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EDITORIAL

Hypoxia-related bioinformatic signatures associated with prognosis and tumor microenvironment of pancreatic cancer: Current status, concerns, and future perspectives

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Abstract

Pancreatic cancer (PC), a highly lethal tumor with nearly identical incidence and mortality rates, has become the sixth leading cause of cancer-related deaths. Hypoxia is an important malignant factor in PC, as it regulates angiogenesis, metabolic reprogramming, tumor progression, and metastasis. Disrupting the hypoxic microenvironment can enhance the efficacy of antitumor therapy and improve the prognosis of patients with PC. With the advent of bioinformatics, hypoxia-related PC models have emerged in recent years. They provide a reference for estimating the prognosis and immune microenvironment of patients with PC and identify potential biomarkers for targeting hypoxic microenvironment. However, these findings based on bioinformatic analysis may not be completely reliable without further experimental evidence and clinical cohort validation. The application of these models and biomarkers in clinical practice to predict survival time and develop anti hypoxic therapeutic strategies for patients with PC remains in its infancy. In this editorial, we review the current status of hypoxia-related prognostic models in PC, analyze their similarities and differences, discuss several existing challenges, and provide potential solutions and directions for further studies. This editorial will facilitate the optimization, validation, and determination of the molecular mechanisms of related models.

Key Words: Pancreatic cancer; Hypoxia; Bioinformatics analysis; Prognosis; Tumor microenvironment

Core Tip: Currently, hypoxia-related bioinformatic models for pancreatic cancer (PC) primarily evaluate their value for prognosis, tumor microenvironment, and antitumor drug screening. However, these studies did not identify a prognostic model with an optimal predictive performance for PC. Moreover, findings based on bioinformatic analyses may not be completely reliable; thus, more experimental evidence is required. With the integration of multiomics data, the emergence of deep learning, and the application of high-quality experimental programs, the limitations of these models can be overcome and further application in clinical practice may be recommended in the future.

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INTRODUCTION

Pancreatic cancer (PC) is a leading cause of cancer-related deaths worldwide. Based on the latest cancer statistics from 2022, there were 510566 new cases of PC and 467005 deaths worldwide[1]. Of these, there were approximately 118700 new cases and 106300 deaths in China in 2022[2]. PC has become the third leading cause of cancer-related deaths in the United States, with an estimated 62200 new cases and 48800 deaths reported each year[3]. Although the incidence varies substantially among countries, global statistics indicate that PC is on the rise, and some scholars predict that it will soon become the second leading cause of cancer-related deaths in Western countries[3]. As a highly lethal and notorious disease, only 15%-20% of patients with PC are candidates for surgical resection. Because of the late diagnosis, rapid progression, early metastasis, and limited treatment options, the 5-year survival rate of PC is approximately 10%, thus posing a major threat to human health[4].

Unlike most solid tumors, the tumor environment of PC is characterized by abundant extracellular matrix rich in stromal cells but lacks extensive angiogenesis, resulting in continuous and severe intratumoral hypoxia[5]. As an important malignant hallmark, hypoxia is involved in the regulation of tumor growth, apoptosis, metabolism, stemness, progression, metastasis, and chemoresistance in PC through the activation of various molecules and signaling pathways [6-8]. Targeting the hypoxic microenvironment of PC is a novel antitumor treatment strategy. It may prevent aggressive progression, enhance the efficacy of chemoradiotherapy, and improve the prognosis of patients with PC.

With a better understanding of the hypoxic microenvironment in PC, researchers have begun to establish hypoxia-related bioinformatic signatures to evaluate prognosis, tumor microenvironment changes, and antitumor drug sensitivity of patients with PC. These signatures provide a reference for predicting the survival time and immune infiltration of patients with PC and provide potential biomarkers for targeting the hypoxic microenvironment of PC, which has attracted significant attention. In this editorial, we review the current status of hypoxia-related prognostic signatures in PC. Furthermore, we discuss several issues associated with these prognostic signatures and provide potential solutions and directions for further studies.

