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Research

Silencing hnRNPD inhibits gastric cancer growth by increasing TXNIP-mediated oxidative stress

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Abstract

Background RNA-binding proteins (RBPs) are essential for controlling gene expression, and their dysregulation is a key factor in tumor development and progression. Heterogeneous nuclear ribonucleoprotein D (hnRNPD), a member of the hnRNP family of RBPs, is aberrantly expressed in various tumors. However, its role and underlying mechanisms in gastric cancer have not been determined.

Methods The expression patterns of hnRNPD in gastric cancer were analyzed using publicly available datasets and clinical specimens. The effects of hnRNPD on gastric cancer cell growth were assessed using the Cell Counting Kit-8 (CCK-8) and colony formation assays. Target genes regulated by hnRNPD were identified through RNA sequencing (RNA-seq) and RNA immunoprecipitation sequencing (RIP-seq).

Results Elevated expression of hnRNPD was observed in gastric cancer, and this overexpression was associated with an unfavorable prognosis. Knocking down hnRNPD could suppress the growth of gastric cancer cells and enhance endogenous oxidative stress. Thioredoxin-interacting protein (TXNIP) was identified as a downstream target of hnRNPD. Further analysis confirmed that hnRNPD diminished TXNIP expression by binding to and destabilizing its mRNA. Moreover, silencing TXNIP reversed the decrease in cell growth and the increase in oxidative stress caused by hnRNPD knockdown.

Conclusion Our study highlights hnRNPD as a major contributor to gastric carcinogenesis. The knockdown of hnRNPD hinders gastric cancer growth by directly interacting with TXNIP, promoting its expression, and inducing oxidative stress. These findings suggest that hnRNPD may serve as a valuable target for the treatment of gastric cancer.

Keywords Gastric cancer · Tumor growth · Oxidative stress · hnRNPD · TXNIP

1 Introduction

Gastric cancer is one of the most prevalent and lethal malignancies worldwide [1]. The etiology of gastric cancer is multifaceted, involving various factors such as *Helicobacter pylori* infection and poor dietary habits [2]. Current approaches to treating gastric cancer include surgery, chemotherapy, immunotherapy, and targeted molecular

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therapy. Despite these therapeutic advances, the prognosis for gastric cancer patients remains unfavorable. Thus, it is essential to elucidate the molecular mechanisms that drive gastric tumorigenesis and progression.

RNA-binding proteins (RBPs) play a pivotal role in the post-transcriptional regulation of gene expression [3]. They are critical for maintaining the cellular transcriptome by controlling RNA processing and transport, including modulating RNA splicing, polyadenylation, mRNA stability, localization, and translation [4]. Increasing studies have suggested that RBPs are aberrantly expressed in multiple cancer tissues and influence numerous cancer-related cellular phenotypes [5, 6]. Additionally, RBPs represent potential targets for a range of anti-cancer therapies [7]. In recent years, there has been growing interest in exploring the relationship between RBPs and gastric cancer [8, 9].

Heterogeneous nuclear ribonucleoproteins (hnRNPs) belong to the large family of RBPs [10]. By interacting with RNA molecules, hnRNPs regulate RNA metabolism from synthesis to degradation. The hnRNP family comprises approximately 20 major members, ranging from hnRNPA1 to hnRNPU. Several studies have demonstrated that hnRNPs are closely related to malignant tumors. For instance, downregulation of hnRNPK inhibited lung cancer cell migration and invasion [11]. Targeting hnRNPU successfully overcame cisplatin resistance in bladder cancer [12]. Silencing hnRNPA2B1 induced apoptosis in melanoma stem cells [13]. These findings provide a compelling rationale for investigating the role of hnRNPs in gastric cancer.

hnRNPD has been implicated as an oncogene in many cancers; however, its specific impact on gastric cancer is still not well defined [14–16]. In this study, we examined the clinical significance of hnRNPD in gastric cancer samples and investigated how hnRNPD affects gastric cancer cell growth. Our study underscores the importance of hnRNPD in gastric carcinogenesis.

2 Materials and methods

2.1 Bioinformatics analysis

Publicly available data were retrieved from well-established repositories, including The Cancer Genome Atlas (TCGA, https://tcga-data.nci.nih.gov/tcga/), the Cancer Cell Line Encyclopedia (CCLE, http://www.broadinstitute.org/ccle), and the Kaplan–Meier Plotter (http://kmplot.com/analysis/).

2.2 Immunohistochemistry

The gastric cancer tissue microarray (HStmA180) used in the present study was purchased from Outdo Biotech (China), which consists of 80 gastric cancer tissue samples and 80 matched adjacent normal gastric mucosa tissue samples. The experiment was approved by the company's ethics committee (Approval No. SHYJS-CP-1801009). All tissue donors provided written informed consent prior to their participation. A primary antibody against hnRNPD (ab61193, Abcam, USA) was used for immunohistochemistry, following previously described protocols [17].

