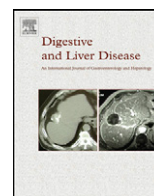




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Review article

A review of mast cells and liver disease: What have we learned?

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ABSTRACT

Background: Mast cells are recognized as diverse and highly complicated cells. Aside from their notorious role in allergic inflammatory reactions, mast cells are being implicated in numerous disease processes from heart disease to cancer. Mast cells have been implicated in liver pathogenesis including hepatitis and host allograft rejection after liver transplantation.

Aims: The aim of this review is to discuss the traditional function of mast cells, their location and anatomy with regards to hepatic vasculature and the role of mast cells in hepatic diseases including liver regeneration and rejection. Finally, we will touch on the role of mast cells in liver cancer. In conclusion, we hope that the reader comes away with a better understanding of the diverse and potential role(s) that mast cells may play in liver pathologies.

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1. Mast cell biology and activation

The history of the mast cell (MC) goes back over 100 years ago when Paul Ehrlich first described them [1–3]. Thirty years after the discovery of these “fat, well-fed” cells, he was awarded a Nobel Prize for his discoveries [4]. Many decades later, research on mast cell biology has continued and these cells are becoming increasingly recognised as “cells without limits”, able to illicit positive or negative effects on tissue and organ function.

Mast cells are derived from pluripotent haematopoietic stem cells in the bone marrow that leave and circulate as immature cells only to mature once they reach their destination [5]. This is distinctly different from basophils that mature in the bone marrow before being released into circulation [6]. Once released, mast cells undergo a maturation process that involves numerous factors including the specific cytokine, stem cell factor (SCF) [1,5,7]. The SCF receptor, c-Kit, is abundantly expressed in mature mast cells and plays a critical role in the maturation, development and secretory action of mast cells [7,8].

As Ehrlich described, mast cells are recognisable by their large granules that, after reaction with aniline dyes, exhibit metachromatic staining [1,2,6]. These granules contain mediators (like histamine or serotonin) that lie in wait until a signal (e.g., an allergic reaction) is sent to the mast cell for their release. In their traditional role, mast cells are key players in immunoglobulin

E (IgE)-associated immune responses via aggregation of the high-affinity IgE receptor, FcεRI, that is expressed on mast cells as a heterotetrameric receptor with subunits that initiate specific signalling events [1,9]. Activation by FcεRI is both highly technical and complicated. Several recent reviews provide a more complete, detailed description of this process [1,7,9].

Both positive and negative effects are elicited by FcεRI including degranulation, gene transcription and eicosanoid production [9]. More recently, it has been noted that mast cells are not regulated solely by IgE-dependent mechanisms. New reports show that mast cells express other surface receptor binding sites such as Toll-like receptors (TLRs) [10], β2-integrins [11], intercellular adhesion molecule-1 (ICAM-1) [11,12], androgen receptors [13], purinergic P2X receptors (P2X1, P2X4 and P2X7) [14] and the serotonin receptor, 5-HT1A [15]. Further studies have shown that mast cells express vascular endothelial growth factors (VEGF A–D) and the receptors VEGFR1 and VEGFR2 [16,17], supporting the role of mast cells in angiogenic processes. It has also been demonstrated that certain lipophilic bile acids (like chenodeoxycholic acid) can play a role in activating mast cells and induce an increased release of histamine [18]. Downstream events investigated in activated mast cells include the activation of the small GTPases, Rho and Ras, via activation by SCF [19]. It has also been shown that mast cells express the receptor for corticotropin-releasing hormone [20] and this hormone induces VEGF release through a cAMP/protein kinase A/p38 mitogen activated protein kinase (MAPK)-dependent pathway [21].

Regardless of whether activation is via traditional IgE-mediated mechanisms or another novel receptor-mediated event, mast cells degranulate and secrete mediators into the surrounding tissue. These mediators include biogenic amines like serotonin or

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histamine, various cytokines and chemokines and leukotrienes [22]. The release of these mediators appears to be dependent upon numerous factors including which protease the mast cell expresses and where the mast cell is located [1,2,6].

2. Mast cell location and heterogeneity

As stated, mast cells are derived from haematopoietic bone marrow stem cells where they present as undifferentiated CD34+, CD117+ progenitor cells [5,23]. The road to their destined tissue is complicated. No two mast cells are alike and this diversity is not limited to species, tissue type or organ [23]. All of these factors can influence the final role played by the mast cell.

