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GAS6/TAM Axis as Therapeutic Target in Liver Diseases

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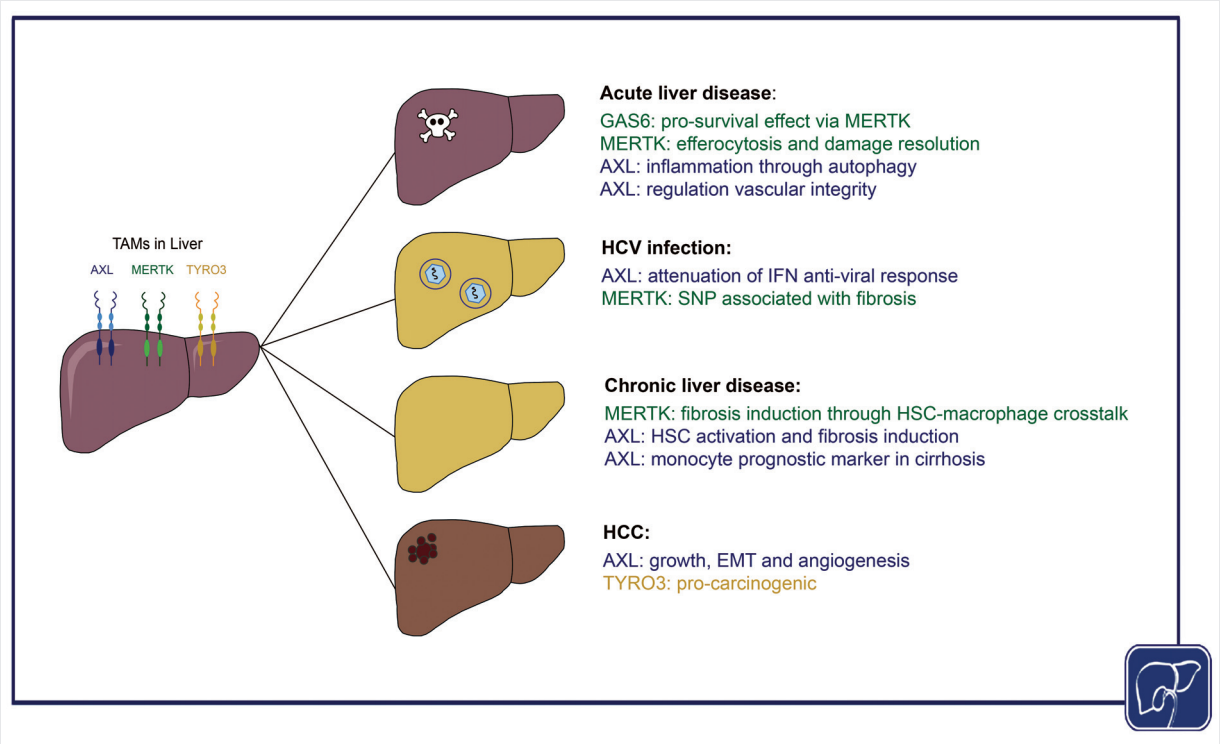
Graphical Abstract



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Abstract

TAM (TYRO3, AXL, and MERTK) protein tyrosine kinase membrane receptors and their vitamin K-dependent ligands GAS6 and protein S (PROS) are well-known players in tumor biology and autoimmune diseases. In contrast, TAM regulation of fibrogenesis and the inflammation mechanisms underlying metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and, ultimately, liver cancer has recently been revealed. GAS6 and PROS binding to phosphatidylserine exposed in outer membranes of apoptotic cells links TAMs, particularly MERTK, with hepatocellular damage. In addition, AXL and MERTK regulate the development of liver fibrosis and inflammation in chronic liver diseases. Acute hepatic injury is also mediated by the TAM system, as recent data regarding acetaminophen toxicity and acute-on-chronic liver failure have uncovered. Soluble TAM-related proteins, mainly released from activated macrophages and hepatic stellate cells after hepatic deterioration, are proposed as early serum markers for disease progression. In conclusion, the TAM system is becoming an interesting pharmacological target in liver pathology and a focus of future biomedical research in this field.

