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Original Article

SOX8 mediates the crosstalk between KRAS and TGF-β pathways to promote the malignant progression of pancreatic cancer

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Abstract: The mechanisms of metastasis and invasion in pancreatic cancer are promoted by the interaction between KRAS mutations and the transforming growth factor-β (TGF-β) pathway. However, the molecular mechanisms linking these pathways remain unclear. Downstream genes of KRAS pathway were identified by RNA sequencing in Panc-1 and MIA-PaCa2 cells. The function of the identified SOX8 was analyzed by using migration assays, western blotting of epithelial-mesenchymal transition (EMT) markers, and chemotherapy sensitivity. The correlation between SOX8 and TGF-β signaling was examined under recombinant TGF-β or TGF-β inhibitor treatment. SOX8 expression was also analyzed in resected specimens. SOX8 expression suppressed by KRAS knockdown, identifying it as a downstream regulated gene. SOX8 knockdown inhibited TGF-β signaling, reduced cell migration, altered EMT marker expression, and enhanced chemotherapy sensitivity. Furthermore, SOX8 knockdown activated the AKT/mTOR pathway, which was reversed by TGF-β inhibition. Clinically, high SOX8 expression correlated with poor prognosis. In conclusions, SOX8 functions as a molecular hub linking KRAS and TGF-β pathways, promoting epithelial-mesenchymal transition (EMT), invasive capacity, and chemotherapy resistance. This novel KRAS-SOX8-TGF-β axis plays the important role in invasion and metastasis of pancreatic cancer, suggesting SOX8 as a useful prognostic biomarker and therapeutic target.

Keywords: SOX8, pancreatic cancer, KRAS, TGF-β

Introduction

Pancreatic cancer has a very poor prognosis, is resistant to conventional treatments, and has an extremely low five-year survival rate of 10-20% [1]. This poor prognosis is largely attributed to the silent onset of the disease, leading to a late-stage diagnosis and its aggressive and metastatic nature. Consequently, elucidating the molecular mechanisms underlying pancreatic cancer progression will lead to the development of better diagnostic methods and treatments.

Pancreatic cancer frequently exhibits Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, which characterize its tumorigenesis [2]. Mutant KRAS plays a central role in oncogenic signaling pathways including the mitogen-activated protein kinase and phosphoinositide 3-kinase pathways, which promote cell proliferation, survival, and drug resistance [3]. In parallel, transforming growth factor-beta (TGF-β) signaling plays a paradoxical role in PDAC. It acts as a tumor suppressor in normal epithelial cells, but in cancer cells, particularly in later stages, it promotes metastasis, evades the immune system, and induces surrounding fibrosis. The intricate crosstalk between these two key pathways is fundamental to the aggressive biology of PDAC.

The SRY-related HMG-box (SOX) family of transcription factors is a critical regulator of embryonic development, cell-fate determination, and tissue homeostasis. However, emerging evi-

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dence suggests that their dysregulation contributes to tumorigenesis in various types of cancers. Specifically, SOX8, a member of the SOX gene family, has been reported to be overexpressed in several cancer cells, including breast cancer and hepatocellular carcinoma, and it accelerates invasion and promotes metastasis [5, 6]. Despite these findings, the role of SOX8 in PDAC remains largely unexplored, which represents a significant knowledge gap.

We hypothesize that SOX8 plays a crucial role upstream of the KRAS pathway and downstream of the TGFβ pathway, potentially acting as a bridge between the two pathways. To date, studies directly linking SOX8 to the K-ras and TGF-β signaling axes in pancreatic cancer are scarce. Therefore, the purpose of this study is to elucidate the extent to which SOX8 plays a crucial role in the mechanisms of pancreatic cancer invasion and metastasis, based on its function within the KRAS and TGFβ pathways. This approach allowed us to establish SOX8 as a novel biomarker for personalized treatment and a potential therapeutic target, paving the way for the development of new strategies to overcome this devastating disease.

Methods

Candidate gene screening via RNA sequencing

To identify potential downstream or upstream targets of KRAS, we performed RNA sequencing of pancreatic cancer Panc-1 cells. The Cells were knocked down for KRAS using small interfering RNA (siRNA), with non-targeting scrambled siRNA used as a control. Forty-eight hours after transfection, total RNA was extracted from both the KRAS knockdown and control cells. The quality and quantity of the extracted RNA were confirmed, and RNA sequencing was performed by Macrogen Japan (Tokyo, Japan). Sequencing libraries were prepared from total RNA, and 150 bp paired-end reads were generated using the NovaSeq 6000 platform (Illumina, CA, USA).

Raw sequencing data were processed to remove low-quality reads and were aligned to the human reference genome (GRCh38). Differential gene expression analysis between the KRAS knockdown and control groups was performed, and genes showing significant changes in expression (adjusted $P < 0.05$) were selected as candidate KRAS-associated genes.

Cell culture, siRNA-mediated gene knockdown, and reagents

The human pancreatic cancer cell lines Panc-1 and MIA-PaCa2 were purchased from the RIKEN BioResource Center (Tsukuba, Japan). The cells were maintained in Dulbecco's modified Eagle's medium (DMEM; Sigma-Aldrich, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (FBS; Thermo Fisher Scientific, Waltham, MA, USA) and 1% penicillin-streptomycin (Nacalai Tesque, Kyoto, Japan) at 37°C in a humidified atmosphere with 5% CO_2.

