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Review

Cytokine Storms and Silent Killers: Immune Dysregulation in Cancer Progression

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Abstract

Cytokines are central mediators of immune communication, orchestrating interactions between innate and adaptive immune cells. In cancer, dysregulated cytokine signaling drives chronic inflammation, immune suppression, and tumor progression. This narrative review synthesizes current mechanistic and clinical insights into cytokine dysregulation, explicitly distinguishing acute systemic cytokine release syndrome (CRS), often observed during CAR-T cell therapy, from chronic, tumor-localized cytokine amplification within the tumor microenvironment (TME). We discuss key signaling pathways including IL-6/STAT3, TNF-α/NF-κB, and TGF-β/SMAD highlighting context-, tumor-, and dose-dependent effects on epithelial-to-mesenchymal transition (EMT), therapy resistance, immune exhaustion, and angiogenesis. The review integrates translational evidence linking cytokine activity to tumor type, biomarkers, patient stratification, and outcomes from both successful and failed clinical trials. Conceptual schematics and tables provide visual summaries of cytokine interactions, immunosuppressive networks, and therapeutic targets. Limitations, including the non-novel nature of the mechanisms discussed, selective clinical coverage, and context-specific variability, are explicitly addressed. By consolidating mechanistic and clinical knowledge, this review offers a focused perspective on cytokine dysregulation, informing translational strategies to modulate the tumor immune landscape.

Keywords

Cytokine storm, Tumor microenvironment, Immune dysregulation, Cancer immunotherapy, Inflammation, Immune checkpoints

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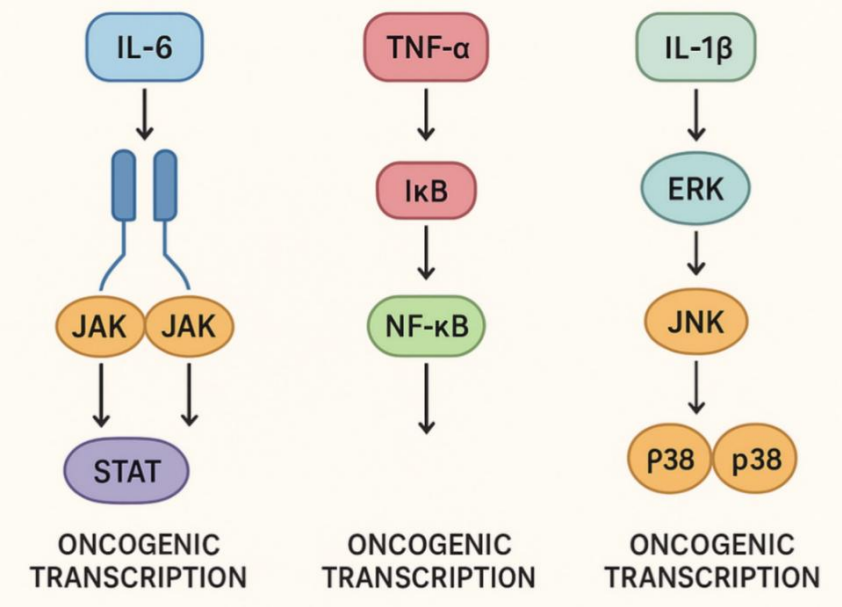
Graphical Abstract

A schematic summarizing cytokine storm mechanisms, immune dysregulation, and therapeutic strategies within the tumor microenvironment (TME), visually linking cytokine signaling, immune checkpoints, and targeted interventions. An overview of these major cytokine signaling pathways, illustrating how IL-6, TNF-α, and IL-1β converge on transcription factors to promote oncogenic transcription, inflammation, and tumor progression.



1. Introduction

Cytokines are pivotal mediators of immune communication, acting as soluble messengers that coordinate the activation, differentiation, and effector functions of immune and stromal cells across tissues. They form a dynamic signaling network that enables rapid and context-specific responses to infection, injury, and stress [1]. Through binding to their cognate receptors, cytokines initiate downstream signaling cascades such as the JAK/STAT, NF-κB, and MAPK pathways that modulate gene transcription essential for inflammation, immune cell recruitment, and tissue repair [2]. In a healthy physiological context, cytokine activity is tightly regulated through temporal control of synthesis, receptor desensitization, and negative feedback loops mediated by suppressors of cytokine signaling (SOCS) proteins [3]. This balance ensures that immune activation is sufficient to eliminate pathogens but restrained enough to prevent collateral tissue damage. However, disruption of this equilibrium can drive pathological immune activation, leading to excessive production of pro-inflammatory mediators such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). Such uncontrolled responses collectively termed a “cytokine storm” are characterized by systemic inflammation, vascular leakage, and multi-organ dysfunction [4].

While cytokine storms were first described in infectious diseases such as influenza and SARS-CoV, accumulating evidence suggests that chronic, low-grade cytokine dysregulation underlies numerous non-infectious pathologies, including autoimmunity, metabolic disorders, and cancer [5]. In the oncological setting, cytokine imbalance is both a driver and a consequence of tumor progression. Malignant cells, along with tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), remodel the cytokine landscape to create an immunosuppressive TME [6]. Within this TME, inflammatory cytokines such as IL-6, IL-8, and TNF-α stimulate pro-survival and angiogenic pathways, while immunosuppressive mediators like TGF-β and IL-10 inhibit cytotoxic T lymphocyte (CTL) and natural killer (NK) cell function [7]. For instance, IL-6 promotes STAT3 activation, leading to enhanced tumor cell proliferation, epithelial-to-mesenchymal transition (EMT), and resistance to apoptosis [8]. Likewise, TGF-β suppresses anti-tumor immunity by promoting Treg differentiation and inhibiting dendritic cell maturation [9]. These signaling dynamics illustrate how cytokine networks serve as a double-edged sword facilitating immune defense under homeostatic control yet promoting tumor survival when chronically dysregulated.

