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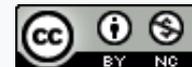


Anatomy and embryology of fish liver and pancreas with a focus on their use in research

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Anatomy and embryology of fish liver and pancreas with a focus on their use in research

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ABSTRACT: Fish liver and pancreas perform indispensable roles related to food digestion, metabolism, and glucose homeostasis. The fish liver fills the cranial part of the celomic cavity and displays variable lobation and degree of coloration across species. Its development from the gut endoderm is regulated by a cascade of signaling factors, including fibroblast growth factor 10 (Fgf10), GATA-binding factor 6 (Gata6), and hepatocyte nuclear factor 6 (Hnf6). The fish pancreas consists of discrete yellow glandular masses that infiltrate the gut mesentery. The pancreatic tissues may also disseminate into the parenchyma of the liver and spleen, forming hepatopancreas and splenopancreas, in several fishes, e.g., cyprinids. The pancreas originates with two buds from the gut wall close to the area of the developing liver. Specification of pancreatic progenitor cells is regulated by the expression of the transcription factor pancreatic and duodenal homeobox 1 (Pdx1), which initiates a downstream cascade of transcription factors important for pancreatic differentiation. Both organs share several anatomical, developmental, and regenerative mechanisms with higher vertebrates, including humans. These shared similarities made them a target of numerous experimental research studies related to embryogenesis, environmental pollution, and endocrine and metabolic disorders. In this article, we summarize the anatomical, histological, and developmental features involving the liver and pancreas in fish. We also discuss strengths and weaknesses of their use for disease modelling.

Keyword: Brokmann bodies; developmental biology; diabetes; fatty liver; fish model; hepatopancreas

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INTRODUCTION

The fish liver performs several functions that include bile secretion, detoxification, and metabolism of carbohydrates, proteins, and lipids (Genten et al., 2009). In female oviparous fishes, it is responsible for production of yolk precursors, e.g., vitellogenin. The latter are of crucial importance for maintaining embryos and nurturing larvae (Yilmaz et al., 2024).

The gross appearance and area occupied by the liver differ significantly among different types of fish (Bertolucci et al., 2008). Anatomically, the liver is located at the most cranial part of the celomic cavity in most teleost. In many species, it appears divisible into a number of lobes that varies according to the species (Franco-Belussi et al., 2012).

The fish pancreas is composed of endocrine and exocrine portions. The endocrine pancreas consists of pancreatic islets that secrete hormones for regulation of blood glucose levels. These islets comprise insulin-producing beta cells, glucagon-producing alpha cells, somatostatin-producing delta cells, and pancreatic polypeptide-producing PP cells. The latter cell type has not been clearly documented in all fish species (Chanet et al., 2023). On the other hand, the exocrine pancreas includes the pancreatic acini that secrete enzymes necessary for digestion and the duct system that conveys them to the intestine. The ductal epithelium also releases bicarbonate-rich secretion into the gut lumen, further aiding in digestion (Ishiguro et al., 2012).

Unlike the liver, which appears well-organized with distinct localization within the celomic cavity, the fish pancreas displays differences in its spatial distribution. In general, pancreatic tissues in many teleosts, e.g., zebrafish (*Danio rerio*), could be identified as discrete glandular masses interspersed among fats of the gut mesentery (Tocher et al., 2008). In a number of species, e.g., grass carp (*Ctenopharyngodon idella*), clusters of pancreatic tissue, mainly of exocrine nature, invade the subcapsular regions of the spleen and surround the main branches of the portal vein within the liver (Mokhtar, 2015).

The embryonic formation of the liver and pancreas in fish is regulated by a complex network of key transcription factors. These factors are spatiotemporally expressed during sequential steps involving induction of hepatic and pancreatic progenitors as well as their specification and subsequent differentiation (Tao and Peng, 2009; Tiso et al., 2009). Interestingly, a number of these factors is reawakened

during damage-induced organ regeneration raising a therapeutic potential for them (Mo et al., 2024).

This review summarizes the structural and developmental events of the liver and pancreas in fish and follows the differentiation process of these organs under control of the transcription factors. It emphasizes the significance of teleost liver and pancreas for disease modeling. The progress in the study of cell lineage will help in creating a role model for better understanding of the disease mechanism and the role of therapeutic agents in minimizing its incidence rate.

LIVER

Anatomical features of fish liver:

The fish liver fills a significant part of the cranial region of the celomic cavity and displays variation in its shape and number of lobes according to species (**Figure 1**). It appears triangular-shaped in Nile tilapia (*Oreochromis niloticus*) (Vicentini et al., 2005) and crescent-shaped in porthole shovelnose catfish (*Hemisorubim platyrhynchos*) (Faccioli et al., 2016). In both species, the liver is bilobed with the left lobe being larger than the right one. Conversely, the right hepatic lobe of grass carp (*Ctenopharyngodon idella*) is more developed than the left hepatic lobe and from which a long process is extended caudally (Mokhtar, 2018). An irregularly shaped liver with three lobes is present in many teleost including zebrafish (*Danio rerio*) and pearl cichlid (*Geophagus brasiliensis*) (Yao et al., 2012). The liver is formed by a single lobe in guppy (*Poecilia reticulata*) (Sousa et al., 2018). In rock goby (*Gobius paganellus*) the liver is pyriform in shape with a smooth dorsal surface and a fissured ventral one (Abusrer and Shtewi, 2023).

