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Review Article

The Role of Proinflammatory Cytokines in Lung Cancer

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Abstract

Lung cancer is one of the deadliest types of cancer worldwide, with high morbidity and mortality rates. In the progression of lung cancer, pro-inflammatory cytokines play a crucial role in chronic inflammatory processes that can facilitate the growth and spread of cancer cells. Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α have been extensively studied due to their association with the pathogenesis of lung cancer. IL-1 triggers inflammatory responses and modulates the tumor microenvironment, IL-6 is involved in cancer cell proliferation and resistance to apoptosis, while TNF-α contributes to and metastasis. The relationship between these pro-inflammatory cytokines and lung cancer indicates that increased levels of these cytokines in the body can worsen cancer conditions by supporting tumor growth, evading immune responses, and promoting metastatic spread. Further research on the specific mechanisms of these pro-inflammatory cytokines is expected to pave the way for the development of more effective new therapies in tackling lung cancer.

Keywords: *interleukin-1, interleukin-6, lung cancer, pro-inflammatory cytokines, tumor necrosis factor alpha*

Abstrak

Kanker paru merupakan salah satu jenis kanker paling mematikan di dunia, dengan angka morbiditas dan mortalitas yang tinggi. Dalam progresi kanker paru, sitokin proinflamasi memainkan peran penting dalam proses inflamasi kronis yang dapat memfasilitasi pertumbuhan dan penyebaran sel kanker. Sitokin proinflamasi seperti IL-1, IL-6, dan TNF-α telah banyak diteliti karena kaitannya dengan patogenesis kanker paru. IL-1 memicu respons inflamasi dan memodulasi mikro lingkungan tumor, IL-6 berperan dalam proliferasi sel kanker dan resistensi terhadap apoptosis, sedangkan TNF-α berkontribusi terhadap invasi dan metastasis. Hubungan antara sitokin proinflamasi tersebut dengan kanker paru menunjukkan bahwa peningkatan kadar sitokin ini di dalam tubuh dapat memperburuk kondisi kanker dengan mendukung pertumbuhan tumor, menghindari respons imun, serta meningkatkan penyebaran metastasis. Penelitian lebih lanjut mengenai mekanisme spesifik sitokin proinflamasi ini diharapkan dapat membuka jalan bagi pengembangan terapi baru yang lebih efektif dalam penatalaksanaan kanker paru.

Kata kunci: *interleukin-1, interleukin-6, kanker paru, sitokin proinflamasi, tumor necrosis factor alpha*

Background

Lung cancer is one of the most common and deadly types of cancer in the world. Based on histology, *lung cancer* is classified into two main types: *small cell* lung cancer (SCLC=KPKSK) and *non-small cell* lung *cancer* (NSCLC=KPKBSK) (Figure 1). KPKSK is rarer in incidence but is known to be highly aggressive and fast-spreading, while KPKBSK is more common and has several subtypes such as adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Major risk factors for lung cancer include smoking, exposure to cigarette smoke, air pollution, and exposure to harmful chemicals such as asbestos and radon. Diagnosis is often delayed due to non-specific symptoms in the early stages, resulting in a poor prognosis for many patients.