The concept of cytokine storms in cancer has expanded beyond systemic hyperinflammation to encompass local, self-perpetuating feedback loops within the TME. Here, tumor cells release cytokines that activate infiltrating immune cells, which in turn produce additional cytokines that further enhance tumor proliferation, angiogenesis, and immune escape [10,11]. This positive feedback mechanism transforms acute inflammatory responses into chronic, tumor-supportive inflammation a defining hallmark of cancer [12]. Persistent cytokine signaling also reprograms cellular metabolism, shifting immune cells toward glycolytic and immunosuppressive phenotypes that favor tumor progression [1]. Moreover, emerging studies reveal that oncogenic mutations can directly modulate cytokine expression. Mutant RAS and MYC, for example, induce IL-6 and IL-1β production, thereby coupling oncogenic signaling with chronic inflammation [13,14].

Similarly, aberrant NF-κB activation in malignant cells leads to sustained secretion of TNF-α and chemokines that recruit immunosuppressive myeloid cells [15]. These interactions establish a self-reinforcing inflammatory circuit linking tumor-intrinsic genetic changes with extrinsic immune dysregulation.

Importantly, cytokine dysregulation contributes not only to tumor progression but also to immune-related adverse effects during therapy. Cytokine release syndrome (CRS), a life-threatening condition observed in CAR-T cell therapy and immune checkpoint blockade, exemplifies the double-edged nature of cytokine-mediated immunity [16,17]. Therapeutic interventions targeting IL-6R (e.g., tocilizumab) have demonstrated clinical efficacy in mitigating CRS while preserving anti-tumor activity, highlighting the therapeutic potential of selectively modulating cytokine pathways [18].

Cytokines occupy a pivotal position at the crossroads of immunity, inflammation, and cancer. Their dysregulation orchestrates a complex interplay between tumor-promoting inflammation and immune suppression, influencing disease trajectory and treatment response. Understanding and precisely targeting chronic cytokine dysregulation offers a promising path toward reprogramming the tumor immune landscape and improving the efficacy of cancer immunotherapies, transforming these persistent inflammatory processes from deleterious drivers into actionable therapeutic targets.

Therefore, cytokines occupy a pivotal position at the crossroads of immunity, inflammation, and cancer. Their dysregulation orchestrates a complex interplay between tumor-promoting inflammation and immune suppression, influencing disease trajectory and treatment response. This review aims to provide an integrative perspective on cytokine-mediated immune dysregulation in cancer progression. Specifically, it explores (i) the mechanistic basis of cytokine storms and their role in shaping the TME, (ii) the crosstalk between cytokine signaling and oncogenic pathways, (iii) the dual roles of cytokines in tumor promotion and immune activation, and (iv) therapeutic strategies aimed at restoring cytokine balance. By understanding these mechanisms, we can design targeted interventions to reprogram the tumor immune milieu transforming cytokine storms from silent killers into therapeutic allies in cancer immunotherapy.

In the context of cancer, the term “cytokine storm” must be applied with conceptual precision. Acute systemic cytokine storms, also referred to as CRS, represent rapid-onset, high-intensity inflammatory responses characterized by elevated circulating cytokines such as IL-6, TNF-α, and IFN-γ, most commonly observed during immunotherapies including CAR-T cell therapy and immune checkpoint blockade. In contrast, tumor-associated cytokine dysregulation is typically chronic and localized within the TME where persistent oncogenic signaling and immune cell reprogramming generate self-sustaining cytokine amplification loops that promote immune suppression, angiogenesis, and tumor progression rather than systemic organ dysfunction. Distinguishing between acute systemic cytokine storms and chronic intratumoral cytokine imbalance is essential for accurate mechanistic interpretation and for the rational design of cytokine-targeted therapeutic strategies in oncology.

2. The Cytokine Storm Phenomenon: Mechanisms and Molecular Drivers

The term cytokine storm describes an excessive and uncontrolled release of pro-inflammatory cytokines that overwhelms normal immune regulatory mechanisms. Although first characterized in infectious diseases such as avian influenza, Ebola, and SARS-CoV, this phenomenon has since been recognized as a pathophysiological process underlying various non-infectious conditions, including autoimmune disorders, sepsis, and cancer [19,20]. Cytokine storms are driven by dysregulated immune activation involving both innate and adaptive immune cells, leading to a self-perpetuating inflammatory cascade that results in widespread tissue injury, metabolic dysfunction, and immune exhaustion.

In the context of cancer, cytokine dysregulation differs fundamentally from acute, infection-driven cytokine storms. While therapy-induced CRS represents a systemic, rapid-onset hyperinflammatory response, tumor-associated cytokine alterations are typically chronic, localized within the TME, and driven by persistent oncogenic signaling and immune cell reprogramming. These chronic cytokine amplification loops sustain inflammation, promote immune evasion, and support tumor progression. Throughout this review, we use “cytokine storm” primarily to describe extreme therapy-induced events, while localized, tumor-driven cytokine dysregulation is framed as chronic amplification to reflect mechanistic and clinical distinctions.

At the molecular level, the initiation of a cytokine storm begins with the activation of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) [21-24], RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs) [25], which detect pathogen-associated or damage-associated molecular patterns (PAMPs and DAMPs) [16,26]. Engagement of these receptors triggers downstream activation of transcription factors such as NF-κB, AP-1, and IRF3, which collectively drive the transcription of pro-inflammatory cytokine genes, including IL-1β, IL-6, TNF-α, IL-12, and IFN-γ [27,28]. Under physiological conditions, this activation is transient and tightly regulated. However, when these pathways are continuously stimulated by chronic infection, tissue necrosis, or tumor-derived danger signals cytokine production becomes sustained, resulting in a vicious cycle of inflammation and tissue injury [29,30].

A key amplifier of cytokine storms is the IL-6/JAK/STAT3 signaling axis, which functions as both a pro-inflammatory driver and a promoter of tumor progression [31,32]. IL-6 activates Janus kinases (JAKs) that phosphorylate and activate STAT3, a transcription factor that upregulates genes involved in survival, angiogenesis, and proliferation [33]. In turn, activated STAT3 promotes further IL-6 transcription, establishing a positive feedback loop that sustains cytokine

overproduction and immune cell hyperactivation. In the TME [34], this loop supports malignant cell growth, inhibits apoptosis, and contributes to immune suppression by promoting the differentiation of MDSCs and Tregs [35,36]. Another central mediator is TNF-α, a pleiotropic cytokine that, when chronically elevated, triggers NF-κB activation, endothelial dysfunction, and necroptotic cell death, thereby perpetuating local and systemic inflammation [37-39]. Persistent TNF-α signaling promotes cancer-related inflammation by inducing reactive oxygen species (ROS) production, DNA damage, and genomic instability, which together accelerate tumor initiation (Colotta et al., 2009). Similarly, IL-1β, produced via activation of the NLRP3 inflammasome, amplifies cytokine cascades by stimulating IL-6 and TNF-α production, reinforcing a chronic inflammatory milieu that favors tumor growth and invasion [40,41].

