MINI REVIEW

Molecular cross-talk of IL-6 in tumors and new progress in combined therapy

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Abstract
IL-6, a cytokine activated by type I interferons (IFNs), is encoded by the IL-6 gene, and secreted by T cells and macrophages. It serves many purposes in the human body and is significant to pathological and physiological activities, such as acute inflammatory responses, autoimmune diseases, and tumor formation. The wide range of IL-6 actions on tumors rely on more than one specific pathway. Advances in modern research have determined that to fulfill its complex physiological functions, IL-6 must be involved in cross-talk with a number of other molecular pathways. Therefore, it is important to clarify the comprehensive pathway network associated with IL-6 activity and to explore the mechanisms to inhibit its pathological activity in order to develop corresponding treatment plans. This study is a simple review of the pathological and physiological actions of IL-6 on the human body. It explains in detail the molecular pathways involved in cross-talk between IL-6 and tumors, summarizing and discussing the latest progress made in IL-6-related internal medicine treatments in recent years, including chemotherapies, targeted therapies, and immunotherapies. Our results provide new insight into the treatment of tumors.

Introduction
Interleukin-6 (IL-6) is a type of cytokine transcribed by the IL-6 gene. It is mainly secreted in the human body by T cells and macrophages. After binding to IL-6 receptors, it forms dimers with CD130 (glycoprotein 130, also known as gp130, IL6ST, IL6-beta) via disulfide bonds, and then activates STAT3 through the JAK/STAT pathway, in turn stimulating the expression of downstream genes to perform a wide range of physiological actions. It serves diverse roles in pathological and physiological activities, such as acute inflammatory responses, autoimmune diseases, and tumor formation.

Physiological activity of IL-6
When first discovered, IL-6 was thought to be a pro-inflammatory cytokine mainly produced after an acute inflammatory response induced Th2 cells. It is involved in humoral immune responses (during which B cells are stimulated to differentiate into plasma cells and produce antibodies), as well as in other immune responses, and in the regulation of existing immune systems. During acute phase protein responses, it induces hepatocytes to synthesize acute phase reaction proteins (APRs) to facilitate the elimination of pathogens from the body.1 Under hypoxia, IL-6 can enhance the activation of hematopoietic stem cells (HSCs), in turn facilitating hematopoiesis, and developing a mechanism for long-term tolerance to hypoxia.2 It can also increase the formation of platelets by increasing the production of thrombopoietin (TPO).3 IL-6 deficiency directly affects bone marrow stromal precursors, resulting in defective hematopoietic support.4 Moreover, IL-6 functions as an endogenous pyrogen that penetrates the blood-brain barrier to stimulate the production of prostaglandin E2 (PGE2) by the hypothalamus to influence the body’s temperature-regulating center, consequently inducing a febrile response.5,6
Pathological activity of IL-6

IL-6 has a bi-directional role. It can activate the immune system during acute phrase responses to eliminate pathogens and facilitate tissue recovery. However, if IL-6-induced activation continues after the infectious factors have been contained, multiple immune system disorders or neoplastic diseases are induced. Tadamitsu Kishimoto was the first to discover and confirm IL-6 activity on rheumatic arthritis. He contributed to the development of the first antibody against the IL-6 receptor (tocilizumab) for the treatment of rheumatic arthritis. Subsequent research determined that IL-6 is also closely related to diseases such as coronary heart disease, schizophrenia, and gestational diabetes mellitus. Recent studies have found that IL-6 is closely linked to the biogenesis and growth of tumors, including those of breast cancer, myeloma, and lung cancer. This study focuses on the latest progress regarding the functions of IL-6 on tumors, with a special emphasis on cross-talk with other molecular pathways and advances with treatment methods.

Relationship between IL-6 and tumors

IL-6 is closely linked to the biogenesis of tumors. By enhancing tumor cell proliferation, it inhibits apoptosis and promotes the invasion, transition, and blood vessel growth of tumors while engaging in immunomodulation and other activities to advance the biogenesis and development of tumors. Its wide range of activity on tumor cells depends on more than one pathway. Advances in modern research have determined that to fulfill its complex physiological functions, IL-6 must be involved in cross-talk with a number of other molecular pathways. Therefore, it is important to clarify the comprehensive pathway network associated with IL-6 activity and explore how to inhibit its pathological actions, so as to devise a new anti-tumor treatment plan.

