

## Application of Cytokines and Growth Factors in Immunotherapy

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### Abstract

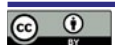
The main goal in cancer treatment is to eliminate tumor cells with minimal harm to healthy tissue. The immune system is ideal for this task as it can identify and eliminate abnormal cells while providing long-term defense against recurrence. Various immune-based cancer treatments activate the immune system or help cancer cells recognize and activate immune cells within the tumor. Immunoregulatory cytokines play a crucial role in treating immune disorders. They regulate macrophage degradation of antigens and promote cellular functions. Lymphocyte interactions can lead to immune cell maturation, while other products limit lymphocyte activation. Cytokines are categorized as interleukins, growth factors, interferons, and colony-stimulating factors. Soluble proteins known as cytokines are essential for mediating and regulating cell interactions in various parts of the body, including the nervous system, gut, and bone remodeling. The study of cytokines' structure and function has proven incredibly beneficial for both immunology and commercial research. By understanding the different domains and analogues of cytokines, researchers have gained important knowledge about how these proteins bind to receptors. Moreover, identifying similarities between various cytokines has offered valuable insights into the workings of cytokine receptors. Understanding the mechanisms behind immunotherapy resistance is important to identify new therapeutic targets. By investigating these pathways, researchers can develop innovative strategies to overcome resistance and improve treatment outcomes. Combining therapeutic modalities to target multiple aspects of the tumor microenvironment simultaneously can overcome the limitations of individual treatments and improve antitumor response. Understanding resistance mechanisms to immunotherapies can lead to the development of tailored strategies to combat treatment resistance and maximize treatment response.

**Keywords:** Cytokine, Cancer, Immunotherapy, tumor vaccine.

### Overview of Immunotherapy in Cancer Treatment

Cancer is one of the deadliest diseases that humans face. At present, surgeons remove tumor tissue from patients and then patients receive chemotherapy

and radiotherapy (1). After these three approaches to tumor treatment, many patients relapse due to residual tumor tissue. In addition, chemotherapy and radiotherapy tend to have systemic toxicity. In



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general, the main causes of disease recurrence are ineffective anti-tumor immunity and inefficiently activated immune system cells (2). Recent years have seen significant progress in understanding how various types of cells respond to different pro-inflammatory cytokines. This understanding has been greatly aided by the measurement of signal-transduction pathway activation, gene expression patterns, and cellular functional responses. While much attention has been given to the activities of pro-inflammatory cytokines, new evidence has emerged showing that other 'suppressive' cytokines can also activate important signaling pathways like NF-kB, MAPK, and STAT (3, 4). This complexity makes it challenging to fully grasp how cells respond to different cytokines, especially when considering the different timeframes over which these responses occur (5). For example, acute-phase pro-inflammatory cytokines can rapidly affect gene expression, while the resolution of inflammation happens much later. The intricate cellular responses to pro-inflammatory cytokines are illustrated through the activation of pathways like NF-kB (6). After treatment with these cytokines, NF-kB is activated through a series of interactions and phosphorylation events, ultimately leading to the regulation of cellular activities (7, 8).

Immunotherapy is a treatment that employs the host immune system to recognize and eliminate cancer cells more effectively than it could do unaided. Tumor immunotherapy aims to enhance anti-tumor immunity by the administration of cytokines, immune checkpoint inhibitors, adoptive cell transfer, and other types of treatment. Recently, tumor vaccines have also been employed in tumor immunotherapy. Many excellent cytokines and growth factors can be used as adjuvants in tumor immunotherapy to enhance the anti-tumor immune response (9).

### **Types of Cytokines and Growth Factors**

Cytokines are small-molecular-weight proteins and glycoproteins that are produced by many types of cells such as fibroblasts, endothelial cells, macrophages, T-lymphocytes, etc. They are produced by virtually all nucleated cells. Interleukins, lymphokines, and monokines are types of cytokines. They can be classified as proteins, glycoproteins, and peptides. Cytokines are regarded as vital soluble mediators of the immune system and inflammatory response to infection, trauma, and inflammation. They are produced by many cell types to combat stress and infection (10). It is indeed a balance of pro-inflammatory, anti-inflammatory cytokines, and other factors that underlie the dynamics of the physiological response to stress and disease. Cytokine action is complex with redundancy of action, and one cytokine may have different effects on different cells, depending on the state of activation of the responding

cell. Many cytokines have been identified which possess activational, chemoattractant, metabolic, and proliferative properties essential for the regulation of host responses (11).

Cytokines can be classified by function, target cells, time of action, source, type of effect, or structure. A classification scheme collects together under broad categories several different, but related, terms. Some classification schemes are simple, making it easy to group cytokines, but arbitrary in that the influence of the structure on the function may not be obvious. Others are more complicated but take account of more than just the structure (12).

