IL-6: A key player in the EGFR-TKI-resistant tumor microenvironment and its therapeutic implications (Review)

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Abstract. IL-6, a pleiotropic inflammatory cytokine predominantly secreted by fibroblasts, myeloid-derived suppressor cells, tumor-associated macrophages and tumor cells, is associated with poor prognosis of and therapeutic resistance in non-small cell lung cancer (NSCLC). The activation of signaling pathways, including the JAK/STAT3, MAPK and PI3K/AKT pathways, promotes tumor survival. Furthermore, the IL-6/JAK/STAT3 signaling axis has emerged as a key driver of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) resistance, orchestrating intricate crosstalk within the tumor microenvironment (TME) to promote cell survival and immunosuppression. The present review synthesized current evidence on the dual role of IL-6 in mediating EGFR-TKI resistance and blunting anti-tumor immunity. The present review highlights the preclinical rationale for combining IL-6 blockade with EGFR-TKI or immune checkpoint inhibitors to overcome refractory disease. The present review also highlights the structure, molecular mechanisms and clinical insights of IL-6 in the TME of *EGFR*-mutant NSCLC and may provide optimized therapeutic strategies for EGFR-TKI-refractory NSCLC.

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Abbreviations: IL-6, interleukin-6; TAMs, tumor-associated macrophages; NSCLC, non-small cell lung cancer; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; TME, tumor microenvironment; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; Gp130, glycoprotein 130; IL-6Rα, IL-6 receptor α; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; Treg, regulatory T cell; NK cell, natural killer cell; CAFs, cancer-associated fibroblasts; OSM, oncostatin M; Arg1, arginase-1; MDSCs, myeloid-derived suppressor cells; PD-L1, programmed cell death ligand 1; PD-1, programmed cell death protein 1; PPI, polyphyllin I

Key words: IL-6, NSCLC, EGFR-TKI resistance, TME, immunosuppressive, immunotherapy

Contents

1. Introduction

The molecular landscape of non-small cell lung cancer (NSCLC) has been revolutionized by the discovery of epidermal growth factor receptor (EGFR) mutations, which occur in 10-35% of Western patients and in ≤50% of Asian patients (1-3). While EGFR tyrosine kinase inhibitors (TKIs) achieve unprecedented initial response rates of 60-80%, the median progression-free survival remains limited to 9-19 months due to the universal development of acquired resistance (4-6). Historically, resistance research has focused on tumor-autonomous mechanisms, including secondary EGFR mutations (for example, T790M and C797S), MET

amplification and phenotypic transformation through epithelial-mesenchymal transition (EMT) (5,7-9).

However, accumulating evidence reveals that dynamic crosstalk between neoplastic cells and their microenvironment contributes considerably to therapeutic evasion (10,11). The tumor microenvironment (TME), comprising immune cells, cancer-associated fibroblasts (CAFs), endothelial cells and extracellular matrix components, establishes biochemical and physical barriers that compromise drug efficacy through multiple mechanisms (12,13).

Cytokines within the TME carry out dual roles in tumorigenesis (14). Among these cytokines, interleukin-6 (IL-6), a multifunctional cytokine produced by tumor and stromal cells, is pivotal in shaping the immunosuppressive TME landscape (15). Clinical cohort studies have demonstrated that elevated serum IL-6 levels are associated with advanced TNM stage, increased metastatic burden and reduced overall survival across diverse malignancies, including NSCLC (16-21). Despite these advances, key knowledge gaps persist regarding the exact involvement of IL-6 in the EGFR-TKI-resistant NSCLC microenvironment.

The present comprehensive review systematically examines the molecular biology of IL-6 signaling networks in EGFR-driven tumorigenesis, the multidimensional role of IL-6 in sculpting therapy-resistant TME architectures, preclinical evidence for IL-6 pathway inhibition in resensitizing refractory tumors and current clinical challenges and future directions for biomarker-driven combination therapies. We hypothesize that targeting IL-6-mediated crosstalk between tumor cells and their ecological niche represents a promising strategy to overcome microenvironment-mediated resistance.

2. Constituents and biology of the IL-6 signaling pathway

IL6 and its receptor. The IL-6 gene, located on chromosome 7p21, encodes a 184-amino-acid protein. Structurally, IL-6 consists of four long α-helices and three loops at their junctions, which maturely form following proteolytic cleavage of its signal peptide (22). IL-6 signaling is mediated by a receptor complex consisting of IL-6, the IL-6 receptor α subunit (IL-6Rα) and glycoprotein 130 (gp130) (23). Specifically, IL-6 first binds to membrane-bound IL-6Rα, an 80 kDa protein featuring an extracellular IL-6 binding domain and a minimal cytoplasmic domain. This IL-6/IL-6Rα complex subsequently recruits gp130 (an IL-6 signal transducer), initiating intracellular signal transduction (24). The structural organization of IL-6 is shown in Fig. 1.