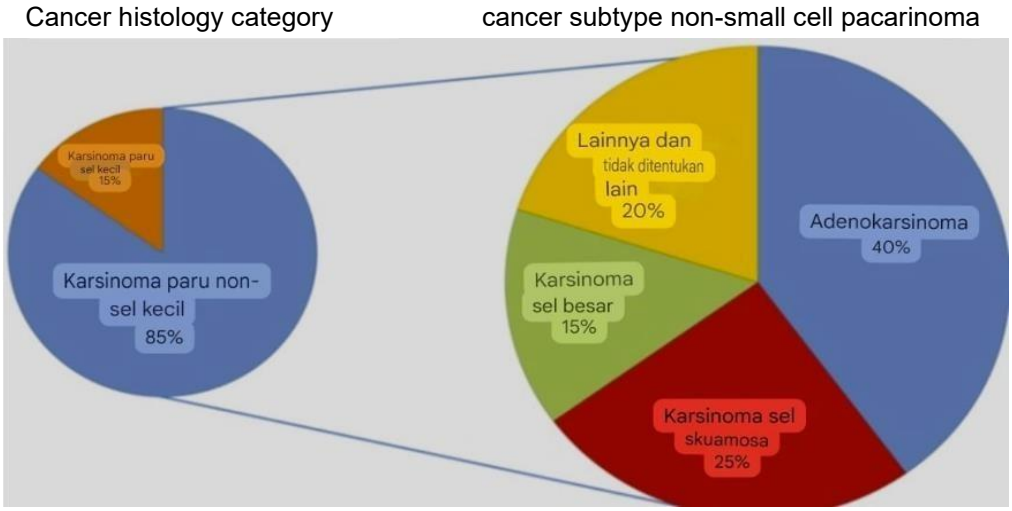

Figure 1. Proportion of lung cancer by type[2]

Molecular mechanisms in lung cancer involve various genetic and epigenetic alterations that trigger uncontrolled cell proliferation, evasion of apoptosis, angiogenesis and metastasis. Major signaling pathways often involved include mutations in the *Epidermal Growth Factor Receptor* (EGFR), *Kirsten Rat Sarcoma Viral Oncogene Homolog* (KRAS) and *Anaplastic Lymphoma Kinase* (ALK) genes (figure 2). Findings about these specific mutations have enabled the development of targeted therapies, such as EGFR and ALK inhibitors, which have shown significant success in prolonging patient survival. More extensive research on these molecular mechanisms may pave the way for the discovery of new therapies and a more personalized approach in the treatment of lung cancer.[1,3]

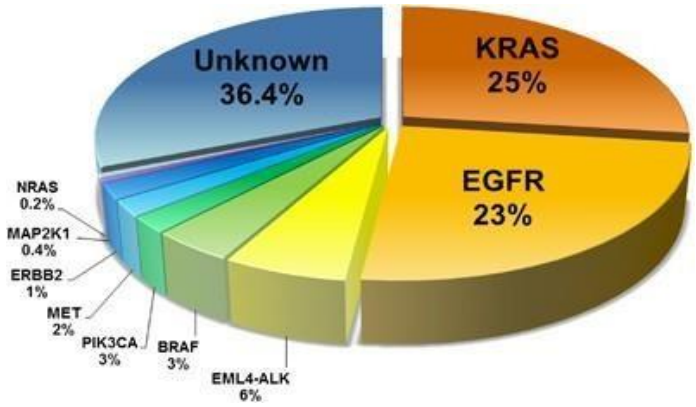

Figure 2. Proportion of genetic mutations in adenocarcinoma based on data from the *National Cancer Institute* Lung *Cancer* Mutation Consortium[4]

Inflammation is the body's natural response to infection or injury, but chronic inflammation can contribute to the development of various chronic diseases, including cancer. In cancer, chronic inflammation can create an environment that is support cancer cell proliferation, invasion and

metastasis. Proinflammatory cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-α) play a key role in mediating this inflammatory process. These cytokines can induce changes in the tumor microenvironment, promote angiogenesis, and inhibit the body's anti-tumor defense mechanisms. Research shows that uncontrolled chronic inflammation contributes to the initiation and progression of many cancers, including lung cancer (figure 3).[5,6]

Several pro-inflammatory cytokines have also been reported to increase the progressivity of lung cancer and facilitate drug resistance. Therefore, targeting inflammatory pathways may be an effective strategy for the prevention and treatment of lung cancer. The main objective of this literature review is to comprehensively examine the role of pro-inflammatory cytokines in the development and progression of lung cancer and explore the specific mechanisms potential therapeutic interventions targeting the inflammatory pathway in the treatment of lung cancer. Due to the large number of cytokines involved in the inflammatory process, this literature review is limited to discussing three proinflammatory cytokines that are widely recognized and have important functions, namely IL-1, IL-6 and TNF-α.[6]

