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## Ductular reaction in non-alcoholic fatty liver disease: When Macbeth is perverted

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### Abstract

Non-alcoholic fatty liver disease (NAFLD) or metabolic (dysfunction)-associated fatty liver disease is the leading cause of chronic liver diseases defined as a disease spectrum comprising hepatic steatosis, non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatic carcinoma. NASH, characterized by hepatocyte injury, steatosis, inflammation, and fibrosis, is associated with NAFLD prognosis. Ductular reaction (DR) is a common compensatory reaction associated with liver injury, which involves the hepatic progenitor cells (HPCs), hepatic stellate cells, myofibroblasts, inflammatory cells (such as macrophages), and their secreted substances. Recently, several studies have shown that the extent of DR parallels the stage of NASH and fibrosis. This review summarizes previous research on the correlation between DR and NASH, the potential interplay mechanism driving HPC differentiation, and NASH progression.

**Key Words:** Ductular reaction; Non-alcoholic steatohepatitis; Hepatic progenitor cells; Cell differentiation; Inflammatory cells; Liver fibrosis

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**Core Tip:** This is the first review focusing on recent advances in the relationship of hepatic cells with ductular reaction (DR), in fatty liver-related steatohepatitis and fibrosis. Recent advances in DR, a common compensatory reaction in liver injury, shed light on the effects of hepatic progenitor cells, hepatic stellate cells, myofibroblasts, inflammatory cells, and their secreted substance. In particular, hepatic progenitor cell differentiation was thoroughly discussed in developing steatohepatitis and fibrosis. This review summarizes the correlation between DR and steatohepatitis and fibrosis, the advanced stages of non-alcoholic fatty liver disease, or metabolic (dysfunction) related fatty liver disease.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), which affects approximately 25% of adults worldwide, is the leading cause of chronic liver diseases[1]. NAFLD refers to a disease spectrum including hepatic steatosis, non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatic carcinoma[2]. In early 2020, an international expert group led a consensus-driven process to develop a more appropriate term for NAFLD, and the term “metabolic (dysfunction) related fatty liver disease (MAFLD)” was recommended[3]. NASH/MASH is characterized by  $\geq 5\%$  hepatic steatosis, hepatocyte injury or necrosis, and inflammation[2,4]. NASH is a critical stage in NAFLD development and is associated with NAFLD prognosis; thus, it has become the focus of NAFLD research. NASH is the second most common indication for liver transplantation in the United States[1]. The occurrence and progress of NASH are related to several factors such as glucose and lipid metabolism, immune response, and gut microbiota[5-7]. The diagnosis and severity classification of NASH depends on histopathological examination. The main pathological features of NASH are hepatocyte balloon degeneration, inflammatory infiltration, Mallory-Den K corpuscle, and zone 3 fibrosis[2,8]. Some studies have shown that neutrophil infiltration and portal inflammatory infiltration are also characteristics of NASH[9,10].

Ductular reaction (DR) is a compensatory reaction commonly detected in various liver injuries[11], involving the participation of hepatic progenitor cells (HPCs), hepatic stellate cells (HSCs), myofibroblasts, inflammatory cells (such as macrophages), and their secreted substances. Among them, the proliferation and differentiation of HPCs are the core of DR[12]. DR is commonly found in the livers of NASH patients. Moreover, there is a parallel relationship between DR and the severity of inflammation and fibrosis in NASH patients[13-15], suggesting that DR has an important role in the progression of NASH.

Based on clinical investigations, the present review summarizes the correlation between DR and NASH. It discusses the shaped HPC differentiation fate in the context of NASH and its influence on NASH progression.

## OVERVIEW OF DUCTULAR REACTION AND CORRELATION BETWEEN HPC AND DR

DR is a compensatory reaction in the portal area caused by biliary diseases, viral hepatitis, NAFLD, acute fulminant liver failure, *etc*[16]. DR is heterogeneous in both pathology and pathophysiology. Desmet divided DR into four types based on pathology: Type 1, Type 2A, Type 2B, and Type 3[17].

Type 1 is predominant in acute complete bile duct (BD) obstruction, alpha-naphthyl isothiocyanate intoxication, and cytokine (*e.g.*, interleukin 6)-induced ductular increase. It results from the proliferation of preexisting cholangiocytes. Type 1 causes the biliary tubes to elongate, branch out, and widen their lumens, allowing them to adjust to the swelling and inflammation of the portal mesenchyme. Type 2A has been interpreted as “ductular metaplasia of hepatocytes.” It is often detected in periportal areas, most characteristically, in chronic cholestatic conditions. In lasting cholestasis, bile acids increase the number of cholangiocytes, which promote the development of pericellular fibrosis, and in this way, it enhances bile ductular metaplasia of hepatocytes. Of note, Type 1 and Type 2A can be reversed when the causative trigger is eliminated; the ductular structures are cleared by apoptosis; and the associated fibrosis is ameliorated to a considerable extent. Prolonged hypoxia induces Type 2B, which manifests in areas of parenchymal hypoxia, specifically in the centrilobular region of liver lobules and the centronodular region of cirrhotic nodules. Although often slower in development, its microscopic pattern is comparable to that of Type 2A in terms of ductular metaplasia or dedifferentiation of mature hepatocytes, which is associated with myofibroblast-induced fibrosis. Type 3 occurs in cases of massive loss of parenchymal cells and is characterized by the activation and proliferation of HPCs located in the



ductules and canals of Hering. As bipotential cells, HPCs can differentiate into hepatocytes and BD cells [17].

