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Research article

LINC00870 promotes imatinib resistance in gastrointestinal stromal tumor via inhibiting PIGR glycosylation modifications

Yuan Li [a,1], Zhiqiang Dai [b,c,1], Zewei Cheng [d,1], Junyi He [b,c], Yirui Yin [b,e], Xinyou Liu [b,e], Jiwei Zhang [d], Guohua Hu [b,c,e], Yueda Chen [b,e,**], Xuefei Wang [b,c,e,f,g,***], Yebo Shao [b,c,e,*]

[a] Central Laboratory, Zhongshan Hospital (Xiamen), Fudan University, Xiamen, 361015, China
[b] Department of General Surgery, Zhongshan Hospital (Xiamen), Fudan University, Xiamen, 361015, China
[c] Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[d] Shanghai Key Laboratory of Compound Chinese Medicines, The MOE Key Laboratory for Standardization of Chinese Medicines, Institute of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China
[e] Xiamen Clinical Research Center for Cancer Therapy, Xiamen, 361015, China
[f] Department of Gastrointestinal Surgery, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[g] Clinical Research Center for Precision medicine of abdominal tumor of Fujian Province, Xiamen, 361015, China

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ABSTRACT

Imatinib is the first-line targeted therapy for gastrointestinal stromal tumor (GIST), but resistance frequently occurs during treatment, limiting its efficacy and clinical application. We performed high-throughput sequencing of tissue specimens from imatinib-resistant GIST patients, and identified significantly high expression of polymeric immunoglobulin receptor (PIGR) in imatinib-resistant cell lines. Further investigation revealed that PIGR binds specifically to LINC00870. The findings from *in vitro* cell functional experiments provide evidence of a strong association between LINC00870 and PIGR and the processes of proliferation and metastasis in GIST. Overexpression of LINC00870 in GIST significantly inhibits the glycosylation modification and secretion of the extracellular region of PIGR, leading to immune dysregulation. The inhibition of PIGR or LINC00870 effectively surmounts imatinib resistance. Our study identified PIGR as a critical molecule in regulating GIST imatinib resistance and elucidated the mechanism by which PIGR promotes imatinib resistance through LINC00870 inhibition of PIGR glycosylation modifications. These findings provide a new theoretical basis for blocking drug resistance and improving prognosis in GIST.

1. Introduction

Gastrointestinal stromal tumor (GIST) is a malignant gastrointestinal tract tumor originating from mesenchymal cells, often in the stomach and small intestine [1]. Unfortunately, GIST is typically resistant to conventional chemotherapy and radiotherapy, leading to

* Corresponding author. Department of General Surgery, Zhongshan Hospital (Xiamen), Fudan University, Xiamen, 361015, China.
** Corresponding author. Department of General Surgery, Zhongshan Hospital (Xiamen), Fudan University, Xiamen, 361015, China.
*** Corresponding author. Department of General Surgery, Zhongshan Hospital (Xiamen), Fudan University, Xiamen, 361015, China.
E-mail addresses: chen.yueda@zsxmhospital.com (Y. Chen), wang.xuefei@zs-hospital.sh.cn (X. Wang), shao.yebo@zsxmhospital.com (Y. Shao).
[1] Yuan Li, Zhiqiang Dai and Zewei Cheng contributed equally to our study.

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a 5-year survival rate lower than 35 %, as well as a high risk of recurrence and metastasis [2,3]. Imatinib, a molecularly targeted drug that effectively inhibits all types of ABL tyrosine kinase activity, has achieved a breakthrough in GIST treatment, significantly improving patient survival [4]. However, the development of drug resistance during imatinib therapy is a major cause of treatment failure and relapse. Thus, it is crucial to investigate the molecular mechanisms underlying imatinib resistance in GIST patients for better treatment and prognosis.

The development of drug resistance in tumor patients arises from intricate interactions among genetic and environmental factors. Several studies have confirmed a strong association between the development of drug resistance and immune dysregulation in oncology patients [5]. PIGR exhibits expression in diverse epithelial cell types and can be induced by inflammatory factors in response to viral or bacterial infections, thereby enabling PIGR to function as an intermediary between innate and adaptive immunity [6–8]. Recent investigations have further revealed an upregulation of PIGR expression during the malignant transformation of epithelial cells, suggesting a plausible association between tumor drug resistance and immune dysregulation [6–8]. Nevertheless, the precise ramifications of aberrant PIGR expression on the surface of tumor cells in GIST patients remain elusive, warranting further elucidation.

In recent years, research on long-stranded non-coding RNA (lncRNA) has advanced significantly, shedding light on their crucial regulatory roles in tumorigenesis and progression. These roles encompass various aspects, including: (1) participation in epigenetic regulation as molecular scaffolds or decoy molecules, broadly influencing DNA methylation and thereby contributing to tumorigenesis [9]; (2) involvement in gene expression regulation by serving as enhancer RNAs that activate or directly pair with DNA in the promoter region to modulate transcription factor activity and influence transcription initiation [10]; (3) engagement in post-transcriptional regulation processes [11]; (4) influence on diverse biological behaviors, such as tumorigenesis, development, invasion, and metastasis [12–14]. Recent investigations suggest that targeting lncRNA may hold promise as a strategy for anti-cancer therapy and has the potential to modulate the responsiveness of tumor patients to existing anti-cancer drugs [15–18]. However, the precise role of lncRNA in GIST patients, particularly in the context of drug resistance, still needs to be more adequately understood.

In this study, we identify PIGR as a critical molecule of resistance to imatinib in GIST patients. Additionally, we have investigated the biological functions of both PIGR and LINC00870 in GIST. Our study elucidates the underlying mechanism through which PIGR mediates imatinib resistance in GIST patients. These findings significantly contribute to our understanding of the specific mechanisms of imatinib resistance in GIST patients, and provide a novel theoretical foundation for developing innovative treatment regimens involving targeted therapy, immunotherapy, and molecular therapy.

2. Materials and methods

2.1. Clinical sample collection

Imatinib treatment-resistant GIST patient samples (cancer and paracancerous tissues) and GIST patient samples (cancer and paracancerous tissues) were obtained from Fudan University Zhongshan Hospital, Shanghai, China (Table S1). This study was approved by the Clinical Research Ethics Committee of Fudan University Zhongshan Hospital.

2.2. Animal and cell lines

Nude mice and NSG mice, female, specific-pathogen-free (SPF) grade, aged 6–8 weeks, weighing 20±2g, were procured from the Experimental Animal Center of Shanghai Cancer Institute (Shanghai, China). The GIST cell lines GIST-T1 and GIST-882 were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA).

