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Research Progress on the Regulation of PD-L1 Expression and Its Role in Tumor Immunity

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Abstract: ***The PD-1/PD-L1 signaling axis serves as a primary mechanism of tumor immunoevasion, wherein the binding of tumor-expressed PD-L1 to its receptor on T cells triggers cellular exhaustion and programmed death. While the clinical introduction of checkpoint inhibitors targeting this pathway has transformed the oncological landscape, the inconsistency of patient response rates highlights a profound need to deconstruct the upstream regulatory networks governing PD-L1 synthesis. By examining the interplay between immune suppression and protein expression, this review aims to identify the specific drivers of tumor escape and evaluate emerging therapeutic strategies designed to optimize the blockade of this critical checkpoint for superior clinical outcomes.***

Keywords: PD-L1, PD-1, immune checkpoint inhibition therapy, regulation of expression, tumor immune response.

1. Preface

In recent years, immunotherapy has created new opportunities for treating cancer. Among these, immune checkpoint blockade therapy has had a tremendous impact on cancer therapy [1]. programmed cell death protein-1 (PD-1) and its ligand, (Programmed death ligand-1) PD-L1, serve as critical immune checkpoints that play a pivotal role in maintaining immune tolerance and preventing autoimmune responses [2]. The interaction between Programmed Cell Death Protein 1 (PD-1) and its ligand, PD-L1, serves as a critical molecular "handshake" that, under normal physiological conditions, maintains peripheral tolerance and prevents the immune system from attacking self-tissues. However, in the chaotic environment of a growing malignancy, tumor cells frequently hijack this regulatory circuit—a phenomenon clinicians often describe as an "immune shield"—to effectively paralyze the host's primary defenders. By overexpressing PD-L1, these cells send a deceptive signal to infiltrating T cells, inducing a state of metabolic and functional exhaustion that allows the cancer to flourish undetected[3]. PD-L1 is expressed in both tumor cells and immune cells, and its expression is controlled by multiple complex factors, such as genetic influences, transcriptional and post-translational changes, along with elements present in the tumor microenvironment [4,5]. However, the control processes and its specific role in tumor immunity still require further investigation. This review aims to delineate the latest research advances in the regulation of PD-L1 expression and its role in tumor immunity, with the objective of providing novel insights for optimizing immune checkpoint blockade therapy. The ultimate goals are to defeat drug resistance, mitigate side effects, and improve treatment effectiveness.

2. Introduction

PD-1 is a membrane-spanning protein made up of a single polypeptide chain, which functions primarily as a surface receptor on T cells. The intracellular region of PD-1 includes an immunoreceptor tyrosine-based inhibitory motif (ITIM) [6]. When PD-1 binds to its ligand PD-L1, phosphorylation is triggered, initiating a downstream signaling cascade that leads to the inhibition of T-cell function. This mechanism helps the body's defense system maintain self-tolerance and control inflammatory responses, but it can also be used by tumor cells to avoid detection by the immune surveillance [7]. PD-L1 acts as a regulator of the immune system that primarily modulates protected against disease responses by attaching to the PD-1 receiver. PD-L1 is a transmembrane protein that includes an extracellular domain, and a segment inside the cell [8]. The extracellular region contains an immunoglobulin-like (Ig-V-like) domain, which mediates the interaction with the PD-1 receptor. PD-L1 is found on many different types of cells, such as macrophages, dendritic cells, and activated B and T lymphocytes, tumor cells, in addition to certain immune cells and normal tissue cells [3].In the tumor microenvironment, PD-L1 present on the surface of tumor cells interacts with PD-1 receptors on T cells, thereby suppressing T lymphocyte activity and enabling tumors to evade the immune system [9]. Consequently, Programmed death-ligand 1 is not only a pivotal molecule in the mechanism of immune response to tumors escape but also a critical treatment focus in cancer immunotherapy.

