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Generation and Regeneration of Cells of the Liver and Pancreas

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Abstract

Liver and pancreas progenitors develop from endoderm cells in the embryonic foregut. Shortly after their specification, liver and pancreas progenitors rapidly acquire markedly different cellular functions and regenerative capacities. These changes are elicited by inductive signals and genetic regulatory factors that are highly conserved in vertebrate evolution. Interest in the development and regeneration of the organs has been fueled by the intense need for hepatocytes and pancreatic β -cells in the therapeutic treatment of liver failure and type I diabetes. Studies in diverse model organisms have revealed evolutionarily conserved inductive signals and transcription factor networks that elicit the differentiation of liver and pancreatic cells, and provide guidance for how to promote hepatocyte and β -cell differentiation from diverse stem and progenitor cell types.

The liver and pancreas coordinately control body metabolism, including the modification of digested nutrients by hepatocytes in the liver and the regulation of blood glucose levels by insulin secreted from β -cells in the pancreas. Liver hepatocytes are large, often polyploid cells that secrete serum proteins, express enzymes that neutralize toxicants, produce bile acids to aid in digestion, and control the bulk of intermediary metabolism. Biliary ducts of cholangiocytes, the other epithelial cell type in the liver, serve primarily as conduits of secreted bile. By contrast, the distinct pancreatic functions are partitioned into many more cell types. Pancreatic cells include insulin (β), glucagon (α), somatostatin, ghrelin, and pancreatic-polypeptide secreting endocrine types, each of which produces a single hormone. The pancreas also contains exocrine cell types, which constitute the bulk mass of the tissue and include acinar cells that produce digestive enzymes and duct cells that provide conduits to the gut for the enzymes. The greater diversity of cell types in the pancreas involves a greater array of regulatory factors and lineage decisions during organogenesis.

Clinical studies have shown that transplantation of hepatocytes can support the functions of a failed liver and correct metabolic liver disease in the long-term (1). Similarly, cadaveric islets can, for several years, support glucose homeostasis in type I diabetic individuals, in whom the β -cells have been destroyed by an autoimmune reaction (2). In both transplantation settings, the quality and amount of donor cells are severely limiting, as is the ability to expand the terminally differentiated cell populations. These limitations have led to a search for other progenitor cell sources of hepatocytes and β -cells and intense interest in how the differentiation of such progenitors can be directed, or “programmed,” efficiently. The programming efforts are founded on understanding how hepatocytes and β -cells are normally generated in the embryo and how they arise during regeneration in adults, in response to tissue damage and

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disease. Here we provide an overview of the cells' development and regeneration and highlight unresolved issues in the field.

Two progenitor domains for each tissue

The liver and pancreas in terrestrial vertebrates each develop from two different spatial domains of the definitive endodermal epithelium of the embryonic foregut. Fate mapping experiments have shown that the liver arises from lateral domains of endoderm in the developing ventral foregut (3,4) as well as from a small group of endodermal cells tracking down the ventral midline (4) (Fig. 1A). During foregut closure, the medial and lateral domains come together (Fig. 1A, green arrows) as the hepatic endoderm is specified. The pancreas is also induced in lateral endoderm domains, adjacent and caudal to the lateral liver domains, and in cells near the dorsal midline of the foregut (5,6) (Fig. 1A). These events occur at 8.5 days of mouse gestation (E8.5), corresponding to about three weeks of human gestation. After the domains are specified and initiate morphogenetic budding, the dorsal and ventral pancreatic buds merge to create the gland. Despite differences in how the different progenitor domains are specified, descendants of both pancreatic progenitor domains make endocrine and exocrine cells, and descendants of both liver progenitor domains contribute to differentiating liver bud cells (3-6). Genetic lineage marking studies are needed to determine the extent to which different descendants within each tissue may differ with regard to functionality and regenerative potential.