In general, the teleost liver is characterized by its reddish coloration due to high vascularization (Bertolucci et al., 2008). The liver color is darker in adult fish compared to juvenile ones (**Figure 2**). The change in liver color occurs in parallel with maturational changes involving other parts of the fish digestive tract (Abdellatif et al., 2024a; Abdellatif et al., 2024b; Fiala et al., 2024). In wild fish, carnivorous species have a reddish-brown liver, while herbivorous species have a light brown one. In farmed fish, especially those of young age, it is lighter in color due to the high fat content of their diets (Taddesse et al., 2014).

It should be noted that in anemia, e.g., those caused by iron deficiency or post-exposure to patho-

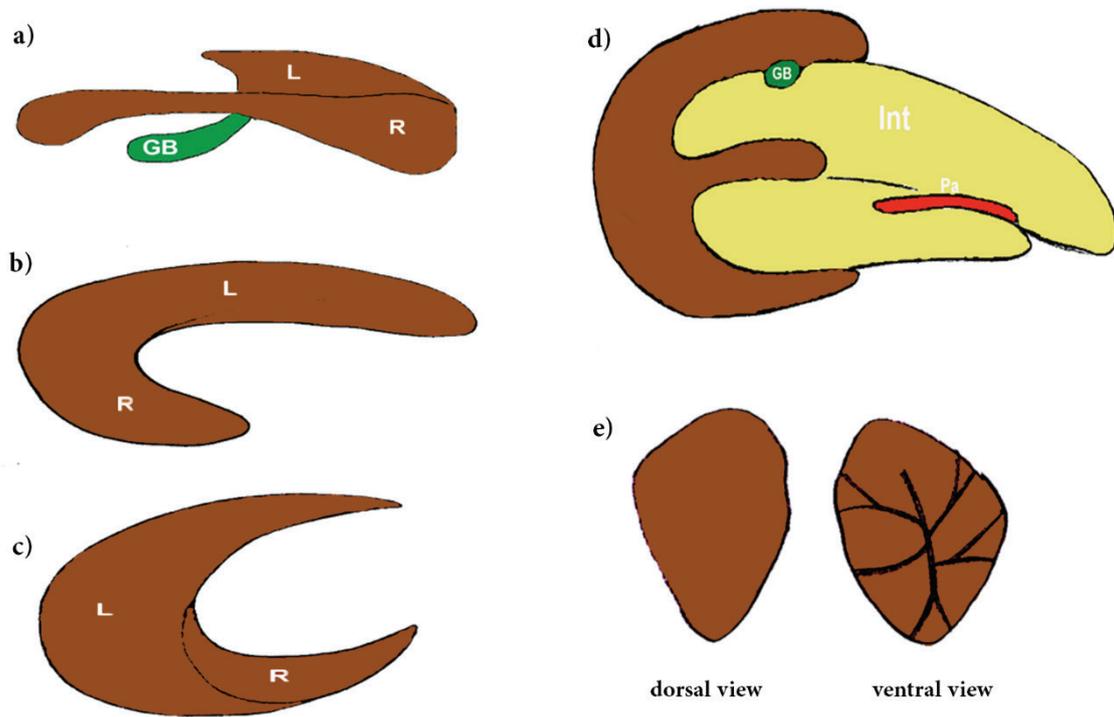


Figure 1. Various forms of liver lobation in teleost. **a)** Grass carp (*Ctenopharyngodon idella*). **b)** Nile tilapia (*Oreochromis niloticus*). **c)** Porthole shovelnose catfish (*Hemisorubim platyrhynchos*). **d)** Zebrafish (*Danio rerio*). **e)** Rock goby (*Gobius paganellus*). GB, gall bladder; Int, intestine; L, left hepatic lobe; Pa, pancreas; R, right hepatic lobe.

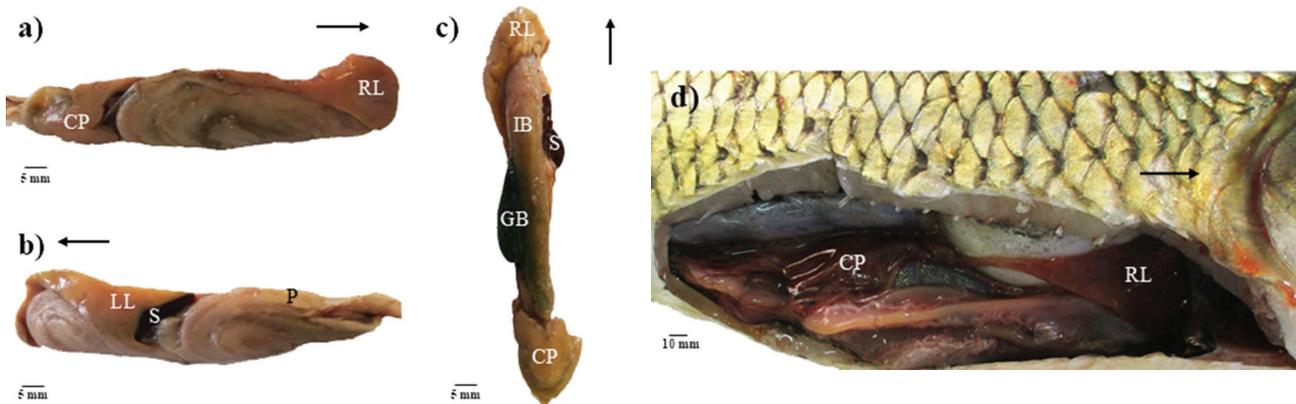


Figure 2. Gross appearance of the liver in juvenile (90 days posthatching) and adult grass carp (*Ctenopharyngodon idella*). Adopted from Fiala (2023). **a)** Right, **b)** left, **c)** ventral views of the liver in juvenile fish. **d)** Right view of the liver in adult fish. The arrow direction indicates the head position. Note the darker coloration of the liver of adult fish compared to that of juvenile ones. RL, right hepatic lobe; LL, left hepatic lobe; CP, caudal process; GB, gall bladder; IB, intestinal bulb; P, pancreas (mesenteric part); S, spleen.

genic viruses, the liver might appear pale in color. However, caution should be applied while interpreting a pale liver color as physiological fluctuations in hepatic glycogen or lipid contents as well as reproductive status can also significantly influence liver color (Buddington and Kuz'mina, 2000).