2.3. Animal model construction

Logarithmic growth phase cells were harvested and adjusted to a concentration of 1×106/ml in serum-free culture medium. Subsequently, each nude mouse was intravenously inoculated with 0.2 ml of the cell suspension. Regular observation of the mice was conducted, and approximately 8–12 weeks post-inoculation, organs were excised, fixed, embedded, and subjected to hematoxylin and eosin (HE) staining. Tumor liver and lung metastases were then assessed under a microscope, and the number of metastatic lesions was quantified.

For the subcutaneous tumor model, logarithmic phase tumor cells GIST-882, GIST-882_PIGR_KO, or GIST-882_LINC0087_KO were collected and adjusted to a concentration of 1×10^7/ml. Each NSG mouse was subcutaneously inoculated with 0.2 ml of the cell suspension. Tumor measurements were conducted every three days, and tumor volume was calculated using formula $V = (L \times W^2)/2$, where V represents volume, L denotes length, and W signifies width.

2.4. RT-qPCR

After total RNA was extracted from tumor tissues and cells, reverse transcription and relative quantitative PCR were performed following protocol from Vazyme. Primers were obtained from Primerbank. The nucleus and cytoplasmic RNA were isolated by nuclear-cytoplasmic separation experiment using Paris Kit (Thermo) in GIST cell lines.

2.5. Western blotting

Proteins were isolated from cells and tissues using RIPA lysate (Beyotime) and quantified by a BCA working kit (Biosharp). The protein was separated by SDS-PAGE gel and electro-transferred. Seal each membrane for 1.5h with 5 % skim milk. After being combined and incubated with the specific antibody, the Immune response band was detected by a secondary antibody and visualized using ECL luminescent solution (Servicebio).

2.6. RNA-fluorescence in situ hybridization and RNA scope

Cells were fixed in 4 % PFA for 15min and permeabilized with 0.5 % TritonX-100 for 15min at 4 °C. Digoxigenin-labeled probes or control probes were mixed and cells were incubated at 55 °C for 4h. The cells were washed 3 times and the specific antibodies were incubated. DAPI was used to counterstain nuclear. Images were observed using a microscope.

2.7. Drug-resistant stable strain establishment

The GIST-882 cell line was selected for drug resistance screening, and the concentrations were set to five experimental groups of DMSO (negative control), 5 μl mol, 10 μl mol, 20 μl mol, and 40 μl mol. When the cells grew to 70%–80 % confluence, the tumor cells in the rhythmic growth phase were placed in a medium containing different concentration of drugs, washed twice with PBS, replaced with a drug-free medium, and cultured routinely until the cells resumed growth. After the cells grew stably and entered the logarithmic growth phase, they were passaged twice. Then the screened enclosures were continued to be cultured in the medium with different concentrations of drugs and the time of action was changed accordingly. After a total of 10 action times (1h, 2h, 3h, 6h, 12h, 24h, 36h, 48h, 60h, 72h) and about 6 months of culture, the cells were able to grow continuously and stably in a specific concentration of drug medium and pass-through generations. Then the cells' biological characteristics and drug resistance indexes were detected after 1 month of discontinuation of drug culture. SDHB was used as an indicator of drug resistance success.

2.8. Construction of knockdown and overexpression vectors and CRISPR-Cas9/dead Cas9 stable strains

Design sgRNAs against the promoter region or first exon start and last exon termination of the target genes (PIGR and LINC00870). The sgRNA sequences with high scores were selected according to the online website (http://crispr.mit.edu/). The sgRNA forward and reverse primers were annealed to form stable double-stranded DNA and ligated to the enzymatically cleaved CRISPR-Cas9/dead Cas9 system vector and verified by sequencing. Transfect 293T cells using Lipofectamine 2000, and replace the medium with fresh medium after 6h. Check the transfection efficiency using the fluorescence microscope after 48h of transfection, and collect the supernatant after 72h. The GIST-882 or GIST-T1 cells were added with the corresponding volume of polybrene 0.5h before the addition of virus infection. The cells were replaced after 12h of infection, after 48h the infection efficiency was observed under a fluorescence microscope.

2.9. Cell migration/invasion assays

The bottom of the Trans-well chambers (BD) was evenly spread with substrate gel and placed in an incubator at 37 °C for 0.5h to allow solidification. After cell counting, the cells were mixed with serum-free DMEM and added directly to the chambers, and the appropriate volume of complete medium was added outside the chambers. The cells were fixed with methanol, stained crystal violet, and photographed under a microscope. The average of five random fields of view per chamber was taken to compare each group's migration and invasion ability. In this experiment, 3–5 replicate wells were set up to test various cells.

2.10. CCK-8 viability assays

The viability of cells was measured *in vitro* using the CCK-8 kit. 2×10^3 cells per well were inoculated in a 96-well plate and incubated for 48h. The 10 % CCK-8 solution was added to each well and incubated for approximately 2h. The absorbance of each well was measured at 450 nm.

2.11. Clone formation experiments

For cell digestion and counting, the suspension was added to a six-well plate for incubation with 1×10^3 cells per well. Clones were observed after 9–14 days. Wash twice with PBS, add 1 ml of methanol to each well for fixation, and leave for 10min at room temperature. Stain with 0.1 mg/ml crystal violet and leave for 10min at room temperature. Dry and count at room temperature.

2.12. RIP-seq experiments

Cell membrane components were isolated from GIST-882 cells of imatinib-resistant strain and tissues of GIST-resistant patients (Beyotime Membrane Extraction Kit and Magna RIP™ RNA-Binding Protein Immunoprecipitation Kit). Total RNA and cell membrane RNA were extracted with TRIZOL reagent, and PIGR endogenous antibody for RIP-Seq experiments. Validation was performed using

RIP-RT-PCR.

2.13. 3′RACE, 5′RACE and northern-blot assays

3′ RACE and 5′ RACE experiments were performed using kits from SMARTer RACE cDNA Amplification Kit (Clontech). Northern-blot assays were performed using the Northern Max® Kit from Thermo Fisher Scientific.

2.14. Protein interaction prediction and protein-coding ability prediction

The online website STRING (https://cn.string-db.org/) was used to predict proteins with potential interactions with PIGR. Based on the Coding Potential Calculator (CPC, http://cpc.cbi.pku.edu.cn/), the Coding-Potential Assessment Tool (CPAT, http://cpc.cbi.pku.edu.cn/), and Phylogenetic Codon Substitution Frequencies (PhyloCSF score), the LINC00870 sequence was analyzed for protein-coding ability.

