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# Mast Cells in Liver Disease Progression: An Update on Current Studies and Implications

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**Abbreviations**

**α-SMA** = α-smooth muscle actin; **ALD** = alcoholic liver disease; **ALDH1A3** = aldehyde dehydrogenase 1 family, member A3; **BDL** = bile duct ligation; **CCA** = cholangiocarcinoma; **CDKN1A** = cyclin-dependent kinase inhibitor p21; **cKit** = stem cell factor receptor**, Col =** collagen; **DKO** = double knockout; **FcεRI** = high affinity receptor for the Fc region of immunoglobulin E; **H1/2/3/4HR** = histamine H1/2/3/4 receptor; **HCC** = hepatocellular carcinoma; **HDC** = 1-histidine decarboxylase; **HFC** = high-fat and high-cholesterol; **HFD** = high fat diet; **HR** = histamine receptor; **IBDM** = intrahepatic bile duct mass; **IgE** = immunoglobulin E; **IL** = interleukin; **LT** = leukotriene; ***Mdr2*$^{-/-}$** = multidrug resistant 2 knocked out, **MMP** = matrix metalloproteinase; **MCs** = mast cells; **miR-144-3p** = microribonucleic acid 144-3 prime; **miRNA** = microribonucleic acid; **NAFLD =** non-alcoholic fatty liver disease; **NASH** = non-alcoholic steatohepatitis**; PBC** = primary biliary cholangitis; **PCNA** = proliferating cell nuclear antigen**; PK** = protein kinase; **PSC** = primary

sclerosing cholangitis; **SCF** = Stem cell factor; **ST2** = suppressor of tumorigenicity; **SYP9** = synaptophysin 9; **TGF-β** = transforming growth factor beta; **TNF-α** = tumor necrosis factor alpha; **VEGF** = vascular endothelial growth factor; **WD** = western diet; **WT** = wild type.

**Abstract:**

Mast cells (MCs) induce the progression of liver diseases including, but not limited to, hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), alcoholic and non-alcoholic fatty liver disease (ALD/NAFLD), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). The effects of MCs during disease progression includes alterations in ductular reaction, steatosis, hepatic fibrosis and inflammation. In addition, there is significant crosstalk between MCs, MC mediators (histamine, tryptase, chymase) and MC-derived cytokines (transforming growth factor beta, tumor necrosis factor alpha, interleukins). Studies have been performed in rodent models, cultured cells, and human tissues to demonstrate the intracellular signaling implications of MC infiltration during liver disease. Targeting MCs may offer novel therapeutic strategies to treat liver disease. Our concise review will encompass the most recent studies involving MCs, their mediators and liver disease with the overall goal to inform the reader about the diverse role of these inflammatory immune cells in liver damage.

## Introduction

Mast cells (MCs) are innate immune cells originating from $CD34^+/CD117^+$ hematopoietic stem cells and regulate liver disease progression (1). With a variety of surface receptors, MC activation is triggered by two main receptor-dependent pathways: IgE/FcεRI and IL-33/ST2 (2). Upon liver damage, MCs are degranulate releasing mediators, including preformed bioactive metabolites (histamine, tryptase, and chymase), newly synthesized cytokines [transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β], and *de novo* lipid mediators (leukotriene (LT)B4, LTD4, prostaglandin) (3) (**Figure 1**). TGF-β1, TNF-α, IL-6, IL-10, and synaptophysin 9 (SYP-9) are released upon liver damage by paracrine interactions between MCs and hepatocytes [through TGF-β (4), TNF-α (5)]; cholangiocytes [through IL-10, TGF-β (6)]; hepatic stellate cells [through SYP-9, TGF-β1 (7)]; and Kupffer cells [through TNF-α, IL-6 (8)]. This review encompasses the most recent studies involving MCs, their mediators and the impact on liver disease.