Lung Cancer

Lung Cancer Epidemiology

Lung cancer is the leading cause of cancer death worldwide, with incidence and prevalence varying globally and regionally. Globally, more than 2 million new cases are diagnosed each year, with a mortality rate approaching 1.8 million. In developing countries, the incidence of lung cancer is increasing with increased smoking and air pollution. In developed countries, despite a decline in incidence due to decreased smoking, mortality rates remain high. The main risk factors for lung cancer include smoking, which is responsible for about 85% of cases, as well as environmental exposures such as asbestos, radon and air pollution. Genetic factors also play an important role, with certain gene mutations increasing a person's risk of developing lung cancer.[1]

Pathogenesis and Progression of Lung Cancer

The pathogenesis of lung cancer involves various complex molecular and cellular mechanisms. Genetic mutations in oncogenes such as EGFR, KRAS, ALK as well as loss of function of tumor suppressor genes such as p53 contribute to uncontrolled cell proliferation, resistance to apoptosis and the ability to invade surrounding tissues. The development of lung cancer occurs through several stages, starting from basal cell hyperplasia, dysplasia, carcinoma in situ, to invasive carcinoma. In the early stages, cancer cells may be confined to the epithelial layer of the lung, but over time these cells can penetrate the basement membrane, enter the lymphatic and circulatory systems and eventually cause metastasis to other organs such as the brain, bone and liver. A deep understanding of these mechanisms is important for the development of more effective therapies and prevention strategies.[3]

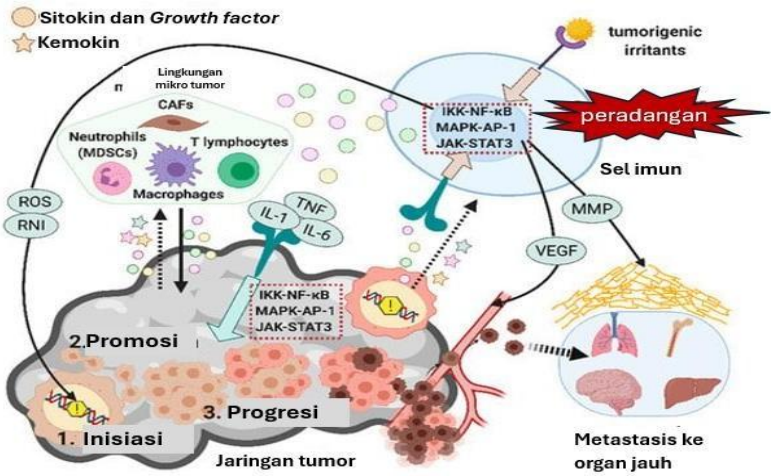

Figure 3. Role of proinflammatory cytokines in the tumor microenvironment[7]

Cytokine Physiology

Definition, Classification, and Mechanism of Action of Cytokines

Cytokines are small proteins secreted by immune system cells to communicate and mediate responses. Proinflammatory cytokines are a subgroup of cytokines that promote inflammation in response to infection or injury. These cytokines play an important role in triggering and maintaining the inflammatory response. The main classifications of proinflammatory cytokines include IL-1, IL-6 and TNF-α. Interleukin-1 is a key mediator in acute inflammatory responses, IL-6 has a role in the regulation of immune responses and chronic inflammation, while TNF-α is a powerful cytokine that can trigger apoptosis but also supports chronic inflammation that can contribute to carcinogenesis.[8]

Proinflammatory cytokines play a critical role in regulating immune and inflammatory responses by stimulating immune cells to migrate to sites of infection or injury, increasing vascular permeability and facilitating communication between immune cells. The mechanism of action of proinflammatory cytokines on target cells begins with binding to specific receptors on the cell surface that trigger various intracellular signaling pathways. These pathways can activate the transcription of genes involved in inflammation, cell proliferation and apoptosis. For example, IL-1 can activate *the Nuclear Factor Kappa B* (NF-κB) pathway involved in inflammatory responses, while IL-6 can activate the *Janus kinase-signal transducer and activator of transcription* (JAK/STAT) pathway involved in cell growth and differentiation. Tumor necrosis factor alpha through its receptor can trigger pathways that lead to apoptosis or in some cases support tumor cell survival and proliferation. [8]

