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The State of Research on PD1/PD-L1 Regulation by Non-coding RNA in Non-small Cell Lung Cancer

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ABSTRACT

Globally, non-small cell lung cancer (NSCLC) is the primary cause of death from cancer. Immunotherapy has advanced significantly in the medical management of NSCLC over the previous couple of decades. Particularly immune checkpoint drugs that target programmed death receptor 1 (PD-1) and its ligand 1 (PD-L1). Meanwhile, miRNAs are crucial for controlling the PD-1/PD-L1 pathway in NSCLC and are an increasingly significant field of investigation at the moment. For these reasons, this paper reviewed the mechanism of the PD-1/PD-L1 pathway in immunological escape from malignant cells and explored how non-coding RNAs (including microRNAs, long-chain non-coding RNAs, and cyclic RNAs) can affect the occurrence as well as growth of NSCLC by regulating PD-1/PD-L1 activity. Argument cites specific miRNAs such as miRNA-200c have the capability to alter the level of PD-L1 expression and thus enhance cancer innate immunity. Beyond that, LncRNA such as NEAT1 affect expression of PD-L1 and evasion of the body's defenses through interaction with miRNAs. In NSCLC, circular RNAs are performing a crucial function in evading immune responses. The article also discusses the efficacy and challenges of our self-developed PD-1 inhibitors in treating advanced NSCLC and emphasizes the need to improve the precision of immunotherapy. Finally, the article highlights the necessity for additional investigation to uncover more upstream modulators to enhance the prognosis and clinical outcomes of NSCLC individuals.

KEYWORDS

Non-small cell lung cancer; PD-1/PD-L1; Immune checkpoint inhibitors; Non-coding RNA; Immunotherapy

1. INTRODUCTION

The International Agency for Research on Cancer (IARC) of the World Health Organization has recently published its latest findings, indicating that in the year 2022, lung cancer accounted for 12.4% of the overall cancers that were recently diagnosed and 18.7% of all fatalities caused by cancer worldwide. Furthermore, it achieved the highest ranking in both male and female populations and has subsequently regained its status as the most typical kind of cancer internationally. Approximately 85% of these illnesses consist of non-small cell lung cancer. Recent advancements in the field of lung cancer treatment have resulted in the emergence of immune therapy as a promising therapeutic strategy for malignant tumors. One notable aspect of immune therapy is the utilization of immune checkpoints, with programmed death 1 (PD-1) and its associated ligand (PD-L1) being prominent examples. Specifically, Pembrolizumab is authorized for the primary healthcare of individuals diagnosed with NSCLC that has metastasized to distant organs and exhibits elevated PD-L1 activity.

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2. PD 1/PD-L 1 OVERVIEW

PD-1, or CD279, a necessary inhibitory molecule that is mainly discovered on the outermost layer of T cell activation. It is made up of 288 amino acids and being assigned to the B7-CD28 superfamily. It shares a sequence similarity of 15% with CD28. Both ligands for PD-1 belong to B7. PD-L1 and PD-L2 are two proteins, with the interaction between PD-1 and PD-L1 being more noticeable within the neoplasm. The liaison between PD-1 and its receptor substance hinders the growth of T cells and cytokines generation, including IFN-γ and IL-2, occurring. In addition, PD-1 has an impact on peripheral immunological tolerance.

Multiple findings indicate that PD-L1 is prominently displayed in numerous kinds of cancerous tumors, especially renal cell cancer, hepatic carcinoma, NSCLC, and others. PD-L1 expression on tumors can be regulated through internal mechanisms, such as the stimulation of the PI3-kinase pathway due to PTEN loss, or extracellular signaling associated with the immune response, such as IFN- γ secretion by peripherally activated T cell lymphocytes [1].

The cytosolic tail of PD-1 has an intracellular immunoreceptor tyrosine switch motif (ITSM) and an immunoreceptor tyrosine inhibitory motif (ITIM). PD-1 phosphorylates the ITSM and ITIM by binding to the ligand, which activates the phosphatase SHP2 (or SHP1) to cause PI3K dephosphorylation and inhibits the phosphorylation of important molecules such as LCK phosphorylated ZAP70, CD3 ς, PKC θ, and other important molecules to inhibit TCR signaling, leading to the Ras / MEK / ERK pathway and the PI3K/AKT/mTOR pathway gaining triggered [2].

