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Review Article

The Biological Effects of Interleukin-6 and Their Clinical Applications in Autoimmune Diseases and Cancers

Abstract

Interleukin-6 (IL-6) is one of the pro-inflammatory cytokines involved in pathogenesis of various autoimmune and chronic inflammatory diseases. IL-6 through binding to its cellular receptor can transduce both classical- and trans-signaling pathways. Overproduction of circulating IL-6 can be detected in patients with different autoimmune diseases. Tocilizumab, a humanized monoclonal antibody against IL-6 receptor, can block IL-6-mediated signaling and has been approved for the treatment of rheumatoid arthritis and Castleman's disease. Besides, expression of IL-6 may promote tumorigenesis and has been detected in various tumors, including multiple myeloma, colorectal cancer, breast cancer, lymphoma, breast cancer and lung cancer. Furthermore, increased levels of circulating IL-6 are associated with poor prognosis and cachexia in cancer patients. Monotherapy with IL-6 blockade or a combination therapy with both IL-6 blockade and conventional chemotherapy may reduce the progression of cancer and improve the status of cachexia in cancer patients. Finally, based upon the known biological effects of IL-6, diseases, other than autoimmune diseases and cancers, potentially to be anti-IL-6 candidates will be briefly discussed.

Introduction

Interleukin-6 (IL-6), composed of 184 amino acids with a molecular weight of 26 kDa, is one of the proinflmmatory cytokine and plays a major role in the progression of systemic and local inflammation. Significant elevation or excessive production of circulating IL-6 usually develops during the disease course of systemic inflammation including infectious or non-infectious diseases [1]. Several studies revealed that IL-6 has multiple functions in immune, inflammation and oncogenesis, and is associated with the promotion of synthesis of acute phase proteins including C-reactive protein (CRP), serum amyloid A, hepatoglobin, fibrinogen and hepcidin [2]. Persistent dysregulation of circulating IL-6 with overproduction may be found in the patients with different autoimmune diseases. Rheumatoid arthritis (RA), one of autoimmune diseases, is a systemic inflammation of polyarthritis, fever, myalgia, malaise and anemia with increasing circulating proinflammatory cytokine including IL-6 [3]. Higher circulating IL-6 is observed in the RA patients and is associated with disease activity, erythrocyte sedimentation rate (ESR), CRP and bony structural damage [4,5]. Increased levels of serum and synovial may be found in the patients with juvenile idiopathic arthritis (JIA) [6,7]. After medication of humanized anti-IL-6 receptor monoclonal antibody (tocilizumab), the clinical manifestations of polyarthritis and serum acute phase proteins are improved. IL-6 targeting therapy serves as a novel therapeutic strategy for the patients with RA and JIA [3,8]. IL-6 can promote osteocalstogensis and induce systemic bone loss with structural bony erosion in the disease course of RA [9]. Among the patients with systemic lupus erythematosus (SLE), increased expression of IL-6 is found, and the clinical manifestations of arthritis and circulating acute phase protein is improved after medication of IL-6 blocker (10). Active systemic inflammation and progressive renal involvement may develop after implication of IL-6 trans-signaling in lupus mice [11]. Elevated concentration of IL-6 is observed in the patients with Castleman's disease and the level is reduced after clinical improvement [12]. These findings prove that IL-6 plays a major role in the pathogenesis of immunological abnormalities and the development of systemic inflammation in different autoimmune disease.

From the previous studies, IL-6 is also involved in the inflammation related tumorigenesis [13]. These cancers associated with abnormal systemic or local elevation of IL-6 involving different organs include breast, lung, ovarian, pancrea, prostate, colon, kidney and hematology [14]. Serum concentrations of IL-6 and CRP may serve as an excellent predicting biomarker of severity of systemic inflammation in

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malignancy. In pancreatic cancer patients, tumor associated macrophages may release IL-6 and it up-regulates cytokine expression, promotes proliferation, immune evasion, angiogenesis and resistance to apoptosis of cancer cells [15]. The levels of serum IL-6 are significantly higher in the patients with active weight loss [16]. Higher levels of serum IL-6 is observed in the patients with aggressive metastatic or recurrent breast cancers [17-19]. Among the hematological cancers including lymphoma and multiple myeloma, elevated serum IL-6 levels are found during the disease course [20-23]. In the patients with prostate cancer, higher serum IL-6 levels are associated with clinical metastasis and hormone-refractory [24,25]. Elevated serum IL-6 levels are observed in other types of cancers including colon, lung, ovarin and kidney [26-30]. Therefore, the pathological involvement of IL-6 is not only inflammation but also has the effect of cancer cells related immune response. IL-6 may be one of the pathogenesis in progression and migration of malignancy, and is essential for inducing cancer related inflammation. IL-6 blockade can suppress the differentiation of Th17 cells and can ameliorate chronic systemic inflammation [14]. The overall clinical and biological effects of IL-6 are shown as Table 1. Blocking the effect of functional IL-6 signaling pathway may thus be of benefit in systemic inflammation related different situations. This review is focused to evaluate the pathological role and clinical practice of anti-IL-6 blocker in numerous autoimmune diseases and cancers.