There is consensus that the fate of HPC differentiation is the core of DR, determining the pathological type of DR and affecting disease development[18]. Epithelial cell adhesion molecule and the neural cell adhesion molecule/sex-determining region Y-Box 9 (SOX9) have been previously considered markers of HPCs, cytokeratin-7 (CK7) and CK19 have been used to identify cholangiocytes, and albumin and hepatic nuclear factor 4- $\alpha$  have been considered markers of hepatocytes[19-21]. HPCs located in the Hering canal typically differentiate into biliary cells in a normal liver[18] but do not lead to DR. HPCs are activated and differentiate into hepatocytes or biliary cells during liver injury. For example, HPCs differentiate into hepatocytes in acute fulminant hepatic failure and contribute to liver regeneration[22, 23]. CK7 immunohistochemistry is also positive in HPCs, which can predict liver injury severity; for instance, HPCs differentiate into CK7+ cells in the portal area in chronic hepatitis C and exacerbate liver injury[13,14,24-26]. Furthermore, a similar phenomenon has been found in hepatitis B virus-injected murine models[27]. In addition, DR is significantly associated with hepatocellular carcinoma peritumoral hepatic inflammation, liver fibrosis, tumor node metastasis classification stage, and poor prognosis[28]. Hepatocyte-derived ductular HPCs can give rise to hepatocellular carcinoma *via* concomitant activation of yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif transcription factors. Autophagy suppresses the formation of hepatocyte-derived cancer-initiating HPCs in the liver[29].

HPCs are activated in the majority of liver diseases[30]. During liver injury, a ubiquitous DR affects the differentiation *vs* dedifferentiation type of HPCs, depending on the severity of the liver injury[31]. Proliferating BDs in DR are misshapen, lack an apparent lumen, and are associated with increased portal inflammation and fibrosis[19,32]. It has been previously demonstrated that HPC activation is sufficient to regenerate a large proportion of the liver parenchyma using targeted deletion of mouse double minute 2 (MDM2) in mouse hepatocytes. This kind of HPC activation may be induced by the tumor necrosis factor-like weak inducer of apoptosis (TWEAK)/fibroblast growth factor-inducible 14 pathway[33]. Interestingly, in the hepatocyte-specific  $\beta$ -catenin knockout model, hepatocytes lose their regenerative capacity, and cholangiocytes still express  $\beta$ -catenin.  $\beta$ -catenin-positive cholangiocytes (differentiated HPCs) differentiate into  $\beta$ -catenin-positive small hepatocytes, which then proliferate and repopulate the liver[34,35]. A previous study reported that YAP levels are increased in NAFLD patients and NAFLD mouse models[36]. A recent study showed that the DR reaction is more intense and hepatocytes trans-differentiate into cholangiocytes protected from cholestatic damage by activating Hippo-YAP in the Tjp2 cKO mouse model (more susceptible to cholic acid-induced liver injury) fed 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)[37]. A murine BD ligation model of liver fibrosis showed that heme oxygenase-1-mediated pro-resolution M2 polarization of macrophages protects the liver from excessive DR and fibrosis with the ligand of numb protein X1 as the key downstream factor[38]. Interestingly, recent studies have shown that HPCs can promote angiogenesis by secreting vascular endothelial growth factor (VEGF) *via* the secretin/secretin receptor/microRNA 125b (miR-125b) axis [39]. However, recent studies have shown that DR cells can promote angiogenesis through slit guidance ligand 2-roundabout 1 signaling channels in various chronic liver diseases (CLDs), contrary to VEGF [40]. Another study showed that the signaling of apelin/APJ (G protein-coupled apelin receptor) can promote intrahepatic angiogenesis[41].

The impact of DR on liver diseases is a double-edged sword. HPCs can be activated and differentiated into hepatocytes to participate in liver regeneration in the case of massive loss of parenchymal cells. Conversely, the activation of HPCs may play a role in the activation of HSCs and the infiltration of inflammatory cells in DR in most CLDs, which can lead to further liver injury, including cirrhosis and tumorigenesis[14,25,42,43].

### Correlation between NASH and DR

A state of NAFLD begins with healthy liver parenchyma (steatosis in < 5% of hepatocytes) and then progresses to steatosis in > 5% of hepatocytes with the initiation of DR. The condition progresses to a severe stage with scar tissue accumulation, elevated steatosis, and hepatic ballooning[43]. In recent years, DR has attracted considerable attention in NASH research. It is worth noting that although DR can assist in repairing liver injury by aiding in HPC activation and differentiation, its impact on the progression of chronic liver disease associated with NASH may not always be favorable, especially when liver regeneration capacity is impaired. In fact, in some cases, DR-induced differentiation may even contribute to the occurrence and progression of inflammation and liver fibrosis in NASH. In 2007, Richardson *et al*[14] analyzed data from 118 liver specimens (107 from NAFLD patients and 11 from normal liver) and found that DR commonly existed in NASH, especially in patients with fibrosis. Multivariate analysis demonstrated that the extent of DR was independently associated with hepatocyte replicative arrest [odds ratio (OR) = 6.5] and fibrosis stage (OR = 17.9). Moreover, they further found that the expansion of HPCs was significantly correlated with NASH activity score[14]. In 2013, based on biopsy specimens from 56 adults with NAFLD (10 with steatosis and 46 with NASH) from Austria and the United States, Skoien *et al*[44] found that both centrilobular fibrosis and portal fibrosis stages were positively associated with the extent of DR. In 2018, multicenter observational studies of 90 NAFLD patients showed that DR was identified in 90% of biopsy samples, and its extent was correlated with

fibrosis stage[15]. Similarly, Gadd *et al*[13] also found that DR appeared in almost all NASH patients, and its grade was significantly associated with pathological liver progression. Similar to the results in adult NAFLD, DR can also be found in pediatric NAFLD, and its extent and/or HPC expansion were significantly correlated with fibrosis degree[44-46].

