Review

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Cytokine Profile in Lung Cancer Patients: Anti-Tumor and Oncogenic Cytokines

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Abstract: Lung cancer accounts for the majority of cancer cases. In recent years, checkpoint inhibitor immunotherapy (ICI) has emerged as a new treatment. A better understanding of the tumor microenvironment, or TMJ, or the immune system surrounding the tumor is needed. Cytokines are small proteins that carry messages between cells and are known to play an important role in the body's response to inflammation and infection. Cytokines are important for immunity in lung cancer. It promotes tumor growth (oncogenic cytokines) or inhibits tumor growth (anti-tumor cytokines) by controlling signaling pathways for growth, proliferation, metastasis, and apoptosis. The immune system relies heavily on cytokines. They can also be produced in the laboratory for therapeutic use. Cytokine therapy helps the immune system stop the growth or kill cancer cells. Interleukins and interferons are two types of cytokines used to treat cancer. This article begins by addressing the role of the tumor microenvironment (TMJ) and its components in lung cancer. This review also highlights the functions of various cytokines such as IL, TGF and TNF.

Keywords: lung cancer; cytokines; therapy; immune system; anti-tumor

1. Introduction

Lung carcinoma, also known as lung cancer, is a type of lung cancer that usually results from uncontrolled cell proliferation of the lungs. Tissue containing epithelial cells that have transformed into malignant cells, or in some cases all epithelial cells, is one type of lung cancer. Abnormal masses or nodules may be seen on chest X-rays [1]. CT scans can also see small lung lesions that X-rays may miss.

Lung cancer is currently the second leading cause of cancer worldwide. Although lung cancer can occur in people who have never smoked, smokers are the group most likely to develop lung cancer. Both the amount and frequency of smoking can affect a person's risk of developing lung cancer. People who quit smoking after smoking for a long time will have a decreased risk of lung cancer. In addition, the risk of lung cancer increases with urban pollution.

To reduce the number of deaths from lung cancer, the best option is to increase the effectiveness of cancer prevention and to use screening strategies for risk assessment and detection in the early stages of lung cancer treatment [2]. According to the study of R. Kuner et al., the estimated number of new cases and deaths from lung and lung cancer in the United States in 2013 was 228,190 and 159,480, respectively. About 55% to 60% of patients have distant metastases and are diagnosed at an advanced, incurable stage. Therefore, the five-year overall survival rate of each stage is between 13% and 16%.

Nonsmall cell lung cancer, also known as NSCLC, is the most common type of bronchial malignancy. Adenocarcinoma and squamous cell carcinoma are the two main histological groups from which they are often separated. Adenocarcinoma and squamous carcinoma cells differ in DNA

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copy number, DNA methylation, gene mutations, transcriptome, proteome, and potential biomarkers.

In lung cancer, cytokines, or proteins, are important to support the immune system. It can promote tumor growth (oncogenic cytokines) or inhibit tumor growth (anti-tumor cytokines) by modulating related factors such as growth, proliferation, metastasis and apoptosis.

1.1. Type and treatment of lung cancer

This is divided into small cell lung cancer (SCLC), which accounts for 15% of patients, and non-small cell lung cancer (NSCLC), which accounts for 85% of patients [70]. Histologically, NSCLC is divided into three subtypes: adenocarcinoma (ADC), large cell lung cancer (LCC), and squamous cell carcinoma (SCC). Both smokers and nonsmokers have been found to have NSCLC, the most common variety that is gender-neutral and affects 40% of ADC victims. ADC consists of type II alveolar cells in the outer lung, which are mucus sealing cells [9].

Other subtypes of SCC occur in flattened squamous cells in the airways, centrally in the lungs, and account for approximately 25% to 30% of the most common causes of smoking [10].

Some asymptomatic cancer patients cannot be accurately diagnosed during conventional treatment. However, approximately 70% of NSCLC patients progress to an advanced stage after diagnosis, either locally or in organ metastases[11]. In other words, early warning signs may be the key to improving cancer patient survival. An important part of the immune system's specific response to dangerous stimuli is inflammation.Many studies have demonstrated the role of inflammation in cancer [12].

Due to the disease's complexity, it develops genetic and epigenetic variants. Tumor differentiation, growth, invasion, and metastasis are generally controlled by these modifications. Approximately 70% to 80% of patients do not believe that surgery, which is considered the best treatment for early-stage NSCLC, is the best option, especially because of locoregional tumor swelling, extrathoracic spread, or poor physical and functional state at the time of diagnosis. Therefore, patients often choose radiotherapy or chemotherapy alone to achieve a better prognosis [13].

