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Research Progress of TMB in Predicting Prognosis and Efficacy of Lung Cancer

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Abstract: Immune checkpoint inhibitors (ICIs) have changed therapeutic paradigms for patients across multiple cancer types and play an important role. However, due to the complexity and individual differences in immunotherapy, not all patients benefit from immunotherapy. New insights into the role of tumor mutational burden (TMB) suggest that their composition, as well as their functionality, might serve as a biomarker to enable optimal patient selection for current systemic therapies and upcoming treatment options. In this paper, we will review TMB as a biomarker for immunotherapy, assess the efficacy of immunotherapy, present several combinations of biomarkers to improve treatment prediction, and further evaluate the limitations of TMB as a biomarker of immunotherapy for lung cancer.
KEYWORDS: Immune Checkpoint Inhibitor, Tumor Mutational Burden, Biomarkers

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1. Introduction

According to the Global Cancer Statistics 2020[1], lung cancer remained the leading cause of cancer death in the world and the leading malignant tumor in China. Its incidence and mortality rates are still increasing year by year, posing a serious threat to national health. Lung cancer is the leading cause of cancer incidence and mortality in men, while women have the third highest incidence rate, just after breast and colon cancer, and the second for mortality, after breast cancer. Meanwhile, there are an increasing number of signaling targets related to the pathogenesis of lung cancer and biological behavior, which are discovered with the rapid development of life science and various detection technologies. With the emergence of targeted therapy and immunotherapy, the routine treatment of lung cancer has made a big step forward. After nearly a decade of development, TMB has emerged an effective genetic marker for screening the benefit groups and predicting the efficacy of ICIs. Therefore, it is particularly important to standardize and effectively select lung cancer patients with high-risk factors to select the correct and most sensitive biomarkers.

2. Overview of TMB

Tumor Mutational Burden (TMB) refers to the number of somatic mutations within the coding region, divided by the total number of non-synonymous mutation sites in the protein-coding region by the total length of the protein-coding region, measured in the unit of mutations/Mb (mut/Mb). Its expression is defined as somatic mutations in each genomic region (in addition to intron and synonymous mutations).

Although the pathological phenotypes of some multiple lesions were consistent, they still differ significantly in the distribution of TMB, for example, in different lesions of a patient. Qiu et al.[2] sequenced sixty-six lung adenocarcinomas (LUAD) by targeted next-generation sequencing to explore the distribution of TMB in different lesions within the tumor, further demonstrating heterogeneity within a tumor and across multiple tumors within a patient. Combining TMB values in specific lesion areas helps to separate the nature of multiple pulmonary lesions. At the same time, tumor cells are genetically unstable and highly somatic mutations, which can generate many new antigens that activate T lymphocytes to proliferate and kill tumor cells. The similarities can be found in Yarchoan and Liontos et al.[3, 4], immune checkpoint molecules on the surface of tumor cells negatively regulate the activation of T cells, resulting in suppression of the immune response by neoantigens and allowing tumor cells to escape from immune surveillance. Tumors with high TMB of immune checkpoint molecules on the surface of tumor cells may respond better to immune checkpoint inhibitors. Therefore, theoretically, TMB could be used as a biomarker for anti-tumor immunotherapy.

The relationships between TMB, MSI, and PD-1/PD-L1 expression

Microsatellite Instability (MSI) refers to the

occurrence/appearance of a new microsatellite allele at a microsatellite site/locus in a tumor due to the insertion or deletion of a repeat unit compared to normal tissue. This phenomenon occurs mostly due to mismatch repair of functional defects in tumor tissue DNA. TMB ≥10mut/Mb [5]is often considered to be in the TMB-High (TMB-H) state. A study from 6004 cases of colorectal cancer (CRC) tumors [6] revealed, nearly all microsatellite instable (MSI-high) (99.7%) patients were classified as TMB-H. The association of MSI-H status with TMB-H was highly statistically significant. In an analysis of microsatellite stable (MSS) patients, TMB-H patients who responded to PD-1 inhibitors were approximately 100× times likely to harbor known and likely variants in POLE (20.7% vs. 0.2%, P value <0.0001) compared to TMB-low (TMB-L) patients. Further work is needed to determine if the checkpoint inhibitor response of MSI-H tumors is associated with TMB-H and MSI-H.

Currently, studies on PD-L1 as a predictive biomarker have been widely carried out, there is a potential correlation between PD-L1 expression level [7] and immunotherapy efficacy, better clinical outcomes were obtained in patients with tumor TMB-H after treated with immune checkpoint inhibitor. In a study against for different histological components and different clinicopathological characteristics in patients with non-small-cell lung cancer (NSCLC)[8], discrepancy in histological components and pathological characteristics may contribute more to the heterogeneous expression of PD-L1. By integrating molecular omics data and real-world pharmaco-vigilance Long et al.[9] found when combined with TMB, CD8 T-cell abundance and homologous repair pathway mutation frequency, it was found that these three indicators not only significantly related the responses and side effects of PD-1 / PD-L1 inhibitor therapy, but also more accurately predicted the benefit-toxicity ratio for treatment response. Therefore, use the information appropriately and receive PD-1 / PD-L1 inhibitors selectively, which may help individualize therapy for patients. In the study by Hodi et al.[10], improved survival was observed with high TMB and absence of BRAF mutation, and the correlations between PD-L1, TMB, and the inflammatory signature were not significant, so combining TMB with inflammatory gene expression signatures and gene mutation status may provide a new idea for predicting advanced tumor response to immune checkpoint blockade.

