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Advances In The Research And Application Of Cytokines In Human Cancer Treatment

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Abstract. Cancer surgery and radiotherapy usually fail to achieve long-term remission due to toxic effects, and tumors remain a major global health burden, while traditional therapies such as chemotherapy have problems with recurrence and immune escape. In recent years, immunotherapy has attracted much attention as a promising alternative therapy, among which cytokines play a key role in regulating anti-tumor immunity. Advances in cytokine biology and bioengineering have promoted the development of recombinant cytokines, fusion proteins, and targeted delivery systems, which can enhance immune activation while reducing systemic side effects according to relevant studies. However, cytokine therapy still faces limitations such as short half-life, off-target effects, and immunosuppressive tumor microenvironment, which limit its efficacy as a monotherapy. This article comprehensively reviews the classification and function of cytokines, focusing on their mechanisms in cancer treatment, and summarizes clinical and preclinical strategies involving monotherapy, combination immunotherapy, and engineered cytokines. This study also explores innovative methods such as nanocarrier delivery, oncolytic virus-mediated cytokine expression, and gene-edited immune cell platforms. Although challenges such as immune modulation and therapeutic resistance remain unresolved, this review provides a reference for future studies focusing on improving delivery efficiency, reducing toxicity, and personalizing treatment based on the tumor immune environment.

Keywords: Cytokine therapy; cancer immunotherapy; interleukins; tumor microenvironment.

1. Introduction

Cancer remains a global health crisis and one of the leading causes of mortality worldwide, with nearly 10 million deaths attributed to cancer in 2020 alone [1]. Despite the widespread use of conventional treatment strategies such as surgery, chemotherapy, and radiotherapy, their therapeutic efficacy remains constrained by non-specific cytotoxicity, high relapse rates, and limited long-term survival.

These deficiencies prompt the need for more targeted interventions that not only eliminate tumour cells but also harness the body's intrinsic mechanisms of tumour surveillance and immune regulation. Over the past two decades, immunotherapy has emerged as a transformative paradigm in cancer treatment. Among the various immune-modulating strategies, cytokines- small secreted proteins that mediate intercellular signalling have garnered particular attention for their central roles in immune activation, inflammation, and tissue homeostasis. The pleiotropic nature of cytokine signalling enables a single cytokine to exert diverse biological effects depending on the cellular context, receptor expression, and environmental cues within the tumour microenvironment (TME). This complexity brings both potential benefits and difficulties to their use in cancer treatment.

Several cytokines, including interferon-alpha (IFN-α), interleukin-2 (IL-2), and granulocyte-macrophage colony-stimulating factor (GM-CSF), have been evaluated in preclinical and clinical settings as therapeutic protein drugs. These cytokines have demonstrated various degrees of antitumor activity by stimulating cytotoxic T cells, enhancing antigen presentation, and reprogramming innate immune responses. Significantly, the FDA's approval of the GM-CSF-expressing oncolytic virus T-VEC, along with cell-based immunotherapies like Sipuleucel-T, highlights the real-world potential

of cytokine-based cancer treatments. However, the efficacy of such therapies is often offset by substantial systemic toxicities, rapid clearance, and the immunosuppressive features of the TME [2].

Considering these challenges, recent innovations in protein engineering and drug delivery systems have sought to optimize the pharmacokinetic and pharmacodynamic properties of cytokine therapies. Given these hurdles, recent advances in protein engineering and drug delivery technologies have aimed to enhance the pharmacokinetic and pharmacodynamic profiles of cytokine therapies. These include engineered cytokine muteins with altered receptor-binding profiles, oncolytic viruses（OVs）that deliver cytokines locally at tumour sites, controlled-release formulations, and nanocarrier based delivery systems designed to achieve spatiotemporal precision and reduce off target effects [3]. In addition, antigen-targeted delivery systems, e.g., ligand-functionalised nanoparticles or cytokine-antibody fusion constructs, provide new opportunities for increasing tumour specificity and restricting systemic exposure. These technological improvements are designed with the aim of widening the therapeutic window and reprogramming the TME into a more immunostimulatory phenotype.