2.1 Genomic Organization and Expression Regulation

The gene that encodes PD-L1 is found on chromosome 9 in humans [10]. Its official designation is CD274 or B7-H1, which encodes the PD-L1 protein. The production of PD-L1 protein is controlled by different cytokines [11]. Among these, Interferon-gamma (IFN-γ) is recognized as one of the most potent inducers, activating PD-L1 gene transcription via the JAK-STAT signaling pathway [12]. Additionally, Multiple tumor-related signaling pathways [13].

Under normal physiological conditions, PD-L1 is present on different types of immune cells, in addition to in specific non-immune cells like vascular endothelial units of living matter and epithelial cells in specific organs [14]. In pathological states, especially within the tumor microenvironment (TME), PD-L1 expression is significantly upregulated, a phenomenon strongly associated with the capacity of cancer cells to avoid detection by the immune system. Byupregulating PD-L1, tumor cells engage the PD-1 receptor on antitumor T lymphocytes, thereby inhibiting T-cell effector functions and promoting tumor growth and dissemination [15]. Consequently, the amount of expression and pattern regarding

PD-L1 are not only a major focus in tumor biology research but also act as a possible indicator in clinical settings.

2.2 Engagement

The binding between PD-L1 and its receptor, programmed cell death protein 1 represents a critical immune checkpoint mechanism that maintains self-tolerance and restricts excessive immune responses [16]. PD-1 is a receptor that suppresses immune responses primarily expressed on the surface of T cells, while PD-L1 is expressed on different kinds of cells, comprising tumor cells as well as immune units of life [17]. This exchange plays a key role in protecting normal tissues from autoimmune attack by limiting T cell activity during inflammatory responses, thereby preventing tissue damage[18].

3. Mechanisms of Regulation

In the tumor microenvironment, the high expression of PD-L1 has been shown to significantly impact tumor prognosis [19]. Studies have revealed that distinct signaling pathways control the axis in different many cells, playing crucial roles in tumorigenesis and progression. The main signaling pathways that regulate PD-L1 are the EGFR pathway and the RAS/RAF/MEK/MAPK-ERK pathway [20].

3.1 Control of PD-L1 Gene Expression

The control of gene expression at the level of transcription of PD-L1 entails a complex process involving multiple signaling pathways and transcription factors. Key transcriptional regulators include NF-κB, STATs, hypoxia-inducible factor 1-alpha (HIF-1α), AP-1, and other factors activated by inflammatory cytokines within the tumor microenvironment [21]. NF-κB acts as a potent transcriptional activator, which is upregulated in response to inflammatory and immune stimuli, directly enhancing PD-L1 expression. For example, upon stimulation by cytokines such as TNF-α or IL-1β, NF-κB translocates to the nucleus and promotes PD-L1 gene transcription [22]. STAT3 also acts as an essential controller of PD-L1 expression and can be triggered by different cytokines and growth factors. Activated STAT3 binds directly to the PD-L1 promoter region, augmenting its expression [23]. HIF-1α, which stabilizes and activates under hypoxic conditions, directly facilitates PD-L1 transcription and represents another crucial factor contributing to increased PD-L1 expression in the tumor microenvironment [24]. Activator protein 1 (AP-1), a heterodimeric complex produced by immediate-early genes, they responds to diverse cellular signals and directly modulates PD-L1 expression.

In addition to these transcription factors, several signaling pathways also participate in the transcriptional control. These pathways influence PD-L1 expression through the aforementioned transcription factors or via other mechanisms [13].

In summary, PD-L1 transcriptional regulation results from the integrated actions of multiple intracellular signals and proteins that regulate gene expression that respond to extracellular and intracellular cues, cytokines, growth factors, and stress conditions,to modulate PD-L1 gene expression. This regulatory network enables PD-L1 to adaptively adjust its expression levels under varying physiological and pathological contexts.

3.2 Post-translational Modification Regulation

The post-translational regulation of PD-L1 involves diverse modification processes, including phosphorylation, ubiquitination, glycosylation, and others, which collectively influence PD-L1 protein stability, cell surface expression, and its interaction with PD-1 [25].