Signals specifying hepatic and pancreatic progenitors

Embryo tissue recombination experiments and genetic approaches in the chick, frog, mouse, and zebrafish have revealed that the liver and pancreas domains are specified within the endodermal epithelium under the influence of inductive signals from nearby mesoderm cells (7,8). Little is known about how the signaling genes in the mesoderm are controlled, but it is remarkable how well the inductive signals are conserved across the vertebrate animal models. Initially, broad suppression of mesodermal Wnt and FGF4 signaling in the foregut enables liver and pancreas induction, whereas active mesodermal Wnt signaling in the posterior gut suppresses these tissue fates (9,10) (Fig. 1B). Retinoic acid signaling, apparently from paraxial mesoderm cells, helps further refine the anterior-posterior position where the liver and pancreas can develop from the gut endoderm (11-14). Subsequently, in the ventral foregut, FGF from the cardiac mesoderm and BMP from septum transversum mesenchyme cells coordinately induce the liver program and suppress the pancreas program (15-18). Curiously, MAPK is activated in response to FGF in the lateral hepatic progenitors well prior to MAPK activation in the medial hepatic progenitors, reflecting apparent differences in patterning (19). During foregut closure, lateral ventral endoderm cells that move caudal to the cardiac domain escape the FGF and can initiate ventral pancreatic development (20). In the dorsal foregut, signals from the notochord that include activin and FGF suppress sonic hedgehog (shh) signaling within the endoderm and allow the pancreatic program (21,22). Notably, all of the above events occur within hours in the vertebrate embryo.

The newly specified hepatic cells in embryos are referred to as hepatoblasts. These cells express serum protein genes specific to hepatocytes, such as *albumin* (*alb1*) and *transthyretin* (*ttr*), and appear to be bipotential and later give rise to hepatocytes and cholangiocytes (23); however, formal genetic lineage studies remain to be performed. The *Tbx3* gene helps expand the hepatoblast population by suppressing *p19^{ARF}* (24). The newly specified pancreatic endoderm is initially marked by the expression of the transcription factor genes *Pdx1* and then *Ptf1a* (25,26), which are crucial for pancreatic development; *Pdx1* is also expressed in adjacent progenitors of the duodenum (27,28).

Changes in signal responses as development proceeds

The cellular responses to inductive signals include the activation and repression of transcription factor genes that, in turn, elicit new gene expression programs required for cell differentiation. Interestingly, the new cell type programs can change the cellular responses to exogenous signals. Such is the case for FGFs, which are needed only transiently to help pattern the foregut endoderm (19,29) and later promote the expansion of the newly specified progenitor cell populations (16,30). Shh signaling initially promotes dorsal pancreatic development in the zebrafish (31,32) and later appears to suppress it (33). Wnt signaling initially inhibits liver induction (9), but shortly afterwards promotes liver bud growth and differentiation (9,34,35). Each of these changes in cellular responses to inductive signals occurs in less than a day of vertebrate embryogenesis. The mechanisms underlying such changes are not known.

Organ morphogenesis and cell type differentiation

After the hepatoblasts and pancreatic progenitors are specified, the respective endoderm cells transition from a cuboidal shape to a columnar one, and then become pseudo-stratified within the epithelium (Fig. 2). This process is similar to the morphogenetic characteristics of neural epithelial development and is controlled in the foregut by the homeobox transcription factor gene *Hhex* (36). The pancreatic epithelium then branches into the stroma, to create the pancreatic bud, whereas for the hepatic epithelium, the basal lamina breaks down and the cells proliferate into the surrounding stroma. These latter morphologic changes are controlled by the homeobox transcription factor genes *Prox1* (37), *Hnf6/OC-1*, and *OC-2* (38) (Fig. 2). *Hnf6* and *OC-2* regulate E-cadherin, thrombospondin-4, and *Spp1*, which control cell adhesion and migration in various contexts. The fetal liver serves as a transient site for hematopoiesis in amniotes. Hence fetal viability is dependent upon proper liver growth.

As the progenitors of both tissues bud into the stroma, they are adjacent to and receive stimulatory signals from nearby endothelial cells (39-41). Interestingly, endothelial cells also promote liver regeneration after tissue damage, apparently by HGF signaling (42). The specific molecular signals produced from endothelial cells in the embryonic context have not been described, but sphingosine-1-phosphate in the circulation, delivered by the endothelium, promotes dorsal pancreatic budding (43). The emerging vascular systems in the liver and pancreatic buds also provide oxygen and nutrients and ultimately allow endocrine function (44).

Neural crest cells migrate into the developing pancreas and, as they develop into neurons, affect the numbers of β -cells (45). The stimulatory roles of endothelial cells and neural crest cells illustrate how crucial is the co-differentiation of the stromal environment with that of the hepatic and pancreatic progenitors.