## Diseases Implicated by MC Presence/Activation

### *MCs and Hepatocellular Carcinoma (HCC)*

MC integration in HCC occurs via the IL family, histamine and regulation of histamine receptors (HRs), tryptase- and chymase-positive MCs, and MC-derived exosomes (**Figure 1**). Three sub-groups of 329 HCC patients were identified based on tumor microenvironment and infiltration of 22 immune cells (including resting and activated MCs) using CIBERSORT software and ConsensuClusterPlus package (9). Decreased resting MCs in HCC patients with fibrosis compared to controls was reported based on the immune cell landscape calculated by CEBERSORT (10).

Increased expression of IL-17 and IL-17 receptor (11), and decreased expression of IL-36α (12) correlated with poor HCC prognosis. MC-derived histamine stimulates the growth of human HCC cell lines and inhibition of H1/H2 HR attenuates HCC proliferation (13). H1HR (14) and H3HR (15) upregulation enhance HCC cell growth and metastasis. H3HR expression is elevated in HCC promoting cell growth and survival via protein kinase/cyclic adenosine monophosphate responsive element-binding/cyclin-dependent kinase inhibitor p21 signaling (16). The increase of tryptase- and chymase-positive MCs in human HCC (17) and the decrease in tryptase serum level in HCC patients after hepatic transarterial chemoembolization (18) suggests a role for these as biomarkers. The

majority of MCs in HCC are inactive and resting MC density is elevated in 305 HCC livers using tryptase immunohistochemistry (19).

*MCs and Cholangiocarcinoma (CCA)*

CCA/MC involvement was demonstrated by increased activity of tryptase and chymase via HDC/histamine/HRs signaling (**Figure 1**). Increased tryptase and chymase expression in xenograft tumor samples was reversed by cromolyn sodium (20). In CCA patients, tryptase-positive MC infiltration (21) and chymase activity in bile (22) increased. Histamine promotes cholangiocyte proliferation (7, 23) and inhibition of MC-derived histamine attenuated CCA growth in xenograft tumors through stem cell factor receptor (c-Kit)/stem cell factor (SCF)-dependent pathway (20). Treatment with cromolyn sodium decreased MC numbers, proliferating cell nuclear antigen (PCNA) expression and CCA (23). MC presence, histamine serum levels, and HDC expression increased in human CCA patients and xenograft tumors that was blocked by HDC or H1HR inhibition (24). Blocking HDC and H1HR suppressed histamine release and cellular proliferation (25), whereas upregulation of H3HR via protein kinase Cα (26) and overexpression of H4HR (27) stunted CCA growth.

*MCs and Alcoholic and Non-Alcoholic Fatty Liver Disease (ALD and NAFLD)*

The link between MCs and ALD is demonstrated by increased activity of tryptase- and chymase-positive MCs and MC-derived TNF-α (**Figure 1**). Tryptase- and chymase-positive MC density increased in ALD liver biopsies (28). In ethanol-induced hepatoxicity, MC density and inflammatory markers, including nuclear factor binding near the kappa light chain gene in B cells were elevated (29). This corroborated with lipid accumulation as the first response to alcohol abuse after binding of MC-secreted TNF-α to hepatocyte TNF receptors (5) implicating TNF-α as a common factor between hepatocytes and MCs.

MC implications in NAFLD/NASH (non-alcoholic steatohepatitis), a significant indication for liver transplant, are focused on enhanced MC presence, MC-secreted chymase, and HDC/histamine signaling (**Figure 1**). Increased tryptase-positive MCs in the periportal and parenchymal regions of stages 3-4 NASH patients (30) was described. Elevated MC presence promoted NAFLD to NASH progression by upregulation of aldehyde dehydrogenase 1 family, member A3 (ALDH1A3) and concurrent downregulation of microRNA-144-3 prime (miR-144-3p) in human NASH livers and

