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<td>著者 (Author(s))</td>
<td>Yuichi, Hori</td>
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<tr>
<td>掲載誌・巻号・ページ (Citation)</td>
<td>Advances in Experimental Medicine and Biology, 777:185-196</td>
</tr>
<tr>
<td>刊行日 (Issue date)</td>
<td>2013</td>
</tr>
<tr>
<td>資源タイプ (Resource Type)</td>
<td>Journal Article / 学術雑誌論文</td>
</tr>
<tr>
<td>版区分 (Resource Version)</td>
<td>author</td>
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<td>権利 (Rights)</td>
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<tr>
<td>DOI</td>
<td>10.1007/978-1-4614-5894-4_12</td>
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<td>JaLCDOI</td>
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<td>URL</td>
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PDF issue: 2019-02-18
Chapter 12

Prominin-1 (CD133) Reveals New Faces of Pancreatic Progenitor Cells and Cancer Stem Cells: Current Knowledge and Therapeutic Perspectives

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Key Words: CD133, cancer stem cell, diabetes, pancreas, prominin-1, tissue-specific stem cell
Abstract

Islet transplantation-based therapies were proven successful for type 1 diabetes mellitus but an extreme shortage of pancreatic islets have motivated recent efforts to develop renewable sources of islet-replacement tissue. Pancreatic progenitor cells hold a promising potential, yet attempts at their prospective isolation are scarce due to the lack of specific marker. We found that prominin-1 (often referred to as CD133 in humans) is expressed by the undifferentiated epithelial cells in the mouse embryonic pancreas. Putative pancreatic epithelial stem and progenitor cells were prospectively enriched in prominin-1+ cell population by cell sorting and characterized. CD133 is also a cell surface marker of human pancreatic cancer stem cells (CSC), which are resistant to conventional treatments such as chemotherapy and radiotherapy. Therefore, a considerable interest in the specific targeting and eradication of CSC is emerging for the cancer therapy, and CD133 may represent a good molecular target. In the present chapter I will summarize our current knowledge about prominin-1/CD133 in mouse and human pancreas.
12.1 Introduction

The pancreas is a glandular organ with dual role in the digestive and endocrine (hormonal) systems. Because of its location and complexity within the body, it is difficult to diagnose the numerous disorders this crucial organ is subjected to, including acute and chronic pancreatitis, diabetes and cancers. Physiologically, the pancreas secrete, as an endocrine gland, digestive enzymes into a network of ducts that finally join the main pancreatic duct. These enzymes pass through the pancreatic ducts and reach the common bile duct in an inactive form. When they enter into the duodenum via the ampulla of Vater and mix with bile, they are activated. These enzymes degrade proteins, lipids, carbohydrates and nucleic acids by the process of luminal digestion. The exocrine tissue also releases bicarbonate ions that neutralize the acidic chyme as it enters the duodenum from the stomach. As an endocrine gland, which consists of the islets of Langerhans, pancreas secrete into the bloodstream polypeptide hormones such as insulin and glucagon that play an essential role in the carbohydrate metabolism. For instance, insulin promotes the uptake of glucose by most cells, and hence, lowers plasma glucose concentration. Glucagon has metabolic effects that oppose the action of insulin. These hormones have also other effects on energy metabolism, growth and development. The insulin is generated from the proinsulin precursor molecule by the action of proteolytic enzymes,
which remove the central portion of the molecule (i.e. C-peptide). The endocrine tissue secretes also somatostatin, which has a wide variety of effects on the gastrointestinal function and may also inhibit insulin and glucagon secretion.

From a therapeutic point of view, the identification of specific cell surface antigen(s) used either for the isolation or the targeting of cells endowed with stem cell properties has recently brought new perspectives in regenerative medicine particularly regarding type 1 diabetes mellitus as well as cancer treatment. The isolation of pancreatic tissue-specific stem and progenitor cells that give rise upon differentiation to insulin-producing cells (IPC) and the identification of cancer stem cells (CSC) harboring prominin-1 as a potential molecular target are good examples.

Prominin-1 (alias PROML1, AC133 antigen or CD133 in humans) is now worldwide recognized as a marker of tissue-specific stem cells or CSC. For further details of the molecular and cellular features of this pentaspan membrane glycoprotein, I invite the readers to look at the first Chapter of this book.

