Stem cells versus plasticity in liver and pancreas regeneration

Janel L. Kopp[1], Markus Grompe[2] and Maike Sander[3]*

Cell replacement in adult organs can be achieved through stem cell differentiation or the replication or transdifferentiation of existing cells. In the adult liver and pancreas, stem cells have been proposed to replace tissue cells, particularly following injury. Here we review how specialized cell types are produced in the adult liver and pancreas. Based on current evidence, we propose that the plasticity of differentiated cells, rather than stem cells, accounts for tissue repair in both organs.

The innate capacity of stem cells to regenerate and replace lost tissue cells has spurred an intense interest in their potential use in regenerative medicine. A central strategy is to treat patients by transplanting stem cells or their differentiated derivatives. An alternative to cell transplantation is to induce cell regeneration by manipulating tissue-resident stem cells or their microenvironment *in vivo*.

Stem cells have been speculated to compensate for tissue loss in many adult tissues, but the term 'stem cell' has been used liberally and rigorous evidence for their existence has been found for only a few tissues. A bona fide stem cell possesses two properties: (1) the ability of long-term clonal self-renewal, so it can go through repeated cycles of cell division while maintaining an undifferentiated state; and (2) multipotency, the capacity to differentiate into more than one specialized cell type (Fig. 1a). Extensive work in the *Drosophila melanogaster* gonad has shown that these intrinsic stem cell properties are induced and maintained by cues from the stem cell niche[1].

To accurately identify stem cells in adult tissues, and to assess their properties, two strategies have been widely used. The first is *in vivo* lineage tracing (the 'gold standard'), in which a putative stem cell is genetically marked *in vivo* to visualize its progeny through time. By following the offspring carrying the genetic mark, it is possible to demonstrate longevity of the stem cell population and identify descendent cell types. True stem cells will produce both undifferentiated and differentiated progeny for the life of the animal (Fig. 1b). Cells with limited self-renewal capacity, such as tissue progenitors, will generate short-lived transient clones that eventually differentiate to contain only specialized cell types. Although *in vivo* lineage tracing can readily distinguish between stem and progenitor cells in tissues with rapid cell turnover, the distinction is difficult to make in tissues with long-lived cell types. Such distinction is more than just semantic, because the limited self-renewal of progenitors can restrict the regenerative capacity when tissue cells are lost due to ageing or injury.

A second strategy for identifying stem cells involves isolating cells using molecular markers followed by *in vitro* culture and/or transplantation into animals. Cells are assessed for multipotency *in vitro* by their ability to generate colonies or 'organoids' that can give rise to differentiated cell types either *in vitro* or after *in vivo* transplantation. Serial passaging of single cells to generate new colonies or organoids is employed to assess their self-renewal capacity (Fig. 1c). The classic example of this method for demonstrating extensive self-renewal is the serial haematopoietic reconstitution assay[2,3]. For many adult tissues and organs, however, similar *in vivo* reconstitution assays are lacking, making it more difficult to prove the existence of a stem cell.

One caveat of *in vitro* assays is that stem-cell-like behaviour can be an artefact of removing cells from their native environment, whereas they may not function as stem cells *in vivo*. As lineage tracing evaluates cell behaviour in a physiological context, it is considered to be the more conclusive test of 'stemness'. Given that there is no universal adult stem cell marker[4], lineage tracing does, however, hinge on the availability of appropriate stem cell markers for the specific tissue or organ under investigation.

In particular, there has been considerable dispute as to the existence and nature of a stem cell in the liver and pancreas[5–10]. In this Review, we use intestinal stem cells (one of the best-documented examples of tissue stem cells) as a reference to examine evidence for the existence of adult liver and pancreas stem cells.

The intestinal stem cell as a prototype adult stem cell

The intestinal epithelium is organized into crypt–villus units, with the villi harbouring short-lived specialized cell types that are continuously replaced. Almost 30 years ago, clonal labelling experiments based on the introduction of random somatic mutations revealed the existence of stem cells in the crypts[11]. These studies, however, were unable to determine the precise identity and location of the stem cell(s).

