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Is Weak Acid Beneficial for Addressing Checkpoint Inhibitor–Triggered Cancer Hyper Progression in Anti-PD1/PD-L1 Immunotherapies?

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Abstract

Numerous cases of checkpoint inhibitor–triggered cancer hyperprogression have been documented. A previous hypothesis attributes cancer onset to the local buildup of hydrogen chloride, jointly mediated by hydrogen bond donors and acceptors and basic amino acids. The anti-PD1/PD-L1 immunotherapies may have caused a surge of protons or chloride ions for the effective treatment of neoplasm, thus giving rise to the local formation of hydrogen chloride and subsequently cancer hyperprogression in some susceptible individuals. It was postulated that the local strength of acidity is critical for tumor growth and metastasis, as the intake of weak organic acids reduces cancer risks. The anti-PD1/PD-L1 immunotherapies can be integrated with weak organic acids to reduce adverse reactions and generate better anticancer outcomes.

Keywords

anti-PD1/PD-L1 immunotherapies, checkpoint inhibitor, cancer hyperprogression, acidity, weak organic acids

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The living environment, dietary, and lifestyle factors are closely related to human health. A large number of patients suffer from cancer due to occupational exposure. Percivall Pott first described the association between scrotal cancer and chimney sweeps in 1775,[1] and bladder cancer frequently occurs in dye workers exposed to benzidine,[2] and asbestos workers are at high risk of bronchogenic carcinoma.[3] Plant-based diet reduces cancer risks, whereas smoking and overconsumption of alcohol increase cancer incidences. *Fusobacterium* species substantially enhance tumorigenesis of the colorectal system, whereas lactic acid bacteria-containing yogurt significantly lowers the rate of malignancies. Some bacteria help tumor to evade immune surveillance. Obesity is a risk factor for neoplasm. Patients with colorectal cancer harbor somatic genetic and epigenetic alterations, including locus-specific CpG island (CGIs) methylation and global DNA or LINE-1 hypomethylation. Global molecular features such as microsatellite instability, CGIs methylator phenotype, global DNA hypomethylation, and chromosomal instability give rise to variations of gene functions on a broad scale.[4] Nonsteroidal anti-inflammatory drugs elicit anticancer effects, whereas vitamin D reduces cancer risk, perhaps via the neutralization of strong acids by calcium salts.[5] Germline and somatic genetic variations have impact on immune function. For example, germline and somatic mutations of TNFAIP3 are key factors in the transformation between autoimmunity and lymphoma.[6]

The efficacy of immune checkpoint inhibitors (ICIs) varies widely among individual patients and tumor types. In a 2012 study, Topalian et al enrolled patients with different cancers to

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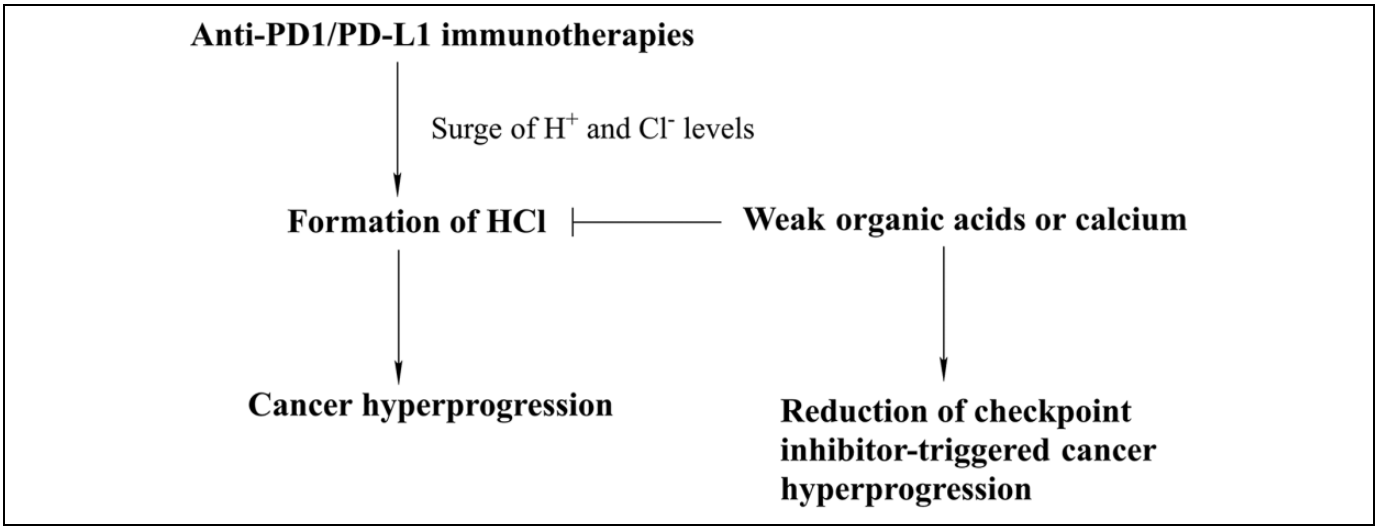