CURRENT RESEARCH STATUS

With an increased understanding of the hypoxic microenvironment in the oncology community, more than ten hypoxia-related bioinformatic models have been established to predict prognosis and tumor microenvironmental changes in patients with PC[9-19]. As shown in Table 1, these studies used hypoxia-related transcriptomic expression profiles and the corresponding clinical data from the Cancer Genome Atlas (TCGA) PC cohort as a training set to construct prognostic models based on Cox regression analysis and least absolute shrinkage and selection operator (LASSO) regression analysis. Subsequently, the accuracy of these models was tested using PC datasets from the Gene Expression Omnibus (GEO) and/or International Cancer Genome Consortium (ICGC) databases. Several common evaluation measures, such as Kaplan-Meier curves, receiver operating characteristic curves, C-index, and calibration curves, as well as univariate and multivariate prognostic risk factor analyses, were used to describe the predictive performance and robustness of the models. Overall, these prognostic models showed low-to-moderate predictive capability for a specific range of patients with PC.

In addition to measuring the predictive performance of these models, researchers also examined the correlation between the risk models and the tumor immune microenvironment (Table 2). Most studies have revealed that patients with high risk scores exhibit lower infiltration of antitumor $CD8^+$ T cells, indicating the depletion of activated T cells and immune escape of tumor cells in the hypoxic microenvironment. Moreover, two studies reported that there may be a higher infiltration of M0 macrophages in the high-risk group[14,17]. Therefore, inducing the differentiation of these macrophages into antitumor M1 macrophages, rather than protumor M2 macrophages, may be necessary for high-risk patients. Nevertheless, the infiltrating levels of M2 macrophages in patients with high risk scores remain controversial based on the results of various hypoxia-related models. Ding *et al*[19] found that high-risk patients exhibited higher M2 macrophage infiltration, whereas the opposite finding was reported by Chen *et al*[18]. This contradiction can be attributed to the different backgrounds of the models and the algorithms used for the immune microenvironment.

Table 1 The main information and prognostic performance of hypoxia-related bioinformatic models in pancreatic cancer