In the present Chapter, I will describe in the first part the enrichment of pancreatic stem and progenitor cells from mice by means of flow cytometry fluorescence-activated cell sorting using prominin-1 as a cell surface antigen, and in the second part, the identification of
human CD133\(^+\) pancreatic CSC, which constitute potential targets in cancer therapy.

12.2 Pancreatic Stem and Progenitor Cells for Regenerative Medicine

12.2.1 Stem Cells for Replacement of Pancreatic \(\beta\)-cells

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia. One of its forms is characterized in terms of etiology and pathogenesis. Type 1 diabetes is the result of the autoimmune destruction of pancreatic endocrine \(\beta\)-cells. This category of diabetes is fatal unless treated with insulin. This means that multiple injections daily or insulin delivery through an insulin pump are necessary for survival. Moreover, patients must test their blood glucose levels several times per day. Nowadays, it is possible to transplant pancreas or islet cells with the result that the patients can live without insulin injections. Advances in the cell-replacement strategy for type 1 diabetes mellitus and the shortage of transplantable tissues have led the community to focus on renewable sources of IPC (1). Although embryonic stem (ES) cells or induced pluripotent stem (iPS) cells hold a promising potential as a source of IPC, IPC-clusters derived from them still have a high degree of cellular heterogeneity, tumor-forming potential, and low-insulin levels compared with pancreatic islets.
Recent studies in the field of regenerative medicine have focused on the isolation of tissue-specific stem and progenitor cells as an alternative source of IPC. Unfortunately, only a few attempts have been made at their prospective isolation from the pancreas, due to the lack of suitable and specific marker and the failure to develop appropriate cell culture strategy to determine their capacity for self-renewal and multilineage differentiation potential. Nevertheless, two interesting studies have reported putative adult pancreatic stem and progenitor cells derived from mice that clonally expanded, while expressing a low-level of insulin and other pancreatic markers (6,7). Although these pioneering works have suggested the existence of stem cells in adult animals the ability of isolated cells to self-renew and to differentiate into functional islets remains to be fully evaluated. On the other hand, Dor and colleagues have reported that after birth new β-cells could be generated by the replication of existing ones rather than by putative pancreatic stem cells (8), thus challenging the existence of adult pancreatic stem and progenitor cells.

In contrast, the existence of pancreatic stem and progenitor cells in the developing pancreas is not controversial. The pancreas develops from the posterior foregut, emerging as buds from the ventral and dorsal area of the gut tube. Although it is thought that pancreatic
and duodenal homeobox 1 (Pdx1)-expressing epithelial progenitor cells give rise to endocrine, exocrine cells and duct (9), clear evidence that isolated clonogenic pancreatic cells possess all stem cell characteristics remains to be confirmed. Transcription factor Pdx1 (also known as insulin promoter factor 1) is a master regulator of pancreas development. To get more insights into these issues, we have recently investigated the possibility to use prominin-1 as a prospective marker for the isolation and characterization of potential pancreatic stem cells.

12.2.2 Prominin-1 Labels Putative Pancreatic Stem and Progenitor Cells Within the Pancreas

Prominin-1 has been recognized as a cell surface antigen of hematopoietic (10) and neural stem cells (11) as well as ES cell-derived progenitors (12), but its specific ligand and function are still a matter of speculation (see Chapter 1). Corbeil and colleagues have previously shown that human prominin-1 (hereafter named CD133 when referring to the human protein) is expressed at the apical plasma membrane of the embryonic gut tube and the neural tube just like previously reported for its murine ortholog. (13). Moreover, an accumulative set of data supports that the general expression of prominin-1/CD133 is far beyond stem cells originating from hematopoietic and neural systems but extends to other tissues/organs (e.g., see Chapters
Furthermore, the cell surface localization of prominin-1/CD133 makes this antigen a promising candidate for the prospective identification and isolation of pancreatic stem and progenitor cells.