Biology of IL-6. IL-6, a pleiotropic inflammatory cytokine predominantly secreted by fibroblasts, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and tumor cells (25-28), signals through four distinct molecular pathways. The classical and trans-signaling pathways constitute the two primary modes of IL-6 signal transduction (29-31), with two additional modalities more recently characterized (32,33). All IL-6-related cytokine receptor complexes (IL-6/IL-6R/gp130) activate an intracellular signal: The JAK/STAT pathway. Furthermore, gp130 phosphorylation triggers secondary downstream pathways, including MAPK-ERK and PI3K-Akt, which synergistically amplify oncogenic signaling (34). The nuclear translocation of activated STAT proteins induces the transcription of tumor-promoting genes associated with proliferation, metastasis and immune evasion (35). Apart from its canonical transcriptional roles in maintaining stemness, survival, metastatic potential and immune evasion across malignancies (36-40), cytoplasmic STAT3 drives tumor progression through non-transcriptional mechanisms. These include metabolic reprogramming and direct interactions with cytosolic signaling effectors, which collectively sustain tumor expansion (41,42). Mechanistically, through classical membrane-bound receptor signaling and trans-signaling via soluble IL-6R, IL-6 activates downstream JAK/STAT3, MAPK and PI3K/AKT pathways, driving the pro-survival signaling, stemness maintenance and immune evasion of tumor cells (43-46) (Fig. 2).

3. IL-6 in the development of EGFR-mutant NSCLC

IL-6 signaling has a key influence on the prognosis of patients with NSCLC. Accumulating evidence has demonstrated that IL-6 is overexpressed across multiple malignancies and is associated with tumor progression (47,48). Mechanistically, IL-6 enhances cancer stemness properties (45,46), whereas pharmacological inhibition of the IL-6/JAK/STAT3 axis suppresses tumorigenic potential (45,49). Notably, IL-6 synergistically interacts with *EGFR* signaling to drive NSCLC progression (50). In *EGFR*-mutant NSCLC cells, treatment with EGFR-TKI paradoxically activates compensatory Src/IL-6/STAT3 signaling, thereby sustaining tumor cell survival (51). Preclinical studies have shown that IL-6 blockade markedly reduces tumor burden (52), while JAK1/2 inhibitors (for example ruxolitinib) effectively suppress the growth of *EGFR*-mutant tumors (53).

Clinical observations further corroborate the oncogenic role of IL-6 in *EGFR*-mutant NSCLC. Elevated IL-6 mRNA levels are consistently detected in NSCLC tissues (54-58) and are independently associated with poor prognosis, establishing IL-6 as a robust prognostic biomarker (54,59,60). Importantly, lower baseline serum IL-6 levels predict prolonged progression-free survival (PFS) and higher objective response rates following EGFR-TKI therapy (61,62).

Collectively, these findings position IL-6 as a key molecular nexus bridging tumorigenesis and clinical prognosis in NSCLC. The IL-6/JAK/STAT3 signaling cascade operates independently of the mutational status of EGFR, exerting pleiotropic effects on tumor cell behavior through both canonical and non-canonical mechanisms.

4. IL-6 mediates EGFR-TKI resistance by remodeling the TME

The majority of patients treated with EGFR-TKI develop acquired resistance within 9 to 14 months of therapy (5). Accumulating evidence highlights the key role of IL-6 in shaping immunosuppressive processes within the TME (63). Furthermore, increasing data indicate a clear association between resistance to EGFR-TKI and IL-6 signaling. IL-6 orchestrates TME immunosuppression, leading to resistance to EGFR-TKI through multiple mechanisms (Fig. 3).

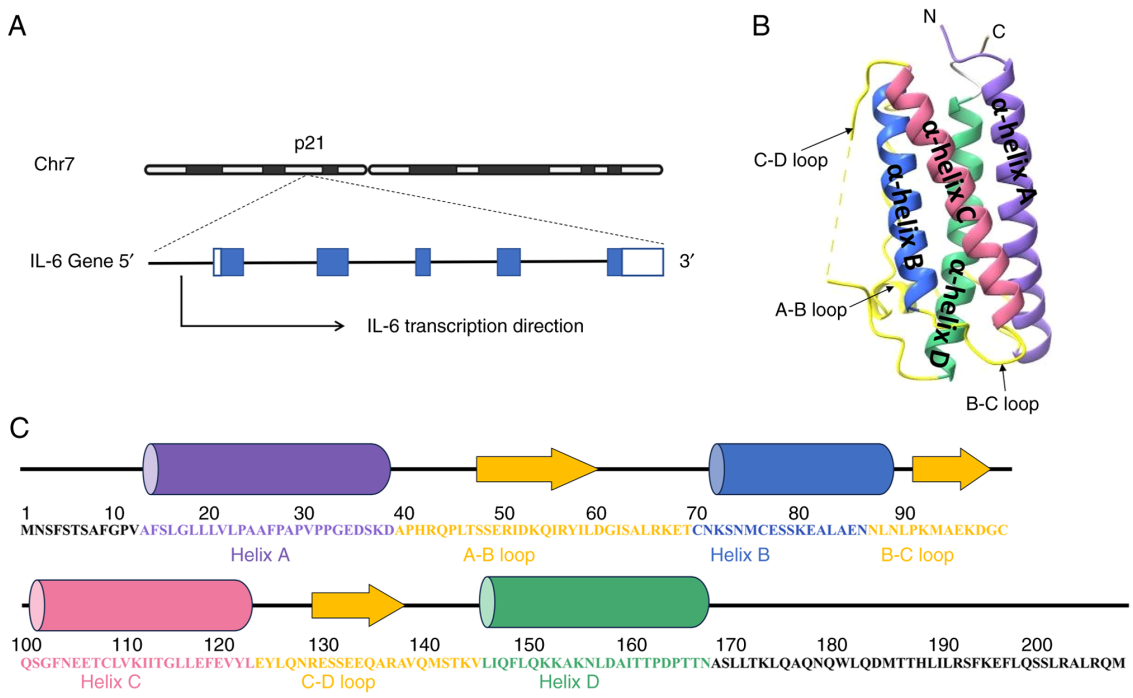

Figure 1. IL-6 Structure. (A) The rectangle illustrates the gene structure of IL-6. (B) Spatial configuration of the IL-6 monomers. The gene structure of IL-6 was obtained from Ensembl (157). The IL-6 amino acid sequence was obtained from UniProt and examined using IBS 2.0 (158). The spatial configuration of IL-6 was obtained from AlphaFold 3 (159). (C) Amino acid sequence of IL-6. IL-6, interleukin-6; Chr, chromosome.