Immunotherapy extensively investigates the PD1/PD L1 immunological examining point, which can activate the immunological system that someone being treated. Within the tumor microenvironment, tumor cells hinder the growth of defense cells and suppress the immune response by increasing the production of PD1/PD-L1. PD-1 attaches to the outer layer of CD8+ T cells that are specific to the carcinoma tissue, rendering them inactive.

Analysis show that PD-1 is expressed an outstanding range in Treg cells while promotes proliferation of Treg cells, converting primary CD4+ T cells to Treg cells. As Treg cells are highly infiltrated in many malignant tumors, they can further inhibit the immune response of the host to produce a highly immunosuppressive tumor microenvironment [3]. Additionally, whereas PD-1 is only expressed by T cells that have been stimulated, the blocking signals that PD-1 generates only affect PD-1+ CD8+ T cells that have already produced a tumor-specific response, hence inhibiting the activity of these immune cells [4]. By applying anti-PD-1/PD-L1 immunosuppression and thus blocking the PD-1/PD-L1 action pathway, not only can it lift its inhibitory state on T cells and restore the T cell function, but also strengthens the tumor's immune system reaction by lowering the quantity of Treg cells present in the malignancy or suppressing their activity in the cancer, so as to achieve the effect of tumor treatment. At present, the four major PD-1 inhibitors in China are toripalimab (Tor), sintilimab (Sin), camrelizumab (Cam), and tislelizumab (Tis). Clinical trial data have shown that this kind of immunosuppressant works well for curing advanced non-small cell lung cancer [5]. However, PD1/PD-L1 inhibitors have a high variability in individual patient treatment and certain patients do not react to inhibitors of PD-1 [6]. Therefore, so as to increase the effectiveness of PD-1 blockers and further beneficiary population, the precision of immunotherapy needs to be improved.

3. NON-CODING RNA

3.1. MicroRNA

MicroRNA usually can cut off the mRNA molecules of target genes or inhibit the translation of target genes by binding completely or incompletely to the complementary regions of target gene mRNAs, thus achieving the function of regulating gene expression after transcription. Some studies have

shown that miRNAs play different functions depending on where they are expressed. In one case, miRNA - 17 - 92 gene groups and miRNA-155, which occur in the amplified zone of the cancer genome play an oncogenic role, while miRNAs located on the deletion chromosome in the cancer gene region (miR-15a and miR-16-1) play a cancer-suppressive role as tumor suppressors [7]. In addition, extracellular miRNAs can work together with components of stromal cells and extracellular matrix to influence intercellular communication to regulate tumor cell function, causing immune escape from the tumor to the host and providing a suitable microenvironment for tumor growth [8]. However, the progress of miRNA in tumor therapy is not smooth. Due to the wide range of miRNA target genes, its drug delivery and cell penetration are poor. It will produce negative damage which human body can not be ignored, so the use of miRNA remains challenging [9].

A recent experimental investigation demonstrated that the presence of miR-138-5p and miR-200c can enhance the infiltration of T lymphocytes in NSCLC tumors by reducing their levels. The upregulation of PD-L1 in the tumors leads to enhanced immunological infiltration of T cells in the malignancies. This study discovered that both miR-138 and miR-200c were able to decrease the levels of PD-L1 in lung cancer cells through experiments conducted on mice. Furthermore, when these two miRNAs were used together, they were able to almost entirely suppress the expression of PD-L1 and decrease the presence of Treg cells in lung cancer tumors by inhibiting the PD-1/PD-L1 pathway. Additionally, the combined treatment induced the growth of CD4+ and CD8+ T cells. The findings suggest that the carcinogenic effect in NSCLC may be caused by the suppression of PD-L1 expression by miR-138-5p and miR-200c [10].

3.2. LncRNA: Long Noncoding RNA (lncRNA)

LncRNA is used as competitive endogenous RNAs of miRNAs that can inhibit protein translation, and mostly regulate gene expression in trans at the post-transcriptional level, and it is involved in a variety of important biological functions such as in the regulation of epigenetic inheritance, cell division and cellular differentiation, and so on. It has been discovered that lncRNA exhibit aberrant expression in a range of tumor types, and there is mounting proof that lncRNA function biologically in many systems via a multitude of distinct routes. For example, (i) interacting with lncRNA proteins; (ii) via the Lncrna-Cerna network; (iii) silencing through Lncrnamirna - mRNA expression; (iv) linking to DNA through cis; (v) connecting to the promoter regions of encoded genes. These actions can regulate modifications to histone proteins, intervene in chromatin remodeling, and obstruct the biological activities of transcription factors, which have a dual role in NSCLC [11].