Keywords

- phagocytosis
- fibrosis
- inflammation
- cytokine regulation
- biomarkers

Lay Summary

The TAM protein family (TYRO3, AXL, and MERTK), activated by the GAS6 and PROS ligands, is known to play a role in cancer and autoimmune diseases. Recent research has found that TAMs are involved in liver diseases like metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and liver cancer. The binding of the TAM ligands GAS6 and PROS to apoptotic cells connects them, principally through MERTK, to liver cell damage, and to liver fibrosis and regulation of inflammation by AXL and MERTK. The TAM system is also involved in acute hepatic injury and soluble TAM-related proteins, particularly soluble AXL, may serve as an early serum marker for disease progression. The TAM system is becoming an interesting topic for future biomedical research in liver pathology and a potential pharmacological target for its treatment.

TAM receptors are key regulators of inflammation and tissue response to damage. Its signaling has been broadly studied in the immune system and cancer, while therapies based on TAM intervention are currently being tested in numerous diseases ranging from melanoma to COVID-19. Besides this well-known TAM activity, recent publications support an emerging and important role in liver homeostasis. TAM receptors, expressed on different liver cells, regulate inflammation, damage resolution, fibrosis, and carcinogenesis. However, the complexity of liver diseases, involving multiple cell types, intra- and intercellular signaling, communication with other organs, and functional diversification of TAMs and their ligands, have hampered the study of their biological relevance. Despite these complexities, recent publications have helped fill some of these gaps, and TAM biology in the liver is becoming clearer and gaining biomedical interest. Hence, this review aims to integrate current knowledge on TAM function in liver homeostasis and disease (►**Table 1**), emphasizing the latest results in the field.

TAM Receptors and Ligands

TAM receptors (TYRO3, AXL, and MERTK) are a subfamily of receptor tyrosine kinases (RTKs) widely expressed among tissues, particularly in cells of the immune system (macrophages, monocytes, dendritic cells, and natural killer cells), platelets, endothelial cells, osteoclasts, Sertoli cells, and the retinal pigment epithelium, among others.[1,2] Protein S (PROS) and growth arrest-specific 6 (GAS6) protein, identified as ligands of TAM receptors,[3,4] contain a C-terminal sex hormone-binding globulin (SHBG) domain that interacts with the membrane receptor, four EGF-type domains in tandem and an N-terminal Gla-domain, characteristic of vitamin K-dependent proteins (VKDPs). This Gla-domain allows their binding to phosphatidylserine (PtdSer) exposed on the surface of apoptotic cells and activated platelets. TAM ligands show different affinities for each receptor: while GAS6 binds to all TAM receptors, with higher affinity for AXL, PROS prefers MERTK and TYRO3.[5–7] In fact, activation of AXL by PROS has recently been observed in particular settings,[8,9] although probably with a much lower affinity than GAS6. Remarkably, binding to PtdSer not only intensifies intracellular signaling but also changes ligand affinities[5] (►**Fig. 1**). TAM heterodimerization[10,11] and interaction with other receptors such as VEGFR, EGFR, or MET[12–14] have been observed and may have important implications in cancer and drug resistance. However, the consequences of these interactions in other pathologies are still under scrutiny and may provide interesting data in the future.

Proteolytic cleavage of MERTK and AXL by the metalloproteinases ADAM10 and ADAM17 has been shown to

