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Tracking Down the Hedgehog's Lair in the Pancreas

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The Hedgehog (Hh) signaling pathway plays a seminal role in developmental patterning, as well as in mature tissue homeostasis.^{1,2} A series of elegant studies published in *Gastroenterology* has elucidated the diverse functions of Hh signaling in morphogenesis, particularly in orchestrating foregut differentiation towards a gastrointestinal fate.^{3–5} In the context of the pancreas, the principal Hh ligand—Sonic Hh (Shh)—is largely excluded from the differentiating pancreatic anlage,⁶ and, until recently, no definitive evidence had been presented for Shh expression in the normal exocrine pancreas. In contrast, ligand-dependent Hh activation plays an important role in mediating epithelial regeneration after exocrine pancreatic injury, as documented by the impaired regeneration that occurs in the setting of genetic or pharmacologic blockade of Hh signaling.⁷ Multiple lines of evidence have also established the association between aberrant Hh signaling and exocrine pancreatic neoplasia. For example, up-regulation of Shh ligand is observed in the noninvasive precursor lesions that precede both human and murine pancreatic adenocarcinomas,^{8,9} and robust pathway activation persists well into metastatic disease.¹⁰ The Hh pathway is implicated in the maintenance of tumor-initiating cells (so-called cancer stem cells) in pancreatic adenocarcinoma,^{10,11} and it is believed that the persistence of these cells might be responsible for disease recurrence and metastases. Finally, recent seminal observations have confirmed the predominantly paracrine nature of Hh signaling in the pancreatic cancer microenvironment,¹² wherein Shh ligand secreted by the neoplastic epithelium binds to the cognate Patched receptor on stromal cells, thereby facilitating stromal expansion (“desmoplasia”)¹³ that, in turn, could act as a physical impediment to efficient drug delivery to the tumor milieu.¹⁴ All of these mechanisms linking aberrant Hh signaling to pancreatic neoplasia underscore the rationale behind ongoing or proposed clinical trials of small molecule Hh antagonists in patients with pancreatic adenocarcinoma.¹⁵

Although the evidence for aberrant Shh ligand secretion by the exocrine pancreas in disease states is unequivocal, establishing a nidus for ligand production in the normal exocrine pancreas has been far more elusive. In this issue of *Gastroenterology*, Strobel et al¹⁶ have identified a specialized compartment comprised of blind outpouchings originating from the proximal ductal system, designated as pancreatic duct glands (PDGs), which might prove to be the proverbial “missing link” between a preexisting Hh axis in the normal pancreas and the profound up-regulation of pathway activity observed in states of chronic injury and neoplasia (Figure 1). In a rather meticulous effort to establish the anatomic proof for blind-ending pouches in 3 dimensions, the authors generated “corrosion casts” of the entire ductal system in mice and in humans, and performed scanning electron microscopy of these casts

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See “Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia,” by Strobel O, Roscow DE, Rakhlin EY, et al, on page 1166.

Conflict of interest

Dr Maitra has previously received research support from Novartis for preclinical evaluation of a small molecule Hh antagonist.

to confirm the ultrastructure of PDGs. In contrast with the normal ductal epithelium, PDGs express the gastric-type apomucin Muc6, and demonstrate expression of Shh ligand, even at “baseline.” Although the authors provide evidence for such out-pouchings in the peripheral parenchyma, for the most part, PDGs seem to be localized in, and adjacent to, the proximal ductal system. Analogous structures can sometimes be observed in an anatomically related conduit—the common bile duct, wherein these gland-like out-pouchings have been referred to as “sacculi of Beale”¹⁷; comparable with their pancreatic counterpart, these sacculi also express abundant Alcian blue–positive mucin. In models of chronic exocrine injury,¹⁸ there is a striking expansion in PDGs, which is accompanied by enhanced expression of Shh and other “embryonal” transcripts like Pdx-1 and Notch gene targets, as well as de novo expression of the apomucin Muc5ac, and rarely, Muc2. These findings in the murine pancreas are mirrored in the setting of chronic pancreatitis in humans, including the predilection for histologic and Hh-related transcriptional alterations to be epicentered on the main duct tissues versus the peripheral parenchyma. The authors surmise that this novel epithelial compartment might play previously unknown function(s) in epithelial repair, metaplasia, and neoplasia.