Histological features of fish liver:

The liver is a parenchymatous organ consisting of parenchyma and stroma. The liver parenchyma is formed mainly by hepatocytes, about 80% of the hepatic parenchyma, which are arranged into hepatic cords, separated from each other by hepatic sinusoids. Phagocytic cells are also found in-between these cords (Franco-Belussi et al., 2012). Except for a limited number of fish species, e.g., lamprey (*Petromyzon marinus*), there is no basal membrane beneath the hepatic sinusoidal lining (Nejedli and Gajger, 2013). Other cells of the liver include Kupffer cells, hepatic stellate cells and endothelial cells which play an important role in proper functioning of hepatocytes (Malik et al., 2002).

The hepatic sinusoids are lined by endothelial cells with spindle-shaped nuclei. Microvillar projections arise from the upper border of hepatocytes and extend into the space of Disse, a space found between the sinusoidal lining and the hepatocytes (Yao et al., 2012).

Typical characteristics of fish hepatocytes include a round central nucleus and eosinophilic cytoplasm containing abundant rough endoplasmic reticulum, lysosomes, and mitochondria (Yao et al., 2012). In female fish the cytoplasm could appear basophilic, especially during breeding season, due to excessive production of vitellogenin. Moreover, the cytoplasm appears vacuolated according to the proportion of the dietary fats (Taddesse et al., 2014). Excessive accumulation of lipid droplets inside the cytoplasm of hepatocytes displaces the nuclei to the periphery of the cells (Azab, 2012).

The hepatocytes display three arrangements: tubular, cord-like, and solid. In the tubular form, the hepatocytes are arranged into a double-layered structure around narrow and irregular sinusoids, e.g., Otocephala. In the cord-like form, the hepatocytes are arranged into a single-layered structure around sinusoids, e.g., Euteleostei. In the solid form, the hepatocytes form several layers around narrow sinusoids, e.g., Elopomorph (Akiyoshi and Inoue, 2004; Noskor et al., 2013).

The liver stroma includes the hepatic capsule and

septa. In plectognathid fishes, e.g., fahaka pufferfish (*Tetraodon lineatus*), the liver is covered by a loose connective tissue capsule with a single layer of squamous cells (Azab, 2012), but in Persian tooth-carp (*Acipenser stellatus*) the liver is enclosed by a dense connective tissue capsule with a layer of cuboidal cells (Monsefi et al., 2010). A meshwork of reticular fibers encircles the hepatic sinusoids and the vascular elements of the liver in grass carp (*Ctenopharyngodon idella*) (Mokhtar, 2018). Noteworthy that the fish liver, except for medaka (*Oryzias latipes*), lacks the typical lobulation pattern frequently seen in mammalian liver due to lack of interlobular connective tissue septa (Hardman et al., 2007).

The arrangement of vascular and biliary tracts of the liver differs between fish and mammals. In mammals, the hepatic cords extend from the portal triad toward the hepatic central vein, but in fish the portal triad is not detected (Akiyoshi and Inoue, 2004; Noskor et al., 2013). Moreover, in mammals, portal triads, collections of branches from the portal vein, hepatic artery, and bile duct, are found around each hepatic lobule. In fish, the bile ducts and the hepatic vascular elements are randomly distributed within the hepatic parenchyma (Figueiredo-Fernandes et al., 2007; Noskor et al., 2013). In zebrafish the hepatic artery is not clearly detected, and the hepatocytes are organized in double-layered cords in a radial manner around the central vein (Yao et al., 2012).

Developmental regulation of fish liver:

The process of liver formation involves three sequential stages: hepatoblast specification, hepatocyte differentiation, and liver growth (Field et al., 2003a) (**Figure 3**). The first steps of zebrafish liver formation involve activation of *Prox1* and *Hhex* in the endodermal cells of the hepatic bud at 22 hpf which in turn induces hepatoblast specification (Jin et al., 2023). The hepatic bud appears dorsal to the yolk sac 32-48 hpf. By 32 hpf, the expression of genes responsible for hepatocyte differentiation such as *ceruloplasmin* and *wnt2bb*, is noticed (Korzsh et al., 2001; Poulain and Ober, 2011). The *Gata6* and *Hhex* further regulate the differentiation of hepatocytes which in turn induces further proliferation of the cells of the developing hepatic bud. The formation of the biliary system is driven by Notch signaling and members of the *Onecut* (OC) family of transcription factors, e.g., *Hnf6*. The liver growth commences 60-72 hpf and continues until the liver reaches its mature size (Chu and Sadler, 2009).

The hepatic primordial cells are bipotent cells.