Inflammation and Cancer

The theory of inflammation as a cause of cancer suggests that chronic inflammation can create a favorable environment for cancer initiation and progression. Chronic inflammation causes oxidative stress, DNA damage and epigenetic changes that increase the risk of mutations and uncontrolled cell proliferation. In carcinogenesis, chronic inflammation plays a role in supporting a tumor microenvironment rich in proinflammatory cytokines, proteolytic enzymes and growth factors that can all promote cancer cell growth and spread. Therefore, chronic inflammation is not only a result of cancer but also contributes to the development and progression of cancer.[6]

Specific Role of Proinflammatory Cytokines

Interleukin-1 (IL-1)

Interleukin-1 is one of the major proinflammatory cytokines that plays an important role in the regulation of immune and inflammatory responses. Interleukin-1 consists of two main isoforms, namely IL-1α and IL-1β, which despite having similar functions are produced and regulated by different pathways. Interleukin-1α is usually found inside cells, whereas IL-1β is mainly released into the extra-cellular environment. Both are produced by various cell types such as macrophages, dendritic cells, fibroblasts, and some types of epithelial cells.

Interleukin-1 acts as a key mediator in the acute inflammatory response, helping the body fight infection and repair damaged tissue (figure 4).[9]

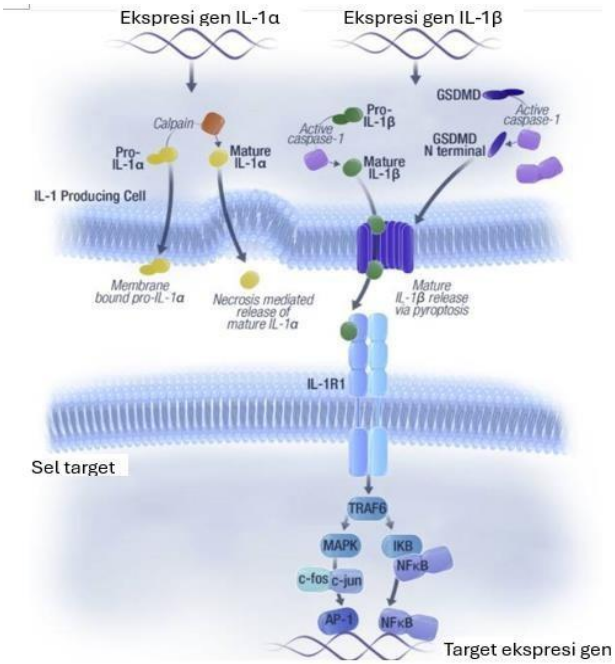

Figure 4. Mechanism of action of IL-1 molecules[10]

The role of IL-1 is not limited to acute inflamma-tory processes. In chronic inflammatory conditions, such as those in autoimmune diseases and cancer, IL-1 can contribute to tissue damage and worsen the disease. For example, in lung cancer, IL-1 plays an important role in tumor initiation and progression. IL-1 can facilitate cancer cell invasion and metastasis by increasing the expression of enzymes that break down the extracellular matrix, such as matrix metalloproteinases (MMPs). Interleukin-1 also stimulates angiogenesis and neovascularization

systems that facilitate metastasis, as well as inhibiting adaptive immune responses and promoting local immunosuppression.[9]
Excessive IL-1 activity can lead to detrimental effects. In chronic inflammation, IL-1 can trigger a sustained immune response, causing tissue damage and favoring the development of chronic diseases such as rheumatoid arthritis and inflammatory bowel disease. IL-1 may also play a role in the induction of fever as part of the body's response to infection. By increasing vascular permeability and stimulating the production of growth factors, IL-1 aids tissue healing, but if not properly regulated, can lead to damaging inflammation. Therefore, regulation of IL-1 activity is key in maintaining the balance between protective and pathological inflammatory responses. [9]

