

# Progress in the research of immunotherapy-related hyperprogression (Review)

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**Abstract.** Immunotherapy has become an effective method for the treatment of a variety of malignant tumors. However, with the development of immunotherapy, the phenomenon of hyperprogression in patients with cancer has gradually attracted attention. Hyperprogression refers to a condition in which the progression of a disease during treatment of a patient with cancer is suddenly accelerated. To date, no reliable marker has been found to predict accelerated tumor growth during immune checkpoint inhibitor (ICI) treatment. The aim the present study was to summarize the definition of hyperprogression and the difference between hyperprogression and pseudocytosis, and investigate the potential mechanisms of hyperprogression including clinical characteristics, potential molecular markers and the immune microenvironment. The effect of macrophage-related different types and factors on tumors in the immune microenvironment was analyzed, and the findings may be used to determine the future directions of research in hyperprogression.

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## 1. Introduction

Malignant tumors are one of the main diseases that seriously threaten human health, with the incidence and mortality rates increasing annually in China. During the past two decades, immunotherapy has become the fourth main method of treating cancer, following surgery, radiotherapy and chemotherapy. Several types of immunotherapy have been developed, such as ICIs, immunomodulatory drugs, monoclonal antibodies, cancer vaccines, and chimeric antigen receptor T cells (CAR-T). Among them, immunotherapy, in the form of ICIs, has been shown to have an unprecedented impact on the prognosis of patients with multiple tumor types. ICIs reactivate the immune response of T cells by inhibiting the activity of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) receptors to exert antitumor effects (1). ICIs have a strong specificity and lasting effect.

However, not all patients have access to ICIs, and a small number of patients have accelerated disease progression following ICI treatment, namely, hyperprogressive disease (HPD) (2). HPD is not limited to immunotherapy; it also occurs in targeted treatment, as well as traditional chemotherapy. The incidence of HPD increases and the overall survival of patients is shortened following immunotherapy, which suggests that the occurrence of HPD seriously affects the prognosis of a patient (3-5). Recently, there have been several hypotheses regarding the development of HPD in immunotherapy, take for example, immune checkpoint blockade which has the potential to functionally stimulate regulatory T cells (Tregs) and locally form an immunosuppressive tumor microenvironment (TME); blockade of immune checkpoints induces polarisation of immunosuppressive cells such as M2 macrophages and dendritic cells that produce high amounts of immunosuppressive cytokines. HPD is both a challenge and an opportunity for immunotherapy. As the current understanding of HPD is very limited, an in-depth exploration of HPD is urgently needed. In the present study, the definition and evaluation criteria of HPD, related influencing factors (clinical and molecular), differential diagnosis and the establishment of clinical plans, were reviewed to provide a reference for further HPD-related research, reasonable prediction and stratification prior to

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clinical treatment, as well as guidance for individualized immunotherapy.

## 2. Discovery process and evaluation criteria of HPD

In 2016, Chubachi *et al* (6) were the first to report that patients with non-small cell lung cancer (NSCLC) receiving navurlizumab exhibited an accelerated disease progression during treatment; this phenomenon was defined as accelerated disease progression following immune checkpoint blockade. Hyperprogression was first recognized at the 2016 Annual Meeting of the European Society of Medical Oncology (7). Lahmar *et al* (7) conducted a single-institution retrospective review of 89 patients with advanced NSCLC who received PD-1/PD-L1 inhibitors. Notably ~10% (9/89) of the patients exhibited rapid progression at the time of the first efficacy evaluation (>50%; expressed as a percentage of the tumor volume gained monthly), and the researchers characterized such progression as ‘paradoxical progressive disease’. The phenomenon of hyperprogression caused by immunotherapy attracted the attention of researchers when in a study by Champiat *et al* (8), at the beginning of 2017, the occurrence of hyperprogression in 9% (12/131) of patients receiving immunotherapy for >20 types of tumors and in 19% (>65) of older patients, was reported.

At present, there is no unified standard for HPD, and its evaluation criteria are mainly based on the following three parameters: Tumor growth rate, tumor growth kinetics (TgK) or time to treatment failure (TTF). Currently, the definition by Kato *et al* is generally accepted: i) TTF <2 months in immunotherapy; ii) tumor load is increased by >50% compared with the baseline; iii) cancer growth rate following immunotherapy is more than double the previous rate (9).

