HIF1α: A Novel Biomarker with Potential Prognostic and Immunotherapy in Pan-cancer

Yonggang Tian, Feihu Bai, and Dekui Zhang

Department of Gastroenterology, Lanzhou University Second Hospital, Lanzhou, Gansu Province, China

The Gastroenterology Clinical Medical Center of Hainan Province, Department of Gastroenterology, The Second Affiliated Hospital of Hainan Medical University, Haikou, China

Correspondence should be addressed to Dekui Zhang; zhangdk8616@126.com

Received 14 April 2022; Revised 15 May 2022; Accepted 2 June 2022; Published 8 July 2022

Cancer is a catastrophic disease that seriously affects human health. HIF1α plays an important role in cancer initiation, progression, and prognosis. However, little is known about the specific role of HIF1α in pan-cancer. Therefore, we systematically and comprehensively analyzed HIF1α using GEPIA, HPA, GeneMANIA, STRING, SMPDB, cBioPortal, UALCAN, and TISDB databases and also 33 cancer and normal tissues in TCGA downloaded from the Genome Data Commons (GDC) data portal. Data and statistical analysis were performed using R software v4.0.3. Our results found that there were differences in the mRNA expression levels of HIF1α in human pan-cancer and its corresponding normal tissues. The expression level of HIF1α correlated with tumor stage in LIHC and also significantly correlated with prognosis in LIHC, LUSC, STAD, OV, PAAD, PRAD, THCA, LUAD, MESO, and READ. The small molecule pathways involved in HIF1α include succinate signaling, fumarate, and succinate carcinogenesis-related pathways. The highest mutation frequency of the HIF1α gene in pan-cancer was head and neck cancer, and the HIF1α methylation level in most tumors is significantly reduced. HIF1α was not only associated with immune cell infiltration but also with immune checkpoint genes and immune regulators TMB and MSI. There were currently 5 small molecule drugs targeting HIF1α.

1. Introduction

As the socioeconomic status and access to health care improve, the disease burden of the population tends to shift epidemiologically: the population appears to have transitioned from contracting primarily communicable diseases to developing primarily noncommunicable diseases [1]. Cancer is a devastating disease among noncommunicable diseases. With an estimated 19.3 million new cancer cases and nearly 10 million cancer deaths worldwide in 2020, the global cancer burden is expected to reach 28.4 million in 2040, a 47% increase from 2020 [2]. Although new technologies and new drugs for the prevention and treatment of cancer are constantly emerging, the prevention and treatment of cancer still cannot meet the needs of the growing number of cancer patients. Therefore, there is still a long way to actively search for specific and sensitive biomarkers for cancer prevention and to develop new drugs.

HIF-1 (hypoxia-inducible factor-1) was first discovered by Semenza and Wang in 1992, and then the structure of HIF-1 was established and the coding sequence of its cDNA was proved [3, 4]. HIF-1 is ubiquitously present in human and mammalian cells and is also expressed under normoxia (21% \( \text{O}_2 \)). The study found that the median oxygen level in most tumors was <2%. Therefore, HIF-1 is often expressed in tumors [5]. Moreover, an increasing number of studies have found that HIF-1 can be involved in metabolic reprogramming [6–8], angiogenesis [7, 9, 10], stem cell [10], and immune regulation [11, 12]. Additionally, HIF-1 activity is associated with increased cancer mortality [13], invasion [14, 15], metastasis...
involvement of HIF1α is an important part of HIF-1 activity, and it consists of four parts: bHLH domain, PAS domain, ODD domain, and transactivation domain. Binding of the ODD domain to pVHL protein under hypoxic level can prevent HIF1α subunit ubiquitination and degradation, thereby increasing the expression level of HIF1α protein, and tumors adapt to the hypoxic environment by expressing high levels of HIF1α protein [23]. To the best of our knowledge, a comprehensive analysis of HIF1α on human pan-cancer clinical prognosis, immune microenvironment, and HIF1α-targeted drugs using bioinformatics remains largely unknown. Herein, we use bioinformatics to comprehensively and systematically study the role of HIF1α in human pan-cancer. Our results suggest that the expression of HIF1α is related to tumor prognosis and immune cell infiltration. In addition, our study also provides information on the involvement of HIF1α in signaling pathways and current drugs targeting HIF1α. In summary, these findings provide insights into the growing interest in HIF1α between the diagnosis and treatment of cancer.

2. Materials and Methods

2.1. GEPIA Database. GEPIA (http://gepia.cancer-pku.cn/) is a web-based tool that provides fast and customizable functionality based on TCGA and GTEx data [24]. In this study, we used the GEPIA database to analyze the expression of HIF1α in tumor tissues and their corresponding normal tissues and displayed them using BodyMap and dot plot, respectively. Subsequently, we also used this database to explore the correlation between HIF1α expression and tumor pathological stage. All of the above use log2(TPM +1) for log scale. In addition, we used the “Survival Plots” module to explore the relationship between HIF1α expression and pan-cancer prognosis.

2.2. HPA Database. HPA (https://www.proteinatlas.org/) database is a large-scale initiative to map the entire human proteome using the integration of antibody-based proteomics and various other omics techniques [25]. In our study, we explored the mRNA expression levels of HIF1α in human cell lines based on the HPA database; the gene expression levels are represented as log2 TPM values.

2.3. GeneMANIA Database. GeneMANIA (http://genemania.org/) analyzes association data including protein and genetic interactions, pathways, coexpression, colocalization, and protein domain similarity [26]. We, in this study, explored the protein-protein interaction network of HIF1α using this database.