Given that the report by Strobel et al¹⁶ represents the first attempt at detailed characterization of this novel compartment in the pancreas, it is anticipated that future studies will address some of the unanswered questions. For example, do PDGs retain a progenitor-like function in the pancreas? Although their expansion in the setting of chronic exocrine injury, concomitant with expression of developmental markers such as Pdx-1, suggests a role in epithelial regeneration, convincing evidence for progenitor-like function would require in vivo lineage tracing studies (eg, by expressing *Cre* recombinase under the control of a Shh or gastric-type apomucin promoter), and/or establishing ex vivo demonstration of multilineage differentiation in isolated PDGs. Although the challenges of conducting such studies are not trivial, they are almost a prerequisite for addressing the function of PDGs in pancreatic homeostasis, and by extension, in pancreatic disease. The pancreas is a unique organ in that multiple terminally differentiated cell types, such as preexisting acini, β -cells, and ductal epithelial cells have all been variously implicated as “facultative” progenitors.^{7,19,20} In other words, these compartments do not harbor a dedicated progenitor function but, rather, in the manner of an “army reserve,” are called into “active service” in the setting of disrupted homeostasis, such as in acute and chronic injury. In fact, it is only very recently that a cell type with dedicated progenitor function has been identified in the centroacinar/terminal ductal location, and it is characterized by expression of the enzyme aldehyde dehydrogenase and the ability for multilineage differentiation.²¹ Of note, and irrespective of their inherent plasticity, all of these pancreatic cell types with progenitor-like function exist in the peripheral parenchyma. PDGs, if indeed these turn out to harbor progenitor-like properties, will be one of the first such examples of a compartment that is predominantly localized in the proximal ductal system.

Another unresolved question vis-à-vis the clinical significance of PDGs lies in their putative connection to pancreatic neoplasia. The authors have postulated that the morphologic resemblance of PDGs to low-grade pancreatic intraepithelial neoplasia (PanINs; so-called²² PANIN-1A) suggests that these structures might account for a subset of early PanIN lesions en route to adenocarcinoma; however, one has to speculate about another intriguing possibility. Given the propensity of PDGs to be localized mainly in the proximal ductal system, rather than in the periphery, these lesions might represent the elusive compartment of origin for intraductal papillary mucinous neoplasms (IPMNs). IPMNs are the most common macroscopic (cystic) precursor lesion of pancreatic adenocarcinoma, but unlike PanINs, tend to be localized in the main pancreatic duct or a branch duct.^{23,24} IPMNs produce copious amounts of mucin, which might reflect their ontogeny within the “cradle of mucinous metaplasia.” Akin to hyperplastic PDGs, most IPMNs also express the apomucin

MUC5AC, and based on the pattern of histologic differentiation in the lining epithelium, MUC2 might either be co-expressed (“intestinal” subtype of IPMN), or be absent (“gastric foveolar” subtype of IPMN).²⁵ Further comparable to PDGs is the evidence of widespread activation of the Hh pathway in IPMNs, including the expression of Shh ligand and Hh gene targets.^{26,27} IPMNs are being increasingly recognized as incidental lesions on imaging of the pancreas, with some estimates suggesting that 1%–5% of the population might harbor such asymptomatic cysts.^{28,29} It is tempting to speculate that PDGs might reflect the source of these precursor lesions, a hypothesis that can be potentially validated in vivo using recently developed autochthonous mouse models of pancreatic cystic neoplasia.³⁰

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References

1. Lees C, Howie S, Sartor RB, Satsangi J. The hedgehog signalling pathway in the gastrointestinal tract: implications for development, homeostasis, and disease. *Gastroenterology* 2005;129:1696–1710. [PubMed: 16285967]
2. Ruiz i Altaba A, Mas C, Stecca B. The Gli code: an information nexus regulating cell fate, stemness and cancer. *Trends Cell Biol* 2007;17:438–447. [PubMed: 17845852]
3. van den Brink GR, Hardwick JC, Tytgat GN, et al. Sonic hedgehog regulates gastric gland morphogenesis in man and mouse. *Gastroenterology* 2001;121:317–328. [PubMed: 11487541]
4. Varnat F, Heggeler BB, Grisel P, et al. PPARbeta/delta regulates paneth cell differentiation via controlling the hedgehog signaling pathway. *Gastroenterology* 2006;131:538–553. [PubMed: 16890607]
5. Kolterud A, Grosse AS, Zacharias WJ, et al. Paracrine Hedgehog signaling in stomach and intestine: new roles for hedgehog in gastrointestinal patterning. *Gastroenterology* 2009;137:618–628. [PubMed: 19445942]
6. Ramalho-Santos M, Melton DA, et al. Hedgehog signals regulate multiple aspects of gastrointestinal development. *Development* 2000;127:2763–2772. [PubMed: 10821773]
7. Fendrich V, Esni F, Garay MV, et al. Hedgehog signaling is required for effective regeneration of exocrine pancreas. *Gastroenterology* 2008;135:347–351. [PubMed: 18619970]
8. Pasca di Magliano M, Sekine S, et al. Hedgehog/Ras interactions regulate early stages of pancreatic cancer. *Genes Dev* 2006;20:3161–173. [PubMed: 17114586]
9. Thayer SP, di Magliano MP, Heiser PW, et al. Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. *Nature* 2003;425:851–856. [PubMed: 14520413]
10. Feldmann G, Dhara S, Fendrich V, et al. Blockade of hedgehog signaling inhibits pancreatic cancer invasion and metastases: a new paradigm for combination therapy in solid cancers. *Cancer Res* 2007;67:2187–2196. [PubMed: 17332349]
11. Mueller MT, Hermann PC, Witthauer J, et al. Combined targeted treatment to eliminate tumorigenic cancer stem cells in human pancreatic cancer. *Gastroenterology* 2009;137:1102–1113. [PubMed: 19501590]
12. Yauch RL, Gould SE, Scales SJ, et al. A paracrine requirement for hedgehog signalling in cancer. *Nature* 2008;455:406–410. [PubMed: 18754008]
13. Bailey JM, Swanson BJ, Hamada T, et al. Sonic hedgehog promotes desmoplasia in pancreatic cancer. *Clin Cancer Res* 2008;14:5995–6004. [PubMed: 18829478]
14. Olive KP, Jacobetz MA, Davidson CJ, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009;324:1457–1461. [PubMed: 19460966]
15. Hidalgo M, Maitra A. The hedgehog pathway and pancreatic cancer. *N Engl J Med* 2009;361:2094–2096. [PubMed: 19923581]