2.15. Data collection, RNA-seq data processing, and analysis

The original data of Sarcoma second-generation sequencing were collected from the TCGA database. All statistical analyses of bioinformatics were performed with Rstudio software (version 4.0.2; http://www.rstudio.com/products/rstudio). The Limma package

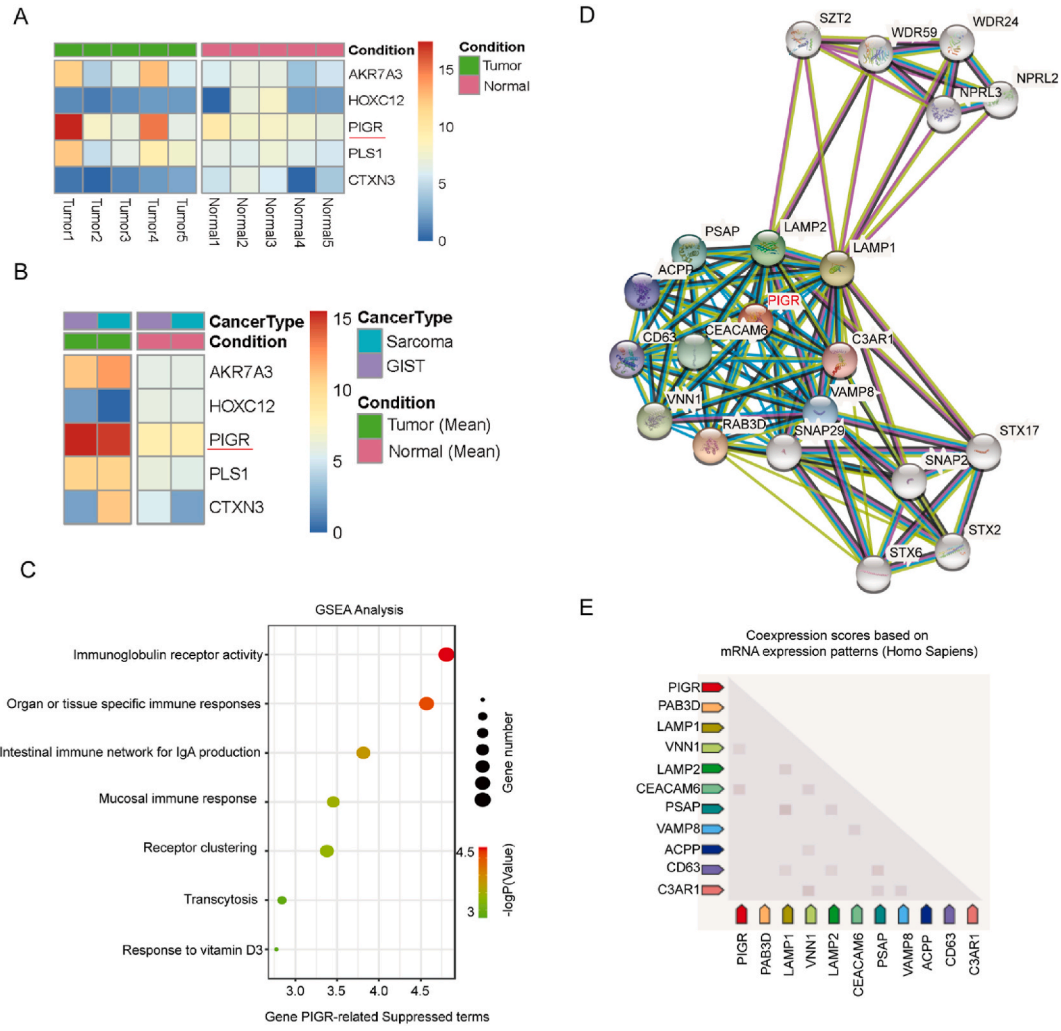

Fig. 1. PIGR as a candidate gene for the study.
(A–B) Hot-map showed the expression profiles of apparently differential genes. **(C)** The analysis of the signaling pathways that regulate PIGR using GSEA. **(D–E)** The online website STRING was used to predict proteins with potential interactions with PIGR and these proteins were analyzed for relevance at the mRNA level using bioinformatics.

was used to analyze the differences in gene expression between tumor samples and healthy samples, and a volcano map and heat map were drawn. R package clusterProfiler (https://guangchuangyu.github.io/software/clusterProfiler) was used to process the GSEA analysis. The correlation analysis and visualization of the gene expression result were processed using ggplot2 in R software.

2.16. Statistical analyses

Statistical analyses were performed using GraphPad Prism 9 (GraphPad, San Diego, California). Statistical analysis was done using the paired Student's t-test, the Pearson correlation, or the Log-rank survival analysis. The p-values less than 0.05 were considered statistically different.

3. Results

3.1. PIGR is significantly correlated with imatinib resistance in GIST

In this study, we performed RNA sequencing analysis on five GIST patients (cancer and paracancerous tissues) who were resistant to imatinib therapy. We combined these results with RNA sequencing data obtained from 263 TCGA-Sarcoma tumor tissues and two normal tissues. Using filtering conditions of $\log_2$Fold change (Tumor/Normal) > 4 and Pearson correlation coefficient ($P < 0.001$), we identified three genes (PIGR, AKR7A3, PLS1) that were highly expressed in GIST patients who were resistant to imatinib therapy (Fig. S1 A-C).

The differential gene expression profiles analysis between the two data sets indicated that the PIGR gene was significantly highly expressed in GIST imatinib-resistant patients (Fig. 1A and B). Further analysis of the signaling pathways closely regulated by PIGR using Gene Set Enrichment Analysis (GSEA) showed that PIGR played an inhibitory role in multiple immune activation pathways, such as immune receptor activation and organ- or tissue-specific immune responses (Fig. 1C). We utilized the STRING online prediction tool to identify potential molecular targets of PIGR and examined their correlation at the mRNA level. Our analysis revealed a significant association between PIGR and VNN1 as well as CEACAM6 (Fig. 1D and E). Vanin-1 (VNN1) has pantetheinase activity and plays a crucial role in tumorigenesis and immune regulation [19–23]. CEACAM6, a carcinoembryonic antigen immunoglobulin family member, is a cell surface adhesion factor that plays a vital role in tumorigenesis, proliferation and metastasis [24]. Based on the results obtained in this study, it is reasonable to infer that PIGR may have a pivotal role in regulating immune responses and promoting tumor progression.