During a cytokine storm, innate immune cells particularly macrophages, dendritic cells, and neutrophils play a central role as both producers and responders of cytokines. Activated macrophages, for instance, release IL-1β, TNF-α, and IL-6, which further activate neighboring immune cells in an autocrine and paracrine manner [42,43]. Activated dendritic cells secrete IL-12 and type I interferons that drive T-helper (Th1) differentiation and IFN-γ production, which in turn stimulates additional macrophage activation, creating a feed-forward inflammatory loop [11]. Neutrophil extracellular traps (NETs), formed during this hyperactivation, contribute to vascular damage and promote metastasis by trapping circulating tumor cells [44]. The adaptive immune system further amplifies cytokine storms through sustained T-cell and NK-cell activation. Continuous T-cell receptor (TCR) engagement and cytokine signaling lead to uncontrolled production of IFN-γ, IL-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Figure 1), which maintain macrophage activation and inflammation [1,27]. This uncontrolled cytokine signaling eventually results in immune exhaustion, characterized by increased expression of inhibitory receptors (PD-1, LAG-3, TIM-3) and loss of effector function [3]. In cancer, such exhaustion is paradoxical: while chronic cytokine stimulation fuels tumor-supportive inflammation, it also blunts anti-tumor immunity, creating a dual-edged scenario that benefits tumor persistence [45,46].

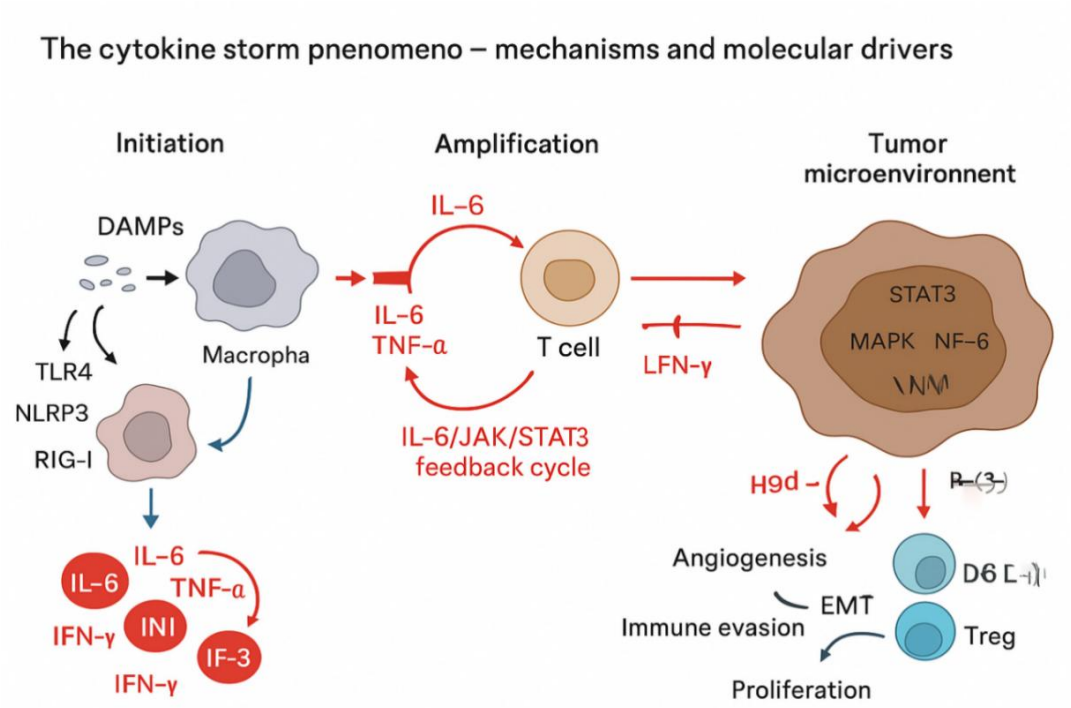


Figure 1. Mechanistic overview of chronic cytokine amplification in cancer.

This figure illustrates how tumor-intrinsic oncogenic mutations (e.g., KRAS, MYC, TP53 loss) initiate sustained cytokine production, activating key signaling pathways such as IL-6/JAK/STAT3 and NF-κB. The resulting chronic cytokine amplification loops promote immune cell reprogramming, including TAM, MDSC, and Treg recruitment, leading to immunosuppression, angiogenesis, and enhanced tumor progression. Arrows indicate feedback loops reinforcing the tumor-supportive microenvironment.

Cytokine storms in the context of tumor biology differ from those observed in acute infections in several critical ways. In cancer, cytokine hyperactivation is often localized rather than systemic and is driven by persistent oncogenic stress and tissue remodeling rather than acute pathogen invasion [47,48]. Tumor-derived cytokines, such as IL-6, IL-8, VEGF, and CXCL12, recruit immunosuppressive myeloid and stromal cells into the TME, where they further amplify cytokine signaling [36]. This establishes a chronic, tumor-promoting inflammatory niche that supports angiogenesis, metastasis, and therapy resistance [49]. Moreover, tumor cells themselves exhibit aberrant cytokine receptor expression and intracellular signaling, rendering them responsive to inflammatory cues. For example, IL-6/STAT3 signaling confers resistance to chemotherapy by upregulating anti-apoptotic genes such as BCL-XL and MCL-1 [50,51]. Likewise, TNF-α and IL-1β signaling promote EMT and invasiveness by inducing transcription factors like SNAIL and TWIST [52]. Thus,

cytokine storms in cancer represent not a transient hyperimmune response but a chronic, self-sustaining inflammatory network that continuously feeds tumor evolution.

