Epidemiology & Public Health

Cytokine and chemokine modulation for immune reprogramming in cancer and neurodegeneration: A comprehensive therapeutic review

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Abstract

Immune reprogramming, the dynamic process by which immune cell phenotypes and functions adapt in response to microenvironmental signals, plays a central role in both cancer progression and neurodegenerative disease pathogenesis. Cytokines and chemokines serve as critical orchestrators of this process, functioning as signaling molecules that coordinate immune system responses. In cancer, malignant cells commandeer these pathways to establish an immunosuppressive Tumor Microenvironment (TME) that recruits pro-tumorigenic cells while inhibiting anti-tumor immunity. Conversely, in neurodegenerative disorders, aberrant cytokine and chemokine signaling drives chronic neuroinflammation, ultimately resulting in progressive neuronal damage.

This comprehensive review synthesizes current literature on immune reprogramming mediated by cytokines and chemokines, with emphasis on therapeutic applications in both disease contexts. We examine diverse therapeutic modalities for modulating these pathways, ranging from traditional recombinant cytokines to contemporary approaches including monoclonal antibodies and novel delivery systems. Critical challenges impeding clinical translation are discussed, including systemic toxicity, context-dependent functions of these molecules, and the formidable barrier posed by the blood-brain barrier in neurological applications.

Finally, we outline future research priorities, emphasizing the need for highly specific targeted therapies and rationally designed combination strategies to restore appropriate immune balance in combating these devastating diseases.

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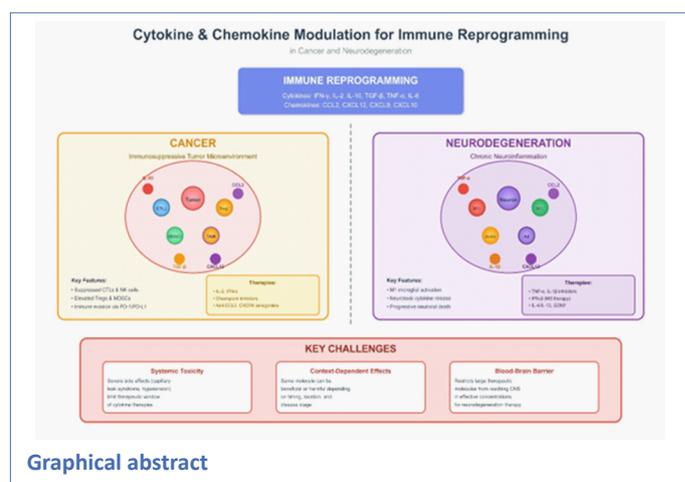
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Graphical abstract

Introduction

The immune system comprises a complex network of cells, tissues, and organs that collectively defend the body against diverse threats, including pathogenic microorganisms and malignant cells. Rather than functioning as a static defense mechanism, the immune system exhibits remarkable plasticity through a process termed immune reprogramming [45]. This process refers to dynamic alterations in immune cell phenotype and function in response to microenvironmental cues, representing an essential adaptive mechanism that becomes detrimental in diseases such as cancer and neurodegeneration [44].

In cancer, immune reprogramming serves as a critical mechanism of immune evasion. Malignant cells possess the capacity to reshape the Tumor Microenvironment (TME), converting immune responses from anti-tumorigenic to pro-tumorigenic. This transformation involves suppressing Cytotoxic T Lymphocytes (CTLs) and Natural Killer (NK) cells while simultaneously recruiting and activating immunosuppressive populations, including regulatory T cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs). This immune dysfunction enables tumors to evade immunosurveillance, facilitating uncontrolled proliferation and metastasis [46].

Neurodegenerative diseases, particularly Alzheimer's Disease (AD) and Parkinson's Disease (PD), similarly exhibit pathological immune reprogramming that drives chronic neuroinflammation. The Central Nervous System (CNS), once considered an immune-privileged site, is now recognized as being actively surveilled by resident immune cells, particularly microglia, the brain's resident macrophages [49]. In neurodegenerative conditions, microglia transition from their homeostatic surveillance state to a reactive inflammatory phenotype, releasing pro-inflammatory mediators that contribute to neuronal damage and disease progression. Understanding these complex immunological changes is essential for developing effective therapeutic interventions.

Cytokines and chemokines represent two critical families of signaling molecules that orchestrate immune reprogramming [51]. Cytokines are small secreted proteins that mediate and regulate immunity, inflammation, and hematopoiesis [94]. This diverse group includes Interleukins (ILs), Interferons (IFNs), and Tumor Necrosis Factors (TNFs), each performing distinct functions in cellular communication. Chemokines constitute a specialized subset of cytokines that primarily function as chemoattractants, directing immune cell migration to specific anatomical locations [43]. The intricate interplay between cytokines and chemokines guides immune cells to sites of infection, injury, or disease. Under physiological conditions, this communication network ensures prompt and effective immune responses [47,50]. However, in pathological states, these signaling pathways become dysregulated with profound consequences.

