Review

Utilizing Therapy-Induced Cytokine Responses for Precision Therapy of Triple-Negative Breast Cancer: A Mini-Review

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Utilizing Therapy-Induced Cytokine Responses for Precision Therapy of Triple-Negative Breast Cancer: A Mini-Review

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Abstract

Triple-negative breast cancer (TNBC) represents the most aggressive breast cancer subtype, characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression. Despite advances in chemotherapy and immunotherapy, treatment resistance and disease recurrence remain significant challenges to effective treatment. Recent evidence suggests that various therapeutic interventions elicit distinct cytokine response patterns within the tumor microenvironment, which critically influence treatment efficacy and patient outcomes. This mini-review synthesizes current knowledge on therapy-induced cytokine responses in TNBC since 2020, focusing on chemotherapy, immunotherapy, targeted therapies, and radiation. We discuss how cytokines, including interleukin-6, interleukin-8, transforming growth factor-beta, tumor necrosis factor-alpha, interferon-gamma, and chemokines, modulate the tumor immune landscape, contributing to both therapeutic resistance and antitumor immunity. Furthermore, we explore emerging precision medicine strategies leveraging cytokine profiling for patient stratification, treatment selection, and therapeutic combinations. Critical research gaps have been identified, including the need for standardized biomarker assays, the optimal timing of cytokine-targeted interventions, and the integration of liquid biopsy platforms. Understanding and manipulating therapy-induced cytokine networks holds promise for developing personalized treatment strategies that enhance response rates and improve survival outcomes in TNBC patients.

Keywords: triple-negative breast cancer; cytokines; immunotherapy; precision medicine; tumor microenvironment; biomarkers

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 15-20% of all breast cancer cases and disproportionately affects younger women and African American populations [1,2]. Defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, TNBC lacks targetable receptors available for other breast cancer subtypes, making it particularly challenging to treat. Patients with TNBC experience higher rates of distant recurrence, visceral metastases, and mortality compared to other breast cancer subtypes, with the majority of recurrences occurring within the first three years following diagnosis.

The therapeutic landscape for TNBC has evolved significantly since 2020, with landmark approvals including pembrolizumab combined with chemotherapy for both early-stage and metastatic disease, sacituzumab govitecan for pretreated metastatic TNBC, and PARP inhibitors in cases with BRCA mutations. Despite these advances, pathologic complete response (pCR) rates following neoadjuvant chemotherapy remain approximately 30-40% for unselected populations, and the majority of patients with metastatic TNBC derive limited benefit from immune checkpoint inhibitors (ICIs) [3,8].

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Emerging evidence suggests that cytokines—secreted proteins that mediate intercellular communication—play a pivotal role in determining therapeutic responses in TNBC [9,10]. Various treatment modalities, including chemotherapy, radiotherapy, immunotherapy, and targeted therapies, induce specific cytokine signatures that reshape the tumor microenvironment (TME) [11,12]. These therapy-induced cytokine responses can either enhance antitumor immunity, promoting tumor regression, or drive immunosuppression and treatment resistance [12,13]. Understanding these complex cytokine networks is essential for developing precision medicine approaches that optimize treatment selection and sequencing.

This mini-review comprehensively examines therapy-induced cytokine responses in TNBC, focusing on research published since 2020. We analyze how different therapeutic modalities alter cytokine profiles, discuss the dual roles of key cytokines in promoting or inhibiting antitumor responses, and explore strategies for leveraging cytokine biology to improve clinical outcomes.

Therapy-Induced Cytokine Responses in TNBC

Chemotherapy-Induced Cytokine Secretion

Anthracyclines

Anthracyclines, particularly doxorubicin and epirubicin, are cornerstone agents in TNBC treatment and potent inducers of immunogenic cell death (ICD) [13,14]. Doxorubicin triggers the release of damage-associated molecular patterns (DAMPs), including high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and cell-surface calreticulin, which activate dendritic cells (DCs) and promote T-cell priming [14,15]. Recent studies have demonstrated that anthracycline treatment significantly elevates plasma levels of interleukin-6 (IL-6), C-C motif chemokine ligand 5 (CCL5), and other inflammatory mediators in TNBC models [15,19]. The cGAS-STING pathway activation by doxorubicin leads to increased production of C-X-C motif chemokine ligand 10 (CXCL10) and type I interferons, creating a proinflammatory TME conducive to immunotherapy [16,21].

In the landmark KEYNOTE-522 trial, neoadjuvant pembrolizumab combined with anthracycline-taxane chemotherapy achieved a pCR rate of 64.8% compared to 51.2% with chemotherapy alone in stage II-III TNBC, with sustained event-free survival benefit at 3-year follow-up. Post-treatment analysis revealed an increase in tumor-infiltrating lymphocytes (TILs) and upregulation of cytotoxic gene signatures, particularly in patients who achieved a pathological complete response (pCR). These findings underscore the synergy between anthracycline-induced ICD and checkpoint blockade [5,17].

However, anthracycline therapy can paradoxically promote resistance through IL-6-mediated pathways [18,19]. Elevated IL-6 activates the JAK2/STAT3 axis, inducing expression of anti-apoptotic proteins including Bcl-2 and Bcl-xL, while stimulating tumor-associated macrophage (TAM)-derived transforming growth factor-beta (TGF-β) secretion. This IL-6-TGF-β crosstalk promotes chemoresistance, ferroptosis resistance, and mesenchymal stem-like phenotypes, which are associated with poor outcomes [18,19].