Cytokines impact the function of a variety of tissues, act directly at a target site, locally control the immune response, control gene transcriptions, autocrine and paracrine signaling, and, in addition, cytokines are responsible for the control of lymphocyte activation and tissue injury (13). This class of molecules includes various interleukins, colony-stimulating factors, interferons, and tumor necrosis factors (14). Responses to cytokines are mediated by specific receptors present in target cells. Cytokines such as tumor necrosis factor and interleukins have effects on endothelial cells which are important in the regulation of angiogenesis (15, 16). Indirectly, interleukins and other cytokines have immunosuppressant functions, engaging in lymphocyte regulation. Many cytokines are pleiotropic, influencing a wide range of target cells and systems (17, 18). Cytokines were initially identified for their role in inflammation, but their biological effects are now known to be much broader. Nowadays, the role of cytokines is also recognized in health and disease (19, 20). Cytokines have untoward effects and their role in the expansion of inflammatory and autoimmune diseases is discussed. In addition, cytokines are attracting interest in their potential use in diagnostics, prognostics, and as therapeutic agents (21, 22).

Using anti-tumor immunity to treat cancer patients is not a new idea. The most common type of immunotherapy has been to induce a tumor-specific immune response using immunogens (23). Surgical tumor resection and chemotherapy, in effect, remove the chloroplast but leave spores when administering cocktails of cytokines and other immunostimulatory compounds to induce a tumor relapse (24, 25). These immunostimulatory cytokines include GM-CSF, IL-2, IL-15, IL-21, and IFN- $\gamma$  (26). These immune-stimulating cytokines can enhance dendritic cell maturation, activate T cell proliferation and survival in vivo, trigger natural killer cell activation, and increase the number of dendritic cells (27). Adoptive cell transfer and immune checkpoint inhibition are also two types of active immunotherapy. In addition, some immune-stimulatory cytokines have also been found to mediate tumor outcomes (25, 28).

### **Role of Cytokines and Growth Factors in Cancer Immunotherapy**

In recent years, it has realized the pivotal role of the immune system in cancer. This has led to new therapeutic opportunities, using cytokines and antibodies to target antigens. Success with monoclonal antibodies targeting CTLA-4 and PD-1 has opened doors for effective treatment (29). However, challenges remain in regulating the immune response without harming healthy tissues. To address these challenges, we need to explore the mechanisms that influence immune cell populations (20, 30). Understanding these interactions can unlock novel strategies for targeted therapies (31). Additionally, research is focused on understanding the balance between immune activation and regulation to minimize adverse effects. This approach has the potential to revolutionize cancer immunotherapy, providing hope to patients and improving outcomes (32, 33).

### **Current Immunotherapeutic Approaches**

Immunotherapy for cancer can be achieved through a variety of methods, including cytokines, growth factors, monoclonal antibodies, adoptive transfer of immune effector cells, vaccines, and gene transfer (34). At present, cytokines and monoclonal antibodies have been the most successful in treating the disease, helping thousands of patients (35). Cytokines such as interleukins, interferons, and colony-stimulating factors can boost a patient's immune response, while monoclonal antibodies directly target cancer cells by identifying tumor antigens (36). Overall, immunotherapy has become an important treatment for various diseases involving infectious agents or abnormal cells, with key players including interferons, interleukins, monoclonal antibodies, immune effector cells, and hematopoietic growth factors (37). Other immune system mediators, like tumor necrosis factors and transforming growth factors, are also likely to play a significant role as therapeutic agents (38, 39).

### **Autoimmune Diseases and Cytokine Therapy**

Autoimmune diseases are long-term illnesses that occur when the body's immune system mistakenly attacks its antigens, leading to tissue damage. These diseases can affect various parts of the body, such as glands, bones, blood, and skin (40). The first recorded case of autoimmunity in humans dates back to ancient Egypt, with diabetes mellitus being the classic example. However, evidence suggests that other civilizations, including the ancient Greeks, Romans, and Chinese, also experienced autoimmune diseases (41). Globally, the prevalence of AID is estimated to be around 5-15%, with conditions like systemic lupus erythematosus, rheumatoid arthritis,

Crohn's disease, alopecia areata, and mucosal lichen being some of the most common. Genetic factors play a role in the development of autoimmune diseases, but environmental influences and other non-genetic mechanisms also contribute (42). The pathophysiology of AID involves a wide range of cells and molecules, with immune and non-immune cells and cytokine secretions all playing a role. Recently, the composition of the microbiota has also been identified as a potential factor in the development of autoimmune diseases, but further research is needed to better understand this connection (43, 44).

### **Cytokine-Based Therapies**

Cytokines are prescription drugs that have a relatively short lifespan in the body, typically lasting only minutes, or in some cases, a few hours. Despite their brief existence, they are constantly being produced by our cells to maintain circulating levels and ensure proper immune system function (45). These tiny protein molecules play a vital role in regulating various cell activities, from controlling the development of secondary sex characteristics to influencing T cell lymphoproliferation and suppressing certain cytokines that may cause inflammation (46). Due to their immense importance in maintaining homeostasis and promoting optimal immune responses, the biotechnical and pharmaceutical industries have taken a keen interest in targeting cytokine activities for potential therapeutic interventions (47).

