

# Interleukin-10 (IL-10) in Cancer Immunotherapy

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## Abstract:

Cancer immunotherapy is an essential therapeutic strategy for the treatment of cancer. In cancer immunotherapy, cytokines, such as interleukin-10 (IL-10), have a vital function. IL-10, synthesized by several types of immune cells, has a vital function in controlling immunological responses, such as subsistence T cells and dendritic cells (DCs), as well as other kinds of cells producing other cytokines. In the immune system, suppressing or reducing the growth and harmful effects of specific immune cells is the main role of this component. Pegylated recombinant human IL-10 and other IL-10 inhibitors can reverse the suppressive impact of IL-10, providing possible ways to control immune responses. IL-10 is mainly recognized for its ability to reduce inflammation and regulate the immune system. However, its involvement in cancer is complex and varies depending on the specific circumstances. IL-10-based treatment has had some degree of success in several forms of cancer. Furthermore, IL-10-derived medications have achieved significant advancements in both animal models and clinical studies, including in humans. While the rate of research progress may fluctuate for various types of malignancies, existing records suggest that IL-10-based immunotherapy shows promising potential.

**Keywords:** Interleukin-10 (IL-10); Cancer Immunotherapy; Cytokine; Cancer.

## 1. Introduction

Immunotherapy, which encompasses T-cell transfer therapy, immune checkpoint inhibitors, monoclonal antibodies, and immune system modulators, is a considerable and widely used cancer treatment type. Immunotherapy is a form of biological therapy that utilizes chemicals derived from living organisms. It enhances the immune system's ability to effectively confront tumors. Cytokine is an important type of immune system modulator, and it plays a great role in immunotherapy. IL10 is a type of cytokine that has shown great potential for cancer treatment recently. It can be produced by almost all kinds of immunocytes, embodying natural killer (NK) cells, dendritic cells (DCs), and all T cell subsets [1]. Initially, IL-10 was believed to be a kind of cytokine that restricts inflammation and promotes humoral and immunological responses [2].

Nevertheless, IL-10 also possesses immune-stimulatory properties, such as its effects on mast cells, B cells, and T cells. Having the capacity to decrease inflammation and cellular infiltrates, IL-10 can also have a therapeutic effect in several animal models of arthritis. The regulatory mechanisms of IL-10 in T cells and dendritic cells (DCs) have been extensively investigated. The concentration of metabolites such as lactate and pyruvate can influence the production of IL-10 by modifying the glycosylation of cell surface proteins. IL-10 can regulate the metabolic pathway in these cells by interacting with IL-10 receptors

and specific signaling cascades within the cell [1].

While IL-10 does enhance the immune response against tumors by altering the efficaciousness of immune cells, for instance, macrophages and CD8 TILs, it often acts as an inhibitor in the tumor-diseased microenvironment. It can suppress the activity of immune cells in those sites of the lesion, hence facilitating tumor growth. In addition, IL-10 can stimulate the proliferation of tumor cells straight forward. However, a specific monoclonal antibody targeting IL-10 can counteract this growth by inhibiting IL-10. This has been demonstrated in studies [3]. Marcon et al. [4] conducted research that found pancreatic ductal adenocarcinoma (PDAC) patients have a decline in the cytotoxic function of NK cells and an elevated expression of IL-10. Trapping IL-10 seems to enhance the effectiveness of cancer treatment in animal models [5]. Another potential therapy involving IL-10 is the use of IL-10 receptor-blocking drugs, which prevent the combination of IL-10 and its receptor. For instance, PEGylated IL-10 treatment has been shown to enhance tumor-specific CD8 T cell responses and inhibit tumor growth.

Furthermore, IL-10 demonstrates promising potential when combined with other immunotherapies, such as CXCL12 trap therapy [6]. Current clinical data indicates a promising outlook for the usage of IL-10 in the treatment of cancer. Research has demonstrated that blocking IL-10 is an effective method for preventing tumor growth, and there are certain medications now available that have

a high level of reliability [7]. An IL-10 inhibiting drug inhibited tumor growth in patients with advanced solid tumors. One kind of human recombinant, IL-10, is PEGylated, sometimes referred to as pegilodecakin, and has demonstrated efficacy in clinical trials.

This review examined the basic principles that govern the IL-10's ability to dominate the immune system to some extent. It also discussed the biological functions of IL-10 within the area of cancer immunotherapy, explored the different effects of IL-10 based methods in various types of tumors, and emphasized the potential future applications of IL-10 in cancer immunotherapy.

