

ARTICLE OPEN



Impaired insulin secretion via the Wnt5a/ β -catenin pathway contributes to diabetes development in pancreatic cancer

Minyoung Lee^{1,2,10}, Ho Seon Park^{3,10}, Hyung Sun Kim⁴, ARim Choi³, Ji Hae Nahm⁵, Beom Jin Lim⁵, Jong Suk Park^{3,6}, Chul Woo Ahn^{3,6}, Younhee Ko⁷, Dong Ki Lee³, Dong Sup Yoon⁸, Joon Seong Park^{4,9} and Shinae Kang^{3,6}

© The Author(s) 2026

Diabetes is highly prevalent in individuals with pancreatic ductal adenocarcinoma (PDAC) and even precedes diagnosis of PDAC; however, the mechanisms of pancreatic cancer-associated blood glucose deterioration remain largely unknown. Here, we constructed a prospective cohort of patients undergoing pancreatectomy to investigate the underlying mechanism of PDAC-associated hyperglycemia. A total of 160 patients who underwent pancreatectomy (72 patients with PDAC and 88 patients without PDAC) were enrolled at a tertiary care hospital. Glucometabolic parameters under oral glucose tolerance test were assessed in both pre- and postoperative periods, and patient-derived blood and pancreatic tissue samples were collected. Compared with patients without PDAC, patients with PDAC showed severe hyperglycemia with impaired insulin secretion before surgery. However, despite identical type of pancreatectomy in both groups, hyperglycemia improved more significantly and insulin secretory function declined less after pancreatectomy in patients with PDAC. Plasma Wnt5a and pancreatic islet β -catenin levels were higher in patients with PDAC and correlated with the degree of hyperglycemia and insulin deficiency. Plasma Wnt5a levels also correlated with tumor size and pancreatic islet β -catenin expression in patients with PDAC. In rodent islets, Wnt5a treatment suppressed insulin release, which was recovered by inhibition of β -catenin. Collectively, impaired pancreatic insulin secretion by aberrant Wnt5a/ β -catenin activation may underlie the hyperglycemia associated with PDAC. Our finding provides insights into the unique molecular mechanism of pancreatic cancer-associated hyperglycemia, paving the way for the identification of potential biomarker and therapeutic targets for this condition.

Experimental & Molecular Medicine (2026) 58:272–283; <https://doi.org/10.1038/s12276-025-01625-8>

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has a very poor survival rate, as most tumors are unresectable at diagnosis¹. New-onset diabetes or worsening of pre-existing diabetes has been reported in a large proportion of patients with PDAC^{1–3}, and possible pathophysiological associations between PDAC and incident diabetes have been described^{4,5}. Therefore, studies to understand the missing link between PDAC and diabetes may enable early detection of PDAC² and provide novel therapeutic targets for PDAC-associated diabetes.

Nevertheless, the distinct glucometabolic characteristics of PDAC-associated hyperglycemia have not been fully understood. A shortage of circulating insulin may partly explain hyperglycemia in PDAC⁴, but whether this reflects reduced β -cells or impaired insulin secretory function remains unclear. Importantly, there has not been adequate translational prospective human studies to investigate PDAC-associated metabolic features, partially because of the limited availability of biochemical

samples from patients with PDAC with an appropriate surgical control group⁶.

To overcome these methodological limitations, we constructed a prospective cohort of 160 patients who underwent pancreatectomy. The database of the cohort contains information ranging from comprehensive glucometabolic parameters under oral glucose tolerance test (OGTT) to patient-derived blood samples and pancreatic tissues. Using this cohort, we investigated the changes in the phenotype of PDAC-associated diabetes before and after PDAC removal, as well as the underlying mechanisms with key molecules, thereby suggesting a potential biomarker for screening and tailored therapeutic targets for PDAC-induced diabetes.

MATERIALS AND METHODS

Study participants

We built a prospective cohort of 160 patients who underwent pancreatectomy, mainly pylorus-preserving pancreaticoduodenectomy

¹Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea. ²Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, South Korea. ³Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. ⁴Department of Surgery, Pancreatobiliary Cancer Clinic, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. ⁵Department of Pathology, Gangnam Severance Hospital, Seoul, South Korea. ⁶Severance Institute for Vascular and Metabolic Research, Yonsei University College of Medicine, Seoul, South Korea. ⁷Division of Biomedical Engineering, Hankyong University of Foreign Studies, Gyeonggi-do, South Korea. ⁸Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. ⁹Department of Surgery and Cancer Research Institute, Seoul National University Hospital, Seoul, South Korea. ¹⁰These authors contributed equally: Minyoung Lee, Ho Seon Park.

✉email: jspark330@gmail.com; SHINAE95@yuhs.ac

Received: 16 September 2024 Revised: 30 September 2025 Accepted: 28 October 2025

Published online: 28 January 2026

(PPPD) (72 patients with PDAC and 88 patients without PDAC), at Gangnam Severance Hospital in Seoul, South Korea, from December 2014 to February 2019 (Supplementary Fig. 1a). The exclusion criteria were as follows: (1) diagnosis of neuroendocrine pancreatic tumor ($n=4$), (2) pancreatic cancer other than adenocarcinoma (for example, mucocystic carcinoma) ($n=3$), and (3) steroid use before surgery ($n=1$). Diabetes and prediabetes were defined according to the American Diabetes Association guidelines⁷. New-onset diabetes was defined as diabetes diagnosed less than 2 years before entry into the cohort, and recently aggravated diabetes was defined as the development of uncontrolled hyperglycemia less than 1 year before entry into the cohort in patients with known diabetes. The characteristics of the 160 patients are summarized in Supplementary Table 1. The human study protocol was approved by the independent institutional review board of Gangnam Severance Hospital, Seoul, South Korea (3-2014-0024).

Mice

Healthy C57BL/6N male mice (8 weeks old) were housed in groups of three mice per cage, with free access to food and water under a strict 12-h light/dark cycle at a controlled temperature ($23 \pm 2^\circ\text{C}$). All the animal experiments were approved by the Institutional Animal Care and Use Committee of Yonsei University Health System (YUHS-IACUC, 2019-0133).

Cells

Insulinoma β -cell line, Min6 cells were maintained in Dulbecco's modified Eagle medium (Gibco, Thermo Fisher Scientific/Gibco) supplemented with 10% fetal bovine serum and antibiotics (100 U/ml penicillin and 100 $\mu\text{g}/\text{ml}$ streptomycin). These were originally received from Prof. Myung-Shik Lee, Yonsei University College of Medicine.

Biochemical measurement of human participants

All patients underwent a 75 g OGTT just before and 2 weeks and 1 year after pancreatectomy. After an overnight fast, sampling was performed at 0, 30, 60, 90, and 120 min after oral intake of 75 g glucose to measure serum glucose and insulin levels. Serum biochemical parameters were evaluated after an overnight fast and 2 h after a normal meal. Serum glucose was measured by the glucose oxidase method using a 747 automatic analyzer (Hitachi). The levels of total cholesterol, triglyceride, and high-density lipoprotein cholesterol were quantified using an enzymatic colorimetric method (Hitachi 747, Daiichi). The low-density lipoprotein cholesterol content was calculated using the Friedewald formula⁸. Glycated hemoglobin A1c (HbA1c) levels were measured using high-performance liquid chromatography (Cobas Integra 800, Roche). Insulin and glucagon levels were measured using a radioimmunoassay method (Roche Diagnostics for insulin; MP Biomedicals for glucagon).

Metabolic assessment of human participants

Hypertension was defined as systolic blood pressure (BP) of ≥ 140 mm Hg or diastolic BP of ≥ 90 mm Hg, current use of BP-lowering medication, or a self-reported history of hypertension. Dyslipidemia was defined as low-density lipoprotein cholesterol levels ≥ 160 mg/dl and/or triglyceride levels ≥ 200 mg/dl and/or high-density lipoprotein cholesterol levels < 40 mg/dl⁹, or current use of lipid-lowering medication. Homeostasis model assessment of β -cell function (HOMA- β) and homeostatic model assessment of insulin resistance (HOMA-IR) were calculated as $(360 \times \text{fasting insulin } (\mu\text{IU}/\text{ml})) / (\text{fasting glucose } (\text{mg}/\text{dl}) - 63)$ and $(\text{fasting insulin } (\mu\text{IU}/\text{ml}) \times \text{fasting glucose } (\text{mg}/\text{dl})) / 405$, respectively¹⁰. The Matsuda index was defined as $10,000 / \sqrt{(\text{fasting glucose} \times \text{fasting insulin} \times \text{mean glucose} \times \text{mean insulin})}$ ¹¹. The insulinogenic index was also calculated as $(\text{insulin } (30 \text{ min}) - \text{insulin } (0 \text{ min})) / (\text{glucose } (30 \text{ min}) - \text{glucose } (0 \text{ min}))$ ¹². The disposition index obtained from the OGTT was used to evaluate the composite degree of insulin secretion in conjunction with insulin sensitivity and was calculated as the Matsuda index \times insulinogenic index¹³.

Pancreatic specimen collection

Specimens from human pancreas were obtained from Gangnam Severance Hospital (Seoul, South Korea) during the surgical procedure of pancreatectomy for histologic analysis. All pancreatic tissues were processed for formalin-fixed, paraffin-embedded and fresh-frozen pancreatic specimens.