[1]Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, British Columbia V6T 1Z3, Canada. [2]Oregon Stem Cell Center, Papé Family Pediatric Research Institute, Oregon Health and Science University, Portland, Oregon 97239, USA. [3]Department of Pediatrics and Cellular and Molecular Medicine, Pediatric Diabetes Research Center, Sanford Consortium for Regenerative Medicine, University of California, San Diego, La Jolla, California 92093-0695, USA. *e-mail: masander@ucsd.edu

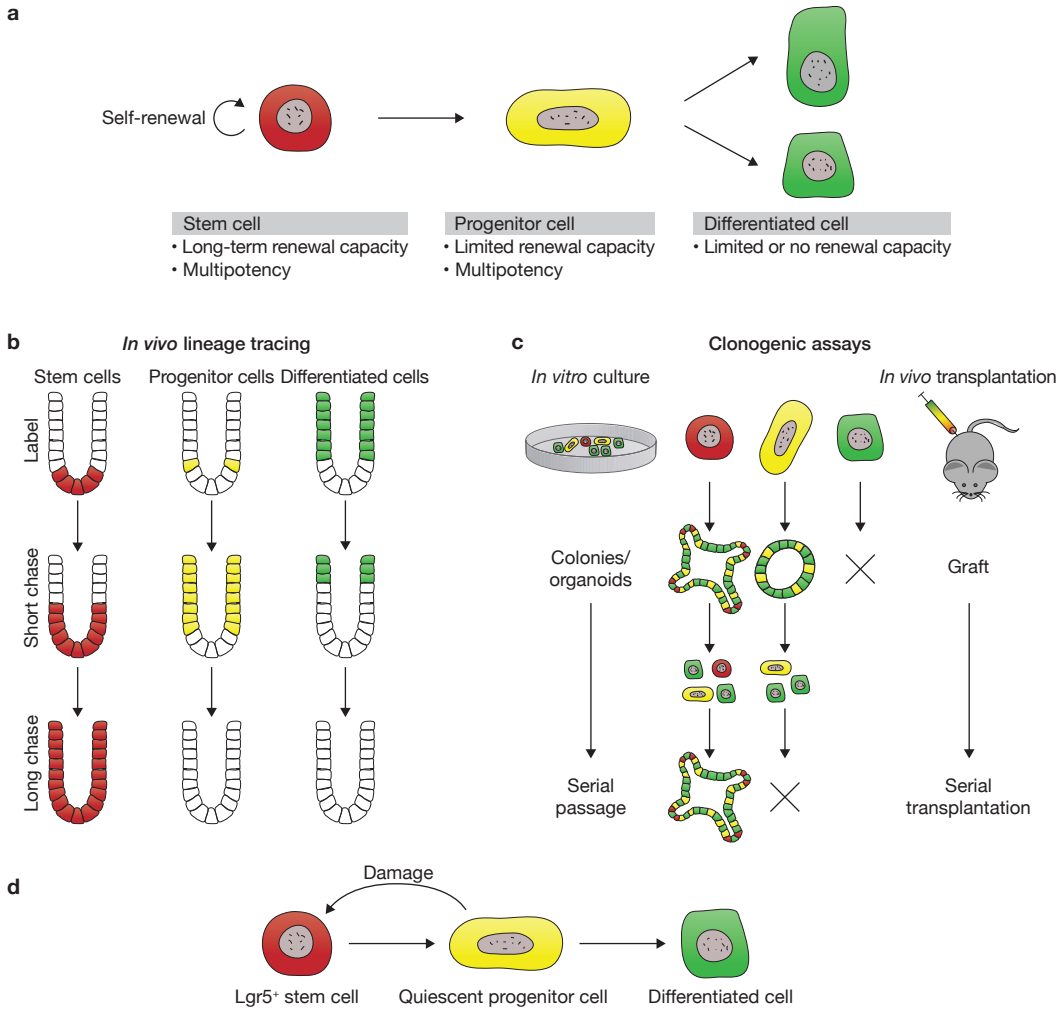

Figure 1 Assays for assessing stem cell properties. (**a**) The classic view of cellular hierarchy in adult tissues. Stem cells (red) divide to give rise to a new stem cell (self-renewal) and a committed progenitor cell (yellow), which in turn produces terminally differentiated cells (green). (**b**,**c**) Functional assays to assess self-renewal and differentiation capacity. Only stem cells can give rise to long-term labelled differentiated cells in lineage-tracing experiments (**b**), or can be serially passaged *in vitro* or transplanted (**c**). (**d**) The concept of a facultative stem cell. During tissue homeostasis, Lgr5$^+$ stem cells give rise to progenitor cells that can persist in a quiescent state (yellow) before differentiating further into mature cells. When the active Lgr5$^+$ stem cell is damaged or lost, this quiescent cell can revert back into a Lgr5$^+$ stem cell state and maintain tissue homeostasis.

