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Inflammatory biomarkers as predictors of cancer progression and treatment response

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Abstract
Inflammatory biomarkers have emerged as critical tools for understanding cancer progression and predicting treatment response. Chronic inflammation plays a pivotal role in tumor development by promoting genetic instability, angiogenesis, and immune evasion. Key biomarkers, such as C-reactive protein (CRP), interleukins (IL-6, IL-10), tumor necrosis factor-alpha (TNF-α), and neutrophil-to-lymphocyte ratio (NLR), have shown significant associations with cancer prognosis and therapeutic outcomes across various malignancies. This review highlights the dual role of inflammatory biomarkers in cancer, acting as both facilitators of tumor progression and potential targets for treatment. Elevated CRP levels, for instance, correlate with advanced tumor stages and poor survival rates. Similarly, IL-6 and TNF-α contribute to cancer cell proliferation and resistance to chemotherapy. Conversely, IL-10 exhibits immunosuppressive effects, which may aid in tumor immune escape. Emerging evidence also underscores the prognostic value of composite markers like NLR in stratifying patient risks and tailoring treatment strategies. In clinical practice, monitoring inflammatory biomarkers provides a non-invasive and cost-effective method to assess disease status and predict responses to interventions such as immunotherapy and targeted therapies. Furthermore, therapeutic modulation of inflammatory pathways holds promise for improving outcomes in patients with resistant or recurrent cancers. Despite significant advancements, challenges remain in standardizing biomarker thresholds and understanding their dynamic interplay with cancer heterogeneity. Future research should focus on integrating inflammatory biomarkers into personalized treatment protocols and exploring their utility in combination with other molecular and genetic markers for a more comprehensive approach to cancer management. This review underscores the potential of inflammatory biomarkers as valuable predictors and modulators of cancer progression and treatment response, paving the way for improved precision oncology.

Keywords: Inflammatory biomarkers, cancer progression, treatment response, chronic inflammation, immunotherapy, prognostic markers

1. Introduction

In the context of cancer research, the interplay between inflammation and cancer demonstrates the widespread utility of inflammatory biomarkers. In 1863, it was observed the presence of leukocytes in neoplastic tissues. Since then, much interest has been generated in the inflammatory microenvironment of a tumor and its association with the progression of the disease. Research has expanded to examine whether inflammatory responses precede the development of cancer, with many studies examining the correlation of pre-diagnostic circulating levels of inflammatory markers and the development of cancer (Yamamoto *et al*. 2021; Kartikasari *et al*.2021; Nøst *et al*.2021) [34, 16, 24].

The most recent development in this historical journey of the relevance of inflammatory biomarkers has been an improved understanding of the mechanisms of action of these biomarkers. It has long been theorized that inflammation itself alters the genetics of cells to promote carcinogenesis through to metastasis. Early mechanistic studies showed the ability of inflammatory biomarkers to potentially alter the genetics of human cells, but recent research now suggests that these biomarkers may sensitize cells to new genetic changes after exposure to a mutagenic agent, further promoting the belief that they are able to drive progression and resistance evolution in cancers. There is now a standing history of four types of inflammatory biomarkers that have been employed in testing: white blood cell differentials, acute phase proteins such as C-reactive protein, cytokines, and neutrophil to lymphocyte ratio (Nøst *et al*. 2021; Hart *et al*. 2020; Hou *et al*., 2021) [24, 10, 14].

It is the intent of this essay to explore the correlation between cancer, the spoils of therapy, and the immune system. Crucially, the purpose of this extended investigation is to identify how various biomarkers associated with inflammation are capable of indicating the progression of cancer in a clinical setting (Yamamoto *et al*. 2021; Kartikasari *et al*. 2021; Nøst *et al*. 2021; Hart *et al*.2020; Hou *et al*., 2021) [34, 16, 24, 10, 14].