Mast cells have been identified in multiple organs and tissues of the body, including lung [24,25], cardiac tissues [26,27], skin [28], gastrointestinal tract [29–31], kidney [32,33] and liver [34,35]. Within these multiple organ sites, there are two well-known human mast cell classes that are distinguished by enzymatic immunostaining for mast cell proteases, tryptase (MC^T) alone or tryptase and chymase together (MC^{TC}) [3,35]. MC^T are found mainly in mucosal sites such as nasal passages whereas MC^{TC} are located within connective tissues like skin [35]. These two populations of mast cells exhibit functional differences. MC^T produce cytokines like interleukin 5 (IL-5) and IL-6, whereas MC^{TC} release IL-4 [36]. Studies on human heart mast cells (HHMC), human lung mast cells (HLMC) and human skin mast cells (HSMC) demonstrate that there is also a functional difference following activation of human mast cells. Patella et al. found that stimulation of HSMC by Substance P induced a release of histamine that was not seen in either HHMC or HLMC, whereas protamine stimulation induced histamine release from HHMC and HSMC, but not HLMC [37].

Like human mast cells, mast cells of the rat are a heterogeneous population exhibiting a phenotype resembling either connective tissue- (CTMC) or mucosal-derived mast cells (MMC) [34,38]. These cells are characterised by staining for two mast cell markers, rat mast cell protease (RMCP) 1 and 2, to distinguish between CTMC (RMCP-1) and MMC (RMCP-2) [34,38]. Rat MMC have also been shown to predominantly contain histamine, whereas rat CTMC have an abundant amount of both histamine and serotonin [39]. These studies strengthened the notion that mast cells cannot be generalised with regard to species, location or function and this heterogeneous quality is likely the tool that mast cells use to adapt to and alter tissue function in response to disease.

3. Mast cell deficient animal models

Studies have reported that mice with naturally occurring mutations occurring at the *Dominant Spotting (W)* locus or the *Steel (Sl)* locus have a significant decrease in tissue mast cells [40–42]. These two strains are designated *Kit^W/Kit^{W-v}* and *Mgf^{Sl}/Mgf^{Sl-d}*, respectively [43–46]. This nomenclature stems from the identification of a point mutation causing exon skipping resulting in the failure of c-Kit to be expressed on the cell surface (*Kit^W*) [43,45], whereas *Kit^{W-v}* is a mutation in the tyrosine kinase domain reducing intrinsic kinase activity [43,46]. *Mgf^{Sl}* describes a deletion of the entire SCF coding sequence (Mgf; mast cell growth factor) [43,45], whereas *Mgf^{Sl-d}* is an intragenic insertion/deletion mutation resulting in a complete lack of SCF coding sequences [43,44]. The site of defect is different in these models; *Kit^W/Kit^{W-v}* mice harbor mutations in the stem cell/mast cell lineage whereas *Mgf^{Sl}/Mgf^{Sl-d}* are defective in the tissue microenvironment required for mast cell development [43]. Whilst these models may be useful, there are significant limitations as these mice are also prone to a multitude of phenotypic abnormalities that are unrelated to mast cell populations [43]. Perhaps a more important discovery was the mast cell “knock-in” mouse [40,41]. Transplantation of bone marrow into *Kit^W/Kit^{W-v}*

mice restores mast cell populations allowing demonstrating that loss of function may be related directly to mast cell deficiency [40,41]. A less popular model engineered to study the importance of mast cells is the mast cell-deficient *Ws/Ws* (white spotting) rat [46–48]. This model has a reduced level of c-Kit tyrosine receptor kinase activity due to a 12-base deletion in the tyrosine kinase domain of c-Kit [47,48]. *Ws/Ws* are deficient in both CTMC and MMC [47–50] and have been used in studies including cardiac function [51], renal fibrosis [52] and systemic anaphylaxis [53].