3.2. PIGR expression levels were significantly elevated in GIST and correlated with prognosis

In light of the crucial role of PIGR in GIST imatinib resistance, we investigated the expression levels of PIGR in imatinib non-resistant cancer samples and their corresponding paracancerous controls, as well as in imatinib-resistant cancer samples and their paracancerous controls. The results revealed significantly higher mRNA levels of PIGR in GIST tumor samples compared to their paracancerous controls (Fig. 2A, $P < 0.001$). Moreover, the mRNA levels of PIGR were markedly higher in imatinib-resistant GIST samples than in non-resistant samples (Fig. 2A, $P < 0.001$). We further categorized the GIST patients into two groups based on PIGR expression levels and examined the correlation between PIGR expression and overall survival time. The data showed that patients with high PIGR expression levels had a poorer prognosis (Fig. 2B). Taken together, these results suggest that PIGR is significantly

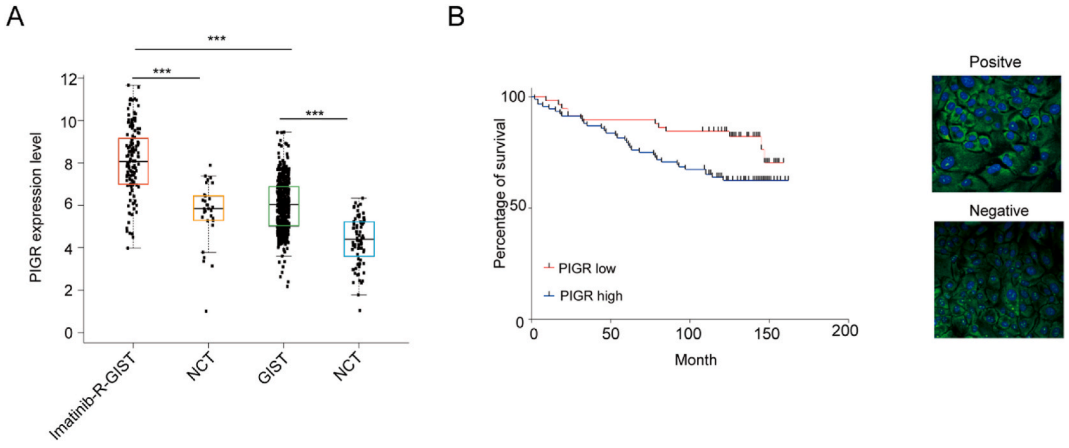

Fig. 2. Expression and prognosis of PIGR in GIST tissues and imatinib-resistant tissues.
(A) The mRNA expression of PIGR in different tissues of GIST. **(B)** Using the log-rank test, the figure on the left shows the survival analysis of PIGR expression differences in GIST patients. The figure on the right shows GIST patients divided into positive and negative groups of PIGR expression by RNA-FISH. ***$P < 0.001$.

upregulated in imatinib-resistant GIST patients, and higher PIGR expression levels are associated with poorer prognosis.

3.3. PIGR functions as an oncogene in GIST

PIGR plays a crucial role in bridging innate and adaptive immunity, suggesting a potential link between imatinib resistance and immune dysregulation [6–8]. To further investigate the specific function of PIGR in GIST, we designed sgRNAs against PIGR sequences and performed endogenous interference using CRISPRdCas9 in GIST-T1 and GIST-882 cell lines, followed by relevant cell function experiments. Our results showed that interfering with PIGR significantly suppressed cell invasion capability, while overexpression significantly promoted it *in vitro* (Fig. 3A and B). Furthermore, in vivo experiments showed that overexpression of PIGR significantly promoted lung colonization and liver metastasis of GIST cells (Fig. 3C and D). These findings suggest that PIGR acts as an oncogene that promotes the malignant phenotype of GIST.

3.4. Specific binding of LINC00870 to PIGR

To facilitate subsequent investigations, we established an imatinib-resistant cell line, GIST-882 (IR-GIST-882), selected based on the SDHB marker as imatinib-resistant [25]. Our results confirmed the successful construction of the stable resistant cell line (Figs. S2A and B). To investigate the molecular mechanisms underlying the role of PIGR in drug-resistant GIST, we extracted RNA from cell membrane fractions of tissues from drug-resistant patients, as well as from cells of drug-resistant strains, for RIP-seq analysis. This analysis aimed to identify RNA molecules specifically bound to PIGR (Fig. 4A). Our study revealed a specific interaction between PIGR and LINC00870 (Fig. 4B), indicating that PIGR may mediate imatinib resistance in GIST through this interaction.

3.5. LINC00870 promotes GIST imatinib resistance via inhibiting PIGR glycosylation modifications

To clarify the transcript sequence information of LINC00870 in GIST cells, we conducted RACE assay and Northern-blot assay, which led us to determine the primary transcript length of 2700bp (Fig. 5A and B). Furthermore, we isolated nucleus and cytoplasmic

