Progress in the application of cytokines in lung cancer treatment

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Abstract. Lung cancer is the most common cancer today and has become the leading cause of cancer death worldwide. Previous common therapy of this disease mainly include surgery, radiation therapy, chemotherapy etc., and the recently most focused solution of immunotherapy, therapy making use of immunity agents such as vaccines, monoclonal antibodies and cytokines. Cytokines, such as gefitinib, the epidermal growth factor receptor inhibitor, and bevacizumab, the VEGF inhibitor, have been widely used in the clinic as targets for the treatment of lung cancer. Another application of cytokines in the treatment of lung cancer is to play the role of biomarkers to provide an important judgment basis for prognosis and diagnosis. However, based on understanding of the advantages and limitations of cytokine therapy, scientists have ceased to make efforts to develop it into a core of the cancer therapy. cytokine's potential to be combined with other therapies and to play indicative roles in cancer treatment still arouses scientists' interest. This passage reviews the common treatments of lung cancer and discusses the progress in the application of cytokines as a component of cancer treatment.

Keywords: Lung cancer; treatment; immunotherapy; cytokine.

1. Introduction

The cytokines are a group of small proteins capable of regulating inflammation and signaling the activation, differentiation and proliferation, which is secreted by a wide range of cells, such as macrophages, B lymphocytes, T lymphocytes etc. [1]. As a key component of the immune system, cytokines promote anticancer response with the stimulation of immune effector cells and stromal cells at sites where cancer is located. Because of this function, cytokines have been applied to cancer treatment settings. For example, there have been a lot of cytokines that have entered clinical trials for advanced cancer patients. These cytokines include IL-18, IL-7, GM-CSF, and IL-21[2]. However, in previous trials about cytokines, the molecules did not fulfill scientists' expectation to become dominant in immunotherapy, due to which scientists have changed the direction of their efforts to the combination of cytokines with other therapeutic agents or new biotechnologies such as genetic engineering to enhance activity of cytokines in cancer treatment [3]. For example, in order to increase the binding affinity in protein-protein interaction of IL-2, there have been studies on computationally designing IL-2 variants that are able to better satisfy the demand [4]. Cytokines can also play a role in immunity. For instance, cytokines and chemokines have been identified to produce local and systematic inflammation. In addition, they are also involved in tumor progression, spread, and therapy resistance. One example of this is tumor necrosis factor-α (TNF-α), which trigger processes like apoptosis resistance, cancer cell proliferation, invasion, metastasis, and angiogenesis. Therefore, cytokines are common target in lung cancer treatment and are considered to have biomarker roles [5].

Lung cancer is a type of malignant tumor starting in the lungs, which is caused by damage to DNA of airway cells. The disease is often caused by cigarette smoking and inhale of damaging chemicals. According to the Cancer Atlas, lung cancer is diagnosed the most today and is becoming the leading cause of cancer death around the world. In a 2018 study, there were 2.1 million lung cancer cases and 1.8 million deaths according to estimates. There are mainly two categories of lung cancer: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) and, of which the latter was more prevalent, accounting for 80% [6]. SCLC is typically located in a peribronchial location with infiltration of the bronchial submucosa and peribronchial tissue [7], while NSCLC locates in the

surface of airways in human lungs [8]. Symptoms of lung cancer include coughing up blood, shortness of breath, bone pain, headache etc. [9]. There have been a lot of studies showing the development of lung cancer is closely correlated with immunological dysfunction. Considering its severity and prevalence, the enhancement of lung cancer treatment is still a focused topic in academia. This passage introduces the application of cytokines on the treatment of lung cancer, focusing on recent advances and future perspectives in this field of research.

2. Overview on cytokines

Cytokines are protein molecules that are secreted by immune cells and some of other types of cells and have different biological functions. Major categories of cytokines include chemokines, interferons, interleukins, tumor necrosis factor etc. Different molecules affect the signaling of the immune system in human body in different ways [1].

Chemokines are cytokines responsible for the mediation of various processes, such as chemotaxis, hematopoiesis, and angiogenesis. Categorization of chemokines is according to positions of sequentially conserved cysteine residues. From the perspective of structure, different sub-families of chemokines have a highly conserved and three stranded α-helix structure or β-sheet tertiary structure but significantly various quaternary structures [10].

