



REVIEW ARTICLE

ADAM and ADAMTS Proteases in Hepatic Disorders

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Abstract

Proteolysis is an irreversible post-translational modification that regulates protein function and signal transduction. This includes remodelling of the extracellular matrix, release of membrane-bound cytokines and receptor ectodomains, as well as the initiation of intracellular signalling cues. Members of the adamalysin protease subfamily, in particular the ADAM (a disintegrin and metalloprotease) and ADAMTS (the ADAM containing thrombospondin motif) families, are involved in these processes. This review presents an overview of how ADAM and ADAMTS proteins are involved in liver physiology and pathophysiology.

Keywords: ADAM; ADAMTS; metzincin superfamily; thrombotic thrombocytopenia purpura; von Willebrand Factor

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Introduction

The liver harbours different cell types, including hepatocytes, cholangiocytes, resident macrophages called Kupffer cells (KCs), sinusoidal endothelial cells (SECs) and hepatic stellate cells (HSCs). Hepatocytes, the liver parenchymal cells, make up the vast majority of cells and fulfil multiple vital body functions such as protein synthesis and storage; detoxification; synthesis of cholesterol, phospholipids and bile salts; and secretion of bile. Bile is then stored in the gallbladder and drained through bile ducts formed by cholangiocytes to aid in the digestion and absorption of dietary fats and fat-soluble vitamins in the duodenum. The liver sinusoids are lined with KCs and SECs, while HSCs represent perisinusoidal cells found in the space of Disse, an area between liver SECs and hepatocytes. In homeostatic conditions, HSCs store fat and fat-soluble vitamins in the liver, in particular vitamin A (retinol, retinoic acid).

Upon acute liver damage, hepatocytes restore the lost liver mass by proliferation and hypertrophy (1). However, under chronic toxic, viral or carcinogenic insult, the proliferation

of hepatocytes is inhibited, and they often become senescent. Under these circumstances, hepatic progenitor cells (HPCs) are activated and observed to proliferate in a variety of chronic liver diseases, including alcoholic liver disease, non-alcoholic fatty liver disease, steatohepatitis and in the iron overload disorder, haemochromatosis. HPCs are small, stem-cell-like cells with unclear origin and have the capacity to differentiate into hepatocytes or cholangiocytes, depending on the underlying injury stimulus (2). Damage signals from cellular compartments lead to the transdifferentiation of HSCs to proliferative and fibrogenic myofibroblasts. These “activated” HSCs respond by depositing collagen, resulting in the formation of scar tissue, which may progress to liver cirrhosis in severe cases. Numerous studies have reported a close temporal and spatial organisation of KCs, HPCs and HSCs, which display an intimate interplay and orchestrate liver regeneration versus disease progression through cytokine and chemokine cross-talk (2–6). These complex signalling networks require precise regulations not only at the cellular level but also at the molecular level. Members of the metzincin

protease family have been shown to be involved in different aspects of chronic liver disease and tumour formation.

The Metzincin Superfamily

The superfamily of zinc proteases or metzincins is characterised by the presence of a protease domain containing an invariant HEXxHxxGxxH zinc-binding motif (7, 8). It is subdivided into four subfamilies: matrixins, adamalysins, astacins and bacterial serralsins. The SVMPs (snake venom metalloproteinases), the ADAMS (a disintegrin and metalloproteinases) and ADAMTs (ADAMs containing thrombospondin motifs) form the adamalysin subfamily (9). The catalytic domains of metzincins share a similar overall structure with the catalytic cleft positioned between an N-terminal subdomain (NSD) and a C-terminal subdomain (CSD) (8). The NSD is anchored by a five-stranded β sheet, followed by a central α helix which contains the HEXxH motif supplying two of the histidines involved in Zn^{2+} -coordination and the glutamate residue that participates in catalysis (Figure 1). C-terminal to the α -helix, a conserved methionine turn is packed against the zinc-binding site (8, 10). Both ADAM and ADAMTS protein structures are thought to exist as “open” or “closed” structures representing another layer of regulation. Currently, this has been shown for the members ADAM17 and ADAMTS4 and 5, respectively (11, 12). In the case of the closed ADAMTS4 conformation, movement of the S2' loop

towards the catalytic centre precludes substrate binding and leads to the release of an additional Ca^{2+} ion (11).

