Editorial

Hypoxia features as potential indicators in prognosis, immunotherapy and drug screening in hepatocellular carcinoma patients

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Primary liver cancer is the 6th most common cancer and 4th leading cause of cancer-related death with over 780,000 new cases annually worldwide (1). Hepatocellular carcinoma (HCC) represents the most common type of primary liver cancer and accounts for around 90% (2). HCC patients present often with advanced hepatic fibrosis or cirrhosis, which are caused by hepatitis virus B or C (HBV or HCV) infections or abuse of alcohol (3-6). Normally, less than 30% of HCC patients are diagnosed at early stage, most HCC patients are diagnosed at very advanced stage (2). Early-stage patients are eligible for resection, transplantation or local ablation surgery, patients at intermediate stage could benefit from chemoembolization treatments, however, patients at the advanced stage could also benefit from first-line systemic treatments, such as sorafenib or lenvatinib, but only with a median survival of 10.7–13.7 months (7-10). Combined treatments of immune-check point blockade (ICB) and VEGF inhibitors have also been in process of clinical trials (11), but advanced HCC patients could not benefit a lot from them, thus, more effective therapeutic tools or methods need to be developed urgently.

Hypoxia is the situation that tissues and cells are deprived of oxygen, it is well known for many years that hypoxia is a main feature of solid tumors (12). Rapid growth of tumor cells leads to a shortage of oxygen supply which induces a hypoxic microenvironment in solid tumors, to survive from that, the tumor cells change numbers of molecular and cellular processes, including cell metabolism, extracellular matrix, metastatic behavior (13,14). Hypoxia-inducible factors (HIFs) are the responsible transcriptional factors that mediate the cellular responses to hypoxia (15). HIFs consist of an alpha and a beta subunit to form the heterodimer and then bind to the hypoxia response elements (HREs) to promote the transcriptions of over 200 genes which regulate cell survival, anti-apoptosis, angiogenesis in response to hypoxia.

Clearly that hypoxia is also the main feature of HCC, HIFs and hypoxia-driven genes have also been reported to be aberrantly expressed and considered as the biomarkers of prognosis in HCC (16).Given the pivotal roles of hypoxia and hypoxia-related genes in the progression of HCC, it is of interest to establish a hypoxia index to study the relations between hypoxia and prognosis in HCC to develop potential therapeutic strategies for HCC patients. A recent study by Luan and Si reported a novel HCC-specific hypoxia score system to predict HCC patients' prognosis and to contribute to the effective therapies for the specific subpopulation of HCC patients (17).

The authors firstly carried out a microarray analysis with different datasets from TCGA to identify a set of hypoxia-

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related genes, with 18 negative signatures and 56 positive signatures screened. The identified hypoxia features were further validated on HCC cells and HCC patients' samples. The clinical features were also detected with the defined hypoxia score that higher hypoxia level is correlated with worse prognosis on HCC patients. These examinations supported that the hypoxia score system could possibly predict the prognosis on HCC patients.

To better improve the hypoxia score system, the authors further analyzed the associations between the hypoxia score groups and the molecular characteristics. Luan *et al.* revealed that the hallmark of angiogenesis, epithelial-mesenchymal transition (EMT), mitotic spindle and WNT-beta catenin signaling elevated in high hypoxia score HCC patients, but fatty acid metabolism, OXPHOS and xenobiotic metabolism diminished (17). Furthermore, the distribution of mutations was also studied with the hypoxia score and identified that lower hypoxia score patients present mutations of CTNNB1 and ALB. Different CNV inclinations were also observed in the low hypoxia score and high hypoxia score groups. These findings further prove that the different hypoxia score groups indeed represent different hallmarks and molecular characteristics in HCC patients. To further study that whether the hypoxia score system could be utilized as an important index of HCC patients' prognosis, the authors explored the relationship between the hypoxia scores and HCC patients' survival with different cohorts. They validated that high hypoxia score group had worse overall survival.