Due to different definition criteria and sample sizes of HPD, the frequency of HPD varies greatly among different cancer and study types. A previous study reported that the incidence of HPD associated with PD-1/PD-L1 inhibitors was 5.9-43.1%, with a combined incidence rate of 13.4% (10). In another study, patients with HPD had a worse prognosis, with a median overall survival (OS) of 3.4 months vs. 6.2 months without HPD ( $P=0.003$ ) (11).

## 3. Pseudoprogression

Pseudoprogression refers to the imaging appearance of tumor progression followed by shrinkage or the emergence of new lesions. It typically refers to the process of tumor growth during immunotherapy and tumor shrinkage following reexamination. This process of ‘first increase and then decrease’ is called pseudoprogression.

Di Giacomo *et al* (12) reported pseudoprogression in a patient with melanoma treated with ipilimumab in 2009. In certain patients, melanoma volume first increased following ipilimumab administration. However, there was a delayed partial response with continuation of treatment. Anti-PD-1 antibody therapy has also been shown to induce pseudoprogression in patients with melanoma, with reported incidences ranging from 2.8-9.7% (12-16). Thereafter, pseudoprogression was also detected in other solid tumors, including NSCLC and squamous cell carcinoma of the head and neck, with

frequencies from 1.3-6.9% (17-20). Pseudoprogression has also been observed in glioblastoma (21), renal cell carcinoma (22), chondrosarcoma (23), gastric cancer (24) and hepatocellular carcinoma (HCC) (25). Patients with pseudoprogression exhibited a significantly improved survival and better overall prognosis compared with patients with real progression (26). In case of pseudoprogression, stopping the drug midway may result in patients missing out on the optimal course of treatment or succumbing to disease. Therefore, it is crucial to accurately differentiate between pseudoprogression and HPD, and it may be necessary to conduct comprehensive and dynamic qualitative and quantitative analysis of different cell communities and factors at multiple time periods.

## 4. Potential influencing factors and mechanisms of HPD

### *Clinical factors and mechanisms*

**Age.** Champiat *et al* (8) reported that HPD status was associated with age. Patients with HPD were older than those without HPD ( $P=0.007$ ). That study also examined the impact of age on Response Evaluation Criteria in Solid Tumors (RECIST) response and found a statistically significant association ( $P=0.036$ ) between age as a continuous variable and RECIST response. The results showed that 19% (7/36) of patients aged >65 years had HPD compared with 5% (5/95) of patients aged <64 years (Fisher's exact test;  $P=0.018$ ). The fact that patients with HPD are older may be due to an altered immunological environment in older people, such as changes in the expression of T-cell costimulatory/co-inhibitory proteins or increased levels of inflammatory cytokines (27,28).

**Sex.** Kanjanapan *et al* (29) reported a higher incidence of HPD in women. Certain scholars maintain that this phenomenon may be due to the higher proportion of male patients smoking, more outdoor work and more ultraviolet exposure. These factors promote a higher immunogenicity and mutation load in male patients once they develop tumors, while the occurrence of tumors in female patients is higher due to adaptive immune escape. However, to better validate this, larger studies, including individual patient meta-analyses, are needed. A meta-analysis of 20 randomized controlled trials with a total of 11,351 patients treated with ICIs by Conforti *et al* (30) reported that men benefited from immunotherapy to a greater extent than women (hazard ratio for overall immunotherapy survival, 0.72 for men vs. 0.86 for women;  $P=0.0019$ ), which suggests that there is a strong possibility of sex influence. On average, female adults have stronger innate and adaptive immune responses. In terms of adaptive immunity, women have higher CD4<sup>+</sup> T-cell counts and higher CD4/CD8 ratios, while often exhibiting greater antibody responses, higher basal immunoglobulin levels, and higher B cell numbers than men. It is hypothesized that females develop more resistant tumors as an adaptation to their intrinsically stronger immune response in comparison with males (31). In addition, through a series of treatments on wild-type, estrogen receptor knockout (ERKO) and PD-1 KO mice, the results revealed that estrogen treatment increased intracellular PD-1 expression in FoxP3<sup>+</sup> Tregs and PD-1, however FoxP3 expression was not sufficient to mediate Treg suppression, suggesting that a role for sex-hormone modulation of the PD-1/PDL1 pathway has

emerged, albeit the published literature is limited to animal studies (32).

**Local recurrence.** In a retrospective study of 34 patients between September 2012 and 2015, Saada-Bouزيد *et al* (33) determined that malignant progression occurred in 10 patients (29%), with at least local recurrence in 9 and distant in 1. Hyperprogression was significantly associated with local recurrence (TGK ratio <2:37% vs. TGK ratio ≥2:90%; P=0.008), but not with local or distant recurrence. Other studies also showed that HPD mostly occurred in the recurrence area following radiotherapy and chemotherapy, which supports this conclusion (6,34,35).