DR also exists in animal NAFLD models. In an 8-wk methionine/choline-deficient (MCD) diet mouse model and a 16-wk western diet mouse model, the number of YAP+, CK19+ reactive-appearing ductular cells, and HPCs were significantly increased with the severity of hepatocyte injury and inflammation[47]. A recent study based on mouse models indicated that during NASH development, YAP activation occurred earlier than DR but they were spatiotemporally correlated. Murine YAP activation may promote hepatocyte dedifferentiation during NASH development[48]. Morell *et al*[49] also established an 8-wk MCD diet mouse model and found that DR extent and HPC number increased steadily over time in the portal and lobular areas. Furthermore, the extent of DR rose significantly in a 12-wk western diet and carbon tetrachloride-treated mouse model, which led to severe NASH-related fibrosis. DR can also occur in other NAFLD animal models, such as rats and monkeys[50,51]. Although some animal models are particularly useful, especially for studying liver regeneration, many features of DR in humans are significantly different from those of animals[18]. The contrasting anatomical features of the two species likely account for this distinction. In humans, cholangiocytes are classified based on the diameter of the biliary tract, which can vary from small to medium to large, resulting in different sizes of the cells. Unlike humans, rodents have small BDs and large BDs, lined by small BDs and large BD cells, respectively, with distinct functional properties[52].

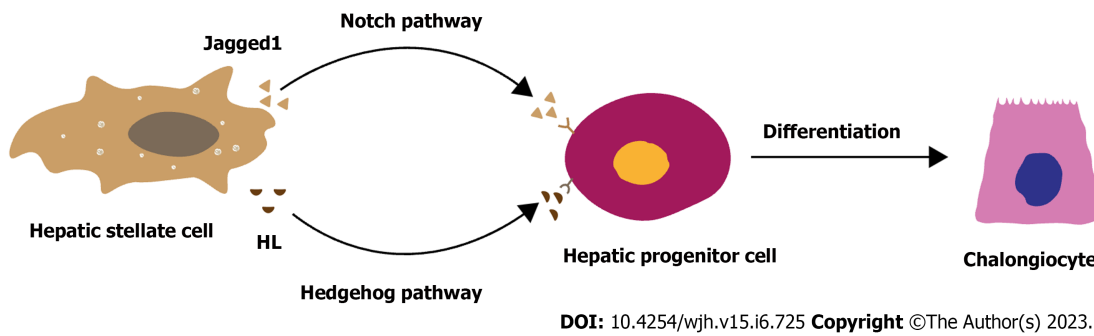
Interestingly, the location of DR varies in different NAFLD patient populations. In pediatric NAFLD patients, DR often appears in the portal/periportal area. In a retrospective study involving 30 children and adolescents with biopsy-proven NAFLD, CK7-positive HPCs localized at the portal-parenchymal interface, *i.e.* the periportal site[45]. Similarly, a cohort study of 32 children and adolescents with biopsy-proven NAFLD showed that DR commonly occurred in the portal area[46]. In another pediatric NAFLD study, the authors gathered 38 biopsy specimens from NASH children in three United Kingdom medical centers. They found DR at the interface between the parenchyma and portal areas in 36 NASH patients[44]. Similarly, portal DR can also occur in adult NAFLD patients[13-15]. However, in adult NAFLD patients, CK7+ cells and/or CK7+ structures can be found in the centrilobular area. Interestingly, CK7+ cells and/or CK7+ structures in centrilobular zones universally occurred in several other CLDs (including chronic viral hepatitis, autoimmune hepatitis, drug-induced liver injury, *etc.*), which was termed centrilobular DR[53-55]. Both centrilobular DR and periportal DR were also found in adult NAFLD studies and showed a significant correlation with NASH progression[15,55,56]. Importantly, centrilobular DR was also located, and the correlation of fibrosis stage with centrilobular DR was much stronger than with periportal DR (regression coefficient: 1.856 *vs* 0.646)[15].

The difference in DR localization between pediatric NAFLD and adult NAFLD is plausible. In children, pediatric NASH is characterized by portal inflammation and/or fibrosis[57-59]. Since it is acknowledged that periportal DR is closely related to NASH progression in pediatric NAFLD, the localization of DR in the portal area is reasonable. The concept of centrilobular DR seemingly contradicts the localization characteristic (portal area) in the classic DR definition in adults. However, this phenomenon might be explained from the following two perspectives. From the pathology standpoint, centrilobular fibrosis, *i.e.* zone 3 fibrosis, is one of the typical pathological features of adult NASH[8]. Therefore, DR – a process related to fibrosis – would emerge in the centrilobular area by fibrosis location. Regarding the underlying pathophysiological mechanism, it has been postulated that CK7+ cells/structures in centrilobular DR might stem from hepatocytes through metaplastic response and/or dedifferentiation[55,60]. Hence, the concept of DR in NAFLD should be expanded to cover centrilobular DR[17]. In a cross-sectional analysis, it was found that centrilobular DR was highly correlated with the stage of fibrosis in adult non-alcoholic steatohepatitis[15]. In addition, centrilobular was the dominant injury pattern, presumably due to pressure induced by mechanical injury[53]. Besides, in NASH, the different underlying impact between centrilobular DR and periportal DR on disease development remains to be clarified.

