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Clinical significance and oncogene function of long noncoding RNA HAGLROS overexpression in ovarian cancer

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Abstract

Purpose To explore the clinical significance and mechanism of long noncoding RNA (lncRNA) HAGLROS in ovarian cancer.

Methods The expression of HAGLROS in ovarian cancer was verified by online databases and quantitative reverse transcription polymerase chain reaction (qRT-PCR), and its relationship with clinicopathological parameters was analysed. Pearson correlation analysis was used to study the correlation between HAGLROS and miR-100 in ovarian cancer. Meta-analysis was used to explore the expression of miR-100 in ovarian cancer. In addition, we used bioinformatics to explore the target genes of miR-100 and perform functional analysis.

Results HAGLROS was significantly upregulated in ovarian cancer ($P < 0.001$) and was closely related to disease stage ($P = 0.033$), tumour size ($P = 0.032$) and poor prognosis ($P = 0.019$). HAGLROS had a certain diagnostic value in ovarian cancer (area under the curve = 0.751). MiR-100 was negatively correlated with HAGLROS ($r = 0.167$, $P = 0.001$) and significantly downregulated in ovarian cancer. Bioinformatics analysis predicted a total of 31 potential target genes that interact with miR-100. These target genes were mainly involved in the regulation of cellular catabolic process, proteoglycan biosynthetic process and positive regulation of proteasomal ubiquitin-dependent protein catabolic process. Among them, mTOR and ZNRF2 are hub genes.

Conclusion HAGLROS is a potential biomarker for early diagnosis and prognosis evaluation of ovarian cancer. It can be used as a molecular sponge of miR-100 to regulate the expression of mTOR and ZNRF2 and affect the signal transduction of the mTOR pathway. HAGLROS is expected to be a new target for the treatment of ovarian cancer.

Keywords Long noncoding RNA · HAGLROS · Ovarian cancer · miR-100 · mTOR signalling pathway · ZNRF2

Introduction

Ovarian cancer is the most deadly female malignancy. Its progression is asymptomatic, and most patients are in an advanced stage at the time of diagnosis. The 5-year survival rate of patients is approximately 30–40% [1]. Currently, surgery and chemotherapy are the main treatments for ovarian cancer, but 80% of patients will eventually relapse [2, 3]. There is an urgent need to further explore the molecular mechanisms of ovarian cancer development to improve the status quo [4].

Long noncoding RNAs (lncRNAs) are noncoding RNAs greater than 200 bp in length, and their major modes of action include regulation of *cis* and *trans* gene expression, scaffolding of subcellular domains and complexes, and regulation of protein activity and abundance [5]. The dysregulation of lncRNA is closely related to human cancer, which is highlighted by the regulation of gene expression by titrating miRNA in a phenomenon called the competitive endogenous RNA (ceRNA) hypothesis [6, 7]. In ovarian cancer, lncRNA can exhibit a variety of biological functions in different pathogenic stages [8]. For example, lncRNA HOTAIR [9], SNHG3 [10] and MLK7-AS1 [11] are involved in the proliferation, metastasis and energy metabolism of ovarian cancer

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cells. HAGLROS is a lncRNA with a length of 699 bp and is involved in the progression of disease in gastric cancer and colorectal cancer [12, 13]. However, its mechanism of action in ovarian cancer remains unclear.

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that responds to a variety of stimuli, including extracellular growth factors, insulin, amino acids and glucose. The mTOR signalling pathway plays an important regulatory role in promoting substance metabolism, participating in apoptosis and autophagy [14]. ZNRF2 can interact with mTOR to participate in the regulation of mTOR complex 1 (mTORC1) signal transduction [15].

This study analysed the expression profile of HAGLROS in various tumours and found that the expression difference of HAGLROS between ovarian cancer and normal ovarian tissue was the most significant. The relationship between HAGLROS and clinical features of patients with ovarian cancer was studied. In addition, we explored the mechanism of action of HAGLROS, analysed the target genes of miR-100 that compete with HAGLROS for binding, and performed functional analysis of the target genes. In conclusion, our research indicates that HAGLROS plays an important role in the development of ovarian cancer and provides a potential target for the diagnosis and treatment of ovarian cancer.

