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(REVIEW ARTICLE)

Targeting the IL-6/STAT3 signaling pathway to reverse chemoresistance in ovarian cancer

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Abstract

Ovarian cancer remains one of the most lethal gynecologic malignancies worldwide, mainly because it is often diagnosed at an advanced stage and frequently develops resistance to chemotherapy. Recent studies have identified the interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling pathway as a key driver of ovarian cancer progression and treatment resistance. This review discusses the biological functions of IL-6 and STAT3 and highlights their roles in ovarian cancer development, progression, and chemoresistance. Activation of the IL-6/STAT3 pathway promotes tumor cell proliferation, survival, angiogenesis, epithelial–mesenchymal transition, invasion, and metastasis. In addition, persistent STAT3 activation contributes to an immunosuppressive tumor microenvironment by reducing anti-tumor immune responses and enhancing immune evasion. The pathway also plays an important role in chemotherapy resistance through the regulation of apoptosis, cancer stemness, metabolic adaptation, and interactions with other oncogenic signaling networks. Given its broad involvement in tumor biology, the IL-6/STAT3 axis has emerged as a promising therapeutic target. Several agents targeting IL-6, IL-6 receptors, JAK kinases, and STAT3 have shown encouraging results in preclinical and early clinical studies, particularly when combined with standard chemotherapy. A better understanding of this signaling pathway may support the development of more effective treatment strategies and improve outcomes for patients with ovarian cancer.

Keywords: Ovarian Cancer; IL-6; STAT3; Chemoresistance; Tumor Microenvironment; Targeted Therapy

1. Introduction

As one of the most lethal gynecologic malignancies worldwide, ovarian cancer causes more than 200,000 deaths annually [1]. The high mortality rate is mainly due to late diagnosis, aggressive behavior, and high recurrence rate [2,3]. Ovarian cancer usually responds well to first-line chemotherapy, however, recurrency rates are high and are usually followed by development of chemoresistance [4]. Nearly 10% of patients with early-stage disease and more than 85% of patients with advanced-stage disease eventually experience cancer recurrence [4,5].

Recent studies highlighted the importance of inflammatory signaling pathways in ovarian carcinogenesis, particularly the interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) pathway [6,7]. Constant activation of this pathway has been associated with tumor proliferation, angiogenesis, metastasis and immune evasion in many cancers [8,9]. Recent evidence indicates that persistent activation of the IL-6/JAK2/STAT3 signaling pathway plays a central role in the development of chemotherapy resistance [10,11]. That is why understanding the molecular

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mechanisms of IL-6/STAT3 signaling in ovarian cancer carcinogenesis may provide better insights into ovarian cancer chemoresistance and potential alternative therapies.

This review aims to discuss the pathophysiological role of the IL-6/STAT3 axis in ovarian cancer. We review the molecular mechanisms of IL-6/STAT3 signaling, particularly its role in the development of chemoresistance in ovarian cancer. In addition, we summarize current therapeutic approaches targeting this pathway in ovarian cancer. Understanding the precise role of the IL-6/STAT3 signaling in ovarian cancer may contribute to the development of more effective therapeutic strategies and improve patient outcomes.

2. Results and discussion

2.1. Interleukin-6 and Its Biological Functions

IL-6 is a pleiotropic cytokine involved in immune regulation, hematopoiesis, inflammation, and tissue homeostasis [12]. The IL-6 gene is located on chromosome 7p21 and encodes a protein consisting of 212 amino acids with a molecular weight ranging from 21–26 kDa due to glycosylation [12,13]. IL-6 is produced by various cell types, including neutrophils, macrophages, monocytes, fibroblasts, endothelial cells, lymphocytes, keratinocytes, and mesangial cells [14,15].

