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Cholangiocytes in the pathogenesis of primary sclerosing cholangitis and development of cholangiocarcinoma☆

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ABSTRACT

Primary sclerosing cholangitis (PSC) is an idiopathic cholangiopathy strongly associated with inflammatory bowel disease (IBD) and characterized by cholestasis, chronic immune infiltration and progressive fibrosis of the intrahepatic and extrahepatic bile ducts. PSC confers a high risk of cholangiocarcinoma (CCA) with PSC-CCA representing the leading cause of PSC-associated mortality. PSC-CCA is derived from cholangiocytes and associated progenitor cells – a heterogeneous group of dynamic epithelial cells lining the biliary tree that modulate the composition and volume of bile production by the liver. Infection, inflammation and cholestasis can trigger cholangiocyte activation leading to an increased expression of adhesion and antigen-presenting molecules as well as the release of various inflammatory and fibrogenic mediators. As a result, activated cholangiocytes engage in a myriad of cellular processes, including hepatocellular proliferation, apoptosis, angiogenesis and fibrosis. Cholangiocytes can also regulate the recruitment of immune cells, mesenchymal cells, and endothelial cells that participate in tissue repair and destruction in settings of persistent inflammation. In PSC, the role of cholangiocytes and the mechanisms governing their transformation to PSC-CCA are unclear however localization of disease suggests that cholangiocytes are a key target and potential regulator of hepatobiliary immunity, fibrogenesis and tumorigenesis. Herein, we summarize mechanisms of cholangiocyte activation in PSC and highlight new insights into disease pathways that may contribute to the development of PSC-CCA. This article is part of a Special Issue entitled: Cholangiocytes in Health and Disease edited by Jesus Banales, Marco Marzioni, Nicholas LaRusso and Peter Jansen.

1. Introduction

Primary sclerosing cholangitis (PSC) is a rare hepatobiliary disease characterized by persistent biliary inflammation, concentric periductal fibrosis (“onion-skin” fibrosis) and in most cases, progression to liver cirrhosis and end-stage liver disease. PSC carries a significant risk of cholangiocarcinoma (CCA) and PSC-CCA represents the most significant cause of patient mortality in PSC [1,2]. By contrast, risk of hepatocellular carcinoma (HCC) is relatively low in PSC [3,4] and underscores the central role of cholangiocytes in the pathogenesis of disease. PSC shows a male preponderance (2 to 1) and affects all ages with a median onset of 30–40 years. Incidence ranges geographically from 0 to 1.3 cases per 100,000 persons per year and prevalence from 0 to 16.2 cases per 100,000 persons [5,6]. In the majority of cases, PSC associates with a distinct form of inflammatory bowel disease (IBD) that bears unique clinical [7] and genetic features to ulcerative colitis and Crohn's disease [8–10]. Up to 25% of PSC patients also develop autoimmune conditions, including autoimmune thyroid disease, type 1 diabetes, rheumatoid arthritis and celiac disease [11]. Heritability is comparable to other complex immune-mediated disorders as first-degree relatives are approximately 10-times more likely to develop PSC compared to unrelated individuals [12]. Definitive diagnosis of PSC is achieved by findings of characteristic biliary strictures using magnetic resonance- or endoscopic retrograde-cholangiography (MRCP/ERCP)

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following the exclusion of secondary sclerosing cholangitis etiologies (e.g. IgG4-associated cholangitis, infections, ischemia, toxins, biliary calculi or trauma) [13]. Owing to a lack of effective medical therapies [14–16], over 50% of patients progress to end-stage disease within 10–15 years of diagnosis which positions PSC as the leading indication of orthotopic liver transplantation amongst cholestatic diseases in Western countries [17,18]. Following transplantation, the 1-year survival rate is 85%, the 5-year survival rate is 72% (United Network for Organ Sharing; www.unos.org) with disease recurring in approximately 25% of cases [19,20].

The localization of immune infiltrate and fibrosis surrounding portal areas strongly suggests that cholangiocytes are key players in PSC, either as a victim or a foe – or both. Cholangiocytes are a heterogeneous group of reactive epithelial cells that line the intrahepatic and extrahepatic bile ducts as well as the peribiliary glands and facilitate the transport of bile constituents from the liver to the duodenum [21,22]. Cholangiocytes express a variety of molecular transporters, aquaporins and ion channels that also enable cholangiocytes to modify the final composition and volume of bile entering the biliary tract [18,23–25]. In PSC, cholangiocytes lining both the intrahepatic and extrahepatic ducts can be affected and inflammation of the biliary tract is linked to cholangiocyte senescence and cholestasis [26,27]. There is also precursor cell activation, with an expansion of the peribiliary gland compartment and likely (although formally not shown) increased mucus production [22]. Impaired cholangiocyte function resulting from a combination of biliary insults (likely involving both inflammation, bile acid toxicity and microbial factors) likely contributes to PSC pathogenesis. It is currently unknown to what extent disturbances in normal cholangiocyte functions are involved in PSC causation, however the possibility exists as shown by sclerosing cholangitis in the context of mutations to the cholangiocyte proteins cystic fibrosis transmembrane conductance regulator (*CFTR*) [27,28], X-prolyl aminopeptidase P1 (*XPNPEP1*) and adducing 3 (*ADD3*) [29–33]. As it stands, the precise etiopathogenesis of PSC is unknown and what we currently believe is that a complex manifestation of multiple genetic and environmental determinants in sum results in the clinical phenotype [34–39]. Similarly, the mechanisms that precipitate the malignant transformation of cholangiocytes in PSC-CCA are poorly understood and it remains to be determined what proportion of PSC-CCA results from the interaction of genetic and environmental factors that initiate PSC versus secondary effects related to cholangiocyte activation, chronic inflammation, bile acid toxicity and cellular senescence that occur during the progression of disease.