In cancer, tumors exploit cytokine and chemokine signaling to recruit pro-tumorigenic immune cells, induce angiogenesis, and suppress anti-tumor immunity, as illustrated in Figure 1. Similarly, in neurodegeneration, aberrant chemokine and cytokine gradients can trigger chronic microglial activation and promote infiltration of peripheral immune cells into the CNS, intensifying neuroinflammation and accelerating neuronal death [55].
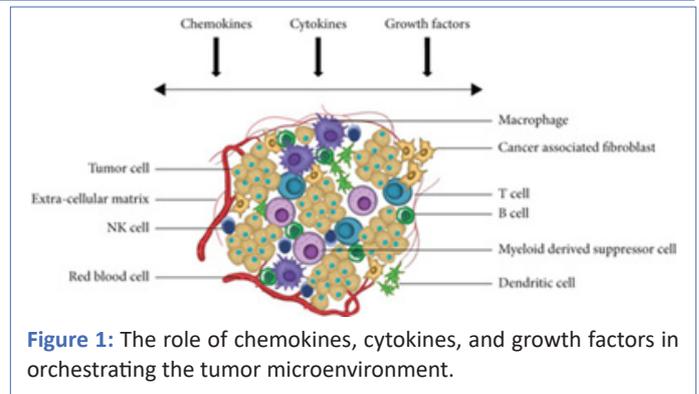

Figure 1: The role of chemokines, cytokines, and growth factors in orchestrating the tumor microenvironment.

This schematic illustrates how tumor cells and stromal components secrete various signaling molecules that collectively shape the immunosuppressive TME. These factors coordinate multiple processes including recruitment of pro-tumorigenic immune cells, promotion of angiogenesis, inhibition of anti-tumor immunity, and facilitation of tumor cell survival and proliferation.

Given the central importance of cytokines and chemokines in shaping pathological immune responses in both cancer and neurodegeneration, targeting these pathways represents a promising therapeutic strategy. Over the past decade, numerous studies and clinical trials have emerged aimed at modulating these signaling molecules. This review provides a comprehensive analysis of current knowledge regarding cytokine and chemokine-mediated immune reprogramming in these two distinct yet interconnected disease areas.

We first examine the specific roles of these signaling molecules in the tumor microenvironment and the CNS, and how they contribute to disease progression. Subsequently, we discuss various therapeutic strategies that have been developed, including recombinant cytokines, small molecule inhibitors, and monoclonal antibodies. We critically evaluate both the clinical successes and, more importantly, the challenges and limitations of these treatments, including systemic toxicity and the complex context-specific actions of these molecules. Finally, we present perspectives on future research directions and how next-generation targeted therapies might be formulated to effectively reprogram the immune system for therapeutic benefit.

Immune reprogramming in cancer

Tumor microenvironment and immune evasion

The Tumor Microenvironment (TME) constitutes a complex ecosystem comprising tumor cells, immune cells, fibroblasts, endothelial cells, and the extracellular matrix. This intricate network serves as a major determinant of tumor progression and treatment response [102]. To evade immune detection and subsequent elimination, tumor cells have evolved sophisticated mechanisms to manipulate the TME, generating an immunosuppressive milieu that promotes tumor survival and expansion.

Immune evasion mechanisms primarily function by suppressing anti-tumor immune responses through multiple strategies. A key mechanism involves activation of immune checkpoints, including the PD-1/PD-L1 axis, which induces T cell exhaustion and functional impairment [18,52].
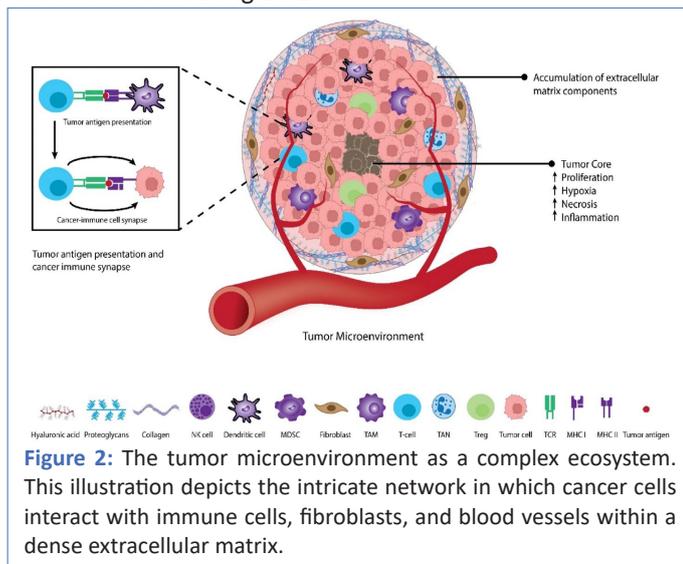
Beyond immune checkpoint engagement, the TME harbors high concentrations of immunosuppressive cell populations. Myeloid-Derived Suppressor Cells (MDSCs) and Tumor-Associated Macrophages (TAMs) are particularly adept at promoting

tumor growth through secretion of immunosuppressive cytokines and growth factors [58,97]. These cells not only suppress effector T cell activity but also stimulate angiogenesis and facilitate tissue remodeling, further contributing to tumor progression (Mano et al. 2013). Additionally, regulatory T cells (Tregs) accumulate within the TME, where they actively suppress anti-tumor immunity through direct cell-to-cell contact and release of inhibitory cytokines (Tommasin et al. 2017).