Taxanes

Paclitaxel and other microtubule-targeting agents induce unique cytokine responses through multiple mechanisms [20,21]. Treatment with paclitaxel induces chromosomal instability and micronucleation, resulting in cytosolic DNA accumulation that activates the cGAS-STING pathway [21,22]. This activation triggers type I interferon production and upregulation of programmed death-ligand 1 (PD-L1) expression on tumor cells, creating a mechanistic rationale for combining taxanes with ICIs [22,23].

Clinical evidence from the IMpassion130 trial demonstrated that atezolizumab combined with nab-paclitaxel improved progression-free survival in PD-L1-positive metastatic TNBC, although

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overall survival benefits were limited. Biomarker analyses revealed that paclitaxel increased stromal TILs and enhanced CD8+ T-cell infiltration in responsive tumors [24,25]. Mechanistically, paclitaxel promotes DC activation by increasing the secretion of CXCL10 and CCL5, thereby facilitating T-cell recruitment to the TME.

Nevertheless, paclitaxel can activate immunosuppressive pathways through TGF-β signaling and NLRP3 inflammasome activation [26,48], the latter of which results in caspase-1-mediated interleukin-1β (IL-1β) secretion, promoting a proinflammatory but potentially tumor-supporting environment. Pharmacological inhibition of NLRP3 with MCC950 enhances the efficacy of paclitaxel by reducing inflammatory cytokine production while maintaining cytotoxicity.

Platinum Agents

Carboplatin, frequently used in neoadjuvant regimens for TNBC, generates distinct immunomodulatory effects [27,30]. Preclinical studies demonstrate that carboplatin combined with anti-PD-1 antibodies increases CCL4 expression, which recruits CD103+ DCs to the TME. These specialized DCs enhance cross-presentation of tumor antigens to CD8+ T cells, driving tumor-specific immunity [28,30]. The combination therapy also elevates systemic interferon-gamma (IFN-γ) levels and reduces myeloid-derived suppressor cell (MDSC) populations [29,30].

The GeparSixto trial demonstrated that adding carboplatin to anthracycline-taxane regimens improves pCR rates in TNBC (53.2% vs. 36.9%), particularly in BRCA-mutated cases where DNA damage repair deficiencies synergize with platinum therapy. Recent analyses suggest that carboplatin-induced cytokine responses, including the upregulation of CXCL10 and IFN-γ, as well as the recruitment of effector T cells, contribute to these enhanced response rates.

Immunotherapy-Induced Cytokine Dynamics

Immune Checkpoint Inhibitors

PD-1/PD-L1 blockade fundamentally alters cytokine networks in TNBC [31,32]. Pembrolizumab and atezolizumab enhance the production of effector cytokines, including IFN-γ, tumor necrosis factor-alpha (TNF-α), and granzyme B, by reinvigorating exhausted T cells. The KEYNOTE-355 trial demonstrated progression-free and overall survival benefits with first-line pembrolizumab plus chemotherapy in PD-L1-positive (Combined Positive Score ≥10) metastatic TNBC.

Biomarker studies reveal that baseline cytokine profiles predict the response to ICI [24,34]. Pre-treatment elevation of CXCL9, CXCL10, and IFN-γ correlates with superior outcomes, whereas high levels of IL-6 and interleukin-8 (IL-8) associate with primary resistance [24,34]. The CXCL9-CXCR3 axis is particularly critical, as CXCL9 expression is essential for T-cell trafficking to tumors and for the successful implementation of anti-PD-1 therapy. CXCR3 knockout mice respond poorly to anti-PD-1 therapy, confirming the non-redundant requirement for this chemokine axis.

Severe adverse events, including cytokine release syndrome (CRS), have been reported following ICI therapy, particularly when combined with radiotherapy. A case report described grade 4 CRS in a metastatic TNBC patient who received hypofractionated radiation therapy 34 days after pembrolizumab, characterized by massive IL-6 elevation requiring tocilizumab intervention. This highlights the need for careful monitoring of cytokine-related toxicities in combination regimens [36,39].

Adoptive Cell Therapies

Cytokine-induced killer (CIK) cells represent an established immunotherapy approach in TNBC. These cells express both T-cell (CD3) and NK-cell (CD56) markers, demonstrating broad antitumor activity through the secretion of high levels of IFN-γ, TNF-α, and perforin. Retrospective studies have shown that adjuvant CIK therapy, combined with chemotherapy, improves 5-year overall survival (94.3% vs. 85.6%, P = 0.029) in postoperative TNBC patients.

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Chimeric antigen receptor T-cell (CAR-T) therapy for TNBC is under active investigation, targeting antigens including transmembrane TNF-α, mesothelin, CSPG4, and ROR1. CAR-T cells targeting transmembrane TNF-α demonstrated potent anti-TNBC activity in preclinical studies, with increased secretion of IFN-γ and IL-2 driving tumor regression. However, while CAR-T therapy can induce robust antitumor responses through the massive release of cytokines, CRS remains a significant concern. Management strategies include prophylactic tocilizumab (anti-IL-6 receptor antibody) administration and careful dose escalation to mitigate severe CRS while maintaining therapeutic efficacy.