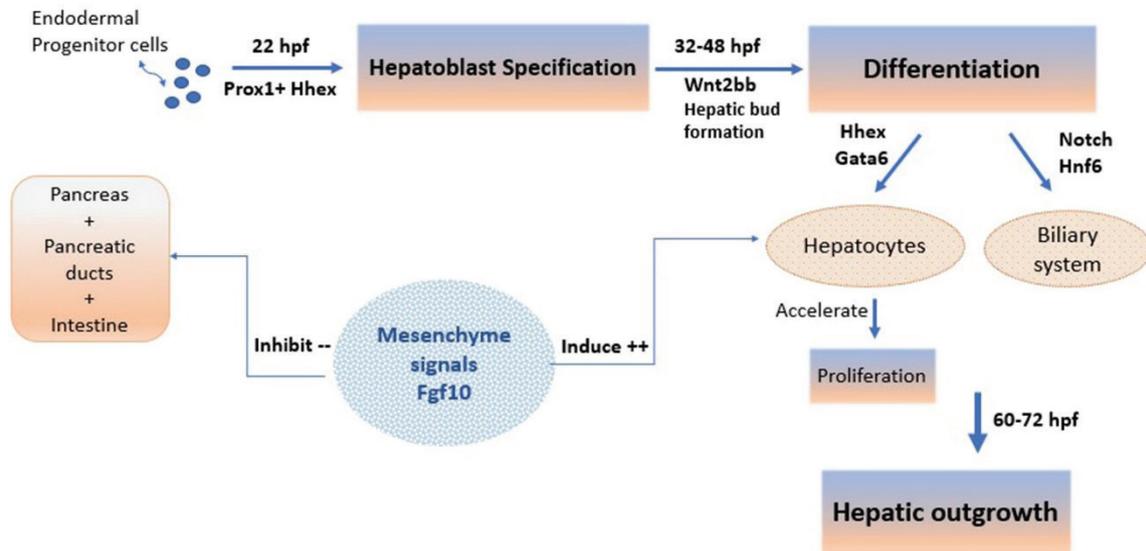


Figure 3. Stages of early development of teleost liver using zebrafish as a model. Fgf10, Fibroblast growth factor 10; Gata6: GATA-binding factor 6; Hhex, Hematopoietically expressed homeobox; Hnf6, Hepatocyte nuclear factor 6; Hpf, hours post fertilization; Prox1, Prospero homeobox protein 1; Wnt2bb, Wingless-type MMTV integration site family, member 2Bb.

They induce the formation of both liver hepatocytes and bile duct cholangiocytes (Gaudio et al., 2009). The precursors of hepatocytes and cholangiocytes detach from the hepatic bud (Duncan, 2003; Zaret, 2002). The hepatic duct is formed from expansion of a stalk connecting the hepatic primordium to the developing gut tube by 34-50 hpf in zebrafish (Field et al., 2003b).

The final stages of hepatic growth require the formation of the vascular tracts (Korzhan et al., 2008). This stage includes three different subdivisions: non-vascular, endothelium-dependent and vascular-dependent growth. The vascular-dependent stage of liver growth needs the circulation of the blood into the sinusoids (Korzhan et al., 2008).

In most vertebrates, the liver and pancreas share the same origin from the foregut endoderm (Deutsch et al., 2001). The release of Fgf10 by the mesenchyme inhibits the hepatic progenitor cells from differentiating into pancreatic cells (Dong et al., 2007; Yan et al., 2015). Further, mesenchymal molecules play a role in the formation of intrahepatic vascular tracts, Ito cells, and hepatic Kupffer cells (Cassiman et al., 2006).

The process of different organ development in zebrafish occurs during the first 24 hours post fertilization (hpf). The fish larvae are capable of swimming

by 24 hpf. Within the first few days post fertilization (dpf) the different systems are formed, and the larvae can depend on external food (Chu and Sadler, 2009).

Using light microscopy, the hepatic primordium is detected from the first day post hatching in port-hole shovelnose catfish (*Hemisorubim platyrhynchos*) and appears composed of clusters of undifferentiated cells (Faccioli et al., 2016). Zadmajid et al. (2019) observed the liver of Levantine scraper (*Capoeta damascina*) larvae as a mass of cells between the yolk sac and the developing gut tube. The liver of tomato clownfish (*Amphiprion frenatus*) exhibited a noticeable increase in the number and size of hepatocytes during the early post hatching stage (Putra et al., 2012). The hepatocytes of European catfish (*Silurus glanis L.*) revealed no signs of lipid accumulation at 3-5 days posthatching, but their cytoplasmic glycogen content was evidenced by the end of the first week concomitant with active utilization of exogenous food (Kozarić et al., 2008).

PANCREAS

Anatomical features of fish pancreas:

The fish pancreas consists of endocrine and exocrine compartments which vary in their anatomical arrangement among the different teleost species (Chakrabarti and Ghosh, 2012; Youson et al., 2006).

The exocrine pancreas contributes to food diges-

tion through the discharge of pancreatic secretions rich in several enzymes including trypsin, amylase, and carboxypeptidase A, into the gut lumen. The endocrine portion contains cells that secrete hormones regulating blood glucose levels (Weinrauch et al., 2022).

The distribution of fish pancreatic tissue shows great variation among different species (**Table 1**). In general, it appears in the form of discrete yellow glandular masses that infiltrate the gut mesentery (Hassan, 2013). In zebrafish (*Danio rerio*), the pancreas is organized into 4 lobes: the gallbladder-spleen lobe, the middle lobe, the left lobe, and the ventral lobe (Chen et al., 2007). In grass carp (*Ctenopharyngodon idella*), the pancreas is detected as dispersed masses within the mesentery. In the latter, and similar to most cyprinids, the pancreas also disseminates within the parenchyma of the liver and spleen, forming hepatopancreas and splenopancreas, respectively (Mokhtar, 2015).