There are three types of interferons: type I interferons were identified according to their antiviral activity, and later were discovered to be responsible for anti-pro iterative and modulation of immune activities, and to modulate non-viral pathogens infection [11]. By contrast, type III interferons were identified later, discovered 50 years later than type I. It has been known that type I III interferons have similar functions to sense pathogens and play the role of activating gene programs of immunity. The most well-known type II interferons are interferon-γ, which is produced by T cells and NK cells, and they are capable of leading to the generation of T cell immune response [12].

Interleukin crucially affects the activation and tuning of immune responses, which is affected by lymphocytes and is usually not produced in large quantities. At least 40 interleukins have already been found and they are classified into different families and subfamilies [13]. From the perspective of receptor types, interleukins are classified into type I, type II, and other type, of which type I includes the most interleukins. Type II includes interleukin-10, interleukin-28 and so on. Other type includes interleukin-1 and interleukin-8. The rest of interleukins all belong to type 1[14].

Tumor necrosis factor (TNF) is a protein molecule mainly produced by activated immune cells. Since first identified in late 1970s, TNF is responsible for the tumor cell suppression and playing different roles in various conditions, such as inflammation, tumor growth, transplant rejection etc. Although TNF can induce cancer death and thus be applied into cancer therapy because of this anticancer property, it is also related to the stimulation of proliferation, survival, migration, and angiogenesis of cancer cells that have developed resistance to cytotoxicity that TNF leads to and thus promote the cancer development, making itself a double-edged sword [15].

3. Common treatments for lung cancer

3.1. Surgery

According to the cancer types, cancer sites and other factors, surgical treatment is one of the treatment options for patients today and mainly involves removing the tissue surrounding the tumor and lymph nodes in the tumor area. During early stages where cancer cells remain localized and are unlikely to spread, surgery will be considered as the best option [16]. Surgical treatment is recommended for patients with lung cancer at early stages [17].

Two common ways of operating surgery are thoracotomy and minimally invasive surgery. A thoracotomy involves cutting in from chest side, ribs and chest wall muscles. It also involves splitting some of the chest wall muscles and gently unfurling two ribs with instruments to allow the surgeon to access the lungs. After the incision is closed, the muscles will be repaired. On the other hand,

minimally invasive surgery includes necessary small incisions to get access to the inside of the chest, and takes advantage of a camera to see the inside of lung so that surgery can be performed [16].

3.2. Radiation Therapy

Radiation can damage the DNA of cancer cell when being used at high doses, and thus radiation therapy can be applied in killing cancer cells or slowing their growth. Currently there are two kinds of radiation therapy that are being used: internal and external beam. Using which type of treatment is usually dependent on the condition of the patients. External beam radiation therapy is a local treatment. For example, for a lung cancer patient, he or she will only have radiation on his or her chest instead of the whole body. By contrast, internal radiation therapy requires a source of radiation to be put inside human body. Both solid and liquid can be radiation sources. Internal radiation therapy with solid sources is called branchytherapy, which puts a radiation source in or near the tumor, while the liquid source in a therapy is called systemic therapy, where the treatment travels in the blood to seek and kill cancer cells.

The limitations of radiation therapy are that it also affects healthy cells, and there are limits to the amount of radiation that some parts of the body can safely receive. Therefore, it is often used in combination with other therapies for optimal results [18].

3.3. Chemotherapy

Chemotherapy works by stopping or slowing the fast growth of cancer cells. The therapy can be applied in treating a wide range of cancer and can be given in multiple ways, including oral, intravenous, injection, intrathecal, intraperitoneal, intra-arterial, topical etc. [19]. The drugs used in chemotherapy include genotoxic drugs, antimetabolites, additional chemotherapy agents, spindle inhibitors etc. [17]. However, without targeting effects, chemotherapy might also kill and affect healthy cells, causing side effects to the patients. Thus, further investigation on more efficient therapy needs to be done [19]. In several randomized studies, the effect of perioperative chemotherapy has been discovered. The results of meta-analysis found that this therapy is beneficial for patients with advanced disease, in which the reduced hazard ratio (HR) is in the range of 0.83-0.92 and absolute survival benefits are of about 5.4-6.9% at 5 years [17].