Importantly, the cross-talk between oncogenic pathways and cytokine signaling acts as a molecular driver of this storm-like state. Mutant KRAS and MYC, for example, induce autocrine IL-6 secretion, which activates STAT3 and NF-κB pathways, reinforcing oncogenic transcription programs. Similarly, TP53 loss promotes NF-κB activation and cytokine secretion, fostering a pro-inflammatory TME [11,53,54]. These interactions blur the line between inflammation-driven oncogenesis and oncogene-driven inflammation, suggesting that cytokine storms and tumor evolution are mechanistically intertwined. In summary, cytokine storms arise from an imbalance between immune activation and regulation, perpetuated by interlocking feedback circuits involving innate sensors, transcriptional regulators, and cytokine networks. In cancer, this dysregulation becomes chronic, rewiring the immune landscape to favor tumor survival, angiogenesis, and immune evasion. Understanding the molecular drivers of cytokine storms particularly the convergence of NF-κB, STAT3, and inflammasome pathways is essential for developing targeted therapies that restore cytokine homeostasis without compromising immune surveillance.

3. Cytokine Imbalance in the TME

The TME represents a dynamic ecosystem composed of tumor cells, immune infiltrates, fibroblasts, endothelial cells, and extracellular matrix components. This complex milieu is sustained by an intricate cytokine network that dictates the balance between immune activation and suppression [7,16,55]. Under normal physiological conditions, cytokines mediate transient inflammatory responses to eliminate damaged or transformed cells. However, in cancer, this balance is disrupted, leading to persistent cytokine secretion that fosters tumor survival, angiogenesis, and immune evasion [56].

3.1 Cytokine Manipulation by Tumor Cells

Tumor cells actively reprogram cytokine signaling to create an immunosuppressive and pro-tumorigenic environment. They secrete a wide range of cytokines, including IL-6, transforming growth factor-beta (TGF-β), interleukin-10 (IL-10), vascular endothelial growth factor (VEGF), and GM-CSF, each contributing to tumor progression through distinct but overlapping mechanisms [28,46,57-61]. Among these, IL-6 is a key driver of tumor-promoting inflammation. Produced by both tumor cells and TAMs, IL-6 binds to its receptor complex (IL-6R/gp130) to activate the JAK/STAT3 signaling pathway [6,62-64]. This leads to transcription of genes involved in proliferation, survival, and angiogenesis [55,65-68]. Sustained STAT3 activation also promotes EMT, enhancing metastatic potential. Furthermore, IL-6 induces VEGF production, stimulating endothelial cell proliferation and neovascularization within the TME [69-74]V(Karin & Clevers, 2016).

Cytokine signaling in cancer is highly context-dependent and varies across tumor types, stages, and microenvironmental conditions. While many cytokines contribute to tumor progression by promoting proliferation, angiogenesis, and immune suppression, their effects are not universal across all malignancies. The functional outcome of cytokine activity depends on tumor genetics, cellular composition of the TME, and the balance between pro- and anti-inflammatory signals. Recognizing this heterogeneity is essential for accurately interpreting cytokine biology and for designing effective, tumor-specific therapeutic strategies.

TGF-β, another central cytokine in the TME, exerts paradoxical roles suppressing tumor growth in early stages but promoting invasion and metastasis in advanced disease [75]. TGF-β signaling induces EMT through upregulation of transcription factors such as SNAIL, ZEB1, and TWIST, enabling epithelial cells to acquire migratory and invasive properties [76,77]. Concurrently, TGF-β suppresses cytotoxic T cell and NK cell functions by downregulating perforin and granzyme B, thereby allowing tumor immune evasion [33]. It also facilitates the differentiation of naïve $CD4^+$ T cells into Tregs, which produce IL-10 and further suppress anti-tumor immunity [1,78,79]. IL-10 plays a critical immunosuppressive role within the TME. While transient IL-10 production helps resolve inflammation, chronic IL-10 secretion by tumor cells, TAMs, and Tregs inhibits dendritic cell maturation and antigen presentation, thereby dampening T-cell priming [1,80-82]. IL-10 signaling via STAT3 further induces expression of PD-L1 on macrophages and tumor cells, leading to T-cell exhaustion [29,49,58,83]. This cytokine acts as a "molecular silencer," ensuring that the immune system remains tolerant to tumor antigens. VEGF, although primarily recognized for its angiogenic functions, also contributes to immunosuppression by inhibiting dendritic cell differentiation and promoting Treg accumulation [84]. Additionally, GM-CSF secreted by tumor and stromal cells recruits MDSCs, which inhibit T-cell activation via arginase-1 and nitric oxide synthase [7,55]. Collectively, these cytokines establish a permissive environment where immune escape, metabolic reprogramming, and angiogenesis proceed in concert.

3.2 Immunosuppressive Cellular Networks: TAMs, MDSCs, and Tregs

The sustained presence of immunosuppressive cytokines supports the recruitment and polarization of suppressive immune subsets. TAMs, MDSCs, and Tregs are principal architects of this immunosuppressive network, orchestrating immune evasion through cytokine-driven crosstalk [59,62,85,86]. TAMs in the TME predominantly acquire an M2-like phenotype under the influence of IL-10 and TGF-β. These M2 macrophages secrete high levels of IL-6, CCL22, and VEGF, promoting tissue remodeling, angiogenesis, and Treg recruitment . Their expression of arginase-1 depletes L-arginine,

impairing T-cell proliferation and activation [87-89]. TAMs also express PD-L1, contributing to T-cell exhaustion and resistance to checkpoint blockade therapies.

MDSCs, derived from immature myeloid cells, are recruited by GM-CSF, IL-6, and prostaglandin E2 (PGE2). Once within the TME, they release IL-10 and TGF-β, further suppressing cytotoxic T-cell responses . MDSCs promote tumor progression by inducing oxidative stress, inhibiting antigen presentation, and facilitating EMT through secretion of matrix metalloproteinases (MMP9) [1,80,90]. Tregs, characterized by the expression of FOXP3, are expanded in tumors through IL-2 and TGF-β signaling. They suppress effector T-cell responses via IL-10 and TGF-β production, as well as through direct cell contact-dependent mechanisms involving CTLA-4 and PD-1. Notably, Tregs enhance the differentiation of TAMs and MDSCs, completing a cytokine feedback circuit that locks the TME in an immunosuppressive state [91]. Together, these cell types and cytokine circuits sculpt the tumor niche into a "cold" immune environment, refractory to T-cell infiltration and resistant to immunotherapy. This cytokine-driven suppression forms one of the principal barriers to effective anti-tumor immunity.