2.3 Cell culture and transfection

Gastric cancer cell lines, including AGS, HGC-27, MKN1, KATO-III, NCI-N87, and MKN74, were acquired from Procell in China. Cells were cultured in DMEM or RPMI-1640 medium supplemented with 10% fetal bovine serum. Short hairpin RNA (shRNA) plasmids targeting hnRNPD were obtained from Vigene (China), and small interfering RNAs (siRNAs) targeting thioredoxin-interacting protein (TXNIP) were produced by Genepharma (China). Transfections were carried out using the jetPRIME reagent (Polyplus, France), according to the manufacturer's instructions. The sequences of siRNAs and shRNAs are provided in Table S1.

2.4 Real-time quantitative-PCR (RT-qPCR) and Western blotting

Total RNA was extracted using an RNA extraction kit (Tiangen, China). Complementary DNA (cDNA) was synthesized with the HiFiScript cDNA Synthesis Kit (CWBIO, China). Quantitative PCR was conducted using the UltraSYBR Mixture

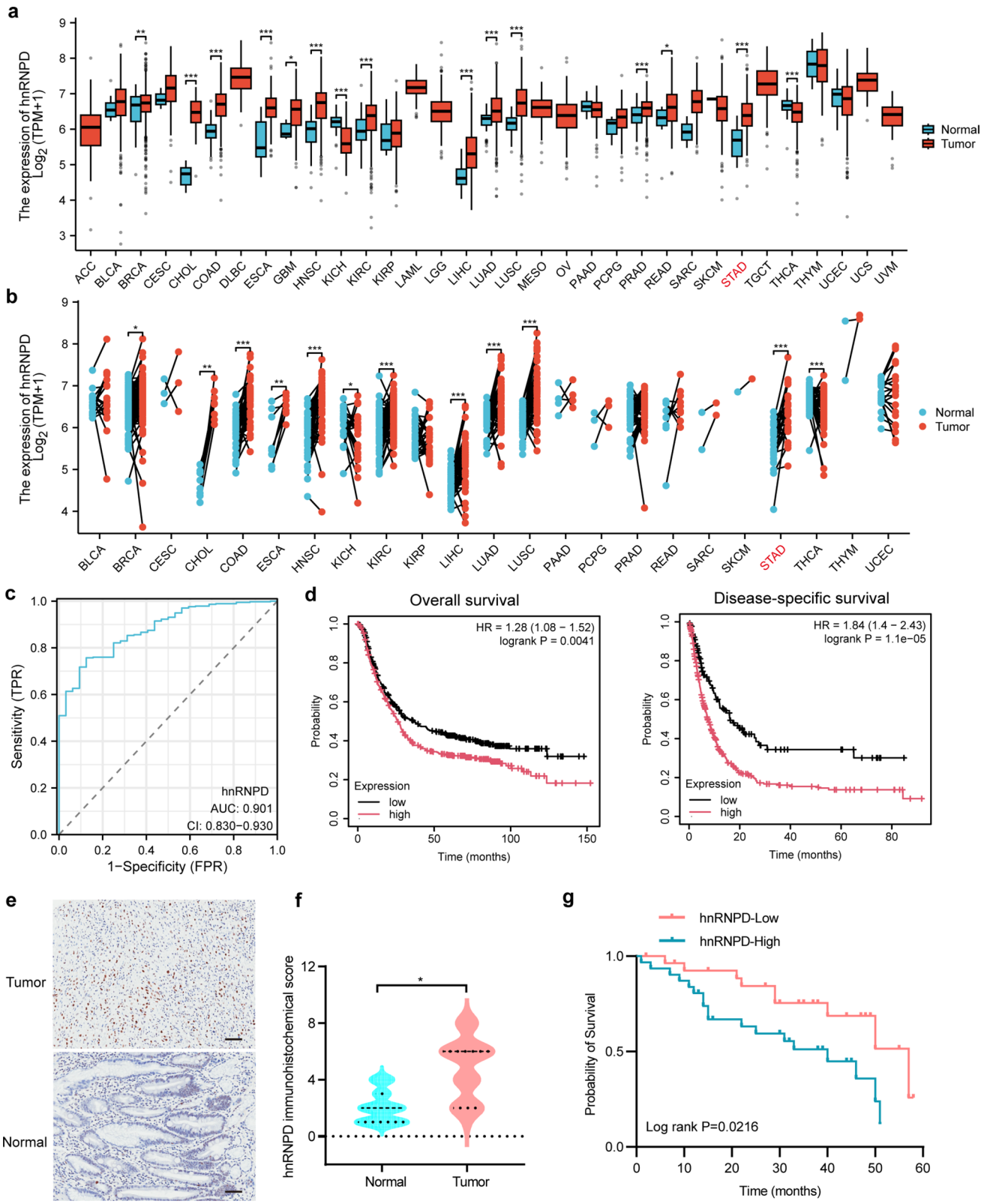


Fig. 1 Expression profile and prognostic value of hnRNPD in gastric cancer. **a** Pan-cancer analysis of hnRNPD across TCGA cohorts. **b** Comparison of hnRNPD expression levels in paired tumor and normal tissues derived from the TCGA pan-cancer datasets. **c** ROC curves illustrating the diagnostic value of hnRNPD. **d** Assessment of prognostic significance using the Kaplan–Meier plotter database. **e** Detection of hnRNPD expression via immunohistochemistry (n = 80). **f** Immunohistochemical scoring of hnRNPD. **g** Survival analysis based on the expression levels of hnRNPD. STAD:stomach adenocarcinoma. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Fig. 2 Effects of hnRNPD knockdown on gastric cancer cell growth. **a** hnRNPD mRNA expression in various cancer cell lines obtained from ▶ the CCLE database. **b** Validation of hnRNPD expression using RT-qPCR. The knockdown efficiency of hnRNPD was assessed by **c** RT-qPCR and **d** Western blotting. hnRNPD expression levels were normalized to GAPDH. **e** CCK-8 and **f** colony formation assays were used to measure cell proliferation. shNC, negative control shRNA; shRNA, specific shRNA targeting hnRNPD. $^{*}P < 0.05$, $^{**}P < 0.01$

