Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

RGC-32 facilitates pancreatic cancer via activating Wnt/β-catenin signaling

Jinli He[#], Guihong Yang[#], Ronglai Cao[#], Liang Zhu[*]

Department of Gastroenterology, the First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, China

[#] These authors contributed equally to this work.

ARTICLE INFO

Original paper

Article history:
Received: June 12, 2023
Accepted: September 22, 2023
Published: December 20, 2023

Keywords:

RGC-32, Pancreatic cancer, Wnt/β-catenin, Cellular vitality, EMT

ABSTRACT

Longitudinal studies have indicated the facilitating effect of RGC-32 during diverse disease progression including pancreatic cancer, yet the systematic and detailed effect of RGC-32 during pancreatic cancer is largely unknowable. For this purpose, we took advantage of the pancreatic cancer cell line (BXPC3) with RGC-32 expression and then modulated its expression by lentivirus-mediated knockdown (shRGC-32) and overexpression (pcDNA-RGC-32). To verify the effect of Wnt/β-catenin signaling in RGC-32-based tumorigenicity, we added the agonist CT99021 to the shRGC-32 BXPC3 cell line and pancreatic cancer mouse model. The deficiency in cellular vitality (cell survival, apoptosis, cell cycle) and migration of BXPC3 were sharply rescued by shRGC-32 in vitro. Notably, the aforementioned phenotypes as well as the expression pattern of EMT-associated biomarkers of BXPC3 with shRGC-32 expression could largely rescued by the agonist of Wnt/β-catenin in vitro and in vivo. Our data indicated the facilitating effect of RGC-32 upon pancreatic cancer cell line and mouse model via activating the Wnt/β-catenin signaling, which collectively suggested the feasibility of RGC-32 as a potent diagnostic and therapeutic target of pancreatic cancer in the future.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.14.26

Introduction

Pancreatic cancer is a highly lethal malignancy that primarily affects men and is characterized by an aggressive disease course (1, 2). It is recognized as a global burden and remains a leading cause of cancer-related deaths worldwide, particularly in developed countries (3, 4). Despite advances in diagnostic techniques such as computed tomography and magnetic resonance cholangiopancreatography, the prognosis for pancreatic cancer patients remains poor. The limited understanding of the underlying pathogenesis has hindered the development of effective diagnostic and therapeutic strategies (5, 6).

One gene that has emerged as a critical player in various disease processes is the response gene to complement (RGC)-32. It has been implicated in tumorigenesis, astrocytosis, extracellular matrix deposition, pulmonary fibrosis, T lymphocyte cell cycle regulation, and Th17 cell differentiation in experimental autoimmune encephalomyelitis (7-9). For example, Cui et al. demonstrated that RGC-32 deficiency can suppress hepatic steatosis by reducing lipogenesis (10). In contrast, Zhu et al. showed that RGC-32 promotes the transition of pancreatic cancer cells to an epithelial-mesenchymal state, thereby promoting tumorigenicity during the epithelial-mesenchymal transition (EMT) (11). However, the specific mechanisms by which RGC-32 contributes to pancreatic cancer progression remain largely unknown.

In this study, we aimed to investigate the role of RGC-32 in pancreatic cancer using the BXPC3 pancreatic cancer cell line and a pancreatic cancer mouse model. By modulating the expression of RGC-32 in BXPC3 cells through lentivirus-mediated knockdown (shRGC-32) or overexpression (pcDNA-RGC-32), we sought to elucidate the impact of RGC-32 on tumorigenicity in vitro. Additionally, we examined the effects of Wnt/β-catenin signaling activation on the cellular vitality and migration of pancreatic cancer cells with RGC-32 knockdown. The Wnt/β-catenin pathway has been implicated in various cellular processes, including proliferation, migration, and differentiation, and its dysregulation has been associated with cancer development and progression.