In more recent years, markers for different cell populations in the crypts have been identified, and genetic lineage tracing experiments were performed to assess their stem cell properties. The first marker to be discovered was Lgr5 (leucine-rich-repeat-containing G-protein-coupled receptor), which marks cycling cells located at the crypt base[12,13]. When Lgr5$^+$ cells were stably labelled, ribbons of labelled cells containing all differentiated cell types were visible in the villi, and persisted long-term[12]. With the identification of Lgr5, it became possible to purify stem cells from the intestine and establish *in vitro* culture systems. In seminal work, Clevers and colleagues demonstrated that a single Lrg5$^+$ cell can generate 3D crypt–villus organoids with similar cell type compositions as seen in the intestine *in vivo*[14]. These organoids could be expanded for multiple passages in the form of new organoids[14,15] and were able to regenerate intestinal epithelium after transplantation into a damaged mouse colon[15].

One surprising feature of Lgr5$^+$ intestinal stem cells is rapid division[12]. It was a long-held dogma that quiescence is an essential property of tissue stem cells; a feature that can be demonstrated by label retention of nucleotide analogues. On this basis, a crypt cell marked by Bmi, Hopx, Lrig1 and Tert expression, and located at the fourth position from the crypt base, was long thought to be the true and only intestinal stem cell[16–18]. Further investigation of label-retaining crypt cells revealed an important concept in adult stem cell biology: the stem cell state is dynamic and influenced by the microenvironment. As the intestine can still regenerate following short-term ablation of Lgr5$^+$ cells[19], other cell populations with stem cell function must exist. In the case of injury, quiescent, label-retaining crypt cells are activated to repopulate the stem cell niche by producing new Lgr5$^+$ cells[19–21]. Under normal physiological conditions, however, lineage tracing of label-retaining cells produced short-lived progeny[20], demonstrating that they function as non-self-renewing, lineage-committed progenitors during tissue homeostasis. Thus, quiescent cells in the intestinal crypts are prototype facultative stem cells, which are called upon in the case of tissue damage (Fig. 1d). These findings illustrate that there is substantial plasticity within the