Alternatively, surgical resection followed the neoadjuvant approach. Radiotherapy (RT) is important in the treatment of lung cancer. According to various studies, approximately 60% of patients received radiation therapy in the early stages of the disease – approximately 44% at diagnosis and approximately 16% in advanced or relapsed state[14]. Chemotherapy is considered a better option for lung cancer treatment because twothirds of patients have cancer or lung cancer at diagnosis [15]. Most FDA approved drugs focus on angiogenesis and immunosuppression to demonstrate the biological and physiological dynamics of the tumor microenvironment and cancer-related symptoms.

1.2. Tumor microenvironment and content: their contribution to NSCLC metastasis

Tumors creates the tumor microenvironment, which is dominated by interactions brought on by the tumor. The anti-tumor potential of different immune effector cells are down-regulated at the tumor site, although they are usually selected in response to signals from the tumor. The chronic infiltration of inflammatory cells seen in human malignancies is enriched with regulatory T cells (Treg) and myeloid suppressor cells (MSC). The lymphocytes, macrophages, dendritic cells and natural killer cells that make up the immune system communicate through cells, surfaces and other mediators (cytokines and chemokines). Innate immunity typically works ahead of schedule during the course of an insusceptible reaction and includes a specific configuration of receptors, with the help of macrophages, neutrophils, and NK cells.

T lymphocytes (CD4+ and CD8+ T cells) and B cells, on the other hand, regulate adaptive immunity. These cells are prepared by antigen-presenting dendritic cells; B cells are activated by antigen entering their local environment; and CD8+ and CD4+ lymphocytes are sensitive to antigen presented as peptides that complex with MHC class I and class II particles, respectively. Germinal gene sequences that produce a large population of T-cell and B-cell receptors can sensitively detect

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multiple targets, resulting in an immune system that takes days to survive and causes strong memory.

The immune response is determined by the cytokine profile transmitted by the immune system: cell mediated immunity is favored by TH1 cytokines such as IL-2, IFN- and tumor necrosis factor (TNF); TH2 cytokines (eg., IL-4, 5, 10 and 13) are important for immunity and well-being; In addition, TH17 cytokines such as IL-17, 22 and granulocyte sedimentation enhancing component (G-CSF) act to elicit responses. It indicates that effector and focused memory T helper type 1 (Th1) and T killer type 1 (Tc1) cells, rather than a humoral immune response, are responsible for defensive long-range resistance against cancer and the ability to combat chronic inflammation.

T cells or NK cells are members of the TNF receptor family (eg. For example, FAS and TRAIL) or performance and degranulation by granzymes, the ultimate result of cancer prevention may or may not be the end of foragers. Similarly, the latter results in the delivery of Th1 cytokines that transform tumor-associated M2 macrophages that secrete arginase and inducible nitric oxide synthase into M1 killer cells that secrete IL-12 and TNFα. In addition, antibodies are effective in inhibiting tumor growth when they bind to oncogenic growth receptors such as HER2/NEU and EGFR and prefer NK or Fc receptors that activate macrophage or complement protein cascades[16]. When cancer cells metastasize, they leave their original site and live elsewhere where they can continue to grow. The tumor and surrounding ME initiates the process of infiltrating, forming, and dividing into different tissues, leading to metastasis. The transformation of a normal cell into a tumor is dependent on the environment, so it may occur in one TME but not in another. TME contains bothcellular and non-cellular components (Figure 1).