Small interfering RNAs (siRNAs) used for the knockdown of target genes were purchased from Invitrogen (Thermo Fisher Scientific). siRNA sequences targeting the following genes were used: FGFR3, SHH, GDF11, SOX8, PAK6, BTC, ETV1, ETV4, ETV5, FOSL1, CBLB, METTL7, and ASB4. A non-targeting scrambled siRNA was used as a negative control. siRNA transfection was performed using Lipofectamine RNAiMAX Reagent (Thermo Fisher Scientific) according to the manufacturer's instructions, as described in our recent publications [7, 8].

To investigate the effects of the TGF-β signaling pathway, cells were treated with TGF-β1 recombinant protein (10 ng/mL; R&D Systems, Minneapolis, MN, USA) or with the selective TGF-β receptor I inhibitor LY364947 (10 μM; Sigma-Aldrich) for 24 h.

Chemomigration assay

A migration assay was performed to evaluate the migratory potential of pancreatic cancer cells using a Transwell system (Corning Inc., Corning, NY, USA), as described previously [8]. Cells (5×10^4) in serum-free DMEM were seeded into the upper chamber of a Transwell insert, and the lower chamber was filled with DMEM containing 10% FBS as a chemoattractant. After 24 h of incubation at 37°C, non-migrated cells on the upper surface were carefully removed using a cotton swab while cells that had migrated to the lower surface were fixed with methanol and stained with 0.5% crystal violet solution. The number of migrated cells in five randomly selected fields was counted under a microscope.

RNA isolation and cDNA synthesis

Total RNA was isolated from cultured cells using an RNeasy Mini Kit (Qiagen, Hilden, Germany) and from human clinical specimens following a previously described method [7, 8]. The quality and quantity of extracted RNA were verified using a NanoDrop spectrophotometer (Thermo Fisher Scientific). For cDNA synthesis, 1 μg of total RNA was reverse transcribed using a SuperScript III First-Strand Synthesis System (Invitrogen) according to the manufacturer's protocol.

Quantitative real-time PCR (qrtPCR)

qRT-PCR was performed on a StepOnePlus Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) using SYBR Green Master Mix (Thermo Fisher Scientific), as described in our previous publications [7, 8]. The expression levels of the target genes were normalized to those of the internal control gene GAPDH.

Western blotting

Cells were lysed using radioimmunoprecipitation assay buffer containing a protease and phosphatase inhibitor cocktail (Roche, Basel, Switzerland). Protein concentrations were determined using the bicinchoninic acid protein assay kit (Thermo Fisher Scientific). Total protein (20 μg) was separated via sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred onto polyvinylidene fluoride membranes. After blocking with 5% skim milk, the membranes were incubated with primary antibodies against p-suppressor of mothers against decapentaplegic (SMAD)2/3, p-SMAD4, p-RAF1, p-protein kinase B (AKT), and p-mechanistic target of rapamycin (mTOR), followed by incubation with horseradish peroxidase-conjugated secondary antibodies. The proteins were detected using an enhanced chemiluminescence detection system (Thermo Fisher Scientific). β-Actin was used as a loading control.

SOX8 expression in clinical specimens

To analyze SOX8 expression in human specimens, total RNA was extracted from surgically resected pancreatic cancer and adjacent nontumorous tissues. All clinical samples were obtained after obtaining informed consent from the patients, and this study was approved by the Ethics Committee of Tokyo Medical University (Approval No. XXX). Gene expression was measured via qRT-PCR as described above, and expression levels were normalized to those of GAPDH.

Statistical analyses

Data are presented as the mean ± standard error of the mean (SEM). Comparisons between groups were made using a two-tailed Mann-Whitney U-test for continuous variables and Fisher's exact test for the comparison of proportions. Correlations were calculated using the nonparametric Spearman's coefficient. All statistical analyses were performed using the SPSS software (SPSS 24.0). Overall survival curves were represented according to Kaplan-Meier estimates and compared using log-rank tests. Statistical significance was set at $P < 0.05$.

Results

Identification of KRAS downstream target genes in pancreatic cancer

To identify the downstream target genes of the KRAS pathway in pancreatic cancer, we performed RNA sequencing of Panc-1 cells following knockdown of KRAS using a specific siRNA (siKRAS) and compared the results with those of cells treated with a non-targeting control siRNA (siGFP). RNA sequencing data revealed significant changes in gene expression between the two groups, as visualized using heat, smear, and volcano plots (**Figure 1A** and **1B**).

From the list of candidate genes with significantly altered expression following KRAS knockdown, we focused on genes known to be involved in signaling pathways associated with cancer invasion and metastasis. The selected genes are listed in **Table 1**.

