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GPX2 is a potential therapeutic target to induce cell apoptosis in lenvatinib against hepatocellular carcinoma

Abstract

Introduction: Lenvatinib has recently become available as the first-line therapy for unresectable hepatocellular carcinoma (HCC), but its molecular mechanism in HCC remains largely unknown.

Objectives: The current study aims to clarify the molecular mechanisms involved in lenvatinib in HCC.

Methods: Gene expression microarrays, flow cytometry, western blot, qRT-PCR, immunohistochemistry and immunofluorescence were used to study the response of HCC cells to lenvatinib. Xenograft tumor of Huh7 cells was also established to detect the anti-tumor effect of lenvatinib *in vivo*.

Results: Herein, we found that lenvatinib could induce apoptosis via increasing reactive oxygen species (ROS) levels in HCC cells. Then, microarray analysis and qRT-PCR results confirmed that GPX2 was a vital target for lenvatinib against HCC. Loss and gain function of experiment showed that regulating GPX2 levels markedly affected the lenvatinib-induced ROS levels and apoptosis in HCC cells. In addition, analyses of The Cancer Genome Atlas (TCGA) database and the qRT-PCR results in our cohort both showed that GPX2 markedly overexpressed in tumor tissues and correlated with poor overall survival in HCC. Mechanistically, our fingdings further demonstrated that GPX2 was a downstream gene regulated by β-catenin, while lenvatinib could prevent nuclear translocation of β-catenin and further inhibit GPX2 expression in HCC cells. More importantly, the correlation of GPX2 expression with lenvatinib response was further analyzed in 22 HCC patients who received lenvatinib therapy, and the results showed that the objective response rate (ORR) in patients with low GPX2 expression was 44.4% (4/9), while the ORR in patients with high GPX2 expression was only 7.7% (1/13). ***Conclusion***: Taken together, our findings indicated that GPX2 plays an important role in lenvatinib-induced HCC cell apoptosis, which might serve as a biomarker for instruction of lenvatinib therapy in HCC patients.

Keywords: Lenvatinib; GPX2; Hepatocellular carcinoma; Apoptosis; ROS.

Introduction

Since most hepatocellular carcinoma (HCC) patients are diagnosed at late stage and loss the chance of radical resection, the application of targeted drugs in recent years has brought new hope for improving the prognosis of these patients. Sorafenib was the first approved targeted drug for advanced HCC in 2007[1, 2]. Over the past decade, many targeted drugs have been tested in HCC[3-5], but only lenvatinib approved as first line and regorafenib approved as second line got positive results in the global phase 3 trials. Lenvatinib, whose targets included FGFR1-4, VEGFR1-3, PDGFRα, and KIT[6-8], was first approved for treatment of advanced thyroid cancer. A recent phase 3 clinical study revealed that lenvatinib showed non-inferior to sorafenib in overall survival in untreated advanced HCC, and it has recently become available as a first-line therapy for advanced HCC in many country[9]. However, the mechanisms of lenvatinib in preclinical studies are limited. It is worthwhile to clarify its molecular mechanisms and identify the predictive biomarkers of lenvatinib therapy against HCC.

Reactive oxygen species (ROS) such as hydrogen peroxide are generated from reduction-oxidation reactions. Low levels of ROS in cells is essential for the regulation of cell survival, while excessive levels of ROS can induce cellular damage and promote cell death through oxidative stress[10]. Therefore, regulation of ROS in cancer cells may represent a viable strategy for cancer therapy[11]. Studies showed that increased ROS levels could enhance radio-sensitivity in breast cancer and lung cancer[12, 13]. Targeted drugs (like erlotinib or sorafenib) were also proved to increase ROS levels and induce cell apoptosis in lung cancer and HCC[14-16]. A recent study revealed that lenvatinib dose-dependently increased apoptosis in anaplastic thyroid cancer (ATC) cells via increasing the caspase-3 activity[17]. However, the precise molecular mechanisms involved in lenvatinib induced HCC cell apoptosis need to be further elucidated.

The anti-oxidant enzyme glutathione peroxidase (GPX) family protects cell survival through reducing the intracellular ROS levels[18]. GPXs have been reported to be involved in the progression of various cancers. Recently, researchers proved that GPX4 is an essential regulator of ferroptosis which could induce cancer cell death[19], and others found that targeting the GPX1 by Vitamin D could suppress tumor progression in salivary adenoid cystic carcinoma[20]. Previous studies also suggested that overexpression of GPX2 was detected in colorectal cancer and HCC[21-23]. Therefore, targeting GPXs and reducing ROS levels could be promising strategies for cancer therapy.