Targeted Therapy and Cytokine Modulation

PARP Inhibitors

PARP inhibitors (PARPi) such as olaparib and niraparib, approved for BRCA-mutated metastatic TNBC, exert immunomodulatory effects beyond direct cytotoxicity [7,40]. PARPi treatment induces a specific type of ICD, termed pyroptosis, characterized by gasdermin-mediated pore formation in the membrane and the release of inflammatory cytokines. In BRCA1-deficient TNBC models, olaparib significantly increased intratumoral CD4+ and CD8+ T cells while reducing expression of exhaustion markers, including PD-1, TIM-3, and LAG-3.

PARPi activates the cGAS-STING pathway by accumulating cytosolic DNA, triggering the production of type I interferons and the upregulation of CXCL10. This creates an inflamed TME characterized by DC maturation, increased antigen presentation, and enhanced T-cell infiltration. The efficacy of PARP inhibitors depends on CD8+ T-cell recruitment via intratumoral STING pathway activation in BRCA-deficient models of TNBC. Combined PARP and WEE1 inhibition synergistically amplifies these effects, increasing calreticulin surface expression and STING-mediated cytokine production in BRCA1/2 wild-type TNBC.

However, PARPi can also recruit immunosuppressive macrophages to the TME. Combination strategies targeting colony-stimulating factor 1 receptor (CSF-1R) to deplete TAMs enhance PARPi efficacy and durably reprogram the TME toward antitumor immunity.

CDK4/6 Inhibitors

Although primarily used in hormone receptor-positive breast cancer, CDK4/6 inhibitors show activity in specific TNBC subsets, particularly luminal androgen receptor-positive tumors. Recent studies have demonstrated that abemaciclib induces cellular senescence, accompanied by a senescence-associated secretory phenotype (SASP), including elevated IL-6 secretion. Therapy-induced senescent cancer cells contribute to PD-L1 induction and anti-PD-1 resistance via RPN1-mediated PD-L1 stabilization.

In BRCA1-mutant TNBC cells, combining abemaciclib with bazedoxifene (an IL-6/GP130 inhibitor) synergistically suppressed proliferation, migration, and invasion while promoting apoptosis. The IL-6-STAT3 pathway mediates resistance to CDK4/6 inhibition by bypassing cell cycle arrest. Dual targeting of CDK4/6 and IL-6 signaling represents a promising strategy for overcoming resistance in TNBC, particularly in molecularly defined subsets [18,45].

Antibody-Drug Conjugates

Sacituzumab govitecan (SG), targeting trophoblast cell-surface antigen 2 (Trop-2), delivers the topoisomerase I inhibitor SN-38 directly to tumor cells. The ASCENT trial demonstrated significant progression-free survival (5.6 vs. 1.7 months, HR 0.41) and overall survival (12.1 vs. 6.7 months, HR 0.48) benefits with SG versus chemotherapy in pretreated metastatic TNBC. Beyond direct cytotoxicity, SN-38-induced DNA damage triggers ICD with the release of DAMPs, including HMGB1, ATP, and calreticulin, activating immune responses. Interestingly, clinical responses to SG occur across Trop-2 expression levels, suggesting additional mechanisms, including bystander effects and immune activation, contribute to therapeutic efficacy.

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Radiation-Induced Cytokine Responses

Radiation therapy (RT) generates complex cytokine responses that can promote both local tumor control and systemic antitumor immunity through the abscopal effect, characterized by the regression of non-irradiated metastatic lesions following local RT. RT induces ICD, characterized by the exposure of calreticulin, HMGB1 release, and ATP secretion, which activates DCs and stimulates cytotoxic T-lymphocyte responses [14,47].

However, RT simultaneously promotes immunosuppressive cytokines, including TGF-β, which recruits MDSCs and enriches regulatory T cells (Tregs). The balance between proinflammatory signals (TNF-α, IL-6, IL-8, type I interferons) and immunosuppressive factors determines the net immune effect [47,48]. Preclinical studies combining RT with TGF-β neutralizing antibodies demonstrate enhanced DC activation, robust CD8+ T-cell responses, and improved control of both irradiated tumors and distant metastases. TGF-β acts as a master regulator of radiation therapy-induced antitumor immunity, and its blockade can convert immunologically "cold" tumors into "hot" tumors responsive to immunotherapy.

Key Cytokines in TNBC Therapy Response and Resistance

Proinflammatory Cytokines: Dual Roles

IL-6: A Double-Edged Sword

IL-6 exemplifies the complexity of cytokine biology in TNBC, exhibiting both tumor-promoting and potentially antitumor effects depending on context [18,19]. Constitutive IL-6 production by tumor cells and stromal components activates JAK2/STAT3 signaling, promoting chemoresistance, cancer stem cell properties, and metastasis [18,19]. Elevated serum IL-6 levels correlate with a poor prognosis and reduced response to chemotherapy across multiple TNBC cohorts. Mechanistically, IL-6 upregulates anti-apoptotic proteins including survivin and Bcl-2, activates DNA repair pathways, and induces drug efflux pumps, collectively conferring multidrug resistance [18,19].