The ADAM Family

In mammals, ADAMs are expressed in a wide range of tissues. Given their numerous substrates, they have diverse functions in development, physiology and pathology (9). The human genome encodes for 22 functional ADAM proteins, of which 10 are considered proteolytically inactive (13). ADAMs without protease activity are thought to facilitate protein folding and protein–protein interactions.

The domain structure of ADAM proteases comprises an N-terminal inhibitory pro-domain, a catalytic metalloprotease domain, a disintegrin domain with a cysteine-rich region, an epidermal growth factor (EGF)-like domain, a transmembrane domain and a cytoplasmic tail (Figure 1a). ADAM proteases are synthesised as catalytically inactive transmembrane proteins of about 750 amino-acid length into the endoplasmic reticulum. The N-terminal pro-domain is thought to have chaperone and inhibitory functions as it interferes with the Zn^{2+} -ion in the catalytic centre. Within the Golgi apparatus, ADAMs undergo further complex glycosylation and are subjected to proteolytic cleavage by the Furin protease, thereby liberating the N-terminal pro-domain. However, for ADAM8 and ADAM28, autocatalytic pro-domain cleavage was demonstrated (14, 15). Recently it has been shown that the recombinant pro-domain of ADAM17 can be harnessed as a specific inhibitor *in vitro* and *in vivo* (16).

The catalytic domain is conserved among the ADAM family members and contains the zinc-binding motif (HEX-GHxxGxxHD) (Figure 1 a and b) (17). The adjacent disintegrin and cysteine-rich domains are suggested to be involved in autoregulation as they fold back and limit access to the catalytic site in the unliganded state (10, 18). The disintegrin domain may also participate in cell–cell adhesion processes and has been shown for ADAM10 to play a role in substrate recognition in concert with the cysteine-rich domain (9, 19). The cytoplasmic tails of transmembrane ADAMs contain phosphorylation sites for several kinases, denoting a role in regulation of protease activity and downstream signalling (9). ADAM-mediated shedding can either be constitutive or activated by G-protein-coupled receptors; Ser/Thr-kinase activity, including protein kinase C (PKC), ERK and p38; and increased intracellular Ca^{2+} (9, 20, 21).

ADAM proteases play a major role in proteolytic ectodomain cleavage, a process termed “shedding” (Figure 2). Functionally diverse proteins have been shown to be subjected to ectodomain shedding with differential physiological consequences. Shedding of receptor molecules such as transforming growth factor (TGF) β receptor abrogates its signalling. Importantly, the soluble ectodomain has the capacity to work as a scavenger and binds the corresponding cytokine (22). The receptor for interleukin 6 (IL-6) is an exception because the IL-6/soluble IL-6R (sIL-6R) complex