2. The Role of Inflammation in Cancer Development

Inflammation plays an important role in cancer development, and many risk factors for developing cancer are linked to chronic inflammatory states. Discussions of how chronic inflammation could lead to tumor initiation and promotion are ongoing, and possible mechanisms include an increased mutagenic load from oxidative damage, proliferation signal generation, modification of angiogenic and metastatic pathways, immune suppression, and cell death subversion. There are many pathways by which inflammatory processes can be involved in carcinogenesis. Major pathways in the development of inflammation-related cancers include the biological response to infectious agents, production of genotoxic free radicals by inflammatory cells, aberrant crypt proliferation promoted by prostanoid production in conditions such as inflammatory bowel disease, and the promotion of angiogenesis and invasion that follows the chronic inflammation-injury-repair cycle. The biological pathways that link inflammation and cancer encompass processes in both the tumor microenvironment and systemic inflammatory responses (Tan *et al*. 2021; Hibino *et al*. 2021; Zhang *et al*., 2021) [31, 11, 36].

Immune cells are present in every tumor and install an inflammatory microenvironment called the tumor immune microenvironment. Besides improving tumor angiogenesis and facilitating the escape from immune surveillance, the biogenesis of this inflammatory microenvironment may lead to supportive actions on cancer cellular functions. Regulatory immune cells act as principal actors in maintaining an immunosuppressive milieu, being responsible for modulating cancer impersonation, metastasis promotion, and dormant cancer oscillation between cancer stem cell states. Macrophages, mast cells, T helper cells, and neutrophils are involved in cancer promotion, invasion, and metastases. The role of inflammation and immune cells in cancer has profound clinical implications, as more biomarkers with a direct or indirect connection with the inflammatory or immune responses are subject to further investigation for potential value as diagnostic, prognostic, and predictive cancer biomarkers. In this review, we will discuss the type 1 and type 2 inflammatory responses linked to specific biomarkers and clinical situations. This will help in the interpretation of the link between inflammation and cancer biology and the significance of therapy for the numerous biomarkers evaluated in large clinical trials (Piotrowski *et al*. 2020; Zhao *et al*. 2021; Khandia & Munjal, 2020; Tan *et al*.2021; Hibino *et al*.2021; Zhang *et al*., 2021) [25, 37, 18, 31, 11, 36].

3. Types of Inflammatory Biomarkers

Inflammatory biomarkers cover a wide variety of compounds that play a critical role in building up the inflammatory status of patients, especially in the context of malignant diseases. Unlike immune-exclusion markers, which do not provide predictive information, the analysis of inflammatory biomarkers deserves great attention in both tumor progression and response to therapeutic approaches, including immunotherapy. They can be divided into four classes, including pro-inflammatory cytokines and chemokines, acute-phase proteins, growth factors and receptors, and prostaglandins (Yamamoto *et al*. 2021; Amin *et al*. 2020; Abraham *et al*. 2021) [34, 2, 1].

Pro-inflammatory Cytokines: Cytokines are small proteins that are secreted by immune cells and are involved in the regulation of immunity, inflammation, and many other functions that underlie various pathologies, including those of cancer. There are two main subtypes of cytokines: the first class includes molecules acting at the level of immunity and inflammation, whereas the second class of cytokines acts mainly at the hematopoietic level. Acute-Phase Proteins (APPs): APPs include serum proteins whose synthesis in the liver undergoes selective regulation in response to inflammatory, injury, or infectious agents. They include C-reactive protein and haptoglobin, and are positive or negative according to the direction of their change following injury, inflammation, or infection. Injecting an agent inducing an acute-phase response will elicit a response involving changes in several genes regulated by pro-inflammatory cytokines. Chemokines: Unlike cytokines, chemokines act almost exclusively locally, such as at the tumor site, recruiting polymorphonucleates, macrophages, monocytes, and lymphocytes, including T immune cells. Early tumor mass: When immune cells arrive at the tumor site and are converted to tumor-associated macrophages, both cell populations secrete a mix of anti- and pro-tumor cytokines and chemokines (Kartikasari *et al*. 2021; Goksel *et al*., 2021; Yamamoto *et al*. 2021; Amin *et al*. 2020; Abraham *et al*. 2021) [16, 8, 34, 2, 1].