IL-6 also suppresses antitumor immunity by inhibiting CD8+ T-cell differentiation, reducing IFN-γ and TNF-α production, and promoting the expansion of MDSCs. In the context of immunotherapy, elevated IL-6 suppresses neoantigen expression by affecting nonsense-mediated mRNA decay, thereby impairing the efficacy of checkpoint blockade.

Conversely, acute IL-6 elevation following specific therapies may reflect activation of antitumor inflammatory responses. Therapeutic blockade using tocilizumab (an anti-IL-6 receptor antibody) or bazedoxifene (an IL-6/GP130 inhibitor) shows promise in preclinical models, reducing tumor growth, metastasis, and chemoresistance. Sequential administration of anti-PD-L1 followed by anti-IL-6R therapy reduced TNBC stemness and M2 macrophage polarization in preclinical studies.

IL-8 and Chemoresistance

IL-8 (CXCL8) drives TNBC progression through multiple mechanisms, including angiogenesis, invasion, and recruitment of immunosuppressive neutrophils and polymorphonuclear MDSCs [49,50]. Autocrine IL-8 signaling activates nuclear factor kappa B (NF-κB), creating a positive feedback loop that sustains aggressive tumor phenotypes. Recent studies demonstrate that IL-8 upregulation associates with a paclitaxel-sensitive but doxorubicin-resistant phenotype in TNBC. Mechanistically, the IL-8/NF-κB feedback loop confers this differential chemosensitivity pattern, with IL-8-driven NF-κB activation inducing pro-survival genes that counteract anthracycline-induced apoptosis but not taxane-mediated mitotic catastrophe.

Elevated serum IL-8 in patients with early and metastatic breast cancer correlates with early dissemination and reduced survival. Targeting IL-8 or its receptors (CXCR1/CXCR2) enhances chemotherapy efficacy and reduces cancer stem cell populations in preclinical models.

TNF-α: Context-Dependent Effects

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TNF-α exhibits paradoxical roles in TNBC biology depending on concentration, duration of exposure, and cellular context [15,38]. While TNF-α can directly induce tumor cell apoptosis and activate cytotoxic immune cells, including NK cells and CD8+ T cells, chronic TNF-α signaling promotes invasion through the upregulation of matrix metalloproteinase-9 (MMP-9) and activation of the NF-κB pathways. The suppression of TNBC aggressiveness by galectin-3-binding protein (LGALS3BP) occurs through the inhibition of TNF-α-mediated TAK1-NF-κB-MMP9 signaling, highlighting the importance of this pathway in metastatic progression.

Targeting transmembrane TNF-α with CAR-T cells demonstrates potent anti-TNBC activity in preclinical studies, with increased IFN-γ and IL-2 secretion driving tumor regression without excessive systemic toxicity. Combined low-dose TNF-α and IFN-γ treatment can enhance NK cell-mediated cytotoxicity against TNBC spheroids, although efficacy varies by molecular subtype.

Immunosuppressive Cytokines

TGF-β: Master Regulator of Immunosuppression

TGF-β is a central mediator of immune evasion in TNBC. TAMs and cancer-associated fibroblasts (CAFs) represent significant sources of TGF-β secretion within the TME. TGF-β suppresses effector T-cell function through multiple mechanisms, including the inhibition of cytotoxic gene expression, the promotion of Treg differentiation and expansion, and the facilitation of M2 macrophage polarization. TGF-β also drives epithelial-mesenchymal transition (EMT) and extracellular matrix remodeling, creating both biochemical and physical barriers to immune cell infiltration.

Therapy-induced senescence in TNBC generates SASP characterized by TGF-β secretion, which paradoxically promotes cancer stem cell enrichment and therapeutic resistance. Senescent cells create an immunosuppressive niche that protects residual cancer cells from immune-mediated elimination. Combining senescence-inducing therapies with TGF-β blockade prevents post-chemotherapy relapse in preclinical models.

Multiple TGF-β inhibitors are currently under clinical investigation for the treatment of solid tumors. Combining anti-TGF-β antibodies with RT enhances DC activation and CD8+ T-cell responses in breast cancer xenografts, improving control of both primary tumors and metastases. TGF-β blockade also overcomes resistance to PD-L1 inhibition by facilitating T-cell penetration into the tumor core. The challenge lies in balancing efficacy with safety, as systemic TGF-β inhibition can cause cardiovascular and inflammatory toxicities.

IL-10: Regulatory Cytokine

IL-10 is an immunosuppressive cytokine that suppresses DC maturation, inhibits T-cell proliferation and cytotoxic function, and promotes immunosuppressive TAM phenotypes [12,48]. TAMs and Tregs represent the primary sources of IL-10 within the TNBC TME. IL-10 downregulates MHC class II expression on DCs and reduces production of immunostimulatory cytokines, including IL-12, thereby limiting antitumor immune responses. The balance between IL-10 and IL-12 production by antigen-presenting cells is critical in determining whether pro-tumor or antitumor immunity predominates [12,48].

Chemokines: Orchestrating Immune Cell Trafficking

CXCL9 and CXCL10: T-Cell Recruitment

The CXCL9/CXCL10-CXCR3 axis is crucial for the recruitment of effector T cells and NK cells to tumors. High intratumoral expression of CXCL9 and CXCL10 correlates with improved survival and enhanced ICI response in TNBC [24,35]. Chow and colleagues demonstrated that intratumoral activity of the CXCR3 chemokine system is required for the efficacy of anti-PD-1 therapy, with CXCR3 knockout mice responding poorly to checkpoint blockade.

