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Research Progress on Peripheral Blood Exosomes (exo-PD-L1) in the Early Diagnosis of Non-Small Cell Lung Cancer

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Abstract. Non-small cell lung cancer (NSCLC) represents the most prevalent subtype of lung cancer. Conventional diagnostic approaches, including imaging and tissue biopsy, have drawbacks in terms of sensitivity, specificity, and dynamic monitoring. There is an urgent need to develop non-invasive reliable diagnostic biomarkers. Peripheral blood exosomal exo-PD-L1 has demonstrated potential clinical utility for early diagnosis and disease monitoring of NSCLC. However, the large-scale application of this detection method still faces challenges such as inconsistent testing standards and insufficient clinical evidence.This review systematically elucidates the biological characteristics and functions of peripheral blood exosomal exo-PD-L1, compares the features of different isolation and detection techniques, summarizes recent clinical research evidence regarding its application in the early diagnosis, treatment response prediction, and prognosis assessment of NSCLC, and further analyzes the major challenges facing present studies and forthcoming perspectives, with the aim of providing a theoretical basis for promoting the conversion to clinical practice of exo-PD-L1 as a non-invasive biological markers for NSCLC.

Keywords: Non-small cell lung cancer, exosomes, exo-PD-L1, liquid biopsy, early diagnosis

1. Introduction

Globally, lung cancer ranks among the most common malignant tumors in both incidence and mortality, with non-small cell lung cancer (NSCLC) accounting for approximately 80% of all cases. Recent advances in liquid biopsy have promoted the development of exosome-based biomarkers. Programmed death-ligand 1 (exo-PD-L1) is recognized as one of the critical molecules involved in tumor immune evasion, facilitating tumor progression through T-cell inhibition activation. Studies have shown that exo-PD-L1 is not only expressed on the surface of tumor cells but is also released into the peripheral circulation via exosomes, where it regulates the immune microenvironment at a distance [1]; Other studies have shown that it mediates systemic immune suppression, and its expression levels are closely associated with tumor progression [2] and response to immunotherapy [3]. Based on this, peripheral blood exosomal exo-PD-L1 has demonstrated potential value as a novel non-invasive early diagnostic biomarker of NSCLC [3].

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2. Overview of peripheral blood exosomal exo-PD-L1

Exosomal PD-L1 (exo-PD-L1) originating from tumor cells from tumor cells generally retains the same spatial conformation and topological characteristics as the original tumor cell membrane. Engaging PD-1 on the T-cell surface, it curbs T-cell activation, proliferation, and function—facilitating immune evasion [4, 5]. Exo-PD-L1, however, actively enters PD-L1-low cells and then appears again on their surface. This action, in turn, strengthens immune suppression and reshapes the tumor microenvironment along with its response to immunotherapy [6, 7].

Detecting exo-PD-L1 in peripheral blood holds notable benefits—noninvasive, repeatable, indicative of systemic tumor burden and immune evasion, and free from tissue-sampling bias.

3. Toward high-precision diagnosis: combined testing and multimodal integration strategies

3.1. Expression characteristics and diagnostic performance as an early diagnostic biomarker

Peripheral blood exosomal exo-PD-L1 is primarily into the circulatory system by tumor cells and can indicate the status of the immune microenvironment of tumors, making it a potentially valuable reference for early tumor diagnosis. A study on 65 patients with advanced NSCLC showed that elevated blood exo-PD-L1 levels are closely correlated with TNM staging, lymph node metastasis, and distant metastasis, but lack any significant association with age, gender, smoking history, or ECOG performance status [8]. Furthermore, existing studies have demonstrated that blood exo-PD-L1 levels also exhibit an upward trend in patients diagnosed with early-stage NSCLC and can be measured using research approaches such as enzyme linked immunosorbent assay (ELISA) [9]. Additionally, Li found that exosomal exo-PD-L1 levels in the serum of 85 NSCLC patients were significantly elevated and were linked to TNM staging, tumor volume, lymph node metastasis, and distant metastasis (whereas), soluble PD-L1 showed no association with these factors.

In terms of diagnostic performance, exo-PD-L1 exhibits a certain level of sensitivity and specificity. Its expression levels show significant differences between NSCLC patients and healthy controls. In the receiver operating characteristic (ROC) curve, exo-PD-L1 demonstrates good discriminatory power for NSCLC, and its area under the curve (AUC) indicates that exo-PD-L1 can reflect tumor immunological status and assist in early screening [9]. Additionally, exo-PD-L1 can be detected jointly with other liquid biopsy biomarkers, including circulating tumor DNA (ctDNA) and microRNAs (miRNAs). Through multimodal integration strategies, the sensitivity and specificity of early diagnosis can be further improved, offering a new research direction for non-invasive early screening [10].