Our preliminary results demonstrate that RGC-32 expression is significantly elevated in the BXPC3 pancreatic cancer cell line compared to a healthy control cell line, HPDE. Knockdown of RGC-32 in BXPC3 cells led to increased expression of GSK-3β, a negative regulator of the Wnt/β-catenin pathway, and decreased expression of β-catenin and WNT1, key components of the pathway. Conversely, overexpression of RGC-32 resulted in decreased GSK-3β expression and increased β-catenin and WNT1 expression compared to control cells. These findings suggest that RGC-32 plays a role in activating the Wnt/β-catenin signaling pathway in pancreatic cancer cells.

To further investigate the tumorigenicity of RGC-32 in pancreatic cancer, we assessed cellular vitality, including cell survival, apoptosis, and cell cycle progression, in BXPC3 cells with RGC-32 knockdown or overexpression. Additionally, we evaluated cell migration and the expression of epithelial-mesenchymal transition (EMT)-associated biomarkers. Notably, we found that the inhibitory effects of RGC-32 knockdown on cellular vitality and the promotion of cell migration could be rescued by activating

* Corresponding author. Email: zhuliang2016zl@163.com

the Wnt/β-catenin signaling pathway in both in vitro and in vivo models.

Materials and Methods

Cell culture

The pancreatic cancer cell line BXPC3 was cultured in RPMI 1640 basal medium with 10% FBS and 100 U/mL penicillin and 100 μg/mL streptomycin addition (denoted as culture medium) under 37°C, 5% CO_2. For cell passage, the BXPC3 cells were dissociated with 1 mL 0.25% Trypsin/EDTA for 1 min, and then the cells were enriched by centrifugation at 37°C, 5% CO_2. For RGC-32 knockdown and overexpression, 2.0×10^5 BXPC3 cells were treated with lentivirus-mediated shRGC-32 and pcDNA-RGC-32, respectively.

Flow cytometry (FCM) assay

To verify the impact of RGC-32 knockdown and overexpression as well as Wnt/β-catenin signal activation upon pancreatic cancer cells, the cells in the indicated groups and time points were turned to FCM assay for cellular vitality analyses, including cell cycle and cell apoptosis. In detail, the single cells were stained with fluorescent antibodies in 0.2% BSA for 30 min in the dark. Then, the cells were washed with 1×PBS twice and turned to FACS Canto II (BD Biosciences) for FCM analysis.

Western-blotting analysis

To determine the expression of the indicated proteins, we conducted a western-blotting analysis as reported before with several modifications (12, 13). In brief, the cells in the indicated groups were collected and washed with 1×PBS twice. Then, the cells were lysed for protein enrichment. After that, we took advantage of the SDS-PAGE electrophoresis and transmembrane for western blot, which were followed by developing and imaging of the indicated bands.

Quantitative real-time PCR (qRT-PCR) analysis

To determine the mRNA expression of the indicated genes, the cells in the aforementioned groups were washed with 1×PBS twice. Then, the cells were lysed by using the TRIZol regent (ThermoFisher, Waltham, MA, USA) for total mRNA collection as described before (12, 14). After that, we utilized the TransScript Fly cDNA Synthesis SuperMix kit (Transgen Biotech, Beijing, China) for cDNA synthesis and the SYBR Green PCR Master Mix (Qiagen, Duesseldorf, Germany) regent for qRT-PCR analysis.

Statistical analysis

Data were statistically analyzed using Statistical Product and Service Solutions (SPSS) 23.0 software (IBM, Armonk, NY, USA). Measurement data were expressed by ($\bar{x}\pm s$) and compared between groups *via* independent-samples *t*-test. Count data were expressed by percentage (%), and compared *by* x^2 test. $P<0.05$ indicated that the data difference was statistically significant.