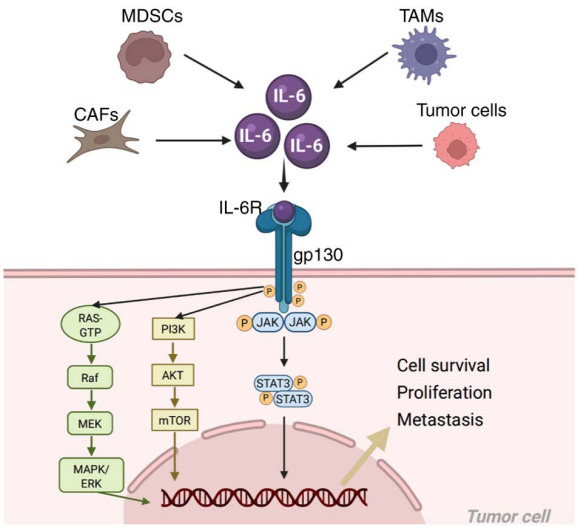

Figure 2. Molecular components of the IL-6 signaling pathway. IL-6 is predominantly secreted by CAFs, MDSCs, TAMs and tumor cells. Activation of the IL-6 signaling cascade drives tumor cell survival, proliferative expansion and metastatic dissemination through autocrine/paracrine mechanisms. CAFs, cancer-associated fibroblasts; MDSCs, myeloid-derived suppressor cells; TAMs, tumor-associated macrophages; IL-6, interleukin-6; Ras, rat sarcoma; GTP, guanosine triphosphate; Raf, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase.

Effect of IL-6 on tumor cells. Elevated IL-6 is consistently associated with adverse clinical outcomes in EGFR-mutant patients with NSCLC treated with EGFR-TKI (64). Specifically, IL-6 positivity by immunostaining (found in 46% of patients in one cohort) associates with notably worse PFS (43). Furthermore, higher pretreatment serum IL-6 levels predict reduced PFS and overall survival (OS) (65). This prognostic link extends to the point of acquired resistance, where IL-6 levels are substantially increased upon resistance development in both gefitinib- and osimertinib-treated patients. Notably, after gefitinib resistance emerges, patients with markedly elevated IL-6 have markedly shorter OS compared with those with lower levels (44). Collectively, these clinical observations substantiate that IL-6 plays a pivotal regulatory role in both outcomes of and therapeutic resistance mechanisms in *EGFR*-mutant patients with NSCLC.

Investigative studies reveal that IL-6 plays a pivotal role in conferring EGFR-TKI resistance through direct effects on tumor cells (66-68). Constitutive activation of the IL-6/JAK2/STAT3 signaling axis is observed in resistant cellular models (69). Mechanistically, this cascade mediates resistance via autocrine IL-6 production and STAT3 positive feedback activation, facilitating tumor cell survival and proliferation both *in vitro* and *in vivo* (67,70). Complementary preclinical investigations reveal that pharmacological inhibition of this signaling axis restored EGFR-TKI sensitivity in murine models, providing therapeutic proof-of-concept (68).

Furthermore, IL-6 contributes to acquired resistance by driving tumor cell-intrinsic EMT progression. Molecular analyses show that IL-6 suppresses E-cadherin and transcriptionally upregulates mesenchymal markers such as Snail and Vimentin (71). The self-sustaining IL-6/IGF-1R/STAT3 autocrine loop has been identified as a key EMT driver (72), with TGFβ cytokine coactivation shown to potentiate IL-6 pathway signaling and subsequent EMT progression. Notably, metformin administration has been shown to suppress EGFR-TKI-resistant xenograft tumorigenesis through dual mechanisms involving a reduction in IL-6 secretion and a reversal of the EMT phenotype (71). These studies illustrate the key role that IL-6 carries out in resistance to EGFR-TKI