The intrahepatic position of fish pancreas has been determined in several fish species including iridescent shark catfish (*Pangasius hypophthalmus*) (Seyrafi et al., 2009), molly (*Poecilia sphenops*) (Hussein et al., 2023), and Nile tilapia (*Oreochromis niloticus*) (Vicentini et al., 2005). The hepatopancreas has been estimated to fill about 5% of total liver area, as in common pandora (*Pagellus erythinus*); that could increase to 14% of total liver area, as in Whiting (*Merlangius merlangus euxinus*) (Nejedli and Gajger, 2013). The splenopancreas has been noted in bassan barbel (*Barbus pectoralis*) (Mahabady et al., 2012), common carp (*Cyprinus carpio*), and binni (*Mesopotamichthys sharpeyi*) (Akoul and Al-Jowari, 2019). In view of this, the fish pancreas has diverse arrangements that may constitute a difficulty during specimen collection and should be thoroughly considered for achieving proper research and diagnostic outcomes.

Table 1. Various forms of pancreas distribution in teleost.

Pancreas form Species	Mesenteric	Hepato-pancreas	Spleno-pancreas	Reference
Zebrafish (<i>Danio rerio</i>)	+			(Chen et al., 2007)
Nile tilapia (<i>Oreochromis niloticus</i>)		+		(Morrison et al., 2004)
Grass carp (<i>Ctenopharyngodon idella</i>)	+	+	+	(Fiala, 2023; Mokhtar, 2015)
Rock Goby (<i>Gobius paganellus</i>)		+		(Abusrer and Shtewi, 2023)
Pearl cichlid (<i>Geophagus brasiliensis</i>)		+		(Sales et al., 2017)
Iridescent shark catfish (<i>Pangasius hypophthalmus</i>)		+		(Seyrafi et al., 2009)
Common pandora (<i>Pagellus erythinus</i>)		+ (~5% of total liver area)		(Nejedli and Gajger, 2013)
Whiting (<i>Merlangius merlangus euxinus</i>)		+ (~14% of total liver area)		(Nejedli and Gajger, 2013)
Molly (<i>Poecilia sphenops</i>)	+	+		(Hussein et al., 2023)
African catfish (<i>Clarias gariepinus</i>)	+			(Karkit et al., 2021)
Long Whiskers Catfish (<i>Mystus gulio</i>)	+			(Ghosh and Chakrabarti, 2016)
Orangefin labeo (<i>Labeo calbasu</i>)	+	+	+	(Ghosh and Chakrabarti, 2016)

Histological features of fish pancreas:

The mesenteric pancreas of fish contains both exocrine and endocrine components. In striped dwarf catfish (*Mystus vittatus*), the exocrine pancreas is composed of serous acini and scattered endocrine islets (Chakrabarti and Ghosh, 2015). In other species, e.g., zebrafish (*Danio rerio*), the endocrine part, often referred to as the Brockman body, is composed of aggregations of several islets, each of which consists mainly of alpha, beta, and delta cells, which are responsible for secretion of glucagon, insulin, and somatostatin hormones, respectively (Yao et al., 2012). These hormone-producing cells were also noticed among the intestinal loops and within the wall of the main pancreatic ducts in common carp (*Cyprinus carpio*) (Akoul and Al-Jowari, 2019; Kong et al., 2002).

The endocrine cells of fish pancreas are characterized by their prominent nuclei and contain abundant smooth endoplasmic reticulum, ribosomes, mitochondria, and zymogen granules within their cytoplasm (Gilloteaux et al., 2008).

In brown spotted grouper (*Epinephelus chlo-rostigma*), the pancreatic acini appear embedded in the mesenteric adipose tissue. These acini are characterized by their granular cytoplasm. While the endocrine pancreatic islets consist of cellular aggregations and are encircled by connective tissue and blood capillaries to convey the hormones directly to the blood stream (Hassan, 2013).

In grass carp (*Ctenopharyngodon idella*), the pancreatic acini of the hepatopancreas are distributed along the course of portal vein branches. These acini are arranged as clusters of pyramidal cells with basal nuclei and prominent nucleoli and contain eosinophilic zymogen granules within their cytoplasm. The acini are separated from the hepatocytes by a thin connective tissue capsule (Figure 4). The intrahepatic part of the pancreas lacks endocrine cells, which appear exclusive to the extrahepatic parts of the pancreas (Mokhtar, 2015).

The distribution of pancreatic acini inside the liver of teleost usually follows the course of portal vein branches; however, they could extend around the hepatic artery and main bile ducts. A species-specific pattern of arrangement has been reported for the intrahepatic pancreas. In Nile tilapia (*Oreochromis niloticus*), the pancreatic acini were detected around the major vascular tracts at the hepatic hilum. These acini follow the venous tract within the hepatic parenchyma and diminish towards the smaller branch-

es, so the efferent vessels appear naked. The hilum is penetrated by the pancreatic-venous biliary arteriolar tract (P-VBAT). This tract is split into smaller tracts such as pancreatic-venous tract (P-VT), pancreatic-venous arteriolar tract (P-VAT), pancreatic-venous biliary tract (P-VBT) and venous tracts (VT) without the pancreas (Akiyoshi and Inoue, 2004; Figueiredo-Fernandes et al., 2007). The perivascular distribution of pancreatic acini were also recorded in grass carp (*Ctenopharyngodon idella*) (Fiala, 2023; Mokhtar, 2015) (Figure 4) and guppy (*Poecilia reticulata*) (Sousa et al., 2018).

Developmental regulation of fish pancreas:

In zebrafish, the pancreas originates from the gut endoderm by two buds: the dorsal and ventral pancreatic buds (Tiso et al., 2009) (Figure 5). The dorsal pancreatic bud is obviously detected at 24 hpf dorsal to the gut tube and formed from primary endocrine cells, arranged in the form of a principal islet. This bud is displaced to the right side after the gut looping. The ventral pancreatic bud appears 34 hpf rostral to the dorsal one and expands to form the exocrine pancreas around the principal islet (Field et al., 2003b). The duct cell, pancreatic acini, and the second wave endocrine cells originated from the ventral bud. The duct system includes the intra- and extrahepatic ducts which contribute to the formation of second wave endocrine cells (late islets) (Moro et al., 2009; Wang et al., 2011). During early stage of pancreatic formation, the expression of *pdx1* is necessary for specification of the endocrine precursors, while *ptf1a* is required for the exocrine precursors (Biemar et al., 2001; Zecchin et al., 2004).