In embryonic pancreas, the majority of the epithelium consists of undifferentiated stem and progenitor cells; Pdx1-expressing epithelial progenitor cells, which are surrounded by mesenchyme. Together with my colleagues we could show by immunohistochemistry that murine prominin-1 is co-expressed specifically on the Pdx1-expressing epithelial cells, while platelet-derived growth factor receptor β (PDGFRβ, CD140b) is expressed on the surrounding mesenchymal cells within the developing pancreas (Fig.12.1A-D) (14).

Using a combination of prominin-1 (as a positive marker) and PDGFRβ (as a negative marker), we demonstrated by flow cytometry the existence of four distinct subpopulations of cells (here named a-d) derived from the embryonic pancreas (14). Their phenotypes were fractionated as followed; (a) prominin-1^{high}PDGFRβ, (b) prominin-1^{dim}PDGFRβ^{-}, (c) prominin-1^{neg}PDGFRβ^{-} and (d) PDGFRβ^{+} (see Fig.12.1E, pink, violet, yellow and blue, respectively). The gene expression analyses by means of reverse transcription polymerase chain reaction (RT-PCR) and microarray of the sorted cells demonstrated that putative markers normally associated with pancreatic stem and progenitor cells such as Foxa2, HNF4a,
HNF6, Pdx1, Hlbx9, Ptf1 and neurogenin3 are enriched in prominin-1\textsuperscript{high}PDGFRβ\textsuperscript{−} fraction (i.e. subpopulation a), whereas markers of terminally differentiated cells including insulin1, preproinsulin1 (β-cell marker), glucagon and preproglucagon (α-cell marker) are enriched in prominin-1\textsuperscript{neg}PDGFRβ\textsuperscript{−} fraction (subpopulation c) (14). In the same line, Oshima and colleagues performed prospective isolation of pancreatic ductal progenitor cells by flow cytometry using prominin-1 (15). Likewise, Sugiyama and colleagues demonstrated that prominin-1/CD133 labeled fetal mouse and human islet progenitor cells (16), and Koblas and colleagues reported that CD133 labeled human insulin-producing progenitor cells (17). Collectively, these independent investigations suggest that prominin-1 as a cell surface antigen could be an ideal marker for the prospective isolation of stem and progenitor cells in developing pancreas and that its expression is decreased through differentiation into mature pancreatic cells notably islet cells. However, since its expression seems to persist at the apical membrane of the peripheral exocrine acini in neonatal and adult pancreas, the use of prominin-1 as a marker of pancreatic stem cells might be more restricted to the embryonic stage (14,15).

12.2.3 Differentiation Potential of Prominin-1\textsuperscript{high} Pancreatic Stem and Progenitor Cells
To determine whether a cell of interest harbors stem and progenitor cell properties, it is imperative to show that it contains a multilineage differentiation potential. In pancreas, for instance, we would expect that the putative stem cells could give rise to endocrine, exocrine cells and duct. Although the culture strategy (including culture conditions and growth factors) for IPC has been intensively investigated especially in regenerative medicine for diabetes mellitus, the experimental conditions for other pancreatic cells have not been established yet.

Together with my colleagues we demonstrated that isolated prominin-1\textsuperscript{high} cells plated on stromal cells during 7 days were generating IPC clusters, but no other pancreatic cell types (14). Indeed, other markers characteristic of endocrine tissue (e.g., glucagon, somatostatin, and pancreatic polypeptide) were detected as mRNA using a sensitive RT-PCR analysis, but contrary to insulin, not as protein by immunohistochemistry, suggesting that both i) their expression levels are very low, and ii) insulin-producing lineage is a default pathway under this culture condition (14).