4. Hepatic mast cells and hepatic vasculature

Since the identification of hepatic mast cells, numerous studies have attempted to expand our knowledge of the location and function of these cells in the liver. Hepatic mast cells have been identified in many areas throughout the liver, however they tend to favour the portal area, including the portal triad and portal tracts [54]. In normal human liver, mast cells have been shown to accumulate, albeit in small numbers, in both portal tracts and within sinusoids of the hepatic lobules [54], suggesting that the appearance of mast cells is not solely dependent upon liver injury, inflammation or damage [55]. Not surprisingly, mast cells were found next to, or in the walls of, blood vessels adjacent to central veins [55]. Hepatic mast cells have also been shown to be mainly associated with connective tissues adjacent to hepatic arteries in both rat and human liver [54,56]. Koda et al. recently discovered a population of mast cells that accumulate near and around intrahepatic large bile ducts and intrahepatic peribiliary glands termed peribiliary mast cells [57]. These cells were found, in normal livers, to congregate under the biliary lining and throughout the ductal walls and periductal tissue [57]. A population of sinusoidal mast cells has also been described that may be derived from myeloid bone marrow cells [58]. Liver mast cells release numerous mediators including histamine, heparin, tryptase, transforming growth factor-beta 1 (TGF-β1), tumour necrosis factor alpha (TNF-α), interleukins, cytokines and basic fibroblast growth factor (bFGF) [58,59].

As this review will focus on hepatic mast cells and their role in liver pathophysiology and given the knowledge that hepatic mast cells are found near blood vessels in the rat liver, we give a brief description of the blood supply to and from the liver as well as microanatomy, including types of liver cells and their role in normal and diseased states. There is a constant flow of blood to the liver via two separate blood supplies: the portal vein and the hepatic artery [60,61]. Terminal branches of the portal vein and hepatic artery come together and the blood mixes entering liver sinusoids [60–62]. Surrounding the hepatic sinusoids are the parenchymal cells of the liver, hepatocytes. The major function of hepatocytes is the initiation and secretion of bile [63]. Hepatocytes are also in direct contact with the blood supply making them a very influential cell type with regard to liver pathology, including hepatocellular carcinoma (HCC) [63,64]. After secretion of bile by the hepatocytes, there is modification of bile before it is pumped out of the liver into the gallbladder. Cholangiocytes, cells lining the biliary tract (or bile duct cells), are responsible for the modification and release of bile from the liver [63] as well as for the transport and metabolism of bile acids [65]. Cholangiocytes are typically the target for a number of cholangiopathies including primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) [66,67].

The blood supply to the biliary tract and cholangiocytes is provided exclusively by the hepatic artery through a structure termed the peribiliary vascular plexus [68,69]. The peribiliary vascular plexus drains into the hepatic sinusoids via a route termed the peribiliary portal system [68,69]. This system has been found to be a source rich in vascular growth factors and other vasoactive substances [69]. Activation of peribiliary mast cells has been shown to induce an increased release of certain vasoactive substances (i.e.

nitric oxide, endothelin, and histamine) during chronic liver disease [57]. This increase in local vasoactive mediator concentration may be responsible for influencing the haemodynamics of the peribiliary vascular plexus and intrahepatic biliary tree.

The flow of blood through the liver is not a passive event and blood flow in and out of the liver directly influences the microanatomy of the liver and how it responds to stress and/or disease. It has been shown in rats with bile duct ligation-induced cholestasis that, after interruption of hepatic artery blood supply via hepatic artery ligation, there is a significant loss of the peribiliary vascular plexus and increased cholangiocyte apoptosis coupled with ductopenia [68]. Ischaemic bile duct injury may also occur during liver transplantation coupled with hepatic artery thrombosis [70]. This event can lead to the development of biliary casts, bile duct death or chronic disease that mimics PSC [70].

The parenchyma of the liver is a complicated structure with numerous cell types having different functions in normal liver function and disease response. These include: Kupffer cells [71,72], hepatic stellate cells [73–75], sinusoidal endothelial cells [71,76], vascular endothelial cells [77], fibroblasts [78] and pit cells [71,79]. As the majority of these cells play a definitive role in liver pathophysiology and presumably interact with hepatic mast cells, we have provided a table (Table 1) outlining these various liver cells and their location as well as their function in the liver. Their interactions with mast cells are discussed in the following sections.

5. Liver pathologies and hepatic mast cells

Hepatic mast cells consistently increase in number with progression of various liver diseases. Studies of cirrhosis, fibrosis, hepatitis and other cholangiopathies demonstrate that, histologically, hepatic mast cell counts generally increase as diseases progress [57,80–82], implicating a significant role for mast cells in hepatic disorders. During systemic mast cell activation syndrome patients with elevated cholesterol levels also display increased liver transaminases and bilirubin levels suggesting that mast cell activation plays a part in liver abnormalities of unknown etiology [83]. These studies, and others, warrant an evaluation of mast cells during liver disease and progression.