3. Predictive value of TMB for immunotherapy

TMB has been extensively studied as a predictor of immunotherapy across tumor types, it was found to serve as a novel and useful candidate biomarker [11] for the clinical outcome of various solid tumors based on treatment. Research shows, compared with other biomarkers, TMB has many advantages. Hellmann et al.[12] examined NSCLC treated with combined PD-1 and CTLA-4 blockade using whole-exome sequencing and found that TMB was not only predictive of improved objective response, durable benefit, and progression-free survival but was not associated with PD-L1 expression, TMB was the strongest feature associated with treatment efficacy in multivariate analysis. This was validated in the results of a subsequent study [13] that TMB could serve as an important independent biomarker for advanced NSCLC. At the same time, compared with PD-L1, TMB can predict response to multiple immunotherapies which can not only predict response to PD-1 / PD-L1 inhibitors, but also anti-CTLA4 such as ipilimumab, as well as adoptive cell therapy[14-16], can provide some predictive utility. TMB ≥10 mut/Mb is [17] considered by to be the threshold for a high likelihood of neoantigen formation, while patients with higher TMB threshold have longer progression-free survival (PFS), thus this also defines TMB-H status. Klempner et al.[18] studies in patients with NSCLC using targeted next-generation sequencing (NGS) have also found, the critical value of TMB fluctuates around 10 mut/Mb. The discovery of a TMB cut-off value that can predict the efficacy of ICIs for patients with NSCLC. In 2020, the FDA approved the PD-1 antibody pembrolizumab for the treatment of TMB-H (TMB > 10 mut/Mb) solid tumors [19]. In general, the more mutations the lesion carries, the higher the TMB and the more responsive the tumor is to immunotherapy. Duffy et al.[20] conclude, the increased productions of neoantigens may render a tumor more immunogenic and thereby improve response to immunotherapy. In some specific cases, TMB-H can also suggest clinical medication efficacy. Among patients with advanced soft-tissue sarcomas (STS) or alveolar soft part sarcoma (ASPS) with metastases, anlotinib combined with toripalimab was shown by [21] to be a very effective treatment and to be more effective in STS patients with TMB-H. At the same time, the situation of TMB-H may suggest a better prognosis in its treatment after sintilimab monotherapy [22]. Multiple studies in advanced and metastatic NSCLC [23, 24] and small cell lung cancer (SCLC) have pointed out that the response to anti-PD-1 treatment correlates with TMB, meanwhile, TMB-H has been associated with improved PFS in advanced and metastatic NSCLC [12, 13, 25], a high recurrence rate in stage III NSCLC patients [26], and increase efficacy in SCLC [16].

Combines multiple biomarkers for predicting treatment efficacy

TMB has been shown to be an effective independent

biomarker and can be used to predict lung cancer immunotherapy. And as research continues to deepen, it is helpful to combine TMB with other biomarkers to improve prediction accuracy.

As noted in multiple studies [27, 28], blood-based assay to measure TMB in plasma (bTMB) has also been shown to be a reliable predictor of ICIs response. In a study [29] on advanced lung squamous cell carcinoma (LUSC), the efficacy of camrelizumab plus chemotherapy can be monitored by bTMB during treatment and its dynamics, and bTMB could be considered as a promising potential prognostic biomarker. Significantly longer PFS [27] were found to be associated with bTMB after atezolizumab. In advanced NSCLC, by anti-PD-L1 monotherapy [28], bTMB was also found to identify patients with significant PFS improvement. Recently, two retrospective studies [30, 31] found that bTMB can be used as a potential biomarker to predict the efficacy of NSCLC patients. Moreover, compared with the problems with histopathological acquisition such as invasiveness and insufficient tumor cells, bTMB can be used as a minimally invasive alternative to avoid these problems. In terms of predicting efficacy, based on the two TMB detection methods of blood and tissue, showed a good linear correlation between the two groups of data, both of which could better quantitatively reflect the gene mutation status of tumor tissue. However, compared with tTMB, the predictive value of bTMB is still controversial [27, 32]. In the study of Klevebring et al. [33], he concluded that bTMB is less predictive than tTMB, an important reason being that it has only a small amount of ctDNA and the amount of ctDNA in circulation is limited, detection of ctDNA from plasma remains challenging [34]. It has also been suggested that malignant pleural effusions (MPE) may be used as an alternative method for liquid biopsy [35, 36]. The proposal of liquid biopsy could provide a new idea in cases where histopathology is not available. However, it has not been confirmed in many tests with the corresponding conclusion in other immunological drugs or disease species. It has not yet been demonstrated whether the selection of its boundaries is the same as that of tissue TMB, which needs further research.