To validate their functional roles, individual knockdowns of these candidate genes were performed using siRNAs and their effects on cell migration were evaluated using a chemomigration assay. As shown in **Figure 1C**, several gene knockdowns suppressed cell migration,

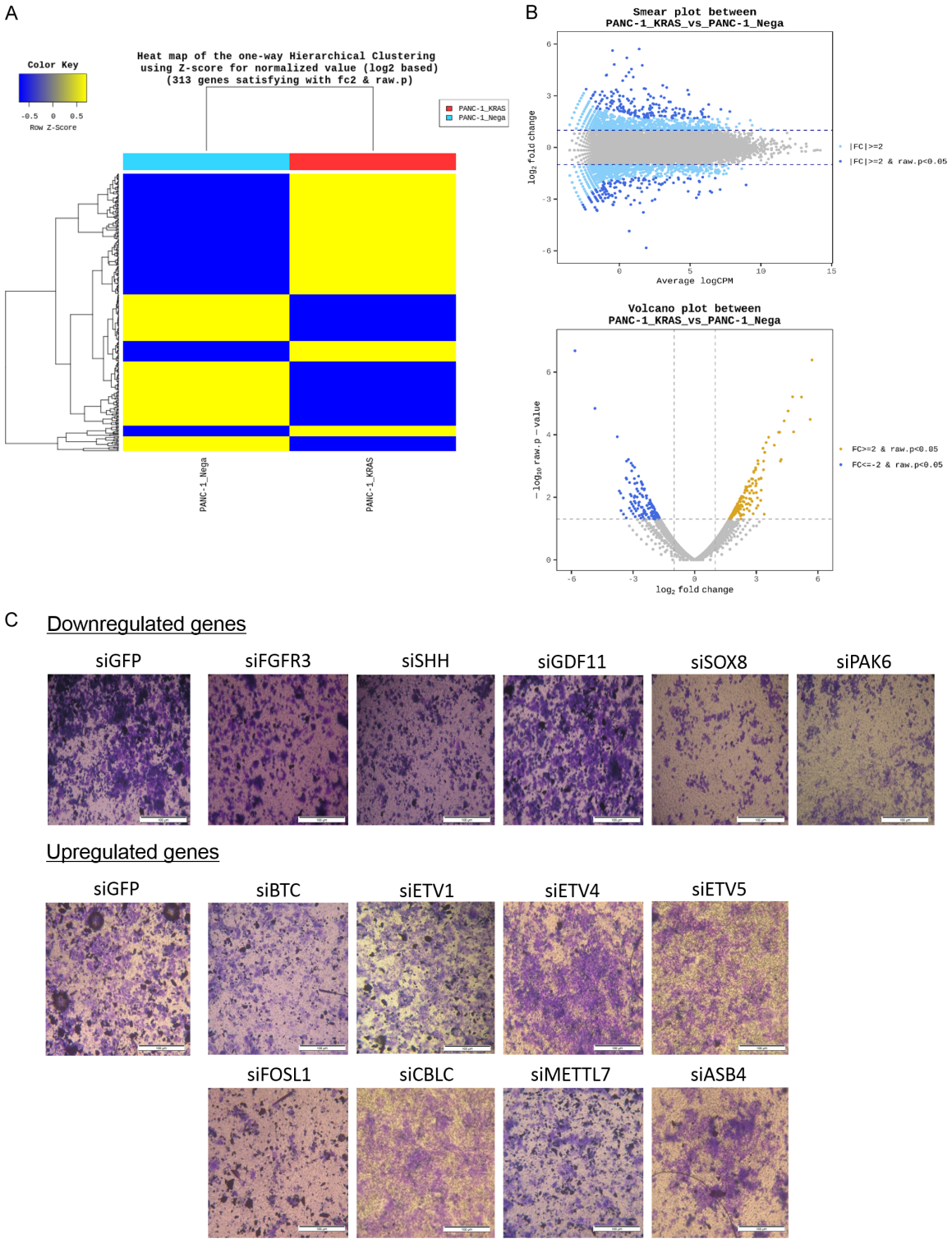

Figure 1. Identification of KRAS downstream target genes in pancreatic cancer cells. A. Heatmap showing global gene expression changes in Panc-1 cells transfected with siKRAS compared with siGFP control, as determined by RNA sequencing. B. Smear and volcano plots illustrating significantly upregulated and downregulated genes following KRAS knockdown. C. Chemomigration assay results following individual siRNA knockdown of selected candidate genes. Several knockdowns reduced migration, with SOX8 knockdown showing the most potent inhibitory effect. Data represent mean ± SEM from three independent experiments.

Table 1. Transcripts per million (TPM) value by RNA sequencing analysis in pancreatic cancer cell line with Kras knockdown

A. Up-regulated genes				
Gene symbol	Gene description	TPM value		*p*-value
		siKras	siGFP	
CEBPA	CCAAT enhancer binding protein alpha	2.703501	0.598164	0.0188
FGFR3	fibroblast growth factor receptor 3	10.821112	2.210374	0.0012
SHH	sonic hedgehog signaling molecule	41.758851	12.122707	0.0401
GDF11	growth differentiation factor 11	4.464186	0.704601	0.0031
SOX8	SRY-box transcription factor 8	1.712243	0.434430	0.0356
PAK6	p21 (RAC1) activated kinase 6	0.427337	0.083488	0.0352
B. Down-regulated genes				
Gene symbol	Gene description	TPM value		*p*-value
		siKras	siGFP	
BTC	betacellulin	0.104320	0.589337	0.0282
ETV1	ETS variant transcription factor 1	0.383163	3.604699	0.0009
ETV4	ETS variant transcription factor 4	1.070625	8.080335	0.0008
ETV5	ETS variant transcription factor 5	7.227534	42.667061	0.0036
FOSL1	FOS like 1	24.975932	94.498147	0.0240
CBLC	Cbl proto-oncogene C	0.330589	1.574987	0.0332
METTL7A	methyltransferase like 7A	0.070791	0.450894	0.0290
ASB4	ankyrin repeat and SOCS box containing 4	0.233694	2.062525	0.0014