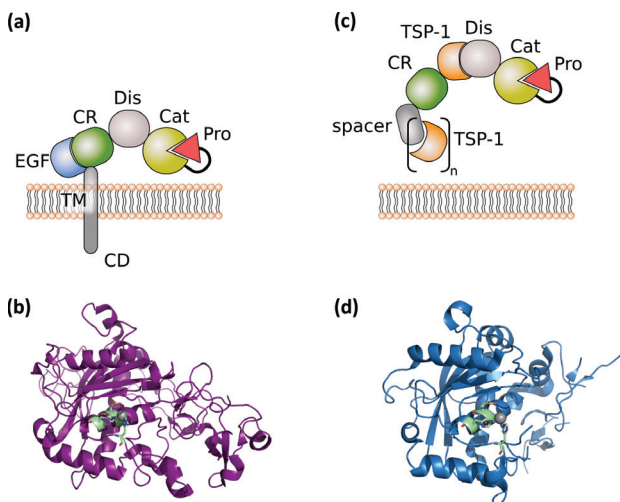


Figure 1. General structure of ADAM and ADAMTS proteases. (a) General domain structure of ADAM proteases. (b) X-ray structure (6BE6.pdb) of ADAM10, including catalytic, disintegrin and cysteine-rich domains. The catalytic zinc is highlighted in grey and the zinc-binding motif in pale green. (c) General domain structure of ADAMTS proteases. (d) X-ray structure of ADAMTS1 (2V4B.pdb), including catalytic and disintegrin domain. The catalytic zinc is highlighted in grey and the zinc-binding motif in pale green.

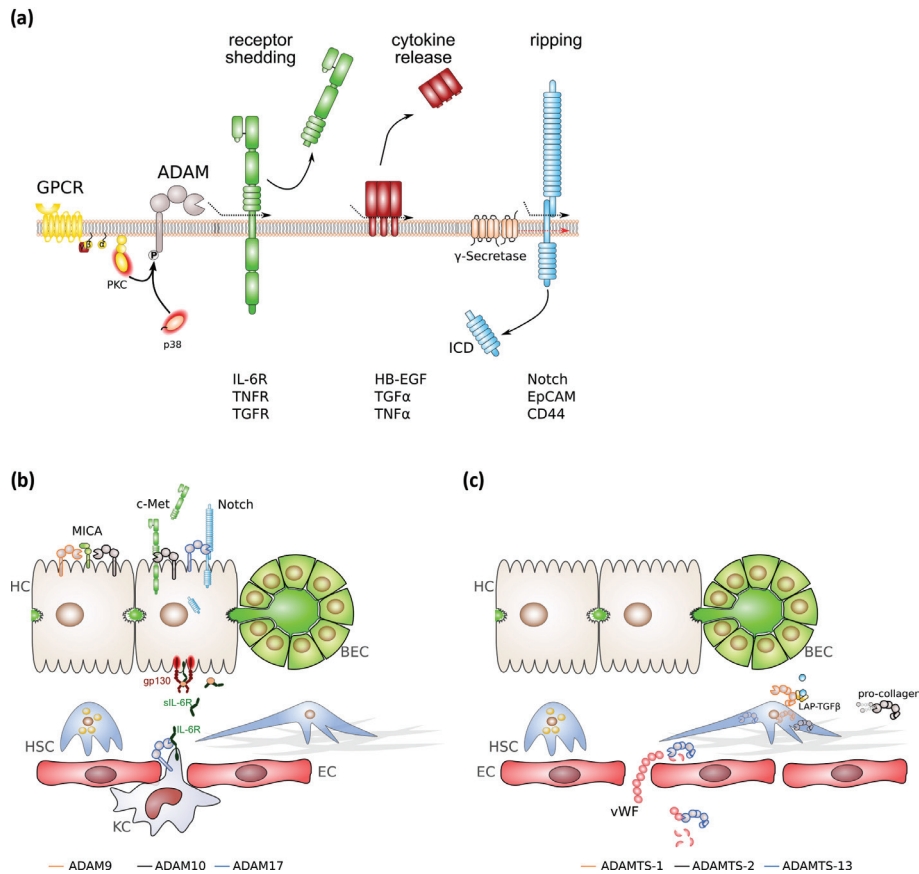


Figure 2. Signal activities of ADAM and ADAMTS proteinases in the liver. (a) ADAM protease activity, ADAM17 in particular, can be regulated by protein phosphorylation. Active ADAM proteases are involved in the release of receptor ectodomains, thereby blunting receptor signalling in most of the cases, the release of membrane-bound cytokines and the initiation of intracellular signalling by regulated intramembrane proteolysis (RIP). (b) Selected proteolytic events of the indicated ADAM proteinases in different cell types of the liver. (c) Selected proteolytic and non-proteolytic events of the indicated ADAMTS proteinases in different hepatic cell types. BEC, biliary epithelial cells; EC, endothelial cell; gp130, glycoprotein 130; HSC, hepatic stellate cells; HC, hepatocyte; ICD, intracellular domain; IL-6R, interleukin 6 receptor; KC, Kupffer cell; LAP-TGF β , latency-associated peptide-transforming growth factor β ; MICA, MHC class I polypeptide-related sequence A; sIL-6R, soluble IL-6R; vWF – von Willebrand factor.