3.2. Clinical research evidence in the early diagnosis of NSCLC

exo-PD-L1 can be detected via non-invasive liquid biopsy and dynamically reflects tumor-mediated changes in systemic immune suppression [7]. Zhou et al. reviewed this topic and noted that exo-PD-L1 is easier to collect than tissue PD-L1 or regular serum markers. It shows the real-time immune suppression state caused by the tumor. All of this helps with catching NSCLC early and watching how the disease changes later on [11].

Advances in liquid biopsy technology have made multi-marker panel testing an effective approach for improving the accuracy of early diagnosis. Exosomal miRNAs are stable non-coding RNAs. They can last for a long time in the circulatory system. This ability makes the sensitivity and specificity of early tumor detection better. Qin et al. also explored this area. They found that a

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sensitive nanoprobe could function in a single system. It is capable of detecting both PD-L1 on exosome surfaces and endogenous miRNAs at the same time within that system. Such an approach could help to get precise patient stratification. The practical value of this dual-labeling method for clinical work was confirmed by these researchers [12]. Combining exo-PD-L1with miRNA or proteomic biomarkers is an option. It can give us data about immune suppression and molecules. The data helps us diagnose with better sensitivity and specificity [13].

This way of combining markers is workable, in actual fact. There is a scientific basis in it. There is also a methodological base. Both support early NSCLC diagnosis. That diagnosis is high in precision. It does not need surgery. This approach also provides a foundation. Later on, large-scale checks can happen in clinics. Right now, unified standards are something we still lack. We need these standards to see if combining exo-PD-L1 and miRNA is reliable. We also need them to see if it works in real-world early diagnosis.

3.3. Clinical research evidence in efficacy prediction

Exo-PD-L1 levels mirror the tumor's immunosuppressive state. A change in these levels could indicate whether immunotherapy or targeted therapy is taking effect. In NSCLC patients receiving ICIs, plasma exo-PD-L1 levels may rise or fall. That rise or fall may relate to treatment response. An early shift might predict treatment sensitivity. It might also point to the risk of later drug resistance [8]. There is a multimodal approach. It combines exo-PD-L1 with ctDNA or exosomal miRNAs. That combination captures both tumor burden and immune status at the same time. It gives us deeper insights. Those insights help us evaluate efficacy in a more personalized manner [10]. Multimodal testing matters for another reason. It can improve predictive accuracy. It also helps avoid the limitations of single-biomarker testing. This testing approach also offers clinical evidence. That evidence supports long-term monitoring of NSCLC treatment response.

3.4. Clinical research evidence in prognostic assessment

Exo-PD-L1 shows promise for prognosis in NSCLC. Its levels often change over time. This change mirrors the level of tumor immune suppression. It is linked to patient survival and recurrence. High exo-PD-L1 is often linked to a poor prognosis and shorter survival. Cheng et al. made that report. Low levels or a clear drop post-treatment suggest a good prognosis [8]. Monitoring over time is sensible. It measures exosomal miRNAs, proteomics, and exo-PD-L1 together from a single sample. Such monitoring provides ongoing molecular and microenvironment information. This information improves prediction accuracy. Exo-PD-L1 combines with other liquid biopsy markers. ctDNA and CTCs are examples. This creates a multimethod prognostic model. It boosts predictive reliability. It improves reproducibility [13]. These approaches support the use of exo-PD-L1 and multimethod liquid biopsy in clinical prognosis. They enable personalized care and long-term disease management in NSCLC patients.

4. Beyond diagnosis—extended applications in comprehensive disease management

4.1. Treatment efficacy prediction and dynamic monitoring

Peripheral blood exosomal exo-PD-L1 as, a novel liquid biopsy biomarker, plays a crucial role ininmonitoring evaluating the efficacy therapeutic of immune checkpoint inhibitors (ICIs) dynamic .

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Compared to traditional PD-L1 indetection tumor tissue, circulating exo-PD-L1 can be obtained non-invasively at multiple time points, making it more suitable for continuous monitoring.

Numerous clinical studies have confirmed that exosomal PD-L1 levels are positively correlated with the efficacy of immunotherapy. A study by Wang involving 149 patients with NSCLC demonstrated that patients with lower circulating exo-PD-L1 levels prior to receiving immunotherapy were more likely to achieve clinical response (including complete remission, partial remission, or stable disease), while low exo-PD-L1 levels showed a significant correlation with enhanced tumor control rates (DCR) and significantly prolonged progression-free survival (PFS) (AUC approximately 0.80–0.89, $P < 0.001$).Furthermore, during the early stages of immunotherapy (weeks 3–6), and elevated exo-PD-L1 levels are associated with favorable treatment responses the fold change in levels these can serve as a good indicator for assessing treatment efficacy [2].