Figure 1. A surge of proton and chloride ion levels may underlie checkpoint inhibitor–triggered cancer hyper progression.

receive anti-PDCD1 (anti-PD1) antibody periodically and quantitatively, among which 36% patients with CD274 (PD-L1)-positive tumors had an objective response but patients with PD-L1-negative tumors were not sensitive to treatment.[7] Le et al reported mismatch repair-deficient (dMMR) colorectal cancers, with a large number of somatic mutations, are more responsive to PD1 blockade than mismatch repair-proficient tumors.[8] However, the antitumor activity of single agent is very limited in various tumors, and it can even lead to accelerated tumor growth. In a recent study, 33.8% of patients with non-small cell lung cancer (NSCLC) who received second-line or later single-agent ICI therapy had experienced rapid progression.[9] Seniors older than 65 years may also be associated with higher rate of hyperprogressive disease (HPD).[10] Hypermethylations of promoter CGIs in tumor suppressors augment tumorigenesis through epigenetic mechanism, signal transduction, or perhaps cation binding in cytosine.[11] Several research groups have reported cases of checkpoint inhibitor–triggered cancer hyperprogression with rates ranging from 7% to 29% in various cancers, and potential mechanisms have been proposed.[12-16]

A biochemical view can complement the biological perspectives. A hypothesis was previously postulated that cancer onset is triggered by the local buildup of hydrogen chloride, comediated by hydrogen bond donors and acceptors, and basic amino acids.[17-19] Red meat is presumed to be slightly carcinogenic as defined by World Health Organization and marked by the presence of myoglobin which harbors around 20% to 21% positively charged basic amino acids, attracting anions such as Cl^- and contributing to the local formation of hydrogen chloride.[17,18] Boiled red meat with denatured proteins retain its carcinogenic potential. Triacylglycerides, glucose, and ethanol harbor oxygen atoms or hydroxyl groups capable of hydrogen bonding and give rise to higher cancer risks in individuals with obesity, diabetes, and alcoholism, respectively.[19-21] Calcium supplement capable of neutralizing strong acids significantly reduces cancer incidences.[5] The noncoastal southern Yunnan Province and nonhumid central provinces in China has low nasopharyngeal cancer prevalence, whereas the humid coastal southern provinces in China and Southeast Asia have high nasopharyngeal cancer rates,[22] suggesting that hydrogen bonding to protons plays a critical role in carcinogenesis of the nasopharyngeal cavity in high-humidity regions. Individuals with regular diarrhea or loose stools are much more prone to develop colorectal neoplasm than individuals with soft stools.[23] Enhanced hydrogen bonding to protons is likely to be the culprit.[17-19] It was proposed that the strength of local acidity is vital for cancer growth and metastasis, since weak acid lowers cancer incidences.[24-26] Chinese vinegar factories reported few cancer cases over decades,[24-26] and the vicinity of these factories also had low cancer incidences,[24] suggesting that the volatile and weak acetic acid may counteract strong acids. The *Homo sapiens* sodium/hydrogen exchanger 1 (NHE1, SLC9A1) is the principle proton efflux machinery in maintaining alkaline intracellular pH in glioma, and the blocking of NHE1 protein sensitized animals to anti-PD1 immunotherapy.[27] Reducing tumor acidity with bicarbonate monotherapy inhibited the growth of some cancers in mice, and integrating bicarbonate therapy with anti-CTLA4 or anti-PD1 enhanced the anticancer effects in several models.[28]

The anti-PD1/PD-L1 immunotherapies may have triggered a surge of protons or Cl^- for the eradication of cancer cells, thus contributing to the local formation of hydrogen chloride. Patients with basic amino acid polymorphisms in basic oncoproteins or/and tumor suppressors may be at relatively high likelihood for checkpoint inhibitor–triggered cancer hyperprogression. Alternatively, patients with cancer with moderate local acidity might be susceptible to the local surge of proton levels or the levels of Cl^- in the anti-PD1/PD-L1 immunotherapies. Weak acid usage can be integrated into these immunotherapies to counteract strong acids and maximize potential benefits (Figure 1). Since over-intake of NaCl may increase local formation of HCl, reduced consumption of salt

can be beneficial to the aforementioned integrated immunotherapies. The reduced consumption of meat during treatment needs to be taken into consideration.

