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Invited Review

Liver and Pancreas: Do Similar Embryonic Development and Tissue Organization Lead to Similar Mechanisms of Tumorigenesis?

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The liver and pancreas are closely associated organs that share a common embryological origin. They display amphicrine properties and have similar exocrine organization with parenchymal cells, namely, hepatocytes and acinar cells, secreting bile and pancreatic juice into the duodenum via a converging network of bile ducts and pancreatic ducts. Here we compare and highlight the similarities of molecular mechanisms leading to liver and pancreatic cancer development. We suggest that unraveling tumor development in an organ may provide insight into our understanding of carcinogenesis in the other organ.

Key words: Hepatocellular carcinoma; Intrahepatic cholangiocarcinoma; Extrahepatic cholangiocarcinoma; Hepatic fibrosis and cirrhosis animal models; Embryonic and postnatal liver development lineage tracing

INTRODUCTION

The liver and pancreas originate from adjacent regions of the definitive endoderm, with liver development being initiated by formation of a tissue bud on the ventral side of the distal foregut, and the pancreas arising from ventral and dorsal endodermal buds located caudally to the liver. Formation of the organ buds and their outgrowth from the distal foregut endoderm are controlled by mesodermal signals, which specify endoderm cells to hepatic and pancreatic fates and promote proliferation of the budding cells[1,2]. Cell proliferation rapidly generates a population of hepatic and pancreatic multipotent progenitors that differentiate to several mature epithelial cell types, namely, hepatocytes and cholangiocytes in the liver, and endocrine, acinar, and ductal cells in the pancreas[3–6]. Importantly, the extrahepatic biliary tract, namely, the gallbladder, hepatic, cystic, and common bile ducts, develop from the same endodermal region as the ventral pancreas[7]. However, as soon as the ventral pancreas starts rotating around the gut to merge with the dorsal pancreas, the extrahepatic biliary tract develops separately from the pancreas while maintaining a connection with the common pancreatic duct.

At the end of organogenesis, the liver and pancreas have developed a tissue organization that allows them to function as amphicrine glands. The endocrine function is ensured by the hepatocytes in the liver and the islets of Langerhans in the pancreas. In both organs, a dense network of fenestrated capillaries enables secretion of hormones and growth factors into the bloodstream. Exocrine functions are exerted by hepatocytes and acinar cells, which contribute roughly to 80% of the mass of their respective organs. They produce bile and digestive enzymes (e.g., amylase, lipases) that are discharged into the duodenum via a ductal network. Ducts are lined by cholangiocytes in the liver and by ductal cells in the pancreas. Notably, hepatocytes secrete most of their protein products directly into the plasma, secreting only bile components to the biliary ducts. In contrast, acinar cells secrete all their protein products through the pancreatic duct system.

In view of the common developmental origin and histological similarities of the two organs, it is not surprising that common transcriptional regulators control the ontogenesis and homeostasis of the liver and

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pancreas. Thus, members of the Forkhead box A (FoxA), Onecut, SRY-related HMG box (Sox), and hepatocyte nuclear factor (HNF) families are essential in developing adult liver and pancreas[8–12]. The similarities between the pancreatic and hepatic developmental programs are also reflected in the fact that acinar cells can transdifferentiate into hepatocytes[13–15].

The liver and pancreas are affected by cancers characterized by poor survival rates. Considering the histological and molecular similarities of fetal and adult liver and pancreas, we reasoned that some mechanisms driving carcinogenesis might be analogous in the two organs. Here we summarize basic concepts about tumorigenesis in the liver and pancreas and discuss how tumor development in an organ may provide insight into our understanding of carcinogenesis in the other organ.

HEPATIC AND PANCREATIC CARCINOGENESIS

In the liver, the most frequent cancers are hepatocellular carcinoma (HCC). Cholangiocarcinoma (CCA) is the second most frequent type of liver cancer, and it accounts for about 10%–25% of all hepatobiliary malignancies. In the pancreas, pancreatic ductal adenocarcinoma (PDAC) is the most frequent pancreatic tumor (85%–95% of cases)[16]. Acinar cell carcinomas (ACCs) are less frequent: they are detected in 1%–2% of adult patients and about 15% of pediatric patients[17]. Pancreatic cystic tumors represent only 1% of cases, but nevertheless account for about 15% of pancreatic cancer resections[18]. These three pancreatic tumor types derive from the exocrine compartment; endocrine tumors are not discussed here. Owing to the similarities discussed above, we here make pairwise comparisons between HCC and ACC, CCA and PDAC, as well as CCA and pancreatic cystic tumors, and highlight the similarities between these cancers at the histological level and with regard to their mutational landscape.

