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Correlative Factors of PD-1/PD-L1 Inhibitors-based Immunotherapy Responses in Non-small Cell Lung Cancer

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Abstract. The use of immunotherapy as a treatment modality in the field of cancer has garnered significant attention since its discovery. Among these, studies have demonstrated the substantial benefits of using programmed death 1 (PD1)/programmed death ligand 1 (PD-L1) inhibitors in the treatment of non-small cell lung cancer (NSCLC). However, as research continues, there are differing advantages and disadvantages to this treatment for NSCLC. Adverse effects related to the immune system and high costs are also faced by patients undergoing this therapy. As a result, the creation of biomarkers is crucial for the immunotherapy of cancer. Numerous studies have examined immunotherapy's side effects in non-small cell lung cancer. Therefore, on the basis of previous studies, this article reviews the factors related to the involvement of PD-1/PD-L1 inhibitors in the immunotherapy response of NSCLC, in order to find candidate drugs and more effective biological treatments for PD-1/PD-L1 inhibitors. Markers provide direction and theoretical basis.

Keywords: NSCLC; PD-1/PD-L1; immunotherapy.

1. Introduction

Lung cancer, a malignant tumor, continues to be one of the leading causes of cancer-related death worldwide in terms of both death and morbidity, among which NSCLC is the most common pathological type. Moreover, patients with advanced NSCLC don't benefit much from traditional chemical and radioactive treatments [1]. Immunotherapy, of which PD-1/PD-L1 have been shown to have broad application prospects, particularly in the treatment of NSCLC, is gradually emerging as a major breakthrough in the treatment of cancer.

PD-1 is a kind of immune inhibiting receptor and its main ligand is PD-L1. When a tumor takes place, the combination of PD-1 and its ligand PD-L1 will result in the immunosuppression of T cells and contribute to tumor immune escape [2]. Blocking the PD-1/PD-L1 pathway thus is considered an important way of immunotherapy in various tumors, with many improvements being achieved in clinical practices. Nonetheless, the number of patients with NSCLC who respond to this therapy are still rather limited, the responses of patients vary from one another, and potential problems like unaffordable prices and immune-related adverse events may come about consequently [3]. So, the use of reliable predictive biomarkers is vital for this immunotherapy. To discover reliable biomarkers, studies on the correlative factors of immune checkpoint therapy outcome are required.

A few studies to find out the correlated factors of immune checkpoint inhibitors (ICIs)-based immunotherapy outcomes have been carried out these years. According to these researches, various kinds of factors can contribute to the outcome of patients undergoing ICIs treatments. Niki Gavrielatou and colleagues showed that PD-1/PD-L1 co-relation is a promising biomarker for the immunotherapy for NSCLC [4]. Xiaoyan Wang and colleagues demonstrated that PDPRD/PDPRT mutation is a positive predictor for immune check point therapy for NSCLC [5]. In addition, Afsheen Raza and colleagues depicted that serum immune mediators' effect on responses of patients to PD-1/PD-L1 blockade [3]. This research classified the already known correlative factors into six different groups, genetic factors, immune checkpoint-related factors, serum immune factors, immune cell related factors, tumor related factors and macrocosm factors, explained the associations with them and the immunotherapy outcomes respectively and also interpreted the possible mechanisms. As a result, a direction for selecting patients with NSCLC that may be suitable for this immunotherapy can

be made and some suggestions for future research on biomarkers of PD-1/PD-L1 inhibitors immunotherapy can be provided.

2. PD-1/PD-L1

First of all, immunoreceptor tyrosine-based switch motif (ITSM) in the cytoplasmic domain is phosphorylated and then the protein tyrosine phosphatases SHP1 and SHP2 is accumulated in the cytoplasm. After that, the phosphorylation of ζ-associated protein of 70 kDa (ZAP70) is suppressed, followed by the dephosphorylation of the downstream signaling molecular phosphatidylinositol-3-kinase (PI3K). This contributes to the phosphorylation of PIP2, with it transforming to PIP3. So, the activation of AKT is depressed consequently, which impacts several significant metabolism pathways in T cells and results in protein synthesis, survival and proliferation decrease [6]. Therefore, the PD-1/L1 inhibitors serve to specifically block the combination of PD-1 and PD-L1 in order to protect immune cells from immunosuppression and restore its capability of killing tumor cells.