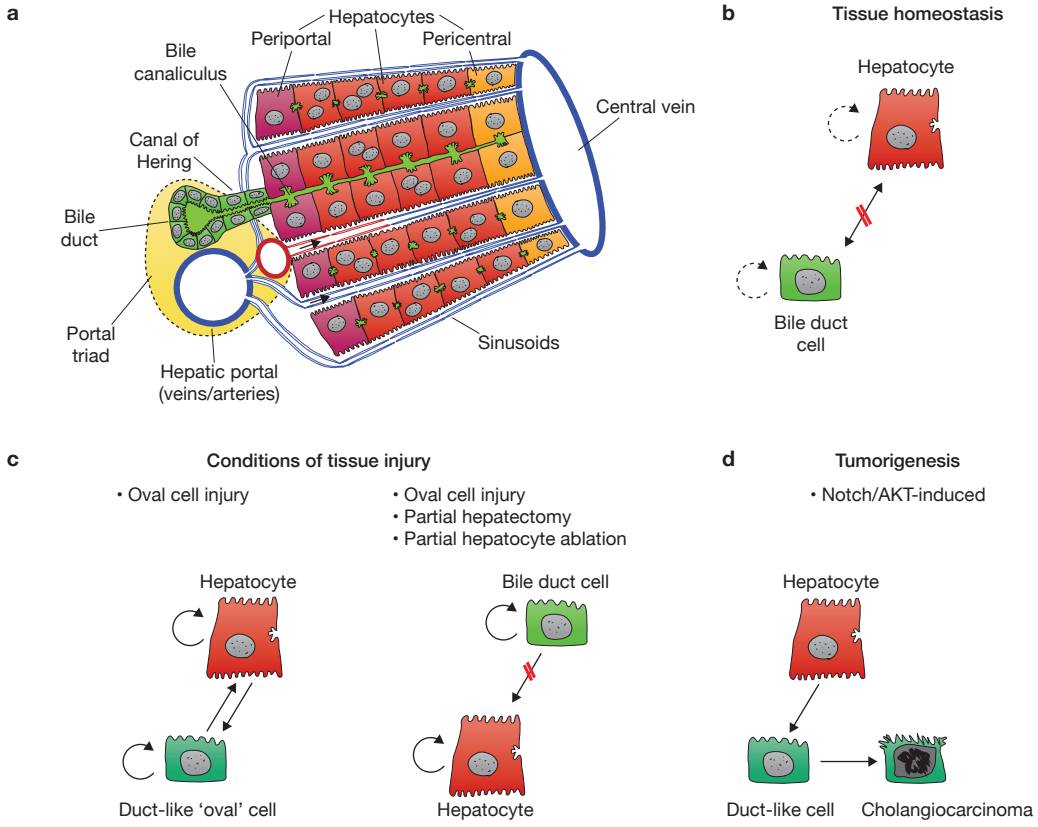

Figure 2 Plasticity and cell interconversion in the liver. (**a**) Cellular architecture of the adult liver. Portal vein and hepatic artery blood enter the hepatic lobule in the portal triad. After mixing, blood flows past the hepatocytes towards the central vein. Bile is secreted into canaliculi by hepatocytes and flows towards the bile duct, located in the portal zone. The canal of Hering consists of cells connecting hepatocytes and the bile duct. (**b**) Cell plasticity during tissue homeostasis. Differentiated hepatic cell types exhibit limited self-renewal (dashed arrows). There is no evidence for interconversion between hepatocytes and bile duct cells. (**c**) Cell plasticity in the injured liver based on lineage tracing in mice. Hepatocytes can undergo ductal metaplasia (dark green) and subsequently revert back to hepatocytes. Biliary cells are highly clonogenic *in vitro*, but do not become hepatocytes *in vivo*. (**d**) In response to oncogenic signals, hepatocytes can undergo ductal metaplasia and give rise to cholangiocarcinoma.

stem cell niche and that injury-induced changes in the microenvironment are sufficient to convert committed progenitors into functional stem cells.

Liver regeneration

The adult liver is the principle site of most intermediary metabolism, and also is a major secretory organ[22]. It contains two main epithelial cell types, the hepatocyte and the bile duct epithelial cell. Hepatocytes perform the metabolic activities, including bile secretion, and the duct cells serve as a conduit of bile to the intestine (Fig. 2a). In the ground state without injury, cell turnover is very slow and less than 1 in 10,000 hepatocytes are mitotic, suggesting a turnover time of at least a year[23]. However, the liver is a highly regenerative organ and is capable of completely restoring its mass after injury[24]. It has been well demonstrated that the hepatocyte and bile duct lineages can both divide extensively in this setting, and that hepatic stem cells are not needed for most injury responses[25]. The liver has long been proposed to also harbour facultative stem cells that can become activated if the injury impairs the ability of the mature cells, especially hepatocytes, to replicate[26–29]. These facultative stem cells are believed to reside near the portal region of the hepatic lobule in the canal of Hering[30]. After activation, the stem cells are thought to proliferate and produce 'oval cells', intermediate cells that have properties of both bile ducts and hepatocytes, which then would differentiate into functional mature hepatocytes.

Clonogenic cells in the liver. Clonogenic growth has been used as an assay to isolate putative stem/progenitor cells in various tissues such as the skin[31] or bone marrow[32]. Such cells were also found in the biliary tree of the adult mouse, which were shown to be bipotential *in vitro*[33,34] — that is, capable of producing cells expressing markers of hepatocytes or bile ducts. As discussed above, the clonogenic growth of Lgr5$^+$ stem cells in intestinal organoids was a highly successful method of delineating stem cells in the intestine[12,35]. Based on their stem cell properties in the intestine, Lgr5$^+$ cells have also been studied in other endodermal organs, such as the adult liver. Although Lgr5 is not expressed in the normal liver during homeostasis, Lgr5$^+$ cells can be found after injury, including oval-cell-inducing injuries[36]. As in the intestine, these cells were found to be capable of extensive clonogenic growth in organoids *in vitro* and displayed significant self-renewal. Unlike their intestinal counterparts, hepatic organoids consist of only a single cell type with ductal characteristics, and do not spontaneously give rise to hepatocytes. With the help of multiple factors, partial differentiation into hepatocyte-like cells can be achieved *in vitro*[36], and *in vitro* differentiated organoids can produce hepatocytes following *in vivo*