Cytokine and chemokine modulation in tumor immunity

Dysregulated cytokine and chemokine signaling lies at the heart of the immunosuppressive TME. Classical pro-inflammatory cytokines such as IFN-gamma and IL-12, typically associated with robust anti-tumor immunity, are frequently suppressed in the TME [90]. Conversely, the TME exhibits elevated concentrations of immunosuppressive cytokines, including IL-10 and TGF-beta [65]. These molecules not only inhibit anti-tumor immune cell activation and proliferation but also promote differentiation of MDSCs and Tregs, further reinforcing the immunosuppressive environment [59].

Chemokines play a crucial role in determining the cellular composition of the TME. Tumor cells and stromal cells secrete distinct chemokines that selectively recruit immunosuppressive cell types while discouraging infiltration of anti-tumor effectors, as demonstrated in Figure 1.

Figure 2: The tumor microenvironment as a complex ecosystem. This illustration depicts the intricate network in which cancer cells interact with immune cells, fibroblasts, and blood vessels within a dense extracellular matrix.

The diagram highlights how this complex architecture enables tumor expansion and creates a hypoxic core. The tumor orchestrates immune evasion by recruiting immunosuppressive cells that inhibit anti-cancer responses, thereby facilitating tumor survival and growth. Key features include the spatial organization of different cell types, the formation of abnormal vasculature, and the establishment of gradients that promote tumor progression while suppressing effective immune surveillance.

For example, CCL2 has been shown to recruit macrophages into the tumor, where they undergo reprogramming into pro-tumorigenic TAMs. Similarly, the CXCL12/CXCR4 chemokine axis plays a pivotal role in tumor cell proliferation, survival, and metastasis by attracting various stromal and immune cell populations to the tumor site (Zu et al. 2020).

Therapeutic strategies targeting cytokine and chemokine signaling

Given their central role in shaping the TME, cytokines and chemokines represent attractive targets for cancer therapy. Therapeutic approaches can be broadly classified into two categories: direct modulation of cytokine or chemokine levels, and indirect intervention through receptor targeting [63]. Recombinant cytokines, including IL-2 and IFN-alpha, were among the earliest immunotherapies applied in cancer treatment. While these agents have demonstrated clinical benefit in select malignancies, their widespread application has been limited by significant systemic toxicity and short half-lives.

More recently, targeted approaches have gained prominence. These include monoclonal antibodies designed to neutralize immunosuppressive cytokines such as IL-10 or TGF-beta, as well as antibodies targeting chemokines that recruit pro-tumorigenic cells [61]. Novel strategies employ oncolytic viruses or gene therapy to deliver cytokines or chemokines directly to the tumor site, thereby minimizing systemic side effects while concentrating immune-modulatory effects where they are most needed. Additionally, accumulating evidence supports combining cytokine or chemokine modulation with other immunotherapies, particularly immune checkpoint inhibitors, to enhance therapeutic efficacy and overcome resistance mechanisms, as detailed in Table 1.

Table 1: List of cytokines and chemokines involved in cancer immunotherapy.

Cytokine/ Chemokine	Main Function in TME	Target Cell Types	Therapeutic Strategy
IFN-γ	Promotes anti-tumor immunity, enhances MHC expression	T cells, NK cells, tumor cells	Recombinant protein, gene therapy (Liao et al. 2019)
IL-2	Activates T cells and NK cells	T cells, NK cells	Recombinant protein
IL-10	Suppresses anti-tumor immunity, promotes Treg function	Tregs, macrophages	Monoclonal antibody (neutralizing)
TGF-β	Inhibits T cell activation, promotes MDSC differentiation	T cells, fibroblasts, MDSCs	Monoclonal antibody, small molecule inhibitor (Arce-Sillas et al. 2016)
CXCL12	Promotes immunosuppressive cells, promotes tumor growth	Stromal cells, tumor cells	Receptor antagonist (e.g., CXCR4 inhibitor) (Li et al. 2020)
CCL2	Recruit's macrophages and MDSCs	Macrophages, MDSCs	Monoclonal antibody, small molecule inhibitor (Chang et al. 2016)

Immune reprogramming in neurodegeneration

Neuroinflammation and immune system changes in neurodegenerative diseases

Neurodegenerative diseases, once viewed solely as disorders of neuronal loss, are now recognized as having a substantial inflammatory component. Neuroinflammation, defined as the inflammatory response within the Central Nervous System (CNS), represents a pathological hallmark of various disorders including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Multiple Sclerosis (MS). This inflammatory state does not merely coincide with neuronal death but actively contributes to disease progression [62].

Microglia, the resident macrophages of the CNS, serve as the primary immune cells of the brain. In healthy brain tissue, microglia maintain a resting or homeostatic state, continuously surveying their microenvironment for pathogens or tissue damage [63]. However, in neurodegenerative diseases, microglia undergo chronic activation, acquiring a reactive phenotype. This activation is triggered by various stimuli, including misfolded protein aggregates such as amyloid-beta in AD and alpha-synuclein in PD, as well as cellular injury [92].

Activated microglia can adopt a spectrum of functional states, ranging from a beneficial, phagocytic phenotype (M2-like) that clears debris and promotes tissue repair, to a detrimental, pro-inflammatory phenotype (M1-like) that secretes neurotoxic molecules and exacerbates neuronal injury. Astrocytes, another major glial cell population, also contribute to this neuroinflammatory milieu through release of pro-inflammatory mediators and disruption of synaptic function [103].