Mouse islet isolation and culture

Islets of 12–15-week-old C57BL/6 male mice were isolated by perfusion of the pancreas, followed by digestion using collagenase P solution in Hank's balanced salt solution¹⁴. Islet cells were collected and cultured.

GO enrichment analyses

In this study, we used a microarray dataset from the public database library of the Gene Expression Omnibus (GEO) associated with pancreatic cancer¹⁵ and diabetes¹⁶. Gene set enrichment analysis (GSEA) and Gene Ontology (GO) enrichment analysis were applied to the differentially expressed genes (DEGs) from these datasets. Gene sets were defined on the basis of GO and hallmark gene sets in the Molecular Signatures Database (MSigDB). GSEA was performed using the Java GSEA version 3.0 platform to generate enriched pathways, and enriched GO terms for DEGs were identified using a hypergeometric test.

RESULTS

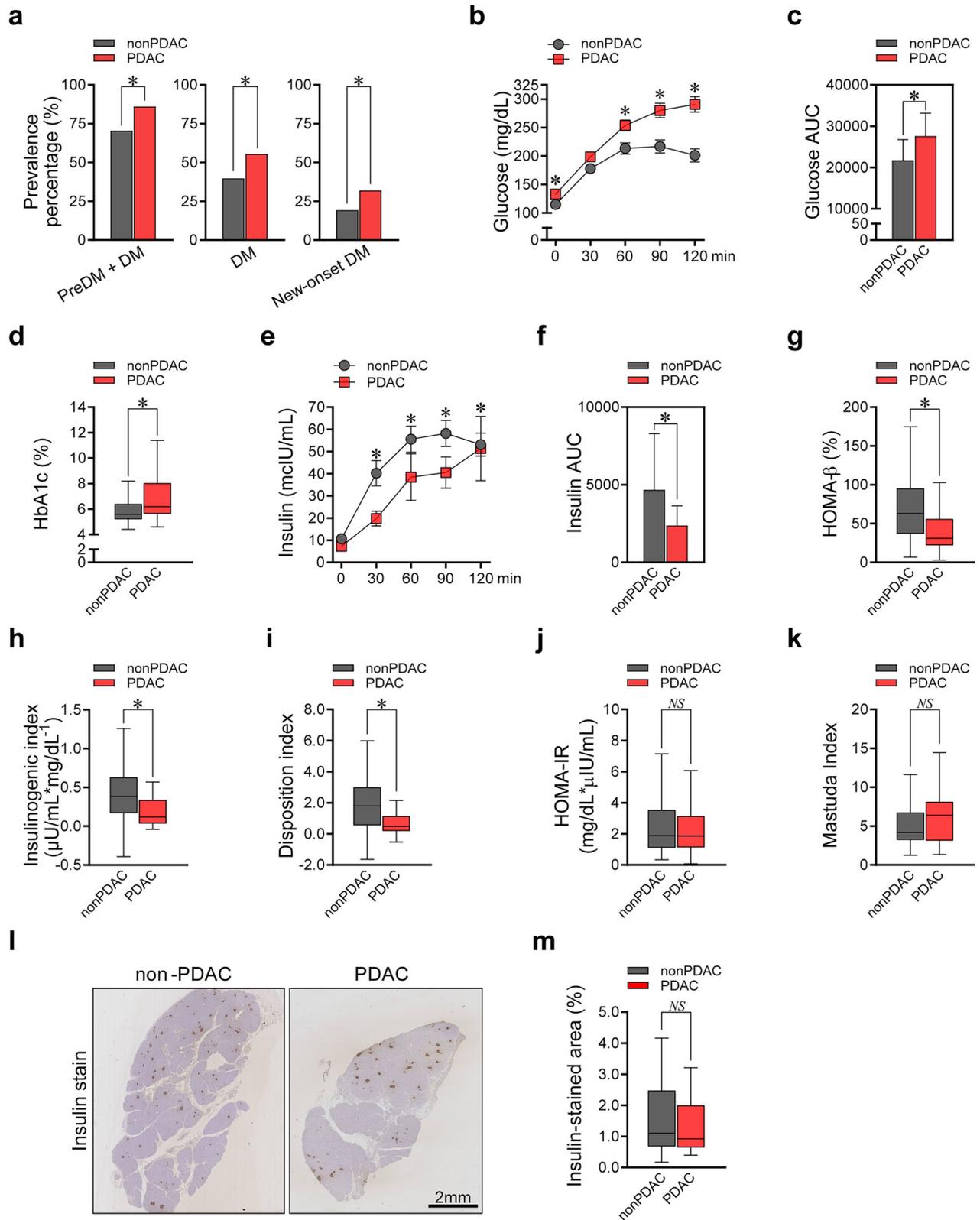
PDAC is significantly associated with worsened hyperglycemia and reduced insulin secretion

Among the 160 patients enrolled prospectively in our pancreatectomy cohort, 88 were patients without PDAC and 72 were patients with PDAC (Supplementary Fig. 1a). The baseline characteristics and metabolic assessments before surgery are presented in Supplementary Table 1. The clinical diagnoses of patients in the non-PDAC group are summarized in Supplementary Fig. 1b. Compared with the patients without PDAC, patients with PDAC had a higher prevalence of a composite of prediabetes and diabetes (70.5% versus 86.1%), as well as diabetes (39.8% versus 55.6%), and new-onset (< 2 years) diabetes (19.3% versus 31.9%) (Fig. 1a). Compared with the patients without PDAC, the patients with PDAC exhibited more severe hyperglycemia, higher fasting and postprandial glucose levels, greater glucose area under the curve (AUC) during OGTT, and elevated HbA1c (Fig. 1b–d). The PDAC group also exhibited significantly lower insulin secretory capacity, with reduced postprandial insulin, insulin AUC during OGTT, HOMA- β , insulinogenic index, and disposition index compared with the non-PDAC group (Fig. 1e–i). No difference was observed in insulin resistance-related parameters, such as HOMA-IR and Matsuda index (Fig. 1j, k). The histological analyses of surgical pancreatic specimens revealed no difference in insulin-stained β -cell area between the PDAC versus the non-PDAC groups (Fig. 1l, m). Altogether, hyperglycemia in patients with PDAC was mainly associated with the impaired insulin secretory function in patients with PDAC compared with patients without PDAC preoperatively.

There were no significant differences between the PDAC and non-PDAC groups in pre-existing metabolic comorbidities other than diabetes, or in nonglycemic metabolic indicators such as waist circumference, weight, body mass index (BMI), BP, and lipid profile (Supplementary Table 1). Therefore, the observed differences in glycemic and insulin secretion markers between the two groups were probably independent of underlying vulnerability to pre-existing metabolic disorders.

Tumor removal recovers hyperglycemia and β -cell dysfunction in patients with PDAC

To address whether hyperglycemia and impaired insulin secretion were caused by pancreatic cancer cells in patients with PDAC, we evaluated the changes of glucometabolic parameters after 'the intervention' of tumor removal. To minimize the impact from the surgical procedure itself on blood glucose levels, we restricted analysis to those who underwent PPPD as their surgical method and enrolled patients without PDAC who underwent the same PPPD surgery as a control group. The comparison before and after surgery was analyzed specifically among 97 patients who underwent PPPD, out of a total of 160 patients who received any type of pancreatectomy.



The changes in glucometabolic profiles at 14 days (Fig. 2 and Supplementary Table 2) and 1 year (Supplementary Fig. 2 and Supplementary Table 3) after PPPD are presented. At 14 days post-PPPD, the BMI decreased significantly in both the PDAC and non-PDAC groups (Fig. 2a), but the degree of BMI reduction did not

significantly differ between the two groups (Fig. 2b). In both the PDAC and non-PDAC groups, the glucose levels during OGTT significantly decreased 14 days after surgery (Fig. 2c); however, the PDAC group showed a significantly greater reduction in post-prandial glucose than the non-PDAC group (-23 mg/dl versus

Fig. 1 Glucometabolic characteristics of patients with PDAC versus patients without PDAC before surgery. a–k The following parameters were compared between patients with PDAC and patients without PDAC before surgery: the prevalence of prediabetes and diabetes, diabetes, and new-onset diabetes (**a**); serum glucose levels during the 2-h OGTT (**b**); glucose AUC during the 2-h OGTT (**c**); HbA1c (**d**); serum insulin levels during the 2-h OGTT (**e**); insulin AUC during the 2-h OGTT (**f**); HOMA- β (**g**); insulinogenic index (**h**); disposition index (**i**); HOMA-IR (**j**); and Matsuda index (**k**). **l, m** Immunohistochemical staining on the pancreatic tissue of the resection margin obtained from PPPD surgery: representative insulin immunostaining image (magnification, 20 \times ; scale bar, 2 mm) (**l**); quantification of the percentage of insulin-positive area in the total pancreatic area (**m**). All data are presented as medians with interquartile ranges, except for **a** (percentages) and **b** and **e** (means with standard error of the mean). * $P < 0.05$ by chi-squared test (**a**), Mann–Whitney U -test (**b** except for differences in glucose at 60 and 90 min, **c–k**, and **m**), or Student's t -test (differences in glucose at 60 and 90 min in **b**); NS, statistically nonsignificant.

–61 mg/dl) (Fig. 2d and Supplementary Table 2). The HbA1c levels also decreased in both groups (Fig. 2e), but to a greater degree in the PDAC group (–0.1% versus –0.4%) (Fig. 2f).