Ref.	Data sources	Modeling methods	Biomarkers	Prognostic performance
Yang *et al*[9]	TCGA, GSE62452	Cox, LASSO	*CAPN2, CCNA2, PLAU*	1-, 3-, 5-year area under the curve (AUC) in the training set: 0.687, 0.749, and 0.796; 1-, 3-, 5-year AUC in the test set: 0.610, 0.849, and 0.765; Calibration curve: Moderate fit; Better predictor than other clinical variables
Ren *et al*[10]	TCGA, ICGC	Cox, LASSO	*LY6D, PCAT2, RP11-80B9.1, RP3-525N10.2, TRIM67, UCA1*	1-, 2-, 3-year AUC in the training set: 0.727, 0.911, and 0.93; 1-, 2-, 3-year AUC in test set 1: 0.635, 0.696 and 0.694; 1-, 2-, 3-year AUC in test set 2: 0.68, 0.756 and 0.689; Better predictor than other clinical variables; Independent prognostic factor
Huang *et al*[11]	TCGA, ICGC, ArrayExpress E-MTAB-6134	Cox, RSF	*LDHA, POM121C*	1-, 3-, 5-year AUC in the training set: 0.716, 0.676, and 0.696; 1-, 3-, 5-year AUC in test set 1: 0.582, 0.642 and 0.657; 1-, 3-, 5-year AUC in test set 2: 0.711, 0.623 and 0.606; Better predictor than other clinical variables; Independent prognostic factor
Li *et al*[12]	TCGA, GSE62452, GSE78229	Cox, LASSO	*KIF23, KRT13, LRP3, LY6D, MMP3, SERPINB7, SEC31B*	1-, 3-, 5-year AUC: 0.763, 0.832 and 0.814; Better predictor than other clinical variables; Independent prognostic factor
Ren *et al*[13]	TCGA, ICGC	Cox, LASSO	*ARID5A, FAM19A2, ICOSLG, IGLV7-46, SPRN*	1-, 2-, 3-year AUC in the training set: 0.77, 0.793, and 0.781; 1-, 2-, 3-year AUC in the test set: 0.675, 0.678 and 0.57; Better predictor than other clinical variables; Independent prognostic factor
Zhou *et al*[14]	TCGA, GSE102238, GSE62452, GSE85916	Cox, LASSO	*BHLHE40, ENO1, SDC4, TGM2*	Calibration curve: Moderate fit; Independent prognostic factor
Sun *et al*[15]	TCGA	Cox, LASSO	*CCAT2, CEP83-DT, CYTOR, DANCR, GAS5, LINC01029, LINC01133, LINC01963, LINC02287, LINC-PINT, LNCSRLR, SH3PXD2A-AS1, TSPOAP1-AS1, UCA1*	1-, 3-, 5-year AUC in the training set: 0.804, 0.89, and 0.915; 1-, 3-, 5-year AUC in the test set: 0.694, 0.769, and 0.866; Calibration curve: Moderate fit; Independent prognostic factor
Tian *et al*[16]	TCGA, GSE62452	Cox, LASSO	*ANKZF1, CITED2, ENO3, JMJD6, LDHA, NDST1, SIAH2, TES*	1-, 3-, 5-year AUC in the training set: 0.936, 0.836, and 0.840; 1-, 3-, 5-year AUC in the test set: 0.814, 0.784, and 0.714; Calibration curve: Moderate fit; Independent prognostic factor
Zhang *et al*[17]	TCGA, ICGC, GSE57495	Cox	*ANXA2, LDHA, TES*	1-, 3-, 5-year AUC in the training set: 0.683, 0.654, and 0.776; 1-, 3-, 5-year AUC in test set 1: 0.670, 0.628 and 0.761; 1-, 3-, 5-year AUC in test set 2: 0.684, 0.612 and 0.647; Independent prognostic factor
Chen *et al*[18]	TCGA, GSE28735, GSE62452, ICGC	Cox, LASSO	*GDF11, IL18, NR0B1, PLAU, PPP3CA, S100A16, SEMA3C*	1-, 3-, 5-year AUC in the training set: 0.76, 0.80, and 0.82; 1-, 3-, 5-year AUC in test set 1: 0.60, 0.83 and 0.79; 1-, 3-, 5-year AUC in test set 2: 0.75, 0.67 and 0.56; Calibration curve: Moderate fit; Better predictor than other clinical variables; Independent prognostic factor
Ding *et al*[19]	TCGA, GSE78229, GSE57495	Cox	*ENO3, LDHA, PGK1, PGM1*	1-, 3-, 5-year AUC in the training set: 0.701, 0.758, and 0.884; 1-, 3-, 5-year AUC in the test set: 0.602, 0.669, and 0.725; Independent prognostic factor

ANKZF1: Ankyrin repeat and zinc finger peptidyl tRNA hydrolase 1; *ANXA2*: Annexin A2; *ARID5A*: AT-rich interaction domain 5A; *BHLHE40*: Basic helix-loop-helix family member e40; *CAPN2*: Calpain 2; *CCAT2*: Colon cancer associated transcript 2; *CCNA2*: Cyclin A2; *CEP83-DT*: Centrosomal protein 83 divergent transcript; *CITED2*: Glutamic acid/aspartic acid-rich carboxyl-terminal domain 2; *CYTOR*: Cytoskeleton regulator RNA; *DANCR*: Differentiation antagonizing non-protein coding RNA; *ENO1*: Enolase 1; *ENO3*: Enolase 3; *FAM19A2*: Family with sequence similarity 19 member A2;