The role of cytokines and chemokines in neurodegeneration

The transition from a homeostatic to an inflammatory state in the CNS is orchestrated by a complex network of cytokines and chemokines. In neurodegenerative diseases, pro-inflammatory cytokines including TNF-alpha, IL-1-beta, and IL-6 are consistently elevated in patient brain tissue [1]. These molecules promote the pro-inflammatory phenotype of microglia and astrocytes, establishing a self-perpetuating cycle of inflammation and cellular damage. In AD, for instance, amyloid-beta plaques stimulate microglia to release these cytokines, which in turn exacerbate plaque formation and neurotoxicity [64].

Chemokines play an equally critical role by directing the migration of both resident and peripheral immune cells. CCL2, for example, is elevated in AD and recruits peripheral monocytes into the CNS, potentially amplifying the inflammatory response [89]. Similarly, the CXCL12/CXCR4 chemokine axis has been implicated in T cell infiltration into the CNS in MS, contributing to demyelination. The intricate interactions among these signaling molecules determine both the magnitude of inflammation and the specific immune cell populations that infiltrate the brain, ultimately influencing disease outcomes [2].

Therapeutic potential of cytokine and chemokine modulation in neurodegenerative disorders

Targeting cytokine and chemokine signaling pathways represents a promising therapeutic avenue for neurodegenerative diseases. Strategies aim either to inhibit detrimental pro-inflammatory responses or to enhance beneficial pro-repair responses. One approach involves neutralizing specific cytokines using anti-inflammatory agents [96]. For example, blocking TNF-alpha or IL-1-beta has been investigated as a means to dampen the inflammatory cascade. However, the interconnected nature of the cytokine network suggests that broad anti-inflammatory strategies may not always prove effective and could potentially produce unwanted side effects [3,4].

An alternative strategy focuses on modulating chemokine receptors to prevent infiltration of pathogenic immune cells into the CNS [4]. Small molecule inhibitors of chemokine receptors have been designed to block immune cell migration. Additionally, anti-inflammatory and neuroprotective cytokines, such as IL-4 and IL-13, are being explored for their potential to promote the beneficial M2-like microglial phenotype and enhance neuronal survival. While still in early developmental stages, these approaches hold promise for establishing a new generation of therapies capable of directly modulating the neuroinflammatory environment [6].

Mechanisms of cytokine and chemokine modulation

Cytokine signaling pathways in immune reprogramming

Cytokines exert their diverse biological effects by binding to specific cell surface receptors, initiating intracellular signaling cascades that ultimately alter gene expression and cellular function. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway represents one of the most prominent cytokine signaling mechanisms [6]. Upon cytokine binding, receptor-associated JAK proteins become activated through phosphorylation, subsequently phosphorylating STAT proteins. These activated STAT proteins then dimerize, translocate to the nucleus, and regulate transcription of target genes involved in immune cell differentiation, proliferation, and activation.

Alternative cytokine signaling pathways include the Nuclear Factor Kappa B (NF-κB) pathway and Mitogen-Activated Protein Kinase (MAPK) cascades [7]. The NF-κB pathway, activated by cytokines such as TNF-alpha and IL-1, plays a critical role in regulating inflammatory responses and cell survival. MAPK pathways, including ERK, JNK, and p38 MAPK, mediate diverse cellular responses including proliferation, differentiation, and apoptosis. The specific signaling pathway activated depends on both the cytokine involved and the cellular context, contributing to the remarkable versatility of cytokine-mediated immune regulation.

Understanding these signaling mechanisms is essential for developing targeted therapeutic interventions. For instance, JAK inhibitors have emerged as effective treatments for various autoimmune and inflammatory conditions by blocking the downstream effects of multiple pro-inflammatory cytokines simultaneously [10]. Similarly, inhibitors targeting NF-κB or MAPK pathways are being investigated as potential therapies for both cancer and neurodegenerative diseases, where aberrant activation of these pathways contributes to disease pathogenesis [25].

Chemokine receptors and immune cell trafficking

Chemokines primarily signal through G Protein-Coupled Receptors (GPCRs), a large family of transmembrane receptors. Chemokine binding to its cognate receptor triggers activation of heterotrimeric G proteins, initiating downstream signaling cascades that predominantly affect cellular cytoskeletal dynamics [9]. This leads to rapid reorganization of actin filaments and formation of a leading edge, enabling cells to migrate along chemokine concentration gradients [66]. This process, termed chemotaxis, plays a fundamental role in directing immune cells (including T cells, B cells, and neutrophils) to sites of inflammation, infection, or tumor formation, as illustrated in Figure 2.

Chemokine-receptor interactions exhibit remarkable specificity, ensuring that immune cell trafficking is highly regulated and directionally controlled [11]. However, this system also displays considerable redundancy, with multiple chemokines capable of binding the same receptor and individual chemokines binding multiple receptors. This complexity provides robustness to immune cell recruitment but also presents challenges for therapeutic targeting.