Kit (CWBIO). Primer sequences are listed in Table S2. Total protein was isolated using a protein extraction kit (Beyotime, China). Western blotting was performed following standard protocols. The primary antibodies used were hnRNPD (No. 12770-1), TXNIP (No. 27429-1), and GAPDH (No. 60004), all obtained from Proteintech (China).

2.5 Cell counting kit-8 (CCK-8) and colony formation assays

Cells were placed in 96-well plates for the CCK-8 assay, and cell proliferation was evaluated using the CCK-8 reagent from Beyotime, according to the provided guidelines. For the colony formation assay, cells were seeded into 6-well plates and incubated for two weeks. Afterward, colonies containing more than 50 cells were stained with crystal violet.

2.6 High-throughput analysis

RNA sequencing (RNA-seq) and RNA immunoprecipitation sequencing (RIP-seq) technologies were employed to identify potential target genes of hnRNPD (Novogene, China). These methods have been extensively described [18]. Differentially expressed genes (DEGs) were analyzed using the edgeR package. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were conducted following sequencing to interpret the functional implications of the data.

2.7 RIP-qPCR

Cells were lysed in RIP lysis buffer (Millipore, USA). Cell lysates were incubated with magnetic beads conjugated to anti-hnRNPD (Abcam) or anti-IgG (ProteinTech). The bound mRNAs were isolated and purified for RT-qPCR detection.

2.8 RNA decay assay

The stability of RNA was assessed using an RNA decay assay. Cells were exposed to actinomycin D (Sigma-Aldrich, USA), an antibiotic that inhibits RNA synthesis, at a concentration of 5 μg/mL for 0, 3, 6, and 9 h. Subsequently, RNA was extracted for RT-qPCR analysis.

2.9 Detection of cellular oxidative stress

Intracellular reactive oxygen species (ROS) were measured using a flow cytometer (Becton–Dickinson, USA) with DCFH-DA (Beyotime). The levels of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) were determined using assay kits, following the manufacturers' instructions (Beyotime).