Under normal conditions, IL-6 maintains homeostasis and regulates cellular proliferation and differentiation [12]. However, in ovarian cancer this cytokine plays an important role in creating a favorable microenvironment for cancer cells [16]. IL-6 is secreted by tumor and stromal cells, including cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and endothelial cells [12,13,16]. IL-6 produced by CAFs contributes to extracellular matrix remodeling and epithelial–mesenchymal transition (EMT) [17]. TAMs secretes IL-6 to promote immunosuppressive environment and immune escape [14,18]. On the other hand, angiogenesis is also stimulated by IL-6 under hypoxic conditions through vascular endothelial growth factor (VEGF) [9,19].

2.2. IL-6 Signaling Pathways

IL-6 initiates intracellular signaling through three major mechanisms: classic signaling, trans signaling, and transpresentation signaling [20,21]. In classic signaling, IL-6 binds to membrane-bound IL-6 receptor (IL-6R), which then activates glycoprotein 130 (gp130) and initiates intracellular signaling. In trans signaling, IL-6 binds to a soluble IL-6 receptor (sIL-6R) that occurs due to proteolytic cleavage by ADAM17. The IL-6/sIL-6R complex activates gp130 on target cells [21]. In trans-presentation signaling, IL-6 bound to IL-6R on dendritic cells is then presented to T cells, resulting in gp130 activation and T-cell differentiation [20,21].

Activation of gp130 induces multiple downstream signaling cascades, including the JAK/STAT3 pathway, PI3K/Akt/mTOR pathway, and Ras/mitogen-activated protein kinase (MAPK) pathway [22]. These pathways regulate multiple cellular responses including proliferation, apoptosis resistance, metabolism, cell differentiation, and angiogenesis [6,22].

2.3. STAT3 Activation and Oncogenic Functions

STAT3 is an essential transcription factor in cell growth, immune regulation, and homeostasis. STAT3 activation is tightly regulated. However, in many cancers, constitutive STAT3 activation is common and usually associated with aggressive tumor behavior [23].

Kinases such as JAK2, SRC, and receptor tyrosine kinases activate STAT3 through phosphorylation of its tyrosine residue Tyr705 [6,24]. After that, STAT3 undergoes dimerization and translocates to the nucleus, where it regulates genes involved in proliferation (cyclin D1, c-Myc), anti-apoptosis (Bcl-xL, survivin), invasion (MMP-9), angiogenesis (VEGF), and cancer cell stemness (CD44, ALDH1) [24–26].

Constitutive activation of STAT3 promotes tumor proliferation, metastasis, angiogenesis, EMT, and resistance chemotherapy. Elevated STAT3 and phosphorylated STAT3 (p-STAT3) has been correlated with advanced FIGO stage, lymph node metastasis, tumor recurrence, and poor overall survival in ovarian cancer patients [27].

2.4. IL-6/STAT3 Axis in Ovarian Cancer

The IL-6/STAT3 signaling pathway plays an important role in ovarian cancer progression. Many studies have demonstrated that IL-6 promotes ovarian cancer cell proliferation, migration, invasion, and angiogenesis [28,29].

Furthermore, constitutive activation of STAT3 is commonly observed in epithelial ovarian carcinoma, particularly aggressive subtypes such as high-grade serous carcinoma and clear cell carcinoma. Overexpression of pSTAT3 has also been associated with advanced FIGO stage, lymph node metastasis, disease recurrency, chemoresistance, and poor overall survival [30–32].

STAT3 expression is often higher in recurrent ovarian tumors compared to primary tumors, suggesting its role in disease recurrence and therapy resistance [33]. Additionally, because of the complex crosstalk between intracellular signalling, therapies targeting other oncogenic pathways, such as PI3K/AKT and MAPK pathway, may unintentionally enhance STAT3 signaling through compensatory feedback mechanisms [34]. This will promote tumor cell survival and therapeutic resistance. These findings highlight the central role of the IL-6/STAT3 axis in ovarian cancer biology.

2.5. The Role of IL-6/STAT3 axis in Ovarian Cancer Progression

2.5.1. Cell Proliferation

IL-6 promotes ovarian cancer cell proliferation primarily through activation of the JAK2/STAT3 signaling pathway. STAT3 activation induces transcription of cell-cycle regulatory proteins, including c-MYC, cyclin D1, cyclin D2, cyclin B1, and survivin, while suppressing cyclin-dependent kinase inhibitors such as p21 and p27 [35–37]. These molecular changes facilitate cell-cycle progression, resulting in uncontrolled tumor cell proliferation.