Results

The activated Wnt/β-catenin signal in pancreatic cancer was impaired by RGC-32 knockdown

To verify the bio-function and underlying mechanism of RGC-32 during pancreatic cancer, we initially took advantage of the pancreatic cancer cell line BXPC3 and the healthy control cell line HPDE. With the aid of qRT-PCR and western-blotting analysis, we found that RGC-32 was highly expressed in BXPC3 (Figure 1A-1B). Then, we constructed RGC-32 cells with RGC-32 knockdown (denoted as shRGC-32 BXPC3) and ectopic overexpression (denoted as pcDNA-RGC-32 BXPC3), respectively. Notably, we found the shRGC-32 BXPC3 showed an increased level of GSK-3β expression whereas with a decline in β-catenin and WNT1 expression (Figure 1C-1D). Conversely, the pcDNA-RGC-32 BXPC3 revealed decreased level of GSK-3β expression whereas with an increase in β-catenin and WNT1 expression compared to the control group (Figure 1C-1D). Taken together, these data indicated the higher level of RGC-32 expression in pancreatic cancer cell line BXPC3, and RGC-32 was adequate for activating the Wnt/β-catenin signaling pathway.

The decline in cellular vitality of shRGC-32 BXPC3 could be efficiently rescued by Wnt/β-catenin signal activation

As mentioned above, RGC-32 knockdown could significantly impair the activation of the Wnt/β-catenin signal in pancreatic cancer cell line BXPC3, yet the detailed impact upon the cellular vitality of BXPC3 was largely

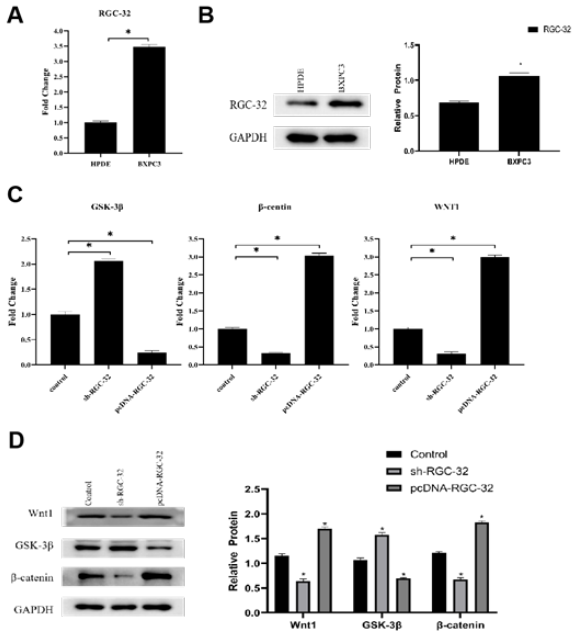

Figure 1. Modulation of RGC-32 expression in BXPC3 and the potent impact upon Wnt/β-catenin signaling pathway. (A) qRT-PCR analysis of the mRNA expression of RGC-32 in pancreatic cancer cell line BXPC3 and healthy control cell line HPDE. (B) Western blotting analysis of the protein expression of RGC-32 in pancreatic cancer cell line BXPC3 and healthy control cell line HPDE. (C) qRT-PCR analysis of the mRNA expression of Wnt signal-associated genes (GSK-3β, β-catenin, WNT1) in pancreatic cancer cell line BXPC3 with RGC-32 knockdown (sh-RGC-32), or RGC-32 overexpression (pcDNA-RGC-32), and the control BXPC3 (control). (D) Western blotting analysis of the protein expression of Wnt signal-associated genes (GSK-3β, β-catenin, Wnt1) in the indicated pancreatic cancer cell line BXPC3, including sh-RGC-32, pcDNA-RGC-32, and the control BXPC3 (control). All data were shown as mean±SEM (N=3 independent experiments). *, P<0.05.