induces signalling via gp130 on target cells. This process has been termed “IL-6 trans-signalling.” (23, 24)

Membrane-bound cytokines and growth factors are also liberated from the membrane by ectodomain shedding (Figure 2). The most prominent example is the family of EGF ligands, comprising heparin-binding EGF (HB-EGF), TGF α , epiregulin and neuregulin, which are shed by ADAM17, and known to play key roles in tumour growth (25). The most prominent substrate of ADAM10 is the Notch receptor, which has been implicated in developmental processes, stem cell growth and differentiation (26). In addition, there is evidence that ADAMs are able to degrade extracellular matrix (ECM) components: ADAM10 cleaves type IV collagen; ADAM13 and ADAM9 degrade fibronectin (27).

ADAM9

ADAM9 processes a wide range of substrate molecules, including amyloid precursor protein (APP), collagen XVII and HB-EGF, and has been linked to cell proliferation, adhesion and migration (28).

Transcriptomic analysis of fibrotic liver tissue revealed that expression of ADAM9 correlated with the activation of HSCs, as assessed by quantitation of alpha-smooth muscle actin (α SMA), independent of the underlying disease aetiology. Northern blots analysis demonstrated that ADAM9 expression was localised to HSCs (Figure 2b) and that expression of ADAM9 significantly increased in activated compared to quiescent HSCs (Table 1) (29). These data suggest that ADAM9 is important for ECM remodelling during hepatic fibrosis progression and may

Table 1. Overview of known ADAM and ADAMTS proteinase activities in the liver and their association with hepatic diseases.

The ADAM family				
Family member	Associated disease	Substrate(s)	Cell type	Reference
ADAM9	Fibrotic liver disease	ECM components	Activated HSCs	(29, 30)
	HCC	MIC-A	Hepatocytes	(32)
	Liver metastasis	Laminin, binding to integrin $\alpha_6\beta_4$, $\alpha_2\beta_1$	Activated HSCs	(33)
ADAM10	Liver homeostasis	pot. indep. of catalytic activity	Hepatocytes, HPCs	(37)
	Liver fibrosis	CX3CL1	Activated HSCs	(38, 39)
	Murine cholestasis	c-Met	Hepatocytes	(41)
	HCC	MIC-A	Hepatocytes	(39)
	Liver metastasis	L1CAM	Tumour cells	(43)
		c-Met	HSCs	(44, 45)
ADAM12	Cirrhotic liver	pot. ECM remodelling	Activated HSCs	(47)
	HCC	pot. ECM remodelling	Activated HSCs	(48)
ADAM17	Liver damage	CX3CL1	Activated HSCs	(38)
	HCC	Notch	Activated HSCs	(53)
		pot. EGFR ligands	Hepatocytes	(50, 51)
		pot. IL-6R	Kupffer cells	(56)
The ADAMTS family				
Family member	Associated disease	Substrate(s)	Cell type	Reference
ADAMTS1	Fibrotic liver disease	Binding to LAP-TGF β	HSCs	(59)
ADAMTS2	Murine liver fibrosis	Pro-collagen	HSCs	(62)
ADAMTS13	SAH	vWF	endothelium	(71)
	ALI, ALF			(72)
	Fibrotic liver disease			(74–78)