**Chemotherapeutics.** A multicenter retrospective study compared disease progression in patients with NSCLC receiving ICI or chemotherapy. A total of 59 patients developed HPD, of which 95% (56 cases) were caused by ICIs, while only 5% (3 cases) received chemotherapy. Patients with two or more metastases were more likely to develop HPD (62.5 vs. 42.6%; P=0.006); Compared with patients who developed progressive disease (PD), those who developed HPD within 6 weeks had a shorter survival time (median OS, 3.4 vs. 6.2 months; HR=2.18; P=0.003). This study showed that HPD is a poor prognostic factor for NSCLC, which is associated with a large tumor load. It also indicated that chemotherapy drugs can cause HPD, but the incidence was markedly lower than that of ICI (11). These may be due to the upregulation of VEGF and TGF-β by radiotherapy, leading to local TME transformation and HPD; however, the mechanisms behind this hypothesis remain unclear.

**Number of metastases.** Ferrara *et al* (11) revealed that PD-1/PD-L1 inhibitor-treated patients with advanced NSCLC were closely associated with the occurrence of HPD in patients with baseline metastasis (≥2), as compared with non-HPD patients. It is hypothesized that ≥2 metastatic foci at baseline may be a predictor of HPD following immunotherapy in patients with NSCLC. A previous study reported that HPD occurrence may be associated with structural characteristics of tumors, but the sample size of this study was limited, and its findings still require confirmation by a large number of prospective studies (36).

The association between clinically-related factors and poor tumor prognosis is presented in Table I.

**Molecular markers.** Current ICIs mainly target PD-L1, PD-1 and CTLA-4 molecules. But there are more than three immune checkpoints. When one immune checkpoint is inhibited by a drug, there may be compensatory activation of other checkpoints, leading to new immunosuppressive effects and rapid tumor growth.

A study involving a variety of tumors showed that mouse double minute 2 homolog (MDM2) gene amplification was linked to the occurrence of HPD (9). A study by Wang *et al* (37) demonstrated that MDM2 can inhibit the activity of p53, while interferon (IFN)-γ can increase the expression of MDM2 and further inhibit the activity of p53. Peng *et al* (38) showed that ICIs can increase the production of IFN-γ at the tumor site, suggesting that the IFN-γ-MDM2-p53

Table I. Association between clinically-related factors and poor tumor prognosis.

Clinically-related factors	Clinical manifestation/treatment	(Refs.)
Age	Older (>65 years)	(7,27,28)
Sex	Female	(29-32)
Local recurrence	High local recurrence	(6,33-35)
Chemotherapeutics/ICIs	ICIs	(11)
Number of metastases	≥2	(11,36)

ICIs, immune checkpoint inhibitors.

axis may be involved in mediating the development of HPD. In a mouse model study (39), PD-1-knockout mice that were infected with *Mycobacterium tuberculosis* produced excessive IFN-γ, resulting in mouse mortality. This study confirmed the association between PD-1 blockade and IFN-γ secretion from another angle, which is still lacking clinical evidence.

Singavi *et al* (40) published a study on MDM2/MDM4 amplification as a molecular marker for HPD population prediction and revealed that genetic variants on MDM2/MDM4, EGFR and 11q13 have links to HPD, however, their use as potential biomarkers of HPD warrants further investigation in larger cohorts.

A meeting abstract of the 19th American Society of Clinical Oncology showed that cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) gene deletion and MDM2 changes are closely linked to immune hyperplasia (41).

Since pretreatment predictors for patients with HPD are one of the key factors in managing patients receiving ICIs, genetic testing (liquid biopsy/tissue test) may be useful for clinical prediction. In the future, ICIs combined with MDM2/4 inhibitors may be a potential treatment strategy.

Concurrently, there are other research views. Kamada *et al* (42) found that patients with advanced gastric cancer without HPD also exhibited genetic changes, such as Erb-B2 receptor tyrosine kinase 2 (ERBB2) amplification, MDM2 amplification, tumor protein p53 (TP53) mutation, KRAS proto-oncogene, GTPase (KRAS) amplification and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation. Genetic alterations such as TP53 mutation, PIK3CA mutation, MDM2 amplification, ERBB2 amplification and KRAS amplification were also identified in patients with advanced gastric cancer who did not have HPD. This is an indication that these alterations may not be HPD-specific.