3.4. Targeted Therapy

Targeted therapy is the therapy targeting on proteins controlling how the cells grow, divide and spread [20]. Discovery of this therapy, which targets on specific oncogenic driver protein, has brought a revolution in the field of cancer therapy [21]. The first discovery revealing the potential of this therapy on lung cancer treatment is the observation of how efficacious gefitinib therapy is in treating patients with sensitizing mutation of EGFR inhibitors. Also, with the development of molecular profiling, the genetic heterogeneity of lung cancers, helping scientists to find the oncogenic driver proteins and apply the discovery in drug development. Now the well-studied targeted driver includes EGFR, ALK, ROS1, and BRAF, targeting on which several drugs have been studied or approved [20].

3.5. Immunotherapy

Another therapy with great promise in meeting the needs of developing more effective targets for cancer therapy is immunotherapy, which works by improving the body's function against the formation of tumor. There have been a range of approached proved effective in trials, which includes immune checkpoint inhibitors, cancer vaccines, CAR-T therapies and cytokine therapies [22].

The most common immunotherapies applied in lung cancer treatment are immune checkpoint inhibitor, cancer vaccine, and adoptive T cell therapies. Immune checkpoint inhibitors play the role of inhibiting checkpoints, molecules that are capable of stopping immune response against pathogens. This therapy has been well investigated and some of the immune checkpoint inhibitors have been approved by U.S. Food and Drug Administration. For example, many of the drugs block the PD-L1

protein and PD-1 receptor on the T cell. In this way, the immune system will be activated to recognize and attack cancer cells.

4. Application of cytokines as targets of the therapy

Cytokines are important components involved in sending signals to promote cancer development. Therefore, scientists have considered developing drugs or therapies that targets on cytokines. For recurrent NSCLC, epidermal growth factor receptor inhibitor, gefitinib has been studied and discovered that it could be a valid treatment for recurrent NSCLC patients. In the large randomized phase III trial, researchers compare the treatment effects of gefitinub to that of placebo in treating recurrent lung cancer patients. From the comparison of survival in the two groups, it was found that gefitinub could be efficacious in treating recurrent NSCLC patients that never smoke, and recurrent patients that are Asian. In addition, erlotinib exhibited capacity in improving survival and quality of recurrent NSCLC patients after chemotherapy. However, in comparison with receiving second-line chemotherapy after first-line chemotherapy, erlotinib treatment did not improve survival of the recurrent NSCLC patients [23].

Another direction of treating NSCLC patients is to control the angiogenesis of cancer cells, which involves the application of angiogenesis inhibitors. The complex process of angiogenesis includes the regulation of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), as well as angiopoietins. Up to date, the only approved therapy of NSCLC targeting on angiogenesis is bevacizumab, inhibitor of VEGF, which was approved for treatment of NSCLC. In a phase III trial, the combination therapy proved to be advantageous regarding response rates, and survival rates. Further study revealed that baseline tumor cavitation as a side effect after bevacizumab therapy can be a significant risk factor. Thus, patients with adenocarcinoma histology tend to get more benefit in receiving bevacizumab treatment. One of the challenges and limitations of anti-VEGF agents is that resistance to the agents could happen to all patients receiving the treatment. Some scientists presumed that the side effect could be caused by increase of compensatory angiogenisis like Platelet-derived growth factor (PDGF) or Fibroblast growth factor (FGF) signaling [23]. However, whether the inhibitors increase the efficacy of chemotherapy in the settings of advanced NSCLC is still unknown, and one of the possible reasons is that in practical settings doses used should be lower in order to reduce toxicities. There are also agents that are with inhibiting activities currently under investigation, like the small molecule inhibitor nintedanib [23].

The third direction is making use of insulin-like growth factor inhibitors. Insulin-like growth factor system consists of two receptors: Insulin-like growth factor 1 receptor (IGF-IR) and IGF-IIR with their respective ligands. These cytokines relate closely to the development of tissues and carbohydrate metabolism, and IGF signaling pathway can lead to the promotion of cell proliferation and differentiation. An example of the inhibitors of these growth factors is monoclonal antibodies and tyrosine kinase inhibitor (TKI) targeting the intracellular domain of the receptor [23].