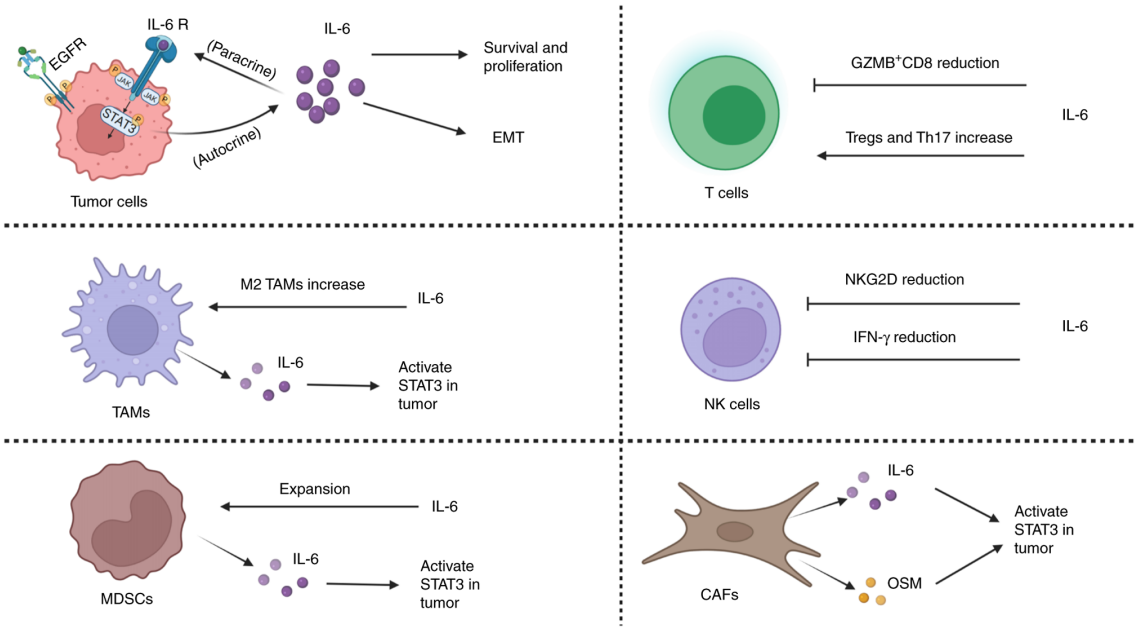

Figure 3. IL-6-mediated resistance to EGFR-TKI occurs via immune-suppressive microenvironment remodeling. IL-6 orchestrates therapeutic resistance in *EGFR*-mutated non-small cell lung cancer through dual mechanisms: transcriptional activation of EMT regulators and pro-survival genes coupled with systemic immunosuppression via TME modulation. EMT, epithelial-to-mesenchymal transition; TAMs, tumor-associated macrophages; NK cells, natural killer cells; MDSCs, myeloid-derived suppressor cells; CAFs, cancer-associated fibroblasts; OSM, oncostatin-M; IL-6, interleukin-6.

mediated by EMT, the IL-6/JAK/STAT3 signaling pathway and other mechanisms, thereby providing potential treatment options against resistance. In addition, IL-6 can regulate transcription factors governing DNA repair fidelity and cell cycle checkpoint control, potentially impairing genomic replication accuracy (73,74). These direct actions of IL-6 on tumor cells underscore its importance in survival, proliferation and resistance development.

Effect of IL-6 on immunosuppression: T cells and checkpoint dysregulation. Lymphocytes are fundamental to antitumor immunity, yet EGFR-TKI resistance is frequently characterized by the depletion of $CD8^+$ T cells and the expansion of immunosuppressive subsets (75,76). IL-6 acts as a central orchestrator of this T-cell dysfunction through distinct molecular mechanisms (52,77-79). Mechanistically, the IL-6 signaling exerts dual immunomodulatory effects by suppressing key cytotoxic mediators (IFN-γ, GM-CSF and CXCL9/10) while concurrently inducing IL-10 secretion and Th2/Th17-polarizing factors, thereby reprogramming $CD8^+$ T-cell differentiation toward dysfunctional states (80). In EGFR-TKI-resistant NSCLC microenvironments, IL-6-mediated downregulation of granzyme B expression considerably impairs $CD8^+$ T-cell cytotoxic capacity, establishing a direct association between cytokine signaling and immune effector dysfunction (81). Importantly, IL-6 drives T-cell exhaustion by engaging the programmed cell death-1 (PD-1)/PD-ligand (PD-L1) checkpoint axis. In the TME, macrophage-derived IL-6 promotes the membrane presentation of PD-1 on T cells via the Rab37/IL-6/STAT3 axis (82). Simultaneously, oncogenic IL-6/JAK/STAT3 signaling in *EGFR*-mutant tumor cells transcriptionally activates PD-L1 expression, thereby conferring a survival advantage through immune escape (83,84).

Beyond $CD8^+$ T cell suppression, IL-6 reprograms $CD4^+$ T-cell differentiation to reinforce the immunosuppressive niche (85). It promotes regulatory T-cell (Treg) differentiation via JAK/STAT3-dependent Foxp3 induction, a process potentiated by adenosine pathway activation (86,87). Furthermore, the IL-6/sIL-6R complex skews the balance toward a protumor Th17 phenotype via coordinated mTOR/STAT3 activation (88-90) while subverting Th1 responses through c-Maf-driven suppression (91). In EGFR-mutant murine models, ablating IL-6 notably reduces intratumoral Treg and Th17 infiltrates and downregulates PD-L1, effectively reversing T-cell exclusion and resistance (52,81).

Effect of IL-6 on immunosuppression: Natural killer (NK) cells. NK cells serve as a primary innate defense, but their surveillance capability is severely compromised in the EGFR-TKI-resistant microenvironment. Distinct from its effects on T cells, IL-6 blunts NK cell effector function by targeting activating receptors. Tumor-derived IL-6 triggers STAT3 phosphorylation in NK cells, which transcriptionally downregulates surface expression of NKp30 and NKG2D, thereby desensitizing resistant cells to NK-mediated lysis (81,92). Additionally, STAT3 binding to the IFN-γ promoter region directly antagonizes IFN-γ production (93). This IL-6-dependent downregulation of recognition receptors and cytokines establishes a specific mechanism of innate immune evasion during therapy.