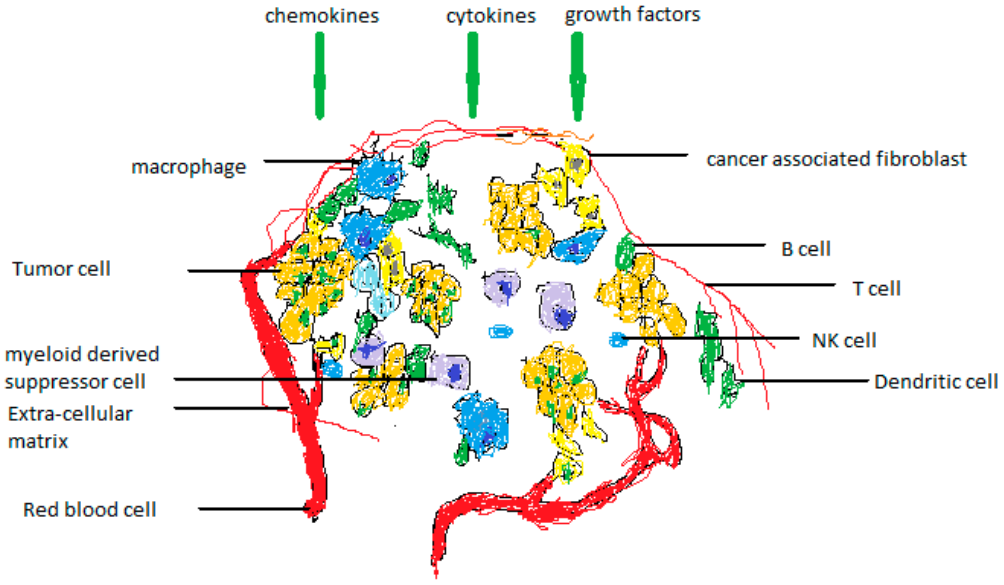

Figure 1. The elements that make up the tumor's microenvironment. The TME is made up of both cellular and noncellular elements. Cancer-associated fibroblasts (CAFs), adipocytes (APs), niche, immune cells, carcinogenic and noncancerous cells, endothelial cells (ECs), mesenchymal stem cells (MSCs), and mesenchymal stem cells (MSCs) are all present in the former and all contribute to the tumor's progression. The mediators that make up the noncellular component include growth factors, cytokines, and chemokines. They could develop independently or promote a cancer cell's growth.

Lung cancer has a complex process of growth, initiation and metastasis. Genetic abnormalities acquired by the tumor lead to the development of the disease and interaction with the immune system leading to localized ME. Immobility and flexibility in TME use different mechanisms. First, it is the main defense mechanism against foreign invaders and consists of dendritic cells (DC) (CD1c (+), natural killer (NK) cells (CD49a, CD69 and CD103), macrophages (CD68+), NK-T cells CD56+ and

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CD3+) and neutrophil phagocyte (NK) cells. Cancer cells promote tumor growth, angiogenesis and metastasis.

If the system is reprogrammed, they also cause tumors to grow. Tumor growth slows from the second phase, which includes B cells (CD20+) and two subsets of T cells, T helper cells (CD4+) and cytotoxic T cells (CD8+) [18]. Tumor infiltrating leukocytes (TILs), which promote anti-tumor responses, account for 67% of TME in lung tumors. This is followed by tumor-associated macrophages (TAMs), followed by small numbers of DC and NK cells [19].

2. Basic properties of cytokines

The balance of the immune system is controlled by cytokines, which are membrane-bound or released proteins that mediate intercellular signals. They are produced by innate and adaptive immune cells in response to tumor antigens and pathogens. Each cytokine has a unique effect on the immune system that is dependent on many factors, including local cytokine concentrations, cytokine receptor expression patterns, and the integration of various pathways into the immune response. The importance of cytokines in tumor immunity is demonstrated by increased tumor frequency in mice lacking type I or type II interferon (IFN) receptors or downstream IFN receptor signaling components [20].

An important aspect of cytokine signaling is pleiotropy, or the ability of a single cytokine to cause different cell types to produce different effects, some of which may lead to resistance (Table 1). This has been viewed as one of the main challenges of IL-2 therapy due to the dual role of IL-2 as a potent activator of the T regulatory and T effector regions. Another important aspect of cytokine signaling is redundancy, or the number of cytokines with the same function. This reactivity makes it difficult to change cytokines for therapy because changing one cytokine may induce the other to compensate.

Table 1. Basic Characteristics of Cytokines.

Cytokine	Primary Cell Source	Primary Target Cell	Biological Activity
IL-1	Monocytes Macrophages Fibroblasts Epithelial cells Endothelial cells Astrocytes	T cells B cells Endothelial cells Hypothalamus Liver	Co-stimulation Cell activation Inflammation Fever Acute phase reactant
IL-2	T cells NK cells	T cells NK cells B cells Monocytes	Cell growth Cell activation
IL-3	T cells	Bone marrow progenitor cells	Cell growth and cell differentiation
IL-4	T cells	T cells B cells	Th2 differentiation Cell growth Cell activation IgE isotype switching
IL-5	T cells	B cells Eosinophils	Cell growth Cell activation
IL-6	T cells Macrophages Fibroblasts	T cells B cells Liver	Co-stimulation Cell growth Cell activation Acute phase reactant