Table 1 Clinical implications of GAS6-TAM signaling in human liver diseases

Disease	Protein	Clinical implications	Ref.
Regeneration	GAS6 and AXL	Contribution of GAS6-AXL signaling in liver regeneration	Ortmayr et al[71]
ALF	MERTK	Increase of resolution-like MERTK$^+$ monocytes and macrophages in blood and liver of ALF patient	Triantafyllou et al[81]
HCV	AXL	Upregulation of AXL following HCV infection in cell cultures and patients	Read et al[86]
	MERTK	Association of *MERTK* rs4374383 G variant with fibrosis progression of HCV patients	Patin et al[87] Rüeger et al[88] Jiménez-Sousa et al[89]
MASLD/MASH	MERTK	Association of *MERTK* rs4374383 G variant with increased prevalence of fibrosis and severe steatosis in MASLD	Petta et al[106] Musso et al[107]
	AXL	Increment of soluble AXL in serum during development of MASLD	Tutusaus et al[104]
Cirrhosis	GAS6 and AXL	Increment of soluble AXL and GAS6 in cirrhotic patients' serum	Bárcena et al[93] Bellan et al[150]
	AXL	Expansion of AXL$^+$ circulating monocytes correlating with infection susceptibility and development of acute decompensation	Brenig et al[99]
Acute on chronic liver failure	MERTK	Increase of MERTK$^+$ monocytes in blood and liver of acute on chronic liver failure patients	Bernsmeier et al[98]
HCC	AXL	Correlation between AXL expression and advanced stages, microvascular invasion and lower overall survival	Liu et al[127] Pinato et al[128] Reichl et al[129]
	AXL	sAXL increment in HCC patients is associated with poor prognosis	Reichl et al[147]
	TYRO3	Significant overexpression of *TYRO3* in tumor samples	Duan et al[140]

Abbreviations: ALF, acute liver failure; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease.

efficiently inactivate TAM receptor signaling.[15,16] In fact, pathological activation of these sheddases may be a possible source of increased soluble MERTK and AXL, which is frequently observed in liver diseases, as will be discussed later.

TAM Receptor Functions

Although each TAM receptor knockout is viable and lacks major defects, deletion of all receptors in mice (TAM KO), apparently normal at birth, results in blindness and splenomegaly after a few months, developing a lupus-like autoimmune syndrome.[17,18] This phenotype revealed the most significant functions of TAM: immune response regulation and clearance of dead cells. Since then, several publications have highlighted the implication of TAM in multiple processes, from coagulation to natural killer cells (NK) differentiation as well as its implication in human pathologies, particularly in cancer.

TAM receptors participate in the control of inflammation and adaptive immunity. TAM activation leads to upregulation of suppressor of cytokine signaling proteins, SOCS1 and SOCS3, which inhibits NF-κB, MAPK, and TRAF3/6 inflammatory signaling downstream Toll-like receptors (TLR) and cytokine receptors, resulting in a reduced production of cytokines.[12] Indeed, upon TLR stimulation, TAM-deficient antigen presenting cells (APCs) produce higher levels of cytokines.[12,19] In addition, AXL also upregulates TWIST, a transcriptional regulator of NF-κB, dampening IFN response and reducing TNF production.[20] The inflammatory activity of NK cells through E3 ubiquitin ligase Cbl-b is also TAM-controlled.[21,22]

During cell death, the PtdSer binding to TAM ligands enables the bridging of apoptotic bodies with phagocytic cells promoting debris removal, a process termed "efferocytosis."[23–25] The regulation of this process by TAMs is crucial for tissue homeostasis. For instance, TAM KO males become infertile at 3 weeks of age[17] due to the accumulation of apoptotic spermatogenic cells. Sertoli cells, responsible of debris removal in testis, require TAM expression for proper testicular development.[26,27] Furthermore, MERTK and TYRO3 deficiency in mice causes blindness and degeneration of photoreceptors due to the impaired engulfment of their distal membranes.[28,29] In APCs, professional phagocytic cells, TAM deficiency reduces clearance of apoptotic bodies but does not affect phagocytosis of pathogens, indicative of an efferocytosis-specific TAM function.[10,30] Interestingly, efferocytosis is associated with immunosuppression[31] which could be promoted to some extent by activation of TAMs. After treatment with apoptotic cells, MERTK signaling inhibits NF-κB pathway reducing the secretion of pro-inflammatory cytokines,[32,33] inducing an immunosuppressive profile,[34] and stimulating a repair response via RhoA and the production of HGF.[35] Therefore, these concurrent functions may explain the implication of TAM in the development of autoimmune diseases.[36,37] Of note, high autoantibody levels, skin lesions, joint swelling, and other features of

