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The role of cytokines as diagnostic biomarkers and therapeutic modulators in cancer management

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Abstract

Cytokines are small signaling proteins that regulate immune responses, inflammation, and cellular communication, playing a critical role in cancer monitoring and treatment response. They can activate or suppress the immune system; thus, they exert both pro-inflammatory and anti-inflammatory effects in disease regulation. However, dysregulation, manifested as altered levels in biological fluids or tissues, is strongly associated with tumor progression, poor prognosis, therapeutic response, and immune restoration. The aim of this study is to evaluate cytokines as diagnostic biomarkers and therapeutic modulators in cancer management, with a focus on their role as indicators of cancer status and treatment response. This comprehensive literature review was conducted using original research articles, reviews, systematic literature reviews, and meta-analyses published between 2020 and 2026 from multiple electronic databases by using "biomarkers" "interleukin," "immunotherapy," and "cytokine" as keywords. The findings indicate that high levels of cytokines, particularly interleukins such as IL-6, IL-8, IL-10, IL-22, and IL-35, are significantly associated with tumor progression, poor prognosis, and therapeutic response across various cancer types. Elevated cytokine levels in biofluids, including blood and cerebrospinal fluid, support their use as minimally invasive biomarkers for early detection and disease monitoring. In conclusion, the findings demonstrate that cytokine level biomarkers are associated with tumor progression, poor prognosis, and therapeutic modulation in different types of cancer. However, their dual role provides significant potential for advancing precision oncology and improving patient outcomes.

Keywords: Biomarkers; interleukin; immunotherapy; Cytokine

1. Introduction

Small signaling proteins called cytokines control inflammation, cell communication, and immunological responses. They are produced by T cells, B cells, and other immune cells, and they help to control the immune response by telling other immune cells either increasing or decreasing their activity. (1) However, in cancer, cytokine networks are often dysregulated, contributing to tumor progression, immune evasion, and metastasis. (2) Cytokines released by the immune cells or tumor cells influenced by the tumor microenvironment; when cancer is present, cytokine levels may be elevated or decreased in blood or tissues. (3) Cytokines can be measured not only in tissues and blood but also in other biological fluids such as cerebrospinal fluid (CSF). (4) In contrast, previously the cancer has been detected and monitored for cancer status or drug response through different biomarkers such as carcinoembryonic antigen (CEA,) prostate-specific antigen (PSA), carbohydrate antigen 125 (CA125), and alpha fetoprotein (AFP), which are responsible for monitoring of cancer metastasis status, and it can be found in tissue or other body fluid. (5) Therefore, the cytokines belonging to various families, comprising more than 40 subfamilies, such as inflammatory interleukins from the same family, can both activate or suppress immune responses aimed at the tumor. (6)

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Currently, the cytokine should act as an immunomodulator due to its capacity to restore the immune system to fight the cancer cells. (1) Its high level of cytokines shows the presence of cancer, and it helps in tracking the cancer stage status during diagnostics. (3) In addition, these are being precisely targeted or altered by increasing advantageous cytokines, modifying the immune response due to its potential to be either antitumor or protumor, but numerous cytokines have both tumor-promoting and tumor-suppressing properties. Meanwhile, their expression is associated with a favorable prognosis in colorectal cancer. (6) In colorectal cancer (CRC) patients, elevated preoperative serum levels of cytokine correlated with a worse prognosis and indicated those who faced cancer recurrence after surgery, while high levels also indicated patients' stage status, like stages I, II, and III in colorectal cancer (CRC), and served as a predictive biomarker. (2) Cytokine-mediated signaling pathways in cancer progression and therapeutic resistance directed by inhibition of cytokine signaling are shown to significantly weaken cancer cell antigenicity. (7) On the other side, the inhibition of cytokine function is a good indicator promoting tumor progression and metastasis reduction. (8)

The cancer therapies modulate the immune system, and changing cytokine levels can serve as dynamic biomarkers to evaluate treatment response and drug efficacy in patients. However, cytokines play a dual and pivotal role in cancer as both biomarkers and immunomodulator targets. (1) While specific cytokine profiles would be elevated or diminished in different types of cancer. (6, 9) The cytokine evaluation provides valuable insights for cancer monitoring and prognosis. (7, 8) Moreover, targeting cytokine signaling pathways offers promising strategies to overcome therapeutic resistance through cytokine control to help to inhibit tumor growth. (8) Therefore, cytokine profiling proves to be a good indicator for cancer diagnosis, biomarker monitoring, and therapeutic assessment to modulate the immune system for providing long survival in cancer patients.