12.2.4 Prominin-1\textsuperscript{high} Pancreatic Stem and Progenitor Cells Have the Ability to Differentiate into Pancreatic Tissues in Mice
To evaluate the potential of prominin-1$^+$ cells to differentiate and produce \textit{in vivo} mature pancreatic cells we have performed a transplantation assay. It is known that the microenvironment (often termed stem cell niche), which is composed of stromal cells and extracellular components, is important to maintain stem and progenitor cell properties. In this context, we engrafted prominin-1$^{\text{high}}$ cells isolated from enhanced green fluorescent protein (eGFP) transgenic mice into the \textit{nude} mice to trace them as well as their progenies (14). One week after engraftment of prominin-1$^{\text{high}}$ cells, but not prominin-1$^{\text{neg}}$ cells, tubular structures expressing Pdx1 in the nucleus and prominin-1 at the apical membrane were identified in the graft, which was similar to that of the embryonic pancreatic epithelium (14). In addition, insulin and glucagon were detected within GFP$^+$ cell clusters (Fig. 12.2A). Specific markers of exocrine (amylase$^+$ or carboxypeptidase A$^+$) or ductal (Dolichos biflorous agglutinin$^+$) cells were also observed (Fig. 12.2B-D). Notably, one month after engraftment, the intracellular C-peptide content in IPC increased and showed levels comparable to that in pancreatic \(\beta\)-cells. Thus, most islet-like cell clusters consisted of IPC in the center and other pancreatic hormone positive cells in the periphery, including glucagon, somatostatin, and pancreatic polypeptide, which is characteristic of mature pancreatic islets (14).
12.2.5 Is Prominin-1 a Specific Marker of Pancreatic Stem and Progenitor Cells?

Engraftment of prominin-1\(^+\) cells resulted in the differentiation in endocrine, ductal, and exocrine cells characteristics of pancreas. However, since the issue of the heterogeneity of the prominin1\(^+\) cell population remains to be elucidated, we are not able at the moment to rule out the possibility that the different cell types detected in the graft arose from distinct progenitor cells. Even in the \textit{in vitro} experiment, we did not detect colonies with evidence of progeny with mixed lineage derived from a single cell (14). Although the general concept of stem cells has been extended from hematopoietic stem cells to many other tissues, only rarely stem cells have been identified as clonogenic precursors that include in their progeny both self-renewing and differentiation potential. Based strictly on this definition, stem cells reported in other systems are not clonogenic. To prove definitively that prominin1\(^+\) cells isolated from pancreas have stem cell characteristics, it is now imperative to transplant single prominin-1\(^+\) cell and reconstitute a pancreas as elegantly shown for hematopoietic or mammary gland stem cells (19,20). Alternatively, we need to employ genetic lineage tracing in mice as established by Dor and colleagues (8) to demonstrate that a single prominin-1\(^+\) cell has a multilineage differentiation potential.
There is a growing body of evidence that pancreatic stem and progenitor cells might be located in the terminal duct. In addition, the phenomenon of “acinar-to-ductal transdifferentiation” should be taken into account. The evidence of adult rodent acinar-to-ductal transdifferentiation and conversion into IPC seems to be promising for cell replacement therapy in diabetes (21,22). More recently, Houbracken and colleagues demonstrated that the human acinar cell had plasticity similar to that described in rodent cells, which might be used to convert them into human IPC (23). However, the plasticity of acinar cell to pancreatic stem and progenitor cells requires additional investigation, and it is obviously an exiting field to explore further.

12.3 Pancreatic Cancer Stem Cells

12.3.1 Human Pancreatic Cancer Stem/Tumor-Initiating/Tumorigenic Cells

Pancreatic cancer is currently the fourth leading cause of cancer-related mortality. The ductal adenocarcinoma that arises within the exocrine component of the pancreas is the most common type accounting for 95% of these tumors. Morphologically, this cancer is typically characterized by moderately to poorly differentiated glandular structures. Other cancers might
develop from islet cells and are classified as neuroendocrine tumors. Unfortunately, pancreatic cancer has a poor prognosis and a high percentage of patients (>80%) will succumb from the disease over the year. The lack of symptoms and the high propensity of early metastasis normally lead to advanced disease at time of diagnosis. Despite our increasing knowledge in tumor biology, the efficacy of treatment of pancreatic cancer has not significantly improved over the last decade.

The current definition of CSC describes them as rare cells within a tumor that are able to self-renew and to produce the heterogeneous lineages of cancer cells (24). The implementation of this concept explains the use of alternative terms in literature, such as “tumor-initiating cell” and “tumorigenic cell” to describe putative CSC. Moreover, CSC are often considered to be resistant to conventional treatment such as chemotherapy and radiotherapy, and treatments that fail to eliminate CSC may allow the tumor to relapse. For more details of CSC including their dynamics and the metastasis initiating cell concept, I refer the readers to an excellent review (25). Therefore, a considerable interest in the molecular targeting and eradication of CSC is emerging for cancer therapy.