Effects of IL-6 on immunosuppression: CAFs. CAFs are key stromal components that drive tumor progression through the secretion of soluble factors, notably IL-6 and TGF-β, orchestrating pro-tumorigenic processes such as angiogenesis, invasive growth and metastatic dissemination (94-98). CAFs themselves represent a notable source of IL-6 within the

TME. IL-6 directly impacts CAF behavior, stimulating the proliferation of normal fibroblasts and inducing a CAF-like phenotype (99,100). Pathophysiological investigations have revealed that bidirectional communication between EGFR-mutant NSCLC cells and CAFs sustains constitutive activation of the IL-6/JAK/STAT3 cascade in malignant cells, thereby conferring therapeutic resistance to EGFR-TKI across preclinical *in vitro* and *in vivo* models (67,101). Targeting the paracrine IL-6/JAK/STAT3 loop between fibroblasts and tumor cells (67) or employing agents such as tranilast that decrease CAFs-derived IL-6, effectively abrogates CAFs-mediated resistance (101). Beyond IL-6, CAFs also express other cytokines such as oncostatin-M (OSM). A preclinical study showed that combination therapy with EGFR-TKI and JAK1 inhibitors (for example, filgotinib) potently inhibits the fibroblast-activated OSMRs/JAK1/STAT3 axis, disrupting stroma-driven pathway crosstalk to prevent adaptive drug resistance (102).

Effect of IL-6 on immunosuppression: Macrophages. TAMs, which predominantly exhibit M2 polarization with a few M1 subpopulations, serve as pivotal mediators of tumor progression, metastatic dissemination and formation of an immunosuppressive microenvironment (103,104). In EGFR-TKI-resistant tissues, IL-6/JAK/STAT3 signaling drives the polarization of TAMs toward a protumor M2 phenotype (105). IL-6/JAK/STAT3 signaling orchestrates three cardinal TAM features, chemotactic migration, survival maintenance and M2 polarization, which are characterized by arginase-1 (Arg1) overexpression coupled with inducible nitric oxide synthase downregulation (106). Concurrently, TAMs can also secrete IL-6 to promote lung cancer progression and metastasis (107,108). Previous mechanistic insights reveal that phase separation of YY1 transcriptional complexes in M2 TAMs enhances chromatin accessibility at IL-6 regulatory regions, amplifying IL-6 transcription and creating a self-reinforcing loop (109). Functional crosstalk analyses also demonstrate that TAM-derived IL-6 activates COX-2/PGE2 cascades in adjacent tumor cells, inducing EMT (110). Thus, IL-6 coordinates a dual mechanism in the myeloid compartment: Promoting M2-mediated tissue remodeling and enforcing intercellular communication.

Effects of IL-6 on immunosuppression: MDSCs. MDSCs are heterogeneous progenitors that markedly contribute to therapeutic refractoriness (111). Elevated cytokine levels in the serum of patients with EGFR-TKI-resistant NSCLC associate with MDSC expansion and poor prognosis (112,113). IL-6 serves as a master regulator of MDSC biology through specific epigenetic and metabolic reprogramming. Mechanistically, STAT3-mediated chromatin remodeling at the Arg1 promoter drives the immunosuppressive polarization of MDSCs (114-120). Concurrently, IL-6 primes MDSCs to undergo metabolic rewiring (enhanced glycolysis/oxidative phosphorylation) and suppresses their antigen presentation machinery (121). These functional alterations collectively potentiate MDSC-mediated T-cell suppression, positioning the IL-6 axis as a strategic target to dismantle the myeloid barrier in resistant tumors.

Taken together, IL-6 serves as a pivotal nexus connecting EGFR-TKI resistance with the immunosuppressive TME. Under persistent selective pressure from EGFR-TKI, surviving tumor cells exhibit markedly upregulated IL-6 secretion. Once released into the microenvironment, IL-6 triggers sustained activation of the intrinsic JAK/STAT3 pathway via either classical or trans-signaling modes. This establishes a self-reinforcing autocrine loop that directly orchestrates resistance-associated phenotypes, including EMT and the expression of pro-survival genes. Importantly, IL-6 also actively induces and sustains an immunosuppressive TME. This landscape is characterized by the functional impairment of effector T cells and NK cells, coupled with the recruitment and polarization of suppressive subsets such as Tregs, TAMs and MDSCs. Notably, this remodeling is not a unidirectional process; immunosuppressive cells and stromal components (for example, TAMs and CAFs) also serve as prolific sources of IL-6, thereby amplifying the signaling cascade. Paracrine IL-6 from these accessory cells feeds back to the tumor cells, further fueling downstream pathways to sustain tumor growth and the resistant phenotype. Within the context of *EGFR*-mutant NSCLC, this reciprocal 'crosstalk' and mutual reinforcement among tumor, immune and stromal cells constitute a vicious cycle that drives EGFR-TKI resistance. Consequently, IL-6 functions as a key bridge, inextricably linking intrinsic TKI tolerance mechanisms with complex immune evasion strategies to establish a synergistic resistance axis. Targeting this IL-6-driven axis thus provides a compelling theoretical rationale for developing novel combination therapeutic strategies to overcome EGFR-TKI resistance.