Materials and methods

Using online databases to query the expression of HAGLROS in ovarian cancer

The Gene Expression Profiling Interactive Analysis (GEPIA) database (https://gepia.cancerpku.cn/) provides genetic sequencing data for tumours and normal samples based on the Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) databases. We extracted the HAGLROS expression profiles of various types of human cancers and normal tissues in the database and verified the differential expression of HAGLROS in ovarian cancer. The Kaplan–Meier Plotter database (https://kmplot.com/analysis/) contains prognostic information for 655 ovarian cancer patients. Patients were divided into two groups according to the optimal cutoff value of HAGLROS expression level to analyse the relationship between HAGLROS and the prognosis of patients with ovarian cancer.

Human samples

From January 2018 to January 2019, 41 ovarian cancer samples and 40 normal ovarian tissue samples were collected from the Department of Obstetrics and Gynecology in People's Hospital of Zhengzhou University. Cancer samples were collected from ovarian cancer patients undergoing surgery, and healthy specimens were collected from patients undergoing adnexectomy due to myoma or uterine prolapse. Specimens were frozen in liquid nitrogen within 5 min after excision and transferred to a − 80 °C freezer. Patients ranged in age from 27 to 76 years with an average age of 54 years. All patients did not have any other tumours and did not receive any preoperative treatment. All experimental protocols were approved by the Ethics Committee of the People's Hospital of Zhengzhou University.

Quantitative reverse-transcription PCR

Total RNA was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). cDNA was synthesised using a Thermo Scientific Revert Aid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Waltham, MA, USA). Quantitative real-time PCR amplification of cDNA was performed using PowerUp^{TM} SYBR^{TM} Green Master Mix (Applied Biosystems, Foster City, CA, USA). The expression of HAGLROS relative to β-actin was determined using the $2^{-\Delta\Delta CT}$ method. The primers used were HAGLROS (forward) 5′-TGTCACCCTTAAATACCGCTCT-3′ and HAGLROS (reverse) 5′-CTTCCTCCCACACAAATACTCC-3′, and β-actin (forward) 5′-CCTGTACGCCAACACAGTGC-3′ and β-actin (reverse) 5′-ATACTCCTGCTTGCTGATCC-3'.

GEO, ArrayExpress, TCGA databases and data acquisition

MiRNA microarrays associated with ovarian cancer were obtained from the National Center of Biotechnology Information (NCBI) GEO (https://www.ncbi.nlm.nih.gov/geo/) and ArrayExpress (https://www.ebi.ac.uk/arrayexpress) databases. Searched keywords were as follows: ("ovarian neoplasms" OR ovarian cancer) AND ("micrornas" OR miRNA) AND "Homo sapiens". The inclusion criteria included the following: (1) the study sample was derived from human tissue, cell lines, exosomes or body fluids. (2) The expression level of miR-100 in ovarian cancer and normal ovarian samples was detected. (3) Each group included more than three subjects. The search deadline was March 1, 2019. RNA-Seq and miRNA-Seq data for ovarian cancer patients were calculated from the IlluminaHiSeq RNASeq and miRNASeq platforms by the TCGA database (https://tcga-data.nci.nih.gov/tcga/). The level of expression of the RNA was normalised for further analysis by the Deseq package of the R language.

Meta-analysis

Meta-analysis of miRNA microarrays was performed using Stata 14.0 (Stata Corp., College Station, TX, USA). The

heterogeneity between studies was assessed by the Chi square and I^2 tests. When the heterogeneity was small ($I^2 \leq 50\%$ and $P > 0.05$), the fixed effects model was used to calculate the point estimate and interval estimate of the effect combination value. When the heterogeneity was significant ($I^2 > 50\%$ or $P \leq 0.05$), the random effect model was used. A funnel plot was used to detect publication bias.

Target gene prediction

Online forecasting software TargetScan7.2 [16] (https://www.targetscan.org/vert_72/), miRDB [17] (https://mirdb.org/), miRWalk3.0 [18] (https://mirwalk.umm.uni-heidelberg.de/), miRTarBase [19] (https://mirtarbase.mbc.nctu.edu.tw/php/search.php) and miRmap [20] (https://mirmap.ezlab.org/) were used to predict the target genes of miR-100.

Functional analysis of target genes

To further explore the potential functions of target genes, Metascape [21] (https://www.metascape.org/) was used for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. The PPI network was constructed using the STRING database 10.5. The interaction pairs in the protein–protein interaction (PPI) network scored greater than 0.4 and the hub genes were obtained from the network.