Despite these efforts, several key questions remain unanswered. For example, cytokine signalling is often entangled with complex feedback loops, such as those mediated by suppressor of cytokine signalling (SOCS) proteins or regulatory phosphatases, which limit sustained therapeutic responses [4]. Moreover, redundancies among cytokine families, and the shared use of signalling intermediates (e.g., JAK-STAT pathways), complicate selective modulation without inducing immune dysregulation. The dual nature of some cytokines exerting both pro- and anti-tumour effects depending on context further challenges their application as monotherapies [1]. Therefore, gaining a deep understanding of how cytokines function across different tumour types and individual immune environments is essential for designing more effective and targeted therapies.

This paper is intended as a broad summary of the biology and therapeutic uses of cytokines in oncology. And also emphasize the latest developments in cytokine-targeting drug discovery, review the strengths and limitations of the approaches adopted so far, and cover some new attempts at combining cytokine treatment with other immune-modulating modalities. This paper also focus specifically on the crosstalk between cytokines and the immune environment around a tumor, as well as novel approaches toward local cytokine delivery.

2. Classification and Functions of Cytokines

2.1. Interleukins

Interleukins (ILs) are a diverse group of cytokines with essential roles in innate and adaptive immunity. IL-2, IL-15, and IL-21 are particularly significant in cancer immunotherapy due to their ability to activate $CD8^+$ T cells and NK cells.

IL-2, secreted by activated T cells, promotes T cell proliferation and differentiation. It was the first cytokine approved by the FDA for cancer treatment, used in high doses for metastatic melanoma and renal cell carcinoma. However, it also expands Tregs and causes toxicities like vascular leak syndrome. Despite these limitations, IL-2 remains useful in adoptive cell therapies such as TIL therapy.

IL-15 shares receptor components with IL-2 but functions differently. It supports NK and memory $CD8^+$ T cell survival without promoting Tregs. Unlike IL-2, IL-15 requires trans-presentation via IL-15/IL-15Rα complexes. In B16 melanoma models, hetIL-15 enhanced $CD8^+$ T cell infiltration by ~10-fold and increased the Pmel-1/Treg ratio from ~0.2 to ~2. It also elevated granzyme B and IFN-γ while maintaining low PD-1 expression [5]. IL-15 is being developed in superagonist and fusion forms to overcome pharmacokinetic limitations.

IL-21, produced by $CD4^+$ T cells and NK cells, boosts cytotoxic function and inhibits Treg induction. In glioma models, IL-21 delivery led to significant tumor regression via NK cells, $CD8^+$ T cells, and antibody-dependent mechanisms [6]. Collectively, IL-2, IL-15, and IL-21 act synergistically to promote effective antitumor responses.

2.2. Interferons

IFN-α, secreted by plasmacytoid dendritic cells, activates DCs and $CD8^+$ T cells and directly inhibits tumor growth. It is approved for melanoma and hematologic cancers, but clinical use has declined due to toxicity and the rise of immune checkpoint inhibitors. Persistent signaling may also impair $CD8^+$ T cell cytotoxicity after radiotherapy [7].

IFN-γ, secreted by T and NK cells, enhances MHC expression, T cell cytotoxicity, and macrophage activation. Mice lacking IFN-γ signaling show increased tumor growth, confirming its surveillance role. Yet, chronic IFN-γ exposure may induce immunosuppressive effects such as PD-L1 upregulation and T cell exhaustion. In ovarian cancer, blocking IFN-γ reduced PD-L1, increased $CD8^+$ T cell infiltration, and prolonged survival ($P = 0.021$) [8]. Though systemic IFN-γ therapy yields modest benefits, localized use remains promising.

IFN-λ (Type III) acts mainly on epithelial and hepatic cells and has shown antitumor effects in preclinical models. It promotes apoptosis, MHC I upregulation, and immune cell infiltration. In a breast cancer model, enhanced IFN-λ signaling reduced tumor burden and extended survival. In cervical samples, low IFN-λ was linked to high-risk HPV infection and abnormal cytology. Given its tissue specificity and reduced systemic toxicity, IFN-λ is a promising candidate for localized immunotherapy.