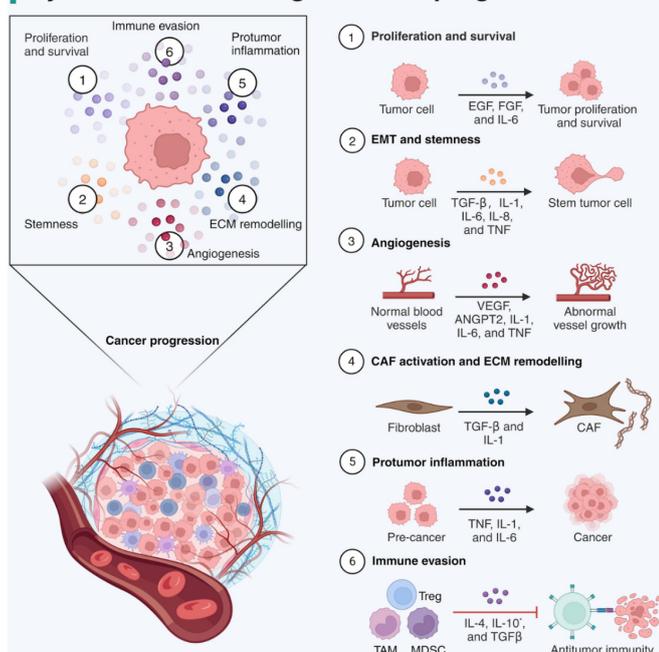## Cytokines contributing to cancer progression

Figure 3: Mechanisms of cytokine action in cancer development. This comprehensive diagram illustrates the multifaceted roles of cytokines in tumor progression within the central tumor microenvironment depiction (labels 1-6 indicate key processes). First, cytokines such as EGF, FGF, and IL-6 drive tumor cell proliferation and survival. Second, TGF-beta, IL-1, IL-6, IL-8, and TNF induce Epithelial-Mesenchymal Transition (EMT) and cancer stem cell properties, promoting a more aggressive phenotype. Third, VEGF, ANGPT2, IL-1, IL-6, and TNF stimulate angiogenesis, providing tumors with essential nutrients and oxygen. Fourth, TGF-beta and IL-1 mediate Cancer-Associated Fibroblast (CAF) differentiation and Extracellular Matrix (ECM) remodeling, facilitating tumor immune evasion and therapy resistance [100]. Fifth, pro-inflammatory cytokines including TNF, IL-1, and IL-6 promote dysregulated inflammation that supports tumor growth. Sixth, immunosuppressive cytokines such as IL-4, IL-10, and TGF-beta inhibit CD8+ T cell function while promoting regulatory T cells (Tregs), Myeloid-Derived Suppressor Cells (MDSCs), and Tumor-Associated Macrophages (TAMs), enabling immune escape.

Table 2: Key cytokine and chemokine receptors and their roles.

Receptor	Ligands	Associated Pathway	Key Role
IFNAR	IFN-α, IFN-β	JAK/STAT	Anti-viral and anti-proliferative response (Umansky et al. 2016)
TNFR	TNF-α, TNF-β	NF-κB, MAPK	Inflammation, cell death, cell survival (Siegel et al. 2022)
IL-2R	IL-2, IL-15	JAK/STAT	T cell proliferation and differentiation (Galdiero et al. 2013)
CXCR4	CXCL12	GPCR	Immune cell trafficking, tumor metastasis (Fridlender & Albelda 2012)
CCR2	CCL2	GPCR	Macrophage and monocyte recruitment (Blattner et al. 2018)
IL-10R	IL-10	JAK/STAT	Immunosuppression (Li et al. 2019)

Notably, while IL-10 typically suppresses immune responses, emerging evidence indicates it can paradoxically enhance tumor-resident CD8+ T cell activation in specific contexts [93].

The interplay between cytokine and chemokine signaling pathways is extensive and bidirectional [12]. Pro-inflammatory cytokines, including TNF-alpha and IL-1, can upregulate expression of various chemokine receptors and chemokines on both endothelial and immune cells, thereby establishing positive feedback loops that amplify immune cell recruitment to inflamed sites (Bellone et al. 2013). Similarly, certain cytokines can activate the JAK/STAT pathway, leading to transcriptional upregulation of chemokine receptors and enhancing immune cell responsiveness to chemokine gradients, as detailed in Table 2.

Cytokine and chemokine therapy in cancer treatment

Cytokine therapy for tumor immunotherapy

Cytokines were among the first therapeutic agents employed in cancer immunotherapy, with the goal of enhancing host anti-tumor immune responses. Recombinant cytokines such as Interferon-Alpha (IFN-alpha) and Interleukin-2 (IL-2) have received regulatory approval for treating specific malignancies. IFN-alpha, one of the earliest immunotherapies, was initially approved for hairy cell leukemia and melanoma [13]. This cytokine exerts multiple anti-tumor effects, including direct inhibition of tumor cell proliferation, enhancement of antigen presentation through upregulation of MHC class I molecules, and augmentation of Natural Killer (NK) cell and T cell activity [14].

IL-2, approved for treatment of metastatic renal cell carcinoma and metastatic melanoma, promotes proliferation and activation of T cells, particularly Cytotoxic T Lymphocytes (CTLs) and NK cells, which are essential for tumor cell destruction. These cells play critical roles in tumor immunosurveillance and elimination.

However, these first-generation cytokine therapies have been hampered by severe systemic toxicity. High-dose IL-2 can induce capillary leak syndrome, hypotension, and multi-organ failure due to systemic inflammatory response syndrome [95]. Similarly, IFN-alpha therapy is associated with flu-like symptoms, profound fatigue, and neurotoxicity. These adverse effects, coupled with the short half-lives of recombinant proteins, have prompted a shift toward more targeted and less toxic therapeutic approaches [14].