In the present study, we detected that lenvatinib induced cell apoptosis and increased intracellular

ROS levels in four HCC cell lines. Then, we demonstrated that GPX2 was an important regulator of ROS and could be markedly inhibited by lenvatinib in HCC cells. Furthermore, we found that GPX2 was significantly overexpressed in HCC tumor tissues, and high expression of GPX2 in HCC cells were more resistance to lenvatinib. Moreover, our results showed that inhibiting GPX2 could increase ROS levels and enhance the anti-tumor effect of lenvatinib. Therefore, our results indicated that GPX2 plays a crucial role in lenvatinib against HCC.

Methods

Cell culture and reagents

Huh7 and HepG2 cells were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). PLC/PRF5 and Hep3B cells were obtained from ATCC (Manassas, VA, USA). HCC cells were cultured in DMEM (Gibco BRL, USA) containing 10% fetal bovine serum (Biological Industries, Israel) at 37 ℃ in a humidified incubator. Lenvatinib were purchased from APExBIO chemicals.

Microarray experiments

Huh7 cells were treated with lenvatinib for 48 h, while the control group was treated with only solvent of lenvatinib. The microarray analysis was performed by KangChen Bio-Tech, and the samples were hybridized on the GeneChip Array (8×60K, ArrayStar, USA). The top ten upregulated and downregulated mRNA altered significantly in both samples are listed in Table S1.

Patients and tissue samples

A total of 95 paired HCC tumor tissues and corresponding adjacent normal tissues were collected at Sun Yat-Sen Memorial Hospital between 2014 and 2017. The histopathological diagnosis was based on the World Health Organization criteria. The clinic pathological characteristics of the patients included in this study were showed in Table S2. Another cohort of 22 HCC patients who were under surgical resection and recurred within 6 months were recommended to receive lenvatinib therapy. Among these 22 patients, 8 patients received lenvatinib alone, 6 patients received lenvatinib plus anti-PD-1 therapy, 4 patients received lenvatinib combined with at least one locoregional treatment of transarterial chemoembolization (TACE), 2 patients received lenvatinib plus anti-PD-1 and TACE, 1 patient received

lenvatinib combined with TACE and radiofrequency ablation (RFA), 1 patients received lenvatinib combined with radiotherapy. The total therapeutic regimens are shown in Table S3. The response assessment was evaluated using contrast-enhanced CT or MRI at 8-12 weeks after the initiation with lenvatinib according to the modified Response Evaluation Criteria in Solid Tumor (mRECIST). All sample tissues collection was approved by the ethics committee of the Sun Yat-Sen Memorial Hospital.

Flow cytometry to detect intracellular ROS and cell apoptosis

Reactive oxygen species assay kit (Beyotime, China) was used to detect the intracellular ROS levels. Briefly, cells were cultured in 12-well plates treated with 20 or 40 μmol/L of lenvatinib for 48 h. Then, the cells were incubated with 2,7-Dichlorodi-hydrofluorescein diacetate (DCFH-DA) for 20 min. The fluorescence intensity of ROS was analyzed by flow cytometry. Cell apoptosis were detected by the flow cytometry using the Annexin V-FITC and propidium iodide (PI).

Immunohistochemistry (IHC)

The immunohistochemistry analyses were performed as previously described. Briefly, after dewaxing and rehydration, the sections were retrieved by boiling in EDTA for 15 minutes, and then incubated with H_2O_2 for 10 min. Subsequently, the sections were blocked with goat serum (CWBIO) for 30 min, and incubated with primary antibody overnight. The next day, tissue sections were then incubated with HRP-conjugated Goat anti mouse/rabbit IgG (Dako Corporation, USA). Finally, the sections were stained with Diaminobenzidine tetrahydrochloride (DAB) and hematoxylin. The staining results were blindly assessed by two researchers according to the score criteria described previously[24].

HCC xenograft models

Huh7 cells (5×10^6) in culture medium were injected into the flank of the BALB/c nude mice. When the tumors grew to ~5 mm in diameter, mice were randomly grouped into three groups (6 mice/group) and administered as the following treatment: control group, 10 mg/kg/d and 30 mg/kg/d of lenvatinib groups. After two weeks' treatment, the mice were killed and the xenograft tumors were removed and weighed. *In vivo* experiments were approved by the Bioethics Committee of Sun Yat-Sen University.