The goal is to develop cytokine-based drugs that can specifically modulate and regulate immune responses, providing targeted treatment options for various diseases. In recent years, significant progress has been made in the development of cytokine-based drugs for the management of chronic inflammation-associated diseases. These diseases, such as asthma, atopy, rheumatoid arthritis, and sepsis, pose significant challenges to patients and healthcare providers alike (48). However, with the introduction of cytokine-based drugs, there is renewed hope for effectively managing these conditions and improving the quality of life for millions of individuals worldwide. Clinical trials evaluating the efficacy of cytokine-based drugs in treating inflammation-associated diseases have shown promising results. These drugs have demonstrated their ability to modulate cytokine levels, dampen excessive immune responses, and alleviate symptoms associated with chronic inflammation (45).

By targeting specific cytokines that are known to contribute to disease progression, these drugs offer a more tailored and personalized approach to therapy. Moreover, the potential of cytokine-based drugs extends beyond their current applications. As researchers continue to elucidate the mechanisms

underlying various diseases, cytokines present themselves as candidates for further investigation and development as antigens for future treatments (49). By harnessing the unique properties of cytokines and leveraging their role in immune regulation, scientists may uncover new therapeutic avenues for an array of conditions (49). Cytokines are remarkable molecules that play a crucial role in regulating cell activities and immune responses. The development and utilization of cytokine-based drugs hold great promise for the treatment of chronic inflammation-associated diseases. With ongoing research and clinical trials, these drugs have the potential to revolutionize the field of medicine and pave the way for more targeted and effective treatments. Using the therapeutic power of cytokines, great progress has been made in the treatment of various diseases, ultimately improving the lives of many individuals (50).

### Challenges and Future Directions

The use of cytokines in clinical treatments is rapidly expanding at an unprecedented rate. Cytokines, which are indispensable proteins utilized to regulate the body's immune system, play an indispensable and pivotal role in combating infections and infectious diseases such as cancer. Despite the remarkable progress that has been achieved thus far, it is imperative to acknowledge that there exists an untapped potential of immense magnitude when it comes to employing cytokines for therapeutic purposes (51, 52). It is of utmost importance to overcome the multitude of challenges that are associated with the therapeutic utilization of these incredible proteins, including but not limited to issues about their biological activity as well as their intricate pharmacological aspects (53).

With amazing advancements in technology, especially in recombinant protein technology and site-specific pegylation, cytokines can now be restructured for a variety of uses. Looking forward, the focus is on finding the most effective combination of cytokines and improving treatment programs (54). In addition, the combination of cytokines with other drugs and the use of delivery methods are expected to make significant progress. It is clear that the field of cytokine therapy has great potential for improvement and offers many opportunities to improve human health (55).

### Limitations of Cytokine-Based Therapies

Although there is tremendous potential in current immunotherapies that aim to activate antitumor-specific responses, they also have a myriad of limitations. These limitations encompass a lack of response in the majority of patients, severe side effects that accompany treatment, the presence of immunosuppressive cells and molecules in the tumor

environment, and the emergence of resistance to these efficacious therapies (56). To overcome these barriers and augment their effectiveness, innovative approaches or combinations of therapies need to be explored (57). A promising avenue for addressing these challenges lies in the development of novel drugs that specifically target immunosuppressive cells, molecules, or cytokines (58). This cutting-edge strategy offers a certain degree of hope for patients, as it holds the potential to unleash the full power of the immune system against tumors. However, it is imperative to acknowledge that simply increasing the dosage of the same agent does not guarantee success (59, 60). This traditional approach, though utilized in some cases, has its own set of limitations, particularly when it involves the administration of cytokines at remarkably high doses (61). Consequently, the scientific community is actively pursuing alternative strategies to enhance the efficacy of immunotherapies (62). One such approach involves combining different therapeutic modalities to create a synergistic effect that targets multiple aspects of the tumor microenvironment simultaneously (63). By doing so, it may be able to circumvent the limitations inherent to individual treatments and bolster the overall antitumor response. These innovative combinations of therapies have the potential to reshape the landscape of cancer treatment and improve patient outcomes (64, 65). Moreover, it is crucial to understand the underlying mechanisms that drive the resistance to immunotherapies. By unravelling these intricate pathways, researchers can identify novel targets for therapeutic interventions, thereby creating innovative ways to overcome resistance (66). This focus on understanding the molecular intricacies of tumor evasion mechanisms opens the door to the development of tailored strategies that effectively combat treatment resistance and maximize treatment response (67).

### Conclusion

In conclusion, while there are inherent limitations in current immunotherapies, the scientific community is steadfast in its pursuit of overcoming these barriers. By exploring novel approaches, combining therapies, and unravelling resistance mechanisms, researchers offer a glimmer of hope for patients and open up new vistas in the fight against cancer. Through these diligent efforts, researchers strive to transform immunotherapies into formidable weapons against tumors, unlocking their true potential in eradicating cancer and improving the lives of countless individuals.

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### Authors' Contribution

Mahnaz Saremi was involved in the conceptualization, design and review, Farnoosh Honarmand was involved in writing the manuscript draft. The authors read and confirmed the final manuscript.

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