unknown. For this purpose, we assessed the cell survival rate of control BXPC3, shRGC-32 BXPC3 and shRGC-32 BXPC3 with CT99021 addition (Wnt/β-catenin signal activation). Notably, shRGC-32 BXPC3 revealed a sharp decline in cell survival rate compared with the control BXPC3, whereas CT99021 addition could efficiently rescue the decline in cell survival rate (Figure 2A). Meanwhile, the significant enhancement of apoptosis in shRGC-32 BXPC3 could be efficiently suppressed by CT99021 addition (Figure 2B). As to the impact of Wnt/β-catenin signal activation on the cell cycle, we observed the moderate enhancement of CT99021 addition to the G2 subpopulation whereas the decline to the G1 and S substages (Figure 2C). Additionally, as shown by the immunofluorescent images of ki-67, the decline in the percentage of ki-67$^+$ cells in shRGC-32 BXPC3 could be efficiently enhanced after CT99021 addition (Figure 2D, P<0.05). Collectively, our data indicated the essential role of Wnt/β-catenin signal activation in rescuing shRGC-32-mediated impaired cellular vitality of BXPC3.

The decline in *ex vivo* migration of shRGC-32 BXPC3 was partially rescued by Wnt/β-catenin signal activation

Having illuminated the Wnt/β-catenin signal activation upon cellular vitality, we next turned to verify the impact upon cell migration of shRGC-32 BXPC3. As shown in Figure 3A, the shRGC-32 BXPC3 revealed a sharp decline in cell invasion according to the transwell assay, whereas the CT99021 addition efficiently rescued the deficiency (Figure 3A-3B). On the basis of the cell scratch assay, we

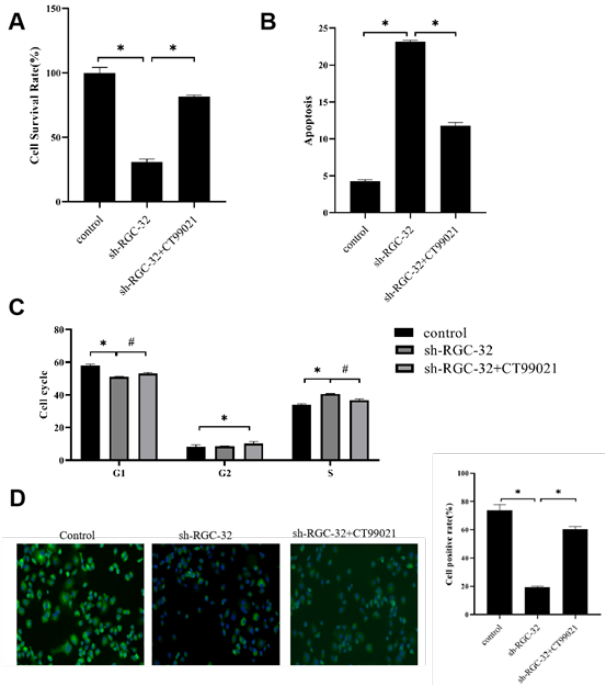

Figure 2. Wnt/β-catenin signal activation efficiently rescued the deficiency of sh-RGC-32 BXPC3 in cellular vitality. (A-B) The cell survival rate (A) and apoptosis (B) of control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition. (C) The distribution of the sub-stages of cell cycles (G1, G2, S) of the indicated BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition). (D) Immunofluorescent staining of Ki-67$^+$ cells in the indicated BXPC3. All data were shown as mean±SEM (N=3 independent experiments). *, P<0.05; #, P<0.01.