Cross-talk pathways associated with IL-6

IL-6 and STAT-3

IL-6 can directly activate STAT-3 through the JAK/STAT pathway. As a downstream pathway of IL-6, STAT-3 is a proto-oncogene per se. It can promote the growth of tumor cells while engaging in the drug resistance process of tumors. Overexpression and continuous activation of STAT-3 are found in nearly 70% of all human tumors. Research on colitis-associated cancer discovered that during tumor biogenesis, IL-6 establishes a close relationship with tumor cell proliferation by activating the STAT-3 pathway, modulating cytokines in the tumor microenvironment at the same time, which reduces anti-tumor IL-12 levels (which activate natural killer and effector T cells), and promotes the secretion of IL-23, thus encouraging tumor formation (by activating TReg cells). Therefore, IL6/JAK/STAT3 pathway activation is an important mechanism of tumor cell survival. A previous study reported that the application of IL-6 blockers to non-small cell lung cancer (NSCLC) treatment can block IL6/JAK/STAT3 pathway activation to inhibit tumor cell growth while exerting no effect on EGFR mutations.

IL-6 and EGFR

EGFR is involved in the IL-6-induced activation of STAT-3. After activation, the repressor protein SOCS3 can block any further activation of STAT-3 through negative regulation. EGFR expression, on the other hand, can inhibit SOCS3 to prolong the activation of STAT-3 downstream genes and produce greater IL-6 through positive feedback. In simple terms, STAT-3 molecules activated by IL-6 undergo rapid degradation after a short interval; however, the EGFR pathway gives rise to the secondary phosphorylation of STAT3, after which STAT-3 can persist in cells for a long period of time, consequently promoting biogenesis and growth of tumor cells. Similarly, in ovarian cancer, EGFR mediates the epithelial-to-mesenchymal transition (EMT) of tumors by activating IL-6 receptors through the JAK2/STAT3 pathway, in turn promoting the peritoneal metastasis of ovarian cancer. A study suggested that the combined use of anti-IL-6 drugs and gefitinib may be effective in treating late-stage ovarian cancer. Research on the interaction between the IL-6 and EGFR signaling pathways revealed the molecular basis of the combined actions of IL-6 and EGFR in promoting tumor biogenesis and development, which brought new insight to anti-tumor targeted therapies. To be precise, the IL6/STAT3 pathway is a new mechanism by which lung cancer cells acquire resistance to EGFR-tyrosine kinase inhibitors (TKIs); blocking this pathway to reverse the acquired resistance resulting from T790M mutations could potentially be a new therapeutic approach for clinical use.

IL-6 and STAT-2/IRF9 pathway

Interferons (IFNs) can activate the STAT-2 pathway. The signal transduction pathway involved is mainly mediated by interferon-stimulated gene factor 3 (ISGF3), a complex formed by STAT1/STAT2/IRF9, among which STAT2 takes effect by modulating IFN-stimulated genes (ISGs) independently. In tumor cells, STAT2 is continuously activated, which leads to the impaired regulation of cellular
transformation; by upregulating the encoding of apoptosis suppressor proteins and cell regulatory factors, it affects various biological activities of tumor cells, including blood vessel formation, proliferation, and cell death. IRF9 and STAT-2 upregulation also boost resistance to anti-tumor drugs.24

For the STAT pathways, STAT1, STAT2, and IRF9 often take effect by forming complexes, namely ISGF3. Related research has shown that STAT2 serves a fundamental role in ISGF3, as it can induce IL-6 transcription independently through IRF9 transposition, without forming ISGF3 with STAT1. Upon activation, STAT2 can directly induce IL-6 gene transcription and expression; at the same time, as a part of ISGF3, it can positively regulate their activation to further enhance IL-6 gene expression.25

In addition, after IL-6 gene expression is induced by the activated STAT2, IL-6 can activate the STAT3 pathway to induce the secretion of more IL-6. As a result, the STAT3 and STAT2 pathways form a positive feedback mechanism through IL-6. Together, they promote IL-6 overexpression, performing a series of physiological activities for the biogenesis and development of tumors.

**IL-6 and NF-kB pathway**

In the tumor microenvironment, cytokines are mainly produced by NF-kB expression, which is activated by tumor-infiltrating lymphocytes (TILs). These cytokines can activate the STAT3 pathway in tumor and immune cells. Among these, IL-6 can also reinforce the activation of NF-kB and STAT3 pathways through the autocrine loop in tumor cells.26

p53 is a vital constituent of NF-kB. Research has found that in a murine model of lung cancer with k-ras mutations, IL-6 deficiency promotes the biogenesis of tumors but decelerates their progression and prolongs the lifespan, while IL-6 activity is weaker in mice with p53 deficiency.27

Furthermore, researchers also found that in NSCLC, both NF-kB and STAT3 pathways can modulate IL-6 expression. TPCA-1 is an inhibitor that can inhibit both pathways and increase the sensitivity of gefitinib; when used in combination with gefitinib it can improve the promotion of tumor cell death.28

**IL-6 and methyl-transferases**

STAT2 expression is closely related to protein arginine methyltransferase 5 (PRMT5).29 PRMT5 reduces the expression of downstream genes and plays an important role in transcriptional regulation by methylating histones H2A, H3R8, and H4R3.30 Wei et al. found that PRMT5 catalyzes the signal-dependent dimethylation of R30 of the p65, which has a significant effect on the ability of p65 to bind to kB elements.31 Therefore, catalysis by PRMT5 is necessary for the complete IL-6 expression induced by STAT2.