How IL-6-mediated biological effects may lead to the pathogenesis of autoimmune diseases and cancers

IL-6 is involved in autoimmunity due to influence of different cells, including T cell, B cell, macrophage, neutrophil, hepatocyte, dendritic cell, fibroblast, endothelial cell and different tumor cell. The circulating activity of IL-6 is complex and may induce both pro-inflammatory and anti-inflammatory effects in the immune system. During the progression of systemic inflammation, autoimmune disease, trauma and infection, increased production of pro-inflammatory cytokine and upregulating the expression of IL-6 usually develops [31]. Normal or tumor related macrophage, fibroblast and endothelial cell have the ability to release IL-6 [15]. Then, activation of IL-6 can contribute to anti-inflammatory or pro-inflammatory through the classical and trans-signaling pathways. In the classical signaling pathway, circulating IL-6 can bind to transmembrane, resulting in the activation of downstream signal via Janus kinase (JAK) in target cells. In the trans-signaling pathway, free IL-6 can bind to soluble IL-6 receptor to precede the downstream signal and amplify IL-6 signaling. The JAK signaling is through the activation of gp130. The gene expression of cell differentiation or proliferation may be activated by transcriptional factors of signal transducer and activator factor 3 (STAT3) or mitogen activated protein kinase (MAPK). IL-6 may induce activation and proliferation of B cell [1]. IL-6 with TGF-β can induce T cells for differentiation of Th17 cell and IL-6 overproduced in vivo inhibits the generation of regular T from naive T cells [32,33]. The differentiation of follicular helper T cell from naïve T cell may be contributed by IL-6 and IL-21. Follicular helper T cells migrate to B cell follicle region IL-6 can activate osteoclast leading to increasing bone resorption and is associated with osteoporosis [34]. IL-6 can promote activation and proliferation of hepatocyte through classic signaling to synthesize acute phase proteins, and these acute phase proteins include CRP, fibrinogen, hepatoglobulin and serum amyloid A. From a recent study, the effect of IL-6 can amplify the inflammatory response through a direct involvement of stromal and innate immunity cells [35]. The development of different systemic inflammation related cytokines and chemokines may be induced in this amplifying process. The multiple physiological effects of IL-6 in the immune system are showed as Figure 1.

Table 1: Clinical and biological effects of IL-6.

Involved category	Effects
Immune	TH17 cells↑ B cells↑ Platelets↑
Inflammation	CRP↑ Serum amyloid A↑ Hepatoglobin↑ Fibrinogen↑ Hepcidin↑
Oncogenesis	Metastasis↑ Hormone-refractory↑

In the patients with RA, proinflammatory cytokines can stimulate the production of IL-6 in rheumatoid synovial fibroblasts through activation of JAK2/STAT3 [36]. IL-6 may block the cartilage repair by inhibiting the differentiation of mesenchymal stem cells into chondrocytes [37]. Castleman's disease is a systemic inflammatory disease characterized by general enlarged hyperplastic lymph nodes. This rare lymphoproliferative disorder has numerous systemic manifestations except polyadenopathy including fever, night sweating, fatigue, malaise, anorexia, weight loss, oranomegaly and edema. Thrombocytosis, leukocytosis, anemia, hypoalbuminemia, hypergammaglobulinemia and elevation of CRP are usually found in the clinical laboratory data. These patients with poor control may develop multiple organ failure and lymphoma. The mechanism of Castleman's disease is not clear, and IL-6 plays a major role in the disease progression [38]. The abnormal expression of other proinflammatory cytokine, such as IL-6, and epidermal growth factor receptor, and vascular endothelial growth factor (VEGF) are observed in these patients. Elevation of circulating IL-6 is observed in the patients with Castleman's disease and is associated with proliferation of B lymphocytes [12]. Activation and proliferation of B lymphocytes can lead to overproduction of IL-6. Increased IL-6 related immune dysregulation may enhance the production of proinflammatroy protein, such as CRP, and the clinical symptoms of anemia and thrombocytosis. At the same time, VEGF and IL-1 might be stimulated due to responsible for IL-6. Abnormal lymphocytic and vascular proliferation develop during the disease course of Castleman's disease [39].