Immunotherapy is gaining continued traction on treatment of kinds of cancers, including HCC (18). Studies of correlation between hypoxia score and the immune system state in HCC would be instructive on the treatments. The authors firstly analyzed the relation between hypoxia scores and extrinsic immune escape and found that patients with high hypoxia scores tend to be in the anti-tumor state but still with some immunosuppressive cells' infiltration. They further studied the association between hypoxia score groups and the intrinsic immune escape in HCC, uncovering that high hypoxia score patients present higher immunogenicity, cytolytic scores, antigen presentation and fibroblasts. Nevertheless, they also found that in high hypoxia score patients present higher T-cell dysfunction in most cases, but with the TIDE tool analysis, they found that all the high hypoxia score groups exhibit high TIDE scores, which means that patients with high hypoxia scores may not benefit a lot from ICB treatment. Further analysis on ICB treated patients illustrated that with low hypoxia scores, patients have significant prolonged survival than the high hypoxia scores. The positive connections between the immunotherapy response and low hypoxia scores were also observed by the authors. Their findings further support that the hypoxia score system could be an instructive tool for the prediction of HCC patients' prognosis and the options of clinical immunotherapies.

Moreover, considering that hypoxia score HCC patients may not benefit a lot from the immunotherapy, the authors constructed a prediction model of drug response and with the differential drug response analysis, they further identified the potential drug of VLX600, which presented high potential to be a promising drug on high hypoxia score HCC patients.

Collectively, in this study by Luan *et al.*, the authors develop a hypoxia score system to estimate HCC patients' prognosis, provide potential recommendation of immunotherapies and screen drugs for high hypoxia score patients (17). The study is interesting and of some clinical relevance. Due to all the studies were based on limited datasets, further studies with more data of HCC patients would be needed to validate and improve the hypoxia score system. The selected drug VLX600 may also need to be further studied with *in vitro* and *in vivo* experiments to validate its potential clinical performance on HCC patients.

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References

1. Tang A, Hallouch O, Chernyak V, et al. Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. Abdom Radiol (NY) 2018;43:13-25.
2. Ahmed I, Lobo DN. Malignant tumours of the liver. Surgery 2009;27:30-7.
3. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.
4. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264-1273.e1.
5. Amaddeo G, Cao Q, Ladeiro Y, et al. Integration of tumour and viral genomic characterizations in HBV-related hepatocellular carcinomas. Gut 2015;64:820-9.
6. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol 2013;10:553-62.
7. Carlomagno F, Anaganti S, Guida T, et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst 2006;98:326-34.
8. Hoffmann K, Franz C, Xiao Z, et al. Sorafenib modulates the gene expression of multi-drug resistance mediating ATP-binding cassette proteins in experimental hepatocellular carcinoma. Anticancer Res 2010;30:4503-8.
9. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
10. Kudo M. Systemic Therapy for Hepatocellular Carcinoma: 2017 Update. Oncology 2017;93 Suppl 1:135-46.
11. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
12. Denko NC. Hypoxia, HIF1 and glucose metabolism in the solid tumour. Nat Rev Cancer 2008;8:705-13.
13. Rey S, Semenza GL. Hypoxia-inducible factor-1-dependent mechanisms of vascularization and vascular remodelling. Cardiovasc Res 2010;86:236-42.
14. Maxwell PH, Dachs GU, Gleadle JM, et al. Hypoxia-inducible factor-1 modulates gene expression in solid tumors and influences both angiogenesis and tumor growth. Proc Natl Acad Sci U S A 1997;94:8104-9.
15. Lum JJ, Bui T, Gruber M, et al. The transcription factor HIF-1alpha plays a critical role in the growth factor-dependent regulation of both aerobic and anaerobic glycolysis. Genes Dev 2007;21:1037-49.
16. Luo D, Wang Z, Wu J, et al. The role of hypoxia inducible factor-1 in hepatocellular carcinoma. Biomed Res Int 2014;2014:409272.
17. Luan M, Si H. Novel hypoxia features with appealing implications in discriminating the prognosis, immune escape and drug responses of 947 hepatocellular carcinoma patients. Transl Cancer Res 2022;11:2097-121.
18. Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol 2022;19:151-72.

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