GAS5: Growth arrest specific 5; *GDF11*: Growth differentiation factor 11; *ICOSLG*: Inducible T cell costimulator ligand; *IGLV7-46*: Immunoglobulin lambda variable 7-46; *IL18*: Interleukin 18; *JMJD6*: Jumonji domain containing 6; *KIF23*: Kinesin family member 23; *KRT13*: Keratin 13; LASSO: Least absolute shrinkage and selection operator; *LDHA*: Lactate dehydrogenase A; *LINC01029/LINC01133/LINC01963/LINC02287/LINC-PINT*: Long intergenic non-protein coding RNA 01029/01133/01963/02287/p53 induced transcript; *LNCSRLR*: Sorafenib resistance associated long non-coding RNA; *LRP3*: Low-density lipoprotein receptor-related protein 3; *LY6D*: Lymphocyte antigen 6 family member D; *MMP3*: Matrix metallopeptidase 3; *NDST1*: N-deacetylase and N-sulfotransferase 1; *NR0B1*: Nuclear receptor subfamily 0 group B member 1; *PCAT2*: Prostate cancer associated transcript 2; *PGK1*: Phosphoglycerate kinase 1; *PGM1*: Phosphoglucomutase 1; *PLAU*: Plasminogen activator urokinase; *POM121C*: Nuclear pore membrane protein 121 transmembrane nucleoporin C; *PPP3CA*: Protein phosphatase 3 catalytic subunit alpha; RSF: Random survival forests; *S100A16*: S100 calcium binding protein A16; *SDC4*: Syndecan 4; *SEC31B*: Secretory protein 31 homolog B; *SEMA3C*: Semaphorin 3C; *SERPINB7*: Serpin family B member 7; *SH3PXD2A-AS1*: SH3 and PX domains 2A antisense RNA 1; *SIAH2*: SIAH E3 ubiquitin protein ligase 2; *SPRN*: shadow of prion protein; *TES*: Testin LIM domain protein; *TGM2*: Transglutaminase 2; *TRIM67*: Tripartite motif containing 67; *TSPOAP1-AS1*: TSPO-associated protein 1 antisense RNA 1; *UCA1*: Urothelial cancer associated 1.

Table 2 The role of hypoxic-related prognostic models in the tumor microenvironment and antitumor therapy and their experimental validation and underlying mechanisms

Ref.	TME changes in a high-risk group	Therapeutic significance	Experimental validation	Mechanism
Yang *et al* [9]	$CD8^+$ T cells, T cells, B cells, plasmacytoid dendritic cells, immature dendritic cells, and cytotoxic cells	Higher sensitivity to cisplatin and paclitaxel in the high-risk group	qPCR: MRNA expression	None
Ren *et al* [10]	$CD8^+$ T cells, $CD4^+$ T cells, and endothelial cells; Macrophages and fibroblasts	Higher sensitivity to paclitaxel, erlotinib, and cisplatin in the high-risk group; No significant difference in TMB, *PD1*, *PD-L1*, *CTLA4* and IPS score	None	None
Huang *et al*[11]	None	*KRAS* mutations are more frequent in the hypoxic subtype	qPCR: MRNA expression	None
Li *et al*[12]	T cell exclusion scores	Lower *PD1* expression in the high-risk subgroup	None	None
Ren *et al* [13]	$CD8^+$ T cells, B cells, macrophage, eosinophil, and monocyte; Immune activation score	Higher sensitivity to paclitaxel and erlotinib in the high-risk group; No significant difference in TMB, MSI, and IPS score	None	None
Zhou *et al* [14]	$CD8^+$ T cells, activated $CD4^+$ memory T cells, naïve B cells, and plasma cells; M0 macrophages; Scores in $CD4^+$ T cell recruiting, Th17 cell recruiting, dendritic cell recruiting, macrophage recruiting, and killing of cancer cells	None	qPCR: MRNA expression; Wound-healing assay: Migration; Transwell assay: Invasion	ChIP assay: *BHLHE40*/*TLR3* axis
Sun *et al* [15]	$CD8^+$ T cells and B cells	None	qPCR: MRNA expression; MTT assay: Proliferation; Transwell assay: Invasion	ChIP assay and luciferase reporter assay: *HIF-1α*/*TSPOAP1-AS1* axis
Tian *et al* [16]	$CD8^+$ T cells and regulatory T cell	Lower *PD1* and *CTLA4* expression in a high-risk group	qPCR: MRNA expression	None
Zhang *et al*[17]	T cells; M0 macrophages	Higher *LDHA* methylation in pancreatic cancer tissues	None	None
Chen *et al* [18]	$CD8^+$ T cells, follicular helper T cells, memory B cells, monocytes, M1 macrophages, M2 macrophages, resting mast cells, and eosinophils; Immune score and stromal score	Higher TMB in the high-risk groups	None	None
Ding *et al* [19]	$CD8^+$ T cells, plasma cells, and naïve B cells; M2 macrophages, resting memory $CD4^+$ T cells, and resting natural killer cells	None	None	None

BHLHE40: Basic helix-loop-helix family member e40; ChIP: Chromatin immunoprecipitation; *CTLA4*: Cytotoxic T-lymphocyte-associated protein 4; *HIF-1α*: Hypoxia-inducible factor 1α; IPS: Immunophenoscore; *KRAS*: Kirsten rat sarcoma viral oncogene homologue; *LDHA*: Lactate dehydrogenase A; MSI: Microsatellite instability; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; *PD1*: Programmed cell death protein 1; *PD-L1*: Programmed death ligand 1; qPCR: Quantitative real-time PCR; TMB: Tumor mutation burden; *TSPOAP1-AS1*: TSPO-associated protein 1 antisense RNA 1; *TLR3*: Toll-like receptor 3.