Chemokine-based approaches to enhance anti-tumor immunity

As master regulators of immune cell trafficking, chemokines offer unique opportunities to reshape the TME for therapeutic benefit. Chemokine-based therapies aim either to recruit anti-tumor immune cells to the tumor site or to prevent recruitment of pro-tumorigenic cells. One strategy involves direct delivery of chemokines to the tumor microenvironment [16]. For example, gene therapy approaches have been explored to introduce genes encoding chemokines such as CXCL9 and CXCL10 into the TME. These chemokines attract CXCR3-expressing T cells and NK cells, which are highly effective at eliminating tumor cells.

This localized delivery strategy aims to create a chemokine gradient that recruits substantial numbers of anti-tumor immune cells to the tumor, effectively converting an immunologically "cold" tumor into an inflamed, "hot" tumor. Conversely, an alternative approach employs chemokine receptor antagonists to block recruitment of immunosuppressive cells. For instance, inhibitors targeting CCR4, CCR5, and CCR6 have been investigated to prevent regulatory T cell (Treg) migration to the TME, thereby reducing T cell suppression and enhancing anti-tumor immunity [17].

Clinical trials and successes in cytokine and chemokine therapy

Despite early setbacks, renewed interest in cytokine and chemokine therapies has emerged, particularly when used in combination with other treatment modalities. One promising strategy involves combining these agents with Immune Checkpoint Inhibitors (ICIs) [18,19]. The rationale is that cytokine pretreatment can increase Tumor-Infiltrating Lymphocytes (TILs), which can then be activated by ICIs that release inhibitory signals. For example, IL-2 has demonstrated improved response rates when combined with ICIs in certain malignancies.

Next-generation cytokine-based therapies currently in clinical trials include engineered cytokines with extended half-lives, fusion proteins combining cytokines with monoclonal antibodies for tumor-targeted delivery, and cytokines delivered via oncolytic viruses [20]. A notable example is talimogene laherparepvec (T-VEC), an oncolytic virus expressing GM-CSF, which has been approved for melanoma treatment and demonstrates the clinical potential of this approach. Similarly, chemokine receptor antagonists are undergoing clinical evaluation for various solid tumors, as summarized in Table 3 [21].

Table 3: Clinical trials using cytokine and chemokine therapy in cancer.

Therapeutic agent	Mechanism of action	Clinical trial phase	Indication	Key findings/Status
Recombinant IL-2 (Aldesleukin)	Activates T cells and NK cells	Approved	Metastatic melanoma, renal cell carcinoma	Approved but high toxicity limits use (Sever et al. 2019)
Recombinant IFN-α	Enhances anti-tumor immunity, inhibits proliferation	Approved	Hairy cell leukemia, melanoma	Approved but associated with severe side effects (Raman et al. 2007)
T-VEC (Talimogene laherparepvec)	Oncolytic virus expressing GM-CSF	Approved	Melanoma	Improves durable response rates, especially in combination (De Sanctis et al. 2016)
Bempegaldesleukin (NKTR-214)	"Prodrug" of IL-2 that selectively activates T cells	Phase 3	Melanoma, renal cell carcinoma	Designed to reduce systemic toxicity, but recent trials have shown mixed results (Gonzalez et al. 2018)
Anti-CCL2 monoclonal antibody	Blocks recruitment of macrophages to TME	Phase 2	Various solid tumors	In trials to reduce immunosuppressive cell infiltration (Kartikasari et al. 2021)
CXCR4 antagonist (e.g., AMD3100)	Blocks tumor cell proliferation and metastasis	Phase 1/2	Hematological and solid tumors	In trials to enhance chemo- and radiotherapy efficacy (Ozga et al. 2021)

Cytokine and chemokine modulation in neurodegenerative diseases

Targeting inflammation and immune reprogramming in Alzheimer's disease

The neuroinflammatory hypothesis of Alzheimer's Disease (AD) posits that chronic inflammation represents a major driver of disease progression, alongside the classical hallmarks of amyloid-beta plaques and neurofibrillary tangles [5]. Microglia and astrocytes primarily mediate this inflammatory process in AD through production of various pro-inflammatory cytokines, including TNF-alpha, IL-1-beta, and IL-6. Therapeutic strategies targeting AD aim either to reduce this chronic inflammatory state or to shift the microglial phenotype toward a more neuroprotective profile [22].

One approach involves neutralizing pro-inflammatory cytokines. TNF-alpha inhibitors, already approved for treating inflammatory conditions such as rheumatoid arthritis, have been evaluated in clinical trials for AD [23]. While early animal studies showed promise in reducing plaque burden and improving cognitive function, clinical trial results in human subjects have been inconsistent, with some studies showing minimal or no cognitive benefit. These challenges stem partly from the limited ability of these large molecules to cross the Blood-Brain Barrier (BBB) and the complex, context-dependent role that TNF-alpha plays in the CNS [24].

An alternative strategy leverages anti-inflammatory and neurotrophic cytokines. IL-4, for instance, induces an anti-inflammatory, pro-phagocytic M2 phenotype in microglia. Preclinical studies have demonstrated that CNS delivery of IL-4 reduces amyloid-beta load and improves synaptic function. Similarly, IL-13 and Granulocyte Colony-Stimulating Factor (G-CSF) are being investigated for their neuroprotective and neurogenic properties [25].