HEPATOCELLULAR CARCINOMA AND ACINAR CELL CARCINOMA

HCC is frequently associated with cirrhosis caused by hepatitis B and C, alcohol abuse, or non-alcoholic fatty liver disease[19]. Several reports indicate that HCC develops from hepatocytes[20], although it has also been suggested that HCC originates from liver stem cells[21]. Macroscopically, HCCs appear as nodular or infiltrative tumors. Generally, nodular tumors are well circumscribed, with trabecular formations composed of cells resembling hepatocytes, whereas infiltrative tumors are poorly differentiated[22]. Pancreatic ACC may originate from acinar cells, as suggested by the expression of acinar-specific enzymes, such as trypsin, lipase, amylase, and carboxyl ester lipase in tumor tissue[23,24]. Histological features are similar to those of HCC: trabecular structures and cells resembling the acinar cell type of origin are observed; poorly differentiated cells are found in some cases. In both HCC and ACC, scant stroma is detected.

Interestingly, in addition to those shared histological features, HCC and ACC are often driven by dysfunctional Wnt/β-catenin pathway. Genomic alterations have been extensively studied in HCC, revealing that 30%–50% of HCCs display perturbed Wnt/β-catenin (*CTNNB1*) signaling, mostly resulting from mutations in *CTNNB1*, *APC*, and *AXIN1*[25–28]. Genomic studies of ACC are less numerous because of the rarity of cases. However, they reveal that *CTNNB1* and *APC* alterations (mutations, gene loss, and/or promoter hypermethylation) are detected in up to 56% in patients[29,30]. Chromosomal imbalances are also recurrent in HCC and ACC, possibly as a consequence of APC loss[25,31,32]. The most frequent amplifications of chromosomal regions are found on 1q, 8q, and 20q in both lesions. This includes amplification of *c-MYC* at the 8q24 locus.

Another striking similarity between HCC and ACC relates to the *KRAS* oncogene. Indeed, despite that *KRAS* is the most frequently mutated oncogene in human cancers, being mutated in 22% of tumors, the frequency of *KRAS* mutations in HCC and ACC is surprisingly low (0% and 1%–2%, respectively)[25,32,33]. This observation extends to the downstream effector of KRAS, BRAF, as well as the epidermal growth factor receptor (EGFR), a receptor whose signaling critically depends on KRAS activity[32,34]. Altogether, this indicates that in both cancer types, the EGFR/KRAS/ERK pathway is not predominantly involved in tumorigenesis, in contrast to many other cancer types.

CHOLANGIOCARCINOMA AND PANCREATIC DUCTAL ADENOCARCINOMA

CCA has a 5-year survival rate of about 10%, and this remains unchanged in the last 20 years[35]. As for HCC, chronic liver inflammation is a common risk factor. In Southeast Asia, CCA development is often associated with infection by *Opisthorchis viverini* or *Clonorchis sinensis*. Based on the anatomical localization, CCAs are classified according to their anatomical localization as intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal (or extrahepatic) CCA (dCCA)[36]. While pCCA and dCCA are mainly mucinous adenocarcinomas, iCCAs are histologically heterogeneous: bile ductular type (mixed) arises from small intrahepatic bile ducts, and bile duct type (mucinous) develops from large intrahepatic bile ducts[37]. Not surprisingly, the diverse anatomical locations of CCA are associated with heterogeneity in the mutational landscape of these tumors[38,39].