Statistical analysis

Student's *t* test was used to evaluate the difference in HAGLROS expression between ovarian cancer and normal ovarian tissue and the relationship between HAGLROS expression and the clinicopathological parameters of ovarian cancer patients. A receiver-operating characteristic (ROC) curve was used to assess the clinical diagnostic value of HAGLROS. Pearson correlation analysis was used to determine the correlation between HAGLROS and miR-100. A P value < 0.05 was considered statistically significant. All statistical analyses were performed by SPSS 22.0 (IBM, Chicago, IL, USA) and GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA).

Results

The expression level and clinical significance of HAGLROS in ovarian cancer

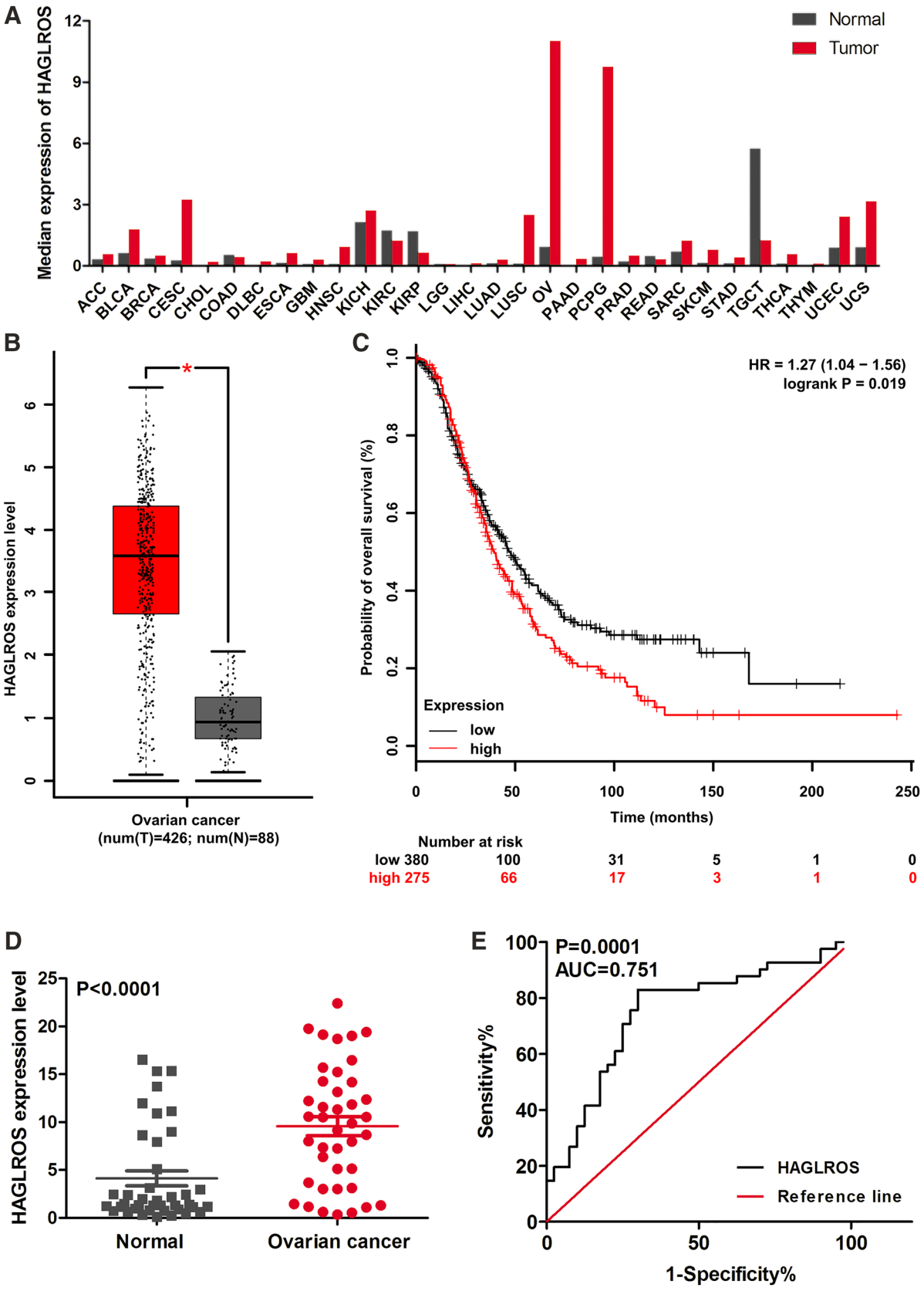
The GEPIA database results showed that HAGLROS was differentially expressed between various tumours and normal tissues, and the expression difference in ovarian cancer was the most significant (Fig. 1a). A total of 426 ovarian cancer tissues and 88 normal ovarian tissue samples were included in the study. The results showed that HAGLROS was significantly upregulated in ovarian cancer ($P < 0.05$, Fig. 1b). Kaplan–Meier Plotter database results showed that the overall survival (OS) of patients with high expression of HAGLROS was significantly reduced ($P = 0.019$, Fig. 1c). To further validate the expression and clinical significance of HAGLROS in ovarian cancer, we collected 41 ovarian cancer samples and 40 normal ovarian tissue samples. qRT-PCR results showed that HAGLROS was significantly upregulated in ovarian cancer ($P < 0.0001$, Fig. 1d). The clinicopathological features and HAGLROS expression levels of patients with ovarian cancer are shown in Table 1. Clinical analysis showed that the expression level of HAGLROS was not significantly different among patients of different ages and pathological types ($P > 0.05$). However, in patients with stage III/IV ($P = 0.033$) and patients with tumours greater than or equal to 10 cm ($P = 0.032$), the expression of HAGLROS was significantly increased. A ROC curve was used to evaluate the diagnostic value of HAGLROS in ovarian cancer with an area under the curve (AUC) of 0.751 (95% CI 0.642–0.860) ($P = 0.0001$, Fig. 1e).