The progenitors of the endocrine and exocrine cells are segregated at the early stage of pancreas development and remain dispersed in the vicinity of the intestinal tract, and some of them remain attached to the hepatic surface (Faccioli et al., 2016).

In many teleost species, the pancreas appears as a cellular mass located between the yolk sac and the gut tube at hatching time. (Falk-Petersen and Hansen, 2003), In gilthead sea bream (*Sparus aurata*) (Elbal et al., 2004) and spotted wolffish (*Anarhichas minor*) (Falk-Petersen and Hansen, 2003), both endocrine and exocrine cells are distinguished at the time of hatching. In Indian walking catfish (*Clarias magur*) the pancreatic primordium was detected on the first day posthatching and the zymogen granules appeared at a later time (Kumari et al., 2021). In yellow catfish (*Pelteobagrus fulvidraco*), the exocrine acini and zymogen granules were clearly detected

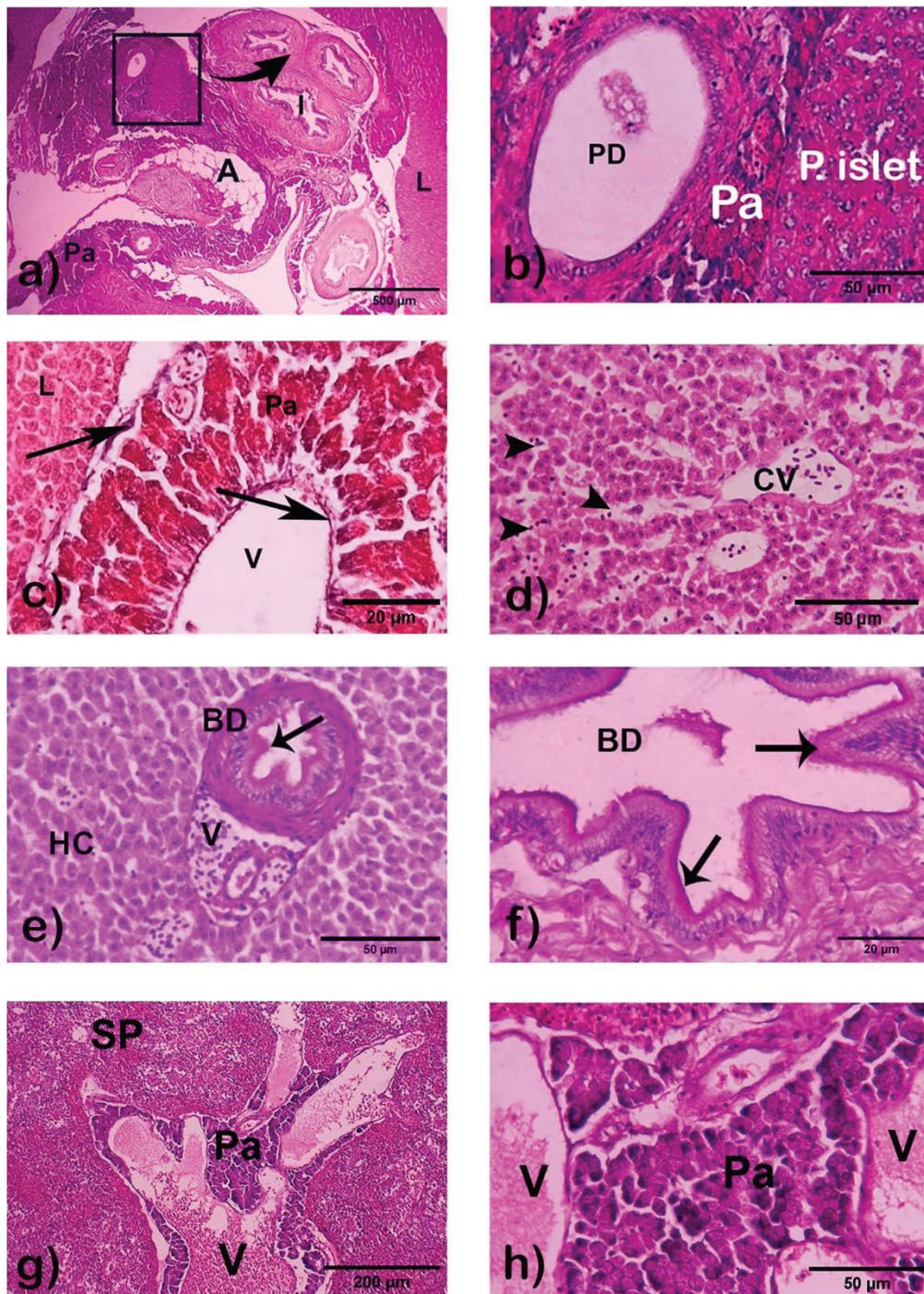


Figure 4. Histological features of the liver and pancreas of an adult grass carp (*Ctenopharyngodon idella*). Adopted from Fiala (2023). **a)** The mesenteric portion of the pancreas consists of pancreatic acini (Pa) in-between the adipose tissue patches (A). I, Intestine; L, liver. H&E stain. **b)** High magnification of Figure 4a showing a large pancreatic islet (P. islet), pancreatic acini (Pa), and a pancreatic duct (PD). **c)** Collagen fibers (arrows) within the wall of an intrahepatic pancreatic-venous tract (P-VT). Masson's trichrome stain. **d)** The hepatic sinusoids (arrowheads) are connected to a centrally located vein (CV). H&E stain. **e, f)** Strong positive PAS staining of apical brush border (arrows) of the intrahepatic (e) and the extrahepatic (f) bile ducts (BD). HC, hepatocytes. PAS stain. **g)** Splenic parenchyma (SP) showing pancreatic tissue, mainly of exocrine nature, (Pa) around branches of the splenic vein (V). H&E stain. **h)** High magnification of Figure 4g showing the structure of an intrasplenic pancreatic-venous tract.