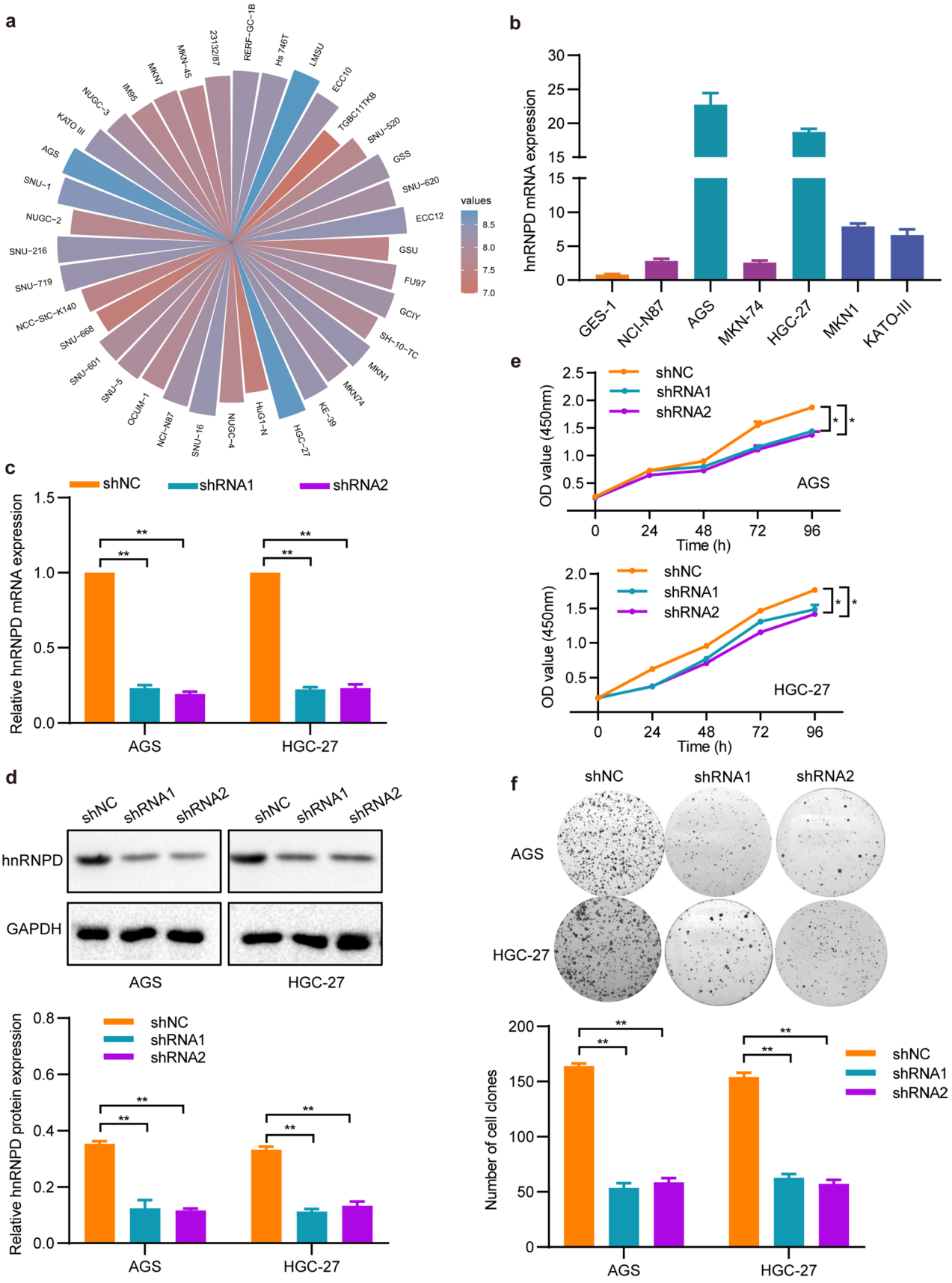
2.10 Statistical analysis

Data are presented as mean ± SD. Statistical significance was determined using one-way ANOVA, Student's t-test, or log-rank test, with a *P*-value of less than 0.05 considered significant.

3 Results

3.1 hnRNPD is upregulated in gastric cancer and its elevation indicates poor prognosis

Using the TCGA database, we analyzed hnRNPD expression patterns across various human cancers. Elevated expression of hnRNPD was observed in several cancer types, including gastric cancer(Fig. 1a, b). According to the Receiver operating characteristic (ROC) diagnostic curve, the expression of hnRNPD effectively distinguished gastric cancer from normal tissues (Fig. 1c). Through the online database Kaplan–Meier plotter, we discovered a negative correlation between hnRNPD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Hs 746T
LMSU
ECC10
TGBC11TKB
SNU-520
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ECC12
GSU
FU97
GCIY
SH-10-TC
MKN1
MKN14
KE-39
HGC-27
HuG1-N
NUGC-4
SNU-16
NCI-N87
OCUM-1
SNU-5
SNU-601
SNU-668
NCC-StC-K140
SNU-719
SNU-216
NUGC-2
SNU-1
AGS
KATO III
NUGC-3
IM95
MKN7
MKN-45
2313287
values
8.5
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hnRNPD mRNA expression
GES-1
NCI-N87
AGS
MKN-74
HGC-27
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Number of cell clones