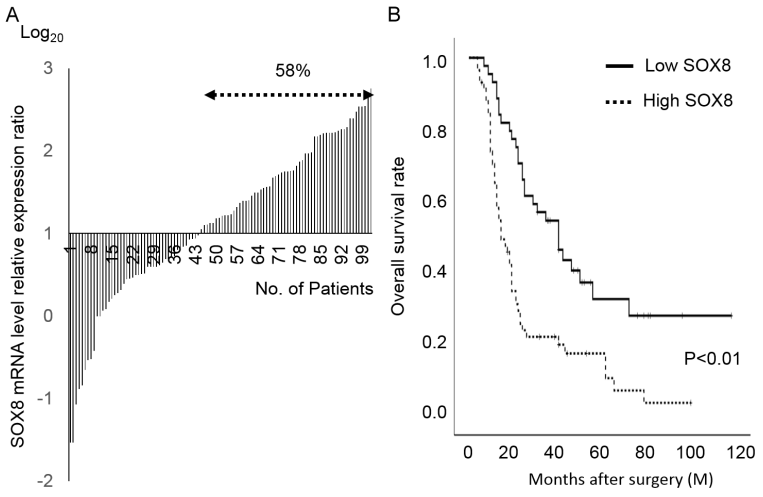

Figure 2. SOX8 expression in clinical pancreatic cancer specimens and its prognostic significance. A. qRT-PCR analysis of SOX8 mRNA levels in surgically resected pancreatic cancer specimens. Approximately 58% of tumors exhibited increased SOX8 expression compared to adjacent non-tumor tissue. B. Kaplan-Meier survival curves stratified by SOX8 expression levels (high vs. low). High SOX8 expression correlated with significantly poorer overall survival (P < 0.01).

with SOX8 knockdown showing the most potent and significant inhibitory effect. These results suggest that SOX8 is a critical downstream effector of KRAS and plays a key role in regulating pancreatic cancer invasion and metastasis.

SOX8 expression in clinical pancreatic cancer specimens and its association with patient prognosis

To investigate the clinical relevance of SOX8, we measured its mRNA expression in surgically resected pancreatic cancer specimens from a patient cohort. qRT-PCR analysis revealed an increase in SOX8 expression in approximately 58% of the pancreatic cancer cases (**Figure 2A**). Based on these expression levels, we set a cut-off value to dichotomize the patient cohort into high SOX8 and low SOX8 groups. Kaplan-Meier survival analysis revealed a significant difference in the overall survival between the two groups, with patients in the high SOX8 group showing a poorer prognosis than those in the low SOX8 group (**Figure 2B**, $P < 0.01$). These findings suggest that SOX8 overexpression is a frequent event in pancreatic cancer and is associated with unfavorable patient outcomes.