As other tumors, recent reports have demonstrated that pancreatic cancer also contains a minute subpopulation of potential CSC. Li and colleagues isolated CSC from pancreatic
cancer using cell surface markers such as CD44, CD24, and epithelial-specific antigen (ESA) (26). Remarkably, cells harboring CD44\(^+\)CD24\(^+\)ESA\(^+\) phenotype (i.e. only 0.2-0.8% of pancreatic cancer cells) had a 100-fold increased tumorigenic potential compared to non-tumorigenic cancer cells. Furthermore, the CD44\(^+\)CD24\(^+\)ESA\(^+\) pancreatic cancer cells showed the stem cell properties of self-renewal and the ability to produce differentiated progeny. More recently, it was reported that CD44 could be co-expressed with CD133 in pancreatic ductal adenocarcinomas raising the possibility that CD133 might be an alternative marker of human pancreatic CSC (27).

### 12.3.2 CD133 is an Alternative Marker of Human Pancreatic Cancer Stem Cells

The expression of CD133 on healthy pancreas was investigated but numerous independent research groups. As reported earlier in the mouse system (see above), Shimizu and colleagues found by means of immunohistochemistry that CD133 is expressed at the apical membrane of ductal cells in human adult pancreas (Fig. 12.3A,B) (28), consistent with a previous report from Karbanová and colleagues (29). Lardon and colleagues have also shown that CD133 including its widely used stem cell AC133 epitope is expressed on all duct-lining cells of human pancreas (30). However, Shimizu and Karbanová studies did not detect CD133
expression on the epithelium of larger interlobular and main ducts (28,29). Indeed, CD133 expression appeared more pronounced towards the acini than larger ducts (31). Given the expression of CD133 within the pancreas (28-31), and its detection in CSC originating from other tissues/organs (see Chapter 1), it is not excluded that particular subpopulation of CD133 + cells on the ductal epithelium might be the source of pancreatic CSC.

In diseased tissues, CD133 was concentrated in ductal metaplasia (the widespread inter-conversion of one cell type into another) of the acinar cells located in the border zone of the tumor (Fig. 12.3C,D) (28). Metaplasia has been associated with pancreatic cancer in both humans and animal models and a metaplasia-ductal adenocarcinoma sequence has been proposed for carcinogenesis in pancreas (32,33). As mentioned above, CD133 expression was also observed in ductal adenocarcinoma cells (Fig. 12.3E,F). Remarkably, Hermann and colleagues isolated human pancreatic CSC using CD133 as a cell surface marker, and found that pancreatic CSC defined by its expression were exclusively tumorigenic and highly resistant to standard chemotherapy (34). Moreover, in the invasive front of pancreatic cancer, double-positive CD133 and chemokine-related receptor-4 (CXCR4) cells were identified as the major metastatic CSC phenotype. Since depletion of this cell population abrogated the metastatic phenotype without affecting their tumorigenic potential, they concluded that a
subpopulation of migrating CD133\textsuperscript{+}CXCR4\textsuperscript{+} CSC is essential for tumor metastasis. It is known that CXCR4 and its ligand the stromal cell derived factor-1\(\alpha\) (SDF-1\(\alpha\), CXCL12) are involved in directional cell migration. A recent study has also proposed that CXCR4/SDF-1\(\alpha\) axis plays a critical regulatory role in the genesis of human islets (35).