2.4. STRING Database. STRING (https://cn.string-db.org/) enables the analysis of sources of protein-protein interaction information [27]. This database was also used in our study to explore the protein-protein interaction network of HIF1α.

2.5. SMPDB. SMPDB (https://smpdb.ca/) is a comprehensive, colorful, fully searchable, and highly interactive database for visualizing human metabolism, drug action, drug metabolism, physiological activity, and metabolic disease pathways [28, 29]. In this study, we used this database to explore the small molecule pathways involved in HIF1α.

2.6. cBioPortal Database. cBioPortal (http://www.cbioportal.org), which provides a web resource for exploring, visualizing, and analyzing multidimensional cancer genomic data [30], was used to explore the HIF1α. 2922 total samples (including 2583 patients) (CGC/TCGA, Nature 2020) were analyzed. mRNA expression z scores (RNA Seq V2 RSEM) were obtained using a z score threshold of ±2.0.

2.7. UALCAN Database. UALCAN (http://ualcan.path.uab.edu/index.html) database enables genomics, bioinformatics, and integrative approaches to understand the molecular basis of cancer [31]. We, in our present work, investigated HIF1α methylation levels in pan-cancer and its corresponding normal tissues based on the UALCAN database. The significance of differences was evaluated using Student’s t-test, and p < 0.05 was considered statistically significant.

2.8. TISIDB Database. TISDB (http://cis.hku.hk/TISIDB/) database is a user-friendly portal that integrates multiple types of data resources in tumor immunology [32]. In our study, the TISDB database was used for the analysis of drugs targeting HIF1α.

2.9. HIF1α Expression Level and Prognosis of Tumor Patients. The data of 33 types of cancer and normal tissues in the TCGA dataset (https://portal.gdc.com) were downloaded from the Genomic Data Commons (GDC) data portal website, using the univariate Cox regression analysis, and the forest was used to show the p value, HR, and 95% CI of each variable through “forest plot” R package. All the analysis methods and R package were implemented by R version 4.0.3. Two-group data was performed by the Wilcoxon test. p < 0.05 were considered statistically significant.

2.10. HIF1α Expression and Immune Cell Infiltration and Immune Modulator Genes. The data of 33 types of cancer and normal tissues in TCGA were downloaded from the Genomic Data Commons (GDC) data portal website. We obtained immune scores using an R package “Immunedeconv” that integrates two state-of-the-art algorithms, including TIMER and xCell. The Spearman correlation analysis heatmaps of HIF1α gene expression and genes associated with immune scores or immune checkpoints in different types of cancers were generated, the vertical axis represents different immune scores, and different colors represent correlation coefficients. R software v4.0.3 was used for statistical analysis. p < 0.05 were considered statistically significant.

2.11. Pan-cancer Analysis of the Correlation between HIF1α Expression and Immune Regulators TMB and MSI. We obtained TMB and MSI scores from the dataset downloaded from TCGA using R software v4.0.3 for statistical analysis and Spearman correlation analysis of TMB, MSI, and HIF1α.
3.1. The mRNA Expression Landscape of HIF1α in Human Pan-cancer

To explore the mRNA expression landscape of HIF1α in human pan-cancer, we comprehensively analyzed the mRNA expression levels of HIF1α in interactive body maps using the GEPIA dataset. We know that, from the overall level of the interactive body map, the median expression levels of HIF1α in most human tumor tissues and their corresponding normal tissues are different, in particular in the brain, blood, lungs, digestive organs (esophagus, pancreas, stomach, and gallbladder), kidneys, thyroid, and other tissues and organs (Figure 1(a)). Based on the previous findings, we, next, studied the mRNA expression levels of HIF1α in 33 tumors and their corresponding normal tissues and organs using the GEPIA database. Unexpectedly, the median level of mRNA expression of HIF1α was high in only 7 tumor tissues (ESCA, GBM, HNSC, LAML, LGG, PAAD, and STAD) compared to normal tissues (Figure 1(b)). Finally, we further
Figure 2: Continued.
analyzed the mRNA expression level of HIF1α from the cellular level using the HPA database. As a result, we found higher levels of HIF1α mRNA expression in these tissue organ cell lines, including the brain, liver and gallbladder, gastrointestinal pancreas, male reproductive system, kidneys and bladder, skin, eyes, proximal gastrointestinal, lungs, female reproductive system, endothelial, muscle, and mesenchymal lymphoid myeloid (Figure 1(c)). Regardless of whether tumor tissue is compared with its corresponding normal tissue, or at the level of organ cell lines, the mRNA expression levels of HIF1α are higher in organs like the brain, digestive organs (esophagus, pancreas, stomach, and gallbladder), and lungs.

3.2. Correlations between the HIF1α Expression and Tumor Pathological Stage. As one of the important indicators of patient prognosis, the pathological stage of the tumor should be looked at closely. Hence, we used the GEPIA dataset to analyze the correlation between HIF1α expression level and tumor pathological stage, including 17 tumors, while other tumors could not be shown in the GEPIA database. As a complete surprise, our results showed that HIF1α expression was only significantly correlated with tumor stage in LIHC ($p = 0.0356$), and there was no correlation between the expression level of HIF1α and the pathological stage of other tumors ($p > 0.05$) (Figure 2). Collectively, these results demonstrate that the expression level of HIF1α is associated with the pathological staging of LIHC, which has a certain guiding significance for guiding the pathological staging of this tumor.