### **DR microenvironment and HPC differentiation fate in NASH**

The DR microenvironment, composed of parenchymal cells, mesenchymal cells, inflammatory cells, and their secreted substances, participates in the activation, proliferation, and differentiation of HPCs[12,61,62]. Different components drive HPC differentiation fate in different directions (Figure 1). Previous studies have indicated that HPCs reside in a specialized microenvironment (niche), which is crucial in determining their cell fate. Laminins, as part of the extracellular matrix (ECM), control the expansion of HPCs in an undifferentiated state, and hence DR, during liver injury. Other studies have demonstrated that HSCs and myofibroblasts might play an essential role in the differentiation of HPCs towards the cholangiocyte cell phenotype, while macrophages may participate in HPC differentiation into hepatocyte phenotypes[12,63]. A previous study showed that estimated glomerular filtration rate (EGFR) ligands were present in the liver microenvironment. In animal models lacking EGFR catalytic activity, the expansion of HPCs can be observed after DDC-induced liver damage, indicating that the lack of EGFR may promote HPC differentiation into hepatocytes, and thus liver regeneration[64]. However, it is noteworthy that the differentiation of HPCs is not modulated by a single factor but by a





**Figure 1** Factors contributing to the differentiation of hepatic progenitor cells in non-alcoholic fatty liver disease and potential pathways associated with hepatic progenitor cells-mediated non-alcoholic fatty liver disease progression.

complicated cellular and molecular network in liver diseases. HPCs tend to differentiate into biliary cell phenotypes in NASH, which may involve the participation of HSCs, myofibroblasts, macrophages, and natural killer T (NKT) cells[13-15,18,44]. At the molecular level, Notch and Hedgehog pathways may be the critical pathways in HPC differentiation into the biliary cell phenotype in NASH patients and mice [16,19,65] (Figure 1).

### **HSC and HPC differentiation fate in NASH**

HSCs, located in the space of Disse, are the critical cells for liver fibrosis development and progression [66,67]. HSCs maintain a quiescent phenotype in normal liver but they can be activated by multiple factors in NAFLD, such as inflammatory cells, damaged hepatocytes, oxidative stress, *etc*[66]. Activated HSCs can acquire a myofibroblast phenotype and increase ECM production, contributing to NASH progression[67].

HSC fibrogenic activation promotes HPC differentiation into hepatocytes to restore mass and function[68]. A subfamily of the inhibitor of apoptosis protein family, survivin (also called baculoviral inhibitor of apoptosis repeat containing-5), has minimal expression in differentiated cells and is associated with cell division. Activated HSCs and HPCs can express survivin. Survivin protein is upregulated with increasing fibrogenic activation of HSCs from their quiescent state. Survivin protein can suppress the fibrotic response of HSCs. At this point, the regenerative capacity of hepatocytes is diminished, followed by replenishment with survivin-expressing HPCs, which differentiate into hepatocytes to promote liver regeneration[68].

HSCs also play an essential role in NAFLD-related DR, possibly by inducing HPCs to differentiate into CK7+ and/or CK19+ cells[12,17,69,70]. In NAFLD, the emergence of DR is accompanied by a significant increase in HSCs and ECM in the DR microenvironment, and the number of HSCs is associated with the DR stage and CK7+ HPC expansion[13]. A similar association between HSC and DR can also be found in other liver diseases, such as hepatitis C infection and primary biliary cirrhosis[13, 16]. Further studies have partially explained the underlying mechanism of HSC-mediated HPC differentiation[25,69].

Primary studies have shown that HSC-mediated HPC differentiation may involve the Notch and Hedgehog pathways. In the DR microenvironment, activated HSCs can upregulate the Notch pathway in HPCs by expressing Jagged1 (a Notch pathway ligand)[60,63], leading to the expression of Notch pathway target genes such as *hes*-related family bHLH transcription factor with YRPW motif 1 and hairy and enhancer of split homolog-1[63,71,72]. Increased Notch target gene expression can further increase the expression of hepatic nuclear factor 1 $\beta$  (HNF1 $\beta$ ) and HNF6, consequently contributing to HPC differentiation into biliary cells and BD formation[73-75]. Similarly, activated HSCs can upregulate the Hedgehog pathway in HPCs by expressing HL (a ligand of the Hedgehog pathway), leading to an increase in the Gli transcription factor family (Gli1, Gli2, and Gli3)[76]. Furthermore, Gli2 can translocate to the nucleus and promote target gene transcription[77,78], whose activation can promote the proliferation and differentiation of HPCs into CK7+ cells[79-83]. Elevated activity of Notch and Hedgehog pathways was analogous to disease severity in studies of both mouse models of NASH and patients with NASH[48,79,84], indicating the potential role of Notch and Hedgehog pathways in HSC-mediated HPC differentiation (Figure 2).