Within the liver and pancreas buds, notch signaling components are important for creating the proper balance in the numbers of hepatocytes and cholangiocytes from hepatoblasts (46,47) and of endocrine and exocrine cells from pancreatic progenitor cells (48-50). Loss of Notch signaling allows the endocrine lineage, which is marked by and requires the transcription factor gene *Ngn3* (25,48,51).

Elegant genetic lineage studies showed that as the pancreatic bud develops into an organ, *Cpal*-positive cells in the distal tips of the branching epithelium are multipotent progenitors that give rise to duct and endocrine descendants along the trunk of the branches, until about E14 in the mouse (52). Afterwards, the *Cpal*-positive cells give rise to acinar cells; this corresponds to the time of the “secondary transition”, when definitive β -cells are generated under the influence of the *Mafa* transcription factor (53,54). Further genetic lineage studies, the transcription factor genes that elicit pancreatic and hepatic cell differentiation, and the

parameters that affect cell growth are shown in Fig. 3 and have been reviewed extensively elsewhere (23,55-57). It is interesting to note the differences in how the dorsal and ventral pancreatic progenitors are specified (Fig. 3), suggesting flexibility in the ways by which pancreas cells could be specified from stem cells.

Liver regeneration

Liver regeneration after most forms of injury does not rely on stem or progenitor cells, but instead involves mitosis of mature cells (58). The regenerative capacity of hepatocytes can be assessed in animal models of liver repopulation, where transplanted cells have a selective advantage over the host (59). Using such systems it has been shown that mature polyploid hepatocytes have stem-cell like regenerative capacity rivaling that of hematopoietic stem cells and are able to divide more than 100 times without loss of function (60). Human hepatocytes are also highly regenerative (61) and, importantly, this capacity for regeneration is established at the earliest embryonic stages (36). Unfortunately, it has not yet proved possible to grow and expand populations of hepatocytes in cell culture or maintain their differentiation. Even with the most sophisticated growth media, hepatocytes de-differentiate extensively within a few hours after plating (62). Thus, the functions of adult hepatocytes, including cell division, appear to depend on complex interactions with other cells in a 3-dimensional matrix. Co-culture systems attempting to mimic this organization show promise in resolving these problems (63).

The adult liver also harbors facultative progenitors which can be activated in response to specific injuries (Fig. 4), usually under conditions of impaired hepatocyte replication. Progenitors give rise to an intermediary cell type, often termed “oval cells,” which are thought to differentiate into both biliary epithelium and hepatocytes (58). However, oval cells are not a homogeneous population (64) and their apparent multipotentiality has not been demonstrated by definitive lineage tracing. In the rat, oval cells resemble embryonic hepatoblasts in that they express both bile duct and hepatocyte markers as well as α -fetoprotein (58). Thus, progenitor cell activation in the adult employs some of the same genetic programs used during development (65). Details about the precise origin of adult liver progenitors and the signals that govern their activation are not clear.

Pancreas regeneration

Whereas hepatocytes are capable of extensive regeneration, the ability of β -cells to expand is more limited, especially in the adult. Some degree of regeneration can occur in young animals after physiologic stimuli such as pregnancy (66) or injury (partial pancreatectomy) (67). However, this partial growth ability is insufficient to permit recovery from cell loss in type 1 diabetes; yet it might, with suppression of autoimmunity (68). The restricted regenerative ability of the endocrine pancreas may be related to the defined number of pancreatic progenitors, which is not capable of compensatory growth in response to cell loss (69). In contrast, hepatoblasts can increase their proliferative rate in response to dysfunctional cells in their midst (36). The lack of regeneration in β -cells has raised considerable interest in the potential of tissue repair by resident stem cells. It remains controversial whether progenitors exist in the adult pancreas. It is clear that the majority of new β -cells derive from pre-existing insulin expressing cells after surgical injury (67,70), but recent work has shown that duct ligation can activate Ngn3 positive β -cell precursors in the ductal epithelium (71). Thus, adult pancreatic progenitors exist and their activation depends on the specific injury, as does oval cell initiation in the liver (Fig. 4).