3.3. The Relationship between HIF1α Expression Level and Prognosis of Tumor Patients. Based on the findings of HIF1α expression level and tumor pathological stage, we further evaluated the relationship between HIF1α expression level and survival prognosis of pan-cancer patients by the Cox regression analysis. Of note, the prognostic indicators in this study mainly include OS and DFS. The Cox regression analysis of the results from 33 types of cancer suggests that the expression level of HIF1α was significantly associated with OS in LIHC, LUSC, MESO, and STAD patients ($p < 0.05$) (Figure 3(a)). In addition, we also found that the expression level of HIF1α was significantly associated with DFS in 4 tumors, including OV, PAAD, PRAD, and THCA ($p < 0.05$) (Figure 3(b)). Next, we used the Kaplan-Meier survival curves to find that high expression of HIF1α in LUAD and MESO has worse OS (Figures 3(c) and 3(d)), while high expression of HIF1α in BRCA has better DFS (Figure 3(e)), and there was no statistical difference between the high and low expression of HIF1α in other tumors and OS and DFS ($p > 0.05$, Supplementary Figure 1 and Supplementary Figure 2).

3.4. Protein-Protein Interaction Network and Small Molecule Pathway of HIF1α. To explore the protein-protein interaction network of HIF1α, our analysis using GeneMANIA databases found that there are 20 genes associated with HIF1α (Figure 4(a)). Furthermore, we explored using the STRING database and found that the number of nodes associated with HIF1α is 11 (Figure 4(b)). We used SMPDB analysis to find that HIF1α in human small molecule pathway includes one protein pathway, succinate signaling (Figure 4(c)), and two disease pathways, the oncogenic action of fumarate and the oncogenic action of succinate (Figures 4(d) and 4(e)).

3.5. Analysis of HIF1α Gene Mutation and Methylation Level in Pan-cancer. To assess the mutation of HIF1α in pan-cancer, we conducted an in-depth study using the cBioPortal database and found that HIF1α was altered in 5% (132/2583) of pan-cancer patients (Figure 5(a)). In addition, we also analyzed the mutation frequency of the HIF1α gene in different types of tumors, and the results showed that the mutation frequency of head and neck cancer (12.5%), lung cancer (10.53%), and pancreatic cancer (10.06%) ranked the top three, respectively. Notably, amplification is the most common type of HIF1α gene mutation (Figure 5(b)). To better understand the mutational map of HIF1α in different cancer types across protein domains, our investigation found that a total of 16 mutation sites were detected, located between 0 and 826 (Figure 5(c)).

Aberrant DNA methylation is an important cause of cancer [33]. Hence, we next used the UALCAN database to explore the level of HIF1α methylation in pan-cancer and its corresponding tissues. Our results indicate that, compared with normal tissues, HIF1α methylation levels were significantly decreased in BLCA, BRCA, CHOL, CESC, COAD, ESCA, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, PAAD, READ, SARC, TGCA, and UCEC tissues (Figure 5(d)).
3.6. Pan-cancer Analysis of HIF1α Expression and Immune Cell Infiltration. Since there is a certain relationship between HIF1α and immune response, we performed a pan-cancer analysis of the relationship between HIF1α expression and immune infiltration levels based on the TIMER database. The data presented here imply that 20 cancers were associated with T cell CD8+, 22 cancers were associated with neutrophils, 20 cancers were associated with Myeloid dendritic cells, 22 cancers were associated with macrophage, and 16 cancers were associated with B cells (Figure 6(a)).

To further identify the relationship between HIF1α expression and infiltration of different types of immune cell subtypes, we used the xCell online tool to provide evidence that, among 38 immune cell subtypes, HIF1α expression was significantly negatively correlated with these subtypes of ACC, CES, HNSC, KIRP, LUSC, TGCT, THYM, and UCEC, whereas HIF1α expression was significantly positively correlated with these subtypes of COAD, KICH, LAML, and LGG. Most remarkable, the expression of T cell CD4+ central memory, T cell CD4+ Th1, and HIF1α has the strongest negative correlation in various cancers (Figure 6(b)).

Figure 3: Association between HIF1α expression and prognosis in cancer patients. (a) and (b) A forest plot of hazard ratios of HIF1α in 33 types of tumors. (c and d) Kaplan-Meier survival curves of OS for patients stratified by the different expressions of HIF1α in LUAD and MESO. (e) Kaplan-Meier survival curves of DFS for patients stratified by the different expressions of HIF1α in BRCA.
Figure 4: Continued.
Figure 4: Protein-protein interaction network and functional enrichment of HIF1A. (a and b) Based on the GeneMANIA and STRING database to explore the protein-protein interaction network of HIF1A, respectively. (c–e) The use of SMPDB to analyze the small molecule pathway of HIF1A in humans.
Queried gene is altered in 5% (132/2583) of queried patients.