5. Targeting IL-6 to overcome EGFR-TKI resistance

IL-6 signaling inhibitors in EGFR-TKI-refractory NSCLC. Multiple preclinical studies and clinical trials examining IL-6 pathway blockade in EGFR-TKI-resistant NSCLC have been summarized in Table I (44,53,68,69,101,102,122-128), some of which are aforementioned. The majority of these studies have focused only on the production of IL-6 and its signaling pathway.

Siltuximab (CNTO328), an IL-6 neutralizing antibody, inhibited the proliferation of H1650 cells, whereas the combination of siltuximab and erlotinib resulted in more pronounced inhibition of tumor growth in a mouse model (122). In *EGFR*-mutant tumor cells that are resistant to gefitinib due to IL-6 induction, miR-206 directly targets the 3'-UTR of intracellular IL-6 messenger RNA to block IL-6/JAK/STAT3 signaling, thereby restoring gefitinib sensitivity (123). Compared with no treatment, the addition of IL-6 to erlotinib-sensitive cells increased drug resistance. Additionally, the presence of IL-6 did not prevent the restoration of cell sensitivity to erlotinib by treatment with P6 (a JAK1/2 inhibitor) (68). The JAK inhibitor AZD1480 showed anticancer and antiangiogenic effects (129,130). AZD1480 alleviated sevoflurane-induced lung metastasis by disrupting the IL-6/JAK/STAT3 pathway (131). Furthermore, in mice bearing *EGFR*-driven lung cancer, AZD1480 showed marked antitumor activity and extended survival time (124). However, erlotinib and momelotinib (JAK1/2 and TBK1 inhibitors) did not appear to provide a greater benefit compared with erlotinib monotherapy in *EGFR*-mutated patients with NSCLC (125).

Table I. Preclinical studies of targeting IL-6-targeted drugs in *EGFR*-mutant lung cancer.

Target molecule	Therapeutic approach	Models	(Refs.)
IL-6/IL-6R	Siltuximab	*In vitro and vivo*	(122)
	miR-206	*In vitro*	(123)
	Tranilast	*In vitro and vivo*	(101)
JAK	P6	*In vitro*	(68)
	Ruxolitinib	*In vivo*	(53)
	AZD1480	*In vitro and vivo*	(124)
	Filgotinib	*In vitro*	(102)
	Momelotinib	Clinical trial (NCT02206763)	(125)
STAT3	Ibrutinib	*In vivo*	(44)
	AZD9150	*In vitro and vivo*	(126)
	HKB99	*In vitro and vivo*	(69)
	WP1066	*In vitro*	(128)
	TPCA-1	*In vitro and vivo*	(127)

Ibrutinib consistently and effectively suppressed the levels of phosphorylated STAT3, which is a powerful inhibitor of IL-6 and laminin α5/FAK signaling. The combination of ibrutinib and osimertinib can reverse resistance to osimertinib and inhibit tumor growth in xenografts (44). Similar findings have been reported for AZD9150 (an inhibitor of STAT3), in which systemic treatment of mice bearing PC-9 tumors with AZD9150 led to the almost complete suppression of tumor growth (126). HKB99 (a PGAM1 allosteric inhibitor) disrupted IL-6/JAK/STAT3 signaling by decreasing the level of phosphorylated (p)-STAT3. Additionally, when combined with osimertinib, HKB99 exerted a synergistic tumoricidal effect and markedly restored the sensitivity to EGFR-TKI (69). A cell experiment revealed that WP1066, a known STAT3 inhibitor, could cause H1650 cells to undergo apoptosis, with an inhibitory effect on tumor growth (128). When EGFR-TKI and TPCA-1, a dual inhibitor of both IKKs and STAT3, are coupled together, *EGFR*-mutated NSCLC is more sensitive to gefitinib (127).

Homoharringtonine possesses anticancer properties, as demonstrated by its ability to reversibly inhibit the IL-6-induced phosphorylation of STAT3 at the Tyr705 site in a mouse model of EGFR-TKI resistance (132). A naturally occurring chemical substance called polyphyllin I (PPI) has anticancer properties and reduces the activation of the IL-6/STAT3 pathway in erlotinib-resistant cells. The combined use of PPI and EGFR-TKI reduces tumor growth and reverses acquired resistance in xenografts (133).

However, following the onset of EGFR-TKI resistance, therapeutic strategies targeting the IL-6/JAK/STAT3 pathway alone often yield suboptimal results. One of the primary hurdles in achieving robust clinical efficacy is the inherent cytokine redundancy within the TME. IL-6 belongs to a larger family of cytokines, including leukemia inhibitory factor, OSM and IL-11, all of which converge on the common signal-transducing receptor subunit, gp130 (48,134-136). Furthermore, the IL-6/JAK/STAT3 axis operates as an integral part of a complex, interconnected network. Tumor cells frequently develop compensatory mechanisms to bypass specific pathway blockade. For instance, the inhibition of JAK/STAT3 signaling may trigger compensatory activation of the PI3K/AKT or MEK pathways, enabling cancer cells to sustain survival and proliferation, thereby limiting therapeutic efficacy (137,138). Clinical data (NCT00841191) from trials of Siltuximab (a chimeric anti-IL-6 monoclonal antibody) have shown that while systemic CRP levels (a surrogate for IL-6 activity) are successfully suppressed, intratumoral p-STAT3 levels often persist, suggesting that the 'gp130-JAK-STAT3' hub remains fueled by alternative ligands. This signaling bypass renders the selective blockade of a single cytokine insufficient to dismantle the pro-tumorigenic niche, necessitating a shift toward targeting the shared gp130 receptor or the downstream STAT3 transcription factor.