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ICI treatment upregulates the expression of CXCL9 and CXCL10 through IFN-γ signaling, creating a positive feedback loop that amplifies T-cell infiltration. However, TGF-β suppresses CXCR3 expression on CD8+ T cells, enabling tumors to evade CXCL10-mediated recruitment even in the presence of high chemokine levels. Combined TGF-β blockade and ICI therapy may overcome this resistance mechanism by restoring T-cell responsiveness to chemotactic signals.

Stabilized formulations of CXCL9 and CXCL10 are being developed to convert immunologically "cold" tumors into "hot" tumors amenable to immunotherapy. Intratumoral delivery of these chemokines maximizes local T-cell recruitment while minimizing systemic toxicity.

CCL2 and MDSC Recruitment

CCL2 (monocyte chemoattractant protein-1, MCP-1) recruits immunosuppressive monocytic MDSCs and TAMs to the TME. High CCL2 expression is associated with a poor prognosis, increased metastasis, and reduced survival in TNBC. CCL2 secretion by tumor cells and stromal elements creates a chemotactic gradient that facilitates recruitment of bone marrow-derived inflammatory monocytes, which differentiate into immunosuppressive TAMs within the TME.

ΔNp63-driven CCL2 and CXCL2 secretion promotes MDSC infiltration in basal TNBC, facilitating metastasis through both immunologic mechanisms (suppression of T-cell responses) and non-immunologic mechanisms (secretion of MMP9 and factors that enhance cancer stem cell function). Targeting CCR2 (the receptor for CCL2) or depleting MDSCs represents a promising therapeutic strategy to enhance the efficacy of chemotherapy and immunotherapy [29,44].

CCL5: Dual Functionality

CCL5 (RANTES) recruits both effector T cells and Tregs, exhibiting context-dependent effects on antitumor immunity [15,30]. Carboplatin, combined with anti-PD-1, increases CCL5 levels, facilitating CD8+ T-cell infiltration and enhancing antitumor responses in preclinical models. However, constitutive CCL5 production can also recruit immunosuppressive cell populations, including T regulatory cells (Tregs), which potentially limit therapeutic responses. The net effect of CCL5 depends on the overall immune contexture of the TME and the relative abundance of different immune cell populations expressing CCL5 receptors (CCR1, CCR3, CCR5) [15,30].

Precision Medicine Strategies Leveraging Cytokine Biology

Cytokine Profiling for Patient Stratification

Emerging evidence supports the use of baseline cytokine signatures to stratify TNBC patients and guide treatment decisions [9,34]. Yang and colleagues established a novel cytokine-related 8-gene signature (CCL25, CXCL13, IL12RB2, IL21, TNFRSF13C, TNFRSF8, CCL7, and GDF5) for predicting prognosis and immune landscape in TNBC . This model successfully classified TNBC patients into high-risk and low-risk groups with distinct survival outcomes. Low-risk patients exhibited higher immune checkpoint gene expression, greater infiltration of CD8+ T cells and activated DCs, and greater sensitivity to both chemotherapy and immunotherapy.

Pre-treatment circulating cytokine levels predict pathologic response to neoadjuvant chemotherapy. Callens and colleagues demonstrated that systemic immune mediators, including CXCL10, reflect tumor-infiltrating lymphocyte density and clinical response in patients with TNBC receiving neoadjuvant chemotherapy. Elevated baseline CXCL10, along with favorable Th1/Th2 cytokine ratios, correlates with pCR achievement. Conversely, high pre-treatment levels of IL-6 and IL-8 are associated with chemoresistance, a higher residual disease burden, and reduced survival [24,34].

Liquid Biopsy Integration

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Liquid biopsy platforms analyzing circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and serum cytokines offer minimally invasive approaches for real-time treatment monitoring and prognostic assessment. Alix-Panabières and Pantel comprehensively reviewed the evolution of liquid biopsy from discovery to clinical application, highlighting the integration of multiple analytes for precision oncology. CTC enumeration predicts prognosis in TNBC, with ≥5 CTCs per 7.5 mL blood associating with significantly worse outcomes. Dynamic CTC assessment during treatment provides an earlier indication of therapeutic efficacy than radiographic imaging.

ctDNA clearance correlates with treatment response and predicts recurrence risk in breast cancer. The integration of cytokine panels with ctDNA and CTC measurements could create comprehensive liquid biopsy platforms for precision therapy guidance, enabling the real-time assessment of both tumor burden and immune contexture.

Therapeutic Combinations Targeting Cytokine Networks

IL-12 Plus MDSC Depletion

Systemic interleukin-12 (IL-12) administration activates NK cells and promotes Th1 differentiation, but has limited efficacy as monotherapy due to MDSC-mediated immunosuppression and dose-limiting toxicities. Combining IL-12 with trabectedin, which selectively depletes MDSCs and M2-like TAMs, demonstrates synergistic antitumor activity in preclinical models of TNBC. This combination increases intratumoral CD8+ T cells, conventional type 1 DCs, and effector cytokines, including IFN-γ and CCL5. Significantly, NK-cell depletion abrogates therapeutic benefits, confirming their essential role in mediating antitumor responses.