## **2. Immunomodulatory Effects of IL-10 on Different Types of Cancer**

### **2.1 Immunomodulatory Effects of IL-10 on liver cancer**

Liver cancer is the term used to describe the growth of malignancies in the liver. Usually, based on its site of origin, liver cancer is categorized into two groups: primary liver cancer and secondary liver cancer. Secondary (metastatic) liver tumors are more prevalent in the United States and Europe than initial tumors. In contrast, the situation is different in numerous regions of Asia and Africa. Improved management of liver cancer is imperative, given that such type of cancer performs a dominant role in mortality, having relevance to cancer around the world.

Moreover, there has been a steady rise in incidence in recent times. Cancer metastasis has a significant impact on the liver, which is vitally responsible for metabolic function among the organs in the human body. Liver cancer mostly arises from the production of cancer metastases. The presence of IL-10 is directly linked to the dissemination of liver cancer throughout the body. Compared to those without liver tumors, individuals with such disease have significantly higher levels of IL-10 [8]. According to Ahmad Mustafa Shiri et al. [9], mice models without the IL10 gene experienced a lower number of liver metastases arising from colorectal cancer (CRC) compared to the control group of mice with the normal IL-10 gene. While a shortcoming in IL-10 may bring about heightened inflammation, animals lacking IL-10 exhibited clear indications of tumor regulation. IL-10 production in the genesis of hepatic metastases was primarily attributed to Foxp3+ Tregs. During the process of creation, IL-10 interacted with foxp3+ Tregs and myeloid cells, triggering a relative signaling pathway to activate. Such a reaction then promotes the development of colorectal liver metastases (CRLM). IL-10 further facilitated PD-L1's expression level in monocytes. As a result, the subsistence of immune cells like CD8+ T-cells and the body's ability to fight against tumors were reduced, which ultimately

facilitated the development of CRLM. When researching the level of IL-10 in tumor conditions, an increasing trend in liver-related disorders, such as liver tumors, was found. This indicates that the growth of tumors is relevant to the level of IL-10. Studies on animal models revealed IL-10's impetus in the survival of liver tumor cells. In this study, the glycoprotein carcinoembryonic antigen was found to promote metastasis by inducing the production of IL-10, thereby inhibiting the anti-tumor response in mice with liver cancer [10]. In addition, the concentration of IL-10 rises during the spread of liver cancer, but when the immune system is enhanced using a modest dose of cyclophosphamide (CTX), it shows a decreasing pattern. IL-10 demonstrated the capacity to hasten those cells expressing PD-L1 in a separate investigation involving liver tumor cells. The unity of inhibitors of IL-10 and PD-L1 demonstrates significant promise, surpassing the efficacy of employing the latter inhibitor alone in the treating area of liver cancer [11]. Confirming the enhancement related to antitumor immunity in hepatocellular carcinoma, the inactivation of ten-eleven translocation-2 was found to be effective in restraining the generation of IL-10. Researchers discovered that IL-10 promotes liver metastases by inducing PD-L1. The text is enclosed in the tag [9].

### **2.2 Immunomodulatory Effects of IL-10 on Pancreatic Cancer**

Early detection can significantly reduce the mortality rate of pancreatic ductal adenocarcinoma (PDAC), much like it does for other forms of cancer. Nevertheless, it is a comparatively lethal form, as it typically advances to the advanced stage upon diagnosis [12]. Furthermore, tumor cells in the pancreas possess the capacity to disrupt and perplex immunoregulation, hence posing additional obstacles for its therapy. A recent study has revealed that IL-10 occupies a crucial part in the immune response to tumors in the pancreas. It can serve as both an indication and a promoter of this specific type of tumor [13]. Recent experiments have shown that both mono- and di-PEGylated IL-10, when attached to its N-terminus, exhibit biological activities. These activities include boosting the production of MHC in macrophages and increasing the level of IFN- $\gamma$  in body parts with tumor lesions. The combination of PEGylated IL-10 and other immunotherapies, such as FOLFOX, can efficiently modulate the anti-tumor immune response, leading to an increased survival rate in pancreatic cancer patients. On the basis of a study conducted by Sideras K et al. [14], IL-10 can regulate the human immune system by decreasing the activity of Th1 responses and increasing the activity of Th2 responses. Pancreatic tumor cells enhance the production of IL-10 in order to disrupt the immunological response against tumors, so evading elimination by the immune system. Researchers

from Fudan University Shanghai Cancer Center (FUSCC) conducted a study on patients with pancreatic cancer and measured their data. They discovered the serum level of IL-10's correlation with the patient's survival rate [13]. When PEGylated IL-10 was combined with FOLFOX in a clinical trial, it outperformed the use of FOLFOX alone in cases of metastatic pancreatic cancer.