Effect of IL-6 combined immunotherapy after EGFR-TKI resistance. Immunotherapy has been among the greatest advances in previous years for the treatment of solid tumors, including NSCLC (139,140). EGFR-TKI resistance upregulates PD-L1 expression in NSCLC, providing a theoretical basis for immunotherapy (Table II). However, negative results from large clinical studies suggest that patients who develop resistance to EGFR-TKI have difficulty benefiting from treatment with immunotherapy alone or immunotherapy combined with chemotherapy (141-143). This poor response to immunotherapy is largely attributed to an immunosuppressive TME. Here, IL-6 carries out a pivotal role. IL-6 levels are substantially increased upon resistance development in EGFR-TKI-treated patients (44,65). IL-6 may orchestrate multifaceted immunomodulatory effects within the TME of *EGFR*-mutant NSCLC through the following mechanisms: First, suppression of antitumor immunity: IL-6 exerts inhibitory effects on effector T cells, NK cells and DCs, with experimental evidence suggesting that IL-6/JAK/STAT3 pathway activation in these immune subsets likely drives downregulation of the antitumor response (144-146). Second, promotion of immunosuppressive networks: Concurrently, IL-6 enhances the expansion and function of immunosuppressive cell populations, including MDSCs and Tregs, while polarizing macrophages toward the M2 phenotype (147,148). Third, immune checkpoint modulation: IL-6 further disrupts immune-tumor crosstalk by upregulating PD-1/PD-L1 expression, thereby fostering an immune-evasive niche (149,150). These effects contribute to a highly immunosuppressive TME, which in turn may mediate resistance to EGFR-TKI. The inhibition of IL-6/JAK/STAT3 signaling can also affect the TME and has implications for antitumor immunity. Consequently, dual targeting of IL-6 signaling and the PD-1/PD-L1 axis represents a promising therapeutic approach to overcome resistance to EGFR-TKI in NSCLC.

Currently, there are Phase I and II clinical trials evaluating the efficacy and safety of the combination of anti-IL-6R and anti-IL-6 with immunotherapy in patients with NSCLC (Table SI). The CANOPY-1 trial demonstrated that elevated baseline plasma IL-6 levels associate with shorter OS in immunotherapy-treated patients with NSCLC (149). Similarly, longitudinal increases in IL-6 levels during PD-1/PD-L1 blockade were associated with diminished therapeutic responses

Table II. Clinical trials on ICI-based treatment strategies for advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs.

Research design	Clinical trials	Treatment regimens	Sample size	PFS (m)	OS (m)
Immunotherapy	WJOG8515L	Nivolumab vs. Pemetrexed plus carboplatin	52:50	1.7 vs. 5.6	20.7 vs. 19.9
Immunotherapy plus chemotherapy	Checkmate 722	Nivolumab plus Pemetrexed plus Cisplatin plus Carboplatin vs. Pemetrexed plus Cisplatin plus Carboplatin	144:150	5.6 vs. 5.4	19.4 vs. 15.9
	KEYNOTE789	Pembrolizumab plus pemetrexed plus choice of cisplatin or carboplatin vs. Pemetrexed choice of cisplatin or carboplatin	245:247	5.6 vs. 5.5	15.9 vs. 14.7
Immunotherapy plus chemotherapy plus VEGF inhibitor	ORIENT-31 cisplatin	Sintilimab plus IBI305 plus pemetrexed and vs. Sintilimab plus pemetrexed and cisplatin vs. Pemetrexed and cisplatin	158:158:160	7.2 vs. 5.5 vs. 4.3	21.1 vs. 20.5 vs. 19.2
	IMpower 150	Atezolizumab plus bevacizumab plus carboplatin and paclitaxel vs. Atezolizumab plus carboplatin and paclitaxel vs. Bevacizumab plus carboplatin and paclitaxel	34 vs. 45 vs. 44	10.2 vs. 6.9 vs. 6.9	26.1 vs. 21.4 vs. 20.3
	ATTLAS	Atezolizumab plus bevacizumab plus paclitaxel and carboplatin vs. Pemetrexed plus carboplatin or cisplatin	151:74	8.48 vs. 5.62	20.63 vs. 20.27
	HARMONi-A	Ivonescimab plus pemetrexed and carboplatin vs. Pemetrexed and carboplatin	161:161	7.1 vs. 4.8	/
Immunotherapy plus VEGF inhibitor	ML41256	Atezolizumab plus bevacizumab	20	2.8	/
	ALTER-L038	Benmelstobart plus anlotinib	55	9.0	28.9

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; PFS, progression-free survival; OS, overall survival; VEGF, vascular endothelial growth factor.

