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A review on biomarkers in cancer immunotherapy: present and future

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ABSTRACT

In recent years, developments in cancer immunotherapy have revolutionized cancer treatment, utilizing the immune system to fight malignancies with unprecedented precision and effectiveness. However, the heterogeneity of responses observed across patients undergoing immunotherapeutic interventions underscores the need for reliable biomarkers that can predict treatment outcomes and guide clinical decision-making. This mini-review explores the evolving role of biomarkers in cancer immunotherapy, focusing on their potential to enhance patient stratification, monitor treatment response, and identify mechanisms of resistance. Our discussion focuses on immunotherapy biomarker research in the present day, highlighting the utility of immune cell profiling, mutational burden analysis, and tumor microenvironment characterization. Moreover, we review the promising use of liquid biopsy-based biomarkers and the integration of advanced omics technologies in refining predictive and prognostic biomarker signatures. As the field of cancer immunotherapy continues to advance, the integration of these biomarkers into clinical practice holds the promise of personalized treatment approaches, improved patient outcomes, and a deeper insight into how the immune system interacts with cancer. This mini-review highlights the importance of ongoing collaborative efforts between clinicians, researchers, and technology developers in shaping the future of cancer immunotherapy utilizing biomarkers.

KEYWORDS

Cancer immunotherapy; Biomarkers; Immune checkpoint inhibitors; Tumor microenvironment; Liquid biopsy; Precision medicine

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Introduction

Cancer immunotherapy has transformed cancer treatment by stimulating the body's immune system to target and eliminate malignant cells. In contrast to traditional cancer therapies, which focus on destroying cancer cells directly, cancer immunotherapy works by inducing the immune system to recognize and attack cancer cells. This paradigm shift from traditional therapies has yielded unprecedented clinical responses across various malignancies, offering durable and often curative outcomes for patients. Immunotherapeutic strategies such as immune checkpoint inhibitors, adoptive T-cell therapy, and cancer vaccines have shown significant potential in cancer treatment and are expected to play an increasingly essential role in cancer care in the future [1].

In cancer treatment, biomarkers provide critical insights into a cancer patient's response to treatment. They play a central role in cancer immunotherapy, acting as guideposts for treatment selection, prediction of therapeutic outcomes, and identification of potential immune-related adverse events. These biomarkers include but are not limited to, the expression of immune checkpoint molecules like PD-L1, the mutational burden of tumors, and the composition of tumor infiltrating immune cells within the tumor microenvironment [2-4].

The use of biomarkers can help oncologists identify patients who will benefit from specific immunotherapies, optimizing treatment decisions and reducing side effects. Additionally, they hold the promise of unlocking personalized immunotherapeutic approaches, ultimately leading to improved patient outcomes [5].

This mini-review offers a comprehensive analysis of the evolving landscape of biomarkers in cancer immunotherapy. We will delve into the diverse roles that biomarkers play, from predicting treatment responses and monitoring disease progression to guiding combination therapies and unraveling mechanisms of resistance. Through this review, we aim to illuminate the pivotal role that biomarkers will play in shaping the future of cancer immunotherapy, paving the way for precision medicine approaches that hold immense promise for cancer patients.

Role of Biomarkers in Cancer Immunotherapy

Biomarkers guide treatment decisions by predicting which patients are likely to respond positively to immunotherapy, help manage potential adverse events, and enable the monitoring of treatment response and resistance. Some of the most promising biomarkers include (Table 1).

Biomarkers as predictors of response to immunotherapy

PD-L1 expression

Programmed cell death ligand 1 (PD-L1) is a crucial immune checkpoint molecule that cancer cells exploit to evade immune detection [6]. It is a transmembrane protein that plays a significant role in immune escape by binding to PD-1 on T cells and promoting immune evasion [6]. Tumors with higher PD-L1 expression are thought to be more susceptible to immune checkpoint inhibitors (ICIs) like PD-1/PD-L1

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inhibitors [7]. PD-L1 expression in tumor tissue, determined through immunohistochemistry, has been used as a predictive biomarker for response to these inhibitors in certain cancer types, including non-small-cell lung cancer (NSCLC), renal cell cancer (RCC), hepatocarcinoma, and melanoma [8]. However, the utility of PD-L1 expression as a predictive biomarker has limitations, and the decision to pursue testing must be carefully implemented for clinical decision-making [2].