5.1. Primary biliary cirrhosis

PBC is classified as an autoimmune disease of the liver that is characterised by the progressive loss of small bile ducts (lined by small cholangiocytes) [66,67]. As these ducts are damaged, bile builds up in the liver over time and damages the tissue. These events can lead to fibrosis and cirrhosis [66,67]. Mast cell quantity has been shown to increase in PBC by staining for either toluidine blue [54] or immunohistochemical staining for tryptase and chymase [59,80], evidence that these cells are presumably MC^{TC}. Increased plasma histamine levels were also found in patients with both PBC and PSC, in contrast to healthy patients, raising the possibility of a role for *in vivo* mast cell activation and mediator release in these diseases [84]. An increase in mast cell number in PBC has also been linked to the secretion of fibrogenic mediators like bFGF, as mast cells positive for bFGF congregated in the fibrotic portal tracts and fibrous septa as well as the fibrotic biliary tree [59]. These cells also had an overexpression of histamine suggesting that the release of histamine and bFGF from mast cells may be responsible for the progression of fibrosis seen in PBC [59]. More recently, in a cholestatic rat model (bile duct ligation-induced), mast cells were found to accumulate in the portal triad and around the proliferating bile ducts [85]. After 14 days of bile duct ligation, mast cell quantity remained similar to sham-operated rats, but increased significantly after 4 days of recanalisation of the ligated common bile duct [85]

with high expression found around the remaining proliferating bile ducts. Coupled with the increase in mast cell quantity was the disappearance of bile ducts via apoptosis suggesting that mast cells contribute to the remodelling of the liver during the progression and resolution of PBC [85].

Studies investigating the mechanisms by which mast cells may be involved (either detrimentally or beneficially) and interact in diseases like PBC are limited. One could speculate that the involvement of mast cells in the resolution of PBC may be related to the increased or decreased release of histamine into the microenvironment caused by the interaction of bile acids [18]. To date, the bile acid ursodeoxycholic acid (UDCA) is the most common treatment choice to slow the progression of PBC [86]. UDCA-induced activation of mast cells produces undetectable amounts of histamine [18], suggesting that this bile acid has a protective effect in regards to PBC progression by inhibiting or attenuating the release of inflammatory mediators like histamine.

5.2. Primary sclerosing cholangitis

Another autoimmune disorder of the liver is PSC. This disease also affects the bile ducts (cholangiocytes) of the liver by increasing inflammation and causing scarring of cholangiocytes [66,67]. Bile flow is impeded leading to cirrhosis and eventual liver failure. PSC is highly associated with inflammatory bowel disease, particularly ulcerative colitis [87] as well as cholangiocarcinoma, cancer of the biliary tree [88]. Similar to PBC, hepatic mast cell expression and quantity have been shown to increase in patients with PSC compared to healthy controls. Increased mast cell infiltration (detected by anti-human mast cell tryptase) has been noted in bile ducts in patients with early stage PSC with a diffuse staining in the fibrous septa in the late stage of PSC [89]. A further study was performed to detect the expression of SCF in damaged bile ducts as well as mast cell expression in relation to portal fibrosis in liver sections from PSC patients. The authors found that SCF was expressed in the epithelia of destroyed bile ducts in patients with PSC and that c-Kit-positive mast cells accumulated and increased in the portal tract of PSC patients [90].

Because PSC is closely associated with ulcerative colitis (up to 70% of patients have both diseases concurrently) it stands to reason that mast cells and their mediators play a role in these autoimmune, inflammatory diseases. The infiltration of mast cells seen in patients with PSC [89] has been likened to that seen in ulcerative colitis [91] and other inflammatory bowel diseases like Crohn's disease, where there is a significant increase in IL-6-positive mast cells [91,92]. Mast cell mediators like histamine, mast cell proteases, heparin, cytokines and platelet activating factor have also been shown to play both helpful and harmful roles in various inflammatory bowel diseases [91]. This information may offer new insights for the treatment options for PSC sufferers, as liver transplantation is currently the only definitive "cure" for PSC [87].

