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Tumor Mutational Burden (TMB) as a Biomarker for Immunotherapy in Cancer

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Abstract

Tumor Mutational Burden (TMB) has gained significant attention as a potential biomarker for immunotherapy in cancer. TMB refers to the number of mutations present within a tumor genome, and higher TMB levels have been associated with an increased likelihood of successful responses to immune checkpoint inhibitors. As the landscape of cancer treatment evolves, immunotherapy has emerged as one of the most promising approaches, especially for cancers with high mutational load. This article explores the role of TMB as a biomarker in immunotherapy, its potential for predicting treatment efficacy, challenges associated with its clinical implementation, and the future directions of TMB research. By understanding how TMB influences immunotherapy outcomes, clinicians and researchers can better identify patients who are most likely to benefit from immune checkpoint blockade therapies, thereby enhancing personalized cancer treatment strategies.

Keywords: Tumor mutational burden; Immunotherapy; Cancer; Biomarkers; Immune checkpoint inhibitors; TMB as biomarker; Personalized medicine; Immunotherapy efficacy; Cancer treatment; PD-1/PD-L1 inhibitors

Introduction

Cancer treatment has undergone significant advancements in recent years, with immunotherapy being one of the most transformative strategies. Unlike traditional treatments such as chemotherapy and radiation, which target cancer cells directly, immunotherapy harnesses the patient's immune system to fight and eliminate tumor cells. The development of immune checkpoint inhibitors, particularly those targeting programmed death-1 (PD-1) and its ligand (PD-L1), has led to remarkable successes in several cancers, including melanoma, non-small cell lung cancer (NSCLC), and others. A major challenge, however, remains predicting which patients will benefit most from immunotherapy. While some patients experience significant and long-lasting responses to immune checkpoint inhibitors, others show little or no response. This unpredictability has spurred the search for biomarkers that can identify patients most likely to benefit from immunotherapy. One such biomarker that has garnered attention is Tumor Mutational Burden (TMB) [1-3].

TMB refers to the total number of somatic mutations found in the coding regions of a tumor genome. Tumors with a high TMB are considered to have a larger variety of mutated antigens, increasing the likelihood of immune system recognition and tumor elimination. As TMB correlates with improved outcomes in certain immunotherapies, it has the potential to be used as a predictor of treatment efficacy. This article provides an overview of TMB, its relationship with immunotherapy response, and the implications of its use as a biomarker for personalized cancer treatment [4].

Description

Tumor Mutational Burden (TMB) is a quantitative measure that reflects the number of mutations within a tumor's genetic material. These mutations may arise from a variety of factors, such as environmental exposures (e.g., smoking), inherited genetic mutations, or errors in DNA replication. High levels of TMB are typically found in tumors that have undergone rapid division, excessive damage, or mutations in DNA repair genes, whereas lower TMB values are often seen in tumors with fewer mutations [5].

Mechanisms of TMB in tumorigenesis

The accumulation of genetic mutations in a tumor occurs as a result of mutations in key genes involved in controlling cell growth and division, including oncogenes and tumor suppressor genes. These mutations can produce new antigens, known as neoantigens, that are presented on the surface of tumor cells. These neoantigens can serve as targets for the immune system. When tumors express higher mutational loads, they generate more neoantigens, which increases the chances of immune recognition and response. Moreover, tumors with high TMB are more likely to benefit from immunotherapies that leverage the immune system, such as immune checkpoint inhibitors. Inhibitors targeting PD-1 and PD-L1, such as pembrolizumab and nivolumab, work by blocking the immune escape mechanisms employed by tumors. The theory is that tumors with more mutations will express more neoantigens, leading to more effective recognition and attack by T cells when PD-1/PD-L1 checkpoints are blocked [6-8].

TMB is typically quantified through next-generation sequencing (NGS) of tumor DNA, which can detect both somatic mutations and genomic alterations across the whole exome or specific genes. NGS technologies are highly sensitive and capable of identifying point mutations, insertions, deletions, and copy number variations in the tumor's genome. The calculation of TMB involves sequencing tumor DNA and determining the number of mutations per megabase (mut/Mb) of the tumor's exonic regions. High-TMB tumors generally exhibit >10 mut/Mb, but the threshold for classification of "high" versus "low" TMB can vary based on cancer type, assay platform, and regulatory context [9,10].