At day 14 post-PPPD, the insulin levels during OGTT decreased significantly in both the patients with PDAC and those without PDAC (Fig. 2g). However, the decline in insulin levels during OGTT was significantly less in the patients with PDAC (Fig. 2h). Although the PPPD procedure itself reduced insulin levels due to the loss of pancreatic volume common to both groups, the relatively smaller decrease observed in patients with PDAC compared with those without PDAC may be explained by partial restoration of insulin secretion following tumor removal in patients with PDAC, as insulin secretion had been suppressed before surgery. This is also supported by additional insulin secretory indices, such as the insulin AUC during OGTT and insulinogenic index, as these parameters significantly decreased only in the non-PDAC group but not in the PDAC group after PPPD (Fig. 2i–l and Supplementary Table 2). Improvements in HOMA-IR and the Matsuda index did not significantly differ between the PDAC and the non-PDAC groups (Fig. 2m–p). The disposition index significantly improved in the PDAC group, while there was no change in the non-PDAC group 14 days after PPPD (Supplementary Table 2). Both PDAC and non-PDAC groups showed a significant reduction in pancreatic volume after PPPD compared with preoperative measurements (Supplementary Table 2). However, there was no significant difference in the amount of volume reduction between the two groups ($P = 0.318$), suggesting the extent of pancreatic resection may not have caused differences in β -cell loss affecting insulin secretory capacity.

At 1 year post-PPPD, participants in both PDAC and non-PDAC groups showed a slight decrease in BMI without any difference between the groups (Supplementary Fig. 2a, b). In both PDAC and non-PDAC groups, the glucose levels decreased (Supplementary Fig. 2c), but the decrease in fasting glucose levels was more pronounced in the PDAC group than in the non-PDAC group (Supplementary Fig. 2d). In addition, the HbA1c level significantly decreased in the PDAC group 1 year after surgery but not in the non-PDAC group (Supplementary Fig. 2e, f). Interestingly, the insulin levels significantly decreased in the non-PDAC group, while they were relatively preserved in the PDAC group at 1 year post-PPPD (Supplementary Fig. 2g, h). Insulin secretory function, determined as HOMA- β , significantly improved in the PDAC group but not in the non-PDAC group (Supplementary Fig. 2i, j). Meanwhile, HOMA-IR did not change 1 year after PPPD in both the PDAC and non-PDAC groups (Supplementary Fig. 2k, l). Collectively, our data suggest a more persistent improvement in glycemic control in the PDAC group than in the non-PDAC group 1 year post-PPPD, which may be attributed to recovery of the insulin secretory function.

Plasma Wnt5a level is increased in patients with PDAC and correlates with the degree of impairment in insulin secretion

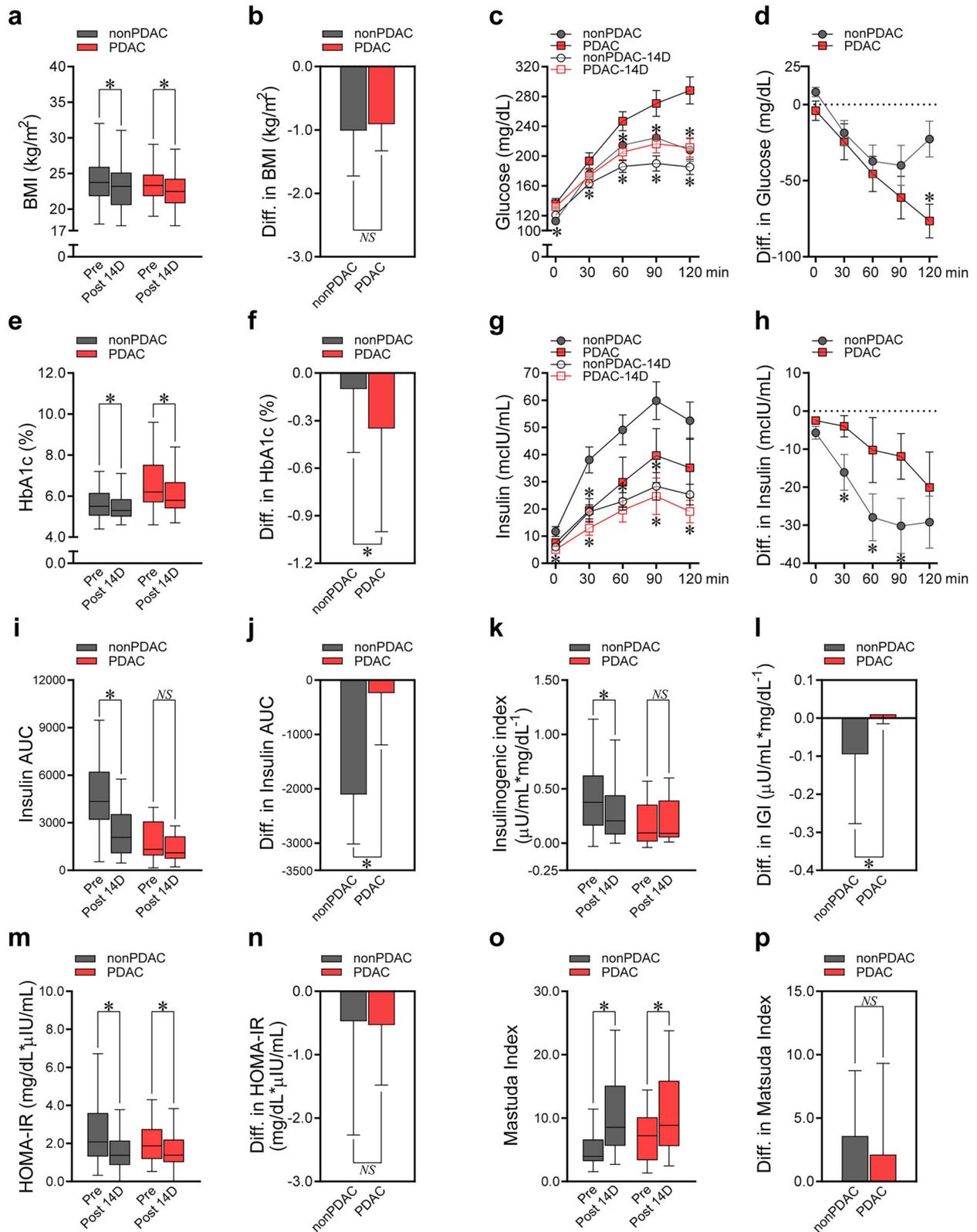
We analyzed the public microarray data from the tumor specimens of patients with PDAC and the islet tissue of patients with diabetes^{15,16} (Supplementary Fig. 3a, b) and found that the Wnt/ β -catenin signaling may be a plausible pathway involved in PDAC-associated diabetes^{17–21}. After preliminary testing of several

molecules of the Wnt/ β -catenin pathway using our cohort sample, we further investigated Wnt5a as a candidate molecule for PDAC-induced hyperglycemia^{22–24}. Wnt5a was highly expressed in the tumor cells arising from the pancreatic duct in the patients with PDAC compared with the normal ductal cells from the patients without PDAC (Fig. 3a). Correspondingly, higher plasma levels of Wnt5a were observed in patients with PDAC (Fig. 3b). Furthermore, plasma Wnt5a levels significantly correlated with the primary tumor size, glucose AUC during OGTT, and HbA1c in patients with PDAC but not in patients without PDAC (Fig. 3c–e). The plasma Wnt5a levels also negatively correlated with insulin secretory parameters such as insulin AUC during OGTT, HOMA- β , and insulinogenic index in the PDAC group but not in the non-PDAC group (Fig. 3f–h). Interestingly, plasma Wnt5a levels also positively correlated with the serum levels of CA19-9, a widely used serum biomarker for pancreatic cancer²⁵ (Supplementary Table 4).

We also evaluated the changes in plasma Wnt5a levels after tumor removal and its association with hyperglycemia and insulin secretion. At 14 days after PPPD, plasma Wnt5a levels were significantly decreased only in the PDAC group (Supplementary Fig. 4a). A greater decrease in plasma Wnt5a at 14 days after PPPD was associated with a larger reduction in HbA1c levels and greater improvement in the insulinogenic index in the PDAC group (Supplementary Fig. 4b, c). At 1 year after PPPD, a higher baseline plasma Wnt5a level was significantly associated with a greater reduction of fasting glucose and HbA1c levels and a greater improvement of HOMA- β in the PDAC group only (Supplementary Fig. 4d–f).