2. Epidemiology of PSC-CCA

CCA is an adenocarcinomatous cancer arising from cholangiocytes. Overall, CCA is rare and accounts for approximately 3% of all gastrointestinal tumors worldwide [40–43]. PSC is a major risk factor for CCA with 10% of CCA cases in the Western world being associated with PSC [44,45]. In patients with PSC, the annual incidence of PSC-CCA is 0.5–1.5% [46–48] and the lifetime risk ranges from 6 to 12% [2,45–52]. Higher frequencies of PSC-CCA (up to 19.9%) are reported in transplant and referral center cohorts but such studies presumably include a greater number of patients with severe PSC phenotypes and likely overestimate the true prevalence of PSC-CCA in the total patient population [46,53]. Similar to the overall incidence of PSC [54–56], risk of PSC-CCA is higher in northern Europe and the United States than populations in southern Europe and Asia (2.8% to 8.4%) [50,57,58]. Pediatric patients and patients with small duct PSC also have a lower risk of PSC-CCA [59–61]. Approximately one third of PSC-CCA is diagnosed within the first year of PSC diagnosis suggesting that undiagnosed PSC precedes the development of PSC-CCA in these cases with symptoms primarily related to PSC-CCA leading to the diagnosis of PSC [2,47,59,62].

Knowledge on predisposing risk factors for PSC-CCA is scarce. The duration and severity of PSC do not seem to correlate with PSC-CCA development [48,63,64] and several proposed factors, including age at diagnosis, smoking and alcohol consumption, a Mayo risk score of more than four, a history of variceal bleeding or colorectal neoplasia and the presence or duration of concurrent IBD confer only small increments to

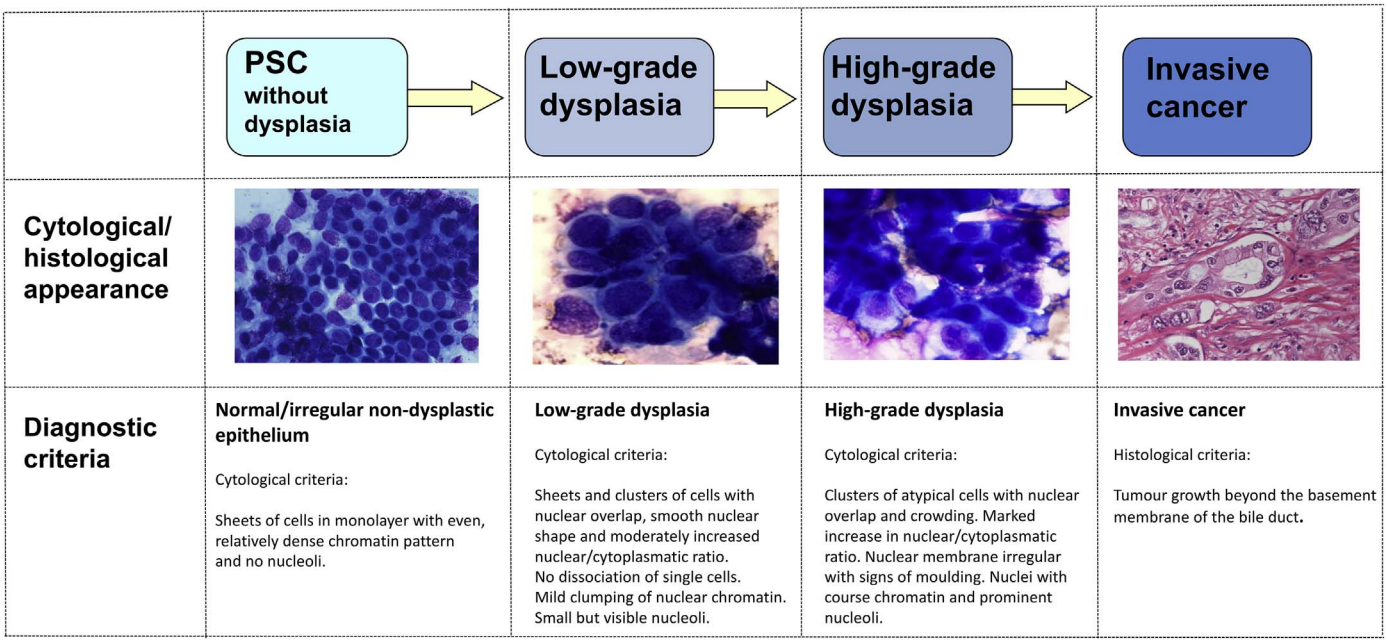

Fig. 1. Several studies support a model of primary sclerosing cholangitis-associated cholangiocarcinoma (PSC-CCA) whereby inflammatory epithelial damage leads to sequential progression from normal non-dysplastic epithelium to low grade dysplasia (LGD), high grade dysplasia (HGD) and ultimately to invasive CCA. In the clinical setting, presence of dysplastic changes in the biliary epithelium is commonly determined based on biliary brush cytology obtained from the bile ducts during endoscopic retrograde cholangiography. Shown are cytological and histological images and generally accepted cytological criteria to classify biliary brush specimens into the following categories: (i) non-dysplastic, (ii) LGD and (iii) HGD. The main criteria for invasiveness are histological (tumor growth beyond the basement membrane), as there are no clear-cut cytological criteria able to distinguish between HGD and carcinoma [149–151]. Cytological and histological images kindly provided by pathologists Peter Jebsen and Henrik M. Reims at Department of Pathology, Oslo University Hospital Rikshospitalet (Oslo, Norway).