Phosphorylation serves as a key mechanism modulating PD-L1 activity. For instance, somethings lead to its proteasomal degradation. Conversely, activation of the PI3K/Akt pathway enhances PD-L1 stability by inhibiting GSK3β activity [26]. Additionally, phosphorylation regulates PD-L1 trafficking and membrane localization. Ubiquitination, another critical post-translational modification, typically targets proteins for proteasome-dependent degradation [27]. PD-L1 is able to be tagged by E3 ubiquitin ligases for subsequent degradation. Studies have revealed that tumor cells often reduce PD-L1 ubiquitination to evade immune surveillance [28]. Glycosylation, particularly N-linked glycosylation, also plays a significant role in PD-L1 regulation by stabilizing its structure and enhancing its binding affinity to PD-1. Glycosylated PD-L1 exhibits increased membrane retention, thereby strengthening immune checkpoint interactions [29].

Beyond these modifications, other mechanisms such as ubiquitin-like modifications, acetylation, and alternative splicing contribute to PD-L1 regulation. These post-translational modifications collectively determine PD-L1's functional fate and represent potential targets for modulating tumor immune evasion and therapy response [30]. Understanding these complex regulatory networks may inform novel therapeutic strategies—for example, enhancing antitumor immunity by targeting PD-L1 phosphorylation or ubiquitination pathways.

3.3 Regulation of PD-L1 Expression by Factors in the Tumor Microenvironment

Multiple factors within the tumor microenvironment (TME) significantly influence PD-L1 expression, with inflammatory cytokines and oxygen concentration being two major contributors [31]. Within the turbulent landscape of the tumor microenvironment, the upregulation of PD-L1 is frequently not an intrinsic tumor event but rather a reactive consequence of immune pressure, driven by a barrage of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and various interleukins. These molecular messengers, predominantly released by infiltrating immune cells attempting to mount an attack, ironically trigger the tumor's defensive shielding by activating key transcription factors like NF-κB and STAT3. This dynamic suggests that high PD-L1 levels often serve as a "biomarker of resistance" in the face of an active, yet thwarted, immune response, blurring the line between tumor aggression and immune recognition. Consequently, tumor cells capitalize on this immune activation by increasing PD-L1 expression, which serves to inhibit immune effector functions and promote immune evasion [32].

Oxygen concentration is another critical factor. Under hypoxic conditions, hypoxia-inducible factor-1α (HIF-1α) stabilizes and accumulates, directly activating PD-L1 transcription [24]. Hypoxia is a hallmark of the TME; it not only promotes adaptive survival of tumor cells but also suppresses T cell-mediated immune responses by upregulating PD-L1 [33].

In summary, inflammatory cytokines and oxygen tension in the TME modulate PD-L1 expression through the activation of multiple signaling pathways and transcription factors [34]. These mechanisms enable tumor cells to survive and proliferate under intense immune surveillance, providing a critical biological basis for tumor immune evasion. Comprehending these mechanisms is crucial for the advancement of efficacious immunotherapeutic approaches targeting PD-L1.

4. The Function in Tumor Immune Response

Neoplastic things utilize many coordinated mechanisms to circumvent immune recognition and elimination [35]. PD-L1 suppresses T-cell activity and hinders immune- mediated tumor elimination [36]. They actively shape a suppressive microenvironment by secreting factors and by recruiting inhibitory cell populations including regulatory T cells and myeloid-derived suppressor cells [37]. Through a process termed immunoediting, tumors selectively promote the outgrowth of clones with enhanced resistance to immune attack. Additionally, tumor metabolism is reprogrammed to deplete critical nutrients like glucose and amino acids from the surrounding environment, which leads to the functional exhaustion of infiltrating immune cells [38]. Aberrant angiogenesis worsens this condition by promoting tumor proliferation. Collectively, these interrelated processes contribute to significant tumor immune tolerance, thereby posing a substantial challenge to the efficacy of immunotherapeutic interventions [39].