Islet β -catenin expression correlates with the degree of hyperglycemia and impaired insulin secretory function in PDAC

To further elucidate the Wnt5a-related mechanism in PDAC-induced hyperglycemia, we evaluated the expression of β -catenin, a part of the canonical Wnt signaling pathway, in the pancreatic islets and analyzed the association between its expression level and various glucometabolic parameters. The identical resection margins of the pancreas from PPPD surgery, whether PDAC or non-PDAC, were used for histological analysis. Both exocrine and islet β -cell areas in the pancreas of patients with PDAC had a significantly higher expression of β -catenin than those of patients without PDAC (Fig. 4a, b). In high-magnification images assessing nuclear translocation associated with β -catenin activation²³, β -catenin within 4',6-diamidino-2-phenylindole (DAPI)-stained nuclei was more evident in PDAC tissues, particularly in the case accompanied by diabetes (Supplementary Fig. 5). Overall, β -catenin showed limited nuclear localization, which needs to be interpreted in the context of membrane-dominant original subcellular distribution and the fasting state at the time of pancreatic tissue collection during surgery, in which β -catenin tends to remain in the cytoplasm^{21,26}. Patients with PDAC who also have diabetes showed an even higher expression of β -catenin than patients with PDAC without diabetes (Fig. 4c). In addition, the plasma Wnt5a level, which was increased in the patients with PDAC compared with patients without PDAC, exhibited a positive correlation with the degree of islet β -catenin expression in the



PDAC group (Fig. 4d and Supplementary Table 5). The expression level of islet β -catenin was significantly associated with the levels of fasting glucose, glucose AUC during OGTT, and HbA1c in the PDAC group, whereas no such association was found in the non-PDAC group (Fig. 4e, f and Supplementary Table 5). The insulin secretory function assessed by insulin AUC

during OGTT, HOMA- β , and insulinogenic index was negatively associated with islet β -catenin expression levels only in the PDAC group (Fig. 4g,h and Supplementary Table 5). Furthermore, the islet β -catenin expression was significantly associated with the primary tumor size in the PDAC group (Supplementary Table 5).

Fig. 2 Different patterns of changes in glucometabolic parameters between patients with and without PDAC before and 14 days after surgery. Changes in the glucometabolic parameters between patients with and without PDAC before and 14 days after surgery. **a, b** BMI. **c, d** Each point of serum glucose levels during the 2-h OGTT. **e, f** HbA1c. **g, h** Each point of serum insulin levels during the 2-h OGTT. **i, j** Insulin AUC during the 2-h OGTT. **k, l** Insulinogenic index. **m, n** HOMA-IR. **o, p** Matsuda index. In **a, c, e, g, i, k, m,** and **o**, glucometabolic parameters before PPPD were compared with those after PPPD for PDAC and non-PDAC groups. In **b, d, f, h, j, l, n,** and **p**, changes in glucometabolic parameters between before and 14 days after PPPD in the PDAC group were compared with those in the non-PDAC group. All data are presented as medians with interquartile ranges, except for **c, d, g,** and **h** (means with standard error of the mean). * $P < 0.05$ by Wilcoxon signed-rank test (**a**, differences in glucose at 0 min in the PDAC group in **c, e, g** except for differences in insulin at 120 min in the non-PDAC group, **i**, differences in the PDAC group in **k, m,** and **o**), paired *t*-test (**c** except for differences in glucose at 0 min in the PDAC group, differences in insulin at 120 min in the non-PDAC group in **k**), Mann-Whitney *U* test (**b**, differences in glucose at 0 min in **d, f, h, j, l, n,** and **p**), or Student's *t*-test (**d** except for differences in glucose at 0 min); NS, statistically nonsignificant. IGI, insulinogenic index; Pre, preoperative status; Post 14D, postoperative status 14 days after surgery.

Alterations in β -catenin-independent, noncanonical Wnt signaling were evaluated in pancreatic islet β -cells by measuring *c-Jun* expression^{27–30} (Supplementary Fig. 6), and no significant difference in the *c-Jun* expression in islets was observed between the PDAC and non-PDAC groups (Supplementary Fig. 6b). In analyses within each group (PDAC and non-PDAC), diabetes status did not influence *c-Jun* expression (Supplementary Fig. 6c). Despite reports of noncanonical Wnt signaling activation in pancreatic cancer²⁷, noncanonical Wnt signaling in β -cells does not appear to explain the diabetes occurring in pancreatic cancer.

Wnt5a-driven β -catenin activation significantly suppresses insulin secretion in association with decreased E-cadherin expression

To confirm Wnt5a-mediated suppression of insulin secretion *ex vivo*, we evaluated glucose-stimulated insulin secretion according to Wnt5a treatment in isolated rodent islets. Wnt5a treatment significantly reduced insulin release both at 5.6 mM and after stimulation with 20 mM glucose (Fig. 5a). Cotreatment with a β -catenin antagonist IWR-1 recovered the Wnt5a-induced insulin secretion impairment (Fig. 5a), implying that the β -catenin pathway mediates decreased insulin secretion by Wnt5a treatment. Wnt5a treatment also significantly decreased the ratio of phosphorylated/total β -catenin protein in rodent islets (Fig. 5b, c) and MIN6 insulinoma cells (Fig. 5d, e), suggesting an activation of the canonical Wnt/ β -catenin pathway^{23,31}. In MIN6 cells stimulated with 25 mM glucose (Fig. 5f), Wnt5a treatment significantly reduced insulin secretion in the siControl condition, whereas knockdown of low-density lipoprotein receptor-related protein 5 (LRP5), the canonical Wnt receptor for Wnt5a³², restored insulin secretion from the Wnt5a-induced decrease. With the addition of Wnt signaling activator, BML-284^{33,34}, the rescue of insulin secretion mediated by LRP5 knockdown was reversed.

Considering that E-cadherin is involved in the vesicular secretion of insulin from pancreatic β -cells³⁵ and is associated with β -catenin signaling^{36,37}, we investigated the changes in cellular expression levels of E-cadherin by Wnt5a treatment. Immunofluorescence staining of rodent islets revealed that E-cadherin was co-expressed along with insulin, and Wnt5a treatment decreased E-cadherin and insulin expression (Fig. 5g). Immunofluorescence staining for E-cadherin and insulin in pancreatic tissues from patients with and without PDAC also demonstrated that the pancreatic expression of E-cadherin was generally decreased in patients with PDAC compared with that in patients without PDAC. Patients with PDAC who also have diabetes showed a more pronounced decrease in E-cadherin expression compared with patients with PDAC without diabetes (Fig. 5h). The link between Wnt5a-induced β -catenin activation and E-cadherin downregulation was further substantiated by LRP5 knockdown in the β -cell line MIN6, which attenuated Wnt5a signaling in the canonical β -catenin pathway (Fig. 5i). Under the LRP5 knockdown condition, Wnt5a treatment did not produce a marked reduction in E-cadherin. Notably, restoration of β -catenin activity with Wnt pathway activator BIO led to a marked decrease

in E-cadherin even under LRP5 knockdown. Alterations in matrix metalloproteinase-7 (MMP-7) as a candidate mediator linking Wnt5a/ β -catenin to E-cadherin downregulation were also examined^{38–40}, and Wnt5a significantly upregulated MMP-7 in β -cells (Fig. 5j, k).

DISCUSSION

New-onset diabetes before detection of pancreatic cancer is frequently observed, supporting a unique causal relationship between pancreatic cancer and diabetes^{1–4}. Thus, studies on the pathophysiological mechanism to understand this relationship may enable early detection of PDAC that is preceded by hyperglycemia and identify potential therapeutic targets for PDAC-associated diabetes. In the current study, we observed that PDAC-associated diabetes was mainly attributable to decreased insulin secretion, a finding that was reversed by PDAC removal. The level of plasma Wnt5a and that of islet β -catenin expression were higher in patients with PDAC than in those without PDAC and correlated with the degree of hyperglycemia and impairments in insulin secretion. *Ex vivo* and *in vitro*, Wnt5a/ β -catenin activation suppressed insulin secretion, possibly by decreasing the expression of E-cadherin. Altogether, impaired insulin secretion via the Wnt5a/ β -catenin signaling pathway in the pancreatic islets may contribute to the development of diabetes in pancreatic cancer (Fig. 6).

While accumulating evidence supports the association between hyperglycemia and PDAC^{6,24}, there has been debate over whether insulin resistance or insulin deficiency plays a more contributory role to this association⁴¹. Insulin resistance was consistently observed in patients with PDAC and resolved after cancer resection in previous reports⁴¹. However, in the present study, the unique glucometabolic profiles in patients with PDAC, distinct from patients without PDAC, were largely explained by an insulin secretory defect. Furthermore, although there was an improvement in the indices for insulin resistance in patients with PDAC after tumor removal, patients without PDAC also showed similar improvements in insulin resistance after PPPD. Therefore, the improvement in insulin resistance in patients with PDAC is probably attributable to the PPPD surgery itself rather than the tumor removal at least in this study cohort. In the present study, the deficient insulin secretion and its recovery after PDAC removal in the patients with PDAC were verified through multiple parameters, including the insulinogenic index measured using OGTT. This allowed delicate assessments of insulin deficiency in humans, which is one of the strengths of this study.