5.3. Hepatic fibrosis and hepatitis

Hepatic fibrosis is a complicated process involving collagen build-up, extracellular matrix turnover and eventual remodelling of the liver. This process encompasses the accumulation of interstitial or "scar" extracellular matrix after liver injury [93]. PBC and PSC can both develop into cirrhosis, the end-stage of progressive fibrosis. A characteristic marker of this end-stage fibrosis are rings of scar that accumulate around the nodules of hepatocytes [93]. Several cell types are implicated in fibrosis progression with the main focus being on the hepatic stellate cell [74]. Years of research have demonstrated that, when activated, hepatic stellate cells take on phenotypes similar to those of myofibroblasts and inflammatory cells and become both proliferative and fibrogenic [94]. In addition,

Table 1
Description of liver cell nomenclature, type, location and function.

Nomenclature and cell type	Location	Function in normal liver	Role in liver pathologies	Interaction with mast cells	References
Cholangiocytes (epithelial cells)	Line the bile ducts	Modification & secretion of bile; transport of bile acids	Cholangiopathies (PBC & PSC) & CCH	MC quantity around inflamed bile ducts	[51,53–55]
Hepatocytes (parenchymal cells)	Surround the hepatic sinusoids	Synthesis of cholesterol; initiates the formation & secretion of bile	Alcoholic cirrhosis, HCC	MC quantity $\uparrow$ as HCC $\uparrow$	
Kupffer cells (NPC, macrophages)	[51,52] Within the hepatic sinusoid	Removal of bacteria and old, unwanted cells	Hepatic toxicity and carcinogenesis	Recruitment of inflammatory mediators	[59,60]
Hepatic stellate cells (HSC) ^a (mesenchymal cells/pericytes)	The space of Disse (between the hepatocyte & sinusoid)	Storage of vitamin A; ECM remodelling; regulator of sinusoidal blood flow	Liver fibrosis; cirrhosis; non-cirrhotic portal hypertension	Recruitment of inflammatory mediators	[50,61,62]
Sinusoidal endothelial cells (SEC)	Make up the lining of the hepatic sinusoid	Filtration; antigen-presenting cells	Liver fibrosis; alcohol-induced cirrhosis	Contribute to the capillarisation of sinusoids; recruitment of inflammatory mediators	[59,63]
Pit cells	Sinusoidal lumen	Eliminate tumour cells	Carcinogenesis	Interaction unknown	[59,66]
Liver-specific NK cells					
Vascular endothelial cells	Line blood vessels	Support & protect vascular bed	Angiogenesis & liver development	Interaction unknown	[64]
Portal fibroblasts	Portal area	Maintenance of homeostatic state	Early biliary fibrosis	Interaction unknown	[65]

PBC=primary biliary cirrhosis; PSC=primary sclerosing cholangitis; CCH=cholangiocarcinoma; HCC=hepatocellular carcinoma; NPC=nonparenchymal cells; ECM=extracellular matrix; NK=natural killer; MC=mast cells.
^a HSC formerly known as Ito (or fat-storing) cells.

tion to hepatic stellate cells, sinusoidal endothelial cells may also lose their fenestrated structure after injury and begin to express pro-inflammatory molecules like ICAM-1, VEGF and other adhesion molecules [75]. Hepatic stellate cells also begin to express ICAM-1, chemokine receptors and TLRs [94]. These qualities, taken on by both hepatic stellate cells and sinusoidal endothelial cells, are very similar to those of mast cells.

During fibrosis and hepatic disease progression (i.e. hepatitis), hepatocytes maintain a close interaction with other resident cell types as well as inflammatory cells. These populations come together to induce “sinusoidal capillarisation” which describes the events that cause the sinusoids to resemble capillaries [95]. Capillarisation inhibits the normal processes of exchange between hepatocytes and plasma and has been found to be a condition that worsens liver function [95]. As hepatocytes undergo necrosis, inflammatory cells are recruited (including mast cells) and Kupffer cells are activated, causing an increase in local cytokine and growth factor release [96,97]. Hepatic stellate cells are the primary target of this event and thus are the most important contributing cell type in extracellular matrix deposition. As the basement membrane components increase, causing the formation of continuous basement membrane-like structures in Disse’s space, there is also a decrease in the amount of endothelial fenestrae [97–100]. A role for mast cells in this process has been investigated. Studies suggest that mast cells contribute to capillarisation by recruiting other liver matrix-producing cells, thus increasing the secretion of cytokines and other mediators during the progression of liver fibrosis [56].