PDAC is one of the deadliest cancers, and the mean survival period after diagnosis has not significantly improved over the last decades. Lifestyle factors, such

as cigarette smoking, excessive alcohol consumption, and obesity, increase the risk of PDAC, likely resulting from chronic pancreatitis[40]. A striking characteristic of PDAC is the prevalence of oncogenic *KRAS* mutations, which varies between 88% and 100%[41,42]. This very high mutation rate suggests that *KRAS* plays a key role in pancreatic tumorigenesis and prompted the development of mouse models with induction of mutated *Kras* in the pancreas[43]. These models revealed that PDAC could originate from acinar cells and not necessarily from ductal cells as suggested by the histological features of the tumors[44–46]. However, the presence of a *Kras* mutation in the acinar genome is not sufficient to initiate tumor development and evolution toward malignancy. Tumor development requires association of a *KRAS* mutation and inflammation[45,47,48] and occurs in a stepwise manner starting with inflammation-induced acinar-to-ductal metaplasia (ADM), during which acinar cells acquire a ductal-like phenotype[49]. When a *Kras* mutation occurs in this inflammatory context, the metaplastic acinar cell transforms into a neoplastic lesion called pancreatic intraepithelial neoplasia (PanIN), which evolves to cancer upon accumulation of other gene mutations, mainly *p53*, *p16*, and *Smad4*[50–53]. Still, this scheme has yet to be confirmed in humans.

In CCA, even though *KRAS* still appears as the most frequently mutated oncogene, its mutation rate is much less important than the prevalence of *KRAS* mutations in PDAC[16] and varies considerably according to the CCA localization[38,54]. Like in mouse models of PDAC, the mere presence of a *Kras* mutation in hepatocytes or cholangiocytes is not sufficient to transform these cells[55,56]. By analogy with the pancreas, it would be interesting to couple the presence of a *Kras* mutation in the liver with the presence of inflammation. Supporting the need for such experiments, bile ductular-type CCA is frequently associated with chronic liver diseases (viral hepatitis or cirrhosis) in which inflammation plays an important part in disease progression and cancer initiation. It should be noted that independent of the presence of inflammation, coupling a *Kras* mutation with mutation in the tumor-suppressor *Pten* results in iCCA development[55].

A central question about CCA development refers to the identity of the cell type of origin. Murine models have shown that iCCA can derive from cholangiocytes or hepatocytes[57–59]. In the latter case, hepatocyte-to-cholangiocyte transdifferentiation requires activation of the Notch pathway, which is comparable to Notch-controlled ADM in the pancreas[60]. Progression to iCCA depends on the combination of Notch activation with hepatotoxin-induced liver fibrosis or activation of the AKT pathway[59,58], whereas activated Notch and activating *Kras* mutations synergistically induce PanIN formation from ADM[44]. Future work will determine the extent of similarities between hepatocyte-derived iCCA and acinar-derived PDAC and whether similar mechanisms operate in humans.

CHOLANGIOCARCINOMA AND PANCREATIC CYSTIC TUMORS

A small proportion of CCA and pancreatic cancers arise from neoplastic lesions called intraductal papillary neoplasm of the bile duct (IPNB) and intraductal papillary mucinous neoplasm of the pancreas (IPMN). Both lesions appear as papillary tumors within dilated duct lumens and are usually associated with the production of mucinous secretions and the presence of cysts[61,62]. IPNB can be detected both in extra- and large intrahepatic bile ducts, and IPMNs are localized in the main pancreatic duct, the branch ducts, or both locations[63–65]. IPNB and IPMN are classified into four identical histotypes: gastric, intestinal, pancreatobiliary, and oncocytic types. IPMN evolves into invasive carcinoma in 20% to 40% of cases and IPNB in 4% to 38% of cases[61,66,67]. Gastric and pancreatobiliary types give rise to tubular adenocarcinoma, whereas intestinal types form mucinous/colloid carcinoma[66,67].