2. Methods

This traditional literature review was conducted using original research articles, reviews, systematic literature reviews, and meta-analyses published between 2020 and 2026 from multiple electronic databases by using "biomarkers" and "interleukin" and "immunotherapy" and "cytokine" as keywords. Inclusion criteria were all clinical, preclinical, cell line research, reviews, systematic literature reviews, and meta-analyses; articles written in English. Exclusion articles published before conference articles and studies unrelated to cancer immunology.

2.1. Cytokines as biomarkers for cancer monitoring indicators

Cytokine expression levels reflect a condition correlated with immune system modulation and the tumor microenvironment. (3, 10) However, peripheral blood biomarkers are minimally invasive and appropriate for dynamic monitoring; they are especially appealing for clinical use. (11) Recent studies indicate that circulating cytokine levels, such as interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-10 (IL-10), are significantly elevated in cancer patients compared to healthy individuals, marked as diagnostic biomarkers in cancer follow-up. (3) Therefore, the observation found in cerebrospinal fluid (CSF) cytokine profiles indicates that IL-6 and IL-10 were elevated in patients with secondary central nervous system lymphoma (SCNSL) in comparison to those in the non-secondary central nervous system lymphoma (non-SCNSL) group. (4) The robust associations among IL-6, TNF-α, and histological characteristics like cellular atypia, mitotic figures, necrosis, and angiogenesis highlight their role in the tumor microenvironment. The elevated sensitivity, specificity, and potential as trustworthy indicators for early cancer identification and prognosis. (3)

2.2. Cytokines as therapeutic modulators

Cytokine expression profiles reflect tumor progression, immune status, and response to therapy, making them valuable tools for diagnosis and prognosis. For instance, elevated levels of interleukin-6 (IL-6) and interleukin-10 (IL-10) have been consistently associated with disease progression and poor clinical outcomes in various cancers. (4) Recent studies demonstrate that IL-6 exhibits significant diagnostic accuracy as a biomarker; therefore, elevation of pro-inflammatory cytokines correlates with poor outcomes and may serve as prognostic biomarkers and therapeutic targets. (4, 12) On the other hand, cytokines are prognostic biomarkers for the effectiveness of immunochemotherapy in advanced gastric cancer AGC patients. Treatment response was substantially correlated with elevated plasma levels of IL-6, IL-8, and IL-10. (10) And also IL-22 is a good indicator for drug monitoring efficacy. (7) Furthermore, it is good for restoring the immune system and demonstrates the ability to enhance immune response. (4, 7, 10, 11)

2.3. Synergistic role of cytokines as a biomarker and therapeutic modulator

Cytokines are essential in cancer by regulating interactions between tumor cells and the immune system in the tumor microenvironment. It has the power to detect, monitor, and treat cancer; however, in combination, it brings restoration of the immune system and improvement in cancer patient outcomes. (13) Cytokines are directly involved in oncogenic

signaling pathways, making them attractive targets for therapy. For instance, IL-6 activates the JAK/STAT3 pathway, which supports tumor growth, metastasis, and resistance to apoptosis. Blocking IL-6 or STAT3 signaling can disrupt these processes and reduce tumor progression due to activation of the immune system. (8) Similarly, in colorectal cancer (CRC), expression of cytokines IL-22 has been shown as a good indicator of drug resistance; stopping the IL-22/STAT3 signaling pathway can enhance the anti-tumor effects both in vitro and in vivo. Therefore, IL-22 could signify a novel target against bevacizumab resistance in colorectal cancer (CRC). (7) However, the high levels of IL-35 in hepatocellular carcinoma (HCC) enhance tumor progression by influencing neutrophil infiltration, angiogenesis, and the exhaustion of CD8+ T cells. Moreover, the anti-IL-35 antibody promoted the infiltration of CD8+ T cells within the tumor. (14) On the other hand, recent studies indicate that IL-6 signaling is associated with a reduced survival rate in pancreatic ductal adenocarcinoma (PDAC) patients, as it fosters tumor formation and spread; further, it is also a recognized immunomodulatory cytokine that supports the growth and anti-tumor effectiveness of chimeric antigen receptor (CAR) T cell therapies, the differentiation of $CD4^+$ T cell subsets, the maturation of cytotoxic $CD8^+$ T cells, and the suppression of inducible Treg formation. The T cell-mediated anti-tumor response to pancreatic ductal adenocarcinoma (PDAC) is strongly enhanced by high IL-6 concentrations by supporting immune responses against tumors through increasing the activity of $CD8^+$ T cells and NK cells, reducing immune tolerance, and improving the proliferation and effectiveness of CAR-T cell therapies. (15) Additionally, necroptosis-related immune activation boosts T cell responses through increased CD69 expression and enhanced IL-6 secretion, leading to heightened PD-L1 expression in cholangiocarcinoma (CCA) cells, demonstrating that the IL-6 signaling-related gene signature can act as a biomarker for patient stratification and individualized therapy in cholangiocarcinoma (CCA). (16) Therefore, IL-6 triggers downstream signaling pathways like JAK/STAT3 and MAPK, enhancing the invasive and metastatic potential of oral squamous cell carcinoma (OSCC) cells; nonetheless, the prognostic and therapeutic significance of the IL-6/IFIT2 axis in oral squamous cell carcinoma (OSCC) opens avenues for future research on targeted treatments in high-risk patient groups. Focusing on IL-6 and associated cytokine pathways may offer therapeutic advantages in the treatment of oral squamous cell carcinoma (OSCC), especially in later stages. (17)