As stated above, mast cells express inflammatory and angiogenic receptors and proteins suggesting that their role in hepatic fibrosis may be equally as important as other resident liver cells. To support this, it has been shown that fibrotic human livers and hepatic stellate cells express and produce SCF, an indication of mast cell activation [101]. Hepatic mast cells have been shown to increase in number in fibrotic tissue compared to normal liver tissue [54] and contribute to the progression of fibrosis via the release of profibrogenic mediators like histamine, tryptase, heparin and bFGF [59]. The link between bFGF and hepatic fibrosis progression has been well documented [102,103] and mast cell-induced release of bFGF may

contribute to extracellular matrix remodelling by interaction with hepatic stellate cells [59]. In PBC over half of the mast cell content of the liver was found in sinusoids (the residence hall for hepatic stellate cells) [54], implying an important relationship between these cells. Co-culture studies of hepatic stellate cells and mast cells demonstrate that hepatic stellate cells interact with mast cells via a mechanism that is blocked (~50%) by neutralizing antibodies to SCF [101]. In a CCl₄-induced fibrosis model, the authors found an increased number of mast cells in portal areas that gradually increased as the degree of fibrosis increased (from 4 to 12 weeks) [104]. They further showed that after treatment with an antioxidant, silymarin, there was decreased expression of portal mast cells that was coupled with activation of hepatic stellate cells and TGF- β ₁ [104]. A recent study in human liver found that there was a high correlation between the number of chymase- (that were also positive for toluidine blue) and angiotensin II-positive cells during the progression of fibrosis [105]. Angiotensin-converting enzyme (ACE) is a well-known angiotensin II-forming enzyme [106] and angiotensin II is thought to induce tissue fibrosis via expression of TGF- β ₁ [107]. However, chymase, like ACE, activates the conversion of angiotensin I to angiotensin II and also activates the precursor of TGF- β ₁. Both angiotensin II and TGF- β ₁ play a role in hepatic fibrosis progression [108,109]. This study demonstrated that angiotensin II formation was chymase-dependent rather than ACE-dependent, implicating a role for chymase-positive cells (i.e. mast cells) in hepatic fibrosis [105]. Taken together, these studies suggest that mast cells may play a critical role in many stages of fibrosis and disease progression.

5.4. Liver regeneration and host allograft rejection

It is commonly believed that the liver is the only organ that can regenerate itself after injury; however new evidence has shown that cardiomyocytes may also be able to perform this function in the heart [110]. Regeneration of the liver is accomplished by the combined effort of numerous cell types that proliferate to compensate for tissue loss. Both cholangiocytes and hepatocytes play a critical role in this process and are activated within hours

Table 2

Location and role of mast cells in liver pathologies.

Liver etiology	Mast cell location	Mast cell role in disease progression	References
Primary biliary cirrhosis (PBC)	Portal triad, proliferating and inflamed bile ducts, biliary tree	↑ release of inflammatory mediators (histamine) & pro-fibrogenic factors (bFGF)	[60,87]
Primary sclerosing cholangitis (PSC)	Damaged bile ducts, fibrous septa and portal tracts	↑ in the secretion of inflammatory mediators like histamine, heparin and cytokines	[91–94]
Hepatic fibrosis and hepatitis	Hepatic sinusoids, around hepatic stellate cells, portal areas and in fibrotic tissue	Contribute to “capillarisation” of sinusoids and increased release of inflammatory mediators	[55,57,60,97–99,107]
Liver transplantation and allograft rejection	Surrounding inflamed and damaged bile ducts	Increased release of inflammatory mediators	[39,56,60]
Liver carcinogenesis	Around damaged cholangiocytes and tumour stromal area (CCH); surrounding destroyed hepatocytes and hepatic sinusoids (HCC)	Both inhibitory and stimulatory effects induced by mast cell mediators via numerous signalling pathways	[114–119]

bFGF = basic fibroblast growth factor; CCH = cholangiocarcinoma; HCC = hepatocellular carcinoma; IL-6 = interleukin 6.

after injury to repair the liver. Other resident liver cells are also implicated in liver regeneration and limited studies now suggest that resident hepatic mast cells and migratory mast cells may affect liver regeneration and, more importantly, rejection [38,55]. In the study by O’Keeffe et al., increased mast cell hyperplasia was found in human patients with chronic rejection, but not in acute states [55]. Because chronic rejection is a condition associated with severe bile duct damage likened to that seen in PBC and PSC, this association with hepatic mast cells and rejection seems logical. As seen before [59], hepatic mast cells were found around inflamed and damaged bile ducts in patients with chronic rejection and although present in healthy, post-transplantation subjects, mast cell quantity did not increase [55].