Despite several studies pointing to paraneoplastic evidence in PDAC-associated diabetes^{42–44}, the majority are supported by animal or cell experiments, not by organized human studies. In search for possible paraneoplastic pathways of PDAC-associated diabetes, we analyzed commonly enriched gene pathways in both pancreatic cancer and diabetes using public microarray data from human tissue^{15,16}. We primarily considered secretory proteins as candidates to identify novel blood biomarkers of PDAC, especially

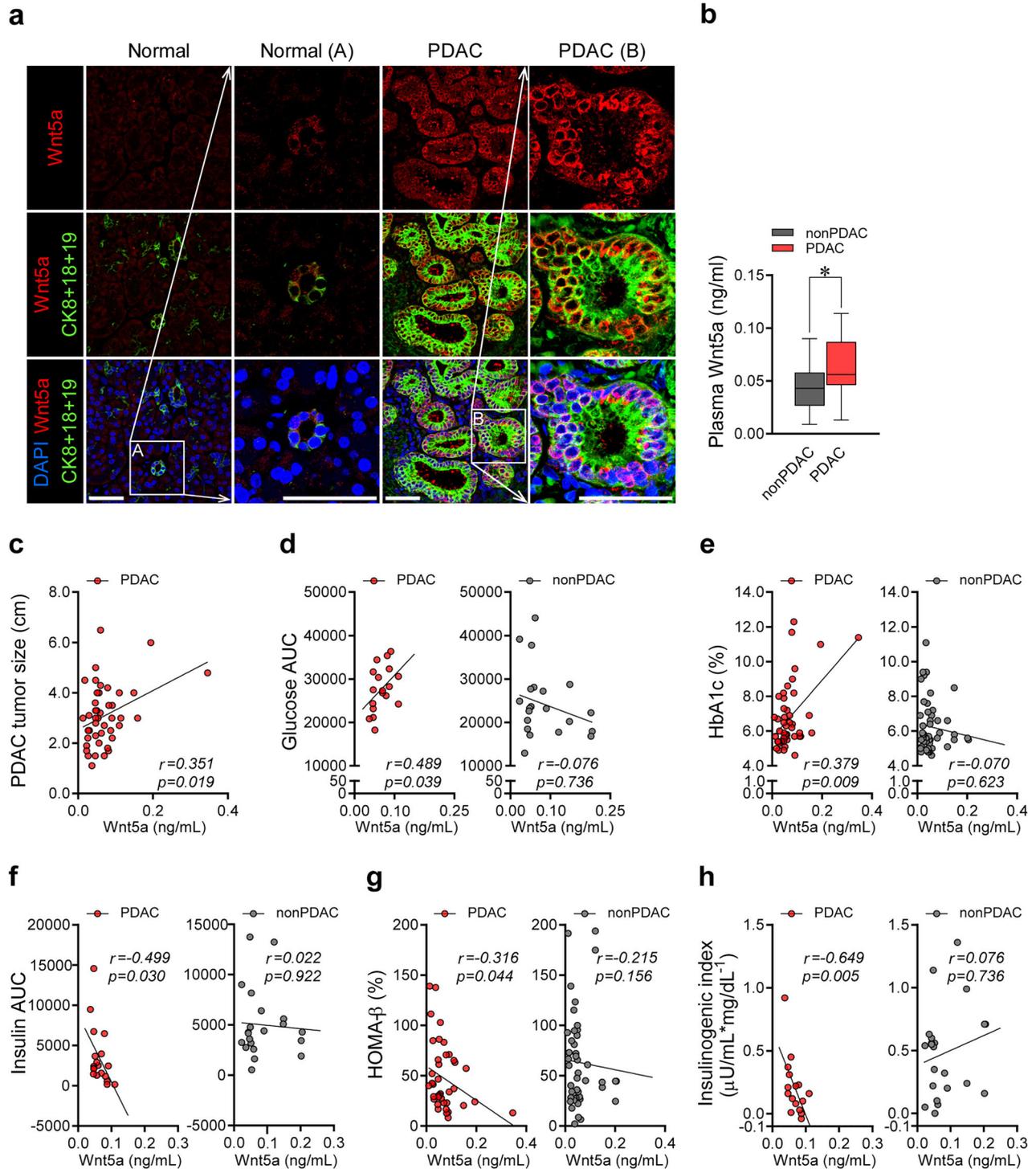


Fig. 3 Plasma Wnt5a level and its association with glucometabolic parameters before surgery. **a** Pancreatic tissue was obtained from the cancer site of patients with PDAC and from the normal site of the patients without PDAC. Representative immunofluorescence staining images for Wnt5a (red) and Cytokeratin 8 + 18 + 19 (green), a marker for pancreatic ductal epithelial cells. Magnification, 400 \times , 1080 \times . Scale bar, 50 μm . **b–h** Preoperative plasma Wnt5a levels measured by ELISA: difference in plasma Wnt5a level between PDAC and non-PDAC groups (**b**); correlation plots showing the associations between plasma Wnt5a and PDAC tumor size (**c**), glucose AUC during 2-h OGTT (**d**), HbA1c (**e**), insulin AUC during 2-h OGTT (**f**), HOMA- β (**g**), and insulinogenic index (**h**) in patients with and without PDAC. * $P < 0.05$ by Mann–Whitney U test (**b**) or Spearman's rank correlation coefficient (**c–h**); NS, statistically nonsignificant.

in those with new-onset or suddenly worsening diabetes. The Wnt pathway is an important mediator in a variety of metabolic diseases⁴⁵ and is a well-known driver of PDAC development²¹. We assessed blood levels of several ligand proteins of Wnt

signaling^{45–47}, a commonly enriched pathway in both pancreatic cancer and diabetes in our analysis, and plasma Wnt5a levels were significantly higher in PDAC patients than in non-PDAC patients. The plasma Wnt5a level and pancreatic β -catenin expression were

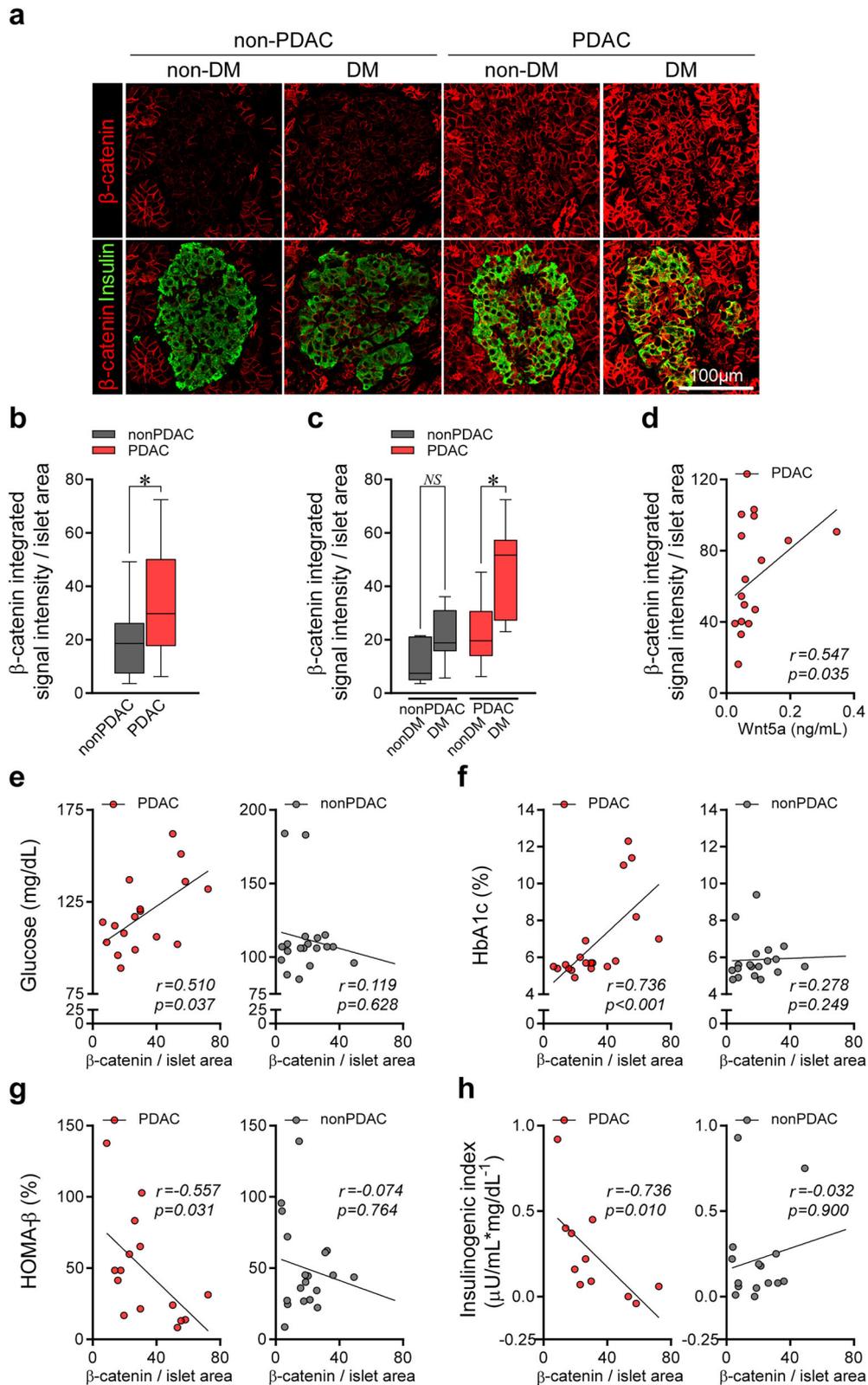
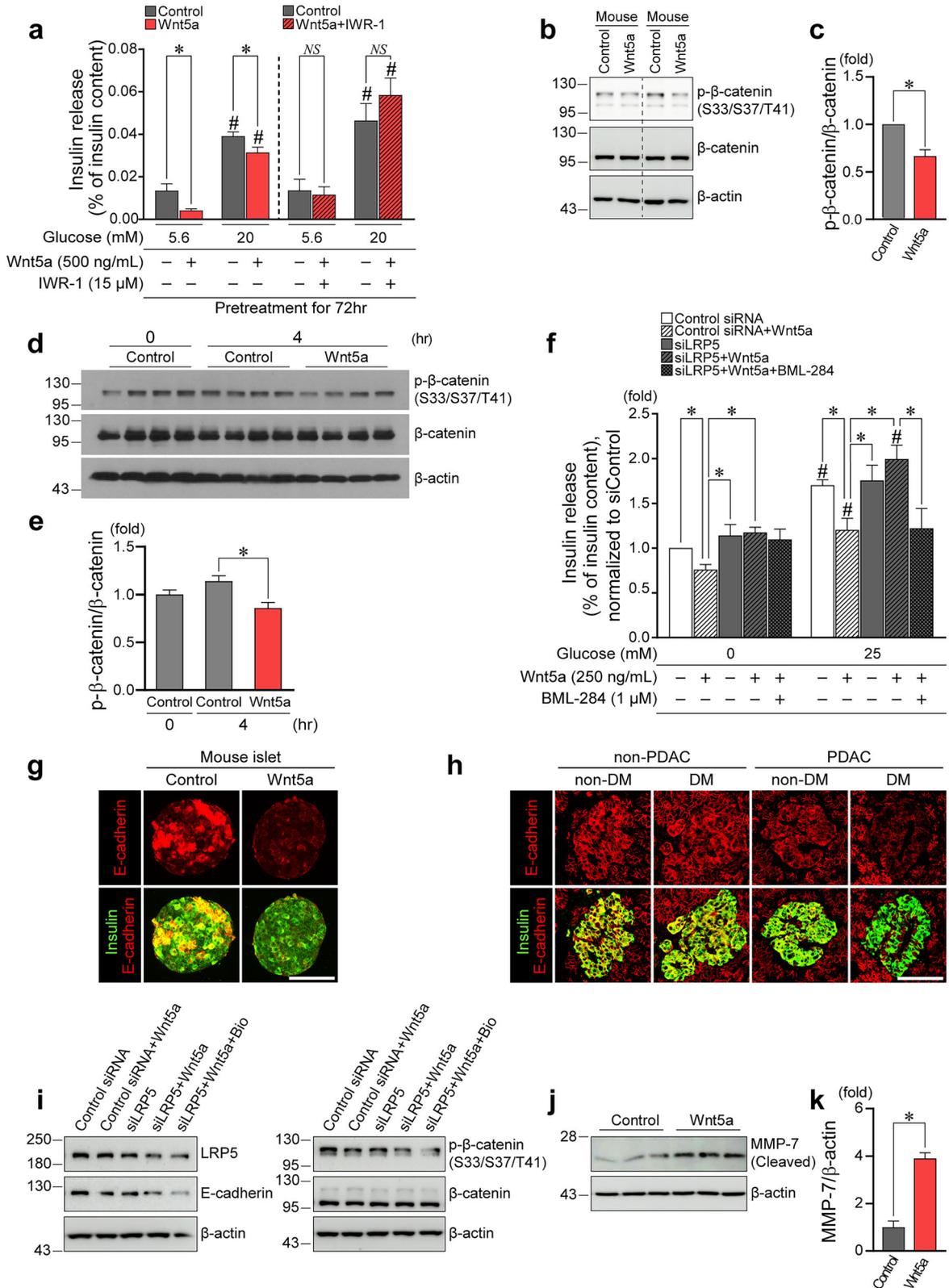