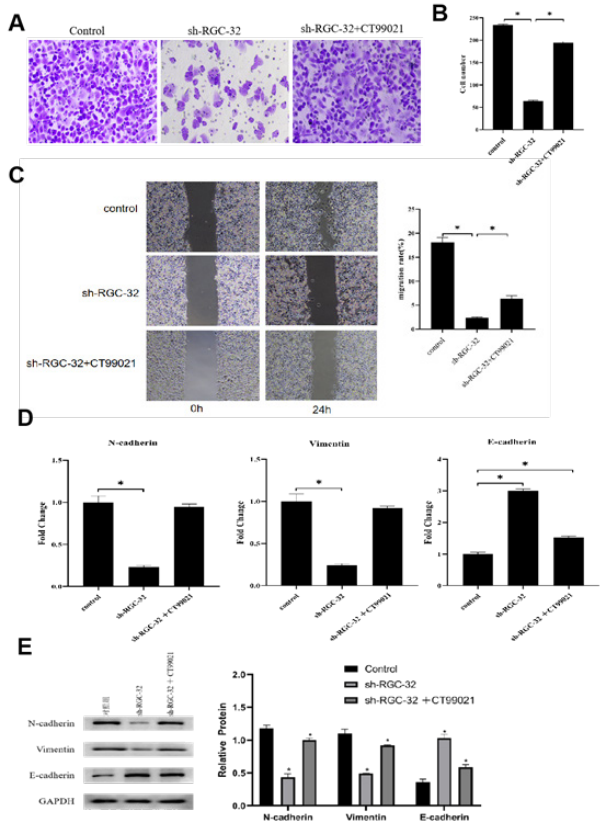

Figure 3. Wnt/β-catenin signal activation partially rescued the deficiency of sh-RGC-32 BXPC3 in migration. (A-B) Transwell assay showed the morphology (A) and cell number (B) of the indicated BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition). (C) The scratch assay revealed the morphology (left panel) and migration rate (right panel) of the indicated BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition). (D) qRT-PCR analysis of the mRNA expression of EMT-associated genes (N-cadherin, Vimentin, E-cadherin) in the indicated BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition). (E) Western-blotting analysis of EMT-associated genes (N-cadherin, Vimentin, E-cadherin) in the indicated BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition). All data were shown as mean±SEM (N=3 independent experiments). *, P<0.05.

observed a significant decrease in shRGC-32 BXPC3 migration compared to the control BXPC3, which could only be partially rescued by CT99021 addition (Figure 3C). Notably, with the aid of qRT-PCR assay and western-blotting assay, we found that the expression of mesenchyme- (N-cadherin, Vimentin) and epithelial- (E-cadherin) associated biomarkers were sharply downregulated and upregulated in shRGC-32 BXPC3, respectively (Figure 3D-3E). Instead, CT99021 addition could efficiently reverse the deficiency of shRGC-32 BXPC3 (Figure 3D-3E). Taken together, these data indicated the Wnt/β-catenin signal activation in rescuing the deficiency in cell invasion and migration.

The decline in *in-vivo* tumorigenesis and migration of shRGC-32 BXPC3 was largely rescued by Wnt/β-catenin signal activation

To further assess the Wnt/β-catenin signal activation upon tumorigenesis and migration of shRGC-32 BXPC3

in vivo, we implanted the aforementioned BXPC3 (control BXPC3, shRGC-32 BXPC3 and shRGC-32 BXPC3 with CT99021 addition) into nude mice of the subcutaneous tumor transplantation model. Distinguishing from those with shRGC-32 BXPC3 transplantation, we noticed the continuous increase in tumor volume and weight after control BXPC3 transplantation (Figure 4A). As to the shRGC-32 BXPC3 with CT99021 addition group, the tumor volume and weight in mice revealed a moderate increase, which was also confirmed by the pathological analyses (Figure 4A-4C). Furthermore, with the aid of western-blotting assay and qRT-PCR assay, we also observed the expression of mesenchyme- (N-cadherin, Vimentin) and epithelial- (E-cadherin) associated biomarkers was sharply downregulated and upregulated in mice tumor tissue with shRGC-32 BXPC3 transplantation, respectively (Figure 4D-4F). Consistently, CT99021 addition could efficiently reverse the deficiency of mice with shRGC-32 BXPC3 transplantation (Figure 4D-4F). Taken together, these data indicated the *in vivo* Wnt/β-catenin signal activation in rescuing the deficiency in cell invasion and migration in null mice.