These studies evaluated the roles of risk models in antitumor drug treatment, particularly immunotherapy (Table 2). Several important immune checkpoints (*e.g.*, programed cell death protein 1, programed death ligand 1, and cytotoxic T-lymphocyte-associated protein 4), immunotherapy-related indicators (*e.g.*, tumor mutation burden and microsatellite instability), and immunological scores (*e.g.*, immunophenoscore and tumor immune dysfunction and exclusion score) were adopted to evaluate the relationship between risk models and immunotherapy response. Unfortunately, no significant findings regarding anticancer immunotherapy efficacy were observed in these studies; however, several chemotherapeutic and targeted drugs, including cisplatin, paclitaxel, and erlotinib, exhibited higher sensitivity in high-risk patients with PC, which to some extent, provide a reference for therapeutic decision-making in future clinical practice.

MAIN CONCERNS

Data inclusion and processing

First, in these hypoxia-related bioinformatic models, the datasets used to construct prognostic signatures were entirely dependent on the TCGA cohort. Because of differences in ethnic and genetic background, data from a single source may fail to meet the universality of the model. Second, batch effects between different datasets should be avoided when building and testing these models, as there may be differences in transcriptomic data formats and sequencing methods. Different sources of raw data without uniform standardization may lead to an unreliable conclusion. Third, clear inclusion and exclusion criteria for patients with PC should be established to ensure the reproducibility of these models. Most deaths during the perioperative period were attributed to severe postoperative complications, such as pancreatic fistula and intraperitoneal infection, rather than PC progression. Therefore, patients who died in the short term after pancreatic surgery should be carefully considered for inclusion in model construction. Otherwise, the predictive performance of prognostic models may remain unchanged, with poor prediction accuracy for 1-year overall survival.

Model construction

The ultimate goal of a study should not be limited to constructing a prognostic model with certain predictive effects. Instead, it should focus on continuously optimizing the model or identifying the model with the best predictive performance in PC. Because existing hypoxia-related prognostic models of PC were mainly constructed by routine Cox and LASSO regression analyses, they may not prove that the prognostic signature based on available data is the optimal model. Various machine learning algorithms have become increasingly popular and should be adopted to develop hypoxia-related models. Moreover, previous studies did not compare the predictive performance of these models.

Experimental validation

Although almost all of these models were validated using external datasets, including GEO and ICGC data, the findings based on bioinformatic analysis may not be completely reliable; thus, they need to be validated with experimental evidence. Unfortunately, relevant experimental validation is not always performed well. Only a few studies have validated the relative mRNA expression levels of potential biomarkers that comprise prognostic models in PC cell lines. There is a lack of additional molecular biological, cytological, immunological, and animal experiments to verify the roles of these biomarkers in PC tumor growth, progression, metabolism, and immune microenvironment. A clinical PC cohort study has not been conducted to determine whether the expression of these biomarkers in tumor tissues affects the prognosis of patients with PC. An animal or hypoxic cell model should be established to clarify whether modulating the expression of these biomarkers can reverse the hypoxic microenvironment and improve PC prognosis. Moreover, the analysis of sensitivity and therapeutic response to anticancer drugs, including chemotherapy, targeted therapy, and immunotherapy, remains in a theoretical stage, as *in vitro* cytotoxicity assays and *in vivo* animal validation have not been reported. Overall, preclinical studies on relevant biomarkers in these prognostic models have substantial progress to make before their incorporation into clinical practice.