3.3 Integrative Model and Therapeutic Perspectives

Cytokine imbalance within the TME represents both a hallmark of tumor progression and a promising therapeutic target. Blocking IL-6 or TGF-β signaling has shown efficacy in preclinical models, restoring T-cell infiltration and sensitizing tumors to immune checkpoint inhibitors [16,92,93]. Similarly, strategies targeting GM-CSF or IL-10 pathways can reprogram MDSCs and macrophages toward anti-tumor phenotypes. However, due to the pleiotropic nature of cytokines, combinatorial therapies that selectively modulate, rather than completely inhibit, cytokine signaling may provide better therapeutic outcomes with fewer side effects (Figure 2) [3,54] (Table 1).

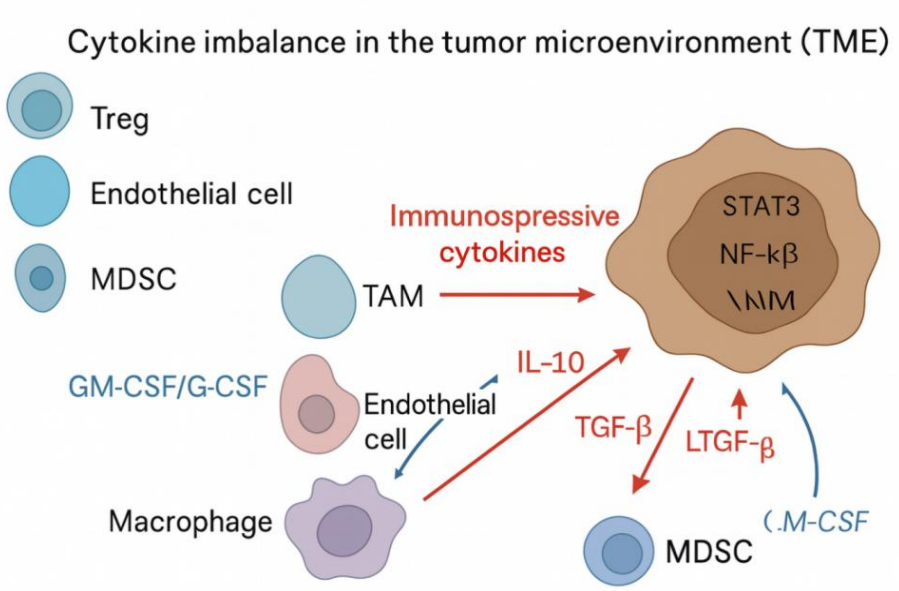


Figure 2. Cytokine imbalance and immunosuppressive networks in the TME.

This figure depicts the major cytokines (IL-6, IL-10, TGF-β, VEGF, GM-CSF) secreted by tumor and stromal cells and their effects on immunosuppressive cellular subsets (TAMs, MDSCs, Tregs). It emphasizes how overlapping cytokine pathways converge to inhibit cytotoxic T-cell function, promote immune evasion, and sustain chronic inflammation within the TME.

Table 1. Cytokines associated with immunosuppression and tumor progression.

Cytokine	Major Cellular Sources	Effect on TME	Key References
IL-6	Tumor cells, macrophages	Activates JAK/STAT3 pathway; promotes angiogenesis and survival	[1,94,95]
TGF-β	Tregs, fibroblasts, tumor cells	Induces EMT, promotes immune evasion and fibrosis	[29,96-98]
IL-10	Tumor cells, TAMs, Tregs	Inhibits antigen presentation, enhances PD-L1 expression	[62,83,99,100]
TNF-α	Macrophages, stromal cells	Promotes chronic inflammation, genomic instability	[46,101]
VEGF	Tumor and stromal cells	Induces angiogenesis, inhibits dendritic cell function	[62,102-104]
GM-CSF	Tumor cells, fibroblasts	Recruits and activates MDSCs, suppresses T-cell immunity	[7,96]

This table summarizes the key cellular sources, functional roles, and clinical relevance of major tumor-associated cytokines, integrating information across cancer types. It highlights dual and context-dependent roles of cytokines and identifies actionable pathways for potential therapeutic targeting.

4. Cytokine Signaling Pathways in Cancer Progression

Cytokine signaling plays a pivotal role in cancer progression by modulating cell proliferation, survival, angiogenesis, and metastasis. Among the myriad of signaling cascades, the JAK/STAT, NF-κB, and MAPK pathways are particularly critical in driving oncogenic processes [2,105,106]. The JAK/STAT pathway is primarily activated by cytokines such as IL-6 and IL-10. Binding of cytokines to their respective receptors triggers the phosphorylation of JAKs, which in turn phosphorylate Signal Transducers and Activators of Transcription (STATs). Activated STATs dimerize and translocate into the nucleus, where they induce transcription of genes involved in cell proliferation, survival, and anti-apoptotic responses. Dysregulation of this pathway, often through persistent IL-6 signaling or mutations in JAK/STAT components, is linked to tumorigenesis in multiple cancers, including hematological malignancies and solid tumors [107-109].

The NF-κB signaling pathway, typically activated by pro-inflammatory cytokines such as TNF-α and IL-1β, orchestrates transcription of genes regulating inflammation, cell survival, and metastasis [110-112]. Chronic NF-κB activation contributes to a pro-tumorigenic microenvironment by promoting angiogenesis, epithelial-mesenchymal transition (EMT), and immune evasion [10,52]. The MAPK pathway, involving ERK, JNK, and p38 kinases, mediates responses to growth factors and stress stimuli. Cytokine-mediated MAPK activation can drive proliferation and survival, while also enhancing invasive behavior and metastasis. An important aspect of cytokine signaling in cancer is the cross-talk with oncogenic mutations. For example, mutant KRAS can upregulate IL-6 production, creating a positive feedback loop (KRAS-IL-6 loop) that sustains STAT3 activation . Similarly, oncogenic MYC amplifies TNF-α-NF-κB signaling, promoting chronic inflammation and tumor progression. Such interactions highlight the intertwined nature of genetic alterations and cytokine-driven signaling in the TME.