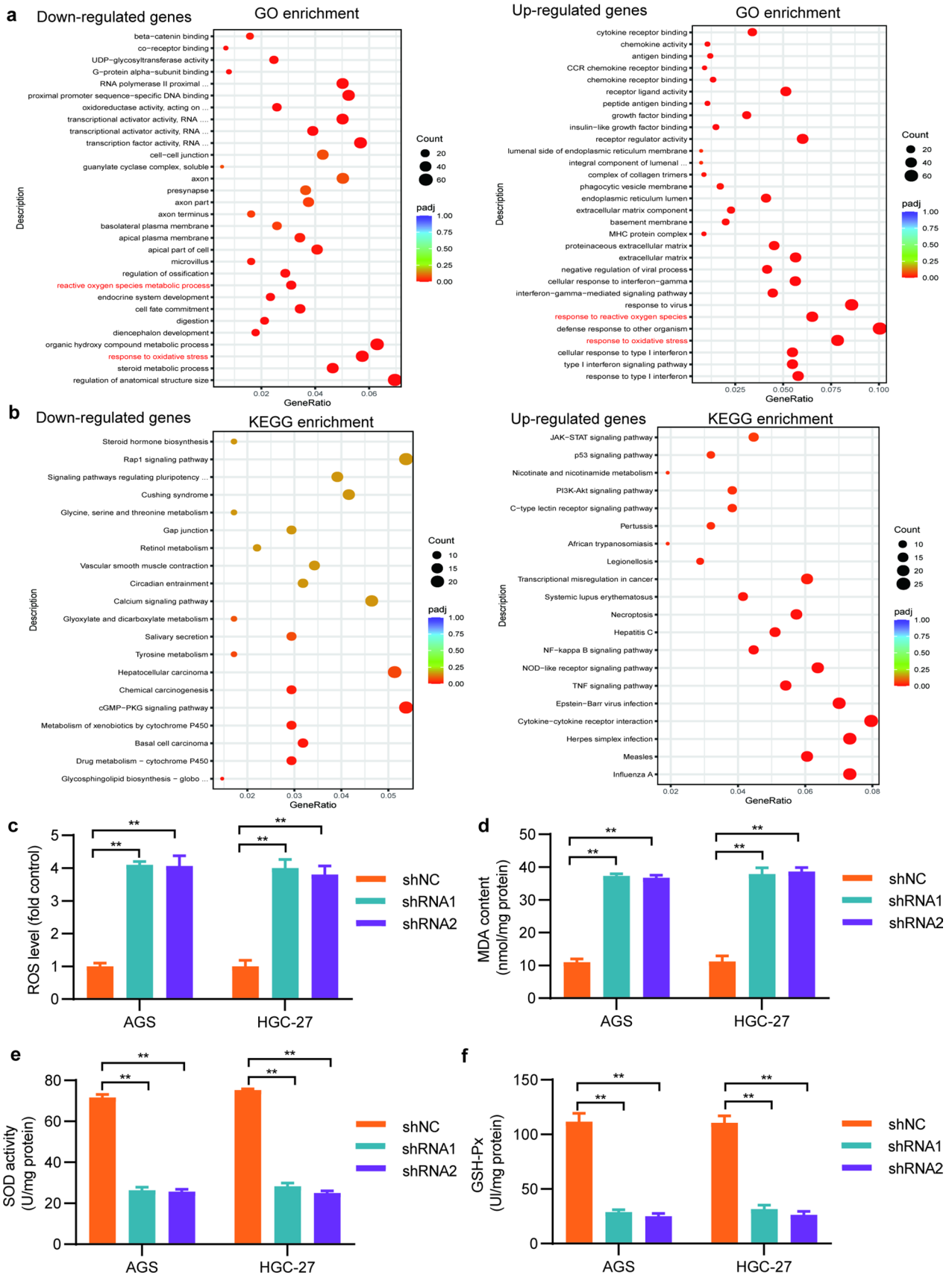


Fig. 3 Effects of hnRNPD knockdown on cellular oxidative stress. **a** GO and **b** KEGG analysis of differentially expressed genes. **c**–**f** Quantitative analysis of oxidative stress and anti-oxidative stress markers (ROS, MDA, SOD, and GSH-Px). *shNC* negative control shRNA, *shRNA* specific shRNA targeting hnRNPD.*$P < 0.05$

expression and both overall and disease-specific survival rates (Fig. 1d). Moreover, tissue microarray analysis showed that hnRNPD was highly expressed in gastric cancer, and its overexpression was linked to poor prognosis (Fig. 1e-g). Collectively, these results suggest that hnRNPD may serve as a potential biomarker for gastric cancer.

3.2 hnRNPD depletion inhibits gastric cancer cell growth

According to the CCLE database, hnRNPD was frequently expressed in gastric cancer cell lines (Fig. 2a). The highest expression was detected in AGS and HGC-27 cells, while moderate expression was observed in MKN1 and KATO-III cells, and low expression was noted in NCI-N87 and MKN74 cells. Similar results were obtained through RT-qPCR (Fig. 2b). hnRNPD was then depleted in AGS and HGC-27 cells using shRNA-mediated knockdown (Fig. 2c, d). The CCK-8 and colony formation assays revealed that silencing hnRNPD inhibited the proliferative and clonogenic abilities of AGS and HGC-27 cells (Fig. 2e, f). These data indicate that hnRNPD may contribute to gastric carcinogenesis.

3.3 hnRNPD depletion increases cellular oxidative stress

To understand how hnRNPD facilitates gastric cancer cell growth, we performed RNA-seq analysis on AGS cells following hnRNPD knockdown (Table S3). Genes exhibiting altered expression were analyzed through GO categories and KEGG pathways (Fig. 3a, b). We discovered that the DEGs were prominently enriched in oxidative stress-related GO terms, such as "reactive oxygen species metabolic process", "response to oxidative stress", and "response to reactive oxygen species" (Fig. 3a; red mark). To explore whether hnRNPD regulates oxidative stress, we evaluated the levels of several indicators related to oxidative stress, including ROS, MDA, SOD, and GSH-Px. We observed that silencing hnRNPD could stimulate the generation of ROS and MDA (oxidative stress biomarkers) in AGS and HGC-27 cells (Fig. 3c, d). However, the activities of SOD and GSH-Px (antioxidative enzymes) were reduced upon hnRNPD knockdown (Fig. 3e, f). These observations imply that the influence of hnRNPD on gastric cancer cell growth is linked to the modulation of oxidative stress.

3.4 hnRNPD directly interacts with TXNIP and negatively regulates its mRNA expression

RIP-seq was employed to identify the mRNAs that specifically bind to hnRNPD in AGS cells (Fig. 4a). By integrating the RNA-seq data (Table S3) with the RIP-seq data (Table S4), we identified 70 candidate genes (Fig. 4b). Among these, the top three candidates with significant fold changes related to oxidative stress were HMOX1 ($Log_2FC = -1.83$), SOD2 ($Log_2FC = -1.73$), and TXNIP ($Log_2FC = 2.26$). Notably, TXNIP was downregulated in gastric cancer, exhibiting a negative correlation with hnRNPD expression (Fig. 4c, d). Hence, TXNIP was chosen for further investigation. The RT-qPCR analysis showed that hnRNPD knockdown resulted in increased TXNIP mRNA expression in AGS and HGC-27 cells (Fig. 4e). The RIP-PCR assay confirmed that hnRNPD was enriched on TXNIP mRNA (Fig. 4f). The actinomycin D experiment demonstrated that the half-life of TXNIP mRNA was prolonged upon hnRNPD silencing (Fig. 4g). Altogether, these results suggest that hnRNPD controls TXNIP expression by affecting the stability of its mRNA.