Understanding the role of different gene mutations in hyperprogression requires further study. Promising potential biomarkers for immunotherapy include liquid biopsies that identify free DNA or circulating tumor DNA (43). For instance, new directions in minimal residual disease techniques have linked chromosomal instability to a poor prognosis and resistance to treatment in a number of malignancies (44).

**Immune microenvironment.** The immune system plays a dual role in the body and may contribute to the development of

cancer through both direct (induced DNA damage and free radical generation) and indirect (angiogenesis and tissue remodeling that promote production of growth factors and inflammatory matrix metalloproteinases) mechanisms.

The development of HPD may involve alterations in the tumor immune microenvironment, exacerbation of innate immune suppression, activation of oncogenic signals, and regulation of tumor-promoting cytokines (45). It has been hypothesized that PD-1 channel blocking could trigger a complex cascade, through mediating the immune system or directly accelerating a tumor growth inhibitory mechanism, altering the tumor immune microenvironment and leading to hyperprogression (46).

Tumor-infiltrating lymphocytes (TILs) are a type of infiltrating lymphocyte isolated from tumor tissue. TILs are a tumor antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T-cell populations found in tumor tissue. The tumor suppressive effect of TILs *in vivo* is limited by CD4<sup>+</sup> CD25<sup>+</sup> Tregs, and the tumor killing activity can be restored following IL-2 stimulation *in vitro*. Following expansion, TILs can be used in adoptive tumor cell therapy in the clinic. Tregs are important suppressor cells and widely exist in TILs. Their function is similar to that of PD-1 signaling to suppress immune response and avoid autoimmune diseases. Tumors also recruit Tregs to their cells and use them to evade attack by the immune system (47). Previous evidence has suggested that high numbers of infiltrating Tregs in tumors are associated with poor prognosis (48). Adeegbe *et al* found that the number of Treg cells increased in the tumors of patients who experienced hyperprogression following the use of PD-1 inhibitors (48). Wen *et al* (49) revealed that the number of Treg mouse lymph nodes resistant to an anti-PD-1 antibody was significantly higher than that of mice sensitive to an anti-PD-1 antibody, suggesting that Tregs may be part of the resistance mechanism of anti-PD-1/PD-L1 antibodies. In addition, Oweida *et al* (50) observed that in a mouse model of squamous cell carcinoma of the head and neck, the accumulation of Tregs could promote tumor recurrence following anti-PD-L1 antibody treatment, in such a manner that the antitumor immunity generated by anti-PD-L1 antibody could not be sustained, that is, drug resistance was generated, and the antitumor immunity mediated by the anti-PD-L1 antibody could be restored following the depletion of Tregs. It was further demonstrated that Tregs were involved in anti-PD-L1 and PD-1 antibody resistance. In addition, Di Pilato *et al* (51) reported that the destruction of the Card9-BCL10-MALT1 signaling complex infiltrating Tregs in mouse tumors would cause them to lose their inhibitory function and exert antitumor effects through the secretion of IFN- $\gamma$ , thus enhancing the efficacy of anti-PD-1/PD-L1 antibodies. Jacquelot *et al* (52) observed that the disruption of inducible nitric oxide synthase inhibited Treg activation in mouse tumors and could maintain the long-term antitumor effect of anti-PD-L1/PD-1 antibody. Tregs are major contributors to anti-PD-1/PD-L1 antibody resistance. The depletion of Tregs or disruption of their inhibitory function can improve the efficacy of anti-PD-1/PD-L1 antibodies. A study by Kumagai *et al* (53) also confirmed that PD-1 inhibitors are often effective when PD-1 is expressed at a high level in effector T cells and at a low level in Tregs in tumors. However, when the level of PD-1 expression on the effector T cells is low and the level of PD-1 expression on the

Tregs is high, the use of PD-1 inhibitors is likely to be ineffective or lead to hyperprogression. Thus, Treg cells inhibit tumor regression, which is one of the mechanisms of hyperprogression in the TME; this is one of the challenges that needs to be resolved by TIL therapy.

At the same time, there is increasing awareness that changes in the TME, such as polarizing certain types of macrophages (such as CD163<sup>+</sup> CD33<sup>+</sup> PD-L1<sup>+</sup> macrophages), could also lead to HPD (54).

Tumor-associated macrophages (TAMs) are important components of the microenvironment of solid tumors, differentiating along a spectrum from M1 tumor-killing macrophages to M2 tumor-promoting macrophages (55). TAMs in the hypoxic microenvironment of tumors are well recognized to confer resistance to a variety of anticancer therapies and to promote cancer recurrence (56). HPD can be classified as a drug-resistant disease.