Several studies have explored the role of PD-L1 expression as a predictive biomarker for cancer immunotherapy [2,6]. A study analyzed all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors and evaluated the primary studies associated with 45 FDA drug approvals from 2011 until April 2019. The study found that PD-L1 was predictive in only 28.9% of cases and was either not predictive (53.3%) or not tested (17.8%) in the remaining cases [2].

Tumor mutational burden (TMB)

Tumor mutational burden (TMB) is a measure of the number of mutations present in the DNA of a tumor cell. It has emerged as a promising biomarker for predicting response to cancer immunotherapy [9]. High TMB (TMB-H) is associated with increased neoantigen production, which can stimulate the immune system to attack cancer cells [9].
TMB-H has shown promise as a biomarker in lung cancer, but the broad applicability of TMB-H as a biomarker of response across all solid tumors is unclear [9]. The FDA has approved the use of TMB as a biomarker for immunotherapy in solid tumors with TMB ≥ 10 mutations/megabase [9]. However, the use of TMB as a universal biomarker across all solid tumors is still under investigation [9].

Several studies have reported that TMB can predict patient response to immune checkpoint inhibitors (ICB) [9,10]. A recent article discussed the limitations of using TMB as a biomarker with a universal threshold across all solid tumors. The article reviewed the relationship between TMB and the tumor immune microenvironment and highlighted the risks of extrapolating evidence from a limited number of tumor histologies to all solid tumors. They propose avenues for future research to address the limitations of TMB as a predictive biomarker.

Immune cell infiltration

Immune cell infiltration is a crucial aspect of the tumor microenvironment that influences cancer progression and response to immunotherapy [11]. Tumor-infiltrating lymphocytes (TILs) are immune cells that infiltrate the tumor microenvironment and play a key role in the immune response against cancer [12]. The presence of TILs is associated with improved survival in several types of cancer, including melanoma, cervical cancer, and NSCLC [13].

A recent review discusses the relevance of immune cell and tumor microenvironment imaging in the new era of immunotherapy [11]. The paper highlights the importance of new therapeutic biomarkers and their *in vivo* evaluation to improve the management of cancer patients. They propose molecular imaging as a non-invasive diagnostic tool for preclinical and clinical purposes to evaluate or predict treatment efficacy *in vivo*.

Another article characterizes different subtypes of immune cell infiltration in the tumor microenvironment and their role in cancer progression and immunotherapy response [12]. The article discusses various types of immunotherapeutic approaches that have been developed, such as vaccine therapy, chimeric antigen receptor (CAR) T cells, programmed cell death 1 (PD-1), and programmed cell death ligand-1 (PD-L1) inhibitors.

Biomarkers as indicators of immune-related adverse events (irAEs)

CTLA-4 biomarkers

CTLA-4 is a protein receptor that plays a crucial role in regulating the immune system's response to cancer cells. In recent years, CTLA-4 biomarkers have been identified as potential predictors of response to immunotherapy [14]. According to a review, several biomarkers have been proposed for predicting the efficacy of immune checkpoint inhibitors (ICIs) targeting CTLA-4 1 [15]. Another review discussed that an immune checkpoint blockade of CTLA-4 improved the survival rate of renal cell carcinoma, melanoma, non-small cell lung cancer (NSCLC), and head and neck squamous cell cancer [16]. This also highlighted the correlation between CTLA-4 expression in regulatory T cells and the response to CTLA-4-based immunotherapies. Another study identified CTLA4 promoter methylation and CTLA-4 protein expression as predictive biomarkers for response to anti-CTLA-4 immunotherapy [17]. Furthermore, an article found that CD4+ and CD8+ memory T cell subsets play an important role in response to anti-CTLA-4 therapy and are potential biomarker candidates [18]. These studies provide valuable insights into the role of CTLA-4 biomarkers in cancer immunotherapy.

Cytokine profiles

Cytokines are small proteins that play a crucial role in the immune system's response to cancer cells. In recent years, cytokine profiles have been identified as potential predictors of response to immunotherapy [19]. According to a study, cytokine therapeutics have shown promise in treating cancer as single agents or in combination with other immunotherapies [19]. Another research discussed the role of cytokines in the modulation of physiological and pathophysiological conditions and their potential as therapeutics [20]. The paper by Li et al. examined the cytokine profile of breast cancer patients. The study measured the levels of 274 cytokines in the serum of breast cancer patients prior to treatment. The results suggest that monitoring cytokine circulating levels in breast cancer could be used to characterize breast cancers and the immune composition of their microenvironment through readily available biological material [21]. These studies provide valuable insights into the role of cytokine profiles in cancer immunotherapy.