Overproduction or overexpression of circulating IL-6 can be found in different types of cancers. There is a direct correlation between IL-6 levels in tumor-associated endothelial cells

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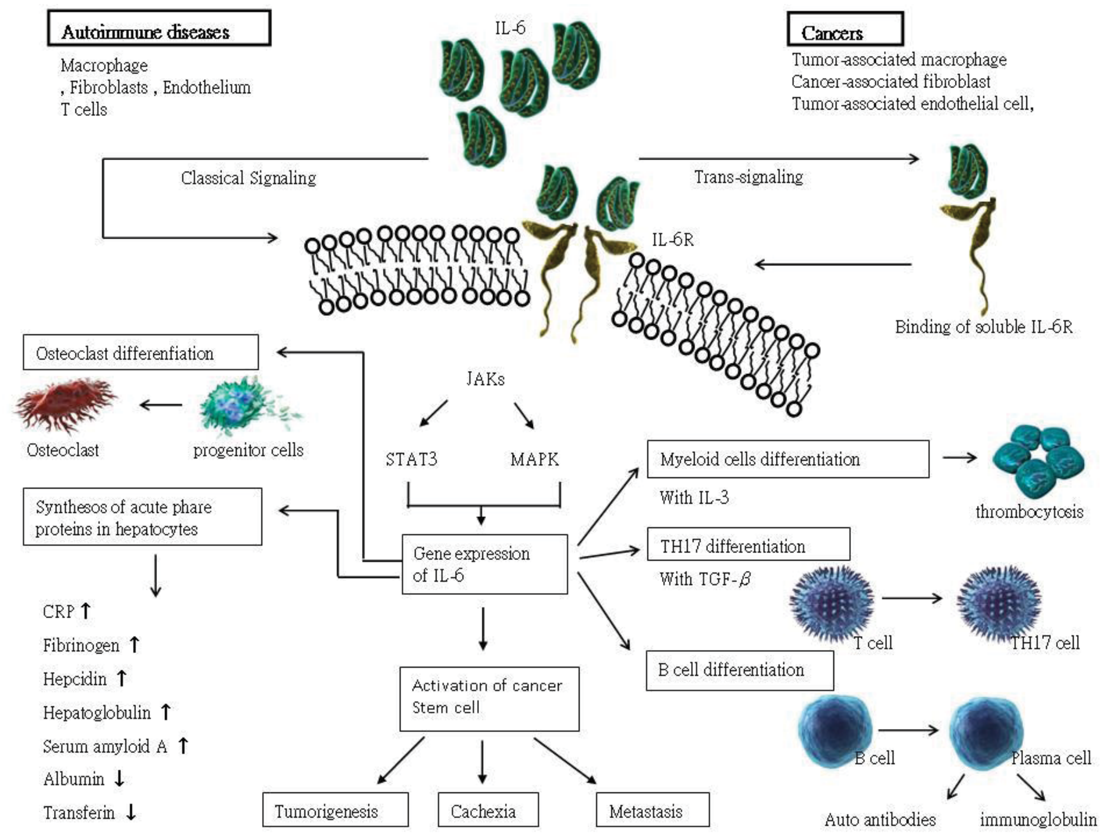

Figure 1: IL-6-medicated signaling and possible biological effects between different cells in the pathogenesis of autoimmune diseases and cancers.

and the tumorigenicity of cancer stem cells [40]. Tumor associated macrophages can induce IL-6 and may contribute to tumor progression associated with the inflammation related tumorigenesis. Tumor associated macrophages produce IL-6 and it promotes expansion of these caner stem cells. Levels of IL-6 in human hepatocellular carcinoma correlate with tumor stage and markers of caner stem cells [41]. IL-6 signaling may affect inflammation related cancer by modulating the resistance of T cells against apoptosis [42]. The imbalance between regulatory T cells and Th17 cells is observed in this progression. Therefore, the biological effect of IL-6 is not only find in autoimmune disorders, but certain malignancies.