Populations of mast cells have also been investigated in liver regeneration after injury. In the rat liver model of partial hepatectomy, where 70% of the liver is removed, it was demonstrated that hepatic mast cell (expressing RMCP-1, an indication of connective tissue mast cell type) quantity decreased per bile ductule at day 3 post-partial hepatectomy, but returned to normal levels after this time point [38]. The authors found that the majority (between 75 and 99%) of recuperated hepatic mast cells (seen after day 3) expressed both RMCP-1 and RMCP-2, suggesting that a migratory population of mast cells appears in the regenerating liver to compensate for the possible loss of resident hepatic mast cells [38]. Thus, it appears from these studies that mast cells are present during liver regeneration. Activation due to an inflammatory response, like host allograft rejection, may cause hepatic mast cells to release unwanted mediators into the environment adding a detrimental effect during regeneration. Although mast cells in other organs have been shown to express angiogenic receptors like VEGFR2 and VEGF3, supporting their role in angiogenesis and remodelling [16,17], there appears to be no information regarding hepatic mast cells and their ability to behave as an ally during liver regeneration. Instead, these few studies have shown that whilst resident hepatic mast cells (as well as migratory mast cells) are present in the regenerating liver after injury, their role is not a supportive one. Understanding how to “deactivate” these cells may shed light on potential new therapies useful for improving regeneration and preventing rejection.

5.5. Liver carcinogenesis

The main immune cell types involved in tumour-associated inflammation include macrophages, dendritic cells, lymphocytes, neutrophils, eosinophils and mast cells [111]. The role of mast cells in carcinogenesis has been studied in numerous types of tumours with contrasting findings. In a study of invasive ductal breast cancer, the authors demonstrated that mast cells engulf and

phagocytose cancer cells, suggesting a protective role for mast cells [112]. However, another study involving human primary breast cancer showed that mast cells play a supportive role in the angiogenic process increasing tumour growth [113]. The role of mast cells in liver carcinogenesis has been investigated, but remains slightly elusive. In HCC, a cancer of hepatocytes, it has been found that both mast cell and Kupffer cell quantity decreased with disease progression that was also coupled with decreased cyclooxygenase-2 (Cox-2) expression [114], suggesting that a decrease in inflammatory cells may aid in inhibition of growth. The mechanism by which this event might occur was not investigated, but does suggest that mast cells (along with other inflammatory cells) may have an inhibitory role in hepatocellular tumour differentiation and proliferation. In contrast, another study involving HCC showed that mast cells played a role in angiogenesis of the tumour microenvironment and increased as the disease progressed throughout the four stages [114]. In human tissue from both HCC and intrahepatic cholangiocarcinoma (ICC), a biliary tract cancer, there was an increase in mast cell quantity compared to normal livers suggesting a role for mast cells in both of these liver cancers [115].

In ICC, mast cells were found mainly in the tumour stromal area, whereas in HCC, mast cells were mostly sinusoidal [115]. Whilst mast cell density and location have conflicting impacts on liver carcinogenesis, there might be beneficial information to be gained from the investigation of mast cell mediators. A study was performed using two different HCC cell lines, HuH-6 and HA22T/VGH [116], which have unique mutations and derivations. The authors investigated the effects of histamine and other mediators spontaneously released by mast cells on HCC growth. Using mast cell releasate obtained from the medium of cultured peritoneal mast cells, they found that in HuH-6 cells, granule remnants and histamine both decreased the growth of this cell line via down regulation of β -catenin, Cox-2 and survivin expression coupled with increased cellular apoptosis. In contrast, in HA22T/VGH cells the release of histamine and granule remnants increased cell proliferation [116]. Further studies were performed demonstrating that blocking certain histamine receptors (H1 and H2) reversed the histamine-induced action in these cells [116]. The H2 histamine receptor antagonist, cimetidine, was shown to decrease HCC growth via epidermal growth factor (EGF) signalling and decrease migratory events in an HCC cell line [117]. With respect to cholangiocarcinoma (CCH), data from Alpini and Francis has shown that histamine stimulation alone has no effect on CCH growth, but activation or inhibition of certain histamine receptors can impact CCH growth by either increasing or decreasing tumour progression [118]. Chronic *in vivo* treatment with histamine in nude mice implanted with CCH cells increased tumour growth [118], whereas long-term treatment with an H3 agonist decreased