Monitoring treatment response and resistance

Circulating tumor DNA (ctDNA)

ctDNA refers to tumor-derived DNA fragments circulating in the bloodstream. Monitoring changes in ctDNA levels can offer insights into treatment response and disease progression [22]. It can reflect the actual tumor burden and specific genomic state of disease and thus might serve as a prognostic and predictive biomarker for ICI therapy [22]. ctDNA has

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been studied as a biomarker for various types of cancer, including NSCLC, colorectal cancer, breast cancer, head and neck cancer, and melanoma [23]. Recent studies have shown that sequential ctDNA analyses allow for the identification of responders to ICI therapy, with a significant lead time to imaging [22]. Developing dynamic changes in ctDNA concentrations as a potential surrogate endpoint of clinical efficacy in patients undergoing adjuvant immunotherapy is ongoing.

Immune cell repertoire dynamics

The immune system is a complex network of cells and molecules that work together to protect the body from infections and diseases, including cancer. The immune cell repertoire refers to the diversity of immune cells that can recognize and respond to different antigens [24]. The dynamics of the immune cell repertoire play a crucial role in cancer immunotherapy, as they determine how well the immune system can recognize and eliminate cancer cells.

Recent studies have shown that the diversity and composition of the immune cell repertoire can predict the response to immunotherapy in patients with various types of cancer [24]. For example, high levels of T-cell receptor (TCR) diversity have been associated with better clinical outcomes in patients with melanoma and lung cancer treated with immune checkpoint inhibitors [24]. In contrast, low TCR diversity has been linked to poor response to immunotherapy in patients with colorectal cancer [24]. Understanding the dynamics of the immune cell repertoire is essential for developing effective cancer immunotherapies.

Table 1. Role of biomarkers in cancer immunotherapy.

Biomarker	Mechanism	Cancer Types
PD-L1 expression	Cancer cells evade immune detection via PD-L1; higher expression correlates with susceptibility to inhibitors	Non-small-cell lung cancer (NSCLC), renal cell cancer (RCC), hepatocarcinoma, melanoma [8]
Tumor mutational burden	High TMB leads to more recognizable mutated antigens for the immune system; associated with improved responses	Lung cancer (promising), various solid tumors (investigation ongoing) [9]
Immune cell infiltration	Tumor-infiltrating lymphocytes (TILs) indicate active immune response; higher levels correlate with better responsiveness	Melanoma, cervical cancer, non-small cell lung cancer (NSCLC) [13]
CTLA-4 biomarkers	Genetic markers and immune profiling predict susceptibility to irAEs associated with CTLA-4 inhibitors	Renal cell carcinoma, melanoma, NSCLC, head and neck squamous cell cancer [16]
Cytokine profiles	Changes in cytokine patterns correlate with the development/severity of adverse events; aids proactive management	Breast cancer, other cancers (investigation ongoing) [21]
Circulating tumor DNA (ctDNA)	Changes in ctDNA levels indicate treatment resistance/recurrence; enables timely therapy adjustments	NSCLC, colorectal cancer, breast cancer, head and neck cancer, melanoma [23]
Immune cell repertoire dynamics	Diversity/composition of immune cells in circulation offer information on treatment response and resistance; aids mechanism identification	Melanoma, lung cancer (positive), colorectal cancer (negative) [24]

Current Landscape of Biomarkers in Cancer Immunotherapy

Overview of FDA-approved biomarkers for immunotherapy

The U.S. FDA has approved several biomarkers that provide valuable insights into patient response to immunotherapy. These biomarkers play a crucial role in patient selection, treatment monitoring, and prognosis. One of the most prominent biomarkers is programmed cell death ligand 1 (PD-L1) expression on tumor cells and immune cells. High levels of PD-L1 expression have been associated with increased response rates to immune checkpoint inhibitors like anti-PD-1 and anti-PD-L1 antibodies [25]. Another FDA-approved biomarker is microsatellite instability-high (MSI-H) status, which indicates deficient DNA mismatch repair and correlates with improved response to immunotherapy across various cancer types [26]. Additionally, TMB has gained attention as a predictive biomarker, with higher TMB being linked to increased immunotherapy efficacy [9].