Mechanism exploration

In addition to clarifying the roles of these prognostic biomarkers in PC, it is necessary to examine the pathways associated with biomarker function. Although multiple gene enrichment analyses have been used to identify risk model pathways in some studies, limited experimental evidence supports these findings. To date, only a few studies have used chromatin immunoprecipitation assays to evaluate the molecular interactions of selected biomarkers[14,15]. However, the mechanisms underlying the regulation of tumor progression, immune cell infiltration, and sensitivity to antitumor drugs through hypoxic microenvironments remain unclear. Notably, we found that lactate dehydrogenase A, a key enzyme that catalyzes the conversion of lactate to pyruvate and regulates lactylation, was repeatedly used when constructing prognostic signatures. The hypoxic microenvironment of PC is closely associated with abnormal metabolic reprogramming, such as enhanced glycolysis and severe lactate accumulation. Therefore, further investigation is needed to determine whether hypoxia-related genes with high-risk expression levels are involved in shaping the tumor microenvironment of PC by regulating histone lactate modification. There is an urgent need to identify the underlying mechanisms of hypoxia-related models, which is important for developing pharmacological targets against the hypoxic microenvironment in PC.

Clinical application

Although many hypoxia-related PC models have been constructed, no relevant clinical applications have been reported yet. This may be mainly attributed to the facts that the predictive accuracy and robustness of these prognostic signatures remain unsatisfactory and the model with the optimal predictive performance is not known. Meanwhile, unlike routine laboratory or clinical examinations of patients with PC, transcriptome sequencing of hypoxia-related genes in tumor tissues from patients with PC is time-consuming, complex, and expensive. In addition, there is currently a lack of more convincing experimental evidence to consider these predictive models for application in clinical practice. Moreover, for patients with advanced PC who do not undergo pancreatic surgery, we cannot predict survival or antitumor drug sensitivity using these models or perform transcriptomic sequencing because the number of tumor tissues may be insufficient. These factors will limit the further development of such models. Liquid biopsy technology may hold promise to address the aforementioned limitation of insufficient pancreatic tissues in patients who cannot undergo surgical resection therapy. Liquid biopsy, a noninvasive frontier technology, can analyze the molecular changes in tumor cells by detecting tumor fragments (*e.g.*, circulating tumor DNA and exosomes) in liquid samples and provide strong evidence for early diagnosis, screening, and prognosis evaluation[20]. Accumulating evidence has indicated that the hypoxic microenvironment can alter the release and content of tumor-derived exosomes, resulting in the enrichment of substantial exosomes in body fluids, which can be used as potential biomarkers for liquid biopsies[21,22]. In light of this, traditional research methodologies should be set aside in favor of high-quality, innovative studies that can lay the groundwork for future clinical practice using these models.

FUTURE RESEARCH DIRECTIONS AND PERSPECTIVES

Single-cell and spatial transcriptomic analyses

Single-cell and spatial transcriptomic sequencing have become important innovative technologies in biological research in recent years[23]. They are widely used to study gene expression at the single-cell level and the cell distribution and expression patterns at the spatial level. With the advent of single-cell and spatial transcriptomic technologies and the continuous breakthroughs in complex data processing and analysis, the construction of tumor prognostic models using single-cell and spatial transcriptomic analyses has become a hotspot in the field of bioinformatics[24,25]. On the one hand, single-cell and spatial transcriptomic data can be used to screen candidate genes in hypoxia-related models of PC. On the other hand, single-cell and spatial transcriptomic analyses may help us understand the expression characteristics of hypoxia-related genes at the single-cell and spatial levels. These analyses can also shed light on the immune microenvironment, cellular communication networks, and pathways associated with hypoxic conditions. Therefore, we should focus on analyzing the available single-cell and spatial transcriptome data for PC to provide new insights for the construction of prognostic signatures and identify the underlying mechanism associated with the hypoxic tumor microenvironment.

Multiomics data integration

Hypoxia-related prognostic models based on traditional omics are analogous to a blind man being instructed to touch an elephant. Hence, accurately describing the prognostic landscape of the entire PC population is challenging. With breakthroughs in high-throughput sequencing technology, high-resolution mass spectrometry technology, and multiomics integration methods, systematic biomedical research has achieved a remarkable milestone[26]. Multiomics analysis can integrate genomics, epigenomics, transcriptomics, proteomics, metabolomics, pathomics, and radiomics in an unbiased manner to systematically analyze the underlying mechanisms of the hypoxic microenvironment and provide a novel paradigm for the establishment of hypoxia-related prognostic signatures. Multiomics integrated analysis and big-data health platforms will be used to construct predictive models for PC in the future. The combination of hypoxia-related multiomics data, clinical information, and radiological data of patients with PC is expected to achieve more accurate survival prediction and individualized treatment strategies, thereby effectively improving the prognosis and treatment of patients with PC.