HLA-I complex and infiltration levels of cytotoxic T cell (CTL) can also be used as biomarkers to predict the efficacy of anti-PD1 and anti-PD-L1 monoclonal antibodies. CASTRO et al. [37] found that patients with HLA mutations tended to have higher TMB and neoantigen levels. Although positive HLA-I expression [38] is independent on PD-L1 status, it is a key factor determining the increase of immune infiltration density, and positive PD-L1 usually indicates the presence of PD-L1 expression in tumor cells or tumor-infiltrating immune cells, therefore, it is suggested that the level of HLA-I protein in lung cancer tissue is related to the level of PD-L1. In addition, studies [39] found that compared with other patients with heterozygous HLA-I locus, patients who were homozygous for at least one HLA locus produced fewer tumor neoantigens. And overall survival (OS) was longer in heterozygous patients for HLA-I than in patients with homozygous alleles. Patients with loss of heterozygosity (LOH) had shorter OS in HLA-I heterozygosity but LOH in at least one locus, especially in the TMB-L population. Although the relationship between HLA LOH and the outcome of immunotherapy in patients has not been proven, the conjoint analysis of TMB can more accurately screen out the population with high benefits.

The establishment of the MicroRNAs(miRNA) model can be used as a new predictive tool to predict the TMB level of patients with advanced cancer. The findings could help identify patients with high TMB receiving immunotherapy. For example, the Li et al. [40] study found that the differential expression pattern between 32 miRNAs and TMB values in patients with colon cancer (COAD) is highly correlated, which can provide a basis for clinicians to predict TMB levels in patients with advanced COAD. Schumacher et al. [17] study indicated that high levels of TMB may cause modification of proteins encoded by mutated genes, meanwhile, these modified proteins are recognized by the immune system as “non-self” and activate specificity, post-transcriptional regulation is required to translate the mutant genes into modified proteins, and miRNAs are important molecules involved in post-transcriptional regulation. So, the differential expression of miRNAs is also licensed to predict TMB levels, helping to identify advanced tumor patients with favorable immunotherapy response, thus enabling individualized precision therapy.

Some studies [41] found that there was a significant interaction between the T cell receptor (TCR) index and TMB, which may provide some guidance on the neoadjuvant treatment of operable lung cancer in the future. At the same time, TMB showed some linear correlation with the TCR index D50, diversity index, and entropy, and this significant correlation was also confirmed in a study [42] focused on breast cancer. Breast cancer pCR refers to a complete pathological response achieved by surgery, whereas in non-pCR tumors, both $CD3^+$ and $CD8^+$ cells increase significantly after neoadjuvant therapy. This would suggest that, even without significant clinical benefit, the immune microenvironment could be improved by recruiting more potent immune cells. The intrinsic reason may be that chemotherapy can further increase immune cell infiltration by inducing cancer cell death and antigen release while modulating intertumoral chemokine

expression[43, 44]. Thus, combining TCR with TMB, perhaps enabling dynamic monitoring of the immune microenvironment, represents a new avenue to predict immune efficacy.

A study of DNA proofreading enzymes [45] found that certain specific mutations of DNA polymerases can lead to higher rates of base substitution mutations. Mutations in these genes are associated with elevated TMB, and screening for these DNA proofreading enzymes may benefit a larger number of patients from ICIs.

Lu et al.[46] studies suggest that CNAs may have better predictive value compared to other features such as PD-L1, MSI, and TMB. Meanwhile, it was found in Liu et al.[47] study that patients with TMB-L and CNA-high（CHA-H） might be the best subgroup to show good response in ICIs therapy. Therefore, TMB-H with CNA-low（CNA-L） may serve as a novel biomarker that is more predictive of ICIs effectiveness than TMB or CNA alone and can be used to partition tumors into different sensitive ICIs treatments, while the combined biomarker of CNA and TMB may better screen and stratify patients, thereby providing a more rational choice for patients treated with ICIs.

Therefore, although TMB is associated with better therapeutic efficacy of ICIs, the specific reasons for the effectiveness of therapy remain unclear, meanwhile, due to the complexity of the immune response, TMB must be considered together with multiple other factors to optimize the prediction of ICIs outcome.

4. Conclusion

In summary, several studies have demonstrated that TMB can be a potential biomarker for predicting the efficacy of immunotherapy, but its efficacy remains controversial and the specific mechanism of TMB is not yet clear. Many questions remain in practice. With the development of the second-generation ICIs research, the existing biomarker detection methods should be further standardized, and more predictive biomarkers based on TMB should be continuously investigated to reduce the relevant effects and further improve the accuracy, so that the therapeutic effects of ICIs can be better predicted by combining TMB with them. The TMB mutations studied are limited to the initial analysis of a few genes associated with tumorigenesis and progression, and a more comprehensive assessment of many genes is needed in the future. The threshold values of high and low TMB were significantly different in the definition of different tumor types and further studies in larger groups on the optimal threshold of TMB is needed in the future to more effectively establish the criteria to distinguish immunotherapy responders from non-responders, and to leverage the most valuable biomarkers to achieve individualized, precise administration for better clinical outcomes.

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