Clinical translation is progressing, with early-phase trials evaluating IL-12-based combinations in solid tumors, including TNBC [10,11]. Careful dose optimization is required to maximize efficacy while minimizing cytokine-related toxicities, including hepatotoxicity, flu-like symptoms, and potential for CRS.

Chemokine Modulation Therapy

Novel approaches combining chemokine modulation (using rintatolimod, celecoxib, and interferon-alpha-2 b) with pembrolizumab aim to reprogram the TME toward immunotherapy responsiveness. Gandhi and colleagues reported that peri-lymphatic cytokine administration can enhance immune checkpoint blockade responses. Phase I data in metastatic TNBC demonstrated that chemokine modulation increased markers of cytotoxic T lymphocytes, with a greater than 10-fold rise in CD8+ T cells and a more than 300-fold increase in the CD8+/FoxP3 ratio in some patients. Phase II trials are evaluating the safety and efficacy of treatments in patients with advanced disease who have exhausted standard therapeutic options.

Senolytic Strategies

Therapy-induced senescence generates SASP characterized by secretion of IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and other proinflammatory cytokines that can promote tumor recurrence and metastasis. Wang and colleagues demonstrated that therapy-induced senescent cancer cells contribute to PD-L1 induction and anti-PD-1 resistance via ribophorin 1 (RPN1)-mediated PD-L1 stabilization. Senescent cells upregulate PD-L1 through glycosylation mechanisms, creating an "immune umbrella" that protects residual cancer cells from CTL-mediated clearance.

Senolytic agents that selectively eliminate senescent cells are under development. Preclinical studies demonstrate that targeting senescent cells prevents chemotherapy-induced stemness, reduces SASP-mediated inflammation, and minimizes the risk of recurrence in TNBC models. Clinical trials evaluating senolytics (including dasatinib plus quercetin) in breast cancer are in early phases.

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Research Gaps and Future Directions

Despite significant advances in understanding therapy-induced cytokine responses in TNBC, multiple critical gaps impede translation into routine clinical practice:

Biomarker Standardization: Current cytokine assays lack standardization across laboratories, with significant inter-assay variability hindering comparison of results and establishment of validated cut-off values [9,24]. The development of certified reference materials, standardized protocols for sample collection and processing, and quality control measures is essential for the clinical implementation of these methods.

Temporal Dynamics: Most studies measure baseline cytokine levels, but therapy-induced changes follow complex temporal patterns with distinct kinetics for different cytokines [24,34]. Serial measurements capturing dynamic cytokine trajectories—before, during, and after treatment—may better predict outcomes than single timepoint assessments. Optimal timing for cytokine assessment relative to treatment administration requires systematic investigation across different therapeutic modalities [11,24].

Spatial Heterogeneity: Circulating cytokine levels may not accurately reflect intratumoral TME composition due to spatial heterogeneity and compartmentalization. Multiplex immunohistochemistry and spatial transcriptomics, which enable the simultaneous assessment of multiple cytokines and immune cell populations within tumor architecture, could provide more granular insights. The integration of tissue and blood biomarkers may optimize predictive accuracy by capturing both local and systemic immune responses [9,17].

Mechanisms of Primary and Acquired Resistance: While PD-L1 expression and TILs associate with ICI response, the majority of biomarker-positive patients still fail to respond [31,32]. Comprehensive profiling of cytokine networks, immune cell phenotypes, epigenetic modifications, and tumor intrinsic factors in resistant cases is needed to identify combinatorial biomarkers with superior predictive value [31,34]. Mechanisms underlying acquired resistance, including clonal evolution, immune editing, and TME remodeling, require longitudinal investigation using serial biopsies.

Optimal Therapeutic Combinations: The vast number of possible cytokine-targeted interventions combined with standard therapies necessitates systematic prioritization [10,11]. Preclinical modeling using patient-derived xenografts, organoids, and humanized mouse models can identify synergistic combinations [10,44]. Adaptive clinical trial designs that allow for real-time optimization based on on-treatment biomarker responses may accelerate the development process.

Safety Considerations: Cytokine-based therapies carry risks of severe toxicities, including CRS, immune-related adverse events, and off-target effects [36,39]. Predictive biomarkers for adverse events (such as baseline IL-6 levels predicting CRS severity), optimized dosing schedules, and practical management algorithms are essential [36,39]. The long-term effects of cytokine modulation, particularly on non-tumor tissues and systemic immunity, remain incompletely understood and warrant ongoing prospective monitoring.

TNBC Molecular Heterogeneity: TNBC encompasses multiple molecular subtypes with distinct biology, immune contextures, and treatment sensitivities [1,3,34]. Cytokine signatures likely vary across Lehmann subtypes (basal-like 1, basal-like 2, mesenchymal, mesenchymal stem-like, immunomodulatory, luminal androgen receptor), and subtype-specific analyses are needed to refine biomarker performance [1,3]. Integration of molecular subtyping with cytokine profiling may enable more precise therapeutic stratification.

Cost-Effectiveness and Implementation: Multiplex cytokine assays, liquid biopsy platforms, and spatial profiling technologies involve significant costs that may limit accessibility. Economic analyses demonstrating improved outcomes relative to costs are required for reimbursement decisions and widespread adoption. Integration into clinical workflows—including specimen handling, turnaround time, result interpretation, and treatment decision algorithms—requires development, validation, and clinician education.