2.3. Tumour Necrosis Factors

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic cytokine secreted by myeloid cells and cytotoxic T lymphocytes. It signals through TNFR1 or TNFR2 to activate diverse pathways, with effects that depend on the cellular context.Pro-apoptotic signaling occurs through activation of caspase-8 via adaptor proteins such as TRADD and FADD, leading to extrinsic apoptosis in tumor cells [9]. This mechanism has been applied clinically in isolated limb perfusion for soft tissue sarcoma. However, systemic use of TNF-α is limited due to severe toxicities, including hypotension, fever, and systemic inflammation.

Conversely, TNF-α strongly activates the NF-κB pathway in tumor and immune cells, promoting cell survival, proliferation, angiogenesis, and inflammatory cytokine production. It also recruits myeloid cells to the tumor microenvironment (TME) and contributes to cancer-associated cachexia by altering systemic metabolism.

TNF-α is further implicated in immune-related adverse events (irAEs) during immune checkpoint blockade therapy. Studies suggest that TNF-α inhibition may alleviate these toxicities and enhance the efficacy of PD-1 or LAG-3 inhibitors by reducing T cell exhaustion and improving immune control [10].

To sum up, TNF-α plays dual roles in tumor progression and immune regulation. Despite its context-dependent complexity, it holds therapeutic potential when precisely controlled in space and time.

2.4. Colony-Stimulating Factors

Colony-stimulating factors (CSFs), particularly G-CSF and GM-CSF, regulate hematopoiesis and innate immune function. G-CSF mobilizes neutrophils and is widely used to treat chemotherapy-induced neutropenia. However, G-CSF–induced neutrophils may suppress T cells and hinder antitumor immunity.

GM-CSF activates neutrophils and monocytes, which may differentiate into either antigen-presenting cells or immunosuppressive MDSCs, depending on context. Some tumors upregulate GM-CSF to promote immune evasion. Despite this, GM-CSF is used in cancer immunotherapy—as an adjuvant in GVAX vaccines, in the oncolytic virus T-VEC, and in Sipuleucel-T for prostate cancer [4].

Though vital for immune recovery, CSFs can also exacerbate inflammation or dampen immunity. Thus, combining them with checkpoint inhibitors requires caution. Current approaches include engineered variants and localized delivery to enhance benefit while limiting side effects.

3. Applications of Cytokines in Cancer Therapy

3.1. Cytokine Monotherapy: Direct Antitumor Effects

Certain recombinant cytokines, such as interferon-alpha (IFN-α), have been used as monotherapies in cancer treatment due to their ability to stimulate immune responses and inhibit tumor cell proliferation.

IFN-α exerts antitumor effects by enhancing antigen presentation, activating dendritic cells, and directly suppressing tumor cell growth. It was once widely applied in the treatment of malignancies such as melanoma and hairy cell leukemia. However, with the advent of more effective and better-tolerated immune checkpoint inhibitors, its clinical use has become limited to niche indications like cutaneous T cell lymphoma [11].

Despite demonstrating the therapeutic potential of cytokine-driven immune modulation, IFN-α faces significant challenges in clinical application. These include dose-limiting toxicities and a narrow therapeutic window. Systemic administration results in widespread distribution, triggering immune activation in non-target tissues and leading to adverse inflammatory reactions. Conversely, insufficient local concentration at the tumor site may reduce its efficacy in reshaping the TME [12]. Moreover, IFN-α may exert context-dependent effects in different TMEs, and in certain chronic inflammatory settings, it could even promote immune evasion.

Prolonged or high-dose exposure to IFN-α may also induce immune tolerance, characterized by T cell exhaustion, upregulation of immune checkpoint molecules such as PD-L1, and impaired dendritic cell function [13]. These changes contribute to an immunosuppressive TME and limit the durability of IFN-α–mediated antitumor responses.

As a result, current efforts are focused on improving IFN-α delivery and pharmacokinetics through engineered proteins, targeted fusion molecules, and localized release strategies, aiming to enhance efficacy while minimizing systemic toxicity.