Therefore, LncRNA own a complex biological regulatory network that can affect multiple signaling pathways [12].

NEAT1, a lncRNA, is a newly identified key oncogene in human cancers, and it has been demonstrated that a worse prognosis for NSCLC is linked to elevated levels of NEAT1 expression. It can be used as a biomarker for NSCLC diagnosis and prognosis [13]. miINA-128-3P, which contains the binding sequences of NEAT1 and HNPNPL, was predicted by bioinformatics, and according to previous studies, the expression of PD-L1 was positively correlated with the expression of heterogeneous cytosolic ribonucleoprotein L (heterogeneous nuclear ribonucleoprotein LHNPNPL,) in prostate cancer. Therefore, it was hypothesized that there is a link between NEAT1, miINA-128-3P, and HNPNPL, PD-L1 pathway. Experiments showed that knockdown of NEAT1 upregulated miR-128-3p, inhibited HNRNPL and PD-L1 expression, reduced NSCLC cell viability, and induced apoptosis, and A549 cells co-cultured with CD8+ T cells were found to activate and inhibit apoptosis of CD8+ T cells while reducing PD-L1 and IFN-γ levels. IFN-γ levels. Therefore, the mechanism of NEAT1-mediated immune escape in NSCLC may be related to the driving effect of miR-128-3p/HNRNPL axis on PD-L1. However, this study did not further validate the mechanism of its action from in vivo experiments, which has certain limitations and is expected to be further explored and improved in future studies [14].

3.3. CircRNA

Circular Ribonucleic Acid (circRNA) is a kind of endogenous RNA widely expressed in eukaryotic cells, and its molecular chain is a ring structure closed by covalent fixation, which makes circRNA not easy to be degraded by RNA enzymes, so circRNA possesses a stronger structure compared to linear RNA. Numerous investigations have consistently revealed the significant involvement of circRNA in the clinical course of NSCLC [15].

circRNA in tumor immunity promotes NSCLC genesis and progression by directly binding to miRNAs, increasing the expression of corresponding target genes regulating post-transcriptional gene expression levels, and enabling the generation of tumor immune escape responses (e.g., circ MET regulates the miR - 145 - 5p / CXCL3 axis to promote the proliferation, metastasis, and immune escape of NSCLC cells [16]).Through the regulation of ubiquitinated proteins involved in the breaking down of IGF2BPs and the awakening of anti-tumor immune responses in NSCLC development, it can also be exploited to increase NSCLC cell growth, cancer metastases, and immune-related escape [17].

It was discovered that human NSCLC tissues had high expression levels of circ USP7, which was mostly released by NSCLC cells via exocytosis. Not only did circUSP7 prevent CD8+ T cells from secreting cytokines like IFN-γ and TNF-α, but it also could suppress CD8+ T cell function by upregulating the expression of protein tyrosine phosphatase 2 (SHP2), which contains Src homology region 2 (SH2), through sponge adsorption of miR-934. Studies have demonstrated that the exosomal circUSP7/miR-934 / SHP2 axis in non-small cell lung cancer (NSCLC) reduces the curative benefit of anti-PD1 therapy. Furthermore, in people with increased circUSP7 expression, SHP2 inhibitors have been shown to lessen the immunosuppressive effects of CD8 + T cell suppression [18].

4. SUMMARY

This paper reviews the mechanism of PD-1/PD-L1 in tumor immune escape and discusses how microRNAs, lncRNA, and circ-RNAs in non-coding RNAs affect PD-1/PD-L1 expression and thus NSCLC development and progression. The drug development of PD-1/PD-L1 immunosuppressants for NSCLC was evaluated from the perspective of non-coding class RNAs and evaluations were provided in anticipation of contributing to the improvement of clinical efficacy in NSCLC. The development of such drugs and disease treatment should be combined with multifaceted research, and further exploration of transcription factors, epigenetic factors and multiple signaling proteins is needed to discover more upstream modulators to further improve the accuracy and beneficiary populations of HSCLC immunotherapy.

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