**HIF1A Genetic alteration**
- Missense mutation (unknown significance)
- Amplification
- Deep deletion
- mRNA high
- mRNA low
- No alterations

**Mutation data**
- Head and neck cancer
- Lung cancer
- Pancreatic cancer
- Colorectal cancer
- Endometrial cancer
- Breast cancer
- Bone cancer
- Melanoma
- Ovarian cancer
- Hepatobiliary cancer
- Bladder cancer
- Prostate cancer
- Thyroid cancer
- Medulloblastoma
- Embryonal tumor
- Cervical cancer
- Acute myeloid leukemia
- Mature B-cell neoplasms
- Essential thrombocythemia
- Soft tissue sarcoma
- Glioma
- Non-small cell lung cancer
- Uterine endometrioid carcinoma

**CNA data**
- T290A
- PAS
- PAS_11
- HIF
- HIF

**Figure 5: Continued.**
Together with the evidence presented here, this suggests that there is a certain correlation between HIF1α expression and the infiltration of various immune cells in the pan-cancer microenvironment.

3.7. Pan-cancer Analysis of the Correlation between HIF1α Expression and Immune Checkpoint Genes and Immune Regulators TMB and MSI. To estimate the association between HIF1α expression and TME in the pan-cancer dataset, we further investigated the relationship between HIF1α expression and two major types of immune regulators. The vast majority of tumors include BLCA, BRCA, COAD, DLBC, ESCA, LAML, LIHC, LUAD, MESO, PAAD, PCPG, PRAD, READ, SARC, SKCM, STAD, THCA, THYM, UCEC, UCS, and UVM, and immune checkpoint genes are positively correlated. Only a few tumors including TGCT and HNSC were negatively correlated with immune checkpoint genes (Figure 7(a)).

TMB and MSI are two emerging biomarkers that are promising predictive biomarkers for immunotherapy in cancer treatment [34]. We first investigated the relationship between HIF1α expression and TMB. Our results suggest that the expression levels of HIF1α significantly correlated with TMB in COAD, BRCA, and LIHC (Figure 7(b)). In addition, in this report, we provide evidence that the expression level of HIF1α is significantly associated with MSI in some tumors, including COAD and DLBC (Figure 7(c)).

3.8. Drugs Targeting HIF1α. The development of drugs targeting HIF1α is critical for the treatment of cancer patients. Therefore, we used the TISDB database to analyze the current drugs targeting HIF1α. In the present study, we observed that there are 5 small molecule drugs targeting HIF1α, including carvedilol, 2-methoxyestradiol, ENMD-1198, PX-478, and FG-2216 (Figure 8(a)). Among them, carvedilol is the drug with the most targets, with a total of 17 targets. It downregulates HIF1α in the myocardium of volume-overloaded heart failure [35]. Remarkably, compared with carvedilol, the other 4 small molecule drugs involve relatively few targets. Of course, Table 1 presents more details on drugs targeting HIF1α.

4. Discussion

HIF is a central regulator for detecting and adapting to cellular oxygen levels, and it regulates oxygen homeostasis and metabolically activated genes through transcriptional activation. In addition to this, HIF affects many other
processes including cancer development [9]. Current research suggests that HIF1α, as one of the most important members of the HIF family, is closely related to the occurrence, development, and prognosis of cancers [38–42]. Thus, we explored the role of HIF1α in human tumors by using bioinformatics methods. We first comprehensively analyze the expression of interacting BodyMap HIF1α in human tumors and their corresponding normal tissues. Second, we provide evidence that HIF1α expression levels are associated with the pathological staging of LIHC and that HIF1α expression levels are associated with prognosis in 11 tumors including LIHC, LUSC, MESO, STAD, OV, PAAD, PRAD, THCA, LUAD, MESO, and READ. In addition, we also found that HIF1α in human small molecule pathways includes 3 pathways (succinate signaling pathway, fumarate carcinogenesis, and succinate carcinogenesis), and HIF1α methylation levels are significantly reduced in most tumors. In addition to the above findings, we further discovered the relationship between HIF1α and immune cell infiltration in the cancer microenvironment and small molecule drugs targeting HIF1α.

In this study, our data suggest that the mRNA expression level of HIF1α was higher in organs such as the brain, as an advanced nerve center, needs a lot of oxygen and energy to maintain its
normal function, the brain is most sensitive to hypoxia [43]. The stomach is an important digestive tract organ, and it is prone to stress-induced gastric ulcer during stress response [44], which is due to the sensitivity of gastric mucosa to ischemia and hypoxia. In addition to the aforementioned sensitivity to hypoxia, tumors grow faster and require more nutrients. Thus, cells like pancreatic cancer [45], liver cancer [46], and lung cancer [47] can activate the transcription of many genes, including those involved in energy metabolism, angiogenesis, and other protein products, by producing many genes, including those involved in energy metabolism, angiogenesis, and other protein products, by producing HIF1 α-related genes all play a role in cancer. For example, a study has found that HIF1α promotes EPO expression at the transcriptional level under hypoxia [59] and achieves antitumor effects by regulating Epo-activated signaling pathways as interfering with the cell cycle of brain tumors [60]. In addition, the HIF1α-related gene ENO1 can bind and degrade the expression of the hepcidin gene, thereby regulating the metabolic homeostasis of intracellular iron ions, affecting ferroptosis, and promoting the occurrence and development of liver cancer [61]. In conclusion, our discovery of HIF1α-related genes provides more new insights for diagnosis and treatment in pan-cancer. In addition, we also used SMPDB analysis to find that HIF1α in human small molecule pathways includes a protein pathway, the succinate signaling pathway, and two disease pathways, fumarate carcinogenesis and succinate carcinogenesis. Previous studies found that hydroxylase activity was inhibited in the presence of low concentrations of O2, high concentrations of

Figure 7: Pan-cancer analysis of the correlation between HIF1A expression and immune checkpoint genes and immune regulators TMB and MSI. (a) Pan-cancer analysis of the correlation between HIF1A expression and immune checkpoint genes. (b) Pan-cancer analysis of the correlation between HIF1A expression and immunomodulators TMB and MSI. *p < 0.05, **p < 0.01, and ***p < 0.001.
tricarboxylic acid cycle intermediates (isocitrate, oxaloacetate, succinate, or fumarate), or chelating agents for Fe (II).