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Cytokine	Primary Cell Source	Primary Target Cell	Biological Activity
IL-7	Fibroblasts Bone marrow stromal cells	Immature lymphoid progenitors	T cell survival, proliferation, homeostasis B cell development
IL-8	Macrophages Epithelial cells Platelets	Neutrophils	Activation Chemotaxis
IL-10	Th2 T cells	Macrophages T cells	Inhibits antigen-presenting cells Inhibits cytokine production
IL-12	Macrophages NK cells	T cells	Th1 differentiation
IL-15	Monocytes	T cells NK cells	Cell growth Cell activation NK cell development Blocks apoptosis
IL-18	Macrophages	T cells NK cells B cells	Cell growth Cell activation Inflammation
IL-21	CD4+ T cells NKT cells	NK cells T cells B cells	Cell growth/ activation Control of allergic responses and viral infections
IL-23	Antigen-presenting cells	T cells NK cells DC	Chronic inflammation Promotes Th17 cells
GM-CSF	Fibroblasts Mast cells T cells Macrophages Endothelial cells	DC Macrophages NKT cells Bone marrow progenitor cells	T cell homeostasis Promotes antigen presentation Hematopoietic cell growth factor
IFN-α	Plasmacytoid DC NK cells T cells B cells Macrophages Fibroblasts Endothelial cells Osteoblasts	Macrophages NK cells	Anti-viral Enhances MHC expression
IFN-γ	T cells NK cells NKT cells	Monocytes Macrophages Endothelial Cells Tissue cells	Cell growth/ activation Enhances MHC expression
TGF-β	T cells Macrophages	T cells	Inhibits cell growth/activation
TNF- α	Macrophages T cells	T cells B cells Endothelial cells Hypothalamus Liver	Co-stimulation Cell activation Inflammation Fever Acute phase reactant

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Cytokines play complex and often antagonistic roles in immune maturation, host defense, and tumor immunobiology. Therefore, the development of cytokine-based immunotherapies for cancer treatment depends on knowing the biological activities and mechanisms of action of these agents.

Table 2. The functions and duties of the cytokine-secreting cells in the tumor microenvironment.

Cell type	Function in TME
Tumour-associated macrophages (TAMs)	TAMs exhibit the M2 macrophage phenotype, which includes protumorigenic characteristics, anti-inflammatory properties, and Th2 cytokine secretion. Help cancer cells invade secondary areas and promote angiogenesis.
Cancer-associated fibroblasts (CAFs)	Stromal cell populations that are active support the desmoplastic tumor microenvironment. By releasing cytokines, one can encourage angiogenesis and control tumor-promoting inflammation.
CD4+ T_h cells	Th1 and Th2 lineages have been divided. Th1 secretes cytokines that are both proinflammatory and antitumorigenic, whereas Th2 secretes cytokines that are both proinflammatory and tumorigenic.
CD8+ T_c cells	Adaptive immune system effector cells that recognize and kill tumor cells by perforin-granzyme-mediated apoptosis.
Mast cells (MCs)	innate and adaptive immune responses to be produced and maintained. Release substances that encourage endothelial cell development to aid tumor cell angiogenesis.
B-cells	Modulators of humoral immunity and secrete cytokines. Alter T_h1:T_h2 ratio.
Natural killer (NK) cells	Without antigen presentation, cytotoxic lymphocytes obliterate stressed cells. Through "missing self" activation and "stress-induced" activation, detect and destroy tumor cells.
Dendritic cells (DCs)	Antigen-presenting cells (APCs) that control the immune system's adaptive response. They increase vascularization in the TME to encourage angiogenesis.
Neutrophils	N1-type cells are pro-inflammatory, anti-tumorigenic, and release Th1 cytokines.

Depending on how they are affected, macrophages can be divided into two types: active M1 type and alternatively activate M2 type. The M1 type secretes Th1 cytokines with pro-inflammatory and anti-tumorigenic properties, while the M2 type secretes Th2 cytokines with anti-inflammatory and pro-tumorigenic properties. Tumor grade and stage correlate with the Th1:Th2 ratio

2.1. Classification of cytokines and their receptors

In order to better define cytokines, many partners and receptors have been identified that define the cytokine problem. To date, seven families of cytokine receptors have been identified (table 3) : type I and type II cytokine receptors, immunoglobulin superfamily receptors, tumor necrosis factor (TNF) receptors, G protein-coupled receptors, transforming growth factor beta (TGF-β), and recently discovered IL -17 receptor. As these hold immediate clinical promise, this section will focus on cytokines that signal through the type I and type II cytokine receptor families.

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Table 3. Classification of cytokine receptors.