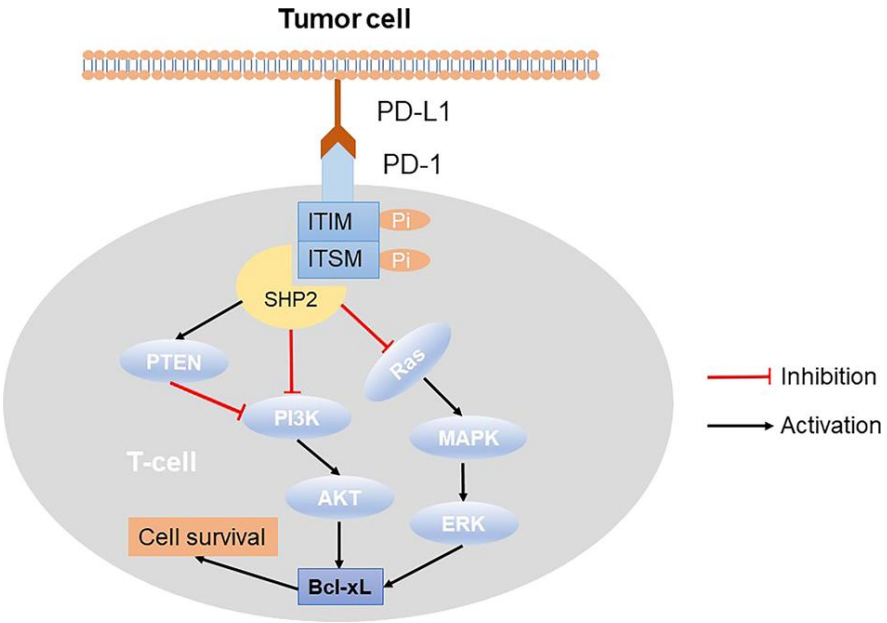

Figure 1. Mechanism of PD-1/PD-L1 [7]

3. Various Kinds of Correlative Factors of Outcomes

3.1. Genetic Factors

Mutations of several genes have been proven to be associated with the responses of patients undergoing ICIs. According to the research launched by Xiaoyan Wang and colleagues, PTPRD/PTPRT mutation is significantly associated with better progression-free survival (PFS) and overall survival (OS) and this association is driven by treatment with immune checkpoint blockade. The mechanism of this can be interpreted with the fact that PTPRD and PTPRT are phosphatase receptors participating in JAK-STAT signaling process which is of vital significance for immune development and mutation of PTPRD/PTPRT can markedly enhance the expression of JAK and STAT. Further research demonstrated that genes connected to antigen processing and presentation are dramatically increased in PTPRD/PTPRT mutants than that in wild types by analyzing mRNA expression, especially chemokines with T cell related effective chemoattractant. Moreover, PTPRD/PTPRT mutation is associated to higher tumor mutation burden, which is another approval factor for immunotherapy outcomes [5].

Apart from that, other mutations like DNA damage response and repair gene (DDR gene) and RAD51B methylation are also connected to improved outcomes in immune checkpoint blockade and potentially valuable as a predictive biomarker [7, 8]. As for the reasons, the mutation of DDR gene

is not only a symbol of high TMB and increased tumor-specific neoantigen but also an activator of some neoantigen-free antitumor immunity pathways such as stimulators of IFN genes pathway (STING pathway) [7]. RAD51B is one of the proteins that have impact on homologous recombination repair pathway of DNA, the defects of which can lead to higher PD-L1 expression. As the result, the methylation level of the gene is a potential biomarker of PD-1/PD-L1 inhibitor immunotherapy [8].