To facilitate immune evasion, malignant cells exploit the biochemical tethering of PD-L1 to the PD-1 receptors found on T cells. This binding event triggers a cascade of suppressive signaling that effectively dampens T-cell priming and blunts their cytotoxic efficacy; by neutralizing these cellular "soldiers," the tumor successfully paralyzes the host's natural ability to seek out and destroy aberrant cells [40]. This interaction recruits phosphatases such as SHP-2, leading to dephosphorylation of key signaling molecules in the TCR pathway and ultimately inhibiting T cell expansion and functional activities [41].

Beyond direct T cell suppression, PD-L1 expression correlates with reduced T cell infiltration into tumor sites, as diminished T cell activity compromises their recruitment and retention within the TME [42]. Moreover, PD-L1 affects additional immune cell populations by promoting the differentiation and functional activity of regulatory T cells (Tregs), thereby enhancing immunosuppressive mechanisms. Additionally, PD-L1 impairs the maturation and antigen-presenting capabilities of dendritic cells (DCs) and macrophages, thus weakening the initiation of antitumor immune responses. For instance, tumor-associated macrophages (TAMs) upregulate PD-L1 under the influence of chemokines, autophagy, or hypoxia-inducible factors, reinforcing avoidance of the immune response [43].

Furthermore, it can be released through exosomes, extending its immunosuppressive effects beyond the local TME to systemic circulation [44]. Recent studies also highlight intracellular PD-L1 signaling, which regulates tumor progression independently of PD-1 binding, such as by promoting nuclear translocation to enhance cancer cell survival [40].

Through these mechanisms, PD-L1 fosters an immunosuppressive niche that not only impedes T cell-mediated tumor clearance but also disrupts the antitumor functions of additional immune cells, collectively driving cancer development and spread [40].

The connection between the levels of programmed death-ligand 1 (PD-L1) expression and tumor outcomes is intricate and varies greatly depending on the context [45]. In some types of cancer, increased abundance of PD-L1 are linked to worse clinical outcomes, probably because PD-L1 suppresses T cell-driven immune responses. By blocking the body's antitumor immune activity, PD-L1 allows cancer cells to escape detection by the immune system, which supports tumor progression and spread [46].

On the other hand, in patients receiving immune checkpoint inhibitors like anti-PD-1 or anti-PD-L1 antibodies, elevated PD-L1 expression might indicate a more favorable treatment response [47]. As a direct therapeutic target, PD-L1 blockade reverses its immunosuppressive effects, restoring T cell-mediated tumor clearance.

Overall, the prognostic value of PD-L1 expression is influenced by multiple factors, including tumor type, tumor microenvironment characteristics, treatment modalities, and the patient's immune status [48]. Consequently, PD-L1 should not be considered an independent prognostic marker but must be evaluated within the specific clinical context of each patient. With advances in personalized medicine, PD-L1 expression levels are increasingly critical for guiding therapeutic decisions and predicting outcomes in cancer immunotherapy.

5. Antitumor Therapies Targeting PD-L1

Their inhibitors belong to a class of immune checkpoint blockers that function by disrupting the interaction between the PD-1 receptor, expressed on the surface of T cells, and its ligand PD-L1, which is often overexpressed by tumor cells [49]. Under normal physiological conditions, this interaction supports immune tolerance and stops the system. However, tumors take advantage of this mechanism by increasing PD-L1 expression to avoid being targeted by the immune system. Inhibitors that block the pathway counteract T-cell suppression, restore antitumor immune responses, and boost the immune system's capacity to destroy cancerous cells[50].

In practice, the inhibitors have received approval for treating various types of cancers, such as non-small cell lung cancer, melanoma, renal cell carcinoma, head and neck cancer, and bladder cancer [51]. These agents are utilized either as initial

treatment or in later stages following the failure of standard therapies, showing notable enhancements in overall survival and quality of life for patients who respond. However, since not all patients experience the same benefits from these treatments, there is a clear need for predictive biomarkers to determine which individuals are most likely to respond.