4. Biomarkers in Predicting Cancer Progression

Inflammatory biomarkers have been valuable in predicting cancer progression. Insights into how cancer drives inflammation, and the molecular and biological relevance of such inflammation, have led to increased interest in biomarker discovery as a potential predictive tool. Systematic profiling of patients who harbor tumors has provided scientific evidence that the overproduction of specific inflammatory mediators can be correlated with the promotion of tumor growth. The relationship of plasma or serum inflammatory mediator levels to different cancer subtypes and disease stages has allowed for the development of predictive models and subsequent correlation to patient outcomes. These types of predictive models have also been used to determine relapse in cancer patients, estimate response to therapy, and inform on prognosis (Kartikasari *et al*. 2021; Karimi *et al*.2021; Nøst *et al*.2021) [16, 15, 24].

The prognostic significance of biomarkers in predicting outcome, response, relapse, case fatality, and survival in cancer patients is important to clinical practice in their accurate risk stratification and subsequent cancer management. As markers of inflammation, well-predicted to play a functional role in cancer progression, biomarkers can be highly informative to a patient's clinical pathway and management. A comparison of several studies has highlighted that tumor stage, tumor site, tumor grade, and treatment regimen are all primary factors in the consideration of a biomarker's predictive utility to patient outcomes. Identifying biomarkers measured by immunoenzymometric assays or immunofluorometric assays, and of which the levels correlate with adverse disease parameters for women with advanced epithelial ovarian cancer, are most likely translatable to patient-relevant outcomes. The interpretation of data on prognostic biomarkers in glial brain tumors is nuanced to the clinical setting for which it is used. When the current management practice is not known, our ability to interpret a relapse-predictive model is severely limited. The optimal biomarker profile in predicting and determining treatment response is unknown, but response to chemotherapeutics appears to have the highest predictive yet clinical relevance. A meta-analysis of predictive models in detecting response to neoadjuvant chemotherapy for women with breast cancer shows that non-pCR is possibly the more reliable predictive, and of the models tested, the prediction of a pCR using serum levels proved most accurate. If we are to move to having these biomarkers predict clinical outcomes, thus impacting our patients' cancer care, biomarker research should be evaluated by both the biological and clinical relevance of a given marker. To gain clinical support, we need to show that the biomarker has a disease-relevant role, is predictive of relevant clinical features, including clinical behavior, can predict an adverse outcome such as relapse, cancer-directed patient fatality, and/or the impact of clinical care in reducing fatality. If the model, including a biomarker, indicates patients who are less likely to benefit from a certain regimen, this will assist in defining a predictive model and allow a personalized treatment regimen to be developed. Integration of these predictive biomarkers gives them relevance to clinical management and improves patient care (Yamamoto *et al*. 2021; Do *et al*., 2020; Kartikasari *et al*. 2021; Karimi *et al*. 2021; Nøst *et al*.2021) [34, 6, 16, 15, 24].

5. Biomarkers in Predicting Treatment Response

In addition to their role for prognostic purposes, inflammatory biomarkers might also indicate the potential response of patients to therapy in the setting of specific clinical trials. The inflammation-engendered mechanisms can affect the efficacy of a specific treatment modality. Systemic inflammation can, therefore, also potentially serve as a useful biomarker for predicting responses to various cancer therapies. This predictive ability spans across various modes of therapies, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy. However, this role will be discussed in detail under each treatment category in the relevant sections to follow. Generally, the presence of these inflammatory markers might indicate an immunosuppressed state in these patients, therefore potentially having a worse response to immunotherapy. Another scenario is the use of biomarkers to develop strategies for personalizing treatment options for the patient. This review will focus on the therapeutic role of these biomarkers by giving their description and the methodology of their assessment, followed by data on their role in predicting individual treatment response in various clinical trials. Clinical trials that have been conducted have shown that using these biomarkers can help discern what treatment a patient might not benefit from, but there are currently very few trials that have incorporated this into their recommendation of alternative strategies for the patients. The data have, however, shown that using these biomarkers has the potential to achieve optimal personalized, patient-specific therapy (Sangro *et al*. 2020; Wang *et al*., 2022; Breiteneder *et al*. 2020; Maniaci *et al*.2021; Drevets *et al*. 2022; Soták *et al*. 2024; Abd-Alwahab *et al*., 2024) [26, 32, 4, 21, 7, 30, 39].