3.5 hnRNPD exerts its oncogenic activity via TXNIP-mediated oxidative stress

TXNIP is recognized as a critical regulator of oxidative stress [19]. We next examined whether the hnRNPD-TXNIP axis impacts oxidative stress in gastric cancer cells. TXNIP expression was silenced in AGS and HGC-27 cells that had undergone hnRNPD knockdown (Fig. 5a, b). We found that the oxidative stress resulting from hnRNPD knockdown was mitigated by silencing TXNIP (Fig. 5c–f). Meanwhile, the reduction in cell proliferation caused by hnRNPD knockdown was reversed when TXNIP was silenced (Fig. 5g, h). Hence, the tumor-promoting property of hnRNPD is partly dependent on TXNIP-mediated oxidative stress.

4 Discussion

hnRNPD is dysregulated in numerous tumors; however, its specific role in gastric cancer has not been previously demonstrated. Here, we discovered that hnRNPD was upregulated in gastric cancer, highlighting its potential as a biomarker for the diagnosis and treatment of this disease. The knockdown of hnRNPD inhibited the growth of gastric cancer cells

Fig. 4 TXNIP is a direct target of hnRNPD in gastric cancer. **a** Identification of hnRNPD-interacting RNAs by RIP-seq. **b** Venn diagram illustrating the overlapping targets of RNA-seq and RIP-seq. **c** The expression levels of hub genes were analyzed using data from the TCGA database. **d** Correlation analysis between hnRNPD and hub genes based on the TCGA database. **e** The impact of hnRNPD knockdown on TXNIP expression was measured by RT-qPCR. **f** A RIP-qPCR assay was conducted to confirm the binding of hnRNPD to TXNIP mRNA. **g** The RNA decay assay was performed to determine the half-life of TXNIP mRNA following hnRNPD knockdown. *shNC* negative control shRNA, *shRNA* specific shRNA targeting hnRNPD. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

by upregulating TXNIP expression, which subsequently increased intracellular oxidative stress. Our findings uncover a potentially novel function for hnRNPD in the process of gastric carcinogenesis.

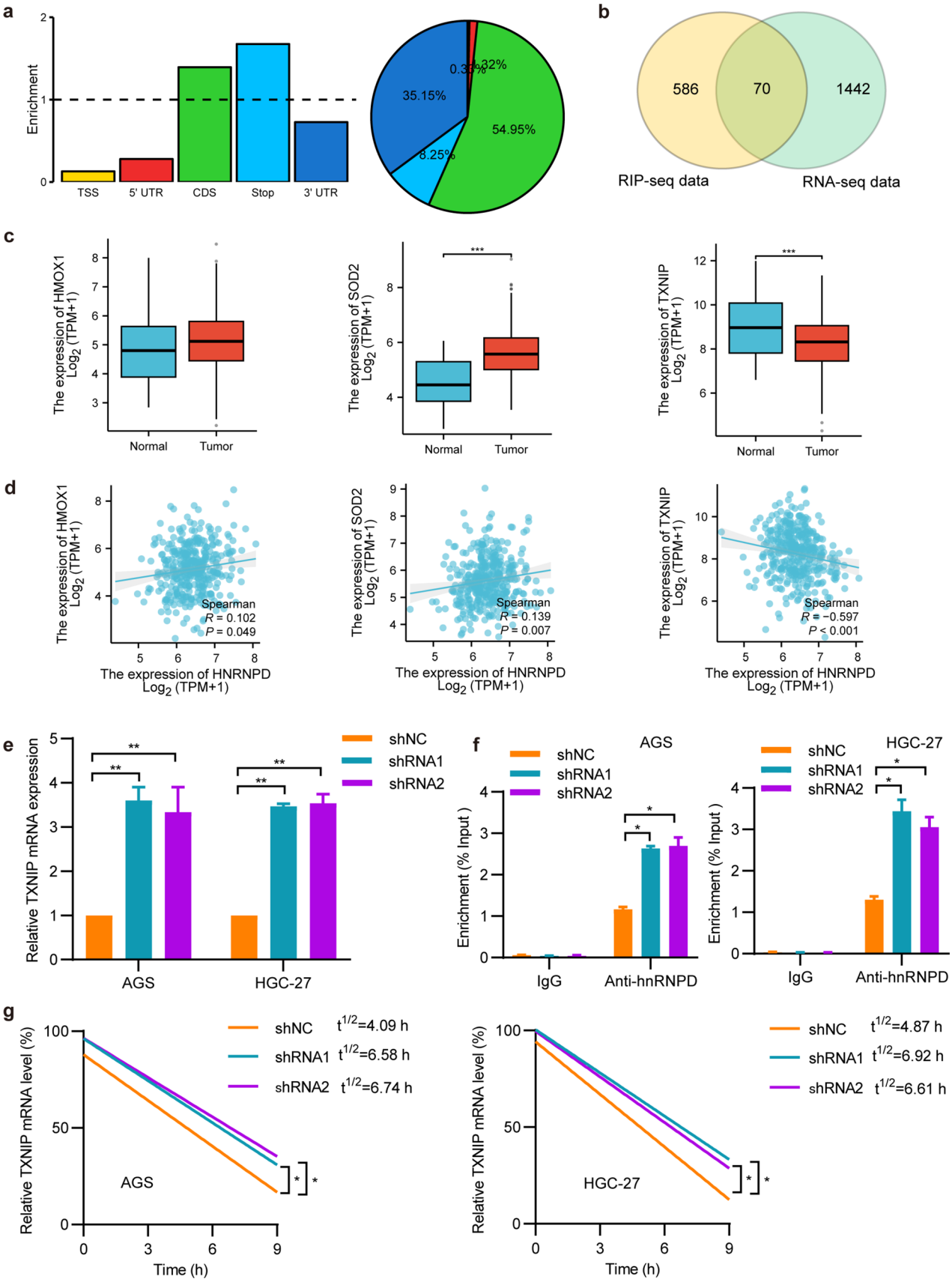
Multiple members of the hnRNP family are involved in the modulation of gastric cancer. For instance, silencing hnRNPA2B1 sensitized gastric cancer cells to chemotherapy [20]. Inhibition of hnRNPU reduced the proliferation, migration, and invasion of gastric cancer cells [21]. Increased expression of hnRNPA1 facilitated the epithelial-to-mesenchymal transition in gastric cancer [22]. The upregulation of hnRNPK contributed to gastric tumorigenesis [23]. The present study utilized bioinformatics analysis and immunohistochemical staining to explore the expression pattern and clinical relevance of hnRNPD in gastric cancer. We observed that gastric cancer exhibited elevated levels of hnRNPD, which were associated with poor prognosis. Loss-of-function experiments indicated that hnRNPD depletion hindered the proliferation and colony formation of gastric cancer cells. Consequently, hnRNPD is an oncogenic factor in gastric cancer and warrants thorough investigation in the future.