Receptor Family	Ligands	Structure and Function
Type I Cytokine Receptors	IL-2 IL-3 Il-4 IL-5 IL-6 IL-7 IL-9 IL-11 IL-12 IL-13 IL-15 IL-21 IL-23 IL-27 Erythropoietin GM-CSF G-CSF Growth hormone Prolactin Oncostatin M Leukemia inhibitory factor	Composed of multimeric chains. Signals through JAK-STAT pathway using common signaling chain. Contains cytokine binding chains.
Type II Cytokine Receptors	IFN-α/β IFN-γ IL-10 IL-20 IL-22 IL-28	Immunoglobulin-like domains. Uses heterodimer and multimeric chains. Signals through JAK-STAT.
Immunoglobulin Superfamily Receptors	IL-1 CSF1 c-kit IL-18	Shares homology with immunoglobulin structures.
IL-17 Receptor	IL-17 IL-17B IL-17C IL-17D IL-17E IL-17F	
G Protein-Coupled Receptors (GPCR)	IL-8 CC chemokines CXC chemokine	Functions to mediate cell activation and migration.
TGF-β receptors 1/2	TGF-β	
Tumor Necrosis Factor Receptors (TNFR)	CD27 CD30 CD40 CD120 Lymphotoxin-β	Functions as co-stimulatory and co-inhibitory receptors.

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2.1.1. Type I cytokine receptors

Type I cytokine receptors, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors, common chain (c), this chain contains specific Janus kinases (The cytokine component of JAK) 1 and 3 that initiates intracellular signaling via coordination of signal transduction and activating T (STAT) molecules (Figure 3). Other type I cytokine receptor subsets include the IL-6 and GM-CSF receptor families, which cooperate through the gp130 receptor to influence multiple signaling pathways at their targets[21].

Various receptor complexes such as IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M, cardiotrophin-1, and ciliary neurotrophic factor use gp130 signaling components to influence immunological, hematopoietic excess activity, and pleiotropic effects[22]. Similarly, receptors of the distinct GM-CSF receptor subfamily, which has a common β chain that binds with the cytokine-specific chain, also recognize IL-3, IL-5, and GM-CSF [23].

2.1.2. Type II cytokine receptors

By use of Type II cytokine receptors, which are made up of a signaling chain and a ligand-binding chain, IFN-α, IFN-β, IFN-γ, and IL-10 actions are mediated. The intracellular domains of type II cytokine receptors frequently interact with Janus kinase (JAK) family tyrosine kinases whose sequences resemble tandem Ig-like domains [24].

2.1.3. Immunoglobulin superfamily receptors

IL-1, IL-18, stem cell factor and monocyte colony stimulating factor receptors are members of the immunoglobulin superfamily and have extracellular immunoglobulin domains.

3. The role of cytokines in immunotherapy and cancer

Since lung cancer outperforms all currently used treatment modalities, it's important to consider some options, especially since the immune system is an important organ of cancer prevention. TILs (immune cells) of the TME, particularly lymphocytes and macrophages, produce cytokines (<30 kDa) that regulate various cellular functions, and high molecular weight nonstructural proteins called chemokines. This process must interact with specific cellular receptors that have an effect on the body through autocrine, paracrine and endocrine types of action. These include metabolism, growth, cell and tissue repair, and chemotaxis [25]. However, cytokines and chemokines are recognized to play an important role in local inflammation and infection.

In addition to treatment, these factors also play an important role in TME for cancer and infection. Considering their role as biomarkers, cytokines (IL-6, 10, 17, 27, 35; TNF-; IFN-; and TGF-) and chemokines (CCL-2, 5, 18; CCR-4; CXCR -4 ; CX3CL) -1; and CXCL-1, 5, 8, 13) are frequently targeted for the treatment of lung cancer[26]. Among other stromal cell types in theTME, macrophages are the major secretors of the cytokine IL-6. When it binds to IL-6R (ligand-binding receptor), its hormonal effects (autocrine and paracrine) are triggered. Its role in TME requires reconciliation of many responses.

It promotes apoptosis, invasion, angiogenesis, EMT and metastasis through the immune system. According to recent research, it also transplants tumor cells into new areas, such as tumor cells containing T lymphocytes [27]. T cells can switch tumors from one state to another, for example from a suppressed state to a reactive state, and also stop the growth and spread of tumors. In addition to innate immunity, TAM-based IL-6 supports the development and repair of cancer stem cells (CSCs). Phosphatidylinositol 4,5-biphosphate 3-kinase/threonine kinase 1/AKT serine (PI3K/AKT) signaling is known to be activated by IL-6 to promote the growth of the A549 brain cancer cell line.

A recent study using in vivo mouse and in vitro human lung tumor models demonstrated that the mechanism by which IL-6 stimulates CCL-2/5 causes EMT and resistance in different stages of lung cancer [26]. Blocking IL-6 modifies TME, complicating the as yet undiagnosed model of carcinogenesis. A number of methods targeting IL-6 signaling have been explored, including blocking STAT3 stimulation with antibodies and peptides, phosphorylating Janus kinase (JAK), and

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using the IL-6, IL-6R, and IL-6-sIL-6R complex. Body [28]. CAFs are important in NSCLC as they enhance EMT signaling to regulate the immune response. IL-10 activity is known to inhibit IL-6 production.