IL-6 and TNF-α are central mediators of tumor-promoting inflammation, primarily through activation of the STAT3 and NF-κB pathways, respectively. IL-6 binds to IL-6R/gp130, triggering JAK-mediated phosphorylation of STAT3, which upregulates genes involved in proliferation, survival, and immune suppression. Persistent STAT3 activation also enhances Treg differentiation, VEGF production, and therapy resistance. Similarly, TNF-α activates NF-κB, promoting chronic inflammation, EMT, and recruitment of immunosuppressive myeloid cells. Rather than discussing these pathways separately in multiple sections, we now present them together to illustrate their interdependent roles in sustaining a pro-tumorigenic microenvironment, emphasizing context-dependent effects and feedback interactions.

5. Cytokine Storms and Cancer-Associated Systemic Syndromes

While cytokines are essential for immune defense, their dysregulated overproduction can lead to systemic syndromes that significantly impact cancer patients. Cytokine storms, characterized by massive release of pro-inflammatory cytokines, are implicated in cancer-associated cachexia, paraneoplastic syndromes, and sepsis-like manifestations [3,20,113,114]. Cachexia, a debilitating syndrome marked by weight loss and muscle wasting, is driven in part by TNF-α, IL-1β, and IL-6, which induce catabolic pathways in muscle and adipose tissue [115-117]. Similarly, paraneoplastic syndromes ranging from fever and fatigue to neurological disorders often result from aberrant cytokine production by tumors or immune cells [1,99,118,119].

The advent of immunotherapies, particularly CAR-T cell therapy and immune checkpoint inhibitors, has brought attention to therapy-induced cytokine storms, also termed CRS. CRS occurs when rapid activation of immune effector cells triggers excessive cytokine secretion, leading to high fevers, hypotension, and multi-organ dysfunction [59,120-124]. Interestingly, the pathological features of therapy-induced CRS closely mirror the systemic effects observed in tumor-driven cytokine dysregulation, highlighting a continuum between endogenous and treatment-related hyperinflammation. Understanding the mechanisms underlying cytokine storms in cancer is crucial not only for improving therapeutic safety but also for identifying potential interventions to modulate excessive cytokine activity without compromising anti-tumor immunity [45].

6. The Dual Role of Cytokines: Anti-Tumor Immunity vs Tumor Promotion

Cytokines exhibit context-dependent effects, acting either as mediators of anti-tumor immunity or as facilitators of tumor progression. This duality is particularly evident for cytokines such as IFN-γ, TNF-α, and IL-2, whose functions vary depending on concentration, timing, and the TME. IFN-γ is central to CTL activation, enhancing antigen presentation and inhibiting tumor cell proliferation [7,62,125-127]. However, chronic IFN-γ signaling can induce expression of immune checkpoints such as PD-L1, driving T-cell exhaustion and facilitating immune evasion. TNF-α, originally identified for its tumor necrosis-inducing properties, can paradoxically promote tumorigenesis under conditions of persistent inflammation [128-130]. Through NF-κB activation, TNF-α contributes to chronic inflammatory signaling, angiogenesis, and EMT, fostering a microenvironment conducive to cancer progression.IL-2 is essential for T-cell proliferation and maintenance of cytotoxic responses. Nonetheless, sustained IL-2 signaling can expand Tregs within the TME, suppressing

effective anti-tumor immunity and promoting tumor tolerance. Table 2 summarizes the dual functional roles of these cytokines, illustrating the delicate balance between protective immunity and pathological consequences in cancer. This duality underscores the need for precise therapeutic modulation of cytokine activity to maximize anti-tumor effects while minimizing immune-related toxicity.

Table 2. Dual functional roles of cytokines in tumor immunity.

Cytokine	Anti-Tumor Role	Tumor-Promoting Role	Mechanism
IFN-γ	Activates CTLs, inhibits proliferation	Induces PD-L1, immune exhaustion	JAK/STAT1
TNF-α	Promotes apoptosis	Enhances chronic inflammation	NF-κB
IL-2	Supports T-cell proliferation	Expands Tregs in TME	STAT5

This table compares anti-tumor and tumor-promoting effects of selected cytokines (IFN-γ, TNF-α, IL-2), illustrating context-dependent outcomes mediated by signaling pathways (JAK/STAT, NF-κB, STAT5). It emphasizes unresolved controversies and highlights implications for therapy design.

7. Cytokine-Immune Checkpoint Crosstalk

The interplay between cytokines and immune checkpoints represents a critical mechanism by which tumors evade immune surveillance. Immune checkpoints such as PD-1, CTLA-4, and LAG-3 function to restrain T-cell activity, preventing excessive immune responses [21,28,57,131,132]. However, tumors exploit these pathways, often in combination with cytokine signaling, to suppress anti-tumor immunity [133]. IL-6 and TGF-β are key cytokines driving this immunosuppressive crosstalk [134-136]. IL-6, through JAK/STAT3 signaling, induces PD-L1 expression on both tumor and immune cells, leading to T-cell exhaustion and impaired cytotoxic responses. Similarly, TGF-β signals via the SMAD pathway, contributing to immune evasion by promoting Treg expansion and suppressing effector T-cell function [6,74,122,137]. This dual regulation of immune checkpoints by cytokines not only facilitates tumor progression but also reduces the efficacy of checkpoint blockade therapies. Given this interplay, combination strategies targeting both cytokines and immune checkpoints are emerging as promising approaches. Clinical trials are investigating IL-6 or TGF-β inhibitors together with PD-1/PD-L1 or CTLA-4 blockade, aiming to overcome resistance and enhance anti-tumor immunity [86,99,133,138,139].

Cytokine-targeted therapies have demonstrated limited success as monotherapies largely due to the redundancy and plasticity of inflammatory signaling networks within the TME. Inhibition of a single cytokine axis, such as IL-6/JAK/STAT3 or TNF-α/NF-κB, often results in compensatory activation of parallel pathways that sustain immunosuppression and tumor survival. Moreover, intratumoral heterogeneity and dynamic immune adaptation further attenuate the durability of response. These limitations underscore the rationale for combination strategies, in which cytokine blockade is integrated with immune checkpoint inhibitors, targeted oncogenic pathway inhibitors, or anti-angiogenic therapies to simultaneously disrupt interconnected pro-tumorigenic circuits and enhance anti-tumor immunity.