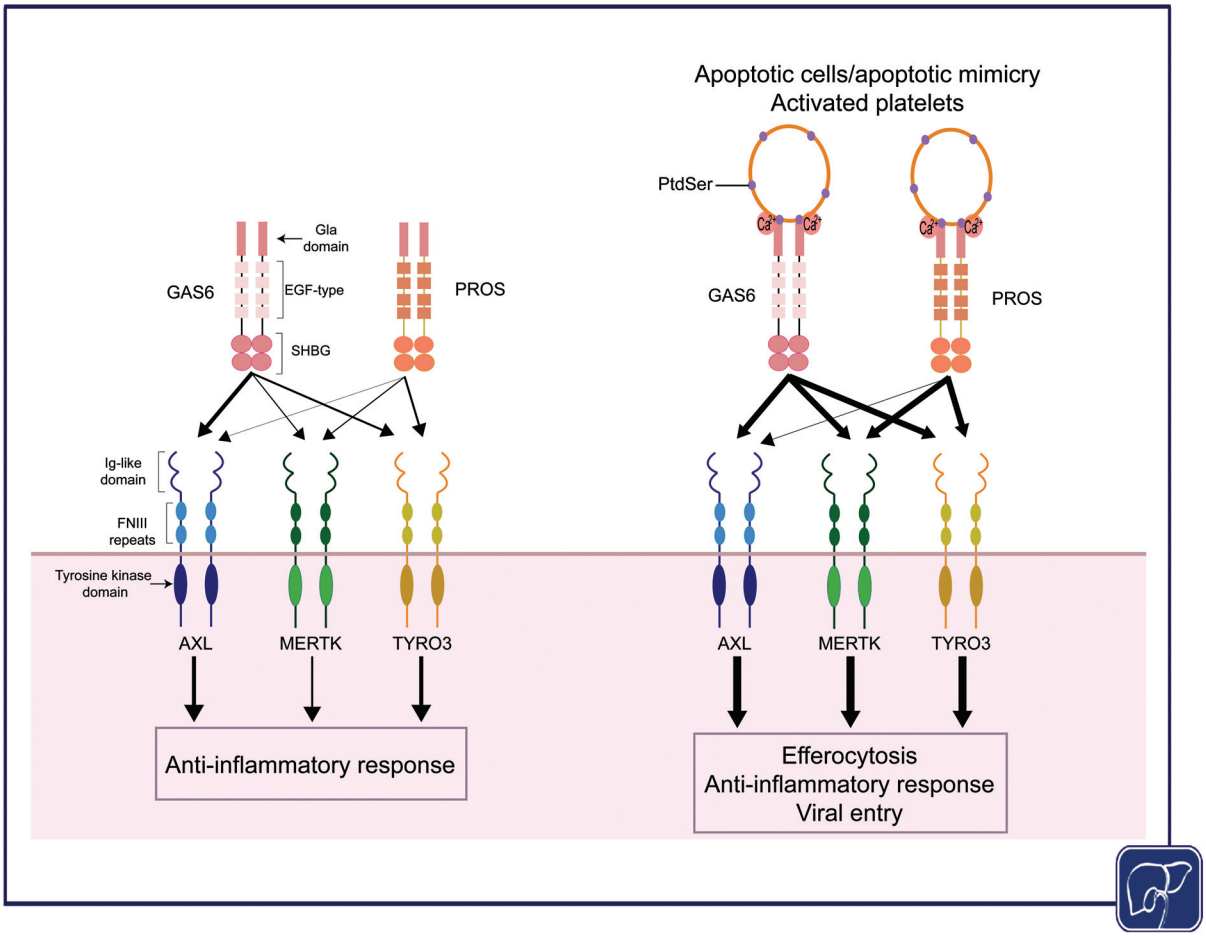

Fig. 1 TAM receptors and their ligands. TYRO3, AXL, and MERTK (TAM) are single-pass transmembrane receptors containing an intracellular tyrosine kinase domain, two fibronectin-type III (FNIII) repeats and two immunoglobulin-like (Ig-like) domains. Protein S (PROS) and growth arrest-specific 6 (GAS6) interact with TAM through their C-terminal sex hormone-binding globulin (SHBG) domain inducing dimerization and intracellular signal transduction. Gla domain allows calcium-dependent binding of TAM ligands to phosphatidylserine (PtdSer), exposed in apoptotic cells, activated platelets and certain enveloped viruses (apoptotic mimicry). Therefore, the Gla domain plays a key role in TAM function, bridging PtdSer exposed cells to enhance efferocytosis or viral entry. The PtdSer–Gla interaction intensifies receptor signaling and changes receptor affinity. Thickness of arrows represents the relative intensity of activation.

autoimmune disease were described in TAM KOs.[18,38] Interestingly, GAS6-TAM system is required for the recognition and phagocytosis of amyloid β (Aβ) plaques by microglia. However, TAM contributes to Alzheimer's disease as the engulfed Aβ material is not processed in lysosome, leading to aggregation of insoluble Aβ fibrils, cell death, and therefore the formation of dense-core plaques.[39]

Another aspect in which the involvement of TAM is being intensively studied is viral entry.[40] PtdSer exposition at the viral envelope activates the phagocytic machinery of target cells, inducing virus internalization.[41] TAM receptor role in this viral "apoptotic mimicry" was first described in vaccinia virus and later observed in several human pathogens such as Ebola, dengue, West Nile virus, and Zika.[42–44] Regarding SARS-CoV-2, AXL does not directly mediate viral entry as proposed[45,46]; however, it enables virus binding to target cell through PtdSer.