The rationale of developing anti-IL-6 for the clinical therapeutic purposes

IL-6 plays a major role in the systemic and local inflammation of autoimmune disease, including RA, JIA, SLE and Castleman's disease [3,43]. In other autoimmune disease, increased expression of serum IL-6 is found among the patients with dermatomyositis [44]. The IL-6 blocker may be sometimes useful in these disease, such as adult-onset Still's disease, amyloidosis, vasculitis, relapsing polychondritis, and systemic sclerosis [43]. These findings suggest that IL-6 is not the only major pathogenesis among these autoimmune diseases. Circulating endothelial cells or progenitor cells are increased in the patient with SLE, and is associated with high INF-α levels and production of autoantibodies. In SLE, the systemic inflammation mediating glomerulonephritis may develop and the IL-6 trans-signaling can exacerbate the systemic inflammation or renal damage. Among SLE patients, plasma IL-6 levels are correlated with CRP and arthritis [10]. During the disease of RA, progressive osteoporosis with bone loss of lumbar spine or femoral neck develops except clinical manifestation of polyarthritis. Circulating IL-6 is positively correlated with the disease activity of RA and negatively correlated with mineral bone density [9]. IL-6 has negative effect on the differentiation of osteoblasts by the inhibition of STAT3 [45]. The medication of anti-IL-6 receptor antibody can prevent the systemic bone loss through inhibiting the migration of osteoclast precursor cells in the model of collagen-induced arthritis [46]. The assays of RA disease activity include DAS28, ESR, CRP and health assessment questionnaire [4], and IL-6 is associated with these clinical assays. IL-6 is important for the development of systemic osteopenia in RA. In autoimmune disease, chronic disease related anemia is due to overproduction of hepcidin through reduction of intestinal iron absorption and blocking the release of iron from macrophages. IL-6 may contribute the induction of hepcidin in anemia of chronic disease. In clinical, the hemoglobin level is increased by the medication of anti-IL-6 receptor antibody in the RA patients [47]. Decreased circulating regular T cells are found among RA patients. After medication of anti-IL-6 receptor antibody, tocilizumb, the clinical disease activity of RA is improved and regular T cells are significantly increased [48,49]. Clinical studies reveal that tocilizumb has effect on control of RA with or without medication of methotrexate. Tocilizumb is still useful for the medication of RA when these patients fail to response TNF-α inhibitor [49]. Monotherapy of tocilizumab is not inferior to tocilizumab combined with methotrexate [50]. The clinical and radiographic effects of tocilizumab may maintain after monotherapy for one year [51]. The subsequent flare will be found after discontinuation of tocilizumab, but the disease can be controlled by re-administration of biologics [52]. Therefore, tocilizumab is one of the most common biological agents for monotherapy [53]. The monotherapy of tocilizumab is superior to monotherapy of TNF-α for reduction of clinical signs and symptoms of RA patients [54].

In autoimmune disease, IL-6 related abnormal presentation of hepcidin is central to anemia of chronic diseases including RA and SLE. Significant elevation of serum IL-6 is found in breast cancer patients when compared with healthy controls [55,56]. Breast cancer cells may secrete IL-6 to support the proliferation of cancer, and reduction of proliferation of cancer is observed after IL-6 knockdown [57]. In another study about breast cancer, the expression of IL-6 is associated with the expression of estrogen receptor [58]. However, the abnormal expression of IL-6 also can be detected in cancer cells without expression of estrogen receptor [59]. Therefore, the increased expression of IL-6 plays a critical role in the development of breast cancer independently. Cancer-associated fibroblasts may promote tamoxifen resistance though IL-6-induced degradation of estrogen receptor-α in breast cancer [60]. In colon cancer cells, mucin 2 can increase the secretion of IL-6 and progress the colonic carcinogenesis [61]. The presence of IL-6 is associated with activation of carcinogenesis and DNA damage by upregulation of CYP1B1 and CYP2E2 in the progression of colonic inflammation [62]. In gastric cancer cells, IL-1β may enhance the invasiveness of cancer cells through the IL-6 expression [63]. The immunohistochemical expression of IL-2 receptor and IL-6 is higher in prostate cancer tissue than in normal tissue [64]. IL-6 gene polymorphism is associated with increased risk of bladder cancer [65]. Among female without history of smoking, genetic polymorphism of IL-6 is associated with the risk of lung cancer risk [66]. Increased expression of serum IL-6 is associated with poor survival in lung cancer [67]. After surgical resection of lung cancer cell, the levels of CRP, TNF-α ad IL-6 are decreased [68]. The anti-IL-6 antibody, siltuximab, has more potent effects on tumor inhibition of lung cancer through influence of cancer-associated fibroblasts [69]. The pathogenesis of IL-6 in the development of cancer is about the direct effect from the cancer stem cells or indirect effect from the systemic inflammation. Cancer stem cells may activate the IL-6 signaling pathway and amplify the expression of circulating IL-6 [70]. In the progression of malignancy, IL-6 is associated with angiogenesis and inhibiting apoptosis of tumors. In conclusion, adequate blocking the IL-6 signaling may disturbance the development of tumor related metastasis and migration. Besides, anti-IL-6 therapy severs as a biological effect for improvement of systemic inflammation in cancer and autoimmune disease.