Cytokine and chemokine approaches in Parkinson's disease and multiple sclerosis

Parkinson's Disease (PD) involves progressive loss of dopaminergic neurons mediated by neuroinflammation, wherein activated microglia release pro-inflammatory cytokines and chemokines. Therapies aimed at modulating this inflammatory response are under active investigation [26]. For example, inhibition of the GM-CSF receptor has been explored as a strategy to reduce microglial activation. Additionally, considerable research in PD has focused on the neurotrophic cytokine Glial Cell Line-Derived Neurotrophic Factor (GDNF) [101]. Although GDNF has demonstrated efficacy in preclinical models, its clinical translation has been hindered by challenges in delivering this large protein to deep brain structures [20,27].

Multiple Sclerosis (MS), an autoimmune disease of the CNS characterized by T cell-mediated demyelination and neurodegeneration, has a more established history of cytokine-based therapies. Interferon-Beta (IFN-beta) has been a cornerstone MS treatment for decades [29]. Its mechanism of action is believed to be multifaceted, including suppression of pro-inflammatory cytokines, enhancement of anti-inflammatory cytokines, and inhibition of T cell proliferation and migration across the BBB. The chemokine receptor CCR6 has also emerged as a therapeutic target, as its inhibition could prevent pathogenic T Helper 17 (Th17) cell migration into the CNS, a process implicated in MS pathogenesis [30].

Challenges in therapeutic development for neurodegenerative diseases

Although cytokines and chemokines have been clearly implicated in neurodegenerative disease pathogenesis, translating these findings into effective therapeutics has proven challenging. The most significant obstacle is the Blood-Brain Barrier

(BBB), a highly selective semipermeable barrier that protects the brain from pathogens and potentially harmful blood-borne molecules [31]. While essential for brain homeostasis, the BBB severely restricts passage of large therapeutic molecules such as recombinant cytokines and monoclonal antibodies into the CNS. This limitation has compromised the efficacy of many promising agents in clinical trials for neurodegenerative diseases, as outlined in Table 4.

Table 4: Potential cytokine and chemokine targets in neurodegenerative diseases.

Therapeutic target	Mechanism of action	Disease	Clinical Trial Status	References
TNF-α	Neutralizes pro-inflammatory cytokine	Alzheimer's, Parkinson's	Mixed results in clinical trials due to BBB penetration and dual role	Altorki et al. 2019
IL-1β	Neutralizes pro-inflammatory cytokine	Alzheimer's, Parkinson's	Preclinical and early-phase clinical trials	Wang et al. 2017
GDNF	Promotes survival and function of dopaminergic neurons	Parkinson's	Clinical trials show limited success due to delivery challenges	Thunnissen et al. 2014
IFN-β	Modulates immune response, anti-inflammatory effects	Multiple Sclerosis	Approved for clinical use, a cornerstone therapy	Jackute et al. 2018
CCR2/5 antagonist	Blocks recruitment of immune cells to CNS	Alzheimer's, MS	Preclinical and early-phase clinical trials	Liu et al. 2019
IL-4/IL-13	Promotes anti-inflammatory M2 microglial phenotype	Alzheimer's	Preclinical studies show promise	Siegel et al. 2019

To circumvent this barrier, researchers are exploring alternative delivery methods, including intracerebroventricular injections, engineered nanocarriers, and cell-based therapies. Additional strategies involve bispecific antibodies that bind both a BBB receptor and the therapeutic target, effectively hitchhiking across the barrier. These next-generation delivery systems are fundamental to realizing the full therapeutic potential of cytokine and chemokine modulation in neurodegeneration [32].

Another major challenge lies in the complex, context-dependent nature of cytokines and chemokines. The same molecule may exert beneficial or detrimental effects depending on timing, location, and concentration. For instance, an initial pro-inflammatory response may be beneficial for clearing misfolded proteins, whereas sustained inflammation causes irreversible neuronal damage. Broad suppression of inflammation, while seemingly logical, may disrupt protective immune functions such as pathogen clearance or debris removal, potentially increasing vulnerability to other insults. Therefore, therapeutic modulation in neurodegeneration requires a nuanced approach that targets specific inflammatory pathways without causing global immune dysregulation [33,34].

Challenges and limitations of cytokine and chemokine therapy

Systemic toxicity and side effects in cancer treatment

While cytokine and chemokine modulation hold considerable therapeutic promise, significant obstacles have hindered clinical implementation, particularly regarding systemic toxicity and adverse effects. First-generation cytokine therapies, such as high-dose Interleukin-2 (IL-2) and Interferon-Alpha (IFN-alpha), exemplify these limitations [35]. Administration of these potent immune activators at therapeutic doses often triggers severe systemic inflammatory responses, resulting in narrow therapeutic windows.

Capillary leak syndrome, a life-threatening condition characterized by fluid extravasation, severe hypotension, and multi-organ dysfunction, commonly occurs in patients receiving high-dose IL-2. Similarly, IFN-alpha therapy is associated with debilitating flu-like symptoms, profound fatigue, and neurotoxicity, frequently necessitating dose reduction or treatment discontinuation [36].

The primary contributor to this systemic toxicity is immune cell activation throughout the body rather than selective activation at the tumor site [98]. Although more recent approaches, including fusion proteins and oncolytic viruses, aim to achieve localized delivery, the risks of off-target effects and systemic inflammatory responses remain substantial concerns. This underscores the critical need for advanced delivery systems and agents capable of selectively targeting pathological cell populations while sparing healthy tissues [37,38].