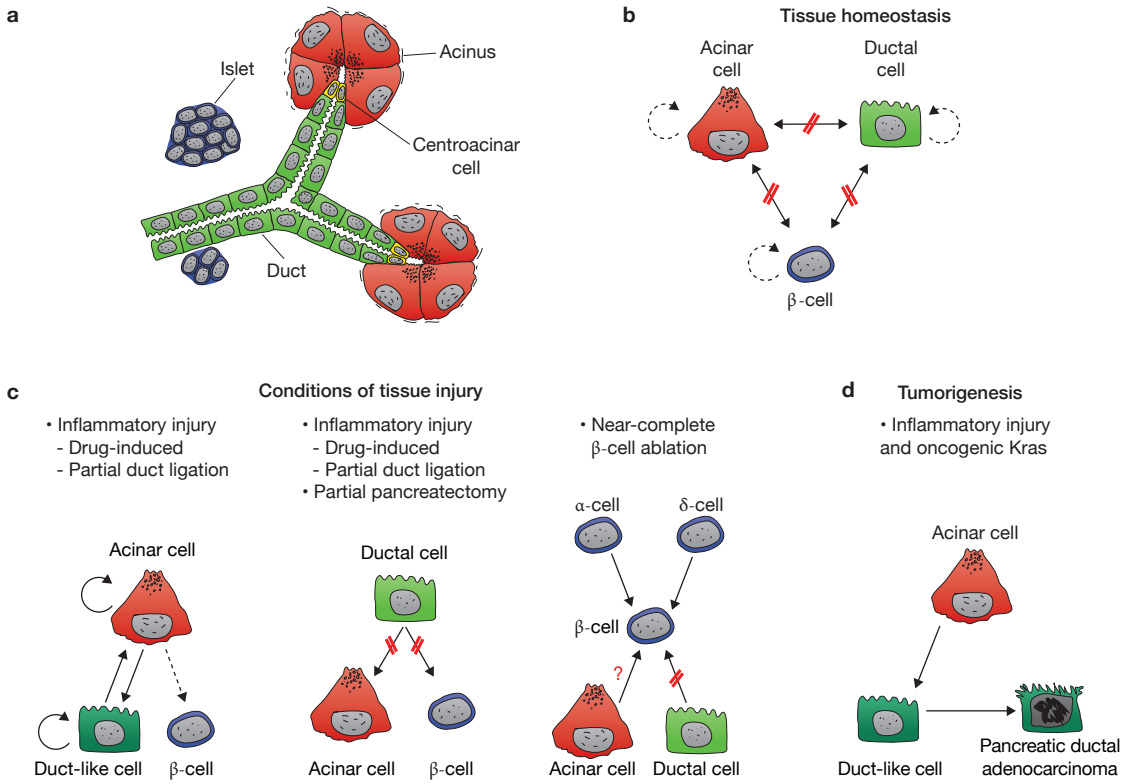

Figure 3 Plasticity and cell interconversion in the pancreas. (**a**) Cellular architecture of the adult pancreas. Acinar (red) and ductal cells (bright green) of the exocrine pancreas form a close functional unit. Centroacinar cells (yellow) lie at the junction of the acinus and its associated terminal ductal epithelium. Endocrine cells (blue) are clustered in islets that are interspersed within the exocrine pancreas. (**b**) Cell plasticity during tissue homeostasis. Differentiated pancreatic cell types exhibit limited self-renewal (dashed arrows). There is no evidence for interconversion of the different pancreatic cell types. (**c**) Cell plasticity in the injured pancreas based on lineage tracing in mice. Acinar cells can undergo ductal metaplasia (dark green). If the injury is short-term, duct-like cells can revert back to an acinar state. Acinar-to-β-cell conversion can occur after long-term inflammatory injury, albeit at extremely low frequency. Pancreatic ductal cells are highly clonogenic *in vitro*, but do not become acinar or endocrine cells *in vivo*. β-Cells can regenerate from other endocrine cell types, but not from ductal cells. (**d**) In response to oncogenic signals, acinar cells can undergo ductal metaplasia and give rise to pancreatic ductal adenocarcinoma.

transplantation[36], although with very low efficiency. Importantly, it has been shown that the precursor to Lgr5$^+$ organoids is biliary in nature and identical to previously reported clonogenic progenitors[37]. Lgr5$^+$ organoids have recently also been generated from human liver[38]. As in the mouse, no spontaneous hepatocytic differentiation occurs and *in vivo* transplantation efficiency is poor compared with true hepatocytes. Genetic lineage tracing of hepatic organoid-forming cells in mice was also conducted, but these cells failed to act as bipotential stem cells *in vivo* (that is, they did not produce hepatocytes following injury)[39]. Overall, the current information indicates that clonogenic cells from the adult liver are not bona fide bipotential hepatic stem cells, but instead are committed to the biliary lineage.

Lineage tracing during normal liver homeostasis. For many years, the 'streaming liver' paradigm had been considered a possibility for hepatic tissue homeostasis[40,41]. This model was analogous to the intestinal stem cell and crypt, with periportal stem cells producing hepatocytes that stream outwards towards the central vein as they age. However, this model was thoroughly debunked by the first genetic lineage tracing studies using retroviral marking of hepatocytes in rats[42,43]. Labelled mature hepatocytes did not stream, and they persisted for very long periods of time. Studies using genetic reporters in adult mice have come to the same conclusion: cell turnover in the liver is very slow and there is no evidence for the contribution of a non-hepatocyte stem cell[44] (Fig. 2b). However, recent work suggests that hepatocytes are heterogeneous and that endothelial-cell-derived niche cues endow pericentral hepatocytes with properties that allow them to maintain hepatocytes during homeostasis[45].

