Human Pathology (2013) **44**, 811–821

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Human PATHOLOGY

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Original contribution

Hilar cholangiocarcinoma and pancreatic ductal adenocarcinoma share similar histopathologies, immunophenotypes, and development-related molecules☆,☆☆

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Received 2 May 2012; revised 7 August 2012; accepted 8 August 2012

Keywords:
Biliary tree;
Cholangiocytes;
Development;
Hilar cholangiocarcinoma;
Pancreatic ductal adenocarcinoma

Summary Embryologically, intrahepatic small bile ducts arise from hepatic progenitor cells via ductal plates, whereas the pancreato-extrahepatic biliary progenitor cells expressing the transcription factors PDX1 and HES1 are reportedly involved in the development of the extrahepatic biliary tract and ventral pancreas. The expression of cellular markers characteristic of the different anatomical levels of the biliary tree and pancreas, as well as PDX1 and HES1, was examined in cholangiocarcinoma components of combined hepatocellular cholangiocarcinoma (12 cases), intrahepatic cholangiocarcinoma (21 cases), hilar cholangiocarcinoma (25 cases), and pancreatic ductal adenocarcinoma (18 cases). Anterior gradient protein–2 and S100P were frequently expressed in hilar cholangiocarcinoma and pancreatic ductal adenocarcinoma, whereas neural cell adhesion molecule and luminal expression of epithelial membrane antigen were common in cholangiocarcinoma components of combined hepatocellular cholangiocarcinoma. PDX1 and HES1 were frequently and markedly expressed in pancreatic ductal adenocarcinoma and, to a lesser degree, in hilar cholangiocarcinoma, although their expression was rare and mild in cholangiocarcinoma components in combined hepatocellular cholangiocarcinoma. The expression patterns of these molecules in intrahepatic cholangiocarcinoma were intermediate between those in hilar cholangiocarcinoma and cholangiocarcinoma components of combined hepatocellular cholangiocarcinoma. Pancreatic ductal adenocarcinoma and hilar cholangiocarcinoma had a similar expression of mucin, immunophenotypes, as well as transcription factors. Pancreatic ductal adenocarcinoma and hilar cholangiocarcinoma showed similar postoperative prognosis. In conclusion, the similar expression of phenotypes related to pancreatobiliary anatomy and embryology may in part explain why these 2 types of carcinoma present similar clinicopathologic features. Further studies on the carcinogenesis of these carcinomas based on their similarities are warranted.

☆ Conflict of interest: There is no conflict of interest for any author.
☆☆ Financial support: This study was supported by a Grant-in-Aid from the Ministry of Health, Labour and Welfare, Japan.
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http://dx.doi.org/10.1016/j.humpath.2012.08.004

1. Introduction

Cholangiocarcinoma (CC) is a primary tumor originating from cholangiocytes (epithelial cells lining the bile duct lumen and also constituting peribiliary glands and their conduits) [1-3]. It seems plausible that cholangiocytes at different anatomical levels present different morphologies and phenotypes, and these differences could reflect heterogeneous clinicopathologic features of CCs, which can be divided into several categories, including bile ductular carcinoma or cholangiolocellular carcinoma, intrahepatic CC (ICC), and hilar CC [1-5].

The biliary tract, particularly the extrahepatic bile duct, and the pancreas are adjacent to each other. The ventral pancreas and biliary system arise from the posterior ventral foregut at almost the same time. The transcription factors hairy and enhancer of split-1 (HES1) and pancreatic duodenal homeobox factor-1 (PDX1) are reportedly involved in the development of the ventral pancreas and extrahepatic biliary system [1,6,7]. In addition, the SRY-related HMG box transcription factor (SOX) 9 is also involved in their development. Recent studies on connections between the biliary tree and pancreas showed that SOX17 is an important molecule driving pancreas formation in one direction and the biliary tree in another and that the extrahepatobiliary system shares a common origin with the ventral pancreas and not the liver [8-10]. Interestingly, Carpino et al demonstrated that the peribiliary glands represent niches of cells with classic phenotypic traits of stem/progenitor cells of endodermal origin, with respect to transcription factors, and surface and cytoplasmic markers [9-11].