in NSCLC cohorts (82). Furthermore, elevated plasma cytokine profiles, including those of IL-6, TNF and IL-8, have been implicated in immunotherapy resistance (151). Preclinical studies substantiate these findings, showing that inhibition of the IL-6 pathway augments immunotherapy efficacy through immune cell modulation within the TME (152,153). For instance, dual administration of anti-IL-6 and anti-PD-1 antibodies in pancreatic cancer murine models enhanced anti-tumor activity and promoted T lymphocyte infiltration (153). Analogously, coordinated blockade of IL-6 and PD-1/PD-L1 signaling in melanoma models upregulates the expression of T-cell-recruiting chemokines and increases the infiltration of IFN-γ-producing $CD4^+$ T cells, yielding synergistic antitumor effects (152). Notably, retrospective analyses revealed that patients with NSCLC with low baseline IL-6 levels in plasma or tumor tissues derived greater clinical benefit from immunotherapy. Preclinically, dual targeting of IL-6 and immune checkpoints attenuated tumor growth and improved survival in NSCLC-bearing mice. Mechanistically, inhibition of IL-6 expression increases $CD8^+$ T-cell infiltration while reducing the numbers of $PD1^+CD8^+$-exhausted T cells and M2 macrophages within the TME (52,82). Moreover, IL-6 blockade sensitized tumors to immunotherapy through the activation of T and NK cells in *EGFR*-mutant genetically engineered mouse model (81). Depletion of IL-6 restored the cytotoxic potential of NK cells in EGFR-TKI-resistant tumors (81). Collectively, these findings suggest that IL-6 is a rational immunomodulatory target for increasing immunotherapy efficacy in EGFR-TKI-resistant NSCLC. However, definitive clinical validation through dose-optimized trials remains imperative.

Effect of IL-6 combined with anti-angiogenic after EGFR-TKI resistance. The hyperactivation of STAT3, a downstream effector of IL-6, a key transcriptional regulator for angiogenic factors, most notably vascular endothelial growth factor, thereby facilitating the neovascularization required for tumor maintenance and dissemination (154,155). Consequently, the IL-6/JAK/STAT3 axis acts as a pro-angiogenic signaling node; its activation not only promotes tumor cell survival but also remodels the vascular microenvironment. Preclinical evidence supports this strategy: the JAK inhibitor AZD1480 has demonstrated dual anticancer and anti-angiogenic properties (129,130). Furthermore, in murine models of EGFR-driven lung cancer, AZD1480 treatment elicits marked antitumor activity and notably extended survival (124), underscoring the potential of targeting this axis to suppress both tumor growth and pathological angiogenesis.

6. Conclusion and future prospects

In conclusion, the IL-6/JAK/STAT3 signaling axis represents a pivotal mechanism of adaptive resistance in *EGFR*-mutant NSCLC, orchestrated through intricate crosstalk between tumor cells, stromal components and infiltrating immune subsets within the TME, leading to improved immunotherapy efficacy. While preclinical data have demonstrated that IL-6 blockade can restore sensitivity to EGFR-TKI and potentially sensitize tumors to immunotherapy, the translation of these findings into clinical practice faces hurdles. Substantial preclinical and clinical research will be needed to determine the exact efficacy of this strategy.

Clinical trials and translational challenges. Currently, large-scale Phase III clinical trials specifically evaluating IL-6/JAK/STAT3 inhibitors in EGFR-mutant NSCLC populations are lacking. The majority of existing evidence is derived from broader NSCLC cohorts or early-phase studies. A considerable challenge observed in immunotherapy trials, such as CANOPY-1, is the variable efficacy of cytokine blockade, underscoring the necessity of identifying specific responder populations. Furthermore, pharmacological interactions pose a translational barrier; for instance, elevated plasma IL-6 concentrations have been associated with reduced metabolic activity of osimertinib, potentially altering drug exposure and efficacy (156). This highlights the need for rigorous pharmacokinetic evaluations when combining IL-6 inhibitors with third-generation EGFR-TKI.

The lack of robust biomarkers for patient stratification remains a major limiting factor. Plasma IL-6 and soluble IL-6R levels have shown prognostic value, where elevated concentrations associate with shorter OS in patients treated with EGFR-TKI or immunotherapy (44,52,149). Tissue p-STAT3 levels serve as a direct indicator of downstream signaling activation. Validating these biomarkers in prospective trials is essential to transition from general cytokine inhibition to precision medicine strategies.

Despite the compelling preclinical rationale connecting IL-6 signaling to EGFR-TKI resistance, several key knowledge gaps must be bridged to facilitate successful clinical translation. First, the spatiotemporal heterogeneity of the IL-6 pathway remains elusive. It is imperative to determine whether the dominant cellular sources of IL-6, and the intensity of signaling, vary between primary tumors and metastatic sites or evolve dynamically from the initial TKI-sensitive phase to the onset of acquired resistance (67,81). Second, the optimal timing of intervention is currently undefined. Future studies must distinguish whether IL-6 blockade yields superior outcomes as an upfront prophylactic strategy to delay resistance or as a salvage regimen upon disease progression. Third, the choice of optimal therapeutic drugs warrants comparative investigation. The efficacy-toxicity profiles of directly neutralizing IL-6, blocking IL-6R, inhibiting JAK, vs. targeting STAT3 downstream, remain to be systematically evaluated in the context of EGFR-mutant NSCLC (see Table I for preclinical agents). Finally, translational success will depend on a holistic understanding of the dynamic crosstalk between IL-6 and other oncogenic pathways, as well as the optimization of dosing schedules and patient selection to manage potential side effects. Addressing these complexities is essential to transform IL-6 inhibition from a theoretical concept into a precise, effective combination strategy for *EGFR*-mutant NSCLC.

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Authors' contributions

QW, CH and YZ wrote the manuscript and designed all the figures and tables in consultation with the other authors. HZ, CQ and ST contributed to the writing and editing of the manuscript. WL, YL and PT developed the concept and reviewed and edited the manuscript. All the authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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