Deep learning based on artificial intelligence

Machine learning technology is a popular and cutting-edge technology in the field of artificial intelligence. It has powerful prediction, classification, and clustering capabilities to complete research tasks using various learning algorithms[27]. Deep learning is an emerging branch of machine learning that can simulate the learning process of the human brain by building multilayer neural network models, such as deep neural networks, convolutional neural networks, recurrent neural networks, and long short-term memory networks, to complete various complex tasks and achieve better prediction performance[28]. Recently, a study described the use of > 70 combinatorial machine learning algorithms to identify differentially expressed genes and construct a prognostic signature associated with programmed cell death in lung adenocarcinoma[29]. Similarly, another group integrated multiomics data and machine learning algorithms to identify three prognostic subtypes for invasive urothelial carcinoma and a consensus machine learning-driven signature with significant implications in prognosis and immunotherapy[30]. These signature-building strategies based on machine learning can provide a reference and experience for constructing hypoxia-related deep learning models in PC. With the continuous progress in computer science and technology, deep learning for the construction of prognostic models will develop rapidly. Using multiomics data and clinical information, various deep learning algorithms and their combinations can be applied to establish and continuously optimize hypoxia-related prognostic signatures until they achieve optimal predictive performance.

High-quality experimental programs

A convincing bioinformatic model requires external datasets to verify accuracy and robustness as well as experimental evidence for validation. Nevertheless, the current hypoxia-related models are not supported by biological experiments; thus, their reliability remains to be determined. We recommend the adoption of high-quality biological experiments in follow-up studies to examine the biological effects and mechanisms of hypoxia-related prognostic models in PC. For example, in addition to using quantitative real-time PCR and western blotting (WB) analyses to examine the expression of RNA and protein, fluorescence in situ hybridization, immunohistochemistry (IHC), and immunofluorescence (IF) are also good alternatives when validating the expression characteristics of hypoxia-related genes in PC. In addition, it is essential to establish a hypoxic PC cell model to examine the effect and mechanism of hypoxia-related genes on PC cell function. A co-culture system of PC cells and immune cells, such as $CD8^+$ T cells and macrophages, should also be established under hypoxic conditions in future studies to examine how hypoxia-related genes influence immune cell function, such as cytokine production, cytotoxic activity, immune cell differentiation, and immune cell survival. Moreover, transplanted PC mouse tumor models should be established to study the role of hypoxia-related gene expression in the tumor immune microenvironment through molecular biological and immunological experiments, such as flow cytometry, IHC, IF, WB, and enzyme-linked immunosorbent assay. Common anticancer drugs and immune checkpoint inhibitors may also be administered to these *in vivo* models to determine the effect of hypoxia-related genes on the efficacy of chemotherapy, targeted therapy, and immunotherapy. Furthermore, the clinical cohorts of patients with PC should be established to verify the relationship between hypoxia-related gene expression in tumor tissues and prognosis and pathological progression.

CONCLUSION

Hypoxia-related bioinformatic models in PC are primarily evaluated in the context of prognosis, tumor immune microenvironment, and antitumor drug efficacy; however, these studies have not successfully identified a prognostic model with optimal predictive performance. Moreover, findings based on bioinformatic computational analyses are often not reliable, indicating that more experimental evidence is needed to identify the underlying mechanisms. With the integration of multiomics data, the application of deep learning algorithms, and the implementation of high-quality experimental programs, the limitations of these hypoxia-related prognostic models can be overcome, and they may be applied to clinical practice in the future.

FOOTNOTES

Author contributions: Jiang J and Li DM designed the overall concept and outline of the manuscript; Cao XY contributed to the discussion and design of the manuscript; Li DM and Jiang J contributed to the writing and editing of the manuscript, illustrations, and review of the literature. All authors have read and approved the final manuscript.

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