### **Macrophages and HPC differentiation fate in NASH**

Emerging evidence suggests that macrophages are a heterogeneous population of cells. There are two types of macrophages: Resident macrophages, *i.e.* Kupffer cells, originating from yolk sac-derived erythroid, myeloid progenitors in the fetal liver; and infiltrating macrophages originating from bone marrow-derived circulating monocytes[7]. In NAFLD, macrophages can be activated and differentiated into two types of macrophages: M1 and M2 macrophages[7]. M1 macrophages secrete pro-inflammatory cytokines and have high phagocytic activity, whereas M2 macrophages secrete immune-suppressive but

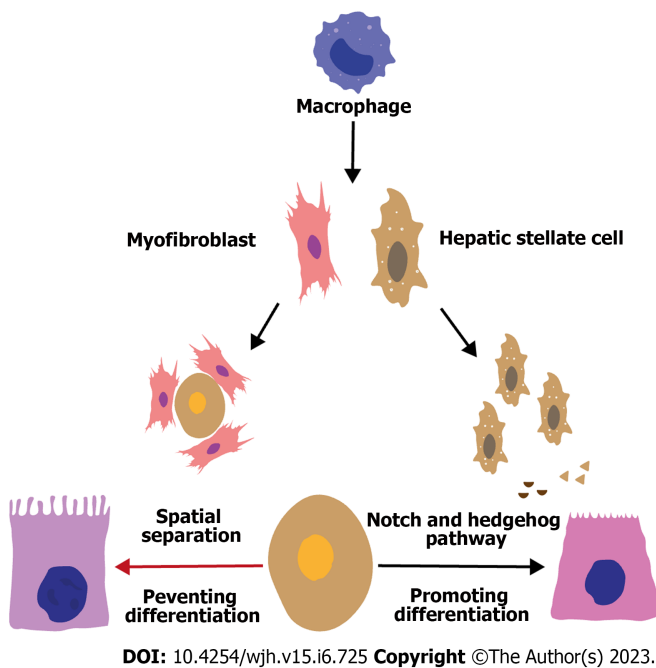


Figure 2 Hepatic progenitor cell-mediated hepatic progenitor cell differentiation may involve the Notch and Hedgehog pathways.

pro-fibrogenic cytokines[85,86].

Although it is universally acknowledged that macrophages play a critical role in NAFLD progression, the relationship between macrophages and HPC differentiation in NAFLD-related DR remains elusive. Macrophages were found to promote HPC differentiation into hepatocytes in the DDC diet mouse model, and the Wnt/ $\beta$ -catenin pathway was the key mechanism in this process[69,83,87]. After phagocytosis of the hepatocyte debris, macrophages increase the expression and secretion of Wnt3a (a ligand of the Wnt/ $\beta$ -catenin pathway), activating the Wnt/ $\beta$ -catenin pathway in HPCs[12,63]. Therefore,  $\beta$ -catenin can translocate to the nucleus and bind its co-activators (*e.g.*, CREB-binding protein), promoting the expression of target genes such as SOX9, MYC, and Twist-related protein 1, all of which are associated with HPC differentiation into hepatocytes[63,88]. Studies have shown that HPCs activate during chronic liver injury when hepatocyte proliferation is insufficient to reach homeostasis. During transforming growth factor (TGF)-induced apoptosis in a fibrogenic environment, HPC expands due to a balance between proliferation and apoptosis, which is favorable in a fibrogenic climate. Mitogens that trigger HPC expansion overlap significantly with pro-inflammatory cytokines released by hepatic macrophages including tumor necrosis factor, interferon gamma (IFN- $\gamma$ ), interleukin 6 (IL-6), and TWEAK. Human amnion epithelial cell-treated NASH mice showed a reduction in both HPC and macrophage numbers and expression levels of HPC mitogens and macrophage-released cytokines[89]. In NAFLD patients, macrophages increased significantly in the DR area, and macrophage infiltration was mainly related to the expansion of CK7+ HPCs and fibrosis stage, indicating the potential role of the macrophage in the HPC differentiation fate[13,46]. However, in the context of liver diseases, the role of macrophages in determining HPC differentiation fate is still unclear. Deduced from the aforementioned basic studies, the increased macrophage infiltration in the DR area of NAFLD patients may promote the differentiation of HPCs into hepatocytes. Nonetheless, according to pathological findings, the actual characteristic of NAFLD-related DR is HPC differentiation into cholangiocytes. Therefore, this seemingly contradictory phenomenon might be explained from the following two perspectives.

The regulation of macrophage-mediated HPC differentiation fate may vary across different disease contexts, which is one potential explanation. Disease pathogenesis in the DDC diet mouse model is highly distinct from NAFLD pathogenesis. Therefore, the functional state of macrophages in NAFLD might be correspondingly specific to that in the DDC diet mouse model. Second, the crosstalk between macrophages and HSCs in NAFLD may predominantly contribute to the differentiation of HPCs into cholangiocytes. It has been well established in NAFLD that macrophages can express multiple pro-fibrotic factors (such as platelet-derived growth factors subunit B and TGF- $\beta$ ), contributing to the proliferation and activation of HSCs and myofibroblasts[7,66,90-92]. Notably, macrophages were near HSCs in the DR area in NAFLD patients, indicating a potential promotive effect of macrophages in driving HPC differentiation into cholangiocytes by activating HSCs[13,46].

Conversely, HSCs might hinder macrophage-mediated HPC differentiation into hepatocytes by interrupting the interaction between macrophages and HPCs in spatial separation. In a biliary regeneration model, HPCs were surrounded by a thick sheath-like layer of myofibroblasts and collagen I, which excluded macrophages from forming a close association with HPCs[63]. Similar sheath-like

structures might also exist in NAFLD; however, further studies in NAFLD patients are needed to validate the potential existence of this structure in the DR area. In summary, macrophages may participate in NAFLD-related DR onset and development through crosstalk with cells such as HPCs and HSCs. However, its specific role and related mechanisms warrant further investigation (Figure 3).