The receptor for activated C-kinase 1 competes with heat shock protein 90 for binding to HIF-1α and mediates O2-dependent ubiquitination and proteasomal degradation [62].

Genetic errors in cancer cells reveal that fundamental biological processes required for cancer to develop and develop go awry. It became clear that cancer genomes contain many additional “passenger” mutations in the process. Driver and passenger DNA mutation patterns derived from cancer genomes provide clues to the different ways cancers manifest as genetically mutated diseases [63]. Interestingly, our data suggest that HIF1α has a mutation rate of 5% in pan-cancer. Therefore, in tumor diagnosis and treatment, some studies have developed HIF1α pharmacogenomic mutation models to study individual changes in the effects of tumor hypoxia drugs [64], which will guide precise treatment. Indeed, DNA methylation analysis is an emerging tool as an aid to improve the accuracy of pathological diagnosis; DNA methylation patterns in circulating tumor DNA hold great promise for minimally invasive cancer detection and classification [65]. We provide preliminary evidence that,
According to the UALCAN database, HIF1α DNA methylation levels are reduced in 17 tumors. A study has confirmed that DNA hypomethylation activates gene transcription and increases tumor proliferation, migration, and metastasis [66]. Therefore, DNA hypomethylation predicts that these tumors tend to have a poor prognosis. In addition, a previous study demonstrated the involvement of HIF1α in the carcinogenesis of fumarate and succinate [67].

Enhancing immune cell function in tumors remains a major challenge in cancer immunotherapy. Hypoxia is a common feature of solid tumors, and cells adapt by upregulating the transcription factor HIF1α [40]. Our results indicate that most cancers are not only related to T cell CD8+, T cell CD4+, neutrophils, myeloid dendritic cells, macrophages, and B cells. And there is a certain relationship with the subtype of immune cells. For instance, our results suggest that, among 38 immune cell subtypes, HIF1α expression was significantly negatively correlated with these subtypes of ACC, CESC, HNSC, KIRP, LUSC, TGCT, THYM, and UCEC, whereas HIF1α expression was significantly correlated with these subtypes of COAD, KICH, LAML, and LGG. There was a significant positive correlation between subtypes. Among them, the expressions of T cell CD4+ central memory, T cell CD4+ Th1, and HIF1α have the strongest negative correlation in various cancers. Of course, a set of previous studies have also demonstrated that HIF1α expression is associated with infiltrating T cells and macrophages [68], Treg [69], and B cells [70].

Given the above findings, we next analyzed the relationship between HIF1α and immunomodulators and found that most tumors were positively associated with immune-checking genes. Only a few tumors, such as TGCT and HNSC, were inversely associated with immune check genes. In addition, we also explored the relationship between HIF1α and TMB and MSI and found that the expression level of HIF1α was significantly correlated with TMB in COAD, BRCA, and LIHC, and the expression level of HIF1α was correlated with MSI in COAD and DLBC. Of course, in addition to our study, a previous study confirmed that HIF1α expresses a new marker that separates the MSI-L group from the MSS and MSI-H groups [71]. In short, regardless of our findings, or those of previous studies, HIF1α is implicated in immune checkpoint genes, TMB, and MSI.

Finally, our study also investigated 5 small molecule drugs targeting HIF1α. Of these, carvedilol, a drug commonly used to treat high blood pressure, has recently been shown to protect the body from sunlight-induced cell damage and skin cancer [72]. Although the cancer preventive activity of carvedilol is independent of β-blockers, we envision whether the anticancer activity of carvedilol is related to HIF1α, which is a major topic for further research in the future.

In conclusion, in this study, our findings highly demonstrate the expression landscape of HIF1α in human pan-cancer and identify the relationship between HIF1α expression levels and tumor immune infiltration and HIF1α-targeting drugs. This may provide a new insight into the use of HIF1α to diagnose and treat human pan-cancer.

5. Conclusion

HIF1α plays an important role in pan-cancer prognosis and immunotherapy, and it may be a novel biomarker with potential prognostic and immunotherapy roles in pan-cancer.

Abbreviations

HIF1α: Hypoxia-inducible factor-1α
ACC: Adrenocortical carcinoma
BLCA: Bladder urothelial carcinoma
BRCA: Breast invasive carcinoma
CESC: Cervical squamous cell carcinoma
CHOL: Cholangiocarcinoma
COAD: Colon adenocarcinoma
DLBC: Lymphoid neoplasm diffuse large B cell lymphoma
ESCA: Esophageal carcinoma
GBM: Glioblastoma
LGG: Brain lower grade glioma
HNSC: Head and neck squamous cell carcinoma
KICH: Kidney chromophobe
KIRC: Kidney renal clear cell carcinoma
KIRP: Kidney renal papillary cell carcinoma
LAML: Acute myeloid leukemia
LIHC: Liver hepatocellular carcinoma
LUAD: Lung adenocarcinoma
LUSC: Lung squamous cell carcinoma
MESO: Mesothelioma
OV: Ovarian serous cystadenocarcinoma
PAAD: Pancreatic adenocarcinoma
PCPG: Pheochromocytoma and paraganglioma
PRAD: Prostate adenocarcinoma
READ: Rectum adenocarcinoma
SARC: Sarcoma
SKCM: Skin cutaneous melanoma
STAD: Stomach adenocarcinoma
TGCT: Testicular germ cell tumors
THCA: Thyroid carcinoma
THYM: Thymoma
UCEC: Uterine corpus endometrial carcinoma
UCS: Uterine carcinosarcoma
UVM: Uveal melanoma
2ME2: 2-Methoxyestradiol
EPO: Erythropoietin
ENO1: α-Enolase 1.