3.2. In Combination with Other Immunotherapies

Cytokines are essential immunoregulatory molecules increasingly being integrated into modern cancer immunotherapy strategies. Rather than functioning as standalone agents, they are now commonly used to augment the efficacy of immune checkpoint inhibitors (ICIs), chimeric antigen receptor T cell (CAR-T) therapies, and cancer vaccines. These combinations aim to overcome resistance mechanisms, improve effector cell persistence, and broaden treatment responses, particularly in immunologically "cold" tumors.

However, the clinical translation of cytokine-based combinations remains challenging. One major limitation is the narrow therapeutic window—systemic administration, even at low doses, can trigger excessive immune activation, leading to toxicities such as cytokine release syndrome or vascular leak syndrome. In solid tumors, poor tissue penetration and off-target immune effects further compromise efficacy.

A notable example is IL-2. Although PEGylated IL-2 (Bempegaldesleukin) was engineered to improve pharmacokinetics and receptor selectivity, a phase III clinical trial combining it with PD-1

blockade failed to demonstrate superiority over PD-1 monotherapy, illustrating the difficulty of translating preclinical promise into clinical benefit [14].

In contrast, localized cytokine delivery has shown more encouraging results. The IL-15 super agonist N-803 (Anktiva), a fusion protein combining IL-15 and IL-15Rα, was recently approved by the FDA for use in combination with BCG in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC). In a multicenter clinical trial involving 77 patients, this combination achieved high complete response rates and showed excellent tolerability, with grade 3/4 adverse events occurring in fewer than 3% of patients [15].

Similarly, IL-21 has shown therapeutic potential when delivered in a targeted manner. Researchers have developed PD-1–IL-21 fusion proteins (e.g., PD-1Ab21) that direct IL-21 specifically to PD-1$^+$ exhausted T cells. In murine tumor models, PD-1Ab21 enhanced tumor-specific memory CD8$^+$ T cell responses, suppressed tumor growth, and avoided systemic toxicity, demonstrating a favorable therapeutic index [16].

Despite these advancements, cytokine therapy continues to face key biological and logistical hurdles. Their pleiotropic effects can unintentionally activate immunosuppressive pathways or expand regulatory T cells (Tregs), reducing therapeutic efficacy. Additionally, the complexity of cytokine manufacturing and the need for specialized delivery systems limit scalability and broad clinical adoption. Therefore, the success of cytokine-based combination immunotherapies will depend on rational therapeutic design, and biomarker-guided patient selection.

3.3. Colony-Stimulating Factors

To address the limitations of native cytokines—such as short half-life, poor tumor selectivity, and systemic toxicity—researchers have developed a variety of engineered cytokine strategies in recent years. These include superkines, cytokine fusion proteins, cytokine–antibody conjugates, conditionally activated formats, and orthogonal cytokine–receptor systems.

Superkines are designed to enhance receptor affinity or alter receptor subtype specificity to achieve more targeted immune activation. For instance, a CD8-targeted IL-2 variant (CD8–IL2), improved antitumor effects in mouse models while minimizing Treg activation [17]. Fusion proteins such as IL-21–PD-1 constructs have been developed to deliver cytokines specifically to exhausted T cells within tumors, enhancing CD8$^+$ T cell function [16]. Other approaches involve conditionally activated cytokines that are only triggered within the TME—such as acidic pH or tumor-associated protease activity—as shown in the split-fusion protein.[18] Orthogonal cytokine–receptor systems restrict cytokine signaling to engineered immune cells such as CAR-Ts, improving safety and precision. Meanwhile, de novo designed cytokine mimetics (e.g., NL-201) have demonstrated favorable pharmacokinetics and cell-type specificity in preclinical studies [19].

Despite these innovations, several challenges remain in clinical translation. Balancing specificity with systemic toxicity is critical, as even engineered cytokines require careful evaluation across tumor types to avoid off-target immune activation. The complexity of conditionally activated systems presents another hurdle, since variations in TMEs may limit consistent activation and therapeutic response. For fusion proteins, stability, half-life, and functional integrity in vivo remain key obstacles that can compromise delivery efficiency and durability. Orthogonal systems, although highly specific, may pose immunogenicity risks in humans that require thorough long-term assessment. Finally, despite promising preclinical data, novel cytokine agonists designed via de novo protein engineering—such as NL-201—may still fail in clinical trials due to insufficient efficacy or unforeseen safety issues.