The recent advances of the experience (clinical benefits and adverse events) of applying anti-IL-6 therapeutics

There are numerous cells can release IL-6 and these cells include macrophages, fibroblasts, endothelial cells and myeloid cells. In the patients with autoimmune diseases, IL-6 may be orientated from these different cells and induce immune reaction through classical or trans-IL-6-signalling pathway. Polyarthritis with systemic inflammatory related manifestations develop in the patients with RA. Aggressive synovial swelling and proliferation over joint space may be observed and the pathogenesis of RA is associated with numerous immune cells including T cells, B cells, fibroblasts, macrophages, endothelial cells, chondrocytes and osteoclasts [71]. Active clinical manifestations of synovial angiogenesis and hypertrophy and osteopenia with bony erosion develop in RA [72]. Traditionally, the medications of non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs may be used for RA. For recent years, novel biological agents by blocking TNF-α, IL-1, IL-6, active B cells and T-cell costimulatory are progressing. IL-6 is one of RA related proinflammatory cytokines. Anti-IL-6 therapy may improve the clinical signs of RA or JIA significantly. Except RA, active arthritis, cutaneous presentations and nephropathy are found in the SLE patients. Diffuse lymphoadnopathy and fever with systemic inflammation are observed among the patients with Castleman's disease. Targeting and blocking IL-6 signaling pathway may improve these clinical systemic inflammations.

In the disease course of malignancy, cachexia is usually found. The biological effect of IL-6 can damage the skeletal muscle, adipose, mucosa of intestine and liver tissue. Therefore, circulating IL-6 may affect the degree of cachexia. At the same time, increased serum IL-6 is observed in different cancers including lung, liver, pancreas, colon, prostate, breast and bladder. Blocking IL-6-signaling pathway can relieve the clinical symptoms of cachexia in cancer patients [73]. IL-6 is one of major transcriptional regulators of hepcidin and chronic anemia with overproduction of hepcidin may contribute to the anemia [74]. Among the multiple myeloma patients with chronic anemia, IL-6 has the activity for acting synergistically with bone morphogenetic protein 2 on the induction of hepcidin [75]. After the blocking medication of IL-6, the anemia is improved by prevention of the induction of hepcidin [74,76]. In summary, different biological effects of IL-6 can be found in autoimmune diseases and cancers. These effects include arthritis, anemia, vascular angiogenesis, autoantibody production, lymphoadenopathy, tumor metastasis and cachexia. The different IL-6 related biological effects are shown as Table 2.

From different studies, IL-6 blockade therapy may be associated with adverse events including infections, infusion reactions, central demyelinating nerve and gastrointestinal perforation [77]. Laboratory abnormalities are found during the medication of IL-6 blockade, and these abnormalities include hyperlipidemia, elevation of liver function and neutropenia [78]. Therefore, adequate evaluation should be performed during anti-IL-6 therapy.

Current knowledge about clinical trials under developing and the aimed illnesses for anti-IL-6

IL-6 is a cytokine with multiple biological functions in the systemic inflammation, and is truly useful in RA, JIA and some clinical symptoms of SLE. Humanized anti-IL-6 receptor

Table 2: Biological effects of IL-6 and their applications in autoimmune diseases and cancers

Effects	Mechanisms	Targeted autoimmune diseases	Targeted cancers	Remark
Arthritis	Th17 differentiation	RA Multiple scleorsis Asthma	Colorectal cancer	IL-6 with TGF-β promote the differentiation of Th17
Anemia	Activated hepatocyte to increase hepcidin	Autoimmune disease related chronic anemia	Malignancy related anemia	Increased circulating hepcidin during systemic inflammation
Osteoporosis	Osteoclast differentiation	RA JIA	Malignancy related bone metastasis and osteopenia	In bone marrow, IL-6 can activate osteoclasts leading to bone resorption
Angiogenesis and vascular permeability	Elevation of vascular endothelial growth factor (VEGF)	RA JIA SLE Castleman's disease	Multiple myeloma Breast cancer Lymphoma Renal cell carcinoma Pancreatic cancer	Overactation of lymphocytes inducing cytokine storm in autoimmune diseases and distant metastasis of tumor
Production of autoantibodies	B cell differentiation	SLE RA Castleman's disease	Lymphoma Leukemia Lung cancer	IL-6 induces the differentiation of plasma cells for production of autoantibodies
Lymphoadenopathy	Hyperplastic lymph nodes Follicular hyperplasia Vascular hyperplasia	Castleman's disease	Leukemia Lymphoma	Activation of myeloid cell with IL-3
Tumor metastasis	Generation of cancer stem cell	None	Breast cancer Lung cancer	IL-6 promotes the generation of cancer stem cells from non-cancer stem cells Cancer-associated fibroblasts mediate drug resistance through IL-6
Liver metastasis	Activated macrophage	SLE RA Castleman's disease	Colon cancer	Activation of macrophages inducing IL-6 secretion of tumor cells
Cachexia	Amplify IL-6 signaling through trans-signaling	RA SLE	Malignancy	IL-6 induces proteasome and autophagy protein degradation