The mechanism of action of IL-1 begins with binding to the IL-1 receptor (IL-1R) located on the surface of target cells. This binding triggers a series of intracellular signaling pathways, including the NF-κB and MAPK pathways, which play a role in the transcription of proinflammatory genes. Activation of these pathways results in the production of more cytokines, proteolytic enzymes and adhesion molecules, all of which contribute to a more robust and sustained inflammatory response. In acute inflammation, these mechanisms help the body fight infection and repair damaged tissues. However, prolonged inflammation can trigger a range of diseases including lung cancer. [9]

In chronic inflammatory conditions, these activation mechanisms can become pathological. Excessive IL-1 activity can lead to sustained inflammation that damages healthy tissues and favors the development of chronic diseases, including cancer. In lung cancer, excessive IL-1 can increase the expression of enzymes such as MMPs, which break down the extracellular matrix and facilitate cancer cell invasion and metastasis. In addition, IL-1 can also promote angiogenesis, which is the formation of new blood vessels that nourish the tumor, thus supporting cancer growth and spread. Understanding IL-1' mechanism of action is important for the development of therapies that target inflammatory pathways in the treatment of chronic diseases and cancer. [9]

In lung cancer, IL-1 plays an important role in various stages of tumor development and progression. The recent *Canakinumab Anti-inflammatory Thrombosis Outcomes Study* (CANTOS) which evaluated the use of anti-interleukin-1β therapy in atherosclerotic disease revealed that interleukin-1β (IL-1β) blockade with canakinumab resulted in a lower incidence of lung cancer. This means that the use of canakinumab, which inhibits IL-1β, also has a positive effect in reducing the risk of developing lung cancer. Studies have also shown that high levels of IL-1 in tumor tissue or blood of lung cancer patients are often associated with a worse prognosis.[11]

Experimental studies have also shown that inhibition of the IL-1 pathway can reduce tumor growth and metastasis in experimental animal models. IL-1 inhibitors or IL-1 receptor antagonists have shown potential in suppressing the tumorigenic activity of IL-1. In addition, therapies targeting IL-1 can be used in conjunction with conventional therapies such as chemotherapy or immunotherapy to improve treatment effectiveness. Thus, IL-1 is not only an important target for basic research but also has meaningful clinical potential in the development of novel therapeutic strategies for lung cancer.[12]

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a proinflammatory cytokine that plays an important role in the regulation of immune and inflammatory responses. Interleukin-6 is produced by various cell types, including macrophages, T cells, fibroblasts and endothelial cells, in response to infection, trauma or other stress. As one of the major mediators of inflammation, IL-6 mediates a variety of biological functions, including T and B cell differentiation, immunoglobulin production, and stimulation of hepatocytes to produce acute phase proteins. Interleukin-6 plays a central role in innate and adaptive immune responses, helping the body fight pathogens and repair damaged tissues. In, IL-6 also plays a role in various chronic inflammatory conditions and autoimmune diseases. For example, high levels of IL-6 have been associated with diseases such as rheumatoid arthritis, cardiovascular disease, and various cancers, including lung cancer.[13]

Interleukin-6 has several key functions in mediating the inflammatory process. One of its main functions is to induce hepatocytes to produce acute phase proteins such as *C- reactive* protein (CRP), which is important for systemic inflammatory responses. In addition, IL-6 plays a role in T cell differentiation into the T *helper* cell (Th17) subset, which is important for defense against infection but can also contribute to autoimmune diseases. Interleukin-6 also promotes the proliferation and differentiation of B cells, increasing the production of antibodies essential for humoral immune responses. Under these conditions, IL-6 can trigger a sustained inflammatory response and damage tissues. Therefore, IL-6 is an important target in the development of therapies to control chronic inflammation and prevent the

progression of more severe diseases.[13]

Excessive IL-6 activity can lead to detrimental effects. In chronic inflammation, IL-6 can trigger a prolonged inflammatory response, causing tissue damage and favoring the development of pathological conditions. Interleukin-6 can have detrimental effects on cancer through several mechanisms. Interleukin-6 is a proinflammatory cytokine that can affect the tumor microenviron-ment in various ways. First, IL-6 can increase cancer cell proliferation by activating signaling pathways that promote cell growth. Interleukin-6 can also inhibit apoptosis or programmed cell death, which is important for controlling cancer cell growth. Interleukin-6 also plays a role in promoting angiogenesis which facilitates tumors to get enough blood supply to grow and spread.[14]