Oxidative stress is widely recognized as a pathological feature across various diseases [24]. Moderate oxidative stress has been reported to support tumor growth, whereas excessive oxidative stress can trigger cellular apoptosis [25]. Oxidative stress is a major risk factor for gastric cancer, contributing to the initiation and progression of cancer cells [26]. Through RNA-seq, we confirmed that hnRNPD was a key regulator of oxidative stress in gastric cancer cells. Oxidative stress primarily arises from the overaccumulation of ROS. Meanwhile, elevated levels of MDA and decreased activities of SOD and GSH-Px are common indicators of oxidative stress. In the present study, we demonstrated that the suppression of hnRNPD led to increased levels of ROS and MDA, whereas the activities of SOD and glutathione peroxidase were reduced. Notably, we reveal for the first time a link between oxidative stress and the growth of gastric cancer cells caused by hnRNPD.

TXNIP, also referred to as thioredoxin-binding protein 2 (TBP2), is an important participant in the regulation of oxidative stress [27]. TXNIP binds to thioredoxin, reducing its antioxidant activity, thereby favoring oxidative stress [28]. Several factors can affect the expression of TXNIP in gastric cancer. For example, TXNIP expression was downregulated by miR-301b-3p [29]. Interference with PTBP1 using siRNA enhanced the expression of TXNIP [30]. This study established a direct connection between hnRNPD and TXNIP through RNA-seq, RIP-seq, RIP-qPCR, and RT-qPCR technologies. Importantly, hnRNPD is known to control the stability and translational efficiency of mRNAs [31]. We confirmed that reducing hnRNPD could upregulate TXNIP mRNA levels by enhancing its stability. Furthermore, suppressing TXNIP reversed both the decline in gastric cancer cell growth and the elevation in oxidative stress due to hnRNPD knockdown. The current study identifies a new regulatory mechanism through which hnRNPD influences TXNIP in gastric cancer.

5 Conclusions

The RNA-binding protein hnRNPD was overexpressed in gastric cancer tissues and facilitated the growth of gastric cancer cells. Mechanistically, hnRNPD bound to TXNIP and negatively regulated its mRNA expression, thereby protecting cells from oxidative stress. Targeting hnRNPD may provide a promising therapeutic strategy for gastric cancer.