In analogy to the stem cell niche, a growing body of evidence is accumulating to show that the tumor microenvironment is essential to maintain CSC. For instance, Moriyama and colleagues demonstrated that CD133\textsuperscript{+} pancreatic cancer cells exhibited a more aggressive behavior, such as migration and invasion, especially in the presence of pancreatic stromal cells (36). They also reported that CXCR4 transcript is overexpressed in CD133\textsuperscript{+} pancreatic cancer cells. Likewise, Hashimoto and colleague have recently found that hypoxia induced the expansion of CD133\textsuperscript{+} pancreatic cancer cells, subsequent tumor aggressiveness, and the expression of CXCR4 (37). In these contexts, CD133 might play a role in the organization and/or polarization of migrating pancreatic cancer cells as it was suggested for CD133\textsuperscript{+} hematopoietic stem cells growing on multipotent mesenchymal stromal cells as feeder cell layer (38). Finally, to prove that CD133\textsuperscript{+} and/or CD133\textsuperscript{+}CXCR4\textsuperscript{+} cancer cells have all stem cell-like characteristics, it will be necessary to engraft a single cell and demonstrate that it reconstitutes the complex heterogeneity of a pancreatic cancer.
In conclusion, the recent effort in the identification and characterization of pancreatic CD133\(^+\) CSC have brought some information concerning the development and spreading of the cancers as well as their resistance to treatment. However, some crucial questions are still opened such as the origin of CSC within pancreas. Further investigation on the molecular and cellular features of CD133 per se could indirectly provide new mechanisms underlying the proliferation of CSC as well as their migration. Likewise, CD133 as a cell surface antigen may become a potential target in the eradication of CSC.
Acknowledgements

I would like to thank Drs. Kazuya Shimizu and Okito Hashimoto for valuable comments on the manuscript. I am also grateful to Norito Fujiwara, Rina Hirai, Yuki Kamino, Nancy Katayama, and Takuma Miura for their technical help. This research was supported by Grants-in-Aid (21591773, 23592007, 24592025) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.
References


**Figure Legends**

**Fig. 12.1** Prominin-1 is expressed on the pancreatic epithelium of murine embryo. (A-D) Prominin-1 is detected at the apical membrane of the Pdx1-expressing pancreatic epithelial cells on embryonic (E) day 11.5 and 13.5, when the majority of the epithelium consists of undifferentiated progenitor cells (A and C), whereas PDGFRβ is expressed by surrounding pancreatic mesenchymal cells (B and D). Both proteins were observed using phycoerythrin-conjugated anti-prominin-1 mAb and biotin-conjugated anti-PDGFRβ mAb (eBioscience), respectively. Scale bars, 50 μm. (E) Flow cytometric analysis of cells derived from embryonic pancreas using mAbs against prominin-1 and PDGFRβ. Four distinct gated cell subpopulations were observed, and the corresponding percentage is indicated as following phenotypes; prominin-1\textsuperscript{high}PDGFRβ\textsuperscript{−} (pink, 15.3 ± 2.8%), prominin-1\textsuperscript{dim}PDGFRβ\textsuperscript{−} (violet, 11.4 ± 2.2%), prominin-1\textsuperscript{neg}PDGFRβ\textsuperscript{−} (yellow, 6.5 ± 1.2%) and PDGFRβ\textsuperscript{+} (blue, 66.8 ± 9.8%). These panels are derived from our work published in Stem Cells in 2008 (14).

**Fig. 12.2** Multilineage potential of pancreatic stem and progenitor cells. (A-D) $5 \times 10^4$
prominin-1+ cells derived from enhanced green fluorescent protein (eGFP) transgenic mice were transplanted in the subcapsular renal space of nude mice, and after 7-days the engrafted cells (visualized with GFP) were processed for immunohistochemistry for the following markers; insulin and glucagon (A), amylase (B) and carboxypeptidase A (C, carbA) as exocrine markers, and Dolichos biflorous agglutinin (D, DBA) as a ductal marker. Nuclei were labeled with 4',6-diamidino-2-phenylindole (DAPI). Scale bars, 50 μm. These panels are derived from our work published in Stem Cells in 2008 (14).

**Fig. 12.3** CD133 expression in normal human pancreas, metaplasia and ductal adenocarcinomas. (A-F) The expression of CD133 in normal human pancreas (A, B), metaplasia lesion (C, D), and in cancer cells of the ductal adenocarcinoma (E, F) were revealed by immunostaining using an anti-human CD133/1 mAb (Miltenyi Biotech) (B, D, F). Adjacent sections were stained with hematoxylin and eosin (HE stain) (A, C, E). Note in the metaplasia lesion, a lobule undergoing a metaplastic transformation is shown adjacent to the normal acinar tissue (C, D). Scale bars, 200 mm. These panels are derived from our work published in Pancreas in 2009 (28).
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