The mechanism of action of IL-6 begins with binding to the IL-6 receptor (IL-6R) on the target cell surface, which consists of the IL-6Rα and gp130 subunits. This binding activates intracellular signaling pathways such as JAK/STAT, *mitogen-activated protein kinase* (MAPK) and Phosphoinositide 3-kinases (PI3K) pathways that play a role in transcription of proinflammatory and anti-apoptotic genes. Activation of these pathways results in increased expression of genes that support cell proliferation, differentiation and survival. For example, the JAK/STAT pathway plays a key role in the regulation of gene expression that controls proliferation and resistance to apoptosis (figure 5).[15]

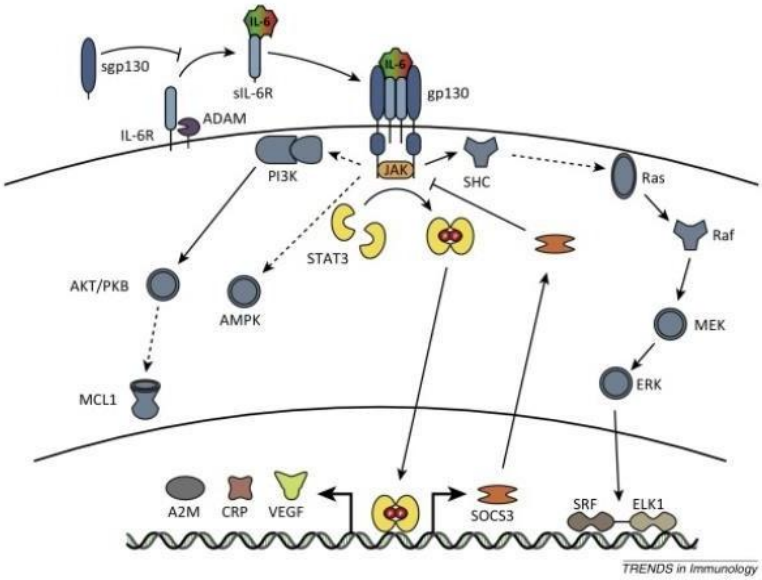

Figure 5. Interleukin 6 mechanism of action[16\]

Research shows that high levels of IL-6 in the serum of lung cancer patients are often associated with a worse prognosis. Interleukin-6 can activate the STAT3 signaling pathway, which plays an important role in cancer cell survival and metastatic ability. Activation of the STAT3 pathway by IL-6 leads to the expression of genes that favor cell proliferation, inhibit apoptotic mechanisms and increase the invasion and metastatic potential of cancer cells. In addition, IL-6 also contributes to the formation of new blood vessels (angiogenesis) around the tumor, providing the necessary nutrients for rapid tumor growth. IL-6 not only serves as an indicator of prognosis but also as a potential target for therapy in lung cancer.[15,17]
Experimental studies have also shown that inhibition of the IL-6 pathway can reduce tumor growth and metastasis in animal models of lung cancer. The use of monoclonal antibodies targeting IL-6 or the IL-6 receptor has shown potential in suppressing tumorigenic activity in cancer models. In addition, therapies targeting IL-6 can be used in conjunction with conventional therapies such as chemotherapy or immunotherapy to improve treatment effectiveness. Thus, IL-6 is not only an important target for basic research but also has meaningful clinical potential in the development of novel therapeutic strategies for lung cancer.[18,19]

Tumor Necrosis Factor Alpha (TNF-α)