A previous study also proved that IL-6 increases lung cancer stem cell proliferation and differentiation by upregulating DNMT1, which inhibits the cell-cycle control system, whereas DNMT3a and DNMT3b have no such effect. This study pointed out that inhibitors targeting the IL-6/JAK2/STAT3 signaling pathway and DNMT1 might represent a new approach for lung cancer treatment.32

**IL6 and NOX4/ROS/Akt**

The enzyme dimer complexes formed by the binding of Nox4 to subunit p22 serve the function of catalyzing the electron transport from NADPH to oxygen molecules. The reaction products are often the final sources of reactive oxygen species (ROS).

Previous research has argued that NOX4 in NSCLC tumor tissues is positively correlated with IL-6 expression; in other words, in NSCLC, exogenous IL-6 notably reinforces the activation of the NOX4/ROS/Akt pathways, whereas NOX4 activates the IL-6/STAT3 pathways, and in turn, promotes IL-6 activation. This finding demonstrated that oxidative stress and IL-6 expression in NSCLC could interact with each other to facilitate the proliferation and growth of tumor cells.33

**IL6 and COX-2/PGE2 pathway**

Previous research has suggested that when macrophages interact with lung cancer cells through β proteins, IL-6 can activate the COX-2/PGE2 pathways in lung cancer cells to induce cell EMT and stimulate tumor cell metastasis. Therefore, inhibiting COX-2/PGE2 pathways may resume the function of macrophages in inhibiting tumor metastasis.

**IL-6-related progress in tumor treatments in internal medicine**

**Application of IL-6 inhibitor to lung cancer treatments**

The research and findings discussed indicate that IL-6 overexpression is closely related to tumor activities, such as biogenesis, development, metastasis, and invasion. Related research has also indicated a significant negative correlation between the prognosis of NSCLC patients and IL-6 concentrations in their serum.34 Therefore, inhibiting IL-6 may be effective for impeding tumor development.
Song et al. found high IL-6 expression levels in NSCLC patients, especially those with squamous cell cancer; the application of the anti-IL-6 antibody, siltuximab, to mouse xenograft models was proven effective in inhibiting tumor growth. Its therapeutic effects positively correlated with IL-6 expression levels. However, no apparent synergistic effect arose from the combined use of gefitinib and siltuximab. Lee et al. found that termed rebeophy, a binding protein with high affinity, binds with IL-6 with great efficacy and specificity, in turn blocking the IL-6/STAT3 pathway. Researchers observed that termed rebeophy is effective for inhibiting the growth of NSCLC tumor cells at the cellular level.

IL-6 and resistance to cisplatin

Currently, chemotherapy remains the leading therapeutic method for treating most tumors, including NSCLC. Cisplatin is the most widely used medication. Despite this, tumors often continue to develop as a result of drug resistance developed during chemotherapy. Cisplatin primarily treats tumors through DNA damage and induces mitochondrial apoptosis. Based on the aforementioned results, it is evident that IL-6 is closely associated with NF-κB, the main physiological function of which is to promote DNA repair.

A study by Duan et al. found that IL-6 high expression in cells could inhibit cellular apoptosis and enhance DNA repair via activation of the MAPK/Stat3/Akt/Erk downstream pathways, thereby resisting the anti-tumor activity of cisplatin. Eventually the tumors develop resistance to cisplatin and continue to grow. Nevertheless, the researchers did not testify whether the use of anti-IL-6 drugs could reverse the resistance to cisplatin. Therefore, the significance of this mechanism to clinical applications remains uncertain.