antibody is used to treat the patients with Castleman's disease, and the clinical manifestations and abnormal laboratory data are improved after three months therapy [79]. Siltuximab, a novel anti-IL-6 monoclonal antibody, has therapeutic benefits in the patients with Castelman's disease. After medication of siltuximab (12 mg/kg every 3 weeks), partial clinical benefit response and tumor response can be found among these patients [80]. In another study, 86% patients with Castleman's disease have clinical and radiological response with significant decreasing CRP after siltuximab therapy [81].

Multiple myeloma is a malignancy disease associated with B-cell proliferation and elevation of circulating IL-6. In vivo, humanized anti-IL6 monoclonal antibody can inhibit the disease activity of multiple myeloma [82]. In the phase 1 study, siltuximab (anti-IL-6 monoclonal antibody) is used in multiple myeloma for recommend dose of 11 mg/kg once every 3 weeks [83]. The addition of siltuximab in the medication of multiple myeloma has no significant different when compared with traditional chemotherapy; but sustained suppression of circulating CRP is observed in the patients with medication of siltuximab [84].

Chronic prostatitis is associated with the progression and development of prostate cancer. One of the proinflammatory cytokines, IL-6, is important for systemic inflammation and may link the aggressivness of prostate cancer [85]. Elevation of IL-6 level is usually found in prostate cancer patients with metastasis or refractory for hormone or radiation therapy through multiple signal pathways including JAK, STAT and MAPK [86-88]. Inhibition of IL-6 can enhance the radiation sensitivity of prostate cancer [87]. IL-6 has a major role in prostate cancer stem cells and may regulate down signaling of STAT3 activation [89]. In the patients with prostate cancer, bone metastasis may develop during the disease course. IL-6 can increase the expression of RANKL and activate the abnormal bone resorption by osteoclasts in vitro. Blocking the IL-6 signaling by tocilizumab may inhibit skeletal tumor growth in vivo and reduce serum RANKL levels in prostate cancer cells [90]. Therefore, the conogenicity and bone metastasis of prostate cancer can be suppressed by anti-IL-6 antibody. Novel therapy about targeting IL-6 seems to fight against prostate cancer.

IL-6 can promote the breast cancer migration and metastasis with activation of STAT3 signaling pathway [91]. From different clinical studies, increased serum IL-6 concentration is associated with advanced tumor stages of various studies including multiple myeloma, lung cancer, colorectal cancer, prostate cancer and breast cancer [92]. Elevation of serum IL-6 is associated with clinical symptoms of depression, anxiety and tumor progression [93]. The initiation of cancers is associated with the activation of cancer stem cells from normal cells. IL-6 can induce the conversion of normal cells to cancer stem cells through the regulation of OCT-4 gene expression [94]. Blocking IL-6 signaling seems to be a potential therapeutic strategy for some cancers with elevation of circulating IL-6. At the same time, resistant of multiple drugs and targeting cancers develop in some patients with breast cancers. In these patients, abnormal elevation and activation of IL-6 are found.

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Neutralizing antibodies against IL-6 may reverse resistance of these chemotherapies (paclitaxel and doxorubicin) [95]. Active IL-6 inflammatory feedback loop may lead to aggressive expansion of breast cancer stem cells, and medication of IL-6 receptor antibody can interrupt this inflammatory loop [96].

In colon carcinoma cells, clonogenic proliferation and invasiveness may be induced by IL-6 through the pathways of MAPK and PI3K [97]. This clonogenic effect can be blocked by IL-6 receptor neutralization antibody. The abnormal elevation of IL-6 has the ability to progress the growth of colon cancers. The liver metastasis of colon cancer is associated with the activated macrophages inducing IL-6 secretion of colon cancer cells in vitro [98]. At the same, overexpression of IL-6 is found the metastatic colon carcinoma cells [99]. Therefore, the pathological effect of circulating IL-6 may be amplified by metastatic tumor cells. Chronic colitis related inflammation may induce the tumorgenesis by mediating IL-6/STAT3 signal pathway. In other study, polysaccharide peptidoglycan complex on Lactobacillus has the effect of inhibiting IL-6 production and may block the development of colitis-associated cancer through inhibition of STAT3 signaling [100].