Tumor Necrosis Factor- α (TNF-α) is a proinflam-matory cytokine that plays an important role in the

regulation of immune and inflammatory responses. *Tumor Necrosis Factor-α* is produced by various cell types, including macrophages, T cells and NK cells, in response to infection, trauma or other pathological conditions. *Tumor Necrosis Factor- α* serves as a key mediator in acute inflammation, helping the body fight pathogens by stimulating a strong immune response. *Tumor Necrosis Factor- α* also induces apoptosis in infected cells or cancer cells, thus playing a role in the control of abnormal cell growth. However, in addition to its protective role, TNF-α is also involved in various chronic inflammatory conditions and autoimmune diseases. Excessive production of TNF-α can cause tissue damage and worsen disease conditions.[20]

Tumor Necrosis Factor- α has several key functions in the mediation of the inflammatory process. One of its main functions is to stimulate the expression of adhesion molecules on endothelial cells, which enhances the recruitment of immune cells to the site of infection or injury. In addition to that, TNF-α stimulates the production of chemokines and other cytokines, which amplifies inflammatory signals and helps attract more immune cells to the site of inflammation. TNF-α also plays a role in inducing fever and the production of acute- phase proteins by hepatocytes, which are part of the body's systemic response to infection. However, excessive TNF-α activity can lead to sustained inflammation that damages healthy tissue and favors the development of chronic diseases, such as rheumatoid arthritis and inflammatory bowel disease.[20]

The mechanism of action of TNF-α begins with binding to TNF receptors (TNFR1 and TNFR2) on the surface of target cells. This binding triggers the activation of a series of intracellular signaling pathways, including NF-κB and MAPK pathways that regulate the expression of proinflammatory and antiapoptotic genes. Activation of these pathways results in the production of more cytokines, chemokines and proteolytic enzymes, all of which contribute to a more robust and sustained inflammatory response. In chronic inflam-mation and cancer, excessive TNF-α activity through this pathway can support tumor growth and spread by creating a microenvironment that favors inflammation, angiogenesis and inhibits cancer cell apoptosis.[20,21]

In lung cancer, TNF-α supports tumor growth by increasing cancer cell proliferation, inhibiting apoptosis, and stimulating angiogenesis. Research shows that high TNF-α levels in the serum of lung cancer patients are often associated with a worse prognosis. *Tumor Necrosis Factor-α* can activate the NF-κB signaling pathway, which plays an important role in cancer cell survival and metastatic ability. Activation of the NF-κB pathway by TNF-α leads to the expression of genes that favor cell proliferation, inhibit apoptotic mechanisms, and increase the invasion and metastatic potential of cancer cells. addition, TNF-α also contributes to angiogenesis around the tumor, providing nutrients necessary for rapid tumor growth. Therefore, TNF-α not only serves as an indicator of prognosis but also as a potential target for therapy in lung cancer.[21]

Conclusions

1. Proinflammatory cytokines such as IL-1, IL-6 and TNF-α play an important role in the development and progression of lung cancer. Interleukin-1 is known to promote cancer cell proliferation and angiogenesis, IL-6 supports tumor growth and metastasis through the STAT3 pathway, while TNF-α affects the tumor microenvironment and promotes chronic inflammation.
2. High levels of proinflammatory cytokines often correlate with poor prognosis in lung cancer patients. The specific mechanisms of how each cytokine affects molecular pathways in lung cancer still require further research for a more complete understanding.
3. Knowledge of proinflammatory cytokines can be applied in the diagnosis and therapy of lung cancer in several ways. Measurement of cytokine levels such as IL- 1, IL-6 and TNF-α in patient serum can be used as biomarkers for early diagnosis and prognosis of lung cancer. In addition, targeting proinflammatory cytokine pathways can be an effective therapeutic strategy. For example, inhibitors of IL-6 or TNF-α have shown potential in reducing cancer cell proliferation and metastasis in preclinical studies.
4. Potential new therapeutic targets based on proinflammatory cytokines pave the way the development of drugs that are more specific and less toxic than conventional chemotherapy.
5. Therapies targeting these cytokines can be used alone or in combination with other therapies such as immune *checkpoint* inhibitors or molecular targeted therapies. As we continue to develop our under-standing of the role of proinflammatory cytokines in lung cancer, it is hoped that more effective and personalized therapies can be found, ultimately improving clinical outcomes for patients.

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