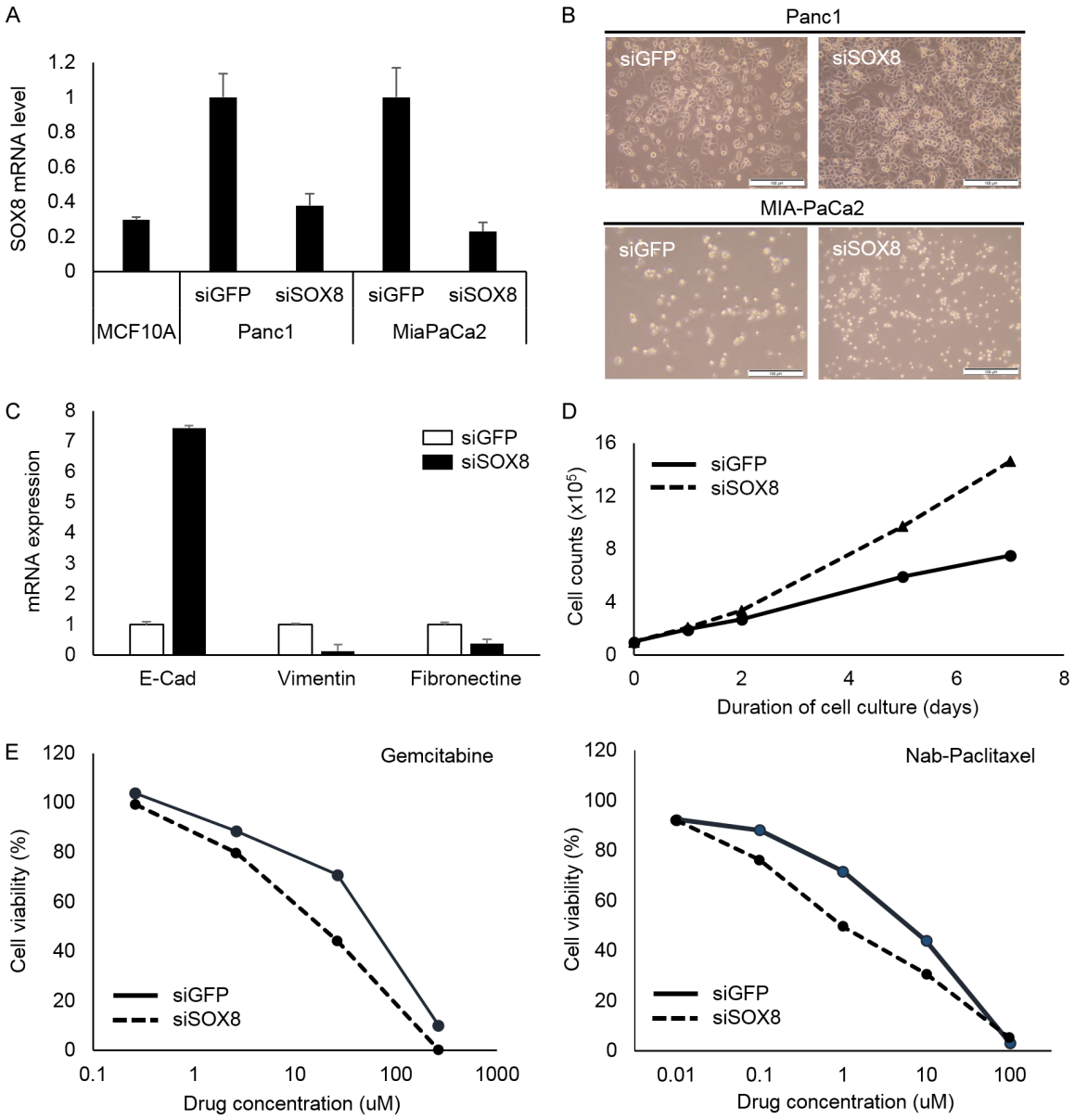

Figure 3. Functional roles of SOX8 in pancreatic cancer cell lines. A. qRT-PCR analysis of SOX8 expression in Panc-1 and MIA-PaCa2 cells compared with non-malignant MCF10A cells. Efficiency of SOX8 knockdown by siRNA is also shown. B. Representative phase-contrast images of cell morphology following siSOX8 transfection. No major morphological changes were observed. C. qRT-PCR analysis of EMT markers following SOX8 knockdown. E-cadherin expression increased, whereas vimentin and fibronectin decreased. D. Cell proliferation assay showing increased proliferation upon SOX8 knockdown. E. Sensitivity to gemcitabine and nab-paclitaxel was also enhanced by SOX8 knockdown.

SOX8 regulates epithelial-mesenchymal transition (EMT), proliferation, and chemosensitivity of pancreatic cancer cells

To investigate the function of SOX8 further, we examined its expression in pancreatic cancer cell lines. Quantitative PCR analysis showed that SOX8 expression was significantly higher in Panc-1 and MIA-PaCa2 pancreatic cancer cells than in the non-malignant mammary epithelial cell line MCF10A (**Figure 3A**). The efficacy of siSOX8 was confirmed by the successful knockdown of SOX8 in these cancer cell lines (**Figure 3A**).

Although SOX8 knockdown did not induce significant morphological changes (**Figure 3B**), it resulted in a clear shift in the expression of

EMT markers. Specifically, SOX8 knockdown resulted in an upregulation of the epithelial marker E-cadherin and a downregulation of the mesenchymal markers vimentin and fibronectin, indicating a partial reversal toward a more epithelial phenotype (**Figure 3C**).

Furthermore, SOX8 knockdown significantly increased the proliferation rate of the pancreatic cancer cells (**Figure 3D**). Concurrently, SOX8 knockdown increased the sensitivity of these cells to the standard chemotherapeutic agents gemcitabine and nab-paclitaxel (**Figure 3E**).

Collectively, these *in vitro* findings suggest that SOX8 plays a crucial role in regulating EMT, proliferation, and chemosensitivity of pancreatic cancer cells, thereby contributing to the malignant phenotype of invasion and metastasis.

SOX8 is a key regulator of the TGF-β signaling pathway

To elucidate the molecular mechanism by which SOX8 promotes invasion and metastasis, we investigated its relationship with the TGF-β signaling pathway, which is known to regulate these processes. As shown in **Figure 4A**, SOX8 knockdown in both Panc-1 and MIA-PaCa2 cells led to a broad suppression of TGF-β signature genes.

Additionally, we examined the expression of key downstream components of the canonical TGF-β pathway. Western blot analysis revealed that SOX8 knockdown resulted in a notable decrease in Smad2/3 and Smad4 phosphorylation (**Figure 4B**), indicating a suppression of the TGF-β signaling cascade. In addition to the canonical pathway, we found that SOX8 knockdown inhibited the expression of several angiogenic factors that are known to be regulated by the TGF-β pathway (**Figure 4C**).

These results suggest that SOX8 is a crucial upstream regulator of the TGF-β signaling pathway and that its effects on cell migration, proliferation, and chemosensitivity are mediated, at least in part, through the activation of this pathway. This finding provides a novel mechanistic link between SOX8 and the well-established pro-tumorigenic functions of TGF-β in pancreatic cancer.