6. Methods for Biomarker Detection and Analysis

Several methods are currently used to investigate putative inflammatory biomarkers in the context of cancer. These include ELISA, immunohistochemistry, PCR, imaging, or digital methods. Several emerging techniques are under development to further refine the detection and analysis of these biomarkers. Although the relative merits of these assays are important to consider, it must be emphasized that assessing these in the clinical context requires a rigid process of standardization and validation, particularly if used to influence treatment. One of the current barriers to the use of inflammatory biomarkers in a clinical setting is the heterogeneity between techniques (Honig *et al*. 2020; Davis *et al*. 2020) [12, 5] (Nakayasu *et al*. 2021; Ladang *et al*. 2023; Zarkali *et al*. 2024; Lateef *et al*., 2024) [23, 19, 35, 38].

Technological advancements in the field of biomarker investigation have expanded the number of ways to detect and analyze circulating or tumor tissue markers, potentially supporting a move toward image-based and multi-feature predictive assays. Furthermore, pairing imaging with genetic and clinical data could be a valuable tool for radiologists and oncologists to enhance tumor characterization. Thus, studies are now emerging that use novel detection methods, configuration, or assessment to predict or assess treatment response or recurrence in a variety of tumor types. However, a major concern in these fields is the availability of the technological resources and infrastructure to support these analyses, and the need for alacrity and caution when moving technologies from in silico or *in vitro* pipelines into the clinical trial setting. In order to maximize the clinical utility of any potential predictive signature, it is increasingly common to validate the relative sensitivity and specificity of these assays with larger clinical sample numbers, but the development pipeline for these technologies will need to change to permit these larger scale screenings. In addition, any potential signatures from these technologies would likely need to be further validated with prospective monitoring against agreed clinical control groups. Overall, despite exciting areas of active investigation, it is essential to remember that accurate detection or rejection of the biomarker remains a necessity to leverage their utility as a predictive or prognostic factor (Menzel *et al*. 2021; Honig *et al*. 2020; Davis *et al*.2020) [22, 12] (Nakayasu *et al*. 2021; Ladang *et al*. 2023; Zarkali *et al*. 2024) [23, 19, 35].

7. Challenges and Limitations in Using Inflammatory Biomarkers

Using biomarkers to predict cancer progression and treatment response offers many possibilities for guiding precision oncology practices. However, there remain considerable challenges and limitations in the use of molecular and inflammatory biomarkers. Cancer is regulated via complex genetic and inflammatory pathways, and therefore, biomarker expression may differ from one tumor to the next. In addition, even a tumor from a single patient can express different biomarker profiles intra-individually. Integrating evidence-based inflammatory and molecular biomarkers into critical care and clinical practice presents an array of challenges and opportunities. Both researchers and clinicians must remain cognizant of bioethics in the use of biomarkers, including issues of consent, data privacy, researcher conflict of interest, financial and industry influence, and so on. Research based on inflammatory and/or molecular biomarkers is methodologically complex and in many ways, unlike the pragmatics required for traditional clinical decision-making. Cohort and case-control studies can validate a hypothesis, but the generalizability of the research in such studies is typically limited. While molecular and inflammatory biomarkers present many possibilities, future research needs to address the methodological limitations present in much of the current biobehavioral research as well as ethical and pragmatic concerns (Loi *et al*. 2021; Kerr *et al*. 2021; Wang *et al*.2021) [20, 17, 33].