Injury responses in the liver. Liver injuries can be divided into two general classes: one that does not involve any stem cells, and another that is thought to activate putative facultative stem/progenitor cells. The latter is termed the oval cell response and involves intense proliferation of periportal ductal (oval) cells. In rodents, numerous protocols for experimental oval cell injury exist[46–48]. The ductular reaction frequently seen in liver cirrhosis has been viewed as the human equivalent of this response[49,50].

Surgical removal of parts of the liver is the prototypical model of stem-cell-independent repair[24]. Classic studies performed by Nancy Bucher with thymidine labelling in the 1960s[51] showed that a majority of hepatocytes divided immediately after hepatectomy and that cell division subsided within days, thereby proving that rare stem cells could not account for tissue regeneration in this model. Subsequent work using BrdU labelling in both rats and mice confirmed these findings[52,53]. Similarly, recent work using genetic lineage tracing of hepatocytes has also ruled out

the involvement of rare stem cells in restoring liver mass after surgical removal of hepatic tissue[44] (Fig. 2c).

The concept of adult liver stem cells is modelled on the properties of the embryonic liver progenitor, the hepatoblast, which is known to be the clonal precursor to both the bile ducts and hepatocytes of the adult[54–56]. In rats treated with a combination partial hepatectomy and chemical DNA damage by 2-acetylaminofluorene (AAF), cells positive for the hepatoblast marker AFP (α-fetoprotein)[57,58] emerge within a short time from biliary type cells in the canal of Hering[47,59]. These AFP$^+$ cells were named oval cells and thought to be hepatic stem cells. Pulse-chase experiments with BrdU strongly suggested that AFP$^+$ oval cells can eventually become mature hepatocytes[59,60], and *in vitro* experiments suggested that oval cells are bipotential, that is, can give rise to both hepatocytes and bile duct cells[61]. Despite the evidence supporting a facultative liver stem cell that becomes active only in specific injury situations, conclusive proof for this model was lacking and lineage tracing studies were needed.

In the 1990s, the work on liver stem cell biology shifted from the rat to the mouse, for which powerful genetic tools were available. As the classic oval cell injury models used in rats had not previously worked in the mouse, alternative injury models were developed. The most prominent was a diet containing the hepatotoxin 3,5-diethoxycarbonyl-1,4-dihydro-collidin (DDC)[48] or choline-deficient ethionine (CDE) supplement[46]. These regimens produce the emergence of duct-like cells, a process that is initiated in the portal zone of the hepatic lobule.

Although AFP$^+$ ducts were never observed in mice, initial experiments using the DDC and CDE diets to induce ductal cell proliferation were all supportive of the facultative liver stem cell hypothesis[62–65]. However, more recent studies from multiple laboratories have consistently shown that biliary precursors do not produce physiologically relevant numbers of hepatocytes in any of the classic mouse 'oval cell' injury models[8,39,66,67] (Fig. 2c). This suggests that facultative liver stem cells may in fact not exist, at least not in the mouse. Two recent papers suggest that putative hepatic progenitors are required for functional recovery after extreme hepatocyte loss[68,69]. Although the data are compatible with the classic notion of a liver stem/progenitor cell in the biliary ducts, neither study used lineage tracing to show that the putative hepatocyte progenitor is in fact derived from biliary cells and not the hepatocytes themselves[70].

Hepatocyte plasticity. In chronic human liver disease, ductular proliferations containing cells that express markers of both hepatocytes and bile ducts are frequently found[49,71–73]. Definitive lineage tracing cannot be done in humans, but some recent experiments in mice have revived the old theory that ductular reactions are derived from hepatocyte transdifferentiation[70,74–76]. When marked hepatocytes were traced during oval-cell-inducing injury, they could produce ductal epithelium if the injury was long-lived (Fig. 2c). Furthermore, hepatocyte-derived duct-like cells have recently been shown to be capable of self-renewal, as well as differentiation into functional hepatocytes[70]. Thus, proliferating ducts derived from injured hepatocytes display the characteristics of the classic oval cell. It seems possible, if not likely, that hepatocytes themselves are bipotential and can therefore be mistaken as stem cells of biliary origin[8]. Ductular plasticity of hepatocytes is also relevant to liver cancers such as cholangiocarcinomas, which in the past were thought to be derived from proposed hepatic stem cells, but can in fact arise from hepatocytes[77,78] (Fig. 2d).