In conclusion, engineered cytokines have opened new possibilities in cancer immunotherapy, but their clinical application demands the resolution of multiple biological and technical challenges. Future efforts should focus on optimizing molecular design, improving delivery precision, and incorporating biomarker-guided patient selection to support broader and safer therapeutic use.

4. Recent Advances and Technological Innovations

4.1. Nanocarriers and Targeted Delivery

The clinical efficacy of cytokine-based therapies is often limited by poor pharmacokinetics, high systemic toxicity, and insufficient tumor accumulation. To address these challenges, recent advancements in nanotechnology have led to the development of various targeted delivery platforms that enhance cytokine stability and intratumoral localization, thereby improving immune activation while minimizing off-target effects. Among these, liposomes, peptide-modified nanoparticles, and antibody–cytokine fusion proteins represent the most widely adopted strategies.

Liposomes are phospholipid bilayer vesicles capable of encapsulating cytokines or cytokine-encoding mRNA, providing protection against enzymatic degradation and enabling passive or active targeting to tumor tissues. Studies have shown that liposomal formulations of IL-2 or IL-12 can significantly extend circulation time, reduce systemic toxicity, and maintain potent immune stimulation [20]. Some designs incorporate pH-sensitive or thermosensitive components to ensure cytokine release specifically within the TME.

Peptide-modified nanocarriers utilize tumor-homing sequences such as iRGD, RGD, or NGR peptides, or immune cell–targeting motifs, to improve delivery specificity [21]. For instance, RGD-modified nanoparticles delivering IL-15 or GM-CSF have demonstrated enhanced uptake by tumor vasculature or dendritic cells, resulting in improved local immune activation and tumor suppression in preclinical models. These systems can also be engineered to respond to enzymatic cues or tumor stromal markers for controlled release.

Antibody–cytokine fusion proteins offer a biologically driven approach to targeted delivery by fusing cytokines (e.g., IL-2, IL-12, IL-21, or TNF-α) to monoclonal antibodies that recognize tumor-associated antigens. This allows for localized immune stimulation at the tumor site. A notable example is L19–IL2, which targets the ED-B domain of fibronectin and has advanced to clinical trials for melanoma and sarcoma, demonstrating reduced systemic toxicity and sustained intratumoral immune activity.

Despite the promising progress, several technical challenges remain. The design of nanocarriers must balance drug loading capacity, release kinetics, and biocompatibility. Additionally, the structural modification of proteins may introduce immunogenicity concerns, and large-scale manufacturing processes require further optimization. Nevertheless, these targeted delivery strategies provide critical support for the clinical translation of cytokine immunotherapies, particularly when used in combination with immune checkpoint inhibitors or adoptive cell transfer therapies.

4.2. OV-based Cytokine Delivery

OVs represent a novel class of immunotherapeutic agents that combine direct tumor cell lysis with immunostimulatory properties. To enhance their immunomodulatory capacity, several OVs have been engineered to express therapeutic cytokines such as GM-CSF or IL-12, thereby enabling localized and sustained cytokine delivery within the TME while limiting systemic toxicity.

One of the most well-established examples is T-VEC (talimogene laherparepvec), a genetically modified herpes simplex virus type 1 encoding GM-CSF. T-VEC has been approved for the treatment of unresectable melanoma and has shown the ability to induce immunogenic cell death while locally recruiting and activating dendritic cells [22]. Clinical data support its capacity to increase tumor-infiltrating lymphocytes and potentially synergize with immune checkpoint blockade [23].

Beyond herpesvirus-based systems, Newcastle disease virus (NDV) is also gaining attention as a delivery platform for cytokine payloads. Recombinant NDV strains expressing GM-CSF or IL-12 have demonstrated potent antitumor activity in preclinical tumor models, driven by enhanced innate immune activation and a shift toward Th1-mediated responses [24]. These viruses offer additional

advantages, including natural tumor selectivity and low seroprevalence in the human population, which may support repeated dosing without rapid neutralization.