Furthermore, the biliary tract and pancreas also show plasticity during development [7,11-13]. Deletion of *SOX17* results in the loss of biliary structures and ectopic pancreatic tissue in the liver bud and common duct, whereas *SOX17* overexpression suppresses pancreas development and promotes ectopic biliary-like tissue throughout the *PDX1*+ domain. *HES1*-deficient mice have gallbladder agenesis and severe hypoplasia of extrahepatic bile ducts; in addition, their biliary epithelium differentiates into endocrine and exocrine cells and forms acini and islet-like structures in the mutant bile ducts.

Recently, signal molecules that regulate the proliferation and differentiation of embryonic stem cells or progenitor cells were reported to be activated in human carcinomas in the pancreas and other organs [13-17]. In this context, it is conceivable that transcription factors related to the development of the pancreas and biliary tract, such as *PDX1* and *HES1*, are involved in the malignant transformation of the pancreas and also the biliary tract. In fact, re-expression of *PDX1* has been identified in pancreatic ductal adenocarcinomas (PDACs) and also their precursor lesions, such as pancreatic intraepithelial neoplasm (PanIN), as well as in CCs and biliary intraepithelial neoplasm (BilIN) [13,17].

Furthermore, recent studies showed that several biliary tract and pancreatic diseases have a similar pathophysiology [6,18-20]. For example, preneoplastic or early intraepithelial neoplasms of the biliary tract, such as BilIN and intraductal papillary neoplasm of bile duct, show similar morphological or genetic changes to their pancreatic counterparts, such as PanIN and intraductal papillary mucinous neoplasm of the pancreas [6]. Our experience suggests that extrahepatic CC including hilar portions and PDAC present similar clinicopathologic features. Both affect the elderly, remain as an intractable malignant tumor, are frequently diagnosed at an advanced and inoperable stage, and show poor postoperative prognosis. However, the reasons why these 2 carcinomas show similar clinicopathologic features remain speculative.

In this study, we attempted to clarify the relationship of hilar CC to PDAC, in comparison with ICC and CC components of combined hepatocellular cholangiocarcinoma (cHC-CC), by examining the expression of mucin and molecules relating to the anatomy and development of the biliary and pancreatic system, such as anterior gradient protein-2 (AGR2), S100P, neural cell adhesion molecule (NCAM), epithelial membrane antigen (EMA), and PDX1 and HES1. CC components of cHC-CC and ICC were chosen for comparison with hilar CC because the former 2 are thought to derive from or to be related to the hepatic progenitor cells (HPC) at bile ductules or the canal of Herings in their development [5,21].

2. Materials and methods

2.1. Anatomy of the biliary tract

The common hepatic and bile ducts, including the right and left hepatic bile ducts, are included in the extrahepatic bile duct. The intrahepatic bile duct, proximal to the right or left hepatic bile duct, is composed of the intrahepatic large and small bile ducts. The former correspond to the first to third branches of both hepatic ducts, whereas the latter, which are recognizable under a microscope, are composed of septal and interlobular bile ducts. The intrahepatic large bile duct and extrahepatic bile ducts are accompanied by peribiliary glands. Glands of the biliary tree (peribiliary glands) are tubuloalveolar glands with mucinous and serous acini, located within duct walls and also in the periductal connective tissue of intrahepatic and extrahepatic bile ducts [22]. The pancreatic ducts are divided into the main ducts and branch ducts.

2.2. Case selection and tissue preparation

We have collected cases of ICC (21 cases), hilar CC (25 cases), cHC-CC (12 cases), and invasive PDAC (18 cases). All ICC cases showed mass-forming growth, and pancreatic and perihilar CC showed nodular sclerosing growth. Intraductal papillary mucinous neoplasm, intraductal papillary neoplasm of bile duct, and carcinomas with neuroendocrine features were not included in this series. All of these