MiR-100 was negatively correlated with HAGLROS and significantly downregulated in ovarian cancer

HAGLROS can competitively bind with miR-100 in gastric cancer and colorectal cancer. Therefore, we included datasets from the GEO and ArrayExpress databases to explore the expression of miR-100 in ovarian cancer. The characteristics of the selected datasets are shown in Table 2, which included a total of 270 ovarian cancer samples and 73 healthy control samples. Meta-analysis results showed that the heterogeneity between the datasets was small ($P = 0.753$, $I^2 = 0.0\%$), and the pooled standard mean difference (SMD) calculated by the fixed effects model was -0.37 (95% CI -0.67 to -0.06, $P = 0.019$) (Fig. 2a). There were no significant publication biases between the datasets (Fig. 2b). The above results indicate that miR-100 is significantly downregulated in ovarian cancer. To further analyse the correlation between miR-100 and HAGLROS, we extracted the expression levels of miR-100 and HAGLROS in 371 ovarian cancer samples from the TCGA database. Correlation analysis showed that miR-100 was negatively correlated with HAGLROS in ovarian cancer ($r = 0.167$, $P = 0.001$).

Target gene prediction and functional analysis of miR-100

The online prediction software TargetScan, miRDB, miRWalk, miRTarBase and miRmap predicted 25, 47, 468, 249 and 804 mRNAs targeted by miR-100, respectively. At least


A
Median expression of HAGLROS
Normal
Tumor
ACC BLCA BRCA CESC CHOL COAD DLBC ESCA GBM HNSC KICH KIRC KIRP LGG LIHC LUAD LUSC OV PAAD PCPG PRAD READ SARC SKCM STAD TGCT THCA THYM UCEC UCS
B
HAGLROS expression level
Ovarian cancer
(num(T)=426; num(N)=88)
C
HR = 1.27 (1.04 − 1.56)
logrank P = 0.019
Probability of overall survival (%)
Expression
low
high
Time (months)
Number at risk
low 380 100 31 5 1 0
high 275 66 17 3 1 0
D
HAGLROS expression level
P<0.0001
Normal
Ovarian cancer
E
P=0.0001
AUC=0.751
Sensitivity%
1-Specificity%
HAGLROS
Reference line

◂**Fig. 1** The expression and clinical significance of HAGLROS in ovarian cancer. **a** Expression profile of HAGLROS in various tumours and normal tissues based on the GEPIA database. **b** Differential expression of HAGLROS between ovarian cancer and normal ovarian samples based on the GEPIA database. $*P<0.05$. **c** High expression of HAGLROS is associated with shorter survival time of ovarian cancer patients based on the Kaplan–Meier plotter. **d** The expression of HAGLROS is significantly increased in ovarian cancer based on qRT-PCR. **e** ROC curve of HAGLROS. HAGLROS has a certain diagnostic value in ovarian cancer