Beyond these histological similarities, IPMN and IPNB share common genetic alterations. In humans, *KRAS* is the most frequently mutated oncogene in both lesions. On average, *KRAS* is mutated in 29%–46% of IPNB and in 61% of IPMN[68,69]. *GNAS*, which encodes the G-protein α stimulatory subunit ($G_{\alpha s}$) of heterotrimeric G proteins, is also frequently mutated in IPNB (50%) and IPMN (56%)[68,70]. Interestingly, *KRAS* mutations are predominant in gastric (65%–73%) and pancreatobiliary subtypes (64%–100%) compared to intestinal subtype (44%–46%), whereas *GNAS* mutations are more typically detected in the intestinal subtype (59%–100%) compared to gastric and pancreatobiliary subtypes (46%–65% and 0%–43%, respectively)[68,71–73], suggesting that mutated *GNAS* promotes intestinal differentiation of IPNB and IPMN. Similarities in the mutational profiles of IPNB and IPMN extend beyond *KRAS* and *GNAS* mutations. Indeed, the third most frequently mutated gene in IPMN, namely, the gene coding for ubiquitin ligase RNF43, with 23% of the mutated cases, also appears mutated at a high frequency in IPNB (12%)[68,74]. Full understanding of the role of *KRAS*, *GNAS*, and *RNF43* in IPNB and IPMN development requires the development of new murine transgenic models. A murine model coupling *Kras* and *Gnas* mutations in the pancreas was generated[75]. These mice develop IPMN, supporting a role of *Kras* and *Gnas* mutations in the development of these lesions. However, the mutations were induced during embryogenesis. Considering the sensitivity of embryonic cells to oncogenic stimuli and the resistance of mature pancreatic cells to such injury, *Gnas* and *Kras* mutations should

ideally be induced in adult mouse pancreas to strengthen the conclusions.

Similar mutational profiles in IPNB and IPMN also suggest that the two lesions originate from the same cell type. Histopathological observations suggest that IPNB and IPMN arise from the biliary and pancreatic ductal cells. However, peribiliary glands (PBGs) and pancreatic duct glands (PDGs) are associated with the large biliary or pancreatic ducts[76,77]. PBG and PDG are proposed to contain stem/progenitor cells[78–80] and may give rise to IPNB and IPMN[61]. The analysis of mouse models supports the hypothesis that IPMN originates from the PDG[81] and that dCCA can originate from the PBG, yet in the latter model, dCCA appeared as an undifferentiated adenocarcinoma, not as a cystic tumor[82].

In conclusion, current data support the notion that the mechanisms of tumorigenesis in the liver and pancreas might significantly overlap (summarized in Fig. 1). Development of new transgenic mouse models, especially to explore the possibility that PBGs and PDGs are a source

	Hepatocellular Carcinoma	Acinar Cell Carcinoma
Histology	- Scant stroma - Trabecular structures	- Scant stroma - Trabecular structures
Frequent genetic alterations	- Wnt-associated factors (*CTNNB1, AXIN, APC*) - Chromosomal imbalances	- Wnt-associated factors (*CTNNB1, APC*) - Chromosomal imbalances
Characteristics	- Most frequent liver cancer - Cellular origin: hepatocytes - No implication of MAPK/EGFR pathways in tumorigenesis	- Rare tumor (1–2% of pancreatic tumors) - Cellular origin: acinar cells - No implication of MAPK/EGFR pathways in tumorigenesis
	Cholangiocarcinoma	Pancreatic Ductal Adenocarcinoma
Histology	- dCCA and pCCA: mucinous adenocarcinoma. iCCA: heterogeneous lesions	- Mucinous adenocarcinoma - Acinar-to-ductal metaplasia followed by PanIN formation
Frequent genetic alterations	- KRAS (less frequently mutated than in PDAC)	- KRAS, SMAD4, P53, CDKN2A
Characteristics	- 10–25% of hepatobiliary malignancies - 3 subtypes of CCA with distinct anatomical localization and distinct mutational spectra - Cellular origin: cholangiocytes, hepatocytes	- Most frequent pancreatic cancer (85–95%) - Cellular origin: acinar cells
	Intraductal Biliary Neoplasms	Intraductal Papillary Mucinous Neoplasms
Histology	- Mucinous lesions - Four histotypes: gastric, intestinal, pancreatobiliary, oncocytic	- Mucinous lesions - Four histotypes: gastric, intestinal, pancreatobiliary, oncocytic
Frequent genetic alterations	- *KRAS*, *GNAS*, *RNF43*	- *KRAS*, *GNAS*, *RNF43*
Characteristics	- 10–25% of hepatobiliary malignancies– - Affects large bile ducts - Possible peribiliary gland origin	- 1% of pancreatic tumors - Affects large pancreatic ducts - Possible pancreatic duct gland origin

Figure 1. Summary of similarities and differences between liver and pancreatic cancers reported in this article.

of IPNB and IPMN and subsequently of cancer, as well as studies of patient-derived xenografts and liver and pancreas organoids[83,84], will enable us to determine to what exact extent pancreas and liver tumorigenesis can be considered similar.

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