ADAM, a disintegrin and metalloprotease; ADAMTS; the ADAMs containing thrombospondin motif; ECM, extracellular matrix; HCC, hepatocellular carcinoma; MIC-A, major histocompatibility class I-related chain A; HSC, hepatic stellate cell; HPC, hepatic progenitor cell; L1CAM, L1 cell adhesion molecule; IL-6R, interleukin 6 receptor; EGFR, epidermal growth factor receptor; LAP-TGF β , latency-associated peptide-transforming growth factor β ; SAH, severe alcoholic hepatitis; ALI, acute liver injury; ALF, acute liver failure; vWF, von Willebrand Factor.

thereby contribute to the establishment of an environment conducive to hepatocellular carcinoma (HCC). Indeed, various studies have reported ADAM9 overexpression in HCC (30–32), and high expression levels of ADAM9 have been linked to tumour aggressiveness (30). Beside its effect on HSCs, ADAM9 was found to promote ectodomain shedding of major histocompatibility class I-related chain A (Figure 2b). Consequently, HCC cells with siRNA-mediated suppression of ADAM9 were more susceptible to natural killer cell-mediated cytotoxicity. Interestingly,

sorafenib-treatment reduced ADAM9 expression, and enhanced major histocompatibility class I-related chain A protein levels and anti-tumour response of natural killer cells (32). An alternatively spliced ADAM9 variant (ADAM9-S), secreted by activated HSCs and stromal liver myofibroblasts, has been shown to promote tumour metastasis to the liver (Table 1). Through its disintegrin domain, ADAM9-S directly binds to $\alpha_6\beta_4$ and $\alpha_2\beta_1$ integrins on colon carcinoma cells and is able to cleave laminin, thereby promoting tumour cell invasion (33).

ADAM10

In most tissues investigated, ADAM10 is the major protease that initiates Notch signalling. In the liver, biliary tree formation (34, 35) and differentiation of HPCs into cholangiocytes (4) are dependent on Notch signalling (Figure 2a). This is also reflected by the finding that patients with Alagille syndrome who suffer from biliary paucity and subsequent cholestasis display mutations in the Notch ligand Jagged-1 (36). We recently investigated the role of ADAM10 under physiological conditions by generating liver-specific ADAM10-deficient mice. Surprisingly, we observed that ADAM10 was dispensable for Notch2 activation *in vitro* in an HPC line, and for biliary tree formation *in vivo* (37), further suggesting that during development, Notch signalling in hepatoblasts does not rely on ADAM10. However, we observed that hepatic loss of ADAM10 leads to the down-regulation of biliary transporters, resulting in spontaneous hepatocyte necrosis (Table 1). Furthermore, loss of ADAM10 resulted in an accumulation of HPCs that might at least, in part, be the consequence of enhanced signalling through the hepatocyte growth factor receptor c-Met (37).

Overexpression of ADAM10 has been reported in chronic liver disease associated with liver fibrosis (38) and in HCC (39, 40) (Table 1). In HSCs, ADAM10 is involved in the release of the soluble chemokine, CX3CL1, thereby facilitating recruitment of inflammatory cells (38). Furthermore, c-Met ectodomain release by ADAM10 from HSCs correlated with hepatic injury in the murine 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) cholestasis model (41). Soluble c-Met has previously been identified as a decoy receptor and might therefore restrict the proliferative response after liver damage (42). SiRNA-mediated suppression of ADAM10 in the human liver cancer cell line, HepG2, decreased cellular proliferation, the ability to grow in semi-solid medium and its tumorigenic potential in xenografts (39, 40). ADAM10 might also be involved in anti-tumour immunity as it has been demonstrated that major histocompatibility class I-related chain A is a substrate for ADAM10 in HepG2 cells (Figure 2b, Table 1), where its surface localisation was enhanced in the absence of ADAM10 (39). Inhibition of ADAM10 might therefore represent an attractive avenue to increase the anti-tumour immune response.