TNF- has been termed a "pyrogenic cytokine" because of its tendency to proliferate in a harsh environment and in response to infection, causing tumor necrosis and cytotoxicity. It binds to its target cells using one of the two receptor families (TNFR1 or TNFR2). According to studies using cancer cells in vivo and in vitro, TNF-- like IL-6 stimulates the process. These include metastasis, angiogenesis, invasion, and anti-apoptosis. Doxorubicin treatment produces TNF-α, while cyclin-dependent kinase inhibitor 1A (CDKN1A) is down-regulated.

This then induces apoptosis in lung tumors lacking TP53. It affects the communication between TNF-TAM and other cells in the TME and controls the survival and growth pathway as well as causing death by TNFR1. Although TNF-- is antitumorigenic because it slows the growth of tumors, its side effects are not normal. Therefore, some studies warn against altering TNF-α, while other studies strongly increase acceptance [29].

The normal regulation of Th1/Th2 T helper cell development was disrupted in 2005 with the identification of T helper 17 (Th17) cells as a third subset of T helper cells.

Th17 cells differ from other T cells in that they produce IL-17, express specific mutations and fulfill specific biological roles. TGF- and IL-6 are required in some cytokine cocktails to differentiate mouse Th17 cells. Additionally, IL-6 promotes the production of IL-21, which helps TGF and IL-23 promote the development of Th17 cells in mice. IL-1 is essential for and promotes the early development of Th17 cells in mice. IL-1 is required for the differentiation of human Th17 cells and together IL-1, IL-6 and IL-23 form a good cytokine environment produced by human Th17 cells.

In addition to cytokine regulation, Th17 development is also influenced by molecular programs of transcriptional regulation. Various, including Th17 cell growth (HIF1-a), signal transducer and activator of transcription 3 (Stat3), retinoid-associated orphan receptor gt (ROR-gt), nuclear receptor ROR-a, IFN-regulated Factor 4 (IRF-4) depends on proteins. .), B cell activating transcription factor (B-ATF) and hypoxia-inducible factor 1 [30].

There is increasing evidence of an association between chronic disease, chronic pain, and cancer. Many immune cells, such as Ab T cells, gd T cells, and natural killer (NK) T cells, can play an important role in tumor prevention and are attracted to local inflammation in the tumor microenvironment. Th17 cells are known to play an important role in the immune system, so they must be present in the tumor microenvironment.

Although Th17 cells are abundant in the tumor microenvironment, it is unclear how they contribute to tumor protection. Most studies investigating the relationship between Th17 cells and cancer have used animal models with varying degrees of success [30].

The IL-12 family of immunosuppressive cytokines includes IL-35. It is the same subunit commonly expressed by regulatory T cells (Treg). STAT1 and STAT4 mediate signaling through IL-35. It does this by binding to the IL-35R receptor. IL-35 inhibits T cell proliferation and effector activity.

Several studies have shown that Tregs induced by IL-35 in TME inhibit CD4 and CD8 function and NK cell antitumor activity. To achieve this, it increases IL-10 and TGF- production. In addition to these results, it has been reported that high plasma IL-35 levels are associated with infection in cancer patients. Potential therapeutic targets include the use of certain monoclonal antibodies to suppress the immune response to IL-35 [31]. B and T cells and activated macrophages release IL-10, a cytokine with protective properties.

It works by binding to the IL-10R receptor. Its main function is to prevent the activation of macrophages. It inhibits the production of proinflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, TNF- and granulocyte-macrophage colony stimulating factor (GM-CSF) [32]. It also reduces the expression of major histocompatibility complex-II (MHC-II) by inhibiting antigen presentation in active macrophages. In addition, IFN- (interferon-) production of Th1 and NK cells is inhibited by IL-10.

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Serum IL-10 uptake can be seen clearly in many diseases, especially in the immune system. In cancer patients, TAM-(M2-)-dependent IL-10 has consistently shown significant clinical significance. While both IL-10 and TAM-based IL-10 have been studied and show some similarities, the signal of the former involves a complex chemical process involving 76 processes and 37 molecules (less extremes) to promote tumor growth [33]. IL-10 from TAMs preferentially promotes lung cancer stalk. In vivo cancer mouse model studies use the NFKB/JAK1/STAT1/NOTCH1 signaling pathway. It also promotes the spread of lung cancer throughout the body. It targets the induction of the CCL-2/CCR-2 and CXC3CL-1/CX3CR-1 axes in the interaction between macrophages and tumor cells. Not only is this IL-10 signaling issue being studied, but many other methods are also being evaluated at the clinical level. Although IL-10 has been extensively studied, its role in cancer therapy remains unclear. Different strategies, such as the development of monoclonal antibodies and peptides that block IL-10, have been tested in various diseases.