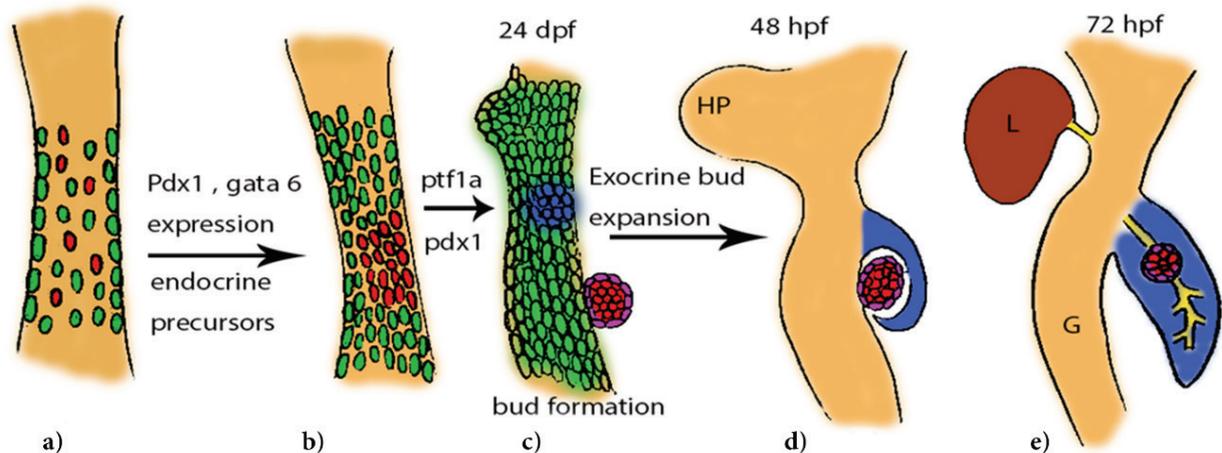


Figure 5. HStages of early development of teleost pancreas using zebrafish as a model. **a, b)** The pancreatic precursors emerge from the gut wall after expression of *pdx1* (pancreatic and duodenal homeobox 1) and *gata 6* (GATA-binding factor 6). **c)** The endocrine bud (red) is displaced posterior to the exocrine one (blue) after the process of gut looping. *Ptf1a* (pancreas transcription factor 1 subunit alpha) induces exocrine acini, duct cells, and secondary endocrine cells. **d, e)** The hepatic primordium (HP) increases in size, and the exocrine bud expands to enclose the endocrine pancreas. The duct system is formed by this stage and connects the pancreas to the gut lumen. G, gut tube; hpf, hours post fertilization; L, liver.

at 4 days posthatching (dph) and the endocrine cells were noticed at 5 dph (Yang et al., 2010).

The appearance of pancreaticocytes shows maturational changes with fish age. In California halibut (*Paralichthys californicus*) (Gisbert et al., 2004) and yellow catfish (*Pelteobagrus fulvidraco*) (Yang et al., 2010), when the larvae start exogenous feeding, the pancreaticocytes reveal a pronounced increase in size and a more basophilic staining.

FISH LIVER AND PANCREAS IN DISEASE MODELLING

Zebrafish has been regarded as an important model for liver embryogenesis studies. Reasons for this include the translucent nature of their eggs, the rapid development of their embryos, and the short incubation time, i.e., the time from fertilization to hatching takes 48-72 hours, making them a more efficient model than other animals with in utero developing embryos (Howe et al., 2013). Zebrafish embryos have been used not only to study molecular factors involving liver development under normal circumstances (Yan et al., 2022; Yi et al., 2018), but also under imbalance of several dietary factors including copper, selenium, and alpha-lipoic acid (Li et al., 2022; Tompach et al., 2024; Zhu et al., 2023).

The structure of fish liver shares several simi-

larities with the human liver in terms of hepatocyte organization and mechanisms of nutrient metabolism (Goldsmith and Jobin, 2012). Studying metabolic and lifestyle factors, e.g., exercise, associated with the incidence of non-alcoholic fatty liver disease (NAFLD) using fish as a model is trending (Chang et al., 2023; Zou et al., 2021; Zou et al., 2023). Several teleost species have also been utilized to monitor various mechanisms involving storage and metabolism of lipids and carbohydrates within the liver. Among these species are white-spotted rabbitfish (*Siganus canaliculatus*) (Li et al., 2008), Japanese puffer (*Takifugu rubripes*) (Xu et al., 2020), European seabass (*Dicentrarchus labrax*) (Palma et al., 2019), and zebrafish (*Danio rerio*) (Lyssimachou et al., 2015; Roy et al., 2020). Out of all these species, zebrafish provided the greatest insights into the understanding of hepatic biology due to the availability of fish strains with targeted genetic mutations of factors involved in nutrient metabolism including stearoyl-CoA desaturase (*scd*) (Xu et al., 2023), liver enriched antimicrobial peptide 2 (*leap2*) and its receptor growth hormone secretagogue receptor 1a (*ghsr1a*) (Fei et al., 2024), and liver-enriched gene 1 (*leg1*) (Wang et al., 2025).