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Conclusion

Therapy-induced cytokine responses represent a double-edged sword in TNBC, capable of either enhancing antitumor immunity or driving resistance and recurrence. The complex interplay between proinflammatory cytokines (IL-6, IL-8, TNF-α, IFN-γ), immunosuppressive cytokines (TGF-β, IL-10), and chemokines (CXCL9, CXCL10, CCL2, CCL5) determines therapeutic outcomes across various treatment modalities [10,12,34,48]. Chemotherapy induces ICD and inflammatory cytokines that can synergize with immunotherapy [5,13,14], while simultaneously activating resistance pathways through IL-6 and TGF-β signaling [18,48]. ICIs reshape cytokine networks by reinvigorating exhausted T cells and promoting the production of CXCL9 and CXCL10 [32,35], but their efficacy is limited by immunosuppressive cytokines and inadequate T-cell infiltration in many patients [31,48]. Targeted therapies, including PARP inhibitors and antibody-drug conjugates, activate immune responses through the ICD and cGAS-STING pathways [6,42], creating opportunities for rational combination strategies.

Precision medicine approaches leveraging cytokine profiling hold significant promise for patient stratification, treatment selection, and therapeutic combination design [9,34]. Baseline cytokine signatures can identify patients likely to respond to specific therapies, enabling the development of personalized treatment algorithms [24,34]. Dynamic monitoring through liquid biopsy platforms enables early detection of resistance and relapse, potentially allowing therapeutic adaptation before radiographic progression. Targeted interventions modulating key cytokine pathways—including IL-6 blockade, enhancement of CXCL9 and CXCL10, TGF-β inhibition, and MDSC depletion [10,29]—demonstrate encouraging preclinical efficacy and are advancing through clinical development.

Critical research gaps remain, including the need for biomarker standardization, elucidation of temporal and spatial cytokine dynamics [17,24], identification of resistance mechanisms, optimization of therapeutic combinations [10,11], and integration into cost-effective clinical workflows. Addressing these challenges through collaborative multidisciplinary research will be essential to realize the full potential of cytokine-based precision therapy for TNBC.

As the field advances, the integration of cytokine profiling with complementary precision oncology tools—such as genomic sequencing, transcriptomic analysis, spatial profiling, and liquid biopsy platforms—will enable increasingly refined treatment algorithms [9,34]. The ultimate goal is to transform TNBC from a uniformly aggressive disease with limited therapeutic options into a collection of molecularly and immunologically defined entities, each amenable to tailored, biomarker-guided interventions that maximize response rates and improve survival outcomes [1,3,34]. Harnessing the power of therapy-induced cytokine responses represents a crucial step toward achieving this vision.

Table 1. Major Therapy-Induced Cytokines and Their Roles in TNBC.

Cytokine	Primary Source	Role in TNBC	Therapy-Induced Changes	References
IL-6	Tumor cells, TAMs, CAFs	Promotes chemoresistance, activates JAK2/STAT3, induces immunosuppression	Increased by chemotherapy (CDK4/6i, anthracyclines)	[18,19,34]
IL-8	Tumor cells, neutrophils	Enhances invasion, angiogenesis, and chemoresistance via NF-κB	Elevated by paclitaxel, doxorubicin	[49,50]
IL-10	TAMs, Tregs, B cells	Immunosuppression inhibits DC maturation and T-cell function	Variable; can be increased by immunotherapy	[12,48]
IL-12	DCs, macrophages	Activates NK and T cells, enhances antitumor immunity	Enhanced by IL-12 therapy + trabectedin	[10,12]
TNF-α	T cells, NK cells, and macrophages	Dual role: promotes invasion (via MMP9) or enhances cytotoxicity	Induced by PARP inhibitors, anthracyclines	[15,38]

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IFN-γ	T cells, NK cells	T-cell activation, Th1 polarization, antitumor immunity	Elevated by ICI + chemotherapy combinations	[24,30,32,35]
TGF-β	Tumor cells, TAMs, CAFs	Immunosuppression, EMT induction, promotes metastasis	Activated by paclitaxel; promotes recurrence	[46,48]
CXCL9	DCs, macrophages	Recruits CXCR3+ T cells and NK cells, enhances ICI response	Upregulated by ICI, PARP inhibitors	[24,35]
CXCL10	DCs, T cells	T-cell recruitment supports antitumor immunity	Increased by pembrolizumab, radiation therapy	[16,24,30,35]
CCL2	TAMs, tumor cells	Recruits MDSCs and TAMs, promotes immunosuppression	Reduced by chemotherapy; increased in resistance	[29,44]
CCL5	T cells, DCs	T-cell and DC recruitment support immune infiltration	Enhanced by carboplatin + anti-PD-1	[15,30]

TAMs: tumor-associated macrophages; CAFs: cancer-associated fibroblasts; DCs: dendritic cells; Tregs: regulatory T cells; NK: natural killer; ICI: immune checkpoint inhibitor; EMT: epithelial-mesenchymal transition; MDSCs: myeloid-derived suppressor cells.

Table 2. Therapeutic Modalities and Associated Cytokine Responses in TNBC.