Fig. 4 Islet β -catenin expression and its association with glucometabolic parameters before surgery. Pancreatic tissue from the same site of resection margin was obtained from patients with and without PDAC and then immunostained for β -catenin and insulin. **a** Representative immunofluorescence staining images for β -catenin (red) and insulin (green) in patients with and without PDAC, with and without diabetes. Magnification, 400 \times . Scale bar, 100 μ m. **b–h** The integrated signal intensity of β -catenin expression per islet area was calculated: difference of islet β -catenin expression between PDAC and non-PDAC groups (**b**); islet β -catenin expression according to diabetes status in PDAC and non-PDAC groups (**c**); correlation plots showing the associations between the islet β -catenin expression and plasma Wnt5a level (**d**), glucose (**e**), HbA1c (**f**), HOMA- β (**g**), and insulinogenic index (**h**) in patients with and without PDAC. * $P < 0.05$ by Mann–Whitney U test (**b** and **c**) or Spearman’s rank correlation coefficient (**d–h**). NS, statistically nonsignificant; DM, diabetes mellitus.



correlated with hyperglycemia and impaired insulin secretion in patients with PDAC. In this study, knockdown of the canonical Wnt receptor at cell membrane, LRP5, reversed the Wnt5a-induced reduction in insulin secretion, providing additional evidence that Wnt5a regulates insulin secretion via the β-catenin-mediated canonical Wnt pathway³². With additional BML-284 treatment, the

effect of LRP5 knockdown was attenuated. BML-284 is a Wnt signaling activator that enhances nuclear β-catenin-dependent transcriptional activation^{33,34}. Thus, Wnt5a's impact on insulin secretion may proceed via the terminal step of the β-catenin signaling cascade, culminating in nuclear translocation and increased transcriptional activity. These findings may suggest that

Fig. 5 Wnt5a/ β -catenin pathway-driven impaired insulin secretion and its association with decreased E-cadherin expression. **a** Degree of insulin release from isolated rodent islet cells in low (5.6 mM) and high (20 mM) glucose condition with/without treatment by Wnt5a (500 ng/ml for 72 h) and β -catenin antagonist, IWR-1 (15 μ M for 72 h) (each group, $n = 5$). **b–e** Western blotting for phosphorylated and total β -catenin after Wnt5a treatment (500 ng/ml for 4 h) in isolated rodent islets and MIN6 insulinoma cells (β -actin was used as a loading control): representative western blotting image of rodent islets (**b**); quantifications of phosphorylated β -catenin per total β -catenin in rodent islets (each group, $n = 8$) (**c**); representative western blotting image of MIN6 cells (**d**); quantifications of phosphorylated β -catenin per total β -catenin in MIN6 cells (**e**). **f** Insulin release from LRP5-knockdown MIN6 cells that were left untreated, treated with Wnt5a (250 ng/ml) alone, or cotreated with Wnt5a (250 ng/ml) and BML-284 (0.1 μ M), under glucose-free (0 mM) and high-glucose (25 mM) conditions (each group, $n = 3$). Wnt5a and the Wnt signaling activator, BML-284, were treated 96 h before and 24 h after siRNA transfection. Insulin release was first calculated as the percentage of total insulin content and then normalized to siControl (= 1.0). **g, h** Isolated rodent islets and human pancreatic tissue were immunostained for E-cadherin (red) and insulin (green) (magnification, 400 \times ; scale bar, 100 μ m): representative immunofluorescence staining images in isolated rodent islets with/without Wnt5a treatment (500 ng/ml for 72 h) (**g**); representative immunofluorescence staining images in human pancreatic tissues from patients with and without PDAC, with and without DM (**h**). **i** Western blotting images of E-cadherin, phosphorylated β -catenin, and total β -catenin in LRP5-knockdown MIN6 cells. At 44 h post-siRNA transfection, cells were treated with Wnt5a (500 ng/ml) with and without BIO (1 μ M) for 4 h. **j** Representative Western blotting image of MMP-7 with and without Wnt5a treatment (500 ng/ml for 4 h) in MIN6 cells. **k** Quantifications of MMP-7 per β -actin (each group, $n = 4$). * $P < 0.05$ by Student's t -test (comparisons between control and treatment groups in **a** and **e**, except the low-glucose control versus Wnt5a+IWR-1 comparison in **a**, and between-group comparisons in **f** and **k**) or Mann-Whitney U test (low-glucose control versus Wnt5a+IWR-1 comparison in **a** and **c**). # $P < 0.05$ by paired t -test (comparisons between low- and high-glucose conditions in **a** and **f**, excluding the control condition used as the comparator for Wnt5a+IWR-1 in **a**) or Wilcoxon signed-rank test (comparison between low- and high-glucose conditions in the control condition used as the comparator for Wnt5a+IWR-1 in **a**). NS, statistically nonsignificant; DM, diabetes mellitus; LRP5, low-density lipoprotein receptor-related protein 5.

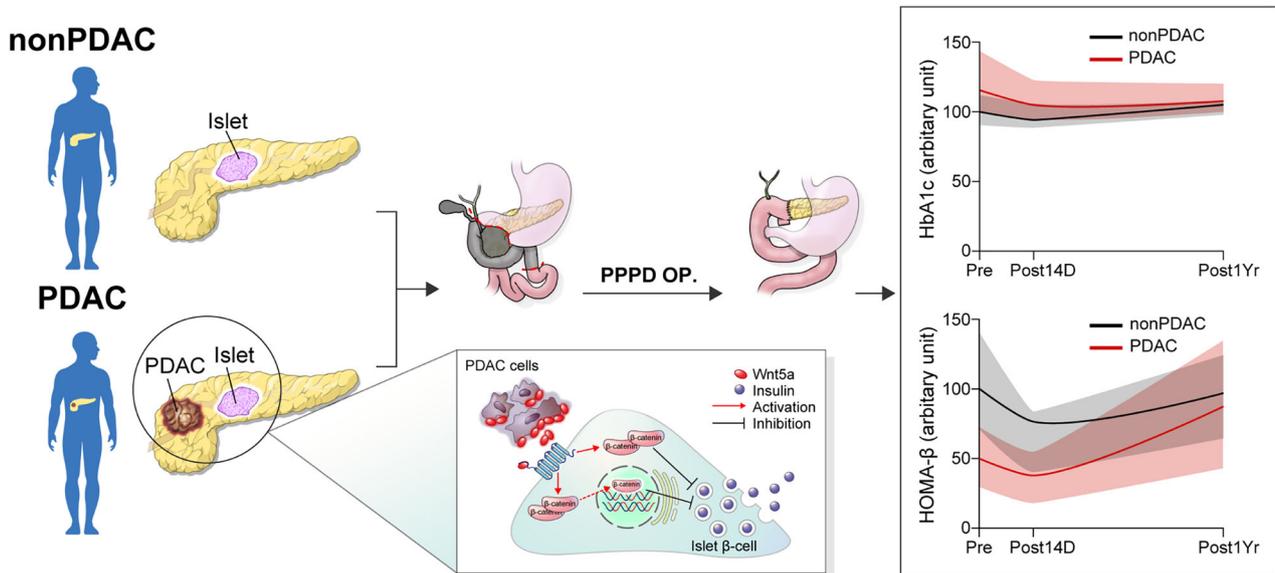


Fig. 6 Graphical overview of PDAC-associated hyperglycemia and its pathophysiological mechanisms. Greater improvement in hyperglycemia after PPPD in patients with PDAC than in those without PDAC may be due to recovery from Wnt5a/ β -catenin pathway-induced impairment of insulin secretion.