Table 1: Prognostic biomarkers across cancer types

Cytokine	Cancer types	Role of biomarker	Therapeutic Modulation	Key Signaling Pathway	References
IL-6	CRC, PDAC, OSCC, HCC, SCNSL	Progression, poor prognosis, therapy response	JAK/STAT3 inhibition; CAR-T enhancement	JAK/STAT3, MAPK	(8,15–17)
IL-8	AGC, NSCLC	Treatment response, poor survival	Chemokine receptor blockade	CXCR1/CXCR2	(3,18)
IL-10	SCNSL, AGC, breast cancer	Diagnostic (CSF), blood, progression	Immunosuppression reversal	STAT3	(3,4,9)
IL-22	CRC	Bevacizumab resistance prediction	Anti-IL-22 antibody	STAT3	(7)
IL-35	HCC	Progression, $CD8^+$ T cell exhaustion	Anti-IL-35 antibody	Not fully defined	(14)

3. Results and discussion

The complex relationship between tumor cell sensitivity and cytokines offers a promising way to improve cancer treatment. Cytokines, in particular, exhibit significant potential as tumor biomarkers for prognosis, treatment assessment, and cancer detection. Elevated amounts of interleukins such as IL-6, IL-8, and IL-10 are strongly associated with tumor progression, poor prognosis, and response to treatment in different types of cancer. Furthermore, cytokines like IL-6 and IL-35 promote tumor growth by influencing the immune system and activating signaling pathways such as JAK/STAT. On the other hand, their inhibition boosts anti-tumor immunity through elevated $CD8^+$ T cell infiltration. Blocking the IL-22/STAT3 signaling pathway can enhance the anti-tumor effect of bevacizumab both in vitro and in vivo. Finally, the cytokine shows the capacity to suppress or boost the immune system; thus, it contributes to the drug's effectiveness or resistance. Tumor biomarkers include various methods for cancer detection, such as early identification, diagnosis, prognosis, prediction, and therapeutic targets, which are crucial for detailing cancer existence, directing cancer management, forecasting treatment response, and recognizing and tracking high-risk individuals. Nevertheless, they are highly sensitive and specific particular tumor biomarkers that should be slowly incorporated

into clinical practice. The collective research findings demonstrate that cytokine and immune-related biomarkers, particularly interleukins such as IL-6, IL-10, IL-8, IL-22, and IL-35, hold significant promise across multiple cancer types. For example, high levels of plasma IL-6, IL-8, and IL-10 have been repeatedly associated with disease progression, low survival rates, and treatment response in non-small cell lung cancer (NSCL), secondary central nervous system lymphoma (SCNSL), breast cancer, and pancreatic ductal adenocarcinoma (PDAC). Furthermore, the observation that cerebrospinal fluid (CSF) levels of IL-6 and IL-10 are associated with diagnosis and treatment response in secondary central nervous system lymphoma (SCNSL) indicates that secreted IL-6 from tumor-associated macrophages (TAMs) stimulates the JAK/STAT pathway in prostate cancer, making it a prognostic marker and a possible therapeutic target. IL-22 plays a role in tumor progression and the upkeep of cancer stem cells, with its signaling inhibition reducing cancer stem cells (CSCs), a result confirmed in animal studies, thus endorsing IL-22 as a predictive and therapeutic biomarker. IL 35 facilitates the advancement of hepatocellular carcinoma (HCC) by attracting neutrophils and diminishing $CD8^+$ T cell infiltration, whereas the anti-IL 35 antibody reinstates $CD8^+$ T cell levels, underlining its significance as both a prognostic and therapeutic target. The cytokine biomarker framework should be incorporated into routine clinical practice for better cancer management systems.

4. Conclusion

The findings demonstrate that a high level of cytokine biomarkers is associated with tumor progression, poor prognosis, and therapeutic response across multiple types of cancer. However, their dual role provides significant potential for advancing precision oncology and improving patient outcomes.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declared that there was no conflict of interest.

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