Apart from the directions above, interleukin-1β is applied as a treatment target as well. IL-1β belongs to IL-1 family and promotes tumorigenesis, including promoting cancer cell migration and invasion, triggering more severe cancer condition, driving immunosuppression, and inducing cancer development and angiogenesis. The mechanism of interleukin-1β to affect cancer cell development is that cancer cells can produce factors causing angiogenesis and cancer progression in response to IL-1. In addition, through IL-1β secretion, cancer associated fibroblast (CAF) and adipocytes promote cancer progression and lead to the induction of angiogenesis. Moreover, IL-1β is involved in in determining myeloid cell infiltrate type in tumor microenvironment. To sum up, IL-1β is related to immunosuppression of TME through its activation and recruit of macrophages, induction of neutrophils, suppression of NK cells, and promotion of angiogenesis and pro-tumorigenic process. In light of this, scientists conduct research on the effect of suppressing IL-1β expression, which turned out to show that the suppression prevent tumor cells from entering the circulation and increase the

tumor infiltration by CD 8+ lymphocytes and decrease tumor suppression [24]. Based on the biological characteristic of interleukin-1β, scientists have studied its application in the treatment of lung cancer. In previous studies, IL-1β has proved to facilitate lung cancer metastasis because of its effect of promoting cytokine production, angiogenesis and tumor development. In a study in 2018, elevated IL-1β serum levels in lung cancer patients have been found to relate to high percentages of myeloid-derived suppressor cell (MDSC). Additionally, increased IL-1β levels cause macrophages to increase the expression of angiogenesis and lymphangiogenic factors. Moreover, IL-1β secretion can make CD 4+ T cells to produce IL-22, which can promote tumor progression, which makes IL-1β to be related to therapy resistance [25].

One evidence of the feasibility of the application of this agent was found in CANTOS trial, where patients with previous myocardial infarction, inflammatory atherosclerosis, and a persistent proinflammatory response were randomly assigned with either placebo or 3 doses of canakinumab, a type of human monoclonal antibody targeting on IL-1β. Canakinumab has been an approved drug to treat fever syndromes and arthritis [24]. The original focus of the study was atherosclerotic disease. However, because the use of immunomodulators may be associated with an increased risk of cancer development in transplant recipients, a secondary analysis was performed which showed that treatment with canakinumab significantly reduced the incidence of lung cancer, and in addition, the risk reduction was dose-dependent. Discovery made in CANTOS trial inspires scientists to further investigate canakinumab's value in treating lung cancer. In the CANOPY clinical program, scientists studied the role of canakinumab in non-small cell lung cancer. Most of the trials are about studies on the combination of therapies targeting IL-1β and PD-L1. In previous studies this therapy proved to be efficacious in bringing a synergistic effect to inhibit the growth of tumor and increase tumor cell infiltration by cytotoxic CD 8+ lymphocytes. Also, in separate studies on mouse models with pancreatic cancer or breast cancer, the combination therapy exhibited great capacity in improving treatment efficacy. However, the observations were not significantly confirmed in CANOPY trials as expected. For example, the study did not show the anticipated overall survival. Yet, the study confirms that the combination of canakinumab and chemotherapeutic drug docetaxel is harmless for patients in trial. Also, the research demonstrated potential improvements in the survival of different subgroups of patients according to inflammatory biomarkers. Thus, canakinumab's potential in treating lung cancer is still the interest of scientists [25].

5. Application of cytokines as biomarkers in treatment

The other application of cytokines in lung cancer treatment is playing the role of biomarkers because of its involving in a wide range of processes in tumor microenvironment. In different clinical trials, a number of cytokines have been tested regarding their potential to be developed into biomarkers, which are important in treatment for providing valuable information for prognosis and diagnosis.

Various interleukins have proved to have the capability to become biomarkers. One of the interleukins is IL-6, which has been analyzed systematically to become a biomarker of immunological responses of NSCLC patients. A study was conduct based on the cytokines' property to alter the response to immune checkpoint inhibitors in tumor patients. The study analyzed promising biomarker cytokines with multi-analyte flow assay, then made comparison between baseline level and actual outcomes to determine whether IL-6 has the potential to become biomarkers. According to the analysis, the expression of PD-L1 and IL-6 was found to be favorable to each other. Also, IL-6 levels were found to be negatively correlated to CD 8+ T cells' activity. Moreover, in the tumor samples, IL-6 levels were found to be positively related to, M2 macrophages, myeloid-derived suppressor cells and regulator T cells. To sum up, based on current scientific findings IL-6 levels will help in the settings of lung cancer treatment prognosis [24]. Scientists have also taken look at IL-8 and IL-1β regarding their biomarker capacities. In a study recruiting 133 patients with lung cancer, researchers collected the subjects' peripheral blood to start an immunoassay, from which levels of IL-8, IL-6 and