### **2.3 Immunomodulatory Effects of IL-10 on Renal Cell Carcinoma (RCC).**

Renal cell carcinoma (RCC) stands for malignancies starting renocortically. Common risk factors for renal cell carcinoma (RCC) include obesity, chronic renal failure, dialysis treatment, hypertension, polycystic kidney disease, diets heavy in sugar and fat, and sickle cell disease. The occurrence of this phenomenon is progressively rising each year [15]. Treatment for RCC has recently been significantly improved. However, there is still an urgent need for medicines targeting advanced-stage RCC, as it remains incurable and causes great suffering to patients. Immunotherapy exerts a significant impact on extending the lifespan of patients and alleviating their suffering. Trials of IL-10-based immunotherapy have achieved favorable outcomes. Research conducted by Naing A et al. [16] indicates that recombinant human IL-10 has efficacy in extending the lifespan of CD8+ T lymphocytes and enhancing their capacity to eliminate cancer cells. Furthermore, the combination of anti-PD-1 with recombinant human IL-10 yielded favorable outcomes [15].

The findings of Chang WS et al. [17] suggest that persons with IL-10 gene mutations have a reduced risk of developing RCC in comparison to those without mutations. Furthermore, for individuals who are currently receiving recombinant human IL-10 (RCC), it has been observed that this treatment can enhance the cytotoxic capabilities of immune-related cells, for instance, CD8+T cells [16]. Furthermore, in combination therapy, uniting IL-10 with PD-1 yielded favorable outcomes in clinical trials, including patients with RCC [15]. Researchers discovered that soluble IL-10, a substance being investigated for its potential to identify renal cell carcinoma (RCC), was not present in the blood of RCC patients. This suggests that while IL-10 may serve as an indicator of RCC, it is not acceptable for blood testing purposes [18].

### **2.4 Immunomodulatory Effects of IL-10 on Melanoma Cancer.**

The majority of cutaneous melanomas originate from melanocytes located near the skin's surface. These melanomas typically develop through two primary mechanisms: the vertical growth phase (VGP) and the radial development phase (RGP). Melanoma cancer can be classified based on these characteristics. In addition, the pigmented patches or plaques of early-stage RGP melanoma lesions

circularly exhibit growth, primarily in a horizontal direction [19]. Immunotherapy is crucial in the treatment of melanoma due to the high immunogenicity exhibited by melanoma tumor cells [20].

Further research is being conducted on IL-10-based immunotherapy. Researchers developed an extracorporeal model of a melanoma tumor. Within this model, IL-10 was observed to alter the differentiation of monocytes, driving them toward an inhibitory M2-like phenotype. This transformation aided melanoma tumor cells in evading elimination by the immune system [21]. In mouse melanoma models where IL-10 was deleted specifically in Treg cells, inhibitory receptors showed a downward trend in the expression of tumor-infiltrating lymphocytes, which resulted in a relatively suppressed tumor growth.

Furthermore, it had a synergistic impact when used with IL-35. Based on a study using mice models, IL-10 demonstrated the capacity to alter the amount of expression of inhibitory receptors, particularly PD-L1 [22]. IL-10 is crucial in immune evasion in the human skin as it alters misguided myeloid differentiation. The researchers identified that IL-10 can promote the growth of M2-like macrophages. This effect may be blocked by using an antibody that targets IL-10 [21]. Currently, there have been advancements in the development of IL-10-based medications, such as pegilodecakin, which have subsequently entered clinical trials. Pegilodecakin demonstrated potential for enhancing patients' circumstances in cases of melanoma, albeit with minimal side effects such as vomiting and diarrhea.

## **3. Summary**

The etiology of various types of malignancies is becoming progressively evident. However, the overall survival rate remains rather poor. The role of IL-10 and its antibody are currently being extensively explored as a potential breakthrough in tumor treatment. IL-10 plays a crucial role in organisms by acting as an immunosuppressant, restraining the immune system from beyond the necessary level of eliminating invaders or abnormal cells, hence averting inflammation. However, this mechanism provides tumor cells with the opportunity to inhibit immune detection and proliferate. Tumor cells developed avenues to avoid being detected or killed through IL-10 relative regulatory pathways. Current IL-10-based therapies are centered around creating medications that specifically target IL-10 or its receptors in order to inhibit immune evasion. Pegilodecakin, a promising medication, has undergone extensive research for several cancer types, both as a standalone treatment and in combination with other therapies. While the available records indicate a promising future for IL-10, the clinical data is still insufficient, and further trials are required to establish IL-10-based immunotherapy as a

validated method.

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