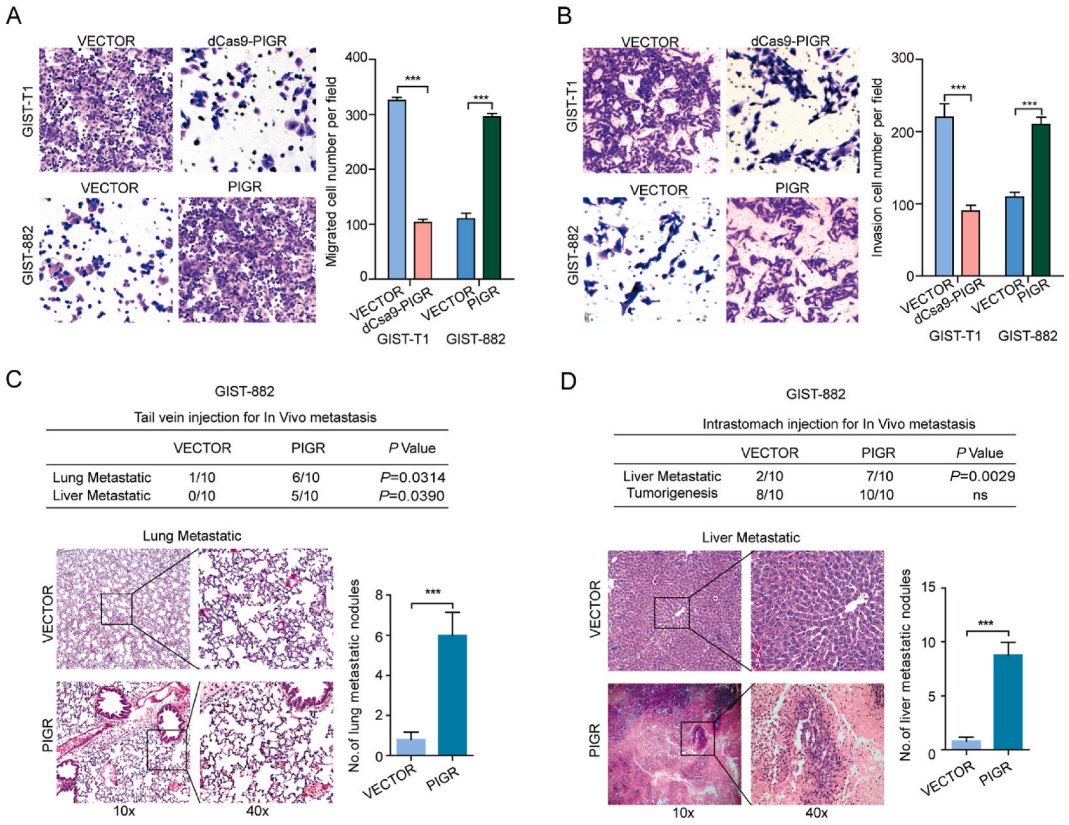

Fig. 3. PIGR functions as an oncogene in GIST.
(A–B) The effect of interfering or overexpressing PIGR on the migration and invasion ability of GIST-T1 and GIST-882 cells. **(C–D)** The effect of PIGR overexpression on the invasive ability of GIST-T1 and GIST-882 cells was analyzed via the tail vein model **(C)** and GIST in situ model **(D)**. Mean ± SEM of 3 independent experiments. ***$P < 0.001$ versus control.

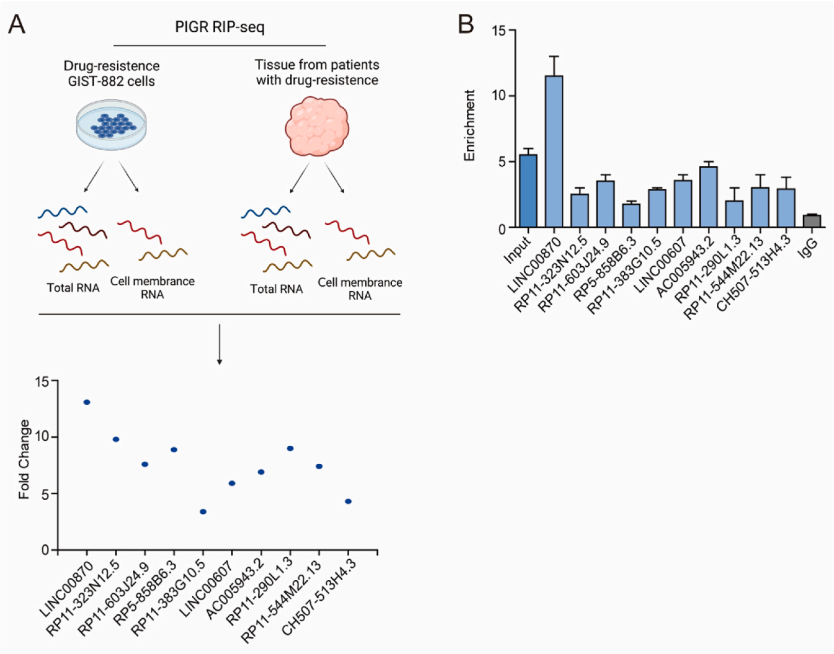

Fig. 4. Exploration of specific mechanisms for PIGR.
(A) The RIP-seq workflow. **(B)** The RNA molecules interacting with PIGR were verified using RIP-PCR. The workflow was created with BioRender.com.

RNA using extraction kits and discovered that LINC00870 was predominantly localized in the cytoplasmic region (Fig. 5C). Using bioinformatics tools such as CPC, CPAT, and phyloCSF sites, we predicted that LINC00870 is a non-coding RNA (Fig. 5D). To confirm the non-coding nature of LINC00870, we assessed overexpressing LINC00870 cells at both RNA and protein levels. Agarose gel electrophoresis confirmed effective RNA expression for both sense and antisense strands of LINC00870 (Fig. 5E). However, Western blot analysis revealed no protein expression, indicating that LINC00870 RNA does not encode proteins (Fig. 5F).

Since lncRNA has been shown to play a crucial role in tumorigenesis and progression [11–14], we constructed LINC00870 knockdown and overexpression stable cell lines in GIST-T1 and GIST-882 cells to explore its function (Fig. 5G). We observed a reduction in cell invasion, migration, and clone formation after LINC00870 knockdown, and an enhancement of these cellular processes after LINC00870 overexpression (Fig. 5H–K). These results suggest that LINC00870 functions as an oncogene in GIST.

We selected two independent cohorts to explore the correlation between PIGR and LINC00870 in GIST imatinib-resistant patient samples to validate our findings. We found a significant positive correlation between PIGR and LINC00870 in two cohorts (Fig. 6A, $P < 0.0001$). Previous studies have shown that PIGR is a transmembrane glycoprotein whose N-terminal glycosylation promotes hydrolysis and secretion in the extracellular compartment, a critical step in the cellular response to the immune response [26]. We investigated the effect of LINC00870 on PIGR by overexpressing it in GIST cells and found a significant decrease in the secretory component content released extracellularly by PIGR (Fig. 6B). This result was consistent with the effect of tunicamycin treatment, which disrupts the extracellular glycan chain of PIGR (Fig. 6C). Our findings suggest that LINC00870 may cause imatinib treatment resistance in GIST by inhibiting the N-terminal glycosylation of PIGR, preventing its extracellular SC region from being released typically and thereby hindering the immune response.

3.6. Inhibition of PIGR or LINC0087 effectively overcomes imatinib resistance

In our final analysis, we demonstrated that inhibition of PIGR or LINC0087 effectively overcomes imatinib resistance. Subcutaneous tumor models were established in BALB/c-nu nude mice using GIST-882 or GIST-882_PIGR_KO resistant cells. Our results indicate that knockout of PIGR in resistant cell lines effectively inhibits tumor growth (Fig. 7A and B). Similarly, knockout of LINC0087 in resistant cells also significantly suppresses tumor growth (Fig. 7C and D). These findings collectively suggest that inhibition of PIGR or LINC0087 represents a promising strategy for overcoming imatinib resistance.