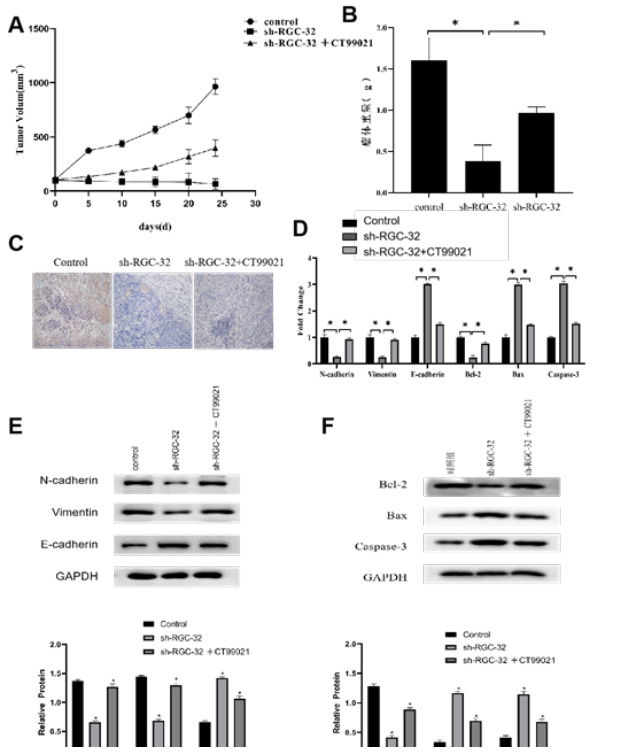

Figure 4. Wnt/β-catenin signal activation effectively rescued the decline of sh-RGC-32 BXPC3 in tumorigenesis. (A-B) The volume (A) and weight (B) of tumors formed by the transplanted BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition) in null mice. (C) The immunohistochemical (IHC) staining of tumors formed by the transplanted BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition) in null mice. (D) qRT-PCR analysis of the mRNA expression of EMT-associated genes (N-cadherin, Vimentin, E-cadherin) and apoptosis-associated genes (Bcl-2, Bax, Caspase-3) in the indicated BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition). (E-F) Western-blotting analysis of EMT-associated genes (N-cadherin, Vimentin, E-cadherin) (E) and apoptosis-associated genes (Bcl-2, Bax, Caspase-3) (F) in the indicated BXPC3 (control BXPC3, sh-RGC-32 BXPC3, and sh-RGC-32 BXPC3 with CT99021 addition). All data were shown as mean±SEM (N=3 independent experiments). *, $P<0.05$.

Discussion

For decades, pancreatic cancer has caused discouraging outcomes and numerous death worldwide, which is largely due to the deficiency in precise diagnosis and the arcane regulatory mechanisms (14). In this study, we took advantage of the in vitro and in vivo models to dissect the RGC-32-based regulatory mechanism in facilitating pancreatic cancer from the aspects of cellular vitality, cell migration and tumorigenesis. Furthermore, we verified the essential role of Wnt/β-catenin signal activation in mediating the oncogenic effect of RGC-32 during pancreatic cancer. Collectively, our data indicated the activation of the RGC-32- Wnt/β-catenin axis in pancreatic cancer.

Longitudinal studies have indicated the pathogenesis of pancreatic cancer from the view of preclinical and clinical investigations, and in particular, the classical Wnt/β-catenin signal (15-17). For instance, Tang *et al* verified the inhibitory effect of m^6A demethylase ALKBH5 (AlkB Homolog 5) during pancreatic cancer tumorigenesis in gemcitabine-treated patient-derived xenograft (PDX) model via suppressing the WIF-1 RNA methylation as well as mediating Wnt signaling (18). Instead, Chen and colleagues identified the facilitating effect of USP28 during pancreatic cancer progression via activating the Wnt/β-catenin signaling pathway and stabilizing FOXM1 (19). Interestingly, Ercan et al and Liu et al put forward the existence of pancreatic cancer stem cells (PCSCs) modulated by signal cascades (e.g., TGF-β, WNT, Hedgehog and NOTCH signal) and upregulation of Wnt receptors (ROR1 and ROR2) in pancreatic ductal adenocarcinoma (PDAC), respectively (20, 21).