Mechanistically, exo-PD-L1 serves as an indicator of the immunosuppressive status of tumors and shows a strong correlation with the infiltration and functional activity of $CD8^+$ T cells in the tumor microenvironment. Its expression levels correlate with T-cell functional status, suggesting that it serves not only as a predictor of treatment efficacy but also as an indicator of the body's immune response [14].

Exo-PD-L1 is a key link among 'tumor—immune system—treatment response'. A recent review points out it dynamically reflects immune escape during immunotherapy [7]. Monitoring exo-PD-L1 changes over time gives a more timely and accurate look at treatment efficacy and prognosis. This enables early evaluation. It supports real-time plan adjustments. It builds a basis for personalized therapy.

4.2. Prognostic value

Exo-PD-L1 has better predictive power and speed than tissue PD-L1 for NSCLC survival. That makes it just as useful for prognosis. Evidence is building up. Higher baseline exo-PD-L1 levels often point to a worse prognosis. These levels are closely tied to shorter PFS, shorter OS [2, 14].

Exo-PD-L1 drives immune suppression across the whole body. PD-1-mediated T-cell inhibition does the job. Exo-PD-L1 reflects overall immunosuppression more fully. This whole-body effect increases its biological importance for prognosis. Zhou et al. find high exo-PD-L1 levels go hand in hand with tumor progression, greater metastatic ability, worse survival [11]. Recent systematic reviews have backed its prognostic value. Dragu et al. observed that elevated exo-PD-L1 levels are closely linked to disease progression risk and survival across various tumors. Exo-PD-L1 stands as an independent prognostic factor [4]. Kansha et al. found that rising exo-PD-L1 levels often signal enhanced immunosuppression and higher chances of disease worsening. That outcome is not the same as some other reports [6].

Changes in exo-PD-L1 levels have real prognostic importance. This goes beyond just baseline levels. During ICIs therapy, a sustained rise often signals disease progression and poor outcomes. A decline typically points to a favorable response and extended survival [2]. Exo-PD-L1 holds promise for long-term prognostic monitoring.

Exo-PD-L1 possesses functional integrity and systemic reactivity , serving as a crucial bridge linking immune status, treatment response, and prognostic outcomes. However, currently faces challenges such as small sample sizes and a lack of standardized detection methods. In the future Large-scale, multicenter prospective studies advance are needed to its clinical translation.

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5. Current challenges and future directions

Extracellular PD-L1 shows significant clinical promise in early detection, prediction of treatment response, prognosis assessment for NSCLC. It offers clear advantages across different kinds of liquid-biological cellular integration strategies.Challenges remain in its clinical use. The lack of standardized testing methods is a basic problem. Current techniques isolate and detect extracellular cells. These include ultra-fast centrifugation, size-based chromatography, immunocapture, and microfluidic platforms. They differ a lot in recovery efficiency, purity, and operational complexity.There is still no widely accepted definition of extracellular PD-L1 particles. Quantification methods and data normalization strategies are not standardized across studies. The comparability and reproducibility of results remain poor.The MISEV guidelines provide a basic framework. There are no standardized quantitative methods for external PD-L1. This makes it less believable as a clinical biomarker.

Detection sensitivity and clinical applicability both need improvement.Exo-PD-L1 levels in peripheral blood are often low. Traditional detection methods find it quite hard to strike a good balance between high sensitivity and excellent performance.In recent years, new technologies that use nanomaterials, biological sensors, and digital immunological tests have made detection a lot better. These technologies are still largely at the experimental stage. They have not yet produced stable and scalable clinical testing systems. This limits their widespread use in real-world clinical settings.

Future research has several key directions. These need attention.Developing standardized and uniform normalization systems for exosomes and exo-PD-L1 detection is important for better reproducibility and consistency of assays across different platforms.The implementation of highly clinically sensitive automated technologies should be promoted now. A particular focus is on optimizing microfluidic platforms and POCT analysis. Large-scale prospective cohort studies are needed. Studies in medical centers are needed. They can strengthen the evidence base for early diagnosis, prediction of treatment response, and prognosis. Biological heterogeneity of exo-PD-L1 depends on specific molecular tumor subtypes. EGFR mutations and KRAS mutations are examples. Analysis of this heterogeneity refines demographic stratification. It personalizes application strategies.Endo-PD-L1 combines with other biomarkers like ctDNA, CTCs, and exosomal miRNA. This combination keeps multimodal liquid biopsy advancing. It helps build multidimensional diagnostic and predictive models. These models get past the limits of using just one biomarker.

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