3 algorithms repeatedly predicted 31 target genes, which are shown in Table 3. GO analysis showed that the target genes were mainly involved in the regulation of cellular catabolic process, the proteoglycan biosynthetic process and the positive regulation of proteasomal ubiquitin-dependent protein catabolic process. KEGG analysis showed that the target genes were mainly enriched in the MAPK signalling pathway and signalling pathways regulating pluripotency of stem cells. The results of the Reactom Gene Set showed that the target genes were mainly involved in the signal transduction of the adaptive immune system and nuclear receptors (Table 4, Fig. 3). In addition, the PPI network revealed the interaction between proteins. Among them, MTOR and ZNRF2 are hub genes (Fig. 4).

Table 1 Relationship between HAGLROS expression and clinicopathological parameters in patients with ovarian cancer

Clinicopathological features	Cases	Expression of HAGLROS	*P*
Age (years old)			
≤ 50	15	10.12 ± 7.01	0.680
> 50	26	9.26 ± 5.97	
Histological type			
Low-grade serous carcinoma and others	10	7.62 ± 3.90	0.149
High-grade serous carcinoma	31	10.20 ± 6.82	
Clinical stage			
Stage I/II	6	4.55 ± 5.19	0.033
Stage III/IV	35	10.43 ± 6.12	
Tumour size (cm)			
< 10	21	7.54 ± 6.61	0.032
≥ 10	20	11.71 ± 5.30	

Discussion

An increasing number of studies have shown that lncRNA plays an important role in the development of cancer [22]. The lncRNA PCA3, which is specifically upregulated in prostate cancer, has been approved by the Food and Drug Administration (FDA) for the diagnosis of prostate cancer [23]. LncRNA HAGLROS is in involved in the development of gastric cancer and colorectal cancer [12, 13], and there are no reports of the role of HAGLROS in ovarian cancer. In this study, we first found that the differential expression of HAGLROS between ovarian cancer and normal ovarian tissue was the most significant, and HAGLROS expression was significantly elevated in advanced patients and patients with large tumour volumes. In addition, high expression of HAGLROS has diagnostic value in ovarian cancer and is associated with poor prognosis. Therefore, HAGLROS can be used as a potential biomarker for early diagnosis and prognosis assessment of ovarian cancer.

The mode of action of lncRNA in cancer was highlighted by the regulation of gene expression by competitive binding to miRNAs. This mode of action plays an important role in the development of ovarian cancer [24]. Chen et al. showed that HAGLROS was mainly located in the cytoplasm and acts as a molecular sponge of miR-100 in gastric cancer and colorectal cancer [12, 13]. To further investigate the mechanism of action of HAGLROS in

Table 2 Characteristics of GEO and ArrayExpress datasets included in the meta-analysis

Series	Country	Year	Platform	Sample source	OC samples	Normal samples
GSE31568	Germany	2011	GPL9040	Peripheral blood	15	19
GSE61741	Germany	2014	GPL9040	Peripheral blood	24	26
GSE48485	Germany	2014	GPL14943	Peripheral blood	5	5
GSE58517	China	2015	GPL18402	Urinary	5	5
GSE76449	USA	2016	GPL19117	Cell	12	2
GSE76449	USA	2016	GPL19117	Exosomes	12	2
GSE103708	Japan	2017	GPL18402	Cell	13	3
GSE103708	Japan	2017	GPL18402	Exosomes	13	3
E-MTAB-1067	Italy	2014	NR	Tissue	171	8