A scientific and clinical gap in applying biomarkers to predict clinical events, such as defining or clarifying the progression of cancer, remains in the current literature. Furthermore, greater clarity is required to demonstrate the link between an elevation in biomarker level, the start, or reactivation of the stress response system, and the initiation, progression, or recurrence of cancer as distinct events. One way forward is to use more reliable endpoints than PFS and hopefully to design non-invasive studies powered to clarify these associations. A review in brain tumors also identified remarkable heterogeneity in methodological designs, biomarkers, and outcomes assessed in association with psychoneuroimmunological studies, indicating significant methodological and outcome variability. Although the selected papers were not associated with any limitations in the methodology-related criteria, mainly because of the initial selection criteria, it remains clearly evident that some of these methodological design and outcome assessment weaknesses are recurrent in several biobehavioral cancer studies. Overall, this review provides a balanced stance on the current status of molecular and inflammatory biomarker research. It will contribute directly to the emerging standards in the genomic and psychoneuroimmunology landscape as well as to the funding and evaluation of cancer biomarker progress. A critical reflection on the current progress and limitations of molecular and inflammatory biomarkers will provide funding bodies with concrete targets and system improvements for assessments and allocations (Sarhadi & Armengol, 2022; Bartha & Győrffy, 2021; Loi *et al*. 2021; Kerr *et al*. 2021; Wang *et al*.2021) [27, 3, 20, 17, 33].

8. Future Directions and Emerging Technologies

Despite substantial advancements in the field of inflammatory biomarkers in cancer, there are still many aspects of research that are crying out to be explored in greater depth and that may well expand our knowledge and clinical toolset considerably. Given the advent of multi-omics and related technology such as genomics, proteomics, and bioinformatics, the opportunity for commercial investment into the production and standardization of related technology is substantial, given the potential customer base in pathology research and diagnostics. Therefore, propositions for regulatory approval and standardization will become imperative over time. Future directions in this research area include further pursuit of mechanistic-based understanding of biomarker significance and targeting, with the current focus being upon such genes as CSF1R. Going forward, clinicians and researchers in this field should vigorously pursue the emerging technologies available and consequently attempt to ascertain their superiority and applicability in relation to established biomarkers. It is possible that in the future, personalized medicine will benefit from such research, allowing tailored ADT and frontline therapies. However, certain barriers do still remain, including a lack of methodology for standardizing serum testing in patients currently, alongside confusion among regulatory bodies on assent for cancer-specific markers, or indeed their interpretation. Emerging technologies, including circulating vesicles and their associated genomics, which are under investigation for their role in the prediction of progression in oncology, will also provide expanded avenues for personalized biomarker testing in the future. (Son *et al*. 2024) [29] (Haghayegh *et al*. 2024) [9] (Singh *et al*. 2023) [28] (Horgan *et al*.2021) [13].

9. Conclusion and Implications for Clinical Practice

This review aimed at investigating the value of inflammatory markers: C-reactive protein, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and Glasgow prognostic score in predicting cancer stage, presence of metastases, response to therapy, and cancer-specific survival. Despite some conflicting evidence, the markers were proposed to be potentially useful in predicting cancer stage and were consistently associated with advanced stage or the presence of distant metastases, worse treatment response, and cancer-specific survival. It is concluded that inflammatory markers showing potential in clinical practice of cancer care are C-reactive protein, neutrophil-to-lymphocyte ratio, and Glasgow prognostic score. These could be potentially used in clinical practice of cancer care. Biomarkers for cancer diagnostics and therapy are playing an increasingly important role in providing the right treatment to the right people at the right time. A potential impact of using well-established systemic inflammatory markers is further described. The systematic use of these markers in clinical practice is recommended. The interest in this field has been increasing recently. These surrogate markers in current use are mainly for demonstrating the prognostic importance in various cancers. The importance of these markers is described regarding the stage of the disease in clinical practice. The field needs more integrated research for exploring associations between circulating markers, the Tumor-Node-Metastasis classification, and patient-related outcomes. This may result in significant progress in the field. The field attracts an increasing research interest; however, it lacks sufficient evidence for recommendation in clinical practice. This field, with the use of circulating biomarkers, is an independent domain and has been omitted from the latest clinical guidelines. The recommendation is for the research to continue providing more reliable evidence about applying this field in clinical practice with the inclusion of an expert multicenter panel for recommendations.

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11. Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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