[47] Indeed, AXL inhibition reduces SARS-CoV-2 infection in cell lines and phase II clinical trial has confirmed the efficacy of the AXL inhibitor bemcentinib for COVID-19 treatment.[48] Of note, GAS6 and TAM evaluation in SARS-CoV-2-positive patients at emergency admission revealed higher plasma GAS6 and AXL levels paralleling COVID-19 severity, and proved AXL inhibition as a cellular tool to control immune response.[49]

Overexpression of TAM receptors has been reported in many cancer types.[50] TAM induction of pro-survival and proliferative signal transducers has been investigated, but more recently, TAM immunosuppressive actions in the tumor microenvironment have gained attention.[51–53] TAM promotes proliferation in cancer cells through RAS and MAPK pathways and survival through upregulation of BCL-2 and downregulation of BAD via AKT signaling.[54–56] Moreover, AXL induces proliferation of vascular smooth muscle cells and endothelial cells leading to the formation of new vessels[57,58] and thus promoting angiogenesis in tumors.[57,59,60] TAM expression in tumor-associated immune cells contributes to an immunosuppressive microenvironment and tumor progression.[61] While clinical trials targeting TAMs were initially designed aiming at cancer cell suppression, recent trials pursue the TAM modulatory effect on both

innate and adaptive immunity in the oncogenic milieu to improve drug efficacy by combination with checkpoint inhibitors.[62,63]

TAMs in the Liver

AXL and MERTK are mainly expressed by Kupffer cells (KC) in mouse and human healthy liver.[64,65] To a lesser extent, these two receptors are also found on endothelial cells, while in quiescent hepatic stellate cells (HSC) AXL expression is reported in mouse.[65,66] In recent single-cell RNA-seq studies, human hepatocytes show a moderate expression of MERTK and scarce AXL expression.[67] Regarding TAM ligands, PROS is produced and secreted by hepatocytes and endothelial cells, while low expression of GAS6 is observed in healthy liver, mostly in endothelial cells and macrophages.