Simultaneously, numerous literatures have also indicated the involvement of transcription factors in pancreatic cancer in combination with the Wnt /β-catenin signaling pathway. For instance, Xu and colleagues demonstrated the inhibitory effect of Cadherin 13 (CDH13) overexpression upon pancreatic cancer progression by suppressing the Wnt/β-catenin signaling pathway and the resultant suppression of epithelial-mesenchymal transition (EMT) (22). Similarly, Zhu and Ding also confirmed the facilitating effect of RGC-32 in inducing the transition of pancreatic cancer in vivo (11). However, the role of comprehensively expressed RGC-32 remains controversial for a long period (23-25). In this study, we took advantage of the pancreatic cancer cell line BXPC3 with RGC-32 high expression and verified the promoting effect upon pancreatic cancer from the view of cellular vitality and cell invasion via activating the Wnt/β-catenin signaling pathway. Meanwhile, we utilized the null mouse model and confirmed the facilitating effect of the RGC-32-Wnt/β-catenin axis during pancreatic cancer by simultaneously orchestrating the EMT-associated factors (E-cadherin, N-cadherin, and Vimentin) and apoptosis-associated factors (Bcl-2, Bax, and Caspase-3).

Collectively, our data highlighted the carcinogenic effect of RGC-32 during pancreatic cancer both *in vitro* and *in vivo* by modulating cellular vitality and migration via activating the Wnt/β-catenin signaling pathway. Our findings will supply new references for the further development of novel diagnosis and drug discovery based on the RGC-32-Wnt/β-catenin axis in the future.

Ethics approval
The ethical approval of the study was approved by the Ethical Committee of the First Affiliated Hospital of Nanchang University (approval no. CDYFY-IACUC-202302QR073).

Consent for publication
Not applicable.

Availability of data and material
All data generated or analyzed during this study, together with the additional files, are included in this published article. Meanwhile, the datasets involved in the current study are available from the corresponding author upon reasonable request.

Competing interests
The authors declare that they have no competing interests and all the coauthors consent to publish the data.

Funding
This work was supported by grants from the project of the Jiangxi Provincial Department of Science and Technology (No. 20202BBGL73109), National Natural Science Foundation of China (No. 82160694), and the project of Jiangxi Provincial Administration of Traditional Chinese Medicine (No. 2023A0021).

Authors' contributions
J.L.H., G.H.Y. and R.L.C.: designed and performed the experiments, collection and assembly of data, manuscript writing; J.L.H., G.H.Y., R.L.C., and L.Z.: data analysis and interpretation, manuscript writing; J.L.H., G.H.Y., R.L.C., and L.Z.: conception and design, revision, final approval of the manuscript. All co-authors have read and approved the final manuscript.

Acknowledgements
The co-authors thank all the doctors and nurses in the Department of Gastroenterology, the First Affiliated Hospital of Nanchang University for their technical support.