SOX8 linked the KRAS and TGF-β signaling pathways

To investigate how SOX8 mediates its effects, we explored its relationship with the KRAS and TGF-β signaling cascades. SOX8 knockdown resulted in the upregulation of key components of the KRAS pathway, specifically AKT and mTOR (**Figure 5**). This upregulation was also observed when cells were treated with the TGF-β inhibitor LY364947, whereas the addition of TGF-β recombinant protein resulted in downregulation (**Figure 5**).

These findings suggest that SOX8 acts as a critical mediator between the KRAS and TGF-β signaling pathways. The reciprocal regulation between SOX8 and the AKT/mTOR pathway, in conjunction with the effects of TGF-β manipulation, indicates that SOX8 likely exerts its influence on KRAS-driven phenotypes through regulation of the TGF-β pathway. This establishes a novel regulatory axis wherein SOX8 modulates the downstream effects of KRAS by regulating TGF-β signaling (**Figure 6**).

Discussion

PDAC is characterized by a complex interplay of multiple signaling pathways. Oncogenic KRAS mutations are a hallmark of PDAC, serving as the central driver for tumor initiation and maintenance [9, 10], while the TGF-β signaling pathway is a critical regulator of cancer progression, promoting EMT, invasion, and metastasis in advanced stages of the disease [4, 11]. However, the molecular mechanisms by which these two powerful oncogenic pathways cooperate to orchestrate the malignant phenotype of PDAC remain largely unknown.

This study provides a crucial link in this context by identifying SOX8 as a novel downstream effector of KRAS that mediates the activation of the TGF-β signaling cascade. The finding that KRAS knockdown alters SOX8 expression and that subsequent SOX8 knockdown suppresses TGF-β signature genes strongly suggests a new signaling axis involving the KRAS pathway, SOX8 gene, and TGF-β pathway. This model provides a paradigm shift in our understanding of PDAC pathogenesis, proposing that KRAS-driven oncogenic signals are integrated into the pro-tumorigenic TGF-β pathway via SOX8.