The expression of PD-L1 has been correlated with patient responsiveness to their inhibitor therapies, positioning PD-L1 as a potential predictive biomarker. Patients with high PD-L1 expression levels are generally more likely to benefit from such treatments [52]. Nevertheless, the ability of PD-L1 to predict outcomes is constrained by its variability and changing characteristics, since PD-L1 levels in tumor tissues can fluctuate over time and differ across various areas within the same tumor. Additionally, some patients with low or undetectable PD-L1 expression still benefit from treatment, indicating the necessity for additional biomarkers to enhance predictive accuracy.

To transcend the predictive ceiling of solitary PD-L1 analysis, future inquiries must pivot toward a holistic integration of complementary biomarkers, specifically weaving tumor mutational burden (TMB) and microsatellite instability (MSI) into the diagnostic framework alongside patterns of immune cell infiltration. This shift moves us from a one-dimensional view to a complex landscape, a transition that is best supported by next-generation technologies like digital pathology and multiplex immunofluorescence; these tools allow us to visualize not just the presence of proteins, but their spatial topography and temporal evolution within the microenvironment [53]. Ultimately, the path forward lies in constructing robust, multi-parameter prediction models that refine patient stratification, ensuring that the potent capabilities of PD-1/PD-L1 blockade are directed precisely toward those most primed to respond.

Although some patients initially respond to their inhibitors, resistance frequently emerges over time. Primary resistance can result from impaired antigen presentation, including MHC-I downregulation, insufficient T-cell infiltration into the tumor, or the presence of immunosuppressive signals within the tumor microenvironment [17]. Acquired resistance frequently entails adaptive modifications, including the increased expression of alternative immune checkpoint molecules, mutations affecting interferon-gamma signaling pathways—specifically the loss of function in JAK1 or JAK2—and the emergence of tumor cell clones exhibiting reduced immunogenicity. The complexity of these mechanisms underscores the necessity for combination therapeutic strategies to overcome resistance.

Their inhibitors can cause immune-related side effects due to unintended activation of the immune system targeting healthy tissues. These adverse events encompass a range of inflammatory conditions, including colitis, hepatitis, dermatitis, and various endocrinopathies such as thyroiditis and hypophysitis, with severity varying from mild to life-threatening [54]. While PD-L1 expression is used as a predictive biomarker, its clinical utility is constrained by factors such as tumor heterogeneity, dynamic changes during treatment, and variability across different tumor regions. Furthermore, treatment responses can still be observed in patients who are PD-L1-negative, emphasizing the importance of incorporating other biomarkers, like tumor mutational burden and microsatellite instability, together with pertinent clinical factors to improve patient selection.

6. Future Outlook

Future research on PD-L1 will focus on elucidating its comprehensive role within the tumor microenvironment and its complex regulatory network, developing more precise detection technologies, and investigating strategies to overcome resistance to immune checkpoint blockade therapy [44].In clinical practice, PD-L1 testing will facilitate personalized medical decisions and optimize combination immunotherapy regimens, thereby enhancing therapeutic efficacy while minimizing unnecessary side effects for more effective cancer management and treatment [55]. By combining multi-omics data, such as genomic, transcriptomic, and proteomic information, predictive models will be developed with PD-L1 detection as a key biomarker. This will help tailor treatment plans specifically to each individual, enhancing therapeutic effectiveness while reducing side effects, thereby improving the overall success of cancer immunotherapy.