Creating hepatocytes and β -cells de novo

The current inability to expand human hepatocytes in vitro is an obstacle not only for cell therapy, but also for pharmaceutical drug development, because of the cells' importance in assessing the metabolism of xenobiotics. Thus, the generation of hepatocytes from expandable precursors is of considerable interest. It is noteworthy that cells with properties virtually identical to hepatic oval cells can also emerge in the pancreas, especially after ablation of acinar cells (72). Upon transplantation, these pancreas-derived "oval cells" can differentiate into functional hepatocytes and bile ducts (73). Several reports have suggested that the reciprocal trans-differentiation is also possible, i.e. the conversion of liver cells toward the pancreatic endocrine fate (74). Forced expression of pancreatic transcription factors elicit insulin expression in the liver and corrects experimental diabetes (75). Together these findings suggest that both the adult liver and pancreas contain cells with epigenetic memory of their common embryonic origin. The existence of potential β -cell precursors in the adult liver is of obvious medical interest. Since pancreatic exocrine cells greatly outnumber β -cells, it is also exciting that they can be reprogrammed to make functional β -cells in vivo by viral delivery of the developmental transcription factors *Pdx1*, *Ngn3*, and *Mafa* (76).

Pluripotent stem cells, including embryonic stem cells (ESC) and induced pluripotent stem cells (iPS), are a potentially abundant source of hepatocytes and β -cells. Numerous groups have been developing ESC differentiation protocols that attempt to mimic normal embryonic development. The first step of both pancreatic and hepatic development is the induction of definitive endoderm by using activin A (77). Further treatment with BMP-4 and bFGF can then direct cells towards the hepatic lineage (78). In a protocol developed for differentiation towards endocrine pancreas, definitive endoderm was treated in sequential stages with KGF, retinoic acid, noggin, and cyclopamine (79,80). Despite remarkable progress, the resulting cells often fail to achieve complete function sufficient for regenerative therapy, remaining only "hepatocyte- or β -cell-like". It is not yet clear how precisely the known developmental signals must be orchestrated to properly program hepatic and pancreatic cells at will, but detailed studies of the activated signaling pathways and their cross-regulatory interactions during embryogenesis will be informative.

Future prospects

Two basic opportunities for medical application of the knowledge of developmental biology of the liver and pancreas have emerged. The first is the application of the precise conditions that exist within the embryo to differentiate pluripotent stem cells. The sequential and exactly timed use of extracellular factors and accessory cell types (such as endothelium and mesenchyme) is predicted to mimic embryogenesis and thus yield highly functional derivatives for transplantation and other applications. In this setting, competent cells respond to extrinsic signals which act upon their epigenome. The second approach is to use genetic reprogramming to directly change cell fates, by taking advantage of transcriptional activators, repressors, and chromatin modifiers. This method can work in vivo as well as in culture and can be applied to adult epigenetic relatives of the desired cell type. Thus, it may be possible to enhance tissue regeneration in situ without the complications of cell engraftment and immunological rejection. However, it will be important to overcome the potential problems of insertional mutagenesis, when stable gene integration is involved, as well as undesired transgene expression changes and physiologic responses to viral gene delivery. In summary, emphasis is required on both approaches to use the signals and regulatory factors from developmental biology to sculpt the differentiation of progenitor and stem cells to liver and pancreas cell fates.

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Fig. 1.

Cell domains and signals for embryonic liver and pancreas specification. A. Fate map of progenitor cell domains prior to tissue induction; view is into the foregut of an idealized mouse embryo at E8.25 (3-4 somite stage). Green arrows indicate movement of lateral progenitor regions toward the ventral-medial region. B. Sagittal view of a mouse embryo several hours later than in A, showing the positions of the newly specified liver and pancreas tissue domains. Signals and cell sources that pattern the endoderm are shown. Dashed blue line indicates plane of view in A.

Fig. 2.

Stages of liver bud organogenesis. Hepatoblasts are stained blue (Hex^{LacZ}⁺); cells with orange nuclei are gut endoderm (FoxA2⁺); and all nuclei were stained green by DAPI. White arrows point to the hepatic cells. Genes and signals that promote each transition are indicated. Similar morphogenetic stages occur during pancreas bud organogenesis. Images are adapted from (36). S, pair somite stage; E, embryonic day.

Fig. 3.

Regulatory factors controlling cell type lineages within the liver and pancreas. Transcription factor genes are shown in bold; their functions have been reviewed in the text and elsewhere (23,55-57), except for *vHnf1* in hepatic development (81). Note that *Pdx1* initially marks duodenum and caudal stomach progenitors (not shown) as well as the pancreatic domains (28).

Fig. 4. Progenitor lineage relationships in adult liver and pancreas. The thickness of the arrows indicates the dominant mode of regeneration. Dashed lines delineate rare or hypothetical cell fate transitions that occur only under specific experimental conditions.