3.2. Immune Checkpoint-related Factors

It's known that the interaction of PD-1/PD-L1 is directly related to the response of patients with NSCLC undergoing treatments with ICIs. PD-L1 expression was mostly used as a biomarker of response in immunotherapy in everyday clinical practice in the past. However, according to documentation evidence and other factors, it is far from a perfect predictive biomarker. In recent years, more efficient factors of PD-1/PD-L1 have been studied. PD-1/PD-L1 co-location, according to the study initiated by Niki Gavrielatou and colleagues, is associated with the clinical outcome. As a surrogate for PD-1/PD-L1 interaction, PD-1/PD-L1 co-location is defined expression in the same pixel, showing positive correlation to response in immune checkpoint blockade [4]. In addition, another research depicted that PD-1/PD-L1 polymorphisms have an impact on clinical outcomes. This research focuses on the single nucleotide rs822339 and revealed that patients with A/A nucleotide in this location have longer OS than that with A/G and G/G genotypes, meaning that this genotype may affect the PD-1/PD-L1 reaction, though the specific mechanism has not been figured out so far [9].

3.3. Serum Immune Factors

Several types of research showed that various soluble serum factors can predict unfavorable outcomes in immunotherapy with PD-1/PD-L1 markers. According to the research accomplished by Li-Na He and colleagues, patients with low baseline and early descent of SAA benefited from a longer OS and progression-free survival. The possible reason for this is that some inflammatory mediators may contribute to the formation and immunosuppression of the tumor microenvironment by inducing TLR2 signaling and then increasing the secretion of TNF-α, while the detailed interaction with inflammatory factors and tumor cell still needs further study [9]. Other serum inflammatory factors like C-reactive protein, Erythrocyte Sedimention Rate and Procalcitonin are also correlated with decreased response in clinical treatment [10]. Apart from the inflammatory factors, a set of immune inhibitory factors in the serum also work as biomarkers to predict the response of patients, for example, only patients with favorable outcomes are found to be with markedly downregulation of some other immune inhibitory biomarkers [11].

3.4. Immune Cell-related Factors

The number of immune cells can represent the outcomes in the ICI treatment for patients with NSCLC, especially the circulating regulatory T cells, which is able to predict pseudo progression and hyperprogression of patients after immunotherapy, according to Da Hyun Kang and colleagues [12]. This is because regulatory T cells are associated with immunosuppression. Moreover, neutrophil-to-lymphocyte ratio (NLR) is another potentially predictive factor, which means patients with lower NLR have a longer survival period. The reason is that high NLR suggests systemic inflammation [13]. Apart from that, products of immune cells like Granzyme B can also serve as a biomarker, showing a positive correlation with the outcomes.

3.5. Tumor Related Factors

Some factors about tumor itself can predict if patients will response to ICIs. It's known that tumor mutation burden is a marker for superior clinical outcomes. What is more, pre-treatment tumor growth rate is related to the clinical outcomes. According to Li-Na He and colleagues, a high pre-treatment tumor growth rate is a reliable predictive factor for poor clinical responses. Although the mechanism remains unclear, it is hypothesized that high tumor growth rate indicates an unfavorable tumor

microenvironment for PD-1/PD-L1 interaction. Reducing of target lesions, however, can represent increased clinical outcomes in patients with NSCLC.

3.6. Macrocosm Factors

macrocosm factors refer to the factors about the structure of body, organs and tissues. According to former studies, patients with better hepatic functions benefit more from the ICIs, enjoying longer OS. Muscle quality is another approval factor of clinical outcome, with higher muscle quality suggesting longer progression free survival and higher objective response rate. Body mass index is also significantly associated with the efficacy of ICIs in patients with NSCLC.

4. Conclusion

Before selecting the candidate for ICIs, detailed physical examination should be adapted to check multiple correlated factors like gene mutation, immune checkpoint interactivity, serum immune factor level and other factors, so that the response rate in the patients can be enhanced.

The PD-1/PD-L1 co-location is not a perfect surrogate for PD-1/PD-L1 interaction, as the PD-1 and PD-L1 expressing in the same pixel do not necessarily interact with each other. As PD-1/PD-L1 interaction is directly associated to the outcomes, more biomarkers linked to the interaction need to be studied.

Though many potential biomarkers of clinical outcomes in ICIs treatments have already been discovered, the mechanism of their interactions with the tumor cell mostly remains unknown. The future study can focus on the specific pathways of the biomarkers to help construct a better understanding of them.

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