a
Enrichment
TSS
5' UTR
CDS
Stop
3' UTR
0.32%
35.15%
54.95%
8.25%
b
586
70
1442
RIP-seq data
RNA-seq data
c
The expression of HMOX1 Log2 (TPM+1)
The expression of SOD2 Log2 (TPM+1)
The expression of TXNIP Log2 (TPM+1)
Normal
Tumor
***
d
Spearman R = 0.102 P = 0.049
Spearman R = 0.139 P = 0.007
Spearman R = −0.597 P < 0.001
The expression of HNRNPD Log2 (TPM+1)
e
Relative TXNIP mRNA expression
shNC
shRNA1
shRNA2
AGS
HGC-27
f
Enrichment (% Input)
IgG
Anti-hnRNPD
g
Relative TXNIP mRNA level (%)
Time (h)
shNC t1/2=4.09 h
shRNA1 t1/2=6.58 h
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shNC t1/2=4.87 h
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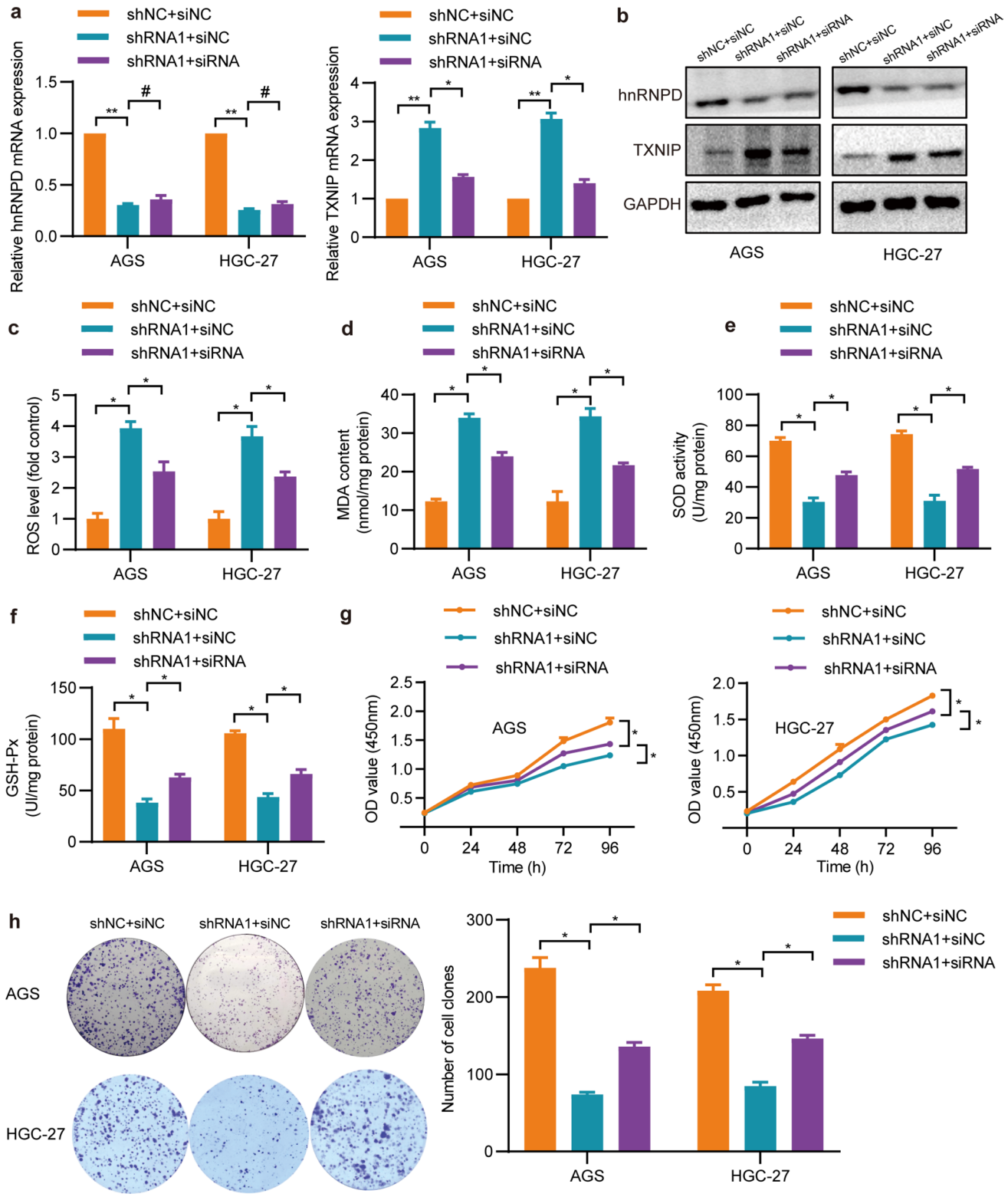

Fig. 5 Effects of the hnRNPD-TXNIP axis on oxidative stress and cell proliferation. **a** The mRNA expression levels of hnRNPD and TXNIP were analyzed using RT-qPCR. **b** The protein expression levels of hnRNPD and TXNIP were monitored by Western blotting. **c**–**f** Quantitative analysis of ROS, MDA, SOD, and GSH-Px levels. **g** CCK-8 assay. **h** Colony formation assay. *shNC* negative control shRNA, *shRNA* specific shRNA targeting hnRNPD, *siNC* negative control siRNA, *siRNA* specific siRNA targeting TXNIP. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{\#}P > 0.05$

Author contributions Xiaoyan Wang wrote the main manuscript text. Xuan Zou, Jin Li, Junshuo Zhou, Qiulei Ren, Kelong Wang. All authors reviewed the manuscript.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate The ethics committee of Shanghai Outdo Biotech Company approved the protocol for handling human tissue samples (No. SHYJS-CP-1801009). Informed consent was obtained from all individual participants included in the study. All procedures performed in the studies involving human participants were in accordance with the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

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