Experimental studies have demonstrated that inhibition of the IL-6/STAT3 axis suppresses ovarian cancer cell growth. Treatment with bazedoxifene, an IL-6/gp130 inhibitor, reduced proliferation in ovarian cancer cell lines such as CAOV-3, OVCAR-3, and SKOV-3 [37,38]. Similarly, suppression of STAT3 expression using small interfering RNA (siRNA) decreased cyclin D1 and survivin expression, inhibited tumor growth, and induced apoptosis [39,40].

STAT3 also contributes to metabolic adaptation in ovarian cancer cells. STAT3 activation enhances expression of glucose-6-phosphate dehydrogenase (G6PD), promoting the pentose phosphate pathway and supporting nucleotide synthesis, antioxidant defense, and resistance to Taxol-based chemotherapy [41,42].

2.5.2. Invasion and Metastasis

Most solid tumors metastasise through blood circulation or lymphatic vessels. However, ovarian cancer cells spread through transcoelomic dissemination within the peritoneal cavity. Ovarian cancer cells can survive and proliferate in ascitic fluid, allowing implantation onto peritoneal surfaces such as the omentum, bowel, and bladder [43].

IL-6/STAT3 axis plays a crucial role in promoting invasion and metastasis of cancer cells. STAT3 stimulates the activation of EMT transcription factors such as ZEB1, SNAIL1, SNAIL2, and Slug, which facilitate EMT and promote invasion [9,44]. During EMT, epithelial cells lose their polarity and the adhesion molecules E-cadherin. The loss of E-cadherin is usually followed by the gain of mesenchymal markers such as vimentin and N-cadherin, which then shifts the epithelial characteristic into mesenchymal phenotype and increases migratory and invasive ability [9].

STAT3 activation also promotes the secretion of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9. MMPs are enzymes that degrade extracellular matrix components and facilitate tumor invasion. Elevated MMP-9 expression has been associated with poor prognosis and decreased survival in ovarian cancer patients [31,45].

Due to rapid growth and lack of vascularisation, the tumor microenvironment tends to be hypoxic. Hypoxia further enhances IL-6/JAK2/STAT3 mediated EMT through interaction with hypoxia-inducible factor-1 alpha (HIF-1α) [46]. This signaling crosstalk strengthens mesenchymal phenotypes and contributes to metastasis and chemoresistance. Additionally, STAT3 signaling contributes to cancer stemness by inducing the expression of stemness markers such as CD44 and ALDH1 which have also been associated with metastatic spread [47].

2.5.3. Angiogenesis and Immune Evasion

Angiogenesis is essential for tumor growth and metastasis because it supplies oxygen and nutrients to tumor tissues. IL-6/STAT3 axis plays a role in angiogenesis primarily through upregulation of VEGF. STAT3 induces VEGF transcription under both normal and hypoxic conditions [48]. Interaction between STAT3 and HIF-1α further amplifies VEGF expression and promotes neovascularization [49].

IL6 and STAT3 are known to regulate immune response in the ovarian tumor microenvironment. IL-6 plays an important role in regulating immune responses, with early IL-6 signaling initially promoting immune cell activation.

However, chronic inflammation and sustained IL-6 activation contribute to an immunosuppressive tumor microenvironment by increasing regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 tumor-associated macrophages (TAMs), while suppressing cytotoxic T-cell and natural killer (NK) cell activity [18,50].

On the other hand, persistent STAT3 activation in immune cells promotes immunosuppressive tumor microenvironment. STAT3 suppresses the activity of cytotoxic CD8+ T cells and natural killer (NK) cells, reduces dendritic cell maturation and antigen presentation, and enhances the expansion of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [51]. These effects collectively impair immune surveillance and facilitate tumor immune escape. STAT3 also regulates macrophage polarization by promoting the M2 tumor-associated macrophage phenotype, which supports tissue remodeling, angiogenesis, and tumor invasion [52]. Additionally, STAT3 signaling increases the production of immunosuppressive cytokines such as IL-10 and VEGF, further reinforcing chronic inflammation and metastatic progression [51,52].