Data Availability

The datasets analyzed for this study such as patient prognosis, genetic mutations, and pathway enrichment can be found in the GEPIA, TIMER, HPA, GeneMANIA, STRING, SMPDB, cBioPortal, UALCAN, TISDB, and TCGA web resources, and requests to further access to datasets can be directed to zhangdk8616@126.com

Conflicts of Interest

The authors declare that they have no conflicts of interest.
Authors’ Contributions

Yonggang Tian, Feihu Bai, and Dekui Zhang conducted data analysis and designed and assisted in writing the manuscript. Dekui Zhang reviewed the manuscript. The final manuscript was read and approved by all authors.

Acknowledgments

This work was supported by the Natural Science Foundation of China (No. 81770525), Gansu Province Colleges and Universities Industry Support and Guidance Project (No. 2019C-21), Cuiyi Science and Technology Program of the Second Hospital of Lanzhou University-Key Cultivation Project (No. CY2018-ZD01), and Hainan Province Clinical Medical Center (No. 2021818).

Supplementary Materials

Supplementary 1. Figure 1: association between HIF1α expression and OS in cancer patients.

Supplementary 2. Figure 2: association between HIF1α expression and DFS in cancer patients.

References

[1] J. Kocarnik, “Cancer’s global epidemiological transition and growth,” Lancet, vol. 395, no. 10226, pp. 757-758, 2020.
[2] H. Sung, J. Ferlay, R. L. Siegel et al., “Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries,” CA: a Cancer Journal for Clinicians, vol. 71, no. 3, pp. 209–249, 2021.
[3] G. L. Semenza, “Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology,” Annual Review of Pathology, vol. 9, no. 1, pp. 47–71, 2014.
[4] G. L. Semenza, “Hypoxia-inducible factor 1: oxygen homeostasis and disease pathophysiology,” Trends in Molecular Medicine, vol. 7, no. 8, pp. 345–350, 2001.
[5] S. R. McKeown, “Defining normoxia, physoxia, and hypoxia in tumours–implications for treatment response,” The British Journal of Radiology, vol. 87, no. 1035, p. 20130676, 2014.
[6] J. Mathieu, W. Zhou, Y. Xing et al., “Hypoxia-inducible factors have distinct and stage-specific roles during reprogramming of human cells to pluripotency,” Cell Stem Cell, vol. 14, no. 5, pp. 592–605, 2014.
[7] P. Lee, N. S. Chandel, and M. C. Simon, “Cellular adaptation to hypoxia through hypoxia inducible factors and beyond,” Nature Reviews. Molecular Cell Biology, vol. 21, no. 5, pp. 268–283, 2020.
[8] F. J. Gonzalez, C. Xie, and C. Jiang, “The role of hypoxia-inducible factors in metabolic diseases,” Nature Reviews. Endocrinology, vol. 15, no. 1, pp. 21–32, 2018.
[9] H. Choudhry and A. L. Harris, “Advances in hypoxia-inducible factor biology,” Cell Metabolism, vol. 27, no. 2, pp. 281–298, 2018.
[10] B. Keith and M. C. Simon, “Hypoxia-inducible factors, stem cells, and cancer,” Cell, vol. 129, no. 3, pp. 465–472, 2007.
[11] L. Schito and G. L. Semenza, “Hypoxia-inducible factors: master regulators of cancer progression,” Trends Cancer, vol. 2, no. 12, pp. 758–770, 2016.
[12] N. Burrows, R. J. M. Bashford-Rogers, V. J. Bhute et al., “Dynamic regulation of hypoxia-inducible factor-1α activity is essential for normal B cell development,” Nature Immunology, vol. 21, no. 11, pp. 1408–1420, 2020.
[13] W. Cheng, Z. Cheng, Z. Yang, D. Xing, and M. Zhang, “Upregulation of hypoxia-inducible factor 1α mRNA expression was associated with poor prognosis in patients with hepatocellular carcinoma,” Oncotargets and Therapy, vol. Volume 12, pp. 6285–6296, 2019.
[14] D. L. P. Brooks, L. P. Schwab, R. Kruttilina et al., “ITGA 6 is directly regulated by hypoxia-inducible factors and enriches for cancer stem cell activity and invasion in metastatic breast cancer models,” Molecular Cancer, vol. 15, no. 1, p. 26, 2016.
[15] L. Xiang, J. Mou, B. Shao et al., “Glutaminase 1 expression in colorectal cancer cells is induced by hypoxia and required for tumor growth, invasion, and metastatic colonization,” Cell Death & Disease, vol. 10, no. 2, p. 40, 2019.
[16] M. H. Yang, M. Z. Wu, S. H. Chiu et al., “Direct regulation of TWIST by HIF-1α promotes metastasis,” Nature Cell Biology, vol. 10, no. 3, pp. 295–305, 2008.
[17] L. You, W. Wu, X. Wang et al., “The role of hypoxia-inducible factor 1 in tumor immune evasion,” Medicinal Research Reviews, vol. 41, no. 3, pp. 1622–1643, 2021.
[18] Q. Zhang, Y. Lou, J. Zhang et al., “Hypoxia-inducible factor-2α promotes tumor progression and has crosstalk with Wnt/B-catenin signaling in pancreatic cancer,” Molecular Cancer, vol. 16, no. 1, pp. 1–14, 2017.
[19] V. E. Theodoropoulos, A. C. Lazaris, F. Sofras et al., “Hypoxia-inducible factor 1 alpha expression correlates with angiogenesis and unfavorable prognosis in bladder cancer,” European Urology, vol. 46, no. 2, pp. 200–208, 2004.
[20] C. Wigerup, S. Påhlman, and D. Bexell, “Therapeutic targeting of hypoxia and hypoxia-inducible factors in cancer,” Pharmacology & Therapeutics, vol. 164, pp. 152–169, 2016.
[21] Z. Ma, L. Z. Wang, J. T. Cheng et al., “Targeting hypoxia-inducible factor-1 mediated metastasis for cancer therapy,” Antioxidants & Redox Signaling, vol. 34, no. 18, pp. 1484–1497, 2021.
[22] G. U. Dachs, A. V. Patterson, J. D. Firth et al., “Targeting gene expression to hypoxic tumor cells,” Nature Medicine, vol. 3, no. 5, pp. 515–520, 1997.
[23] L. Iommarini, A. M. Porcelli, G. Gasparre, and I. Kurelac, “Non-canonical mechanisms regulating hypoxia-inducible factor 1 alpha in cancer,” Frontiers in Oncology, vol. 7, p. 286, 2017.
[24] Z. Tang, C. Li, B. Kang, G. Gao, C. Li, and Z. Zhang, “Gepia: a web server for cancer and normal gene expression profiling and interactive analyses,” Nucleic Acids Research, vol. 45, no. W1, pp. W98–w102, 2017.
[25] A. Digre and C. Lindskog, “The Human Protein Atlas-spatial localization of the human proteome in health and disease,” Protein Science, vol. 30, no. 1, pp. 218–233, 2021.
[26] M. Franz, H. Rodriguez, C. Lopes et al., “Genemania update 2018,” Nucleic Acids Research, vol. 46, no. W1, pp. W60–w64, 2018.
[27] D. Szklarczyk, A. L. Gable, D. Lyon et al., “String V11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets,” Nucleic Acids Research, vol. 47, no. D1, pp. D607–d613, 2019.
[28] A. Frolkis, C. Knox, E. Lim et al., “SMPDB: the small molecule pathway database,” Nucleic Acids Research, vol. 38, suppl_1, pp. D480–D487, 2010.
T. Jewison, B. A. Aksoy, U. Dogrusoz et al., “Integrative analysis of complex cancer genomics and clinical profiles using the CBioPortal,” Science Signaling, vol. 6, no. 269, p. p11, 2013.