In addition to its role in fibrotic liver disease and HCC, ADAM10 seems to have a role in the establishment of liver metastasis. The neuronal cell adhesion receptor L1-CAM, which is expressed on colon cancer cells, is proteolytically processed by ADAM10, generating a L1-CAM intracellular domain (ICD). An increased L1-CAM ICD formation through enhanced ADAM10 activity resulted in enhanced liver metastasis (Table 1) (43). Furthermore, tumour cell-secreted tissue inhibitor of metalloproteinase (TIMP) 1 was shown to inhibit ADAM10-mediated c-Met processing (Figure 2b) and thereby c-Met signalling in liver metastasis. Suppression of TIMP-1 lowered the metastatic potential of

tumour cells, while circulating TIMP-1 levels correlated with an increased risk for liver metastasis formation (44, 45). Very recently, the same group demonstrated that TIMP-1 secreted from pancreatic premalignant lesions activates HSCs in the liver via binding to the tetraspanin CD63, thereby preparing a hepatic premetastatic niche (46).

ADAM12

Due to alternative splicing, ADAM12 can be expressed as a long (ADAM12L) or as a short (ADAM12S) form. The latter is soluble due to its lack of transmembrane and cytoplasmic domains (47). Both ADAM12 isoforms were found to be up-regulated upon TGF β stimulation in activated HSCs but not in hepatocytes. Furthermore, expression of ADAM12 was increased in cirrhotic livers and liver cancer and localised to cells of the tumour stroma, presumably HSCs (Table 1) (30, 48). ADAM12 was also detectable in circulation and correlated with overall survival (48). Interestingly, in another study, overall patient survival and ADAM12 expression correlated with the expression of the Tetraspanin Tspan8 (49), which is often up-regulated in HCC (50). Down-regulation of Tspan8 in HCC lines reduced ADAM12L expression and tumourigenicity in a mouse xenograft model (49). However, more in-depth analysis is needed to identify definite substrates of ADAM12 and decipher its potential role in tumour stroma dynamics and ECM remodelling.

ADAM17

Reports using *in vitro* experiments demonstrated that ADAM17 mediates the release of EGFR ligands in hepatocytes upon exposure to tumour necrosis factor (TNF) α (51) or TGF β (52), suggesting that ADAM17 on hepatocytes might be involved in liver regeneration (Table 1). Furthermore, release of CX3CL1 from HSCs was also shown to be mediated by ADAM17, correlating with enhanced inflammatory cell infiltration upon liver damage (38). However, a clear *in vivo* evidence for a role of ADAM17 in liver regeneration is still lacking.

Overexpression of ADAM17 has been reported in human HCC and diethylnitrosamine (DEN)-induced murine HCC model (53). In tumour cells, ADAM17 is essential for Notch signalling (Figure 2b), resulting in the maintenance of a cancer stem cell phenotype (54) with enhanced migratory abilities through activation of integrin β 1 (53, 55). Interestingly, it was shown that formation of hepatic metastases is enhanced by the release of soluble Notch ligands from endothelial cells, which in turn activates Notch on colorectal cancer cells. *In vitro* experiments using small molecule inhibitors suggested that proteolytic release of Notch ligands might be mediated by ADAM17 (56). However, the question whether ADAM17 is also important for Notch signalling under physiological conditions, in particular in the liver, remains unanswered.

ADAM17 is a major protease for the membrane-bound IL-6R, leading to the release of soluble IL-6R (Figure 2b).

In contrast to many other soluble receptors, sIL-6R is able to bind IL-6 and induce signalling through the signal-transducing subunit, gp130 (24). This process is called IL-6 trans-signalling. We recently demonstrated that IL-6 trans-signalling is critically involved in HCC tumour initiation and tumour angiogenesis (56). Taken together, liver tumourigenesis appears to depend on ADAM17 proteolysis. However, more detailed *in vivo* analyses are needed to clarify if ADAM17 can be harnessed as a potential target in HCC therapy.