Recent studies have also shown that treatment with PARP inhibitor (PARPi) increased STAT3 activation in ovarian cancer cells, tumor-associated immune cells, and CAFs. This promoted an immunosuppressive tumor microenvironment by reducing IFN-γ and Granzyme B expression while increasing IL-10 production, potentially contributing to tumor progression and recurrence [53].

2.6. IL-6/STAT3 axis in Chemoresistance

Most ovarian cancer patients initially respond well to first-line platinum-based chemotherapy. However, acquired resistance to platinum and taxane chemotherapy develops during repeated treatment cycles of chemotherapy. [22]

Elevated IL-6 and IL-6 receptor (IL-6R) expression in ovarian cancer cell lines such as OVCAR-3 and SKOV-3 has been associated with multiple chemotherapeutic agents resistance such as carboplatin, cisplatin, gemcitabine, and vincristine [54]. Inhibition of IL-6 signaling using tocilizumab, an anti-IL-6R monoclonal antibody, combined with carboplatin has demonstrated reduced tumor cell proliferation, suggesting that blockade of IL-6 signaling may restore chemosensitivity [37].

The IL-6/JAK2/STAT3 pathway contributes to chemoresistance through multiple interconnected molecular mechanisms. One important mechanism underlying chemoresistance involves the formation of polyploid giant cancer cells (PGCCs), which is usually found in high-grade serous carcinoma following chemotherapy. Chemotherapeutic agents such as paclitaxel disrupt mitotic spindle formation, causing mitotic arrest and triggering endoreplication. This process leads to the development of PGCCs that exhibit stem cell-like properties. IL-6 facilitates PGCC formation through autocrine signaling loops that reprogram tumor and stromal cells to create a protective tumor microenvironment that supports cell survival during chemotherapy.[55]

Furthermore, activation of STAT3 leads to upregulation of anti-apoptotic genes and modulates drug transporters which affect the efficacy of chemotherapeutic agents such as doxorubicin [35,53].

Activation of STAT3 also leads to activation of multiple pathways including MAPK and PI3K/AKT pathway. These pathways suppress stress induced autophagy and reduce apoptosis by chemotherapeutic agents such as cisplatin. It has been found that drug resistance is related to decreased expression of autophagy markers including pPERK, peIF2α, ATF6α, and IRE1α. Furthermore, evidence suggests that therapies targeting alternative oncogenic pathways may unintentionally enhance STAT3 activation through compensatory feedback mechanisms. Inhibition of pathways such as PI3K/AKT or MEK/ERK can paradoxically increase IL-6/JAK2/STAT3 signaling, contributing to therapeutic resistance and tumor cell survival. [34,45,56]

Cross-talk between JAK2/STAT3 signaling and oncogenic pathways involving p53 and RAS also enhances resistance. Wild-type p53 counteract STAT3 mediated resistance by promoting autophagy and stress responses, whereas RAS mutations enhance STAT3 activation and resistance mechanisms.[57]

2.7. Emerging Therapeutic Strategies Targeting IL-6/STAT3 Pathway

Given its central role in ovarian cancer progression and chemoresistance, the IL-6/STAT3 pathway is a potential therapeutic target. Multiple strategies targeting different components of this signaling cascade are currently under investigation.