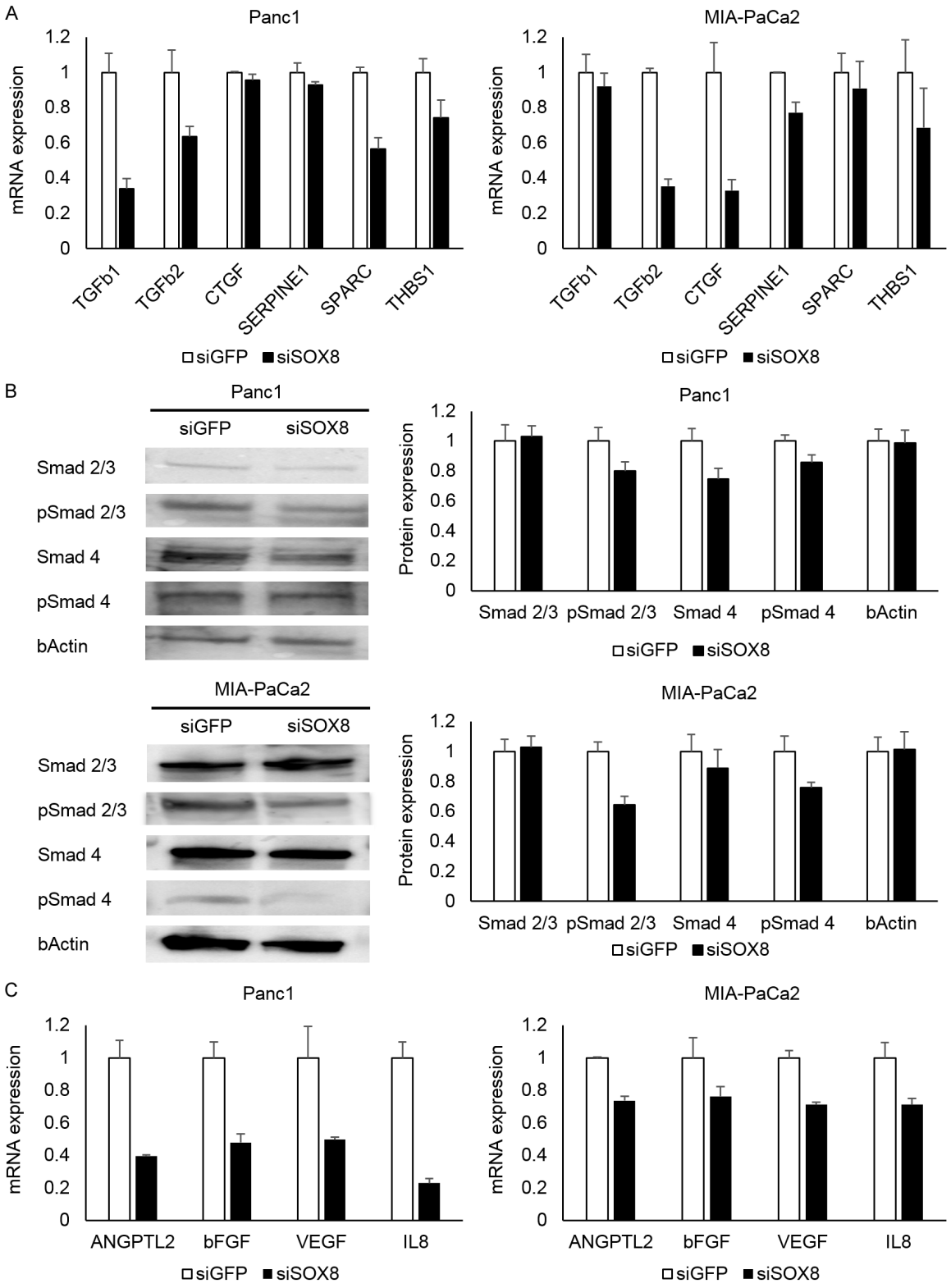

Figure 4. SOX8 regulates the TGF-β signaling pathway in pancreatic cancer cells. A. qRT-PCR analysis of TGF-β signature gene expression in Panc-1 and MIA-PaCa2 cells following siSOX8 transfection. B. Western blot analysis of canonical TGF-β signaling components. Phosphorylation of Smad2/3 and Smad4 was markedly reduced after SOX8 knockdown. C. Expression of angiogenic factors regulated by TGF-β signaling was suppressed following SOX8 silencing.

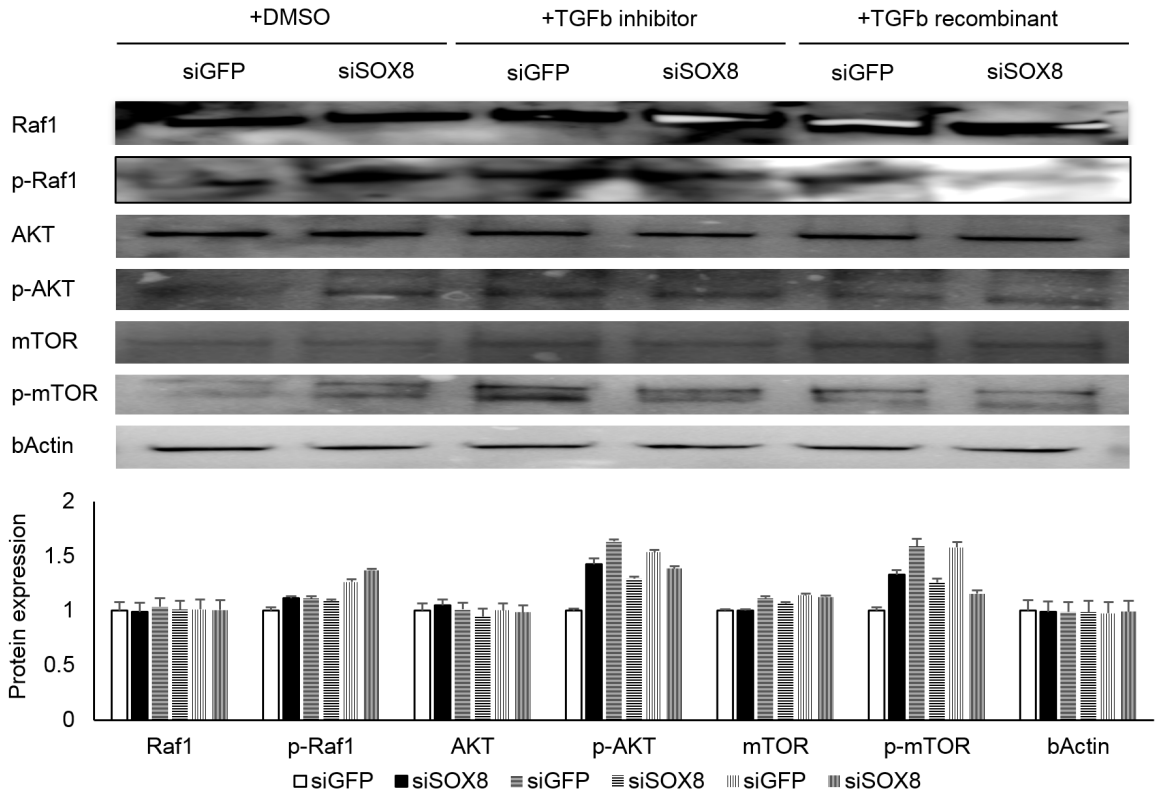

Figure 5. SOX8 links the KRAS and TGF-β signaling pathways. Western blot analysis of AKT and mTOR expression after SOX8 knockdown, treatment with the TGF-β inhibitor LY364947, or stimulation with recombinant TGF-β protein. Reciprocal regulation of AKT/mTOR components suggests that SOX8 mediates KRAS-driven phenotypes through modulation of the TGF-β signaling pathway.