Heterogeneity of the tumor environment has become a major research focus. There are significant differences in gene regulation and protein expression among different cancer types and tumor stages, which may be important factors leading to tumor hyperprogression. Wang *et al* (57) used single-cell RNA sequencing to dissect unique immune signals between lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD), the two main subtypes of NSCLC. Fatty acid-binding protein 4 (FABP4) macrophage was found to be the predominant component of macrophages in LUAD, but the predominant component of macrophages in LUSC was identified to be secreted phosphoprotein 1 (SPP1). The results demonstrated that macrophages and lymphocytes are important factors for the immuno-heterogeneity of lung cancer subtypes and revealed the unique function of the macrophage subcluster in the immuno-heterogeneity of lung cancer subtypes. Concurrently, a new lymphocyte-associated macrophage cluster was defined and it was labeled selenoprotein P (SELENOP)-macrophage. This subset expressed SELENOP, folate receptor beta, interleukin 32, CD3 delta subunit of T-cell receptor complex and leukotriene C4 synthase at high levels, indicating that they are closely associated with lymphocyte-related functions, and this subset was revealed to be involved in peptide metabolism, protein trafficking, and cytokine secretion and is critical for both LUAD and LUSC. These studies lay the foundation for the potential clinical development of new therapeutic targets in lung cancer in the TME.

Cleaver-1/stabilin-1 is widely found on lymphocytes, vascular endothelial cells and certain subtypes of M2 macrophages as a scavenger receptor and adhesion molecule. In patients with advanced colorectal cancer, patients with high expression of cleaver-1/stabilin-1 had a shorter survival and worse prognosis. A clinical study by Patten *et al* confirmed that cleaver-1 promotes tumor angiogenesis and regulates T-cell activity. The inhibition of cleaver-1 can increase the secretory activity of TAM proinflammatory cytokines and reactivate the antitumor activity of CD8<sup>+</sup> T cells through antigen presentation, thereby overcoming the immunosuppressive TME (58).

Considering the complex microenvironment and highly heterogeneous characteristics of HCC, Liu *et al* (59) investigated the expression of various protein cells in the TME and revealed that the proportion of plasmacytoid dendritic and natural killer, T and B cells was significantly reduced, and

Table II. Association between the expression of various genes and poor tumor prognosis, identified using single-cell RNA sequencing.

Subtype	Expressed by cells	(Refs.)
FABP4-M $\phi$	M $\phi$	(56)
SPP1-M $\phi$	M $\phi$	(56)
Cleaver-1/stabilin-1	Lymphocytes, vascular endothelial cells and certain subtypes of M2 macrophages	(57)
SPP1 and CD44	Tumor cells (hepatocellular carcinoma)	(58)
LILRB4	Antigen-presenting cells	(59-64)
LILRB2	Myeloid cells	(65)

FABP4, fatty acid-binding protein 4; M $\phi$ , macrophages; SPP1, secreted phosphoprotein 1; LILR, leukocyte Ig-like receptor.

the proportion of macrophages was significantly elevated in the tumor tissue. The level of expressed SPP1 and CD44 in HCC was also examined, and the findings indicated that the expression of SPP1 and CD44 in HCC tissues was markedly upregulated compared with that in normal tissues. Protein expression of CD44 as well as SPP1 was shown to be markedly higher in HCC than in healthy tissues by immunohistochemistry. Survival results showed that the prognosis of those with dual high expression of SPP1 and CD44 was poor, indicating the tumor-promoting roles of the SPP1/CD44 axis during HCC progression.

The leukocyte Ig-like receptor (LILR) family is one of the most important target groups for tumor progression. It has 13 members (including two pseudogenes) and is one of seven leukocyte immunoglobulin-like inhibitory receptors. LILRB4 is a type of suppressor receptor that has an important function in immunological checkpoint pathways. In patients with cancer, LILRB4 inhibits the proliferation of CD4<sup>+</sup> T cells and promotes tumor growth and invasion by combining with its ligand CD166 and CD8<sup>+</sup> CD28 T cells (60-63). Studies have revealed that LILRB4 plays a critical role in tyramine and in activating the tyramine receptor (64). In view of the role of LILRB4 in tumorigenesis, this discovery emphasizes the association between LILRB4 and tumors (65). Increasing evidence suggests that LILRB4 may be a regulator of tumor progression through the inhibition of the Akt signaling pathway. Thus, LILRB4 is considered a marker of malignancy. In solid tumors, LILRB2 can interact with major histocompatibility complex, class I, G, angiopoietin-like family, semaphorin 4A and CD1d-related ligands in the TME, causing myeloid cells to allow or promote tumor growth, and promote tumor immune escape. A previous study revealed that LILRB2 may act as a myeloid immune checkpoint. It reprograms tumor-associated myeloid cells and stimulates antitumor immunity (66). Several therapies targeting LILRB4 are currently in clinical development, including inhibitory antibodies, antibody-drug conjugate (ADC) and CAR-T cell therapies. With the in-depth study of LILRB4, a broader prospect in tumor application and hyperprogression research may be revealed for LILRB4.