The liver of both larval and adult fish has been extensively used to evaluate the effect of various

deleterious agents on vertebrates' biology. These agents include endocrine disruptors (e.g., bisphenols) (Liu et al., 2023); heavy metals, e.g., cadmium (Chen et al., 2024); micro- and nanoplastics (Brandts et al., 2022; Wang et al., 2022); organic solvents (e.g., toluene) (Sayed et al., 2023; Su et al., 2023); and fire suppressants (Annunziato et al., 2020; Li et al., 2023). Fish species used for these investigations included zebrafish (*Danio rerio*), Japanese medaka (*Oryzias latipes*), and fathead minnow (*Pimephales promelas*).

The fish pancreas displays considerable morphogenetic and endocrine similarities to the human pancreas, especially those related to the basic organization of endocrine cells as well as developmental pathways governing their development and function (Löhr and Hammerschmidt, 2011). Several researches have utilized fish pancreas as a model for studying vertebrate pancreas biology during diabetes (Krishnan and Rohner, 2019). The availability of genetic manipulation tools pertinent to the zebrafish pancreas has enabled the establishment of therapeutic gadgets for diabetes treatment by defining new sources for insulin production from non-beta cell origins (Ye et al., 2015; Yu et al., 2023).

Various areas of research involving the liver and pancreas of fish are shown in **Figure 6**.

CONCLUSIONS

Morphological and developmental features of fish liver and pancreas, as well as their importance in research studies related to lipid storage and metab-

olism, regeneration in response to damage-induced toxicity, and diabetes, have been reviewed. The diverse localization of fish pancreas across various fish species suggests caution during representative sampling of the whole organ to achieve sufficient outcomes. Although zebrafish remains an excellent model for most of these studies, characterizing additional fish models warrants future studies.

Understanding the developmental events involving the pancreas will help to improve studies focusing on transdifferentiation of pancreatic endocrine cells. Moreover, characterizing the liver biology of several teleost models will enable researchers to test various therapeutic agents and enrich the field of comparative toxicology. Lastly, broadening the spectrum of knowledge related to the functional anatomy of fish liver and pancreas will accelerate screening of novel approaches for the purposes of hepatic regeneration and experimental diabetes.

LIST OF ABBREVIATIONS

Dph: Day posthatching
 Fgf10: Fibroblast growth factor 10
 Gata6: GATA-binding factor 6
 Ghr1a: Growth hormone secretagogue receptor 1a
 Hhex: Hematopoietically expressed homeobox
 Hnf6: Hepatocyte nuclear factor 6
 Hpf: Hour post fertilization
 Leap2: Liver enriched antimicrobial peptide 2
 Leg1: Liver-enriched gene 1
 NAFLD: Non-alcoholic fatty liver disease
 Oc: Onecut
 Pdx1: Pancreatic and duodenal homeobox 1

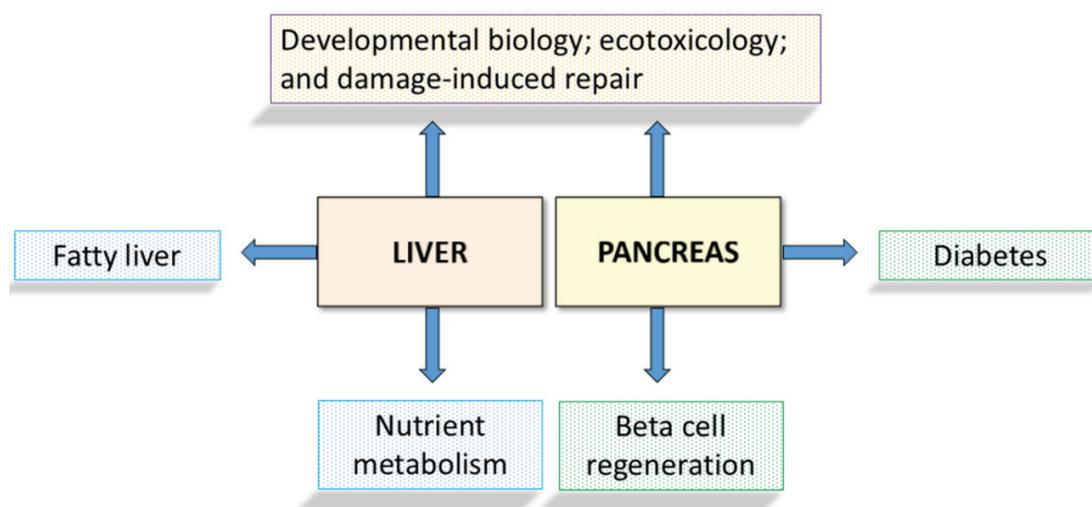


Figure 6. Summary of various research areas involving fish liver and pancreas.

PP: Pancreatic polypeptide
Prox1: Prospero homeobox protein 1
Ptf1a: Pancreas transcription factor 1 subunit alpha
P-VAT : Pancreatic-venous arteriolar tract
P-VBAT: Pancreatic venous biliary arteriolar tract
P-VBT : Pancreatic-venous biliary tract
P-VT: Pancreatic-venous tract
Scd: Stearoyl-CoA desaturase
VT: Venous tract
Wnt2bb: Wingless-type MMTV integration site family, member 2Bb

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Data availability

All data are included in the published article.

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Conflict of interests

The authors declare no conflict of interest.

Authors' contributions

EF, AA prepared the figures and drafted the manuscript. MS, SE revised the manuscript. All authors accepted the final version of the paper.

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