Although the clinical utility of these biomarkers has been demonstrated in ample clinical trials, many variables involved in using these biomarkers have posed serious challenges in daily practice. Furthermore, the predicted responders by these

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three biomarkers only have a small percentage of overlap, suggesting that each biomarker captures different contributing factors to ICI response. The review article also discusses four novel gene signature biomarkers: T-cell inflamed gene expression profile (GEP), T-cell dysfunction and exclusion gene signature (TIDE), melanocytic plasticity signature (MPS), and B-cell focused gene signature [25]. The GEP and TIDE have shown better predictive performance than PD-L1 and PD-L1 or TMB, respectively.

Limitations and challenges of current biomarkers

While FDA-approved biomarkers have significantly advanced personalized cancer immunotherapy, several limitations and challenges must be addressed to further enhance their clinical utility.

Heterogeneity of tumor microenvironment

Tumor microenvironment heterogeneity poses a challenge as biomarker expression may vary across different regions of the tumor [27]. This variability can lead to inaccurate assessment of biomarker status and subsequent treatment decisions [27].

Lack of standardized assays

The absence of universally accepted assay protocols for biomarker assessment results in inconsistent data interpretation. Standardization is crucial for ensuring reliable biomarker evaluation and treatment selection across different laboratories and clinical settings.

Dynamic nature of biomarker expression

Biomarker expression within tumors is not static; it can change over time due to tumor evolution, treatment-induced alterations, and immune responses [28]. This dynamic nature complicates the reliability of single-time-point biomarker assessments, necessitating the development of strategies to monitor changes in real time [28].

Emerging Biomarkers in Cancer Immunotherapy

There are several emerging biomarkers that promise to enhance treatment outcomes and tailor therapies to individual patients in cancer immunotherapy.

Neoantigens and personalized vaccines

Neoantigens, derived from tumor-specific mutations, have gained traction as crucial indicators of immunotherapy response [29]. Personalized cancer vaccines, adoptive T-cell therapy, and immune checkpoint inhibition rely on an understanding of the patient-specific neoantigen profile in order to guide personalized therapeutic strategies [29]. Prioritization of immunogenic neoantigens is key to enhancing cancer immunotherapy through the development of personalized vaccines, adoptive T-cell therapy, and the prediction of response to immune checkpoint inhibition. Genomic approaches to predicting and prioritizing immunogenic neoantigens are rapidly expanding, raising new opportunities to advance these tools and enhance their clinical relevance.

Gut microbiome composition

The composition of the gut microbiome has emerged as a potential influencer of immunotherapy outcomes. Certain bacterial species have been associated with improved response rates to immune checkpoint inhibitors, demonstrating the microbiome's role in modulating systemic immune activation [30]. Harnessing this knowledge could lead to strategies for optimizing patient microbiota to enhance treatment responses.

Peripheral blood immune cell profiling

Profiling peripheral blood immune cells offers a non-invasive means to monitor a patient's immune status during immunotherapy. Specific immune cell subsets and their activation states can serve as dynamic biomarkers, reflecting the treatment's impact on the immune system [31]. This enables clinicians to make timely adjustments and tailor interventions based on the patient's immune profile.

RNA-based biomarkers

RNA-based biomarkers are a promising area of research in cancer immunotherapy [32]. Cabús et al. discussed the challenges and best practices for cell-free long RNA biomarker discovery [33]. The field of cell-free RNA biomarkers has mostly focused on the study of microRNAs (miRNAs) as biomarkers of disease in the circulation due to their higher stability in blood. However, there is a rising interest in the study of long RNAs (>200nt), including but not limited to messenger RNAs (mRNAs) and long non-coding RNAs (lncRNAs). The article also highlights the importance of identifying RNA-based biomarkers for early detection of cancer.

Integrative Approaches to Biomarker Discovery and Validation

Biomarkers play a pivotal role in modern medicine, aiding in early disease detection, prognosis assessment, and treatment response monitoring. Integrative approaches that combine various technologies and methodologies have emerged as powerful strategies for biomarker discovery and validation. This article provides a concise overview of three key aspects within this domain: multi-omics analysis, machine learning and artificial intelligence (AI), and the prospects of liquid biopsies (Table 2).

Multi-omics analysis for comprehensive biomarker identification

Multi-omics analysis has revolutionized biomarker discovery by enabling a comprehensive view of biological systems. It involves the simultaneous analysis of various biological molecules, such as genomics, transcriptomics, proteomics, and metabolomics. This approach facilitates the identification of novel biomarkers that could be missed by analyzing individual omics data sets [34]. Integrating data from multiple omics platforms allows researchers to unveil intricate molecular interactions and pathways that contribute to disease progression. By comparing healthy and diseased samples, researchers can identify commonalities and differences in omics profiles, leading to the discovery of robust biomarker candidates. For instance, in cancer research, multi-omics analysis has uncovered biomarkers associated with tumor development, metastasis, and treatment response [35].