The elevation of circulating IL-6 develops in the patients with lung cancer. The pathogenesis of lung cancer is associated with activation of macrophage with elevation of IL-6 and the development of epithelial to mesenchymal transition [101]. Active migration of lung cancer cells can be induced by IL-6 though JAK/STAT3 pathway [102]. Therefore, IL-6 is important for the metastasis of lung cancer. In vitro, the medication of anti-IL-6 antibody may reverse the induction of epithelial to mesenchymal transition in lung cancer cells [101]. Among the patients with lung cancer, serum IL-6 levels are higher in the patients with cachexia and poor response for chemotherapy [103]. The blocking agent for activity of IL-6 has the potential of improving disease prognosis and cachexia in lung cancer. A humanized anti-IL-6 antibody (ALD518) can improve the lung cancer related anemia and cachexia in Phase I and II clinical trial [104]. A chimeric anti-IL-6 monocolonal antibody, siltuximab, is used in the patients with advanced solid tumors including colorectal, ovarian and pancreatic cancers. Improvement of chronic anemia and systemic inflammation are observed, but adverse events of hepatic function abnormalities, fatigue and neutropenia are also found [76]. The clinical responses of IL-6 blockade in autoimmune diseases and cancers are shown as Table 3.

How to improve the anti-IL-6 therapeutics from both basic and clinical aspects

Tocilizumab is a humanized monoclonal antibody with consistent of complementary determining regions of mouse anti-IL-6 receptor antibody and human IgG1 portion. Tocilizumab may block IL-6-mediated signaling by binding to circulating soluble or transmembrane IL-6 receptors [105]. The disease activity of RA can be controlled by inhibition of Th17 differentiation through targeting IL-6 blocking. Direct down regulation with decreasing concentration of circulating IL-6 is the major target point about the therapy of Castleman's disease. In the patients with SLE, targeting IL-6 may block the abnormal B cell proliferation and regulate the expression of regular T cells. In the cancer related systemic inflammation, increased levels of circulating IL-6 is a poor prognostic factor and is associated with higher mortality and drug resistance. Targeting IL-6 therapy may improve the drug resistance, chronic anemia and cachexia in cancer patients. The approved indications for anti-IL therapy include RA, systemic juvenile idiopathic arthritis and Castleman's disease. The off-label applications of anti-IL-6 therapy include SLE, systemic sclerosis, polymyositis, systemic vasculitis and adult onset Still's disease. The medication of targeting IL-6 therapy is about the systemic inflammation of autoimmune disease. Active systemic autoimmune disease is associated with upregulation of proinflammatory cytokine and IL-6 is one of the most involved common cytokines. Significant improvement of arthritis and circulating parameter of systemic inflammation (including CRP and ESR) are often observed when IL-6 blocker is used in these autoimmune diseases with active inflammation. IL-6 also plays a major role in the pathogenesis of chronic anemia. In the cancer related systemic inflammation, different degree elevation of IL-6 is usually found. Metastasis, active resistant chemotherapy, migration and higher mortality are major issues related upregulation of IL-6 signaling in cancers.

In conclusion, anti-IL-6 therapy has a useful strategy for selective autoimmune inflammation diseases, such as RA, Castelman's disease, SLE and JIA. Among the patients with cancers, levels of circulating IL-6 are associated with metastasis, prognosis and chronic inflammation. Targeting IL-6 therapy may improve the systemic inflammation related complications due to cancers. Therefore, improvements and benefits of systemic inflammation related clinical manifestations (such as anemia, cachexia and fever) are observed in the cancer patients. Anti-IL-6 therapy may be used for the combination therapy for malignancy. The traditional therapy such as chemotherapy or target therapy cannot be replaced by anti-IL-6 therapy.

Conclusion

The biological effects of IL-6 are multiple functional and are important in the autoimmunity of systemic inflammation. Elevation of systemic or local IL-6 is observed in numerous autoimmune or rheumatic diseases. The administration of targeting anti-IL-6 is useful in RA, Castleman's disease and juvenile idiopathic arthritis. Limited biologic effects of IL-6 blocking are observed in SLE, systemic sclerosis and polymyositis. The clinical improvements include decreasing serum CRP, arthritis and anemia in these limited responses of autoimmune diseases. Therefore, elevation of circulating IL-6 is not always the major pathogenesis of all autoimmune diseases. IL-6 has a complex role in the pathogenesis of various autoimmune diseases. Sometimes, IL-6 may be the secondary presentation of systemic inflammation in these autoimmune diseases. Except autoimmune diseases related inflammation, cancers related inflammation is usually associated with the systemic effect of circulating IL-6. In almost clinical trial, the serum CRP levels are significant reduced after anti-IL-6 therapy. The clinical manifestations of systemic inflammation including fever, cachexia and anemia are improved. However,