IL-1β and were tested. From the comparison with baseline data, the results show that the levels of IL-8, IL-6 and IL-1β in lung cancer group patients are higher when compared to control. Additionally, in the study IL-8 was discovered to relate positively to clinical stage of cancer. In the further statistical analysis on the interleukins' potential to be diagnostic biomarker, IL-6 and IL-8 showed a great promise regarding AUC (Area under curve) value under certain confidence interval and Youden index respectively. The studies also showed the efficacy of the three interleukins in the prediction of lung cancer metastasis including lymph node metastasis and distant metastasis, from which only IL-8 was found to have the ability for prediction [26].

Another example of application focuses more on the overall cytokine levels, which includes levels of T helper 1 and 2 cytokines and proinflammatory cytokines. Th1 and Th2 are two families of cytokines. Th1 cytokines are capable of eliciting cell mediated responses, while Th2 is responsible for the protective process of the direction of T-cell response away from phenotype of Th1. In situations where malignant tumors grow, the balance is disrupted, which favors an immunosuppressive tumor microenvironment. In order to confirm the assumption of the two molecules' application potential, more studies were carried out. In the study, researchers compare serum levels of the three types of cytokines in SCLC patients with baseline in healthy people. The subjects in the study are two independent groups of SCLC patients. All of them were treated with standard chemotherapy, with some of them treated with anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody ipilimumab and others not. According to the data collected, IL-1β, IL-5, macrophage inflammatory protein-1α (Mips-1α), and TNFα levels in SCLC patients were significantly lower than in healthy individuals. In the following steps, researchers studied how the levels change when treatment started. According to the results, patients receive a global increase in assessed cytokine levels after immunotherapy started. Although IL-8 levels did not change significantly before and after the treatment, IL-2 levels proved to be capable of predicting sensitivity to ipilimumab. The median OS of patients with high serum IL-2 concentration was 30.5 m, and that of low groups 8m. As for IL-6, high concentration group has a median value 9.5 m and while lower group has 18.5 m. lastly when it comes to TNFα, higher groups medium is 7.8 m while those with lower levels had 18.5 m. When changing the density of the population, the results remain the same. Therefore, it can be concluded that high levels of IL-2 correlate to how sensible patients are to ipilimumab therapy and IL-6 and TNFα are positively related to resistance to ipilimumab. Besides, IL-4 in the study has been identified as related to the outcome in SCLC. In the study, patients received only chemotherapy, meaning that their IL-4 levels increased significantly, received a worse treatment outcome, which is significantly different from that of immunotherapy group. The results indicate the potential of IL-4 to be developed into biomarkers in prognosis in lung cancer treatment [27].

Another serum cytokine level that has been identified to be helpful in treatment is macrophage inhibitory cytokine-1(MIC-1) belonging to the superfamily of transformation growth factor-β. In a study enrolling 152 patients of early stage of NSCLC who have received surgical resection, 48 benign pulmonary disease (BPD) patients and 105 healthy people as controls, scientists measured the serum MIC-1 level and determined the associations between clinical and prognostic features. In the end they found that MIC-1 levels are higher in NSCLC patients than in other two groups, and that MIC-1 levels relate negatively to the overall 3 year-survival rate [28].

6. Summary

As the leading type in mortality chart of cancer among people across the world, lung cancer treatment is still a project of global burden for humankind. Due to cytokines' wide involving in the development of cancer cells, they have been long viewed as with promise for application. However, because of the fact that cytokines are molecules that have pleiotropic effects and relatively low half-life, it seems that cytokine therapy will hardly be developed into the core of scientists' solution of the problem of lung cancer treatment. However, cytokines can still play important roles as treatment targets and biomarkers. Considering the variety of cytokine molecules, the future of using cytokines

for treatment is promising. For example, the progress in machine learning and nanosensor technologies enable scientists to find a larger range of cytokines that are able to be applied as biomarkers. With advanced tools in scientific research, researchers will be allowed to discover more in the direction of making cytokines biomarkers. Also, since there is still much unknown about cytokine properties, it is reasonable to believe that in the future more cytokines targets can be found and thus benefit lung cancer treatment.

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