Machine learning and AI in biomarker prediction

Machine learning and AI have transformed biomarker prediction by handling the complexity and high-dimensional nature of omics data. These technologies can identify patterns

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Table 2. Integrative approaches to biomarker discovery and validation.

Integrative approaches to biomarker discovery and validation	Key aspects	Role and significance
Multi-omics analysis	Comprehensive view of biological systems	Simultaneous analysis of genomics, transcriptomics, proteomics, metabolomics Identifies novel biomarkers missed by individual omics analysis Reveals molecular interactions and pathways contributing to disease Unveils robust biomarker candidates through comparisons of omics profiles
Machine learning and AI	Handle complexity of high-dimensional data	Identifies patterns and relationships in massive omics datasets Predicts biomarkers with high accuracy using existing data Distinguishes between healthy and diseased states; predicts outcomes Integrates diverse data types for enhanced biomarker predictions
Prospects of liquid biopsies	Non-invasive, real-time disease monitoring	Analyzes biofluids for biomarkers released from diseased tissues Detects circulating tumor DNA, exosomes, microRNAs in blood and more Promising for cancer detection, treatment monitoring, and genetics Eliminates need for invasive tissue biopsies; enables longitudinal monitoring

and relationships within massive datasets that are beyond the scope of manual analysis. Machine learning algorithms can learn from existing data and predict biomarkers with high accuracy [36]. Classification and regression models are commonly used to distinguish between healthy and diseased states and to predict disease outcomes. AI-driven approaches also enable the integration of diverse data types, enhancing the accuracy of biomarker predictions [37].

Prospects of liquid biopsies in biomarker detection

The prospects of liquid biopsies have reshaped the landscape of biomarker detection by offering non-invasive and real-time monitoring of disease progression. Liquid biopsies involve the analysis of biofluids such as blood, urine, or cerebrospinal fluid to detect biomarkers released from diseased tissues [38]. Circulating tumor DNA, exosomes, and microRNAs are among the molecules commonly analyzed. Liquid biopsies are particularly promising for cancer detection and monitoring, as they provide insights into tumor genetics and allow for tracking treatment response and the emergence of resistance mutations [38]. These minimally invasive techniques eliminate the need for invasive tissue biopsies, reducing patient discomfort and enabling longitudinal monitoring.

Clinical Implications and Future Directions of Biomarkers

In the age of personalized medicine, biomarkers offer profound clinical implications and have the potential to shape the future of healthcare. This article presents a concise overview of key aspects in this domain: tailoring immunotherapy, guiding combination therapies, adaptive clinical trials, and addressing ethical considerations.

A. Tailoring immunotherapy based on biomarker profiles has revolutionized cancer treatment. Biomarkers such as PD-L1 expression or tumor mutation burden help identify patients who are more likely to respond to immune checkpoint inhibitors [39]. This precision approach minimizes unnecessary treatments and reduces adverse effects, optimizing patient outcomes.
B. Combination therapies guided by biomarker insights offer a promising avenue for enhanced therapeutic efficacy. Biomarker profiling enables clinicians to identify synergistic drug combinations targeting specific molecular pathways, thereby improving treatment responses and overcoming resistance [40].

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C. Adaptive clinical trials and real-time biomarker assessment are reshaping the research landscape. Biomarker-guided trials allow for dynamic treatment adjustments based on patient responses, expediting drug development and increasing trial success rates [41].

Conclusions

In this comprehensive exploration of biomarkers and their role in cancer immunotherapy, we have reviewed various dimensions that highlight the significance of these molecular signatures in shaping the future of personalized medicine. Through integrative approaches such as multi-omics analysis and the application of machine learning and artificial intelligence, we have shown a deeper understanding of disease mechanisms, enabling the identification of robust biomarker candidates. Liquid biopsies have emerged as a promising way, offering non-invasive monitoring and real-time insights into disease progression.

In conclusion, biomarkers play a crucial role in cancer immunotherapy. They are essential in patient stratification, treatment selection, and monitoring. A growing collaboration between researchers, clinicians, industry stakeholders, and regulatory agencies is leading to the development of biomarkers that will redefine healthcare in the future, making precision medicine a reality for countless patients.

Disclosure statement

No potential conflict of interest was reported by the author.

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