The ADAMTS Family

Unlike ADAM family proteins, members of the ADAMTS protease family contain neither transmembrane nor cytoplasmic domains and are synthesised as extracellular proteins. Instead, all family members contain at least one thrombospondin (TSP) type-1 repeat (TSR) that comprises approximately 50 amino-acids and is similar to the type-1 repeats in TSP-1 and TSP-2 (57). The human ADAMTS family contains 19 members that can be clustered into eight different evolutionary clades, depending on their domain organisation and known functions. The aggrecanase and proteoglycanase clades contain members (ADAMTS1, 4, 5, 8, 15, 9, 20) that are involved in the processing of hyaluronan-binding chondroitin sulphate proteoglycan extracellular proteins, including versican and aggrecan. Another clade encloses pro-collagen N-propeptidases (ADAMTS2, 3, 14) that confer maturation of triple helical collagen fibrils (57).

The overall domain organisation of ADAMTS proteins can be structured into a metalloproteinase domain and an ancillary domain (Figure 1c). The metalloproteinase domain consists of a pro-domain, the catalytic metalloprotease domain and a disintegrin-like module. The catalytic domain of ADAMTS members contain a HExxHxBG(N/S)BxHD consensus motif, with B as a large non-polar residue and three histidines that coordinate the Zn²⁺ metal ion (Figure 1c and d) (8, 57, 58). To date, no ADAMTS protein has been identified to associate with integrins. In contrast, crystal structure data suggest that the disintegrin-like domain is an integral part of the catalytic core of ADAMTS proteins (11, 59). The composition of the ancillary domain varies between the different ADAMTS members; however, all have at least one TSR motif in common (Figure 1c). ADAMTS proteins display multiple functions during tissue development and homeostasis, and their dysregulation has been associated with various diseases. During development, members of the aggrecanase and proteoglycanase clade process the ECM component versican ensuring enough structural support on the one hand, while allowing dynamic remodelling on the other hand (57).

ADAMTS1 and ADAMTS2

The aggrecanase/proteoglycanase group member ADAMTS1 is involved in the processing of ECM components (60).

Expression of ADAMTS1 positively correlated with progression of hepatic fibrosis to cirrhosis. ADAMTS1 was localised to HSCs. Interestingly, ADAMTS1 expression is elevated in activated HSCs and is associated with latency-associated peptide (LAP)-TGF β , resulting in TGF β activation (Figure 2c, Table 1). Consequently, a KTRF sequence-containing peptide derived from ADAMTS1 was sufficient to reduce collagen deposition in the murine carbon tetrachloride cirrhosis model (61). ADAMTS2 cleaves the pro-peptides of type I and type II pro-collagens prior to fibril formation. Its prominent role in collagen maturation has been further emphasised by the discovery of ADAMTS2 mutations in Ehlers-Danlos syndrome type VIIC (62), which is characterised by extreme skin fragility and joint laxity, among other symptoms. The impact of ADAMTS2 on liver biology has been previously shown in experimental liver disease using carbon tetrachloride (Table 1). While the initial parenchymal damage was similar, HSC activation and collagen deposition were significantly reduced in ADAMTS2^{-/-} mice compared to appropriate controls (Figure 2c, Table 1) (63).

ADAMTS13

ADAMTS13 is the sole member of the von Willebrand Factor (vWF)-cleaving protease (vWFPC) clade. The vWF is a pro-thrombogenic glycoprotein, produced constitutively as ultra-large, multimeric protein by endothelial cells (64). After endothelial injury, vWF binds on one side to sub-endothelial collagen and on the other side to platelet glycoproteins, gpIb/IX/V, leading to platelet tethering at the injury site. Under fluid shear stress, vWF gets proteolytically processed. Thus, ADAMTS13 generates smaller, non-functional vWF fragments (Figure 2c) (65). Loss of ADAMTS13 catalytic activity, either by recessive mutations (66) or by inhibitory auto-antibodies (67), leads to the accumulation of ultra-large vWF and the formation of platelet-rich microthrombi in the micro-vasculature causing a life-threatening rare disorder called thrombotic thrombocytopenia purpura (68, 69). Low levels of ADAMTS13 are also found in patients with sepsis-induced disseminated intravascular coagulation and are associated with increased mortality (70).