Context-dependent functions and immune system dysregulation in neurodegeneration

In neurodegenerative diseases, the challenges of cytokine and chemokine therapy are compounded by the delicate immune balance within the Central Nervous System (CNS). Individual molecules may exhibit dual or even multiple functions, with effects varying based on cellular context, disease stage, and local microenvironment [39]. A molecule may act as neuroprotective under certain conditions while proving neurotoxic in others. For instance, an initial pro-inflammatory response may prove beneficial for clearing misfolded protein aggregates, whereas chronic inflammation inevitably leads to irreversible neuronal damage [40].

Broad anti-inflammatory interventions, though seemingly rational, carry significant risks. Complete inhibition of major inflammatory cytokines such as TNF-alpha may compromise essential immune functions, including pathogen clearance and cellular debris removal, potentially increasing brain vulnerability to additional insults. Moreover, systemic immunosuppression could increase infection risk and impair tissue repair mechanisms. Consequently, therapeutic modulation in neurodegeneration demands precise, carefully calibrated approaches that target specific pathological inflammatory pathways while preserving physiological immune system functions [41].

Overcoming delivery challenges in cytokine and chemokine therapy

The Blood-Brain Barrier (BBB) represents one of the most formidable obstacles for therapeutic agents targeting the CNS. This highly selective semipermeable barrier protects the brain from bloodborne pathogens and potentially harmful molecules [42,48,55]. However, this protective function simultaneously prevents large therapeutic molecules, including recombinant

proteins and monoclonal antibodies, from reaching the CNS in therapeutically relevant concentrations. This limitation has severely restricted the clinical efficacy of numerous promising candidates in neurodegenerative disease trials [54].

To overcome this barrier, researchers are investigating innovative delivery strategies. These include nanocarrier systems engineered to transport therapeutic molecules across the BBB, as well as gene therapy and cell-based delivery approaches wherein genetically modified cells produce and secrete therapeutic cytokines or chemokines directly within the CNS [38]. Bispecific antibodies, designed to bind both BBB receptors and therapeutic targets, represent another promising strategy for facilitating transcytosis across the barrier. Additionally, focused ultrasound techniques can transiently disrupt the BBB, permitting enhanced drug penetration. These next-generation delivery platforms are essential for unlocking the full therapeutic potential of cytokine and chemokine modulation in neurodegenerative diseases, and their continued development represents a critical research priority [53].

Conclusion

This comprehensive review has illuminated the pivotal and multifaceted roles of cytokines and chemokines in both cancer and neurodegenerative diseases. These signaling molecules function not as passive mediators but as active orchestrators of immune reprogramming that fundamentally drives disease progression. In cancer, malignant cells co-opt these pathways to establish an immunosuppressive microenvironment, recruiting pro-tumorigenic cells while simultaneously suppressing anti-tumor immunity. Conversely, in neurodegeneration, dysregulated cytokine and chemokine signaling perpetuates chronic neuroinflammation, contributing to progressive neuronal damage and clinical deterioration.

We have examined diverse therapeutic approaches designed to modulate these pathways for clinical benefit, ranging from conventional recombinant cytokines to more sophisticated targeted therapies including monoclonal antibodies and small molecule inhibitors. While significant progress has been achieved, particularly in cancer immunotherapy, substantial challenges remain. Systemic toxicity continues to limit the therapeutic window of many cytokine-based therapies, while the blood-brain barrier poses a formidable obstacle for CNS-targeted interventions. Moreover, the context-dependent and often paradoxical functions of these molecules necessitate careful consideration of timing, dose, and delivery methods.

The future success of cytokine and chemokine-based therapies depends critically on addressing these key challenges. Priority research areas should include development of highly specific agents capable of distinguishing pathological from physiological signaling. Personalized medicine approaches, utilizing patient-specific biomarkers to tailor therapy and predict treatment response, will prove increasingly important. We anticipate continued advancement in sophisticated delivery systems, including engineered nanocarriers and cell-based therapies, to circumvent the blood-brain barrier and other delivery constraints.

Combination therapies, integrating cytokine and chemokine modulation with other immunotherapies such as immune checkpoint inhibitors or CAR-T cell therapy, represent particularly promising strategies with potential for synergistic effects. Additionally, temporal modulation strategies that account for disease stage and dynamic changes in the immune microenvironment may enhance therapeutic efficacy while minimizing adverse effects. Ultimately, success will require deeper understanding of the spatiotemporal complexity and context-specific nature of immune signaling networks.

Final remarks

The fields of cancer immunotherapy and neurodegeneration therapeutics are advancing at an unprecedented pace. While the path toward safe and effective treatments remains challenging, the potential to achieve therapeutic immune reprogramming through cytokine and chemokine modulation is increasingly tangible. As ongoing research continues to unravel the complexities of these signaling networks, we are approaching a new era of precision medicine capable of restoring appropriate immune balance to combat these devastating diseases. The integration of cutting-edge technologies, including artificial intelligence for biomarker discovery, advanced biomaterials for targeted delivery, and sophisticated imaging techniques for real-time monitoring, promises to accelerate progress toward this goal. With continued interdisciplinary collaboration and sustained research investment, cytokine and chemokine-based therapies hold substantial promise for transforming clinical outcomes in both cancer and neurodegenerative diseases.

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