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Letter to Editor open access

Is Cellular Senescence Involved in Progressive Loss of Canals of Hering in Primary Biliary Cirrhosis?

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Introduction

Liver progenitor/stem cells (LPCs) play important roles for regeneration or replacement of hepatocytes and also cholangiocytes in some hepatobiliary diseases [1], and it has been reported that the LPCs activation is associated with a hepatic fibrosis and inflammation in several chronic liver diseases, such as chronic viral hepatitis and non-alcoholic steatohepatitis (NASH) [2,3]. Canals of Hering (CoH) are considered to be a niche of LPCs and they locate in between hepatocyte canaliculi and bile ductules.

Primary biliary cirrhosis (PBC) is an autoimmune liver disease which mainly affects interlobular bile ducts, and progressive and sustained loss of interlobular bile ducts with chronic nonsuppurative destructive cholangitis eventually leading to progressive fibrosis and prolonged cholestasis followed by liver failure [4,5]. Recently, the destruction of CoH has been reported to occur at early stage of PBC [6,7]. We also demonstrated that the number of CoH was already low in early stage of PBC [8]. Furthermore, CoH loss was correlated with the progression of histological stage and liver dysfunction, and CoH decreased in follow-up biopsies showing stage progression with advance of bile duct loss and chronic cholestasis. These facts suggest that the number of LPCs of PBC patients decreases in accordance with disease progression, different from chronic viral hepatitis or NASH patients. LPCs shortage may cause insufficient supply of biliary committed cells to the bile ductules and interlobular bile ducts, followed by sustained loss of interlobular bile ducts and then disease progression of PBC.

So, how and why does CoH loss occur progressively in PBC? While the exact mechanism(s) for progressive CoH loss remains speculative, there are several interesting hypotheses: i) CoH or bile ductules being destroyed by an immune attack [6] or ii) cellular senescence leading to impaired replacement and eventual loss of bile ductules and CoH [9,10].

In the former, the immune attacks similar or identical to those on interlobular bile duct, may occur on these canals where LPCs are located, at a relatively early stage, and these attacks may continue and eventually lead to progressive loss of CoH [6,8]. Otherwise, cellular senescence is a state of irreversible cell cycle arrest a cell at the G0 phase of the cell cycle as a DNA damage response and has no longer the ability to proliferate. Although these cells are metabolically still active, this process is followed by eventual loss of affected cells. Recent studies showed that cellular senescence was implicated in several biliary diseases and also premature or stress-induced senescence was discussed with respect to senescence-associated secretory phenotype (SASP) which is associated with microenvironments of affected cells or tissues [11,12]. Interestingly, Sasaki et al reported that bile ductules showed cellular senescence in PBC, and that sustained cellular senescence might lead to the eventual loss of bile ductules and CoH loss [9,10]. It is, moreover, reported that senescence is propagated through positive feedback by nearby senescent cells, causing senescence of adjacent bile ductules and CoH in PBC [11,12]. Recently, we have reported that cellular senescence may play an important role in the pathogenesis of fibrosing cholangiopathies including PBC, and senescence of biliary epithelial cells may be induced by several senescent stimuli, particularly impaired autophagy and oxidative stresses [11]. Alpini et al also reviewed cellular senescence and cholangiopathy, indicating that cellular senescence of cholangiocytes may be linked to the development of cholangiopathies of several biliary diseases, particularly PBC, primary sclerosing cholangitis, biliary atresia and chronic allograft rejection [12]. While exact mechanisms for occurrence of cellular senescence of CoH remains speculative, multiple senescent stimuli including autophagy or oxidative stress might be involved in this critical process leading to progression of stage of PBC.

In this context, the prevention of sustained or locally propagated cellular senescence at the level of CoH may be effective for slowing or even recovering the progression of bile duct loss and the progression of PBC.

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