E. Cerami, J. Gao, U. Dogrusoz et al., “The cbio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data,” Cancer Discovery, vol. 2, no. 5, pp. 401–404, 2012.

B. Ru, C. N. Wong, Y. Tong et al., “DNA methylation and gene silencing in cancer,” Nature Clinical Practice. Oncology, vol. 2, Suppl 1, pp. S4–11, 2005.

C. Luchini, F. Bibeau, M. J. L. Ligtenberg et al., “HIF-1α regulated pathways in hepatocellular carcinoma (review),” Oncology Reports, vol. 35, no. 2, pp. 2402–2402, 2019.

S. B. Baylin, “DNA methylation and gene silencing in cancer,” Cell Stress & Chaperones, vol. 25, no. 2, pp. 265–275, 2020.

P. Huang, W. Tang, R. Shen et al., “Analysis of candidate biomarkers and related transcription factors involved in the development and restoration of stress-induced gastric ulcer by transcriptomics,” Cell Stress & Chaperones, vol. 25, no. 2, pp. 265–275, 2020.

Y. Guo, Z. Xiao, L. Yang et al., “Hypoxia-inducible factors in hepatocellular carcinoma (review),” Oncology Reports, vol. 43, no. 1, pp. 3–15, 2020.

A. A. Tirpe, D. Gulei, S. M. Ciortea, C. Crivii, and I. Berindan-Neagoe, “Hypoxia: overview on hypoxia-mediated mechanisms with a focus on the role of HIF genes,” International Journal of Molecular Sciences, vol. 20, no. 24, p. 6140, 2019.

Y. Baba, K. Nosho, K. Shima et al., “HIF-1α overexpression is associated with poor prognosis in a cohort of 731 colorectal cancers,” The American Journal of Pathology, vol. 176, no. 5, pp. 2292–2301, 2010.

F. Simon, M. Bockhorn, C. Praha et al., “Deregulation of HIF1-alpha and hypoxia-regulated pathways in hepatocellular carcinoma and corresponding non-malignant liver tissue–influence of a modulated host stroma on the prognosis of HCC,” Langenbeck’s Archives of Surgery, vol. 395, no. 4, pp. 395–405, 2010.

Y. Zhang, J. Wang, and Z. Li, “Association of HIF-1A gene polymorphisms with advanced non-small cell lung cancer prognosis in patients receiving radiation therapy,” Aging (Albany NY), vol. 13, no. 5, pp. 6849–6865, 2021.