secreted Wnt5a from the PDAC is a potential diabetogenic factor that suppresses insulin secretion. Wnt5a/ β -catenin signaling pathway needs further validation as a candidate of screening for PDAC-associated diabetes, which presents with a distinct insulin secretory dysfunction.

Cadherin molecules support the release of insulin vesicles³⁵, and the loss of E-cadherin in β -cells impairs glucose-stimulated insulin secretion⁴⁸. β -Catenin forms a complex with E-cadherin that promotes insulin vesicle pooling and trafficking, enabling insulin secretory granules to be released in response to glucose in β -cells³⁵. However, the link between Wnt5a-induced β -catenin activation and E-cadherin downregulation in β -cells has not previously been addressed, especially in the pancreatic cancer microenvironment. Here, we suggested that decreased E-cadherin induced by Wnt5a and subsequent β -catenin-dependent canonical Wnt pathway activation could underlie insulin secretory defect in PDAC-associated diabetes. This phenomenon may be partly mediated by MMP-7 upregulation. In pancreatic cancer cells, β -catenin is associated with the overexpression of MMP-7³⁸, which

degrades E-cadherin, thereby weakening cell–cell junctions and facilitating tumor invasion and metastasis³⁹. However, although MMP-7 expression has been detected in pancreatic β -cells⁴⁰, there has been no evidence that its expression is modulated by Wnt signaling; this study demonstrates that Wnt signaling can increase MMP-7 expression in β -cells. Restoration of decreased E-cadherin mediated by aberrantly activated Wnt/ β -catenin pathway could be a potential therapeutic strategy to ameliorate impaired insulin secretion-induced diabetes. Further mechanistic work dissecting MMP-7, E-cadherin, and β -cell insulin secretory function is also warranted.

We evaluated the metabolic outcomes after tumor removal at 14 days post-surgery and with an extended follow-up to 1 year among patients who underwent PPPD. The average duration of hospital stay after PPPD in Korea is around 14 days⁴⁹, and the first analysis was conducted on the 14th day after surgery to observe early postoperative changes right before discharge. Differences in glycemic parameters including HbA1c were noted within a week after surgery⁵⁰, suggesting that at least 1 week post-PPPD may be

adequate for evaluating early metabolic alterations. The timing of the late postoperative follow-up was determined by considering the schedule of adjuvant chemotherapy and the overall survival. To minimize the influence of adjuvant chemotherapy on glycemic control, it was reasonable to ensure at least a 6-month interval after surgery^{51,52}. Given that the median overall survival after PDAC resection is 1–2 years^{51,52} and the 1-year survival rate is approximately 70%⁵¹, the 1-year mark was considered appropriate for follow-up in a substantial proportion of patients. Compared with the non-PDAC group, the PDAC group showed more severe hyperglycemia before surgery which was reversed even within 2 weeks after tumor removal and lasted for 1 year. The more pronounced glycemic improvement and preservation of insulin secretory function observed in the PDAC group compared with the non-PDAC group after PPPD may not be explained by differences in the pancreatectomy volume and the resulting β -cell loss or remnant intestine⁵³. The PDAC and non-PDAC groups had comparable β -cell mass per unit area of the pancreas before surgery, and due to the standardized nature of the PPPD procedure performed in both groups⁵⁴, there was no significant difference in the volume of pancreas resected between them. This supports our research hypothesis that specific molecules produced by PDAC may play important roles in impaired insulin secretion and the development of diabetes.

This study investigated the molecular link between PDAC and diabetes using patient-derived specimens and glucometabolic tests including OGTT, a gold-standard test for evaluating metabolic status. However, there are several limitations. First, postoperative metabolic features 1 year after PPPD were investigated with an insufficient number of patients. A larger number of patients with a longer follow-up duration would be helpful. Second, we addressed only Wnt5a as a candidate player in PDAC-associated diabetes. Other signaling molecules may also be involved and require further elucidation. Third, the detailed molecular mechanisms underlying Wnt5a pathway in PDAC-induced hyperglycemia should be evaluated using genetically engineered animal model in separate studies to specify therapeutic targets for PDAC-induced hyperglycemia. Fourth, the generalizability of these results to other populations may be limited, as this study was conducted in participants of Asian ethnicity.

In conclusion, using human samples from patients with pancreatic cancer and rodent islets/cells, we elucidated the underlying mechanisms of pancreatic cancer-associated diabetes. We evaluated the changes in glucometabolic profiles before and after tumor removal in patients with PDAC and compared them with those of an appropriate surgical control group: patients without PDAC who underwent the same PPPD surgery as the patients with PDAC. We demonstrated that hyperglycemia in pancreatic cancer can be explained by the aberrant Wnt5a/ β -catenin activation-induced insulin secretory defect. Our findings highlight the potential of this pathway for developing novel blood biomarkers of PDAC-associated diabetes, as well as therapeutic targets to restore insulin secretion and reduce hyperglycemia in PDAC.

DATA AVAILABILITY

Supplementary Fig. 3 was generated from the publicly available GEO database under accession codes GSE20966 and GSE16515. The remaining data can be found in the the Article or its Supplementary Information.

REFERENCES

- Ntala, C., Debernardi, S., Feakins, R. M. & Crnogorac-Jurcevic, T. Demographic, clinical, and pathological features of early onset pancreatic cancer patients. *BMC Gastroenterol.* **18**, 139 (2018).
- Sharma, A., Smyrk, T. C., Levy, M. J., Topazian, M. A. & Chari, S. T. Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. *Gastroenterology* **155**, 490–500 e492 (2018).
- Molina-Montes, E. et al. Deciphering the complex interplay between pancreatic cancer, diabetes mellitus subtypes and obesity/BMI through causal inference and mediation analyses. *Gut* **70**, 319–329 (2021).
- Andersen, D. K. et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. *Diabetes* **66**, 1103–1110 (2017).
- Hart, P. A. & Chari, S. T. Diabetes mellitus and pancreatic cancer. *Pancreas* **42**, 1207–1209 (2013).
- Singhi, A. D., Koay, E. J., Chari, S. T. & Maitra, A. Early detection of pancreatic cancer: opportunities and challenges. *Gastroenterology* **156**, 2024–2040 (2019).
- American Diabetes Association. Standards of medical care in diabetes—2019 Abridged for primary care providers. *Clin. Diabetes* **37**, 11–34 (2019).
- Friedewald, W. T., Levy, R. I. & Fredrickson, D. S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin. Chem.* **18**, 499–502 (1972).
- Jin, E. S. et al. Dyslipidemia fact sheet in South Korea, 2022. *Diabetes Metab. J.* **47**, 632–642 (2023).
- Matthews, D. R. et al. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419 (1985).
- Matsuda, M. & DeFronzo, R. A. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* **22**, 1462–1470 (1999).
- Stumvoll, M. et al. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care* **23**, 295–301 (2000).
- Oh, T. J. et al. Oral glucose tolerance testing allows better prediction of diabetes in women with a history of gestational diabetes mellitus. *Diabetes Metab. J.* **43**, 342–349 (2019).
- Kang, S. et al. Endothelial progenitor cell cotransplantation enhances islet engraftment by rapid revascularization. *Diabetes* **61**, 866–876 (2012).
- Pei, H. et al. FKBP51 affects cancer cell response to chemotherapy by negatively regulating Akt. *Cancer Cell* **16**, 259–266 (2009).
- Marselli, L. et al. Gene expression profiles of β -cell enriched tissue obtained by laser capture microdissection from subjects with type 2 diabetes. *PLoS ONE* **5**, e11499 (2010).
- Bordonaro, M. Role of Wnt signaling in the development of type 2 diabetes. *Vitam. Horm.* **80**, 563–581 (2009).
- Chocarro-Calvo, A., García-Martínez, J. osem., Ardila-González, S., De la Vieja, A. & García-Jiménez, C. Glucose-induced β -catenin acetylation enhances Wnt signaling in cancer. *Mol. Cell* **49**, 474–486 (2013).
- García-Jiménez, C., García-Martínez, J. M., Chocarro-Calvo, A. & De la Vieja, A. A new link between diabetes and cancer: enhanced WNT/ β -catenin signaling by high glucose. *J. Mol. Endocrinol.* **52**, R51–R66 (2014).
- Lee, S. H. et al. Islet specific Wnt activation in human type II diabetes. *Exp. Diabetes Res.* **2008**, 728763 (2008).
- Zeng, G. et al. Aberrant Wnt/ β -catenin signaling in pancreatic adenocarcinoma. *Neoplasia* **8**, 279–289 (2006).
- Bo, H., Gao, L., Chen, Y., Zhang, J. & Zhu, M. Upregulation of the expression of Wnt5a promotes the proliferation of pancreatic cancer cells in vitro and in a nude mouse model. *Mol. Med. Rep.* **13**, 1163–1171 (2016).
- Griesmann, H. et al. WNT5A-NFAT signaling mediates resistance to apoptosis in pancreatic cancer. *Neoplasia* **15**, 11–22 (2013).
- Relling, I. et al. Role of wnt5a in metabolic inflammation in humans. *J. Clin. Endocrinol. Metab.* **103**, 4253–4264 (2018).
- Kim, J. et al. Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers. *Sci. Transl. Med.* **9**, eah5583 (2017).
- Choi, S. W., Song, J. K., Yim, Y. S., Yun, H. G. & Chun, K. H. Glucose deprivation triggers protein kinase C-dependent β -catenin proteasomal degradation. *J. Biol. Chem.* **290**, 9863–9873 (2015).
- Chen, Y. F., Chen, Z. X., Tang, Y. & Xiao, Q. The involvement of noncanonical Wnt signaling in cancers. *Biomed. Pharmacother.* **133**, 110946 (2021).
- He, P. et al. Trophoblast glycoprotein promotes pancreatic ductal adenocarcinoma cell metastasis through Wnt/planar cell polarity signaling. *Mol. Med. Rep.* **12**, 503–509 (2015).
- Takahashi, R. et al. Therapeutic effect of c-Jun N-terminal kinase inhibition on pancreatic cancer. *Cancer Sci.* **104**, 337–344 (2013).
- Chmielowiec, J. et al. Human pancreatic microenvironment promotes β -cell differentiation via non-canonical WNT5A/JNK and BMP signaling. *Nat. Commun.* **13**, 1952 (2022).
- Mahdi, T. et al. Secreted frizzled-related protein 4 reduces insulin secretion and is overexpressed in type 2 diabetes. *Cell Metab.* **16**, 625–633 (2012).