wild-type (WT) mice fed Western diet (WD) (31). WD fed MC-deficient, *Kit*$^{W\text{-}sh}$ mice had ameliorated NAFLD phenotypes, along with a switch to macrovesicular steatosis (31). Apolipoprotein E- and MC-deficient (*Kit*$^{W\text{-}sh/W\text{-}sh}$) mice displayed reduced hepatic steatosis and interleukin production compared to *ApoE*$^{-/-}$ mice demonstrating a protective role in the absence of MCs (32). The chymase activity, matrix metalloproteinase and TGF-β levels were attenuated in a high-fat and high-cholesterol model treated with TY-51469 (chymase inhibitor) (33). Enhancement in MC chymase activity in NASH was observed (34) and TY-51469 treatment reduced hepatic steatosis and fibrosis by decreasing angiotensin II, collagen (Col) I, Col III, and α-smooth muscle actin (α-SMA) expression (35). High fat diet (HFD) decreased intrahepatic biliary mass (IBDM) and cholangiocyte senescence in *Hdc*$^{-/-}$ HFD mice via dysregulated histamine/leptin signaling evidenced by reduced histamine secretion and increased leptin resistance, suggesting the importance of HDC/histamine signaling in obesity-induced liver damage (36).

*MCs and Primary Biliary Cholangitis (PBC) and Primary Sclerosing Cholangitis (PSC)*

Portal MC infiltration, plasma histamine level, density of hepatic tryptase-positive and chymase-positive MCs, and liver chymase concentration increased in PBC patients (1) (**Figure 1**). Ketotifen, a MC stabilizer, increased hepatic mucosal MC presence in cholestatic rats while decreasing MC population in the mesenteric lymphatic complex, levels of TGF-β1 and vascular endothelial growth factor (VEGF) (37).

The interplay between MCs and PSC is mediated through the HDC/histamine/HRs and SCF/TGF-β1 axes (**Figure 1**). A reduction in MC-derived histamine, IBDM, and VEGF expression was observed in BDL *Hdc*$^{-/-}$ compared to BDL WT mice, indicating a link between HDC and histamine in PSC (38). This agreed with amelioration of hepatic damage and fibrosis in the novel double knockout (DKO) mouse model combining *Mdr2*$^{-/-}$ and *HDC*$^{-/-}$ mice, which display attenuated phenotypes relative to *Mdr2*$^{-/-}$ mice, and when DKO mice were treated with histamine, PSC phenotypes increased demonstrating that histamine induces hepatic damage (8). Cromolyn sodium treatment reduced hepatic MC number near cholangiocytes after BDL compared to control (23) and attenuated PSC phenotypes in *Mdr2*$^{-/-}$ mice that was coupled with decreased bile flow and total bile acid (TBA) content (7). Ursodeoxycholic acid treatment ameliorated MC-secreted histamine and biliary damage in *Mdr2*$^{-/-}$ mice and human PSC (39). The differential action on biliary damage of

H1/H2HR antagonists in *Mdr2*$^{-/-}$ mice was demonstrated by reduced proliferation of small and large cholangiocytes (24). When *Mdr2*$^{-/-}$ mice were treated with an H2HR Vivo-Morpholino, PSC phenotypes and MC activation were reduced (40). HRs, HDC, and serum histamine levels decreased in BDL *Kit*$^{W\text{-}sh}$ mice relative to BDL WT mice (41) supporting the importance of HDC/histamine/HR signaling in cholestasis.

There is increased SCF biliary expression/secretion in human PSC and targeting SCF using Vivo-Morpholino decreased MC migration, biliary damage and fibrosis in *Mdr2*$^{-/-}$ mice (42). TGF-β1 is a significant factor in PSC progression, and cromolyn sodium treatment decreases TGF-β1 levels in cholestatic rodents (6, 7, 23). In DKO mice treated with histamine, TGF-β1 signaling was enhanced demonstrating that histamine directly impacts TGF-β1 (8). MC activation in *Mdr2*$^{-/-}$ mice increased fibrosis evidenced by elevated expression of TGF-β1, α-SMA, fibronectin, and Col I (7, 24). Enhanced fibrosis was ameliorated in BDL *Kit*$^{W\text{-}sh}$ mice compared to BDL WT mice (41). Reintroduction of MCs lacking TGF-β1 into WT, DKO or *Kit*$^{W\text{-}sh}$ mice reduced PSC phenotypes compared to control MC injections (43). When MCs lacking farnesoid x receptor signaling, mice had significantly decreased TBA levels and PSC phenotypes compared to mice injected with control MCs (44). These studies demonstrate that manipulation of MCs *in vitro* impact *in vivo* phenotypes and support the role of SCF/TGF-β1 signaling in PSC.