Although both CAR-T-associated CRS and cancer-associated cytokine dysregulation involve elevated cytokine levels, their underlying pathophysiology differs fundamentally. CAR-T-associated CRS represents an acute, systemic inflammatory reaction initiated by rapid activation and expansion of adoptively transferred T cells, followed by secondary amplification through monocytes and macrophages that release large quantities of IL-6, IL-1β, and IFN-γ, often leading to fever, hypotension, and multi-organ dysfunction. In contrast, cancer-associated cytokine dysregulation is a chronic and predominantly localized process within the TME, driven by persistent oncogenic signaling and reciprocal interactions among tumor cells, TAMs, MDSCs, and Tregs. This chronic cytokine imbalance promotes immune suppression, angiogenesis, and tumor progression rather than acute systemic toxicity. Recognizing these mechanistic differences is critical for interpreting inflammatory signatures in cancer and for designing therapeutic strategies that selectively modulate cytokine pathways without compromising antitumor immunity.

8. Therapeutic Targeting of Cytokine Dysregulation in Cancer

Targeting cytokine dysregulation offers a rational approach to modulate the TME and improve therapeutic outcomes. Current strategies include neutralizing antibodies, receptor antagonists, and small-molecule inhibitors. Anti-IL-6 therapies (e.g., tocilizumab) block IL-6 receptor-mediated JAK/STAT3 signaling and are clinically approved for managing CAR-T therapy-induced CRS [140,141]. Anti-TNF therapies (e.g., infliximab, etanercept) neutralize TNF-α, mitigating chronic inflammation and associated tumor-promoting effects [142,143]. TGF-β inhibitors (e.g., galunisertib) interfere with SMAD signaling, reducing immunosuppression and fibrotic remodeling in the TME. JAK inhibitors target downstream signaling of multiple cytokines, limiting hyperactivation of pro-tumor pathways [32]. Emerging trends in cytokine modulation include bispecific antibodies that simultaneously block cytokines and checkpoint molecules, cytokine traps that sequester multiple cytokines, and nanoparticle-mediated cytokine delivery, enabling spatial and temporal control of immune modulation. The main challenge in cytokine-targeted therapy remains balancing anti-tumor immunity with safety, as excessive inhibition can impair protective immune responses (Table 3).

Table 3. Summarizes selected clinical interventions targeting cytokine signaling in cancer.

Cytokine	Primary Cellular Sources	Functional Role in Cancer	Dual / Context-Dependent Effects	Therapeutic Relevance / Actionable Pathways
IL-6	Tumor cells, TAMs, T cells	Promotes proliferation, angiogenesis, survival	Sustained STAT3 activation drives tumor growth; transient IL-6 can support anti-tumor immunity	Targetable via IL-6/IL-6R blockade (e.g., tocilizumab); JAK/STAT3 inhibitors
TGF-β	Tumor cells, Tregs, fibroblasts	Induces EMT, immune suppression, fibrosis	Tumor-suppressive in early stages, tumor-promoting in advanced disease	TGF-βR inhibitors (e.g., galunisertib); modulates Treg expansion
IL-10	TAMs, Tregs, tumor cells	Immunosuppressive, inhibits antigen presentation	Can resolve inflammation but chronic IL-10 promotes T-cell exhaustion	Potential target in combination with checkpoint inhibitors
TNF-α	Macrophages, stromal cells	Drives chronic inflammation, genomic instability	Acute TNF-α may induce apoptosis; chronic elevation promotes tumor progression	TNF inhibitors (e.g., etanercept, infliximab) under investigation
IFN-γ	CTLs, NK cells, Th1 cells	Enhances antigen presentation, CTL activation	Chronic signaling induces PD-L1, T-cell exhaustion	Considered in immunotherapy modulation; timing and dosing critical
VEGF	Tumor and endothelial cells	Angiogenesis, immune suppression	Promotes vessel formation but may enhance immune cell infiltration when normalized	Anti-angiogenic therapy (e.g., bevacizumab)
GM-CSF	Tumor cells, fibroblasts	Recruits MDSCs, supports tumor immune evasion	Low levels enhance DC function; high levels suppress T cells	Potential target to reprogram MDSCs and enhance immunotherapy

Key Takeaways:

- ✓ Chronic cytokine amplification in the TME is tumor-promoting, but effects are highly context-dependent.
- ✓ IL-6, TGF-β, and TNF-α represent the most clinically actionable pathways.
- ✓ IL-10 and IFN-γ illustrate unresolved duality and require careful consideration in therapy design.
- ✓ Targeting cytokine pathways should consider tumor type, disease stage, and immune context.

In order to clarify the distinctions between acute systemic cytokine storms and chronic tumor-associated cytokine dysregulation, we provide a comparative overview in Table X. Infection-induced CRS, including CAR-T therapy-related events, is characterized by rapid-onset, systemic hyperinflammation driven by activated T cells and myeloid cells, often resulting in fever, hypotension, and multi-organ dysfunction. In contrast, cancer-associated cytokine dysregulation represents a chronic, localized process within the TME, sustained by reciprocal interactions among tumor cells, TAMs, MDSCs, and Tregs. These differences in trigger, timing, localization, and cellular mediators underscore the importance of context-specific mechanistic interpretation and therapeutic targeting of cytokine pathways in oncology (Table 4).

Table 4. Comparison of infection-induced CRS vs cancer-associated cytokine dysregulation.

Feature	Infection-Induced Cytokine Storm (CRS)	Cancer-Associated Cytokine Dysregulation
Trigger	Acute infection or immunotherapy (e.g., CAR-T cells, checkpoint inhibitors)	Chronic tumor-intrinsic signaling and TME interactions
Onset	Rapid, hours to days	Slow, persistent over weeks to months
Localization	Systemic	Primarily localized within the TME
Key Cytokines	IL-6, IL-1β, IFN-γ, TNF-α (high systemic levels)	IL-6, TGF-β, IL-10, VEGF, GM-CSF (local gradients)
Clinical Manifestations	Fever, hypotension, organ dysfunction, vascular leakage	Immune suppression, tumor progression, therapy resistance
Immune Cell Involvement	Activated T cells, NK cells, monocytes/macrophages	Tumor cells, TAMs, MDSCs, Tregs
Duration	Transient, resolves with intervention or immune adaptation	Chronic, self-sustaining
Pathophysiology	Acute hyperactivation of innate and adaptive immune responses	Persistent cytokine amplification loops, immune exhaustion, pro-tumor inflammation
Therapeutic Considerations	Cytokine blockade (e.g., tocilizumab), corticosteroids, supportive care	Targeted modulation of TME cytokines, checkpoint inhibitors, combinatorial approaches

