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REVIEW PAPER

IMPROVED CYTOKINES FOR THERAPY

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Abstract:

Cytokine treatments have the potential to revolutionize the treatment of infectious, autoimmune, and cancer diseases. But their shorter half-life, widespread pleiotropic signaling, and systemic toxicity have restricted the clinical use. Mechanistically, they enhance T cell proliferation, differentiation, and effector functions by modulating key signaling pathways, enabling precise control of Th1, Th2, Th17, and Treg responses. The engineered cytokines show improved stability, a longer half-life, and activity that targets specific tissues while still providing strong immune-stimulating effects. In preclinical models, they demonstrate better effectiveness compared to wild-type cytokines. However, Recombinant cytokines frequently cause dose-limiting side effects that limit their therapeutic window, such as capillary leak, immune overactivation, hypotension, and flu-like symptoms. To overcome these limitations, we have altered these cytokines to achieve their maximum therapeutic potential.

Keywords: *Cytokines, T cells, Bioavailability, Therapy.*

1. Introduction

Innate and adaptive immune responses are synchronized by cytokines, which are tiny, soluble signaling proteins that regulate immune cell communication. Through strictly controlled signaling networks, they regulate vital biological processes like immune cell activation, proliferation, differentiation, and survival. Several pathological conditions, such as cancer, autoimmune diseases, chronic inflammatory disorders, and infectious diseases, are characterized by irregular cytokine signaling. Cytokines like interleukins, interferons, tumor necrosis factors, and colony-stimulating factors have been systematically studied as therapeutic agents that can improve immune-mediated disease control or restore immune balance because of their fundamental role in immune regulation [1-4].

Recombinant cytokines' early clinical development reported compelling proof of their therapeutic potential. While interferon-α (IFN-α) demonstrated effectiveness in viral infections and hematological malignancies, high-dose interleukin-2 (IL-2) therapy produced long-lasting responses in subsets of patients with metastatic melanoma and renal cell carcinoma [4]. Noteworthy dose-limiting toxicities, such as capillary leak syndrome, hypotension,

cytokine release syndrome, and severe flu-like symptoms, severely restricted clinical use despite these achievements. Moreover, many cytokines' short half-lives in circulation require frequent or high-dose administration, which increased systemic toxicity and decreased patient tolerability [6]. These restrictions made it clear that better cytokine designs were required in order to maintain therapeutic efficacy while reducing side effects [1-4].

Innovations in protein engineering, structural biology and immunology have sparked a resurgence of attention in cytokine-based treatments. The development of cytokines with improved stability, extended half-lives, receptor-selective signaling, and tissue-specific activity is made possible by modern techniques. Improved cytokines can selectively boost positive immune responses while preventing harmful systemic inflammation by modifying cytokine-receptor interactions or limiting cytokine activation to diseased tissues. These next-generation cytokines are promising agents in precision immunotherapy for cancer, autoimmune diseases, and chronic infections because preclinical and early clinical research shows that they have better therapeutic indices than wild-type molecules [7–9].

2. Limitations of conventional cytokine therapy

2.1 Short serum half-life

The very short serum half-life of the majority of native cytokines is a significant disadvantage of traditional cytokine therapy. Renal filtration and metabolic pathways quickly clear cytokines from circulation due to their small molecular size and high susceptibility to proteolytic degradation. In order to sustain biological activity, therapeutic administration frequently necessitates high systemic concentrations or repeated dosing. This pharmacokinetic disadvantage raises the possibility of dose-dependent toxicity in addition to limiting long-term immune modulation. According to clinical research, rapid cytokine clearance causes exposure levels to fluctuate, which lowers therapeutic efficacy and makes optimal dose control more difficult [1, 2, 10,11].

2.2 Systemic toxicity

The biggest barrier to the extensive clinical application of recombinant cytokines is still systemic toxicity. Serious side effects, such as capillary leak syndrome, hypotension, fever, chills, flu-like symptoms, cytokine release syndrome, and immune-mediated organ damage, are often brought on by high-dose cytokine administration. Extensive immune and endothelial cell activation causes these toxicities, which result in vascular permeability, systemic inflammation, and hemodynamic instability. For example, vascular leak syndrome is closely linked to interleukin-2 therapy, whereas systemic inflammatory symptoms are frequently brought on by interferons and other pro-inflammatory cytokines [12–14].

2.3 lack of target specificity

The lack of target specificity in native cytokine therapy is another basic problem. Cytokines are pleiotropic molecules that act on a variety of immune and non-immune cell types. Although this wide range of activity is necessary for physiological immune regulation, it presents a noteworthy hindrance in therapeutic contexts. Systemic administration causes inflammation. Therapeutic accuracy and safety may be compromised by this non-selective signaling [15].

3. Mechanisms and engineering strategies of improved cytokines

3.1 Enhancing pharmacokinetics: Stability and half-life extension

In order to improve stability and extend circulation time, cytokines have been modified using techniques like PEGylation, Fc fusion, and albumin-binding domains [1, 2, 16]. These changes delayed renal filtration, increase

hydrodynamic size, and protect cytokines from proteolytic digestion. We and other found that half-life-extended cytokines improve therapeutic indices and reduce negative systemic effects by achieving sustained immune activation at lower doses [1-4, 17, 18]. Selective shielding of receptor-binding sites has been made possible by rational PEGylation techniques, preserving desired signaling while reducing off-target interactions [19].

3.2 receptor biasing and selective signaling

Receptor Biasing (modification in cytokines to selectively activate particular receptor complexes) has become a potent approach to increase safety and efficacy. Designed to selectively signal through the IL-2Rβγ complex, engineered interleukin-2 (IL-2) and IL-15 variations minimize activation of regulatory T cells (Tregs) while encouraging the proliferation of effector T cells and natural killer (NK) cells [20 -22].

3.3 tumor targeting and context-dependent activation

Cytokine engineering studies are increasingly concentrated on limiting cytokine activity to disease areas in order to further reduce systemic toxicity. By combining cytokines with antibodies or ligands that identify tumor-associated antigens, tumor-targeted cytokines, also known as immunocytokines, are produced. This concentrates immune activation inside the tumor microenvironment [1-4]. While reducing peripheral exposure, this targeted activation improves antitumor effectiveness [23]. Furthermore, pro-cytokines, also known as masked cytokines, have been created that stay inactive in the bloodstream but are specially triggered by inflammatory signals or tumor-associated proteases in ailing tissues [24, 25]. Innovative delivery systems are being investigated to improve cytokine therapy beyond protein-level engineering [26].

Conclusion and Future Perspectives

Among the most potent endogenous modulators of immune responses, cytokines have shown considerable therapeutic promise in the treatment of infectious illnesses, cancer, and autoimmune diseases. Many of the issues have been resolved by developments of improved cytokine, including as half-life extension, receptor biasing, and targeted delivery [1, 27]. Precision immune regulation via thoughtful design and regulated delivery is required for cytokine therapy. Improved cytokines with programmable and context-dependent activity can be achieved by integrating structural biology, computational protein engineering, and synthetic biology [1, 28].

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