OC ovarian cancer, *NR* not reported

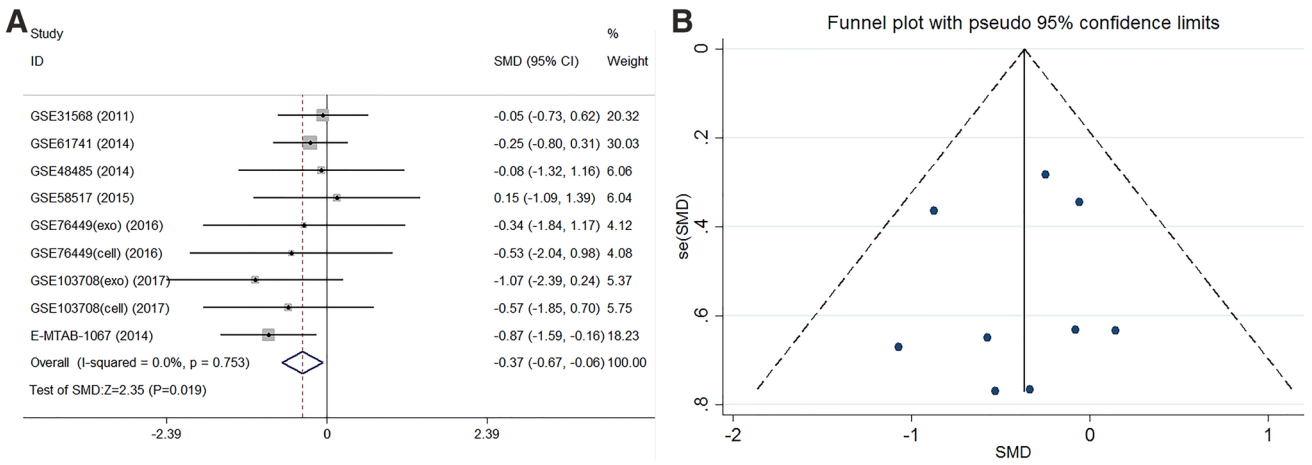


Fig. 2 Meta-analysis of miR-100 expression in ovarian cancer. **a** Forest plot of datasets evaluating HAGLROS expression between ovarian cancer and normal ovarian samples. **b** Funnel plot of datasets detecting publication bias in our study

Table 3 Predicted targets of miR-100 by various online prediction algorithms

Algorithms	Jointly predicted target genes	Number
TargetScan, miRDB, miRTarBase, miRmap	*MTOR, ZNRF2, THAP2, HS3ST2, KBTBD8, SMARCA5*	6
miRDB, miRTarBase, miRmap, miRWalk	*RNF144B*	1
TargetScan, miRDB, miRmap, miRWalk	*TRIB2*	1
miRDB, miRTarBase, miRmap	*HOXA1, FGFR3, TRIB1, RAP1B, CTDSPL*	5
TargetScan, miRDB, miRmap	*EPDR1, ZZEF1, FZD8, TAOK1*	4
miRDB, miRWalk, miRmap	*HES7, HS3ST3B1, MTMR3, AP1AR*	4
TargetScan, miRmap, miRTarBase	*ZBTB7A, FKBP5, BMPR2, PPP1CB*	4
TargetScan, miRWalk, miRmap	*CLDN11, RASGRP3, CYP26B1, TMEM135*	4
TargetScan, miRDB, miRWalk	*AGO2*	1
miRTarBase, miRmap, miRWalk	*IFIT3*	1

Table 4 Functional enrichment analysis of target genes

ID	Category	Description	Count	Log P
GO:0031329	BP	Regulation of cellular catabolic process	8	−5.28
GO:0030166	BP	Proteoglycan biosynthetic process	3	−4.06
GO:0032436	BP	Positive regulation of proteasomal ubiquitin-dependent protein catabolic process	3	−3.79
GO:0,048,705	BP	Skeletal system morphogenesis	4	−3.64
Hsa04010	KEGG	MAPK signaling pathway	4	−3.52
R-HSA-1280218	Reactom gene sets	Adaptive immune system	6	−3.45
GO:0031667	BP	Response to nutrient levels	5	−3.44
GO:0043408	BP	Regulation of MAPK cascade	6	−3.43
GO:0002521	BP	Leukocyte differentiation	5	−3.36
Hsa04550	KEGG	Signaling pathways regulating pluripotency of stem cells	3	−3.13
GO:0071695	BP	Anatomical structure maturation	3	−2.94
R-HSA-9006931	Reactom gene sets	Signaling by nuclear receptors	3	−2.68
GO:00048511	BP	Rhythmic process	3	−2.26

GO gene ontology, *BP* biological process, *KEGG* Kyoto Encyclopedia of Genes and Genomes