Therapeutic Approach	Key Cytokine Responses	Impact on Tumor Microenvironment	Clinical Evidence in TNBC	References
Anthracyclines (Doxorubicin)	HMGB1, ATP, calreticulin release; IL-6↑, CCL5↑, CXCL10↑	ICD induction, DC activation, enhanced T-cell priming	KEYNOTE-522: pCR 64.8% vs 51.2%; improved EFS	[5,13–15,17,19]
Taxanes (Paclitaxel)	IFN-I↑ via cGAS-STING; IL-1β↑, PD-L1↑	Micronucleation, cGAS activation, and increased TILs	IMpassion130/KEYNOTE-355: PFS benefit with ICI	[20–25]
Platinum agents (Carboplatin)	CCL4↑, CXCL10↑, IFN-γ↑; recruits CD103+ DCs	CD8+ T-cell infiltration, reduced MDSCs	GeparSixto: pCR 53.2% vs 36.9% with carboplatin	[27–30]
Immune Checkpoint Inhibitors (Pembrolizumab, Atezolizumab)	CXCL9↑, CXCL10↑, IFN-γ↑; variable IL-6 changes	Enhanced T-cell infiltration reverses exhaustion	FDA-approved for PD-L1+ mTNBC	[5,31–33,35]
PARP Inhibitors (Olaparib, Niraparib)	IFN-γ↑, TNF-α↑ in CD8+ T cells; STING activation	Increased CD4+/CD8+ T cells, reduced Tregs, and DC maturation	FDA-approved for BRCA-mutant mTNBC; synergy with ICI	[7,40–43]
Antibody-Drug Conjugates	DNA damage → ICD; SN-38-	Cytotoxic payload delivery with immune modulation	ASCENT: PFS 5.6 vs 1.7 mo; OS 12.1 vs 6.7 mo	[6,14]

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(Sacituzumab govitecan)	induced cytokine release			
CAR-T Cell Therapy	IL-2, IFN-γ, TNF-α release; risk of CRS (IL-6 storm)	Cytokine-mediated tumor killing, potential toxicity	Preclinical; CRS is manageable with tocilizumab	[37–39]
Radiation Therapy	Type I IFN, TNF-α, IL-6, IL-8; HMGB1 release	Abscopal effect, systemic immune activation	Case reports of CRS: synergy with ICI	[14,36,47,48]
CDK4/6 Inhibitors + IL-6 blockade	IL-6-driven senescence → SASP; synergy with IL-6 blockade	Overcomes CDK4/6i resistance via IL-6 pathway inhibition	Preclinical; targets BRCA1-mutant TNBC	[18,45,46]

ICD: immunogenic cell death; pCR: pathologic complete response; EFS: event-free survival; TILs: tumor-infiltrating lymphocytes; mTNBC: metastatic triple-negative breast cancer; PFS: progression-free survival; OS: overall survival; CRS: cytokine release syndrome; SASP: senescence-associated secretory phenotype; mo: months.

Table 3. Cytokine-Based Precision Therapy Strategies and Research Gaps in TNBC.

Strategy/Application	Current Approach	Precision Medicine Potential	Key Research Gaps	References
Cytokine Profiling for Patient Stratification	8-gene cytokine signature (CCL25, CXCL13, IL12RB2, IL21, etc.)	Identify high-risk vs. low-risk patients; guide therapy selection	Validation in large prospective cohorts; optimal cut-offs	[9,34]
Predictive Biomarkers	Pre-treatment IL-6, IL-8, CXCL10 predict pCR and ICI response	Baseline cytokines predict chemotherapy and ICI efficacy	Standardization of assays; dynamic vs. baseline measurements	[9,24,34]
IL-6 Pathway Blockade	Tocilizumab for CRS; Bazedoxifene + CDK4/6i	Overcome resistance, manage adverse events (CRS)	Optimal timing, dosing, and combination with other therapies	[18,36,39]
CXCL9/CXCL10 Enhancement	Recombinant chemokines or inducers to enhance T-cell recruitment	Convert cold tumors to hot, enhance ICI response	Clinical-grade formulations; delivery methods	[35,48]
TGF-β Inhibition	Anti-TGF-β mAbs + radiation/ICI combinations	Reduce immunosuppression, prevent metastasis	Balance efficacy with safety; biomarkers for patient selection	[46,48]
IL-12 + MDSC Depletion	Trabectedin + IL-12 to deplete MDSC and activate NK cells	Synergistic antitumor immunity in ICI-resistant TNBC	Clinical trials needed; optimal dosing schedules	[10,29,44]

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Combination: ICI + Chemotherapy	Carboplatin/paclitaxel + pembrolizumab (FDA-approved)	Maximize pCR rates, improve EFS, and OS	Biomarkers beyond PD-L1; mechanisms of primary resistance	[5,31,33]

pCR: pathologic complete response; ICI: immune checkpoint inhibitor; CRS: cytokine release syndrome; CDK4/6i: CDK4/6 inhibitor; mAbs: monoclonal antibodies; MDSC: myeloid-derived suppressor cells; NK: natural killer; EFS: event-free survival; OS: overall survival; SASP: senescence-associated secretory phenotype; ctDNA: circulating tumor DNA; CTCs: circulating tumor cells.

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