Statistical analysis

Data analyses were conducted by SPSS software (version 20.0). Student's t-test or two-way analysis

of variance (ANOVA) with Bonferroni correction was applied to compare the statistical difference between different groups. *P < 0.05 was considered statistically significant.

Results

Lenvatinib induced ROS related apoptosis and inhibited tumor growth in HCC

To evaluate the cytotoxicity of lenvatinib against HCC, we treated four HCC cells (HepG2, PLC/PRF5, Huh7 and Hep3B) with various concentration of lenvatinib for 48 h. Cell viability dose dependently decreased in all the four HCC cells, in which Huh7 and Hep3B cells were more sensitive to lenvatinib than HepG2 and PLC/PRF5 cells (Fig. S1A-D). Then, we investigated the level of apoptosis in these four HCC cells treated with lenvatinib by flow cytometry. The results showed that 20 and 40 μmol/L of lenvatinib both significantly induced apoptosis in Huh7 and Hep3B cells (Fig. 1B and Fig. S1F). However, the results in HepG2 and PLC/PRF5 cells showed that 20 μmol/L of lenvatinib had limited role on inducing apoptosis (Fig. 1A and Fig. S1E). Similar results were also found in the intracellular ROS levels that lenvatinib markedly increased the ROS levels in Huh7 and Hep3B cells, but not HepG2 and PLC/PRF5 cells (Fig. 1C-D and Fig. S1G-H). We also examine the anti-tumor activity of lenvatinib against HCC *in vivo*, and the results in Figure 1E and 1F showed that lenvatinib at concentrations of 10 and 30 mg/kg/d both displayed effective anti-tumor effect on Huh7 xenografts. The tumor weight in 10 and 30 mg/kg lenvatinib group were 64.5% and 29.6% to that of control group, respectively (Figure 1G).

Lenvatinib inhibited the expression of GPX2 in HCC cells

In order to explore the targets of lenvatinib in HCC, we examined the transcriptome of Huh7 cells exposed to lenvatinib (40 μmol/L, 48 h) with microarrays. We identified 634 differentially expressed mRNA, including 343 upregulated and 291 downregulated genes. The hierarchical clustering heatmap showed the top 20 mostly increased and decreased mRNAs in Figure 2A, among which the anti-oxidant enzyme glutathione peroxidase 2 (GPX2) was one of the most downregulated genes with over 22-fold change. Then, we detected the RNA level of GPX2 in the four HCC cells. The results revealed that HepG2 and PLC/PRF-5 exhibited much higher levels of GPX2 than that of Huh7 and Hep3B cells (Fig.

2B). Additionally, qRT-PCR and western blot further confirmed that lenvatinib could dose dependently downregulate GPX2 expression in HCC cells (Fig. 2C-D). Next, the IHC results proved that lenvatinib markedly inhibited GPX2 expression *in vivo*. In addition, the percentage of Ki-67-positive cells were also decreased a lot in the groups treated with lenvatinib (Fig. 2E-F).

The expression of GPX2 was upregulated in HCC tissues and correlated with poor overall survival

We analyzed TCGA database and revealed that GPX2 was markedly over-expressed in various types of digestive system tumors, including HCC (Fig. S2A-B). Then, we further validated the expression of GPX2 in our cohort. As shown in Figure 3A, GPX2 was significantly upregulated in HCC tumor tissues. Besides, we also conducted Kaplan-Meier analysis for overall survival (OS) and recurrence free survival (RFS), and the results showed that patients with higher levels of GPX2 correlated with poorer OS and RFS (Fig. 3B-C). Moreover, Cox regression analysis demonstrated that GPX2 expression, microvascular invasion and BCLC stage were independent risk factors of OS in HCC (Table 1), while only BCLC stage was independent risk factors of RFS in HCC (Table 2).

GPX2 played an important role in ROS related apoptosis induced by lenvatinib in HCC cells

To explore its important role in HCC, GPX2 was markedly inhibited by GPX2 specific siRNA in HepG2 cells, and significantly upregulated by lentivirus vector carrying the GPX2 gene (Fig. 3D-E). We furtherly explored the role of GPX2 and ROS related apoptosis in HCC cells. The results demonstrated that downregulating GPX2 markedly increased the ROS levels in HepG2 cells, while overexpression of GPX2 significantly decreased the ROS levels in Huh7 cells (Fig. 3F). Moreover, we found that inhibiting the expression of GPX2 could sensitize HepG2 cells to lenvatinib, while Huh7 cells with overexpression of GPX2 became more resistant to lenvatinib (Fig. 3G-H). Taken together, these results suggested that HCC cells with high levels of GPX2 were more resistant to lenvatinib.