### **Mast cells and HPC differentiation fate in NASH**

According to recent studies, NAFLD/NASH development is primarily influenced by the interaction between DR and mast cells (MCs)[93,94]. MCs may promote NAFLD/NASH progression by activating Kupffer cells and HSCs with histamine[94]. Recruitment of MCs is a characteristic of BD injury. It has been proven that knocking down or inhibiting the expression of MCs can effectively reduce DR[95,96]. MC-derived TGF- $\beta$ 1 is a critical regulator of hepatobiliary damage, and blockage of TGF- $\beta$ 1 can ameliorate DR and other features of cholestatic liver injury[97]. MCs were found to promote microvesicular steatosis development *via* the miR-144-3p/aldehyde dehydrogenase 1 family, member A3 (ALDH1A3) signaling pathway in a Western diet mouse model with NASH[98]. Reduced ALDH1A3 expression promotes lipid peroxidation associated with liver fibrosis and steatosis and a reduction in  $\beta$ -oxidation of free fatty acids[99].

Moreover, miR-144-3p showed increased expression in insulin resistance in NASH. Meanwhile, DR expansion in mouse models of Western diet with NASH is more sensitive. The phenotypic changes are associated with the secretion of insulin-like growth factor 1 by cholangiocytes, driving peribiliary infiltration and MC activation. Consistent with this finding, MCs from NASH patients accumulate in the portal area, directly correlating with fibrosis stage[93]. A more relevant study discovered that inhibiting MCs reduced DR, inflammation, fibrosis, and recovery from liver injury after MC injection[94].

Previous studies have demonstrated that elevated farnesoid X receptor (FXR) expressed by MCs can be detected in primary sclerosing cholangitis, primary biliary cholangitis, and NAFLD[100-102]. MC-FXR plays a critical role in liver injury and DR in a cholestasis model, where MCs express FXR and infiltrate the liver promoting liver fibrosis during cholestasis and triggering biliary injury. After migration and activation, MCs induce DR and senescence through paracrine interactions with cholangiocytes. Moreover, the MC-FXR signaling pathway modulates the biliary senescence/senescence-associated secretory phenotype and histamine H1- and H2-receptor signaling pathways to regulate total bile acid and then affects DR and liver injury[103]. According to these studies, MCs are correlated with DR in various liver diseases and may affect the differentiation of HPCs through macrophages, HSCs, and fibroblasts. However, the mechanism by which MCs influence HPC differentiation remains obscure.

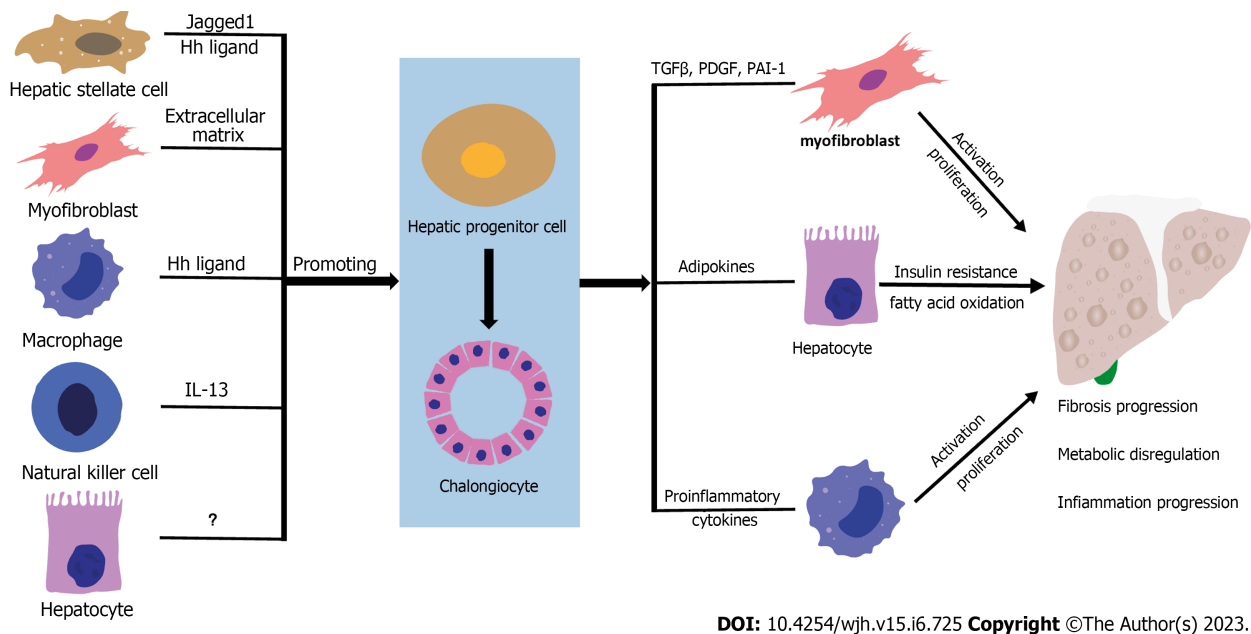
### **ECM and HPC differentiation fate in NASH**

ECM – a supporting structure for organs, tissues, and cells-represents a complex protein network including fibrillar and non-fibrillar collagen, laminin, fibronectin, *etc*[104]. ECM proteins can play a vital role in HPC differentiation fate. For example, loss of the basement membrane, a cell-supporting structure, is correlated with the increased level of HNF4 in HPCs, indicating the differentiation of HPCs into hepatocytes[105]. In addition, laminin can upregulate the expression of the biliary marker gene and downregulate hepatocyte transcription factor C/EBP $\alpha$  in HPCs, driving HPC differentiation into cholangiocytes[106]. A recent study based on mouse models of chronic parenchymal damage showed that iloprost reduces laminin deposition and enhances the differentiation of HPCs into hepatocytes[107]. The disruption of integrin  $\beta$ 6, an adhesion receptor that interacts with fibronectin and TGF- $\beta$ 1, inhibits the response of HPCs to tissue damage. Significant ECM deposition, such as collagen deposition, is commonly found in NAFLD-related fibrosis[67,108]. Therefore, the accumulation of ECM during the development of NAFLD may contribute to HPC differentiation and the formation of DR.