**Conclusions/Future Perspectives**

The dynamic interplay between MCs and liver diseases is highlighted by increased MC infiltration, elevated MC-secreted bioactive metabolites, MC-derived cytokines, and the regulation of key signaling pathways such as HDC/histamine/HRs, SCF/TGF-β1, and miR-144-3p/ALDH1A3. In addition to antihistamines, MC stabilizers, and tryptase/chymase inhibitors, novel and natural compounds have emerged as promising approaches to target MCs in liver disease (**Table 1**). Further studies are required to elucidate the crosstalk between MCs and resident liver cells and understanding MC activation and infiltration mechanisms in liver diseases.

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**Figure legends:**

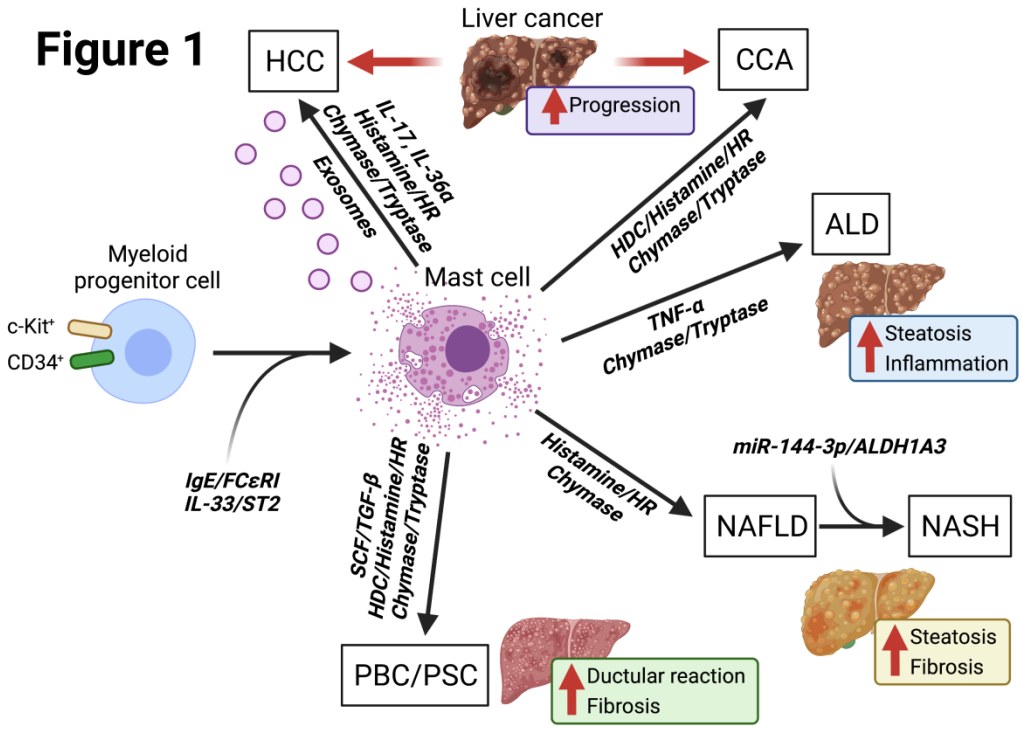
**Figure 1: Diseases implicated by increased MC presence/activation.** Immature MC progenitors circulate in the lymphatic and vascular systems and develop to the mature form once they reach the peripheral organs upon activation via IgE/FcεRI and IL-33/ST2 receptor-dependent pathways. MCs implication has been demonstrated in a diverse spectrum of liver disease (HCC, CCA, ALD/NAFLD, PBC, PSC) through increased MC presence/infiltration; elevated secretion of histamine, tryptase, and chymase; upregulated expression of TGF-β, TNF-α, and IL-17; and activation of three principal MC-mediated signaling pathways including HDC/Histamine/HRs, SCF/TGF-β1, and miR-144-3p/ALDH1A3.