Future Directions and Conclusions

With the advent of immune checkpoint-blocking antibody, marked advance has been made in the treatment of cancer. To date, several ICIs are now approved for therapy, ipilimumab was the first agent to be used for melanoma treatment,[29] and nivolumab, pembrolizumab, cemiplimab, and so on were approved subsequently. Due to the limitations of single-agent therapy, combination therapy possesses some advantages. The 5-year survival rate was 18.2% for patients with advanced melanoma treated with ipilimumab plus dacarbazine, twice as patients treated with placebo plus dacarbazine.[30] Larkin et al also demonstrated that the combination of PD1 and CTLA4 blockade was more effective than single-agent therapy in previously untreated patients with metastatic melanoma.[31] By analyzing the progression-free survival curves of different treatments, Suda suggested a possible strategy that HPD after immunotherapy can be avoided with the combination of PD1/PD-L1 inhibitors and cytotoxic chemotherapy.[32]

In addition to the combination therapy strategies, the role of biomarkers is under intense scrutiny. As a tumor biomarker, tumor mutation burden (TMB) has been shown to be an independent predictor of response to immunotherapy. Hellmann et al found that TMB strongly predicted the efficacy in patients with NSCLC treated with PD1 and CTLA4 combination blockade.[33] Molecular pathological epidemiology should be adopted to find effective biomarkers to address checkpoint inhibitor–triggered cancer hyperprogression in immunotherapies.[4,34] Identified biomarkers related to HPD have been discussed in detail by Wang et al, including tumor cell biomarkers, tumor microenvironment biomarkers, laboratory biomarkers, and clinical indicators.[14]

Oncoproteins and tumor suppressors usually have over 10% to over 20% basic amino acids, accounting for their tumorigenicity when additional disease-causing polymorphisms are present. The lactic acid-containing yogurt or organic acid-rich plant-based diet reduces cancer risks,[7] perhaps via the attenuation of local acidity. Modest calcium supplement can be integrated with immunotherapy since insoluble calcium salts counteract hydrogen chloride, which could also decrease checkpoint inhibitor–triggered cancer hyperprogression. Clinical trials should be conducted for the integration of weak organic acids to immune-therapies before medical applications.

Authors' Note

Ethical approval is not applicable in this commentary, as no animal or human subject was involved.

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References

1. Azike JE. A review of the history, epidemiology and treatment of squamous cell carcinoma of the scrotum. *Rare Tumors*. 2009; 1(1):e17.
2. Walker B, Gerber A. Occupational exposure to aromatic amines: benzidine and benzidine-based dyes. *Natl Cancer Inst Monog*. 1981;(58):11-13.
3. Woodworth CD, Mossman BT, Craighead JE. Squamous metaplasia of the respiratory tract. Possible pathogenic role in asbestos-associated bronchogenic carcinoma. *Lab Invest*. 1983; 48(5):578-584.
4. Ogino S, Chan AT, Fuchs CS, et al. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut*. 2011;60(3):397-411.
5. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354(7):684-696.
6. Nocturne G, Boudaoud S, Miceli-Richard C, et al. Germline and somatic genetic variations of TNFAIP3 in lymphoma complicating primary Sjogren's syndrome. *Blood*. 2013;122(25): 4068-4076.
7. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
8. Le DT, Uram JN, Wang H, et al. PD1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26): 2509-2520.
9. Zhang L, Bai L, Liu X, et al. Factors related to rapid progression of non-small cell lung cancer in Chinese patients treated using single-agent immune checkpoint inhibitor treatment. *Thorac Cancer*. 2020;11(5):1170-1179.
10. Champiat S, Dercle L, Ammari S, et al. Hyper progressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin Cancer Res*. 2017;23(8):1920-1928.
11. Wang Y, Wang Z, Cui L, et al. Why some circulating DNA methylation markers can be used for diagnosis and prognosis of cancers. *Science*. 2018. Accessed June 17, 2020. http://science.sciencemag.org/content/354/6314/843.6/tab-e-letters