In addition, efforts are being made to develop molecular inhibitors and receptor blocking (IL-10R) strategies that target JAK/STAT3 signaling [34]. Several results indicate that IL-10+ Bregs (regulatory B cells) suppress human lung cancer, particularly in ADCs. They have been shown to be involved in cancer. In addition, IL-10 is thought to be important for maintaining the homeostasis of inflammation-fighting regulatory T cells (Treg). In addition, it is important for the suppression of proinflammatory T cells (Th17) that express the IL-17 gene [64].

Control of tumor growth depends on different T cell populations that maintain a balance between pro-inflammatory and anti-inflammatory factors [35]. Despite its many functions, IL-10's ability to downregulate MHC I renders tumor cells more susceptible to NK. This indicates that IL-10 works in concert with excitatory cytokines such as IL-2, which can increase NK cell-mediated responses to tumor cells. However, conflicting data on the role of IL-10 in cancer are beginning to emerge. According to Konjevi et al.

A plausible explanation for why its function is not regulated by environmental stimuli is cytokine homeostasis [36].

Myeloid-derived suppressor cells (MDSCs) support peripheral immunity by acting as anti-inflammatory agents. Because of its complexity, the role of IL-10 in preventing cancer has been controversial since its discovery in the 1990s. While decreased IL-10 levels have been shown to increase the risk of gastric adenocarcinoma and prostate cancer, it is known to increase tumor growth in various types of cancer (HIV-positive cancer). According to research by Lee and colleagues, IL-10 slows tumor growth by blocking the effects of the IL-6/STAT3 axis on MDSCs.

Among T lymphocytes, IL-10 is thought to have both stimulating and inhibitory effects. According to Fujii et al.'s research, administration of IL-10 immediately after vaccination can enhance immunity and increase the effectiveness of vaccination. Splenocyte-based transfection studies showed that IL-10 can better regulate CTL activity by reducing CD+ T lymphocytes. This finding suggests that IL-10 has a negative effect on immune and immune-promoting CD4+ and CD8+ T lymphocytes, respectively.

The secondary function of IL-10 suggests that it could be used in the development of increasingly complex anti-inflammatory drugs [37]. Several studies have shown impaired IL-10 signaling in young cancer patients, and other studies have shown that IL-10 mutant animals exhibit an increased risk of cancer. These studies highlight the impact of IL-10 deficiency on the perception of tumor-promoting inflammation and the importance of IL-10 in the control of inflammation [38].

IL-27, another anti-inflammatory cytokine, is recognized for its ability to reduce tumor growth. This immunostimulatory two-chain cytokine, together with IL-12, promotes CD4+ T cell proliferation, Th1 cell differentiation and IFN- production. It has pleiotropic effects, including EB13 and IL-27p28 subunits. IL-27 mainly activates STAT1 and STAT3, gp130 chain and IL-27R.

It slows the growth of NSCLC while promoting apoptosis. In xenograft models, in addition to downregulatory and EMT-related genes, IL-27 forced intratumoral myeloid cells to show anti-tumor activity [39]. The COX2 inhibitor called apricotoxib combined with IL-27 prevents EMT in NSCLC cells in a STAT1-dependent manner. One study showed that IL-27 inhibits proliferation, migration and invasion of NSCLC cells. Another anti-cytokine is IL-37 with 5 variants (IL-37a to IL-37e).

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IL-37 is a member of the IL-1 family. The second type, IL-37b, is the most studied isoform as it is widely expressed in many human tissues and brain tumors. It has been reported to reduce pain and fatigue. It is known that proinflammatory factors such as IL-1/, IL-6 and TNF- are inhibited by it. The mechanisms underlying IL-37 activity are thought to be modulation of the IL-6/STAT3 pathway, inhibition of β-catenin, inhibition of the pSmad3C/P21 tumor signaling pathway, and recruitment of CD57+ NK cells[40].

M2 macrophages release tumor growth factor (TGF-), another anti-inflammatory cytokine that promotes angiogenesis and metastasis. It uses type I and type II transmembrane serine/threonine kinase receptors to regulate its biological processes. These macrophages produce VEGF and COX-PGE2, as well as other mediators that promote tumor growth. IFN-, a cytokine that promotes inflammation, reactive nitrogen and oxygen intermediates, inducible nitric oxide synthase production, and NSCLC-associated MHC molecules secreted by another macrophage subtype called M1 [41]. The role of its signaling is pleiotropic.