### **Hepatocyte senescence and HPC differentiation fate in NASH**

Cellular senescence, a cell cycle arrest response, is mediated by the induction of cyclin-dependent kinase inhibitors p21 and p16[109,110]. In NAFLD, hepatocyte senescence involves multiple factors, such as oxidative stress and inflammation, and is characterized by increased p21 levels[111,112]. Interestingly, hepatocyte senescence, *i.e.* replicative arrest, may activate HPC proliferation and differentiation. Oxidative stress induces hepatocyte senescence with consequent cell cycle arrest and impaired regeneration[113]. A recent study demonstrated that oxidative stress can affect HPC differentiation, and the redox is regulated by various transcription factors, of which nuclear factor (erythroid-derived 2)-like 2 (NRF2) plays a crucial role in HPC differentiation, and its activation can inhibit oxidative stress. As stemness is maintained in HPCs through constitutive NRF2 activation, it is inhibited when HPCs are activated during liver injury, *e.g.*, NASH.

Interestingly, NRF2 inhibition increases the transplantation efficiency of human HPCs[114]. In an MDM2-deleted mouse model, severe hepatocyte senescence was characterized by a high p21 level and resulted in significant HPC proliferation and differentiation into hepatocytes[33]. However, in NAFLD patients and the choline-deficient and ethionine-supplemented (CDE) diet mouse model, mild hepatocyte senescence was also identified by a lower p21 level and was positively correlated with DR stage and CK7+ HPC expansion, conversely indicating a potential role of hepatocyte senescence in HPC differentiation into cholangiocytes[14,33]. To reconcile these apparently conflicting findings, some



**Figure 3** Potential role of macrophages in hepatic progenitor cell differentiation fate in non-alcoholic fatty liver disease.

experts have suggested that the absence of hepatocyte senescence may enable hepatocytes to undergo self-regeneration without relying on HPC-mediated regeneration[33]. In addition, hepatocytes are the primary source of liver regeneration in a healthy liver, while HPCs do not participate in normal liver regeneration. Therefore, it might be further speculated that aging and healthy hepatocytes may regulate HPC differentiation. Nevertheless, the mechanism by which aging hepatocytes and/or healthy hepatocytes regulate HPC differentiation fate is yet to be elucidated.

#### **NKT cells and HPC differentiation fate in NASH**

NKT cells – a type of innate immune cell in the liver – can participate in the development of liver inflammation and fibrosis[115]. In NAFLD, NKT cells significantly increase in the DR area, and their infiltration extent correlates with both NASH severity and DR stage[80,116]. Conversely, liver biopsies of HBV patients often reveal a pronounced DR and diminished expression of IFN- $\gamma$ , which is caused by NKT cells. Nevertheless, treatment with IFN- $\gamma$  has been shown to ameliorate DR in these patients[117]. However, the role of NKT cells in HPC differentiation fate is unclear in NAFLD-related DR. There is evidence suggesting a promotive role of NKT cells in HPC differentiation into cholangiocytes in liver injury models. In these studies, NKT cells increased the expression of IL-13 and the production of Hedgehog ligands, which may drive HPC differentiation into cholangiocytes[80,118-121]. Nevertheless, it is unclear whether NKT cells are required for HPC differentiation into biliary cells in NASH.

#### **Potential role of HPC differentiation in aggravating NASH**

In addition to the impact of the NASH-related DR microenvironment on HPC differentiation fate, differentiated HPCs can aggravate inflammation and fibrosis progression in NASH. As aforementioned, there is a close correlation between HPC expansion and NASH progression, indicating the potential role of differentiated HPCs in aggravating NASH. Moreover, the promotive role of differentiated HPCs in NASH inflammation and fibrosis progression has been proven in NASH-related animal models. Although the underlying mechanism has yet to be fully understood, it may involve the participation of HSCs, macrophages, adipokines, and the epithelial-mesenchymal transition (EMT) (Figure 1).

Differentiated HPCs may participate in HSC-mediated NASH-related fibrosis by promoting HSC activation and proliferation. Increased hepatic levels of several factors, such as PDGF, connective tissue growth factor (CTGF), and Hedgehog ligands, have been found in NAFLD animal models[60,122,123]. In basic studies, HPCs are one of the sources of PDGF, CTGF, and Hedgehog ligands[81,122]. The promotive role of these molecules in enhancing HSC proliferation, accumulation, and ECM production has been well established[81,124-126]. Therefore, these pathways may be involved in HPC-mediated HSCs activation in NASH aggravation.