4. Discussion

GIST is the most common type of gastrointestinal mesenchymal tumors. Their pathogenesis is primarily driven by gain-of-function mutations in the KIT gene (accounting for 75–80 %) and mutations in the platelet-derived growth factor receptor alpha (PDGFRA) (<10 %). Additionally, abnormalities in genes such as SDH, NF1, KRAS, and HRAS have been implicated in GIST development. GIST

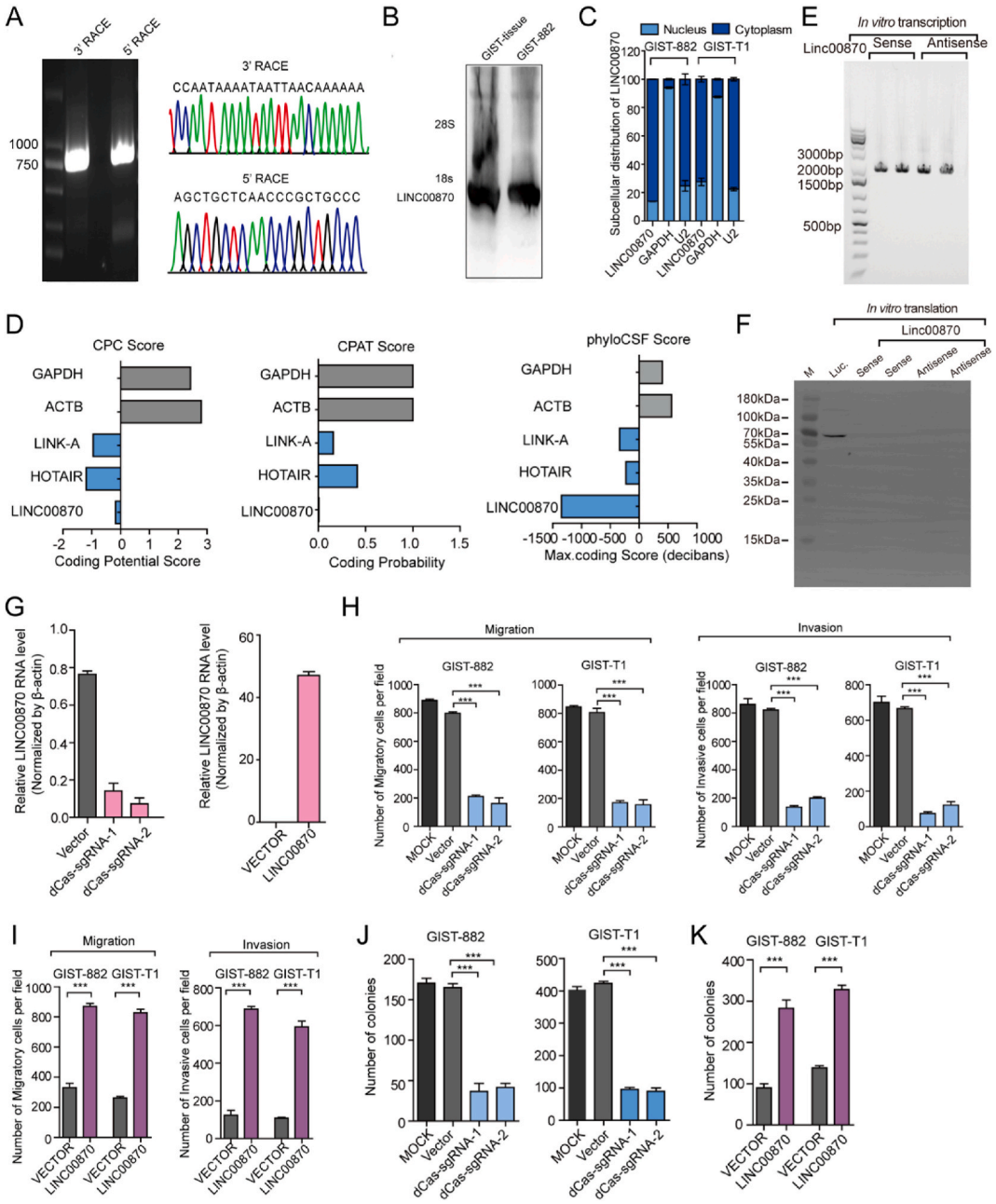

Fig. 5. Basic characteristics and biological functions of LINC00870.

(A) LINC00870 sequence information and length were analyzed using 3′RACE and 5′RACE experiments. The uncropped gel image can be found in Supplementary Figure 3. **(B)** The number and length of LINC00870 transcripts in GIST cell lines and tissues were determined by a Northern blot assay. The uncropped Northern blot image can be found in Supplementary Figure 4. **(C)** The distribution of LINC00870 in GIST cell lines. **(D)** The sequence protein-coding ability of LINC00870 was predicted using the prediction website. (E) Agarose gel electrophoresis was utilized to determine the length of LINC00870 in GIST-882 cells overexpressing either the sense or antisense strands. The uncropped gel image can be found in Supplementary Figure 5. **(F)** Western blot analysis was performed to evaluate the protein-coding potential of LINC00870 in GIST-882 cells overexpressing either the sense or antisense strands, with a luciferase plasmid used as the control. The uncropped Western blot image can be found in Supplementary Figure 6. **(G)** The identification of LINC00870 interference and overexpression efficiency. **(H–I)** The effect of interfering **(H)** or overexpressing **(I)** LINC00870 on GIST cells' invasive and migratory capacity. **(J–K)** The effect of interfering **(J)** or overexpressing **(K)** LINC00870 on the ability of GIST clone formation. Mean ± SEM of 3 independent experiments. $^{***}P < 0.001$ versus control.

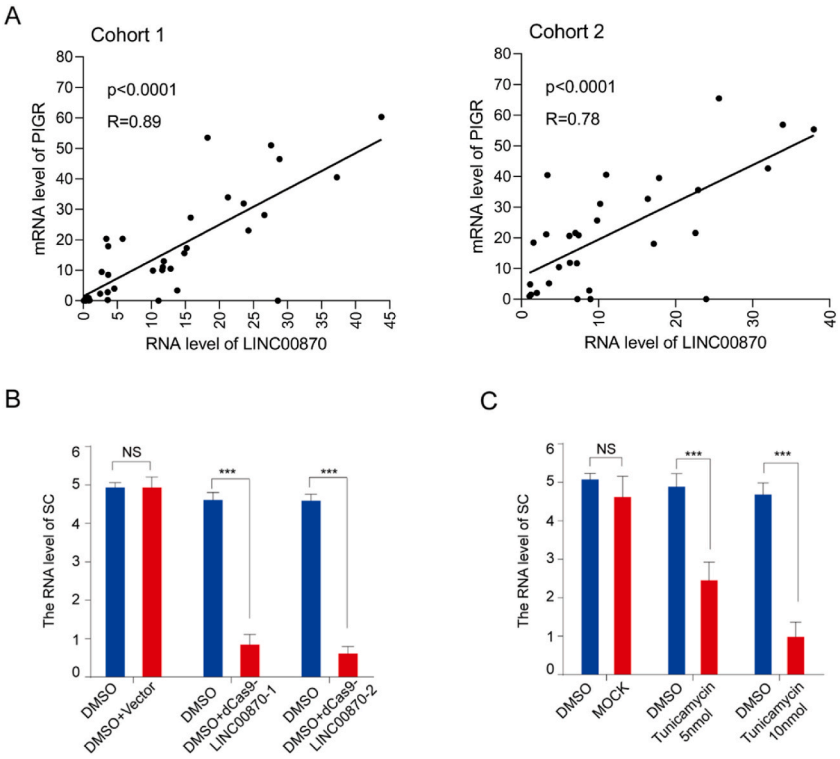

Fig. 6. Correlation and mechanism study of PIGR and LINC0087.
(A) The correlation analysis between PIGR and LINC00870 at the mRNA level in GIST imatinib-resistant patients. The unadjusted original results can be found in Supplementary Figure 7. **(B)** The expression content of PIGR extracellular secretory structure SC in cell supernatants after overexpression of LINC00870. **(C)** The expression content of PIGR extracellular secretory structure SC in cell supernatants after treatment of cells with tunicamycin. Mean ± SEM of 3 independent experiments. ***$P < 0.001$ versus control.