12. Kamada T, Togashi Y, Tay C, et al. PD1^{+} regulatory T cells amplified by PD1 blockade promote hyperprogression of cancer. *Proc Natl Acad Sci USA*. 2019;116(20):9999-10008.
13. Kaiser J. New drugs that unleash the immune system on cancers may backfire, fueling tumor growth. *Science*. 2019. doi:10.1126/science.aax5021.
14. Wang X, Wang F, Zhong M, et al. The biomarkers of hyperprogressive disease in PD1/PD-L1 blockage therapy. *Mole Cancer*. 2020;19(1):81.
15. Kanjanapan Y, Day D, Wang L, et al. Hyperprogressive disease in earlyphase immunotherapy trials: clinical predictors and association with immune-related toxicities. *Cancer-Am Cancer Soc*. 2019;125(8):1341-1349.
16. Saada-Bouzid E, Defaucheux C, Karabajakian A, et al. Hyperprogression during anti-PD1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. *Ann Oncol*. 2017;28(7):1605-1611.
17. Tang M, Zhou Y, Li Y, et al. Hydrogen donors and acceptors and basic amino acids jointly contribute to carcinogenesis. *Med Hypotheses*. 2017;98:42-44.
18. Zhang J. Appearance of somatic mutations can be subjected to the influences of inherited factors. *Science*. 2017. Accessed April 23, 2020. http://science.sciencemag.org/content/355/6331/1330/tab-e-letters
19. An S, Li X, Tang M, et al. Functional duality of ethanol on cancer. *Med Hypotheses*. 2019;122:124-125.
20. Zhang X, An S, Wu X, Li X, Qiuyun L. How to prevent obesity-triggered heart disease. *Eur J Prev Cardiol*. 2018;25(16):1790.
21. An S, Zhao B, Zhang X, Qiuyun L. How to prevent diabetes-triggered heart disease. *Eur J Prev Cardiol*. 2018;25(16):1789.
22. Wan Y, Zhang J, Li X, Wang Y, Liu Q. Cellular states and secondary chemical bonding: a biochemical view of major human diseases. *Biochem Insights*. 2019;12(6):1178626419877846.
23. Wan Y, Wen L, Liu Q. Who will benefit from colorectal cancer prevention measures? *Eur J Cancer Prev*. 2019;28(5):459-460.
24. Wan Y, Li J, Liu Q. Vinegar production and cancer risk. *Eur J Cancer Prev*. 2019;28(4):82.
25. Shi Y, An S, Wan Y, Fan Y, Qiuyun L. How to best use acetic acid for the prevention of heart disease and cancer. *Eur J Prev Cardiol*. 2019;26(1):437-438.
26. An S, Li X, Tang M, et al. The role of acetate in the antagonism of oxalate—a potential causative molecule for heart disease and cancer death. *Nat Prod Commun*. 2020;15(3):1-4.
27. Guan X, Luo L, Begum G, et al. Elevated Na/H exchanger 1 (SLC9A1) emerges as a marker for tumorigenesis and prognosis in gliomas. *J Exp Clin Cancer Res*. 2018;37(1):255.
28. Pilon-Thomas S, Kodumudi KN, El-Kenawi AE, et al. Neutralization of tumor acidity improves antitumor responses to immunotherapy. *Cancer Res*. 2016;76(6):1381-1390.
29. Lipson EJ, Drake CG. Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma. *Clin Cancer Res*. 2011;17(1):6958-6962.
30. Maio M, Grob J, Aamdal S, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. *J Clin Oncol*. 2015;33(10):1191-1196.
31. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.
32. Suda K. The ABCs of preventing hyper progressive disease after immunotherapy: awareness, biomarkers, and combination. *J Thorac Dis*. 2019;11(3):S347-S351.
33. Hellmann MD, Nathanson T, Rizvi H, et al. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. *Cancer Cell*. 2018;33(5):843-852.
34. Ogino S, Nowak JA, Hamada T, et al. Insights into pathogenic interactions among environment, host, and tumor at the crossroads of molecular pathology and epidemiology. *Annu Rev Pathol*. 2019;14(2):83-103.