In addition to directly promoting HSC and myofibroblast activation, HPCs may undergo the EMT towards myofibroblasts, consequently leading to hepatic fibrosis progression. EMT is a cell reprogramming process from the epithelial to mesenchymal phenotype[76,77,127]. EMT in hepatocytes, cholangiocytes, and HSCs can be found in various liver diseases and is related to hepatic fibrosis[76,128,129]. A proportion of HPCs can go through the EMT, which is characterized by the upregulation of mesenchymal cell markers [such as alpha-smooth muscle actin ( $\alpha$ -SMA) and S100 calcium-binding



protein A4) and downregulation of epithelial cell markers (such as CK7 and CK19)[130-133]. Differentiated HPCs (CK7+) that highly express  $\alpha$ -SMA can be found in NAFLD, indicating the presence of HPC-originated EMT and its potential contribution to fibrosis pathogenesis[79]. The onset of EMT in HPCs may involve the Hedgehog pathway activity and TGF- $\beta$ [79]. Notably, whether high expression of  $\alpha$ -SMA or collagen in HPCs can be regarded as the EMT remains controversial. This is because a recent lineage tracing study, using an  $\alpha$ -fetoprotein Cre mouse model, provided strong evidence against the existence of HPC-myofibroblast transition[134]. Therefore, further basic studies regarding the origination of  $\alpha$ -SMA and CK7 double-positive cells are warranted.

Differentiated HPCs can promote macrophage-mediated inflammation in NASH. Studies have shown that macrophages play an essential role in NASH aggravation[7]. As previously mentioned, significant macrophage infiltration was detected in the NAFLD-related DR area. The number of macrophages is significantly associated with the extent of DR and HPC expansion, indicating that HPCs have a potential role in macrophage recruitment[13]. Primary studies have proven that multiple factors, such as chemokines and pro-inflammatory cytokines, are involved in HPC-mediated macrophage recruitment [7,135-137]. For example, HPCs can contribute to macrophage recruitment by increasing C-C motif chemokine ligand 2 and C-X3-C motif chemokine ligand 1 expression and promote macrophage polarization into M1-type by secreting IL-1, IL-6, and IFN- $\gamma$ , consequently exacerbating hepatic inflammation[7,135-137]. Therefore, these cytokines may participate in HPC-mediated macrophage infiltration and activation in NASH.

Metabolic dysregulation is a major hallmark in the pathophysiological process of NAFLD, and differentiated HPCs exacerbate by causing dysregulation of the secretion of adipokines, leading to an increase in NASH progression. Adipokines, including adiponectin, leptin, and resistin, contribute to NAFLD development by modulating glycolipid metabolism, inflammatory response, and HSC activation[138]. Although adipokines are mainly produced by adipose tissues, they have also been found to secrete adiponectin and resistin[45,139]. Notably, in NASH, differentiated HPCs increase resistin expression and downregulate adiponectin expression. Moreover, resistin expression in HPCs is positively correlated with the severity of NAFLD.

By contrast, adiponectin expression in HPCs was found to be negatively correlated with the severity of NAFLD, indicating that adipokines play a role in HPC-mediated NASH progression[45]. Adiponectin can suppress hepatic lipogenesis and the production of proinflammatory cytokines but can stimulate insulin secretion and fatty acid oxidation in the liver[140,141]. By contrast, resistin reduces peripheral insulin sensitivity and promotes the expression of proinflammatory cytokines[138,142]. In NASH, adipokine dysregulation aggravates insulin resistance, worsening liver inflammation and injury, which also increases HSC activation, thereby aggravating NASH[45,143-145]. Therefore, the NAFLD-related microenvironment can cause the dysregulation of adipokine expression in HPCs, leading to NAFLD-related metabolic dysregulation.

## CONCLUSION

Studies conducted in the past 100 years have shown that DR may be a compensatory reaction to liver injury, but the correlation between DR and NAFLD needs to be sufficiently studied. The expected prevalence of DR in NAFLD patients, and more importantly, the close relationship between DR and the progression of inflammation and fibrosis in NASH, remain to be clarified. Although DR promotes liver regeneration[54,146], it remodels the NASH microenvironment, which aggravates rather than alleviates NASH severity, similar to the initially upright “Macbeth” getting perverted under a corruptive lure. In NAFLD, HPC proliferation and differentiation, the core processes in DR pathogenesis, might be triggered by NAFLD-related liver injury. The cells (such as HSCs and macrophages) and their secreted substances may drive the differentiation of HPCs into cholangiocytes. Conversely, differentiated HPCs may, in turn, aggravate NASH through multiple pathways, which may involve the participation of HSCs, macrophages, adipokines, and the EMT. The involvement of these cells in the interaction between DR and NASH pathogenesis may form a ‘vicious circle,’ presumably leading to further progression of hepatic inflammation and fibrosis.

However, the bilateral interaction between DR and NAFLD remains to be further verified. For the DR caused by NAFLD, the majority of previous findings about NAFLD-related DR were primarily obtained through observational studies. Several signaling pathways are involved in DR (*e.g.*, Notch, Hedgehog, TWEAK), and it was recently discovered that long non-coding RNA/p300 could influence DR progression[147]. However, how these pathways promote the pathogenesis of DR in the context of NAFLD remains unclear. We are still determining whether the pathways mentioned above are involved in DR-related NAFLD. The key factors driving HPC differentiation in NAFLD need to be further investigated. In addition, in terms of the impact of DR on the pathogenesis of NAFLD, considering our limited understanding of the core molecular mechanism driving DR, it is difficult to provide a direct and exact intervention towards the DR onset, which hinders establishment of a causal effect of DR on NAFLD progression. Therefore, we need further investigations to deepen our understanding of the core and characteristic pathways of DR, to achieve the development of DR-targeted intervention in NAFLD-



related studies. More importantly, the underlying mechanisms of both NAFLD-caused DR and HPC-mediated NAFLD progression may be important targets for treating NAFLD.

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