7. Conclusion

This review has outlined the regulatory processes controlling PD-L1 expression, its essential function immune evasion mechanisms in malignancy, and the interventional paradigms aimed at PD-L1. The PD-1 and PD-L1 interaction is a key mechanism by which tumors evade the effector cells system, allowing cancer cells to survive and grow despite immune defenses. he clinical application of inhibitors targeting the axis has undeniably revolutionized cancer management, offering a survival advantage that is often—though not exclusively—tied to high tumoral PD-L1 expression; yet, real-world outcomes reveal a stark dichotomy where many patients remain unresponsive despite favorable biomarker profiles. This discrepancy underscores the limitations of relying solely on ligand presence to predict efficacy, suggesting that the determinants of immune recovery are far more multifaceted than initially understood. Consequently, the focus of contemporary investigation has shifted from merely validating these agents to rigorously dissecting the patient specific factors that dictate response, with the ultimate goal of engineering novel strategies that can circumvent acquired resistance and extend the benefits of immunotherapy to currently refractory populations.

References

[1] Chow A, Perica K, Klebanoff C A, et al. Clinical implications of T cell exhaustion for cancer immunotherapy [J]. Nat Rev Clin Oncol, 2022, 19(12): 775-790.

[2] Zhang H, Liu L, Liu J, et al. Roles of tumor-associated macrophages in anti-PD-1/PD-L1 immunotherapy for solid cancers [J]. Mol Cancer, 2023, 22(1): 58.

[3] Borgeaud M, Sandoval J, Obeid M, et al. Novel targets for immune-checkpoint inhibition in cancer [J]. Cancer Treat Rev, 2023, 120: 102614.