Analogous to the suggestion that hepatocytes abutting the central vein could be responsible for maintaining the hepatocyte population during homeostasis[45], hepatocyte heterogeneity may also be important during liver repair. A recent study found that hepatocytes in the periportal region have high regenerative capacity during injury and are resistant to becoming cancerous[79]. Although the possibility of niche-dependent hepatocyte heterogeneity requires further investigation, it is important to consider that much literature refutes the notion of either portal-to-central or central-to-portal hepatocyte streaming during homeostasis[42,43].

Pancreas regeneration

Like the liver, the pancreas is comprised of long-lived cell types. Acinar cells and endocrine islet cells secrete digestive enzymes and blood-glucose-regulating hormones, respectively. Both cell types proliferate at a rate of less than 0.2% per day and are estimated to survive more than a year in mice[80–82]. Ductal cells, which carry the digestive enzymes from the acinar compartment to the duodenum (Fig. 3a), exhibit similarly low proliferation rates[80]. However, in terms of its regenerative capacity, the pancreas is not similar to the liver. Although acinar and endocrine cells increase their division rate after injury[83–85], tissue mass is not fully restored[86–92]. Generally, there has been much debate as to whether division of existing cells accounts for cell regeneration or whether there is a role for a stem/progenitor cell[5–7], an idea that has been especially favoured in the context of endocrine cell regeneration. As small endocrine cell clusters are frequently found adjacent to ducts[93], especially after injury[94–99], putative stem/progenitor cells have been thought to reside in the pancreatic ducts. Moreover, endocrine cells originate from duct-like structures during foetal life[100–103] and it was assumed that this process would continue after birth.

Clonogenic cells in the pancreas. Rare clonogenic cells with multilineage potential have been reported in islets[104–106], but the best-characterized clonogenic population has been identified in isolated pancreatic ducts, from both mice and humans[106–113]. Whether clonogenic cells are exclusively restricted to a specific aspect of the ductal tree is not known. Yet, it has been shown that centroacinar cells, located at the junction of an acinus and terminal duct (Fig. 3a), have sphere-forming potential[113]. Centroacinar cells proliferate *in vivo* in response to injury, and are enriched for the expression of stem cell markers[113]. The cardinal tissue stem cell marker Lgr5 is not expressed in centroacinar cells, and as in liver, Lgr5 is absent from the adult pancreas, but induced by injury in a subset of ductal cells[112]. Lgr5 is also induced when ductal cells from the uninjured pancreas undergo colony formation *in vitro*[112]. This shows that removing cells from their native niche alters cellular state, illustrating the profound impact of the microenvironment on cell properties.

Similar to findings in liver, duct-derived 'pancreatospheres' are capable of significant clonogenic growth *in vitro* and exhibit self-renewal capacity, at least for a few passages[37,104,110,111,113]. Some studies also reported endocrine and acinar cell differentiation in a subset of duct-derived colonies *in vitro*, albeit with very low efficiency[110,113]. Others achieved limited endocrine differentiation only by co-transplanting the spheres with 'helper cells' from the embryonic pancreas into mice[112]. As of yet, there is no convincing evidence to claim that these clonogenic cells are pancreatic stem cells. For example, it is unclear whether secondary or tertiary colonies can form organoid-like structures with multi-lineage potential as shown for intestinal stem cells[14]. The most striking argument

against these cells being tissue stem cells comes from *in vivo* lineage tracing experiments. When the very same ductal cell population that gives rise to organoids *in vitro*[112] was traced *in vivo*, no differentiation into other cell types was observed, not even after injury[101]. Thus, similarly to bile duct cells in the liver, clonogenic cells in the pancreatic ducts are not bona fide stem cells, but are committed to the ductal lineage.

Lineage tracing during normal pancreas homeostasis. The concept that new endocrine cells arise from stem/progenitor cells in the ducts of the adult pancreas was first proposed more than a century ago[114] and is largely based on anatomic proximity. However, seminal lineage tracing studies by Dor and colleagues[115] refuted this model. After stably labelling endocrine β-cells in young mice, the researchers tested whether the fraction of labelled β-cells changes over a one-year chase period. If new β-cells were produced from stem/progenitor cells, the frequency of labelled β-cells would gradually decrease. However, they found that the labelling index remained unchanged, providing evidence that the majority of new β-cells arise by self-duplication and not from non-β-cell stem cells. Similar studies with acinar cells provided no evidence for them being replaced by a non-acinar cell source[116,117]. Thus, during postnatal life, β-cells and acinar cells are produced by the division of pre-existing cells (Fig. 3b).