cells originate from interstitial cells of Cajal or their precursor cells and their survival is dependent on the expression of KIT [27,28]. KIT mutations predominantly occur in the juxtamembrane (JM) domain (encoded by exon 11) and in the extracellular domain near the membrane (encoded by exons 8 or 9), with approximately 85–90 % of KIT-mutant GIST exhibiting these characteristics. These mutations confer oncogenic properties to the KIT gene, promoting tumor formation primarily through the PI3K-AKT, JAK-STAT, and RAS-RAF-MEK-ERK (MAPK) signaling pathways [29–33].

Currently, imatinib remains the first-line targeted therapy for progressive or unresectable GIST. Nevertheless, both primary and secondary drug resistance frequently arise, leading to diminished therapeutic efficacy, increased tumor recurrence, metastasis, and elevated mortality rates. Thus, elucidating the molecular mechanisms underlying drug resistance in GIST is essential for enhancing therapeutic strategies and prognostic outcomes. Approximately 90 % of GIST cases are driven by activating mutations in receptor tyrosine kinases, primarily KIT or PDGFRA [34]. Research on imatinib resistance has highlighted several key factors: KIT mutations result in sustained protein activation, which impacts the genomic context and activates alternative signaling pathways [35,36]. Patients with the PDGFRA-D842V mutation exhibit primary resistance to imatinib [36,37]. For BRAF/KRAS mutations, while imatinib inhibits the mutated KIT receptor, it does not affect the downstream RAS-RAF signaling pathways associated with BRAF/KRAS mutations [38,39]. Additionally, inhibiting KIT signaling can lead to the release of FGF-2, further worsening tumor malignancy [40]. In terms of metabolism, succinate dehydrogenase (SDH) deficiency results in the stabilization and accumulation of HIF1-α under normoxic conditions, promoting angiogenesis and glycolysis, thereby facilitating tumor growth [41,42]. Given the extremely limited treatment options for imatinib resistance, there is an urgent need to investigate new mechanisms to combat this challenge.

Our high-throughput sequencing of tissue specimens from imatinib-resistant GIST patients identified PIGR as a significantly differentially expressed gene. While PIGR has been found to exhibit differential expression in various cancers, there is no conclusive evidence regarding its role in the prognosis of tumor patients [43–50]. Our study discovered that PIGR is remarkably highly expressed in GIST tumor tissues. The role of PIGR in tumors remains controversial, possibly owing to tumor heterogeneity or different action mechanisms. Studies in colorectal cancer revealed that PIGR could act as a prognostic marker and inhibit tumorigenesis through LAMB3-AKT-FOXO3/4 signaling [51]. Transcriptome sequencing analysis revealed that PIGR was downregulated in breast cancer, and overexpression of PIGR in breast cancer cells inhibited their adhesion and proliferation [52]. PIGR controlled tumor progression in lung cancer by downregulating the differentiation suppressor gene NOTCH3 [53]. In hepatocellular carcinoma, extracellular vesicles carrying PIGR activated the AKT/GSK3β/β-linked protein signaling cascade response, promoting cancer stemness, tumorigenesis, and metastasis [54]. Other studies have revealed that PIGR promoted hepatocellular carcinoma by activating Smad and Yes-MEK/ERK

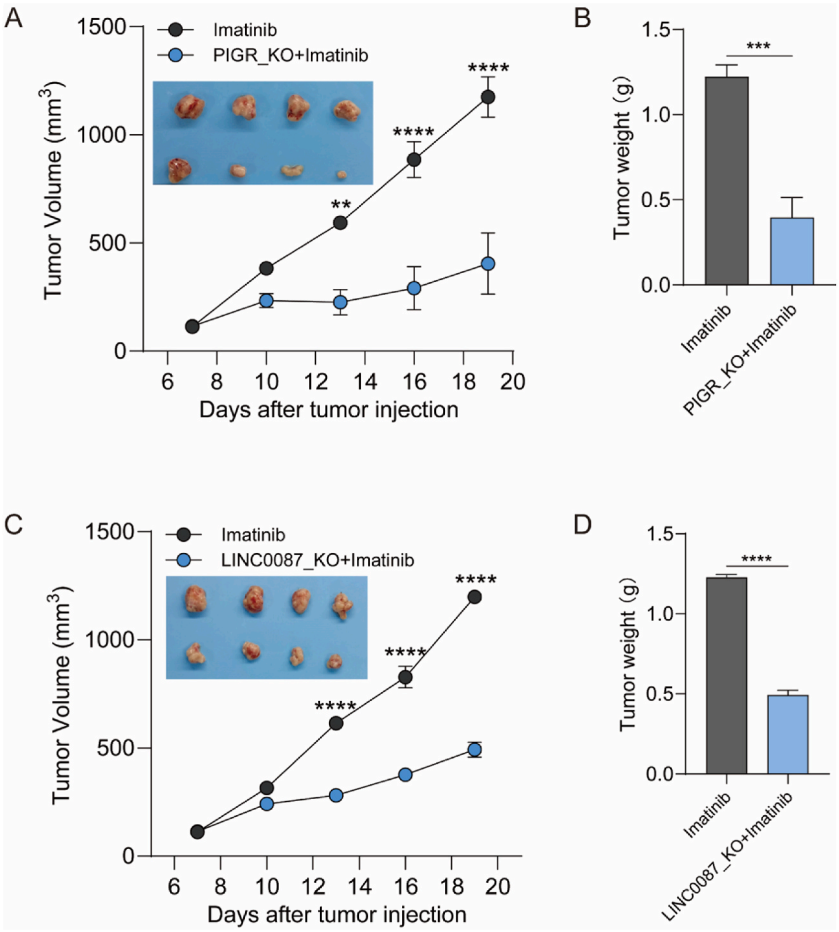

Fig. 7. Inhibition of PIGR or LINC0087 effectively overcomes imatinib resistance.
(A–B) Subcutaneous tumor models were established in BALB/c-nu nude mice using GIST-882 or GIST-882_PIGR_KO resistant cells, and tumor growth was monitored **(A)**. Tumor weight was measured at the end of the experiment **(B). (C–D)** Subcutaneous tumor models were established in BALB/c-nu nude mice using GIST-882 or GIST-882_LINC0087_KO resistant cells, and tumor growth was monitored **(C)**. Tumor weight was measured at the end of the experiment **(D)**. Mean ± SEM of 3 independent experiments. $^{***}P < 0.001$ versus control.