ADAMTS13 expression is predominantly found in the liver but also to some extent in skeletal muscles, placenta and the lung (71). It is therefore not surprising that patients with severe alcoholic hepatitis (SAH) display reduced plasma activity of ADAMTS13 and reduced vWF proteolysis (Table 1). In SAH patients with multiorgan failure, ADAMTS13 levels were markedly reduced, resulting in increased platelet clumping and subsequent multiorgan failure (72). Similarly, patients with acute liver injury and acute liver failure displayed an imbalance between vWF and ADAMTS13 (Table 1), and low ADAMTS13 levels were associated with higher grades of encephalopathy and lower survival rates potentially linked to microthrombus formation (73).

A more detailed analysis localised ADAMTS13 expression to α SMA-positive HSCs in a patient with hepatitis C-related chronic hepatitis, suggesting a role in fibrotic liver disease (74). Accordingly, ADAMTS13 expression levels were increased not only in activated rat HSCs *in vitro* but also in HSCs *in vivo* in carbon tetrachloride-injured rats (75). Patients with liver cirrhosis displayed increasing levels of vWF with increasing severity according to Child-Pugh classification, while collagen-binding activity of vWF was decreased in these patients, partially correlating with increased ADAMTS13 activity (76). However, two other studies detected decreased ADAMTS13 levels in cirrhotic livers, linking ADAMTS13 levels to an increased platelet thrombi formation (77, 78). A very recent study demonstrated that while ADAMTS13 did not correlate with the Child-Pugh score in cirrhotic patients, low levels of ADAMTS13 were associated with portal vein thrombosis (79). In contrast, in patients with non-alcoholic fatty liver disease, the increased risk in thrombosis was not linked to aberrant ADAMTS13 levels or hyperactive haemostasis (80).

Conclusion

As summarised above, selected members of ADAM and ADAMTS proteinase families display altered expression in different liver pathologies, and a mechanistical role in the pathology has been shown for some members. However, we are still far from fully understanding the complex nature of ADAM and ADAMTS proteinases and their impact on liver physiology and pathology. Substrate analysis on a proteomics level will help to unveil how ADAM and ADAMTS proteinases regulate liver biology.

Further studies will also show if ADAM and ADAMTS expression and activity can be harnessed for diagnostic or therapeutic purposes. ADAMTS13 activity is already routinely assessed for the diagnosis of thrombotic thrombocytopenia purpura. Extended studies will determine the utility and benefit of ADAMTS13 activity measurement in the clinical management of acute and chronic liver disease. Albeit overexpression of some ADAM proteases has been shown in liver pathologies, more extended human studies, and experimental *in vivo* studies using targeted deletion, in particular hepatic cell types of the liver, are warranted to better understand the role of ADAM proteases in liver pathologies and targeted diagnosis and therapeutics.

There have been numerous research activities in the past to develop small molecule inhibitors for ADAM17 to treat chronic inflammatory diseases such as rheumatoid arthritis. However, the first chemical entities displayed musculoskeletal and hepatic toxicities and therefore did not proceed beyond phase I/II clinical trials (81). A recently developed dual-specific ADAM10/17 inhibitor, INCB7839 (25), is a promising candidate that is currently in a clinical trial phase I/II study (NCT02142451) for the treatment of diffuse large B-cell

non-hodgkin lymphoma. In addition, very recently, the recombinant pro-domain of ADAM17 has been developed as a specific ADAM17 inhibitor *in vitro* and *in vivo* and might represent a novel strategy to specifically inhibit ADAM and ADAMTS proteinases (16). In summary, the world of ADAM and ADAMTS proteinases remains a rich but largely underexplored sea of therapeutic opportunities.

Conflict of interest

The authors report no conflict of interest with respect to research, authorship and/or publication of this article.

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