IL-6 and resistance to EGFR-tyrosine kinase inhibitors

The IL-6/STAT3 pathway is a new mechanism through which lung cancer acquires resistance to EGFR-TKIs. Blocking this pathway to reverse the acquired resistance to EGFR-TKIs could potentially become a new therapeutic approach in clinical practice. Li et al. discovered that during both in vitro and in vivo experiments metformin could reverse the acquired resistance to EGFR-TKIs in tumor cells by inhibiting IL-6 signaling and EMT. As a cheap medication with low toxicity, metformin can be used in combination with TKIs for the treatment of NSCLC with acquired resistance to EGFR-TKIs to reverse the resistance and extend patient life. Homoharringtonine (HHT) is applicable for the treatment of all acute non-lymphocytic leukemia (ANLL); it is also effective in treating other diseases, such as myelodysplastic syndromes (MDS), chronic granulocytic leukemia (CGL), and polycythemia vera. HHT can reversibly block the IL-6-induced phosphorylation of STAT3 at the Tyr705 site, and reduce anti-apoptotic protein expression. The murine model of NSCLC resistance to EGFR-TKIs also verified that HHT had the same anti-tumor functions during in vivo experiments.

Polyphyllin I (PPI) is a natural chemical compound isolated from the rhizomes of Paris polyphylla. It possesses anti-cancer activities and can reverse EMT by blocking the IL6/STAT3 pathway to overcome NSCLC cell resistance to EGFR-TKIs. The combined use of PPI and erlotinib can possibly reverse the acquired resistance to EGFR-TKIs and prolong patient life.

IL6 and radiotherapy

During radiotherapy, IL-6 can upregulate the members of the chemokine CC subfamily, CCL2 and CCL5, to intensify the macrophage infiltration of tumors and promote tumor development. Blocking CCL2/CCL5 activation can significantly reduce the number of macrophages migrating to the tumor cells after radiation exposure. Therefore, blocking IL-6 signaling or CCL2/CCL5 molecule activity during regular radiotherapy may inhibit radiation-mediated macrophage infiltration and slow tumor development.

Chen et al. found that during radiotherapy for treating NSCLC, IL-6 promotes the differentiation and proliferation of CD133+ cancer stem cells, while enhancing DNA repair to inhibit tumor cell apoptosis and protect CD133+ cancer stem cells from the damage of radiotherapy. When compared to patients that have not undergone radiotherapy, patients with radiation pneumonitis have significantly higher contents of IL-6 in their serum after radiotherapy. Therefore, in patients that have received radiotherapy, their risk of radiation pneumonitis is proportional to the IL-6 levels in their serum.

Based on these observations, incorporating IL-6 inhibitors and their downstream pathways in radiotherapy can possibly reduce the adverse reactions of radiotherapy and improve the therapeutic effects, thereby prolonging patient life.

IL6 and immunotherapy

PD-1 and PD-L1 can effectively block the actions of tumor-infiltrating T and B cells, resulting in tumor immune escape.

Recent studies have reported that EGFR can upregulate PD-L1 expression through the IL-6/JAK/STAT3 pathway.
Using EGFR-TKIs to treat tumor cells blocks the activation of this pathway, thus downregulating PD-L1 expression. Blocking PD-L1 expression in NSCLC decreases the proliferation of tumor cells and promotes their apoptosis. Thus, for NSCLC treatment, a combined regimen of EGFR-TKIs and anti-PD-L1 drugs may enhance the anti-tumor activity of the medications.44

In NSCLC cell lines A549 and H157, radiotherapy activates the IL-6-MEK/Erk pathway to increase PD-L1 expression and reduce the expression of NKG2D ligands. Both effects can lead to tumor immune escape from NK cells. When compared to the use of a single inhibitor, the combined use of PD-L1 antibodies and MEK/Erk inhibitors intensifies NK cell activity against radiotherapy-resistant cells. Therefore, for patients undergoing radiotherapy or with radiotherapy-resistant cancer, the combined use of PD-L1 antibodies and MEK/Erk inhibitors could potentially improve the anti-tumor efficacy of medication.45

In two clinical trials using mice, an IL-6 inhibitor was used together with a PD-L1 antibody to treat prostate and liver cancers. Both experiments showed that the combination could enhance the anti-tumor activity of the medication. Therefore, using the inhibitor of IL-6 or its downstream pathway with an anti-PD-L1 antibody could be a potential method for treating tumors.46,47

Recent research shows that IL-6 has wide-spectrum roles in physiological and pathologic activity in the human body, and benefits from abundant downstream target genes and complex interaction with other signaling pathways. IL-6 plays a crucial role in tumor invasion and metastasis, and contributes to drug resistance by widely interacting with regulating factors. We have found a number of drugs that block IL-6 and its downstream pathways, but these are extremely limited in their application, with the exception of in rheumatoid arthritis. No mature therapy has been developed based on IL-6, particularly for tumors. We believe that IL-6 has a bright future for the synergistic therapy of tumors. It not only offers a positive prospect to solve the worldwide problem of drug resistance in chemotherapy and targeted therapy, but also in the synergistic activity of radiotherapy and immunotherapy.

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Disclosure

No authors report any conflict of interest.

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