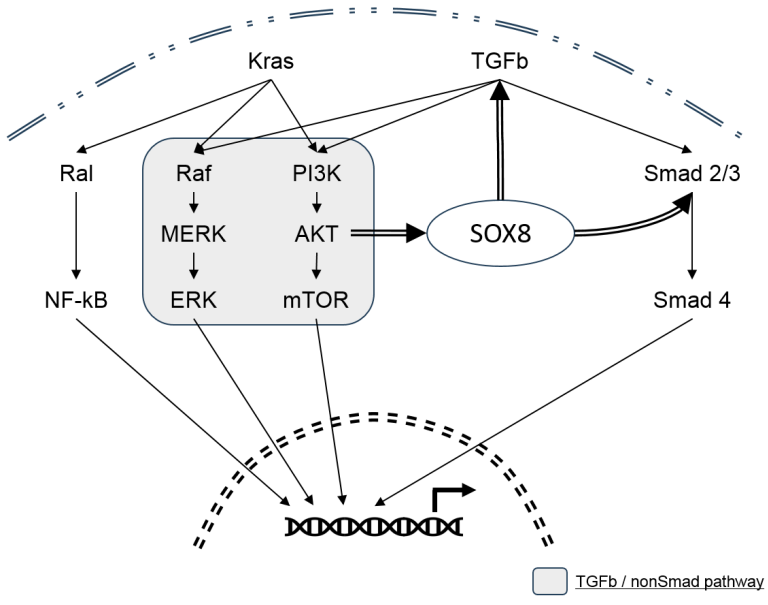

Figure 6. Hypothetical model of SOX8 as a mediator between KRAS and TGF-β signaling in pancreatic cancer. Schematic illustration showing the proposed regulatory axis in which SOX8 functions downstream of KRAS and promotes TGF-β signaling. Collectively, these findings suggest that SOX8 acts as a critical mediator linking the KRAS and TGF-β pathways, thereby facilitating epithelial-mesenchymal transition, proliferation, invasion, and chemoresistance in pancreatic cancer cells.

The SOX gene family comprises transcription factors that are crucial for embryonic development and cell fate determination. Among them, SOX8 has recently drawn attention because of its aberrant expression and involvement in the malignant progression of various tumors. SOX8 has been shown to promote cancer cell invasion and metastasis in numerous cancer types. For instance, high SOX8 expression is associated with a poor prognosis in breast cancer and hepatocellular carcinoma, as it enhances the migratory and invasive potential of cancer cells [12-14]. Moreover, SOX8/EZH2/SPARC signaling induces primary chemoresistance to albumin-bound paclitaxel in PDAC [15]. This is linked to its

function as a master regulator of EMT, a key process by which cancer cells lose their epithelial characteristics and acquire a migratory and invasive mesenchymal phenotype. Our findings also suggest that SOX8 mediates this transition by activating a panel of EMT-concerned genes. Furthermore, SOX8 has been implicated in the maintenance of self-renewal and stem-like properties of cancer cells. Cancer stem cells are considered the primary cause of tumor recurrence and therapeutic resistance. Several reports showed that SOX8 regulates the expression of cancer stem cell markers and enhances tumor-forming ability, suggesting its involvement in both tumor malignancy and chemoresistance [12, 16].

Interestingly, we identified a reciprocal relationship between SOX8 and the KRAS downstream pathway. Knockdown of SOX8 suppresses TGFβ signaling while simultaneously upregulating AKT and mTOR, downstream effectors of KRAS. This finding suggests a negative feedback mechanism that suppresses the TGFβ pathway, thereby activating the KRAS-AKT/mTOR axis. Furthermore, our results with the TGF-β inhibitor LY364947, which also suppressed AKT and mTOR expression, indicate a more complex regulatory network. This suggests that SOX8 regulates the AKT/mTOR pathway not only through its influence on TGF-β signaling but also via an independent mechanism that remains to be identified. Elucidating the precise nature of this crosstalk is critical for future research. Understanding this intricate feedback loop is essential for addressing a major challenge in PDAC therapy, that is, the limited success of targeting single pathways, such as KRAS [17, 18]. Cancer cells often develop drug resistance through the activation of alternative pathways. Our findings suggest that SOX8 acts as a central hub, orchestrating a complex signaling network that allows for this adaptive response. Therefore, targeting this hub could be a comprehensive therapeutic strategy.

The results of the present study have important clinical implications. The finding that high SOX8 expression in clinical specimens correlates with poor patient prognosis indicates that SOX8 may serve as a valuable new prognostic biomarker for PDAC. Moreover, given its role as a central mediator between the two major oncogenic pathways, SOX8 may be a promising new therapeutic target. Future research should focus on developing strategies to inhibit SOX8 directly or target its downstream signaling. Exploring the efficacy of combining SOX8 knockdown with conventional chemotherapy (e.g., gemcitabine and nab-paclitaxel) in *in vivo* models is a crucial next step toward clinical translation. Furthermore, the upstream regulation of SOX8 by KRAS and the detailed molecular mechanisms of its crosstalk with both the TGF-β and KRAS signaling pathways warrant further investigation.

Despite the findings, this study has some limitations. First, most of our findings were based on *in vitro* experiments using established pancreatic cancer cell lines. Although these models are valuable for uncovering molecular mechanisms, they may not fully recapitulate the complex tumor microenvironment and cellular heterogeneity present in human pancreatic cancer. Second, although we demonstrated that SOX8 is a downstream target of KRAS and that it activates the TGF-β pathway, the precise molecular mechanism remains to be fully elucidated. The direct transcriptional targets of SOX8 that are responsible for TGF-β pathway activation have not been identified. Third, although our analysis of SOX8 expression in clinical specimens demonstrated a strong correlation with patient prognosis, a relatively small cohort was used. Finally, although we established the new KRAS-SOX8-TGFb axis, the complex feedback loop and alternative signaling pathways regulated by SOX8 remain unclear. The finding that SOX8 knockdown influences the AKT/mTOR pathway independently of TGF-β signaling suggests the existence of other regulatory mechanisms.

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All study participants provided informed consent.

Disclosure of conflict of interest

None.

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