[4] Gao C, Chen J, Bai J, et al. High glucose-upregulated PD-L1 expression through RAS signaling-driven downregulation of PTRH1 leads to suppression of T cell cytotoxic function in tumor environment [J]. J Transl Med, 2023, 21(1): 461.
[5] Damei I, Trickovic T, Mami-Chouaib F, et al. Tumor-resident memory T cells as a biomarker of the response to cancer immunotherapy [J]. Front Immunol, 2023, 14: 1205984.
[6] Zhou Q, Meng Y, Li D, et al. Ferroptosis in cancer: From molecular mechanisms to therapeutic strategies [J]. Signal Transduct Target Ther, 2024, 9(1): 55.
[7] Chen Y, Guo D Z, Zhu C L, et al. The implication of targeting PD-1: PD-L1 pathway in treating sepsis through immunostimulatory and anti-inflammatory pathways [J]. Front Immunol, 2023, 14: 1323797.
[8] Roy D, Gilmour C, Patnaik S, et al. Combinatorial blockade for cancer immunotherapy: targeting emerging immune checkpoint receptors [J]. Front Immunol, 2023, 14: 1264327.
[9] Wang B, Chen C, Liu X, et al. The effect of combining PD-1 agonist and low-dose Interleukin-2 on treating systemic lupus erythematosus [J]. Front Immunol, 2023, 14: 1111005.
[10] Zhang T, Yu-Jing L, Ma T. Role of regulation of PD-1 and PD-L1 expression in sepsis [J]. Front Immunol, 2023, 14: 1029438.
[11] Klement J D, Redd P S, Lu C, et al. Tumor PD-L1 engages myeloid PD-1 to suppress type I interferon to impair cytotoxic T lymphocyte recruitment [J]. Cancer Cell, 2023, 41(3): 620-636.e629.
[12] Li L, Zhang Y, Hu W, et al. MTHFD2 promotes PD-L1 expression via activation of the JAK/STAT signalling pathway in bladder cancer [J]. J Cell Mol Med, 2023, 27(19): 2922-2936.
[13] Iqbal M J, Kabeer A, Abbas Z, et al. Interplay of oxidative stress, cellular communication and signaling pathways in cancer [J]. Cell Commun Signal, 2024, 22(1): 7.
[14] Chen S, Saeed A, Liu Q, et al. Macrophages in immunoregulation and therapeutics [J]. Signal Transduct Target Ther, 2023, 8(1): 207.
[15] Knopf P, Stowbur D, Hoffmann S H L, et al. Acidosis-mediated increase in IFN-γ-induced PD-L1 expression on cancer cells as an immune escape mechanism in solid tumors [J]. Mol Cancer, 2023, 22(1): 207.
[16] Ibis B, Aliazis K, Cao C, et al. Immune-related adverse effects of checkpoint immunotherapy and implications for the treatment of patients with cancer and autoimmune diseases [J]. Front Immunol, 2023, 14: 1197364.
[17] Khosravi G R, Mostafavi S, Bastan S, et al. Immunologic tumor microenvironment modulators for turning cold tumors hot [J]. Cancer Commun (Lond), 2024, 44(5): 521-553.
[18] Landi D, Navai S A, Brock R M, et al. A Checkpoint Reversal Receptor Mediates Bipartite Activation and Enhances CAR T-cell Function [J]. Cancer Res Commun, 2025, 5(3): 527-548.
[19] Bagley S J, Binder Z A, Lamrani L, et al. Repeated peripheral infusions of anti-EGFRvIII CAR T cells in combination with pembrolizumab show no efficacy in glioblastoma: a phase 1 trial [J]. Nat Cancer, 2024, 5(3): 517-531.
[20] Cui J W, Li Y, Yang Y, et al. Tumor immunotherapy resistance: Revealing the mechanism of PD-1 / PD-L1-mediated tumor immune escape [J]. Biomed Pharmacother, 2024, 171: 116203.
[21] Guo Q, Jin Y, Chen X, et al. NF-κB in biology and targeted therapy: new insights and translational implications [J]. Signal Transduct Target Ther, 2024, 9(1): 53.
[22] Liu C, Yin Q, Wu Z, et al. Inflammation and Immune Escape in Ovarian Cancer: Pathways and Therapeutic Opportunities [J]. J Inflamm Res, 2025, 18: 895-909.
[23] Xue C, Yao Q, Gu X, et al. Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer [J]. Signal Transduct Target Ther, 2023, 8(1): 204.
[24] Chen Z, Han F, Du Y, et al. Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions [J]. Signal Transduct Target Ther, 2023, 8(1): 70.
[25] Zhong Q, Xiao X, Qiu Y, et al. Protein posttranslational modifications in health and diseases: Functions, regulatory mechanisms, and therapeutic implications [J]. MedComm (2020), 2023, 4(3): e261.
[26] Tang X, Sui X, Weng L, et al. SNAIL1: Linking Tumor Metastasis to Immune Evasion [J]. Front Immunol, 2021, 12: 724200.
[27] Gupta R, Sahu M, Srivastava D, et al. Post-translational modifications: Regulators of neurodegenerative proteinopathies [J]. Ageing Res Rev, 2021, 68: 101336.
[28] Li J, Liu J, Zhou Z, et al. Tumor-specific GPX4 degradation enhances ferroptosis-initiated antitumor immune response in mouse models of pancreatic cancer [J]. Sci Transl Med, 2023, 15(720): eadg3049.
[29] He X, Xu C. Immune checkpoint signaling and cancer immunotherapy [J]. Cell Res, 2020, 30(8): 660-669.
[30] Li J J, Wang J H, Tian T, et al. The liver microenvironment orchestrates FGL1-mediated immune escape and progression of metastatic colorectal cancer [J]. Nat Commun, 2023, 14(1): 6690.
[31] Daniel S K, Sullivan K M, Labadie K P, et al. Hypoxia as a barrier to immunotherapy in pancreatic adenocarcinoma [J]. Clin Transl Med, 2019, 8(1): 10.
[32] Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications [J]. Cell Mol Immunol, 2020, 17(8): 807-821.
[33] Wu Q, You L, Nepovimova E, et al. Hypoxia-inducible factors: master regulators of hypoxic tumor immune escape [J]. J Hematol Oncol, 2022, 15(1): 77.
[34] Nishida N, Kudo M. Oncogenic Signal and Tumor Microenvironment in Hepatocellular Carcinoma [J]. Oncology, 2017, 93 Suppl 1: 160-164.
[35] Yu P, Zhang X, Liu N, et al. Pyroptosis: mechanisms and diseases [J]. Signal Transduct Target Ther, 2021, 6(1): 128.
[36] Dhatchinamoorthy K, Colbert J D, Rock K L. Cancer Immune Evasion Through Loss of MHC Class I Antigen Presentation [J]. Front Immunol, 2021, 12: 636568.
[37] Mao X, Xu J, Wang W, et al. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives [J]. Mol Cancer, 2021, 20(1): 131.