Lenvatinib suppressed GPX2 expression by preventing nuclear translocation of β-catenin

Previous researches have demonstrated that β-catenin could directly activate the promoter of GPX2 in HepG2 cells[25]. To explore the regulation of β-catenin/GPX2 axis, we found a GEO dataset (GSE94858), which explored the gene expression profiling of HepG2 cells after knockdown of β-catenin. By analyzing the GSE94858 with the GEO2R, we found that GPX2 was significantly downregulated after knockdown of β-catenin (Fig. 4A). qRT-PCR results confirmed that specific knockdown of β-catenin significantly decreased GPX2 mRNA levels in HepG2 cells, while overexpression of β-catenin markedly increased GPX2 mRNA levels in Huh7 cells (Fig. 4B-C). In addition, we also confirmed that the mRNA levels of β-catenin (CTNNB1) was markedly upregulated in HCC tissues by analyses of TCGA database (Fig. 4D). Moreover, we also detected that lenvatinib significantly suppressed GPX2 expression, while overexpression of β-catenin markedly impaired its effect on GPX2 inhibition in HCC cells (Fig. 4E). To investigate whether lenvatinib could modulate the activation of β-catenin, we used western blot and immunofluorescence to detect the nuclear translocation of β-catenin. The results demonstrated that lenvatinib prevented the nuclear translocation of β-catenin in HepG2 and Huh7 cells (Fig. 4F-G).

β-catenin drived GPX2 expression and decreased lenvatinib sensitivity in HCC cells

Since the above results demonstrated that GPX2 could modulate ROS levels, we also explored the regulation of β-catenin and ROS levels in HCC cells. The results revealed that downregulating β-catenin markedly increased the ROS levels in HepG2 cells, while upregulating β-catenin significantly decreased the ROS levels in Huh7 cells (Fig. 5A-B). In addition, to explore β-catenin and the sensibility of lenvatinib in HCC cells, HepG2 cells were transfected with siRNA (si-β-catenin) and then treated with lenvatinib. The results demonstrated that inhibiting β-catenin could markedly enhance the cell apoptosis in HepG2 cells, while increasing β-catenin impaired the anti-tumor effect of lenvatinib in Huh7 cells (Fig. 5C-D). The illustrative model of Figure 5E showed that lenvatinib induced ROS related apoptosis by regulating the β-catenin/GPX2 axis.

Low expression of GPX2 in HCC tissues conferred better efficiency to lenvatinib treatment in patients

To further explore the treatment response to lenvatinib and the GPX2 levels in HCC patients, we analyzed the expression of GPX2 in 22 patients who received lenvatinib. The evaluation of the lenvatinib efficiency using CT or MRI was performed at 8-12 weeks according to mRECIST. Based on mRECIST criteria, one patients achieved complete response (CR), four patients achieved partial response (PR), nine patients achieved stable disease (SD), and eight patients achieved progression disease (PD), respectively. Taken together, the objective response rate (ORR) in our cohort was 22.7% and disease control rate (DCR) was 63.6%. To our interest, 44.4% (4/9) of HCC patients with low GPX2 were responders (CR+PR), while most patients (12/13) with high GPX2 were non-responders (SD+PD) (Fig. 6). Therefore, these findings suggested that GPX2 might be a biomarker for predicting the efficiency of lenvatinib in HCC patients.

Discussion

In the present study, we found that lenvatinib could increase ROS levels and induced cells apoptosis via inhibiting GPX2 expression in HCC cells. HCC cells with high levels of GPX2 was more resistant to lenvatinib. We also found that GPX2 was overexpressed in HCC tissues in TCGA database and our cohort of HCC patients. In addition, we demonstrated that GPX2 was a downstream gene regulated by β-catenin. Mechanistically, our results showed that the mechanism of lenvatinib against HCC might be through preventing the nuclear translocation of β-catenin, and targeting β-catenin or GPX2 could enhance the effect of lenvatinib against HCC.