2.7.1. IL-6 and IL-6R Inhibitors

Direct inhibition of IL-6 is one of the most promising approaches. Siltuximab, a monoclonal antibody targeting IL-6, has demonstrated the ability to suppress IL-6 signaling and inhibit cancer stem cell formation. Although early-phase clinical trials showed acceptable tolerability, clinical efficacy in advanced ovarian cancer remains limited. This highlights the complexity of advanced tumor oncogenic pathways. [37,58]

Targeting the IL-6 receptor has also shown promising results. Monoclonal antibodies such as tocilizumab, sarilumab, and satralizumab have demonstrated anti-tumor activity in preclinical studies. Tocilizumab, in particular, has been shown to restore sensitivity of carboplatin resistant ovarian cancer cells and induce apoptosis when combined with chemotherapy. [59,60]

2.7.2. STAT3 Inhibitors

STAT3 acts as a major downstream effector of the IL-6 signaling. Direct inhibition of STAT3 has become a major focus of targeted therapy research. Several small-molecule inhibitors targeting STAT3 phosphorylation, dimerization, or DNA-binding activity have demonstrated promising preclinical efficacy.

WP1066 suppresses STAT3 phosphorylation and sensitizes ovarian cancer cells to cisplatin. HO-3867 inhibits STAT3 activation and suppresses tumor growth, angiogenesis, invasion, and metastasis. Additional inhibitors such as Stattic, OP-B, indirubin, AG490, ruxolitinib, and YHO-1701 target either STAT3 domains or upstream kinases including JAK2. [61–63]

LLL12B, a novel selective STAT3 inhibitor, directly binds the SH2 domain of STAT3 and prevents Tyr705 phosphorylation and dimerization. Combination therapy using LLL12B together with cisplatin or paclitaxel demonstrated synergistic anti-tumor effects, including reduced cell viability, migration, and proliferation. [64]

JAK inhibitors such as ruxolitinib are also promising therapeutic agents because they block phosphorylation of STAT3. Inhibition of JAK2/STAT3 signaling not only suppresses tumor growth but also restores autophagy, reverses EMT, and improves chemosensitivity. [65]

2.7.3. RNA Interference and Oligonucleotide-Based Therapy

RNA interference (RNAi) based therapeutic approaches have gained increasing attention. Small interfering RNA (siRNA) and antisense oligonucleotides (ASOs) targeting STAT3 significantly reduce expression of proliferative and survival-associated genes including CCND1, BIRC5, and VEGF. In ovarian cancer cell lines such as SKOV3 and OVCAR3, specific siRNA suppresses proliferation and induces apoptosis.[40]

Decoy oligodeoxynucleotides are also another innovative strategy. These short DNA fragments competitively bind STAT3 and prevent interaction with promoter regions of target genes. STAT3 decoy oligodeoxynucleotides reduce invasion, migration, metastasis, and resistance to paclitaxel while simultaneously suppressing expression of proteins associated with drug resistance such as Akt, P-glycoprotein (P-gp), and EMMPRIN. [66]

2.7.4. NF-κB and Tyrosine Kinase Inhibitors

NF-κB also regulates IL-6 signaling. Inhibiting NF-κB may reduce IL-6 production and suppress downstream activation. Bortezomib, an NF-κB inhibitor widely used in multiple myeloma, has been investigated in recurrent ovarian cancer, although toxicity remains a significant limitation. [67,68]

Tyrosine kinase inhibitors such as dasatinib, saracatinib, and bosutinib may also interfere with IL-6-related signaling by suppressing multiple pathways including MAPK/ERK and NF-κB pathway. [69]

3. Conclusion

The IL-6/STAT3 signaling pathway plays a central role in ovarian cancer progression and chemoresistance. Constitutive activation of this pathway promotes tumor cell proliferation, survival, EMT, angiogenesis, and immune escape. Several studies have demonstrated that inhibition of this pathway can restore sensitivity and enhance apoptosis in ovarian cancer models. Targeted therapies have shown promising preclinical activity, particularly when combined with conventional chemotherapy.

Future therapeutic approaches should focus on combination strategies integrating IL-6/STAT3 inhibition with platinum-based chemotherapy, PARP inhibitors, immunotherapy, or other targeted therapies to overcome compensatory signaling pathways. Further studies are also needed to identify predictive biomarkers for patient selection and treatment response. Advances in molecular profiling and precision medicine may improve the treatment strategies for ovarian cancer patients especially with recurring disease.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflict of interest to disclose.

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