In addition to immunity, these activities affect cell growth, differentiation, death, motility and invasion. TGF stimulates differentiation, induces immunosuppressive cells, and subsequently suppresses the activity of T cells and anergic NK cells in the TME. The main source of TGF- is also an anti-inflammatory agent. TGF-β can be used as an effective therapeutic agent to promote NK cell-mediated anti-tumor protection by modifying the TME, thereby promoting tumor growth and metastasis. TGF-β induces EMT in lung tumors using the JAK/STAT3 signaling pathway [42].

Another cytokine, IL-17, is dysregulated in many human diseases such as cancer and inflammation. IL-17A to IL-17F is a family of six cytokines with different homology and roles in the immune system. These cytokines bind to IL-17 receptors (IL-17R, IL-17RA to IL-17RE), which function as homodimeric or heterodimeric complexes. IL-17A, the oldest member of the IL-17 family, is produced by Th17 cells [63]. Its overproduction is associated with cancer as well as autoimmune and inflammatory diseases [43].

The IL-17B/IL-17RB pathway is a signal that promotes not only cancer survival but also growth and spread. Tumor-promoting activity of the IL-17B/IL-17RB pathway is unique and complex due to ongoing tumor processes and unexpected mechanisms that cause TME modification. Various in vitro and in vivo studies have demonstrated that IL-17B signaling is essential to support tumor health and growth. All studies have shown that the IL-17B/IL-17RB axis is blocked by inhibiting receptor expression in tumor cells, eliciting anti-IL-17RB antibodies, and restoring chemosensitivity in vitro and in vivo [77]. Surprisingly, IL-17RB signaling along the ERK/GSK-3 β/β-catenin pathway has been associated with EMT in lung cancer [95].

Both human cancer patients and mouse tumor models showed tumor-promoting therapeutic activity via IL-17 and Th17. The main role in the tumor-promoting activity of IL-17 or Th17 cells ultimately leading to the promotion of tumor growth is angiogenesis and cytokine activation in the tumor microenvironment. IL-17 has been shown to promote human cervical cancer in nude mice. This effect was associated with increased IL-6 and IL-8 levels and recruitment of macrophages to the tumor site. In addition, research using a mouse model of colon adenocarcinoma has shown that the anti-inflammatory effect of IL-17 is associated with the activation of various angiogenic factors from fibroblasts and tumor cells, including VEGF, PGE2, keratinocyte-derived factor. Talent. promotes tumor angiogenesis and nitric oxide.

According to the same research group, IL-17 promotes CXCR2-dependent angiogenesis in vivo by increasing net angiogenic activity and growth in human non-small cell lung cancer. In addition to its role in angiogenesis, IL-17 can also stimulate the synthesis of IL-6, which activates oncogenic Stat3 signaling and increases expression of genes that promote survival and angiogenesis [86].

4. Conclusions and future directions

Cytokines have been shown to be effective in the treatment of cancer, but it is not yet clear that some effective targets affect the different immune system. For cell populations that have been extensively studied, such as T cells, the labeling and role of surface receptors is well understood, and researchers use the same set of CD markers to identify the populations at hand using flow cytometry.

However, the difficulty of detecting the receptor set increases with the level of the immune system being studied, making it difficult to compare results and identify patterns for a long time.

By analyzing changes in the activity and expression of surface markers of all different types of immune cells after immunotherapy, evaluation of treatment can be made easier and more consistent. This analysis can also use surface markers of the immune system in cancer patients to predict the effectiveness of the immune system.

It is important to examine the role and surface markers of the immune system in tumors and to pursue cytokine-based immunotherapy, but the main purpose of the article is to provide detailed information about the prospects of cancer cytokine therapy. One of the most important features of cytokines as modulators of the immune system is their pleiotropic effects. Each cytokine has a different effect on the immune system, enabling it to promote both pro-inflammatory and anti-tumor responses.

Therefore, for the future of cytokine-based cancer therapy, it will be important to develop a combination strategy that will enhance the anti-inflammatory effect while inhibiting the tumor-enhancing immune system. High doses of cytokines are required to induce a beneficial response in cancer patients, but doing so leads to many problems, including their short lifespan and toxicity (pro-inflammatory and autoimmune response). New technologies are coming in that improve the targeting of cytokines and alter their pharmacokinetics, such as cellular or other delivery systems based on transporters and drug transfer proteins Voluntarily helping to solve many of the shortcomings of cytokine therapy. According to the latest developments in cancer prevention, they will become the most important part of the treatment when used together with other drugs such as cytokines, anti-inflammatory drugs, oncolytics or as part of the immune response of DC and tumor cells.

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