Sorafenib served as the only first-line targeted drugs for nearly ten years, and recently lenvatinib became the second targeted drug as first-line therapy for HCC. The questions about how to choose the targeted drugs for HCC patients needed further discussion. Compared with sorafenib, lenvatinib might display its superior anti-tumor effect through targeting FGFRs[6, 26]. Increasing evidences suggested that FGF signaling pathways were commonly activated in HCC and contributed to sorafenib resistance[27-29]. Recently, studies demonstrated that lenvatinib displayed selective anti-proliferative activity in HCC cells with high levels of FGF19, and higher FGFR4 expression could serve as biomarkers for combined therapy of lenvatinib plus anti-PD-1[30, 31]. More interestingly, our microarray gene expression analysis in

Huh7 cells exposed to lenvatinib also demonstrated that FGF19 was significantly downregulated (data not showed). These findings suggested that FGF19 might be one of the molecular biomarkers for choosing targeted drugs in HCC patients.

As a first line therapy for HCC, lenvatinib is now widely applied in clinic and prolongs the prognosis of advanced HCC patients. Lenvatinib was recommended orally for unresectable HCC patients at 12 mg/day for ≥60 kg and 8 mg/day for <60 kg[9, 32]. However, the results of REFLECT trial and real-world studies showed that the ORR was less than 30%[9, 33]. Therefore, exploring the potential biomarkers to predict the therapy response and to guide the selection of dosage of lenvatinib are urgently needed. The present study demonstrated that lenvatinib could dose-dependently suppress GPX2 expression in HCC cells, but only relative high dose of lenvatinib could induced cell apoptosis in HepG2 and PLC/PRF5 cells (with high levels of GPX2). Our results confirmed that HCC cells with high expression of GPX2 was more resistant to lenvatinib. In addition, we also conducted a retrospective analysis of 22 lenvatinib-treated recurrent HCC patients. Consistent with previous studies, the ORR in our cohort was 22.7% (5/22) for all the patients. It means that there are over 70% HCC patients who could not benefit from the treatment of lenvatinib. To our interest, the results showed that the ORR was 44.4% (4/9) in patients who expressed lower levels of GPX2, while the ORR was only 7.7% (1/13) in patients who expressed higher levels of GPX2. These results provide evidence that those HCC patients with low levels of GPX2 might benefit from lenvatinib treatment, while those patients with high expression of GPX2 should be suggested with higher dosage of lenvatinib or combined therapy to improve the prognosis.

The oncogenic role of GPX2 has been documented in various cancers and is associated with tumor progression[34, 35]. It was reported that GPX2 levels were associated with metastasis formation and resistance to current systemic therapy in colorectal cancer, and increasing ROS levels through targeting GPX2 may be an effective anti-tumor therapy[22]. Others also showed that YAP promoted ROS accumulation through downregulation of GPX2, thus triggering cell growth inhibition in lung squamous cell carcinoma[21]. In addition, researchers demonstrated that GPX2 was up-regulated in HCC tumor tissues and associated with early hepatocarcinogenesis[23]. Our study also proved that GPX2 was overexpressed in HCC tumor tissues by analyses of TCGA-LIHC database and the qRT-PCR results in our cohort of HCC patients. We further showed that GPX2 played an important role in ROS-mediated regulation of cell apoptosis in HCC. As we known, this is the first study to demonstrate the correlation

between GPX2 inhibition and ROS related apoptosis in HCC.

Inhibiting degradation of β-catenin could accumulate its nuclear translocation and interacts with the transcription factors (TCF/LEF) to regulate target genes[36]. Activation of Wnt/β-catenin pathway is highly involved in the progression of HCC. The present study also confirmed the oncogenic role of CTNNB1 in HCC tissues by analysis the TCGA database. It was reported that β-catenin/TCF4 directly bind to the promoter of GPX2 in HepG2 cells[25], which was consistent with our result that GPX2 was a target of β-catenin by loss and gain function of experiment. We also demonstrated that lenvatinib could provent the nuclear translocation of β-catenin in HCC cells. The current data revealed a potential mechanism of lenvatinib, and demonstrated its ability to inactive β-catenin in HCC.

In conclusion, our study demonstrated that GPX2 played an important role in lenvatinib against HCC, which might serve as a biomarker for lenvatinib treatment for HCC patients. Moreover, this finding also provide evidence to further evaluate the potential application of anti-GPX2 therapy combinated with lenvatinib for improving the survival of HCC patients. Since the limited HCC samples we collected, the exact role of GPX2 in lenvatinib sensibility still need further investigation, and we will keep focusing on this issue in our future studies.

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