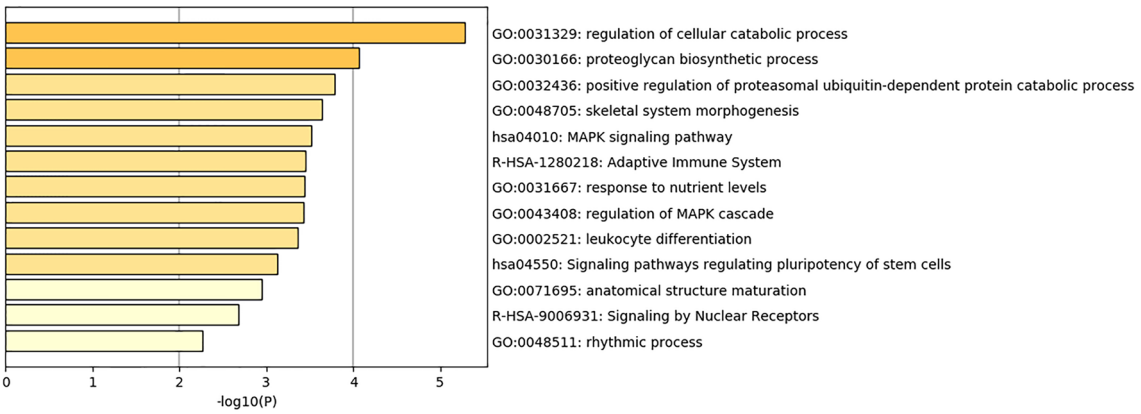


Fig. 3 Top 13 representative enrichment terms for functional enrichment analysis of target genes

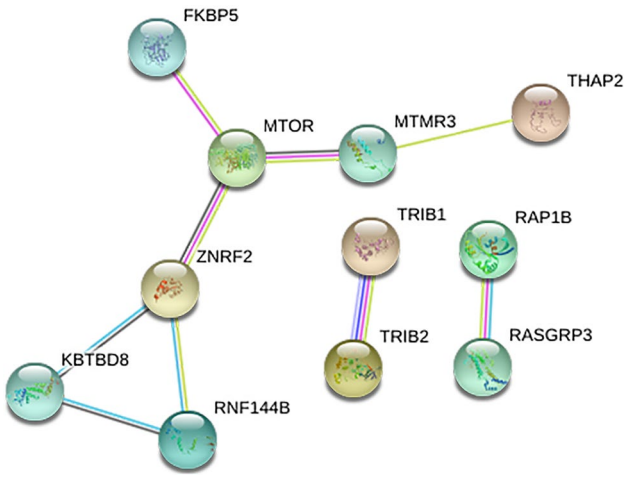


Fig. 4 The PPI network of the target genes. Connections between nodes represent the relationship between gene-encoded proteins. A bold line indicates a higher confidence level

ovarian cancer, we explored the expression of miR-100 in ovarian cancer. MiR-100 was significantly downregulated in ovarian cancer and negatively correlated with HAGLROS. We speculate that it is consistent with gastric cancer and colorectal cancer. In ovarian cancer, HAGLROS can competitively combine with miR-100 to regulate the expression of target genes. Bioinformatics analysis showed that the target genes are mainly involved in the regulation of cellular catabolic processes, proteoglycan biosynthetic processes and the positive regulation of proteasomal ubiquitin-dependent protein catabolic processes. mTOR and ZNRF2 are hub target genes. mTOR is an evolutionarily conserved serine/threonine kinase that binds to other proteins to form mTORC1 and mTOR complex 2 (mTORC2), in which the mTORC1 signalling pathway is an important pathway involved in the regulation of many cellular functions [25]. Abnormal mTORC1 signalling is present in ovarian cancer [26]. ZNRF2 is a membrane-associated E3 ubiquitin ligase that promotes amino acid-stimulated mTORC1 translocation to lysosomes to activate mTOR signalling and thereby promotes substance metabolism by interacting with mTOR on the membrane [15].

In conclusion, our study indicates that the lncRNA HAGLROS is significantly upregulated in ovarian cancer and is a potential biomarker for early diagnosis and assessment of prognosis in ovarian cancer. HAGLROS can competitively bind with miR-100 to promote the expression of mTOR and ZNRF2, thereby activating the signal transduction of the mTOR pathway to promote the development of ovarian cancer. This study reveals the clinical significance and mechanism of HAGLROS in ovarian cancer and provides a new target for the research and treatment of ovarian cancer in the future.

Author contributions All the authors contributed to the study conception and design. MY performed the experiments and ZZ collected and analysed the data. YW and YZ contributed to the quality control of data and algorithms. The first draft of the manuscript was written by MY and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethics Committee of the People's Hospital of Zhengzhou University.

Informed consent Informed consent was obtained from all individual participants included in the study.

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