32. Yadav, R. & Patel, B. Insights on effects of Wnt pathway modulation on insulin signaling and glucose homeostasis for the treatment of type 2 diabetes mellitus: Wnt activation or Wnt inhibition? *Int. J. Biol. Macromol.* **261**, 129634 (2024).
33. Liu, J. et al. A small-molecule agonist of the wnt signaling pathway. *Angew. Chem. Int. Ed.* **44**, 1987–1990 (2005).
34. Ahadome, S. D., Zhang, C., Tannous, E., Shen, J. & Zheng, J. J. Small-molecule inhibition of Wnt signaling abrogates dexamethasone-induced phenotype of primary human trabecular meshwork cells. *Exp. Cell Res.* **357**, 116–123 (2017).
35. Dissanayake, W. C., Sorrenson, B. & Shepherd, P. R. The role of adherens junction proteins in the regulation of insulin secretion. *Biosci. Rep.* **38**, BSR20170989 (2018).
36. Nelson, W. J. & Nusse, R. Convergence of Wnt, beta-catenin, and cadherin pathways. *Science* **303**, 1483–1487 (2004).
37. Ripka, S. et al. WNT5A-target of CUTL1 and potent modulator of tumor cell migration and invasion in pancreatic cancer. *Carcinogenesis* **28**, 1178–1187 (2007).
38. Li, Y. J., Wei, Z. M., Meng, Y. X. & Ji, X. R. β -catenin up-regulates the expression of cyclinD1, c-myc and MMP-7 in human pancreatic cancer: Relationships with carcinogenesis and metastasis. *World J. Gastroenterol.* **11**, 2117–2123 (2005).
39. Sommariva, M. & Gagliano, N. E-cadherin in pancreatic ductal adenocarcinoma: a multifaceted actor during EMT. *Cells* **9**, 1040 (2020).
40. Segerstolpe, Å et al. Single-cell transcriptome profiling of human pancreatic islets in health and type 2 diabetes. *Cell Metab.* **24**, 593–607 (2016).
41. Sah, R. P., Nagpal, S. J., Mukhopadhyay, D. & Chari, S. T. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat. Rev. Gastroenterol. Hepatol.* **10**, 423–433 (2013).
42. Basso, D. et al. The pancreatic cancer cell line MIA PaCa2 produces one or more factors able to induce hyperglycemia in SCID mice. *Anticancer Res.* **15**, 2585–2588 (1995).
43. Wang, F., Larsson, J., Adrian, T. E., Gasslander, T. & Permert, J. In vitro influences between pancreatic adenocarcinoma cells and pancreatic islets. *J. Surg. Res.* **79**, 13–19 (1998).
44. Chari, S. T., Zapiach, M., Yadav, D. & Rizza, R. A. Beta-cell function and insulin resistance evaluated by HOMA in pancreatic cancer subjects with varying degrees of glucose intolerance. *Pancreatology* **5**, 229–233 (2005).
45. Nie, X., Wei, X., Ma, H., Fan, L. & Chen, W. D. The complex role of Wnt ligands in type 2 diabetes mellitus and related complications. *J. Cell Mol. Med.* **25**, 6479–6495 (2021).
46. Kang, Y. E. et al. Serum R-Spondin 1 is a new surrogate marker for obesity and insulin resistance. *Diabetes Metab. J.* **43**, 368–376 (2019).
47. Nusse, R. & Clevers, H. Wnt/beta-catenin signaling, disease, and emerging therapeutic modalities. *Cell* **169**, 985–999 (2017).
48. Wakae-Takada, N., Xuan, S., Watanabe, K., Meda, P. & Leibel, R. L. Molecular basis for the regulation of islet beta cell mass in mice: the role of E-cadherin. *Diabetologia* **56**, 856–866 (2013).
49. Kim, Y. J. et al. Clinical outcomes of pancreaticoduodenectomy for pancreatic ductal adenocarcinoma depending on preservation or resection of pylorus. *Ann. Hepatobiliary Pancreat. Surg.* **24**, 269–276 (2020).
50. Lee, J. S., Sohn, M., Kim, K., Yoon, Y. S. & Lim, S. Glucose regulation after partial pancreatectomy: a comparison of pancreaticoduodenectomy and distal pancreatectomy in the short and long term. *Diabetes Metab. J.* **47**, 703–714 (2023).
51. Chikhladze, S. et al. Adjuvant chemotherapy after surgery for pancreatic ductal adenocarcinoma: retrospective real-life data. *World J. Surg. Oncol.* **17**, 185 (2019).
52. DePeralta, D. K. et al. Completion of adjuvant therapy in patients with resected pancreatic cancer. *HPB* **22**, 241–248 (2020).
53. Kang, C. M. & Lee, J. H. Pathophysiology after pancreaticoduodenectomy. *World J. Gastroenterol.* **21**, 5794–5804 (2015).
54. Kim, S. W., Kim, K. H., Han, J. K. & Park, Y. H. Pylorus-preservation decreases the extent of atrophy of the remnant pancreas after pancreatoduodenectomy. *HPB* **1**, 65–70 (1999).

ACKNOWLEDGEMENTS

We thank Medical Illustration & Design (MID), a part of the Medical Research Support Services of Yonsei University College of Medicine, for providing excellent support with medical illustration of graphical abstract.

AUTHOR CONTRIBUTIONS

M.L.: writing – original draft, conceptualization, methodology, investigation, formal analysis, data curation. H.S.P.: writing – original draft, methodology, investigation, formal analysis, data curation. H.S.K.: methodology, investigation, resources. A.C.: methodology, investigation, data curation. J.H.N.: methodology, investigation, resources. B.J.L.: methodology, investigation, resources. Jong Suk P.: writing – review and editing. C.W.A.: writing – review and editing. Y.K.: writing – review and editing, methodology, investigation, formal analysis. D.K.L.: writing – review and editing. D.S.Y.: writing – review and editing, methodology, investigation, resources. Joon Seong P.: writing – review and editing, supervision, conceptualization, methodology, investigation, resources. S.K.: writing – original draft, supervision, conceptualization, methodology, investigation, funding acquisition, resources.

FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government Ministry of Science and ICT (MSIT) (grant no. 2019R1A2C1086148), a faculty research grant of Yonsei University College of Medicine (grant no. 6-2018-0166), and grants from the Core Innovation Research Group (grant no. DHD000116, D-2025-0020), Gangnam Severance Hospital, Yonsei University College of Medicine.

COMPETING INTERESTS

M.L. has received lecture honoraria from JW Pharmaceutical Corporation, Boryung Corporation, Eli Lilly and Company, Merck Sharp & Dohme, HK inno.N, Servier Korea, Handok Inc., Daewoong Pharmaceutical, Kukje Pharm Co., Ltd., GC Biopharma Corporation, Jeil Pharmaceutical Co., Ltd., and Boehringer Ingelheim. All other authors have no conflicts to disclose and no other relationships or activities that could appear to have influenced the submitted work.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s12276-025-01625-8>.

Correspondence and requests for materials should be addressed to Joon Seong Park or Shinae Kang.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2026