Together, these virus-cytokine constructs offer an attractive strategy to reshape the TME and overcome immune exclusion. Their ability to trigger local inflammation, improve antigen presentation, and support effector T cell infiltration may help convert immunologically "cold" tumors into "hot" ones, thereby enhancing the effectiveness of other therapies such as ICIs or adoptive cell transfer.

However, challenges remain. Host antiviral immunity can limit viral persistence and repeat administration, and large-scale manufacturing requires stringent control to ensure safety and consistency. Nonetheless, OVs equipped with cytokines represent a promising platform for localized immunotherapy, with increasing evidence supporting their integration into multimodal cancer treatment regimens.

4.3. Combination Therapies and Personalized Immunomodulation

Given the multifaceted nature of tumor immune evasion, monotherapy with a single cytokine often results in limited efficacy due to compensatory immunosuppressive mechanisms or insufficient T cell activation. To address these shortcomings, a growing number of studies have explored the synergistic use of multiple cytokines to orchestrate more effective and durable antitumor immune responses. Among these, the combination of IL-2, IL-15, and IL-21 has drawn particular attention due to their complementary effects on T cell and NK cell biology.

IL-2 promotes the expansion of effector T cells but also activates Tregs, often limiting its therapeutic window. In contrast, IL-15 supports memory $CD8^+$ T cells and NK cells without expanding Tregs, while IL-21 enhances the cytolytic activity of $CD8^+$ T cells and can suppress Treg induction. When used in combination, these cytokines can potentiate cytotoxic immunity while limiting immunosuppression. Preclinical models have demonstrated that co-delivery of IL-15 and IL-21 enhances T cell persistence, tumor infiltration, and effector function more effectively than either cytokine alone. Early-phase clinical trials are also evaluating the co-administration of IL-2 variants with IL-15 superagonists in adoptive T cell therapies, including TIL and CAR-T protocols.

In parallel, advances in gene editing technologies such as CRISPR-Cas9 are opening new avenues for personalized cytokine modulation. Through precise editing of cytokine genes, their receptors, or downstream signaling regulators, it is now possible to rewire immune cell behavior to overcome tumor-induced suppression. For instance, engineered T cells with disrupted IL-2Rα (CD25) or PD-1, combined with IL-15 transgene expression, have shown improved proliferation and persistence in vivo [25]. CRISPR has also been used to knock out SOCS family genes to enhance cytokine signaling sensitivity, or to insert inducible cytokine expression cassettes that activate only in the TME.

Several of these strategies are under active investigation. A recent study reported the first-in-human use of CRISPR-edited T cells lacking endogenous TCR and PD-1 [26], combined with engineered TCR targeting NY-ESO-1 antigen in sarcoma patients, laying the groundwork for further integration of cytokine pathways. Meanwhile, clinical trials are exploring the co-delivery of IL-12 or IL-18 in CAR-T cells, with ongoing efforts to use gene circuits that allow conditional cytokine release based on tumor antigen recognition [27].

Altogether, cytokine combination therapies, coupled with gene editing and patient-specific design, represent a promising strategy to overcome current limitations in immunotherapy. Their rational use may enable better control over immune cell phenotype, improve safety profiles, and ultimately tailor treatment to the immunogenetic context of each tumor.

5. Conclusion

This review provides a comprehensive overview of the classification, function, and therapeutic application of cytokines in cancer treatment. The review explores the roles of key cytokines such as interleukins, interferons, TNF-α, and colony stimulating factors, and elaborates on their mechanisms of action in immunomodulation and tumor suppression. In addition, the review explores the use of cytokines as monotherapy and in combination with other immunotherapies such as checkpoint inhibitors, chimeric antigen receptor-T cells, and cancer vaccines. In addition, the review discusses emerging strategies such as engineered cytokine variants, nanocarrier systems, antibody-cytokine fusion constructs, and OVs to achieve more targeted and effective delivery.

However, the complexity of cytokine signaling, the potential for immune-related toxicity, and the differences between different tumor types need to be further studied. In addition, the interaction of cytokines with patient-specific immune profiles remains understudied. Future research should focus on improving delivery strategies, developing context-based cytokine formulations, and combining cytokine therapy with genomic and biomarker-based precision medicine. Further research explores how cytokines interact with the TME and other immune modulators.

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