signaling pathways [55,56]. Ohkuma et al. found that PIGR overexpression was associated with poor prognosis after surgical resection in patients with pancreatic cancer [46]. Our study found that GIST patients with high PIGR expression had a poor prognosis, and overexpression of PIGR significantly promoted GIST cell invasion, lung colonization, and liver metastasis, suggesting that PIGR functions as an oncogene in GIST. Our animal experiments also confirmed that interfering with PIGR expression in imatinib-resistant cell lines helps inhibit tumor growth, suggesting that the application of PIGR inhibitors in clinical settings may improve survival in imatinib-resistant patients. However, PIGR plays a critical role in mediating the transcytosis of polymeric IgA and IgM from the basolateral surface to the apical surface of epithelial cells, subsequently secreting these immunoglobulins into the mucosal fluid [57–59]. Therefore, the sole use of PIGR inhibitors could potentially disrupt normal mucosal immunity. If it is possible to specifically interfere with PIGR at tumor sites, for example, through the use of antibody-drug conjugates (ADCs), it may achieve better therapeutic outcomes while reducing side effects for patients [60,61]. Of course, these conclusions are based solely on animal models, and further challenges must be addressed before clinical application.

Our findings suggest that PIGR plays a crucial role in imatinib resistance in GIST, as evidenced by the significantly higher mRNA expression of PIGR in imatinib-resistant GIST samples than in non-resistant samples. Furthermore, we identified a specific binding between PIGR and LINC00870 through the RIP-seq assay. In recent years, there has been increasing research interest in the regulatory role of lncRNA in tumor development and progression [11–14]. The significance of lncRNA in various pathological and physiological processes is well established [62], although no studies have reported on the regulatory mechanisms of LINC00870 in GIST drug resistance and immunity. We established an imatinib-resistant cell line, IR-GIST-882, through a high-dose gap-action approach, which provided an effective tool for studying imatinib resistance. Furthermore, by overexpressing LINC00870 in GIST-882 and GIST-T1 cell lines, we observed increased invasion, migration, and cladogenesis of GIST cells, suggesting that LINC00870 functions as an oncogene in GIST. LncRNAs are pivotal as regulatory and predictive factors in cancer treatment resistance and can be used as adjunctive therapeutic agents to enhance the efficacy of existing therapies, such as chemotherapy, radiotherapy, immune checkpoint inhibitors,

and targeted therapy [63,64]. Their substantial dysregulation across various cancer types, coupled with their heterogeneous expression, positions them as ideal biomarkers and therapeutic targets for personalized medicine [65]. Despite their potential, the clinical application of LncRNAs-based therapies faces challenges, including issues of tolerance, toxicity, and off-target effects, which necessitate further investigation.

The cell lines and drug-resistant variants used in our study are derived from human sources. However, due to interspecies differences, in vivo studies often utilize immunodeficient mouse models, which have significant limitations, particularly the absence of immune cells that may influence assessments of immune dysregulation. Current cellular models in tumor immunology include human peripheral blood mononuclear cell (Hu-PBMC) and human CD34 (Hu-CD34) humanized mouse models, which effectively reconstruct the immune system within immunodeficient mice, thereby enabling the examination of tumor dynamics within an immune-enriched microenvironment [66,67]. To investigate the roles of LINC00870 and PIGR within the immune cell microenvironment, employing humanized mouse models would provide more reliable results. While this study proposes a potential strategy to overcome imatinib resistance through the inhibition of PIGR or LINC00870, it is essential to draw insights from other research to further validate its feasibility and safety in clinical settings [68–70]. Additionally, the pharmacokinetics and pharmacodynamics of these strategies should be investigated to optimize dosing regimens, enhance therapeutic efficacy, and minimize side effects [71,72]. We hope that the GIST-imatinib resistance-related targets identified in this study will provide valuable references and assistance for the treatment of GIST patients with imatinib resistance.

In summary, our study investigated the mechanisms underlying resistance to targeted therapies in GIST patients and identified the PIGR-LINC00870 complex as a potential key factor in inducing drug resistance. These findings suggest that targeting this complex could offer a promising approach to the comprehensive treatment of GIST by combining targeted therapy, immunotherapy, and molecular therapy. This study provides valuable insights into the clinical management of GIST and offers potential clinical applications for improving patient outcomes. Further studies are warranted to validate the clinical significance of this complex and explore its potential as a therapeutic target for GIST.

CRediT authorship contribution statement

Yuan Li: Writing – original draft, Formal analysis, Data curation. **Zhiqiang Dai:** Formal analysis, Data curation. **Zewei Cheng:** Formal analysis, Data curation. **Junyi He:** Software, Methodology. **Yirui Yin:** Software, Methodology. **Xinyou Liu:** Software, Formal analysis. **Jiwei Zhang:** Writing – review & editing. **Guohua Hu:** Data curation. **Yueda Chen:** Writing – review & editing, Supervision, Funding acquisition. **Xuefei Wang:** Writing – review & editing, Supervision, Funding acquisition. **Yebo Shao:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Informed consent statement

Not applicable.

Data availability statement

All datasets involved in this study can be viewed in the Gene Expression Omnibus (GEO number: GSE155800) or data availability part of the corresponding articles. All data pertinent to this study, whether generated or analyzed, are comprehensively presented in this manuscript and its supplementary information. For any additional inquiries or requests, interested parties are encouraged to contact the corresponding authors.

Ethics statement

The animal research was approved by the Institutional Animal Care and Use Committee of Shanghai Immunocan Biotechnology Co., Ltd (Approval Number: YMNK-IACUC-F006, Approval Date: November 14, 2022). The human research was approved by the Clinical Research Ethics Committee of Fudan University Zhongshan Hospital (Approval Number: B2023-199, Approval Date: November 19, 2023). Additionally, it should be noted that at our teaching hospital, all patients admitted for surgical procedures are required to sign consent forms allowing for the use of their surgical specimens for research purposes. Therefore, research involving surgical specimens is exempt from the requirement for explicit informed consent.

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of abdominal tumor of Fujian Province.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41934.

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