9. Emerging Technologies for Cytokine Profiling and Single-Cell Immunomics

Advances in single-cell RNA sequencing, spatial transcriptomics, and multiplex cytokine profiling are revolutionizing the understanding of cytokine heterogeneity within the TME [144-146]. These technologies allow mapping of cytokine production at the resolution of individual cells, revealing the complex network of immune and stromal cell interactions that drive tumor progression and immune evasion [62]. Spatial transcriptomics enables localization of cytokine-producing cells, providing insight into microenvironmental niches of immune suppression or activation [147]. Multiplex cytokine assays allow simultaneous quantification of dozens of cytokines, helping delineate signatures associated with therapy response or resistance [62]v. Moreover, computational modeling and AI-driven approaches are increasingly applied to predict cytokine-immune cell dynamics and identify optimal intervention points for targeted therapy [1,5,60]. Integration of multi-omics datasets combining transcriptomic, proteomic, and spatial information offers a systems-level understanding of cytokine networks and therapeutic vulnerabilities [148-151].

In revising this review, emphasis has been placed on integrating landmark mechanistic and clinical oncology studies that directly define the roles of cytokine signaling and immune regulation in cancer progression and therapy response. Primary research articles elucidating pathways such as IL-6/JAK/STAT3, TNF-α/NF-κB, and TGF-β-mediated immune suppression, as well as pivotal clinical investigations of cytokine modulation in immunotherapy, now form the principal evidentiary foundation of the manuscript. Reliance on secondary or tangential sources has been minimized to ensure that conclusions are grounded in authoritative and field-defining evidence, thereby enhancing both scientific rigor and translational relevance.

To provide a clinically relevant perspective, Table 5 summarizes the relationships between major cytokines, tumor types, therapeutic interventions, and observed clinical outcomes. For example, IL-6 is associated with poor prognosis and therapy resistance in multiple myeloma and certain solid tumors, whereas targeting IL-6/IL-6R signaling with tocilizumab has been effective in mitigating CAR-T therapy-induced CRS. Similarly, TGF-β contributes to immune suppression and metastasis in advanced cancers, with TGF-β inhibitors under investigation to enhance immunotherapy efficacy. IL-10 and GM-CSF are highlighted for their dual context-dependent roles, influencing both tumor progression and therapeutic response. This clinically anchored table provides a concise reference linking cytokine biology to tangible outcomes in oncology, supporting translational interpretation of the mechanistic pathways discussed in the review.

Table 5. Clinical associations of key cytokines in cancer.

Cytokine	Tumor Type(s)	Therapy / Intervention	Clinical Outcome / Relevance
IL-6	Multiple myeloma, ovarian cancer, colorectal cancer	IL-6/IL-6R blockade (e.g., tocilizumab); JAK/STAT inhibitors	High IL-6 correlates with poor prognosis, therapy resistance, and enhanced tumor proliferation; blockade mitigates CRS and may improve therapy response
TNF-α	Breast cancer, melanoma, hepatocellular carcinoma	TNF inhibitors (e.g., infliximab, etanercept)	Chronic TNF-α promotes inflammation, EMT, and genomic instability; acute TNF-α may enhance tumor apoptosis in some contexts
TGF-β	Pancreatic cancer, lung adenocarcinoma, colorectal cancer	TGF-βR inhibitors (e.g., galunisertib); combination with checkpoint blockade	Mediates immune suppression, metastasis, and fibrosis; inhibition can enhance T-cell infiltration and therapy response
IL-10	Non-small cell lung cancer, ovarian cancer	Investigational cytokine modulation; checkpoint inhibitors	Chronic IL-10 contributes to T-cell exhaustion and PD-L1 upregulation; may also resolve inflammation transiently
GM-CSF	Melanoma, pancreatic cancer	GM-CSF neutralization; DC vaccines	High GM-CSF recruits MDSCs, suppressing T-cell immunity; low/moderate levels can enhance dendritic cell function
IFN-γ	Melanoma, renal cell carcinoma, lymphoma	Checkpoint blockade (PD-1/PD-L1, CTLA-4)	Supports CTL activation and antigen presentation; chronic signaling can induce PD-L1 and immune exhaustion
VEGF	Renal cell carcinoma, colorectal cancer, glioblastoma	Anti-angiogenic therapy (e.g., bevacizumab)	Drives angiogenesis and immune suppression; normalization can improve immune cell infiltration

10. Conclusions and Future Perspectives

Cytokine dysregulation is a central driver of cancer progression, immune escape, and therapy resistance. The dual roles of cytokines mediating both anti-tumor immunity and tumor-promoting inflammation underscore the need for context-specific and personalized modulation strategies. Future therapeutic approaches are likely to combine cytokine-targeted interventions with immune checkpoint inhibitors and metabolic modulators, creating multifaceted strategies to restore immune balance while minimizing systemic toxicity. Advances in single-cell immunomics, spatial profiling, and AI-based modeling will further enable precision targeting of the “silent killers” within the tumor immune microenvironment.

Ultimately, integrating these approaches represents the next frontier in precision immunology, aiming to transform cytokine signaling from a driver of disease into a therapeutic leverage point for durable cancer control.

11. Limitations

This review integrates mechanistic and clinical insights on cytokine dysregulation in cancer, several limitations should be acknowledged. The manuscript is a narrative synthesis and does not present novel experimental data; many mechanisms discussed such as IL-6/STAT3 and NF-κB signaling, EMT induction, immune suppression, and therapy resistance are already well-characterized, and the review primarily consolidates existing knowledge. Cytokine effects are highly context- and tumor-specific, influenced by genetic background, microenvironment, and exposure dynamics, which may not be fully captured. Coverage of clinical data, including patient stratification, biomarkers, and trial outcomes, is necessarily selective, and citation bias may influence emphasis. Finally, conceptual figures and tables provide pedagogical support but do not generate new experimental insight. These limitations highlight the scope and constraints of the review while framing its contribution as a perspective integrating mechanistic and translational evidence.

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Conflict of Interest

There is no Conflict of interest.

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The author declares that no Gen AI was used in the creation of this manuscript.

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