16. Strobel O, Roscow DE, Rakhlin EY, et al. Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia. *Gastroenterology* 2010;138:1166–1177. [PubMed: 20026066]
17. Frierson HF Jr. The gross anatomy and histology of the gallbladder, extrahepatic bile ducts, Vaterian system, and minor papilla. *Am J Surg Pathol* 1989;13:146–162. [PubMed: 2644853]
18. Strobel O, Dor Y, Alsina J, et al. In vivo lineage tracing defines the role of acinar-to-ductal transdifferentiation in inflammatory ductal metaplasia. *Gastroenterology* 2007;133:1999–2009. [PubMed: 18054571]
19. Xu X, D'Hoker J, Stange G, Bonne S, et al. Beta cells can be generated from endogenous progenitors in injured adult mouse pancreas. *Cell* 2008;132:197–207. [PubMed: 18243096]
20. Inada A, Nienaber C, Katsuta H, et al. Carbonic anhydrase II-positive pancreatic cells are progenitors for both endocrine and exocrine pancreas after birth. *Proc Natl Acad Sci U S A* 2008;105:19915–19919. [PubMed: 19052237]
21. Rovira M, Scott SG, Liss AS, et al. Isolation and characterization of centroacinar/terminal ductal progenitor cells in adult mouse pancreas. *Proc Natl Acad Sci U S A*. 2009 Dec 19; Epub ahead of print.
22. Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001;25:579–586. [PubMed: 11342768]
23. Singh M, Maitra A. Precursor lesions of pancreatic cancer: molecular pathology and clinical implications. *Pancreatology* 2007;7:9–19. [PubMed: 17449961]
24. Crippa S, Fernandez-Del Castillo C, Salvia R, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiological characteristics. *Clin Gastroenterol Hepatol*. 2009 Oct 14; Epub ahead of print.
25. Adsay NV, Merati K, Basturk O, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an “intestinal” pathway of carcinogenesis in the pancreas. *Am J Surg Pathol* 2004;28:839–848. [PubMed: 15223952]
26. Satoh K, Kanno A, Hamada S, et al. Expression of Sonic hedgehog signaling pathway correlates with the tumorigenesis of intraductal papillary mucinous neoplasm of the pancreas. *Oncol Rep* 2008;19:1185–1190. [PubMed: 18425375]
27. Ohuchida K, Mizumoto K, Fujita H, et al. Sonic hedgehog is an early developmental marker of intraductal papillary mucinous neoplasms: clinical implications of mRNA levels in pancreatic juice. *J Pathol* 2006;210:42–48. [PubMed: 16794990]
28. Winter JM, Cameron JL, Lillemoe KD, et al. Periapillary and pancreatic incidentaloma: a single institution's experience with an increasingly common diagnosis. *Ann Surg* 2006;243:673–680. [PubMed: 16633003]
29. Fasanella KE, McGrath K. Cystic lesions and intraductal neoplasms of the pancreas. *Best Pract Res Clin Gastroenterol* 2009;23:35–48. [PubMed: 19258185]
30. Siveke JT, Einwachter H, Sipos B, et al. Concomitant pancreatic activation of Kras(G12D) and Tgfa results in cystic papillary neoplasms reminiscent of human IPMN. *Cancer Cell* 2007;12:266–279. [PubMed: 17785207]

Figure 1. Pancreatic duct glands (PDGs) are blind outpouchings originating predominantly from the proximal ductal system, and are characterized by Shh ligand expression and a distinct apomucin profile. A striking expansion of PDGs is observed in the setting of chronic injury, including increased Shh ligand expression. PDGs might contribute to epithelial regeneration and serve as a nidus for pancreatic exocrine neoplasia, particularly neoplasms centered on the proximal ductal system.