Injury responses in the pancreas. Pancreatic ductal cells acquire, at least partially, a progenitor-like state in response to injury[96,101,118–120]. This observation gave rise to the long-held paradigm that tissue damage activates facultative stem/progenitor cells in the ducts[121]. For example, when pancreatitis is induced by caerulein or constriction of the main duct through partial duct ligation, ductal cells reactivate expression of the embryonic progenitor cell markers Pdx1 and/or Ngn3[96,101,118–120,122–126]. Moreover, Wnt signalling, which acts in the embryonic but not the adult pancreas[127–130], is activated in response to partial duct ligation[112]. These gene expression changes were thought to reinstate mechanisms used in the embryonic pancreas, where endocrine cells differentiate *de novo* from bipotential progenitors capable of producing both endocrine and ductal cells[100–103]. In the past decade, the idea that ducts harbour a facultative stem/progenitor cell has been thoroughly tested by *in vivo* lineage tracing experiments.

Both an indirect approach (assaying for the influx of unmarked cells into a specific cell compartment[83,84,115–117,122–124,131,132]) and a direct labelling approach (looking for a contribution of marked cells to another cell compartment[65,83,101,102,117,125,126,132–137]) have been used in the context of pancreas injury. As a whole, these lineage tracing studies provide little, if any, evidence for a contribution of facultative stem/progenitor cells to endocrine or acinar cell regeneration in classic pancreatic injury models, including partial β-cell ablation, partial pancreatectomy, partial duct ligation or caerulein treatment[65,83,84,101,102,115–117,124,131,132,134–137] (Fig. 3c). Numerous research groups labelled ductal cells directly using inducible Cre lines, but observed no contribution of marked cells to the β- or acinar cell compartment in these classic injury models[65,101,102,134,135]. Although a few studies reported evidence in support of a stem/progenitor cell[122,123,125,133], in some cases the lineage tracing tool proved inadequate to test the question[138]. In sum, lineage tracing studies strongly argue against ductal cells being a significant source of new β- or acinar cells in the context of injury and call into question the very concept of a facultative stem cell in the pancreatic ducts.

Pancreatic cell plasticity. In conditions of pancreatic inflammation, ductular structures with characteristics of both acinar and ductal cells are frequently found[139]. Similarly, cells co-expressing different endocrine hormones are observed in the face of metabolic stress[140]. Lineage tracing experiments in mice suggest that these hybrid cells are not produced from specialized stem/progenitor cells but instead represent transdifferentiation events[83,126,132,140–142], similarly to hepatocyte-to-ductal cell conversions observed in the liver. In some instances, the process is transient and reversible once the insult is eliminated — as during early stages of acinar-to-ductal metaplasia induced by inflammation, where acinar cells transiently convert into proliferative duct-like cells, which then redifferentiate into acinar cells to repair tissue damage[142] (Fig. 3c). Likewise, β-cell dedifferentiation seems to be initially reversible when the adverse metabolic environment is corrected[140]. If, however, the insult is severe or long-lasting, transdifferentiation events can become permanent. In the extreme case of experimental near-complete β-cell ablation, other endocrine cell types transdifferentiate into β-cells and restore, at least partially, β-cell mass[83,137] (Fig. 3c). Acinar-to-endocrine[126] and possibly also ductal-to-endocrine[122] interconversions have been observed in other models of extreme tissue injury. All the emerging evidence suggests that if the insult is severe enough, differentiated cells dedifferentiate, in some cases reverting back to a stem-like state, and participate in tissue repair. Although this can have beneficial effects, the inherent plasticity of pancreatic cells also bears a risk for disease. The prime example for this is acinar-to-ductal metaplasia, which becomes irreversible in the context of oncogenic mutations and can lead to pancreatic cancer[142,143] (Fig. 3d).

Concluding remarks

Current evidence indicates both differences and similarities of cell regenerative mechanisms in the liver, pancreas and intestine. Whereas the intestine relies on specialized stem cells to replenish and repair tissue cells, a stem cell may not even exist in the liver and pancreas. Instead, these organs depend primarily on mature cell types for cell regeneration under both homeostatic and injury conditions. It is not yet known whether all mature cell types contribute equally to tissue regeneration; a multicolour clonal fate mapping approach, as previously employed in the intestine[144], could provide valuable information. Tissue insults to the liver and pancreas, particularly if severe, render differentiated cells plastic, and revert mature cells to a stem-like state to ensure tissue regeneration. An important area of future research will be to identify niche signals that control cell plasticity in the liver and pancreas, as this could help develop methods of tissue repair and cancer therapy.

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ADDITIONAL INFORMATION

Supplementary information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence should be addressed to M.S.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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