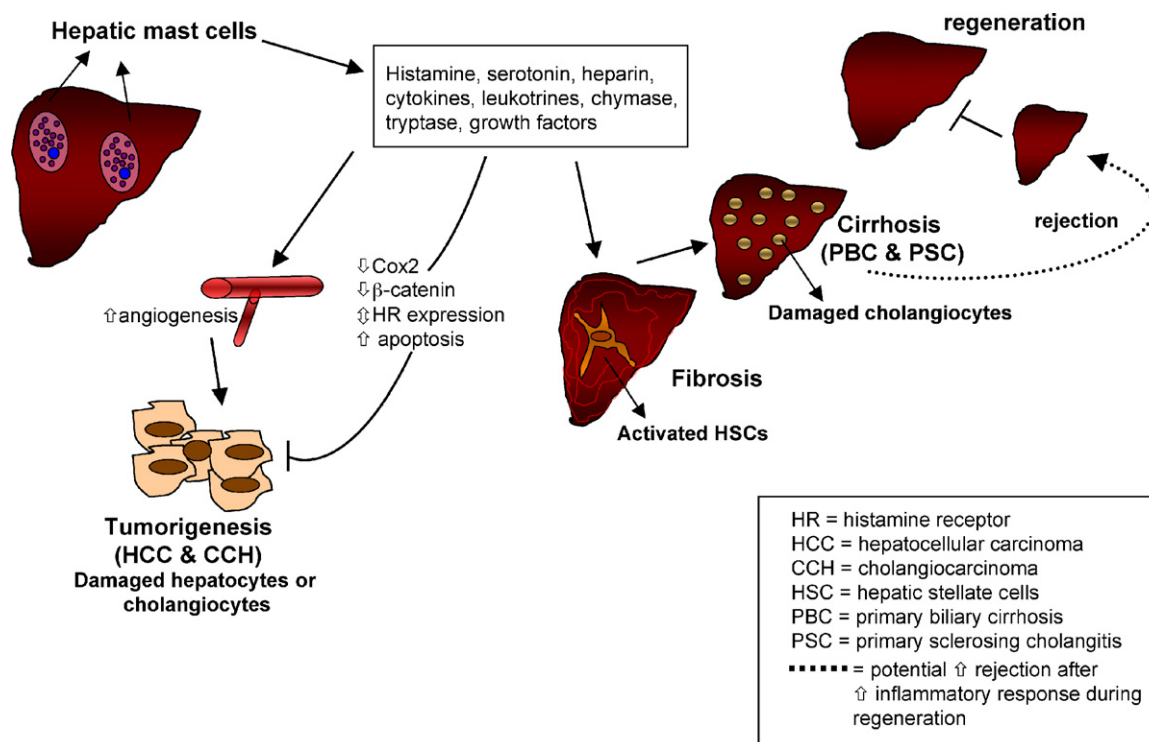


Fig. 1. A graphic depiction of mast cell localisation in the liver and the associated mast cell mediators and effects on liver pathologies.

tumour promotion [119]. Whilst the role of mast cells and mast cell mediators has yet to be unraveled fully in these devastating cancers, there is promise that these cells and, more importantly, their contents may prove to be useful therapeutic targets in the future (Table 2).

6. Concluding remarks and future perspectives

Research involving mast cell biology and function has exponentially exploded during the last decade. Acceptance of mast cell involvement in disease pathologies besides allergic reactions is becoming more prevalent. No longer considered a passive cell, mast cells are shedding new light on the way that we think about disease progression, whether it is cardiac dysfunction or cirrhosis of the liver. From recent works mentioned in this review, it appears that mast cells do not always play a helpful role in liver pathogenesis (Fig. 1). However, whilst behaving in a detrimental fashion in the majority of studies performed, mast cells are not the sole contributor to these diseases. It cannot be ignored that mast cell-deficient rats (*Ws/Ws*) still develop fibrosis suggesting that mast cells may not be the only cells stimulating fibrosis but may work in association with other resident liver cells to promote disease [120]. The findings from these studies have provided helpful information whilst generating further unanswered questions that add to our confusion regarding these cells and their role in healthy processes. If they are only present to aide in disease advancement, then why are they present at all? What is their role in normal, healthy processes of the liver? Questions like these and others remain to be answered and it is completion of these quests that will hopefully provide the insight necessary to find new treatments for patients suffering from liver disease.

Conflict of interest statement

None declared.

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