that target TAMs, such as interfering with TAM-related pathways, reducing infiltration of TAMs, and reprogramming the macrophage phenotype, could enhance the anti-tumor effect of EGFR-TKIs.

Author contributions

DC, KG, and XY wrote the original draft of the article and drew the illustration. RC, BW, WZ, CF, and MJ contributed to the conceptualization and revised the draft. All authors participated in the revision of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Science and Technology Project for Youth Talent of Changzhou Health Commission (QN201703), Young Talent Development Plan of Changzhou Health Commission (CZQM2020024), Major Science and Technology Project of Changzhou Health Commission (ZD202004, ZD202007), and China Postdoctoral Science Foundation (2020M670064ZX).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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