**Table 1: Compounds targeting MCs in liver disease***

| Name | Function | Disease/Effects | Models | (Ref #)/ Year |
|---|---|---|---|---|
| Mepyramine/ Ranitidine | H1HR antagonist H2HR antagonist | PSC/ Reducing tumor growth, serum histamine, angiogenesis and EMT. | *Mdr2*$^{-/-}$ male mice | (24)/2018 |
| Cimetidine | H2HR antagonist | Hepatic ischemia–reperfusion injury/ Protective effect by inhibiting the activity of P450 and decreasing the generation of endogenous ROS. | Rat hepatocytes BRL-3A cell + 24 h hypoxia + 4 h reoxygenation | (45)/2013 |
| RAMH | H3HR agonist | CCA/Inhibiting CCA growth by activating PKCα. | CCA cell lines BALB/c nude mice | (26)/2009 |
| Clobenpropit | H4HR agonist | CCA/Decreasing CCA proliferation via $Ca^{2+}$ dependent pathway. | Xenograft mice injected with Mz-ChA-1 cells | (27)/2011 |
| Cromolyn sodium | MC stabilizer | PSC/Ameliorating cholangiocyte proliferation, bile flow and MC infiltration by decreasing HDC expression and histamine secretion. | *Mdr2*$^{-/-}$ mice BDL male rats MC line | (7)/2016 (23)/2014 (6)/2016 |
| Ketotifen | MC stabilizer | Hepatotoxicity caused by CYC/Ameliorate effects by decreasing oxidative stress, inflammation, and apoptosis. | Albino Wistar rats Adult male injected with CYC | (46)/2020 |
| Doxantrazole | MC stabilizer | Alcohol hepatic toxicity/Protective effects by impairing the intestinal barrier permeability. | Sprague-Dawley rats + ethanol + | (47)/2006 |

| Name | Function | Disease/Effects | Models | (Ref #)/ Year |
|---|---|---|---|---|
| | | | dextrose | |
| TY-51469 | Chymase Inhibitor | NASH/Ameliorating hepatic steatosis and fibrosis by attenuating the MC presence and expression of Col I, Col III, and α-SMA. | MCD diet-fed hamsters | (34)/2010 |
| TY-51469 | Chymase Inhibitor | NASH/Ameliorating hepatic steatosis and fibrosis by attenuating the expression of TGF-β, angiotensin II, and MMP-9. | HFC diet-fed rats | (33)/2017 |
| APC 366 | Tryptase Inhibitor | PSC/Reducing hepatic fibrosis, collagen content, and expression of PAR-2 and α-SMA. | BDL rats + APC 366 | (48)/2014 |
| UDCA | Natural bile acid | PSC/Ameliorating biliary damage, fibrosis and inflammation by reducing MC activation. | Human PSC *Mdr2*$^{-/-}$ mice | (39)/2018 |
| Zingerone | Bioactive ingredient extracted from ginger root | ALD/Ameliorating hepatoxicity by decreasing the MC density and expression of NFκB, COX-2, TNF-α, and IL-6. | Male albino Wistar rats post orally supplemented 30% ethanol for 60 days | (29)/2016 |

* COX-2 = cyclooxygenase-2; CYC = cyclophosphamide (common chemotherapy agent); EMT = epithelial mesenchymal transition; HFC = high fat and high cholesterol; MCD = methionine-and choline-deficient; RAMH = (*R*)-(α)-(−)-methylhistamine dihydrobromide; ROS = reactive oxygen species; UDCA = ursodeoxycholate.

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