G. Pasello, L. Urso, M. Mencoboni et al., “MDM2 and HIF1alpha expression levels in different histologic subtypes of malignant pleural mesothelioma: correlation with pathological and clinical data,” Oncotarget, vol. 6, no. 39, pp. 42053–42066, 2015.

R. Xiao, S. Wang, J. Guo et al., “Ferroptosis-related gene NOX4, CHAC1 and HIF1A are valid biomarkers for stomach adenocarcinoma,” Journal of Cellular and Molecular Medicine, vol. 26, no. 4, pp. 1183–1193, 2022.

W. Shen, H. L. Li, L. Liu, and J. X. Cheng, “Expression levels of PTEN, HIF-1α, and VEGF as prognostic factors in ovarian cancer,” European Review for Medical and Pharmacological Sciences, vol. 21, no. 11, pp. 2596–2603, 2017.

M. Jiang, Y. Cheng, D. Wang et al., “Transcriptional network modulated by the prognostic signature transcription factors and their long noncoding RNA partners in primary prostate cancer,” EBioMedicine, vol. 63, p. 103150, 2021.

M. H. Kim, T. H. Lee, J. S. Lee, D. J. Lim, and P. C. W. Lee, “HIF-1α inhibitors could successfully inhibit the progression of differentiated thyroid cancer in vitro,” Pharmaceuticals (Basel), vol. 13, no. 9, p. 208, 2020.

I. Akagi, H. Okayama, A. J. Schetter et al., “Combination of protein coding and noncoding gene expression as a robust prognostic classifier in stage I lung adenocarcinoma,” Cancer Research, vol. 73, no. 13, pp. 3821–3832, 2013.

J. L. O’Donnell, M. R. Joyce, A. M. Shannon, J. Harney, J. Geraghty, and D. Bouchier-Hayes, “Oncological implications of hypoxia inducible factor-1α (HIF-1α) expression,” Cancer Treatment Reviews, vol. 32, no. 6, pp. 407–416, 2006.
K. Hirota, “HIF-A prolyl hydroxylase inhibitors and their implications for biomedicine: a comprehensive review,” *Biomedicines*, vol. 9, no. 5, p. 468, 2021.

M. Buemi, C. Caccamo, L. Nostro, E. Cavallaro, F. Floccari, and G. Grasso, “Brain and cancer: the protective role of erythropoietin,” *Medicinal Research Reviews*, vol. 25, no. 2, pp. 245–259, 2005.

T. Zhang, L. Sun, Y. Hao et al., “ENO1 suppresses cancer cell ferroptosis by degrading the mRNA of iron regulatory protein 1,” *Nature Cancer*, vol. 3, no. 1, pp. 75–89, 2022.

Q. Ke and M. Costa, “Hypoxia-inducible factor-1 (HIF-1),” *Molecular Pharmacology*, vol. 70, no. 5, pp. 1469–1480, 2006.

S. J. Chanock, “The paradox of mutations and cancer,” *Science*, vol. 362, no. 6417, pp. 893-894, 2018.

V. Balasubramaniam and P. K. K. Namboori, “Development of HIF1a pharmacogenomic mutation models to study individual variations in drug action for tumor hypoxia: an in silico approach,” *Journal of Pharmacy & Bioallied Sciences*, vol. 13, no. 4, pp. 387–393, 2021.

A. Papanicolaou-Sengos and K. Aldape, “DNA methylation profiling: an emerging paradigm for cancer diagnosis,” *Annual Review of Pathology*, vol. 17, no. 1, pp. 295–321, 2022.

M. Kulis and M. Esteller, “DNA methylation and cancer,” *Advances in Genetics*, vol. 70, pp. 27–56, 2010.

J. F. Wentzel, A. Lewies, A. J. Bronkhorst, E. van Dyk, L. H. du Plessis, and P. J. Pretorius, “Exposure to high levels of fumarate and succinate leads to apoptotic cytotoxicity and altered global DNA methylation profiles in vitro,” *Biochimie*, vol. 135, pp. 28–34, 2017.

N. J. Brouwer, A. P. Wierenga, G. Gezgin et al., “Ischemia is related to tumour genetics in uveal melanoma,” *Cancers (Basel)*, vol. 11, no. 7, p. 1004, 2019.

L. B. Jarvis, D. B. Rainbow, V. Coppard et al., “Therapeutically expanded human regulatory T-cells are super-suppressive due to HIF1a induced expression of CD73,” *Communications Biology*, vol. 4, no. 1, pp. 1–4, 2021.

K. E. Lee, M. Spata, L. J. Bayne et al., “HIF1a deletion reveals pro-neoplastic function of B cells in pancreatic neoplasia,” *Cancer Discovery*, vol. 6, no. 3, pp. 256–269, 2016.

Z. Arabsorkhi, H. Sadeghi, E. Gharib, L. Rejali, H. Asadzadeh-Aghdaei, and E. Nazemalhosseini-Mojarad, “Can hypoxia-inducible factor-1a overexpression discriminate human colorectal cancers with different microsatellite instability,” *Genes & Genetic Systems*, vol. 96, no. 4, pp. 193–198, 2021.

S. Liang, M. A. Shamim, A. Shahid et al., “Prevention of skin carcinogenesis by the non-β-blocking R-carvedilol enantio- mer,” *Cancer Prevention Research (Philadelphia, Pa.)*, vol. 14, no. 5, pp. 527–540, 2021.