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Discussion

Several studies have shown that tumors with high TMB may be more responsive to immune checkpoint inhibitors. TMB has been correlated with better outcomes, including higher rates of progression-free survival (PFS) and overall survival (OS), in patients treated with immune checkpoint inhibitors. The rationale behind this correlation lies in the concept that a higher number of mutations increases the presence of neoantigens on the tumor surface, making the tumor more "visible" to the immune system. When immune checkpoint inhibitors are used to block PD-1 or PD-L1, the tumor's ability to escape immune recognition is diminished, allowing the immune system to recognize and target these neoantigens more effectively.

For instance, in cancers like non-small cell lung cancer (NSCLC) and melanoma, which often harbor high mutational loads, patients with elevated TMB have shown significantly better responses to checkpoint inhibitors like nivolumab and pembrolizumab. Similarly, high TMB is associated with positive outcomes in other cancers, such as gastric cancer and head and neck squamous cell carcinoma. Beyond the mutational burden, the tumor microenvironment (TME) plays an essential role in determining the efficacy of immunotherapy. The TME consists of various cell types, extracellular matrix components, blood vessels, and immune cells. A high TMB may suggest an increased immunogenic potential, but a tumor's ability to evade immune surveillance depends significantly on its TME.

Factors such as immune cell infiltration, presence of immunosuppressive cells (e.g., regulatory T cells), and cytokine profiles can influence treatment outcomes. Tumors that are more immune "hot" (i.e., contain higher levels of immune infiltrates) are generally more responsive to immune checkpoint inhibition, while immune "cold" tumors (those with low immune cell infiltration) are less likely to respond to these therapies, even with high TMB. While TMB offers a potential biomarker for immunotherapy response, its predictive value is not perfect. Not all patients with high TMB will respond to immune checkpoint inhibitors, and some patients with low TMB may still exhibit durable responses. Therefore, researchers are exploring combination therapies to improve treatment outcomes.

One promising strategy is combining immune checkpoint inhibitors with other immunotherapy approaches, such as cancer vaccines, adoptive cell therapy, or oncolytic virus therapies. These approaches may enhance the immune system's ability to recognize and attack tumor cells, especially in cases where TMB alone does not predict a response. In addition, TMB may be used alongside other biomarkers, such as PD-L1 expression, microsatellite instability (MSI), and gene expression profiles, to develop a more comprehensive picture of a patient's immunotherapy suitability. Integrating TMB with these biomarkers may offer more precise predictions of treatment success, guiding personalized treatment strategies.

Despite its promise, there are several challenges in using TMB as a reliable biomarker for immunotherapy response

There is no universally agreed-upon threshold for what constitutes "high" versus "low" TMB. The cutoff value for TMB varies among cancer types, testing platforms, and research settings. This lack of consistency presents challenges in translating TMB measurements across different clinical contexts. TMB can vary not only across different patients but also within different areas of the same tumor. Tumor heterogeneity complicates the interpretation of TMB measurements, as biopsies from non-representative regions may underestimate the true mutational burden. While there is evidence to support a positive correlation between high TMB and response to immune checkpoint inhibitors, it is not a perfect predictor. Some patients with low TMB may still respond to immunotherapy, while some with high TMB may not. This highlights the need for complementary biomarkers or more refined definitions of TMB. The regulatory adoption of TMB as a biomarker is evolving. The U.S. Food and Drug Administration (FDA) approved pembrolizumab for use in patients with high TMB across all solid tumor types in 2020. This approval marked a significant milestone in incorporating TMB into clinical decision-making, especially for tumors that are traditionally difficult to treat. However, regulatory bodies continue to evaluate how TMB and other biomarkers can be incorporated into personalized treatment regimens for broader clinical use.

Conclusion

Tumor Mutational Burden (TMB) represents a promising biomarker for identifying patients who may benefit from immune checkpoint inhibitors. Tumors with higher TMB levels are more likely to harbor a greater number of neoantigens, potentially enhancing immune recognition and response to immunotherapy. Several cancers, including melanoma, lung cancer, and gastric cancer, have demonstrated better treatment responses when high TMB is present. Despite its potential, the use of TMB as a standalone biomarker faces challenges, including standardization issues, tumor heterogeneity, and limited predictive accuracy. To overcome these limitations, combining TMB with other biomarkers, leveraging immune microenvironment data, and exploring combination therapies may improve patient selection for immunotherapy. As research and clinical validation continue, TMB holds significant promise as an integral part of personalized cancer treatment, driving more effective and targeted immunotherapeutic approaches. Ultimately, TMB can play a key role in guiding decision-making for immunotherapy, improving treatment outcomes, and enhancing cancer care in the coming years.

Acknowledgement

None

Conflict of Interest

None

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