[38] Riera-Domingo C, Audigé A, Granja S, et al. Immunity, Hypoxia, and Metabolism-the Ménage à Trois of Cancer: Implications for Immunotherapy [J]. Physiol Rev, 2020, 100(1): 1-102.
[39] Yegutkin G G, Boison D. ATP and Adenosine Metabolism in Cancer: Exploitation for Therapeutic Gain [J]. Pharmacol Rev, 2022, 74(3): 797-822.
[40] Jiang X, Wang J, Deng X, et al. Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape [J]. Mol Cancer, 2019, 18(1): 10.
[41] Saeidi A, Zandi K, Cheok Y Y, et al. T-Cell Exhaustion in Chronic Infections: Reversing the State of Exhaustion and Reinvigorating Optimal Protective Immune Responses [J]. Front Immunol, 2018, 9: 2569.
[42] Ayers M, Lunceford J, Nebozhyn M, et al. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade [J]. J Clin Invest, 2017, 127(8): 2930-2940.
[43] Jia X, Yan B, Tian X, et al. CD47/SIRPα pathway mediates cancer immune escape and immunotherapy [J]. Int J Biol Sci, 2021, 17(13): 3281-3287.
[44] Baghban R, Roshangar L, Jahanban-Esfahlan R, et al. Tumor microenvironment complexity and therapeutic implications at a glance [J]. Cell Commun Signal, 2020, 18(1): 59.
[45] Reck M, Rodríguez-Abreu D, Robinson A G, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer [J]. N Engl J Med, 2016, 375(19): 1823-1833.
[46] Wu S Z, Al-Eryani G, Roden D L, et al. A single-cell and spatially resolved atlas of human breast cancers [J]. Nat Genet, 2021, 53(9): 1334-1347.
[47] Mariathasan S, Turley S J, Nickles D, et al. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells [J]. Nature, 2018, 554(7693): 544-548.
[48] Zhang L, Bai H, Zhou J, et al. Role of tumor cell pyroptosis in anti-tumor immunotherapy [J]. Cell Insight, 2024, 3(3): 100153.
[49] Yi M, Zheng X, Niu M, et al. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions [J]. Mol Cancer, 2022, 21(1): 28.
[50] Lv B, Wang Y, Ma D, et al. Immunotherapy: Reshape the Tumor Immune Microenvironment [J]. Front Immunol, 2022, 13: 844142.
[51] Gordon S R, Maute R L, Dulken B W, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity [J]. Nature, 2017, 545(7655): 495-499.
[52] Baba Y, Nomoto D, Okadome K, et al. Tumor immune microenvironment and immune checkpoint inhibitors in esophageal squamous cell carcinoma [J]. Cancer Sci, 2020, 111(9): 3132-3141.
[53] Vasaturo A, Galon J. Multiplexed immunohistochemistry for immune cell phenotyping, quantification and spatial distribution in situ [J]. Methods Enzymol, 2020, 635: 51-66.
[54] Da L, Teng Y, Wang N, et al. Organ-Specific Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitor Monotherapy Versus Combination Therapy in Cancer: A Meta-Analysis of Randomized Controlled Trials [J]. Front Pharmacol, 2019, 10: 1671.
[55] Mitchell M J, Billingsley M M, Haley R M, et al. Engineering precision nanoparticles for drug delivery [J]. Nat Rev Drug Discov, 2021, 20(2): 101-124.