Hyperprogression has been revealed to always be the result of a combination of complex factors. Li *et al* (67) suggested that the intersection of immune and tumor metabolic pathways drives cancer hyperprogression during immunotherapy. In animal models, T cell-derived IFN- $\gamma$  has been revealed to

promote tumor FGF2 signaling, thereby inhibiting PKM2 activity and reducing NAD<sup>+</sup>, resulting in sirt1-mediated decreased  $\beta$ -catenin deacetylation and enhanced  $\beta$ -catenin acetylation, thereby reprogramming tumor stemness (67). In preclinical models, targeting the IFN $\gamma$ -PKM2- $\beta$ -catenin axis was demonstrated to prevent HPD. Therefore, the interaction of core immunogenicity, metabolism, and oncogenic pathways through the IFN $\gamma$ -PKM2- $\beta$ -catenin cascade is the basis of immune checkpoint blockade-associated HPD (67). The association between the expression of various genes and poor tumor prognosis is revealed in Table II.

## 5. Conclusions

The clinically relevant factors, biomarkers and possible effects of the immune microenvironment on hyperprogression, described in the present review, have attracted increasing attention. HPD associated with ICI treatment usually predicts poor clinical prognosis (11). It is therefore necessary to explore predictors of HPD, with the aim of undertaking early treatment decisions without delays. The present review summarized the current findings of possible factors associated with hyperprogression. Clinically-relevant factors, such as individuals >65 years, women, greater local recurrence and number of metastases, as well as ICI treatment, indicate higher rates of hyperprogression. Biomarkers such as MDM2/MDM4, EGFR, CDKN2A/B, STK11, JAK3 and SOX9 are also closely associated with HPD, however the exact associations remains controversial. The major components of the immune microenvironment, such as FABP4 macrophages, SPP1 macrophages, cleaver-1/stabilin-1, SPP1, CD44, LILRB4 and LILRB2, all indicate the possibility of marked HPD. In cases where the cause of HPD is not clear, the characteristics of patients with accelerated progression compared with the clinical outcome may be investigated in reverse order, to identify the characteristics of patients with high risk of HPD, in order to reduce HPD-induced mortality. In recent years, the increasingly in-depth study of the immune microenvironment has provided novel insights into the abnormal hyperprogression of tumors, particularly the heterogeneity of various types of macrophages and marker proteins such as cleaver-1/stabilin-1 and LILBR family proteins in tumor progression. Therefore, it is considered that these factors may greatly influence the occurrence of tumor hyperprogression. Further studies with

a greater number of cases and a more detailed genetic and protein analysis of patients with HPD need to be conducted urgently, to better understand the mechanism of HPD and thus reduce the incidence of HPD and improve the prognosis of patients with HPD. During immunotherapy, particularly during the first 6-8 weeks of immunotherapy, close attention should be paid to symptoms and physical changes.

In conclusion, hyperprogression is a relatively specific adverse immunotherapy-related phenomenon, not uncommon in immunotherapy, whose specific mechanism remains unknown. However, accelerated progression should not influence the selection of immunotherapy as a treatment option. Immunotherapy remains a promising antitumor strategy, and the discovery of hyperprogression should not prompt patients to abandon this treatment. Greater in-depth study of immunotherapy should be carried out, clarifying the occurrence and development mechanism of hyperprogression, in order to improve immunotherapy in the fight against tumors.

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### Authors' contributions

Literature collection and analysis were performed by RQ. XC is the corresponding author and contributed to the study conception and design. The first draft of the manuscript was written by RQ. LY, XZ, LH and PZ contributed to the writing of previous versions of the manuscript and YW aided with language editing. All authors read and approved the final manuscript. Data authentication is not applicable.

### Ethics approval and consents to participate

Not applicable.

### Patient consents for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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