References

1. Goral V. Pancreatic Cancer: Pathogenesis and Diagnosis. Asian Pac J Cancer Prev 2015; 16(14): 5619-5624.
2. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011; 378(9791): 607-620.
3. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastro Hepat 2021; 18(7): 493-502.
4. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroentero 2016; 22(44): 9694-9705.
5. Chu LC, Goggins MG, Fishman EK. Diagnosis and Detection of Pancreatic Cancer. Cancer J 2017; 23(6): 333-342.
6. Cai J, Chen H, Lu M, et al. Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. Cancer Lett 2021; 520: 1-11.
7. Tegla CA, Cudrici CD, Nguyen V, et al. RGC-32 is a novel regulator of the T-lymphocyte cell cycle. Exp Mol Pathol 2015; 98(3): 328-337.
8. Luzina IG, Rus V, Lockatell V, et al. Regulator of Cell Cycle Protein (RGCC/RGC-32) Protects against Pulmonary Fibrosis. Am J Resp Cell Mol 2022; 66(2): 146-157.
9. Rus V, Nguyen V, Tatomir A, et al. RGC-32 Promotes Th17 Cell Differentiation and Enhances Experimental Autoimmune Encephalomyelitis. J Immunol 2017; 198(10): 3869-3877.
10. Cui XB, Luan JN, Chen SY. RGC-32 Deficiency Protects against Hepatic Steatosis by Reducing Lipogenesis. J Biol Chem 2015; 290(33): 20387-20395.
11. Zhu L, Ding Y. RGC-32 induces transition of pancreatic cancer to epithelial mesenchyme in vivo. Pancreatology 2018; 18(5): 572-576.
12. Zhang L, Wang H, Liu C, et al. MSX2 Initiates and Accelerates Mesenchymal Stem/Stromal Cell Specification of hPSCs by Regulating TWIST1 and PRAME. Stem Cell Rep 2018; 11(2): 497-513.
13. Wei Y, Hou H, Zhang L, et al. JNKi- and DAC-programmed mesenchymal stem/stromal cells from hESCs facilitate hematopoiesis and alleviate hind limb ischemia. Stem Cell Res Ther 2019; 10(1): 186.
14. Zhang L, Wei Y, Chi Y, et al. Two-step generation of mesenchymal stem/stromal cells from human pluripotent stem cells with reinforced efficacy upon osteoarthritis rabbits by HA hydrogel. Cell Biosci 2021; 11(1): 6.
15. Farooqi AA, Nayyab S, Martinelli C, et al. Regulation of Hippo, TGFbeta/SMAD, Wnt/beta-Catenin, JAK/STAT, and NOTCH by Long Non-Coding RNAs in Pancreatic Cancer. Front Oncol 2021; 11: 657965.
16. Cai K, Deng L, Zheng D, Li L, He Z, Yu C. MICAL1 facilitates pancreatic cancer proliferation, migration, and invasion by activating WNT/beta-catenin pathway. J Transl Med 2022; 20(1): 528.
17. Aguilera KY, Le T, Riahi R, et al. Porcupine Inhibition Disrupts Mitochondrial Function and Homeostasis in WNT Ligand-Addicted Pancreatic Cancer. Mol Cancer Ther 2022; 21(6): 936-947.
18. Tang B, Yang Y, Kang M, et al. m(6)A demethylase ALKBH5 inhibits pancreatic cancer tumorigenesis by decreasing WIF-1 RNA methylation and mediating Wnt signaling. Mol Cancer 2020; 19(1): 3.
19. Chen L, Xu Z, Li Q, et al. USP28 facilitates pancreatic cancer progression through activation of Wnt/beta-catenin pathway via stabilising FOXM1. Cell Death Dis 2021; 12(10): 887.
20. Liu D, Sharbeen G, Phillips P, Ford CE. ROR1 and ROR2 expression in pancreatic cancer. Bmc Cancer 2021; 21(1): 1199.
21. Ercan G, Karlitepe A, Ozpolat B. Pancreatic Cancer Stem Cells and Therapeutic Approaches. Anticancer Res 2017; 37(6): 2761-2775.
22. Xu D, Yuan H, Meng Z, et al. Cadherin 13 Inhibits Pancreatic Cancer Progression and Epithelial-mesenchymal Transition by Wnt/beta-Catenin Signaling. J Cancer 2020; 11(8): 2101-2112.
23. Fazeli F, Ahanjan M. The capacity of stem cells in treatment of diabetes. Cell Mol Biomed Rep 2022 Dec 1;2(4):230-44. doi: 10.55705/cmbr.2022.357066.1060.
24. Azeez SH, Jafar SN, Aziziaram Z, Fang L, Mawlood AH, Ercisli MF. Insulin-producing cells from bone marrow stem cells versus injectable insulin for the treatment of rats with type I diabetes. Cell Mol Biomed Rep 2021 Apr 1;1(1):42-51. doi: 10.55705/cmbr.2021.138888.1006.
25. Zhu L, Qin H, Li PY, et al. Response gene to complement-32 enhances metastatic phenotype by mediating transforming growth factor beta-induced epithelial-mesenchymal transition in human pancreatic cancer cell line BxPC-3. J Exp Clin Canc Res 2012; 31(1): 29.