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Table 3: Targeted diseases under developing for anti-IL-6

Anti-IL-6 regimens	Rationale	Clinical response	Targeted diseases	References
Tocilizumab (Anti-IL-6 receptor antibody) 4-8 mg/kg iv every month	Direct inhabitation of circulating IL-6 Decreasing systemic acute phase protein	Suppression of disease activity and radiographic progression	RA	[50-52]
Tocilizumb 8-12 mg/kg every 4 week	Direct inhabitation of circulating IL-6 Decreasing systemic acute phase protein	Sustained improvement of disease activity	JIA	[8,106,107]
Siltuximab (anti-IL-6 antibody) 12 mg/kg iv every 3 weeks	Suppression of IL-6-induced STAT3 signaling	CRP suppression Partial clinical benefit response	Castleman's disease Non-Hodgkin lymphoma Multiple myeloma	[81,108]
Tocilizumb 4-8 mg/kg every 4 weeks	Blocking IL-6 trans-signaling with selective inhibition of B cells, inflammation and innate immune system	Improved clinical manifestation of arthritis and mild disease activity of SLE Decreased anti-dsDNA levels	SLE	[109]
Siltuximab (anti-IL-6 antibody) 12 mg/kg iv every 3 weeks	Blocking the overproduction of IL-6	Significant clinical benefits response	Castleman's disease	[80]
Siltuximab (anti-IL-6 antibody)	Prevention of cachexia Inducing apoptosis of cancer cells and reduced cellular proliferation	Inhibition of tumor growth and metastasis	Prostate cancer	[110]
Neutralizing antibodies against IL-6	Blocking the expression of IL-6 from breast cancer stem cells	Reversed the drug resistance to paclitaxel and doxorubicin	Breast cancer	[95]
ALD518 (anti-IL-6 antibody)	Blocking the IL-6 related inflammatory pathway	Prevention of related anemia and cachexia Decreased resistance to EGF-pathway inhibitors	non-small cell lung cancer	[104]
Siltuximab (anti-IL-6 antibody)	Suppression of IL-6-induced STAT3 phosphrylation and nuclear translocation	Improvement of dry resistant recurrent tumors and metastasis	Ovarian cancer	[111]
Siltuximab (anti-IL-6 antibody) 11-15 mg/kg iv every 3 weeks for monotherapy	Blocking IL-6/STAT3 signaling	Decreased CRP level and increased hemoglobin level. No significant suppression of tumor	Lung cancer Colorectal cancer Pancreatic cancer Ovarian cancer Head and neck cancer	[76,112]
Anti-IL-6 receptor antibody	Reduction of clonogenic growth and invasiveness by blocking MAPK and PI3K pathway in vitro	Inhibition of tumor metastasis	Colon cancer	[97]

the clinical response and disease control are not always seen in some autoimmune inflammation diseases. This phenomenon of substantive reducing CRP is also observed in the cancer patients after the medication of anti-IL-6 therapy. No significant suppression of tumor migration or metastasis is found. The progression of cancer related clinical manifestations is still proceeding. In some studies, the combination of anti-IL-6 therapy may improve the resistance of chemotherapy in malignancy.

In summary, anti-IL-6 therapy is useful in the autoimmune diseases with systemic inflammation, and these autoimmune diseases include RA, Castleman's disease, JIA and SLE. Significant improvement of circulating acute phase protein, disease activity and anemia is observed in these effective autoimmune diseases. However, the effect of anti-IL-6 therapy is not significant in other autoimmune diseases including polymyositis, systemic sclerosis, psoriasis and systemic vasculitis. In these non-effective autoimmune diseases, decreased circulating CRP and anemia is still found, but no significant improvement of disease activity is observed. Besides, there is no significant improvement of metastasis, prognosis and mortality after anti-IL-6 therapy in the patients with cancers. However, IL-6 still plays a major role in systemic inflammation of numerous cancers including breast cancer, prostate cancer, lung cancer, colon cancer and multiple myeloma. Anti-IL-6 therapy may improve the clinical manifestations of malignancy related systemic inflammation. These effective clinical manifestations of chronic systemic inflammation include fever, anemia and cachexia. Targeting IL-6 antibody for IL-6 inhibition may sensitize tumor cells to irradiation and chemotherapy. These involved organs of malignancy include breast, prostate and colon. Thus, the circulating IL-6 level might severe as a predictor of the radiation or chemotherapy response in these tumor cells.

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