The liver is repeatedly exposed to harmful insults leading to cell damage, death, and inflammation. In this regard, TAM receptors play an essential role in liver homeostasis and tissue repair. For instance, TAM KO mice show increased transaminases and autoantibodies levels in serum as well as immune cell infiltration in the liver already at 6 months of age.[68] Consistently, TAM deficiency induces progressive liver inflammation and damage resembling autoimmune hepatitis.[68] Recently, similar results have been described in aged *Axl*$^{-/-}$*Mertk*$^{-/-}$ mice. At 7 to 12 months of age, higher transaminases and cytokine levels were detected in these mice compared with WT but also an increase in cleaved caspase3. Besides liver damage, the enhanced staining of the scavenger receptor MARCO points out to an unsuccessful clearance of apoptotic cells despite macrophage infiltration and activation.[65]

Liver Regeneration

Early in 1994, upregulation of *Gas6* expression was described as an inflammatory response in a liver regeneration model.[69] At that time, GAS6 function was not clear, but 10 years later Couchie et al confirmed the increase of GAS6 and its role during liver regeneration.[70] After partial hepatectomy (PH), a widely used regeneration model, *Axl* and *Gas6* mRNA expression, was upregulated in liver progenitor cells (LPCs). Moreover, GAS6 treatment increased cell survival rather than proliferation in a LPC cell line.[70] In the same way, an increase in soluble AXL (sAXL) and GAS6 serum levels was observed after liver resection in cancer patients suggesting a strong contribution of GAS6-AXL signaling in liver regeneration.[71] Moreover, these changes were not observed in patients with high preoperative levels of sAXL and GAS6, which correlated with higher risk of liver dysfunction and worse clinical outcome.

MERTK has also been related to liver regeneration. Santamaria-Barria et al reported a modest delay in liver regeneration after MERTK pharmacological inhibition in the PH model.[72] The study described a subset of MERTK-expressing KC in which cytokine production is critical for the onset of liver regeneration. In contrast, this delay was not reproduced in *Mertk*$^{-/-}$ mice after PH, maybe indicating a certain degree of molecular compensation in the KO mice or off-target effects of the MERTK inhibitor used; so, further studies are needed to decipher MERTK's role in this model.

Acute Liver Diseases

Involvement of TAM in the initiation and resolution of acute liver injury has been discussed in several studies. In the hepatotoxic model induced by acute administration of CCl_4, GAS6 is upregulated and secreted by KC and HSC.[66] Using GAS6-deficient mice, defective wound healing was noticed after CCl_4 administration without differences in liver damage.[73] Moreover, attenuated inflammation and monocyte infiltration were detected and the chemoattractant potential of GAS6 was proved in vitro.[73] Actually, a previous publication demonstrated that GAS6 promoted leukocyte extravasation by enhancing the interactions between endothelial cells and leukocytes.[74] Nevertheless, *Gas6*$^{-/-}$ liver showed overexpression of AXL and consequent SOCS1 upregulation that might explain the limited inflammation and delayed repair observed in the CCl_4 acute model.[73] The major contribution of this work was the finding of AXL expression in HSC cells and its pro-survival effect, which plays an important role in chronic liver disease, as detailed below.

GAS6 pro-survival effect was also assessed in hepatic ischemia-reperfusion (I/R) injury.[75] In hepatocyte cultures, GAS6 treatment induces AKT phosphorylation and cell viability under hypoxic conditions. Accordingly, partial hepatic I/R was lethal in *Gas6*$^{-/-}$ mice (90% of death vs. 10% in WT mice at 12 hours) showing an increase in hepatocellular cell death, transaminase levels, and inflammatory cytokines. Phosphorylation of MERTK and AKT, but not AXL, was detected only in WT liver samples, suggesting an hepatoprotective role of GAS6-MERTK signaling during liver damage.[75] Recently, Wang et al corroborated the reduction of phosphorylated AXL in liver-transplanted patients and mice undergoing I/R.[76] Both studies showed that administration of recombinant GAS6 attenuated hepatic ischemia; however, Wang et al supported that AXL, via SOCS1 upregulation, protects against hepatic I/R injury. Of note, MERTK expression or activation was not assessed.

An additional role has been attributed to AXL in acute liver damage: the regulation of inflammation through autophagy. Recent literature establishes autophagy as a key regulator of inflammasomes through degradation of its components[77] and, as mentioned earlier, efferocytosis, which requires the machinery of autophagy,[78] prevents the inflammatory response in APCs via TAM.[79] Han et al reported the relation between AXL and autophagy via MAPK14 leading to inflammasome inhibition in macrophages.[80] In this line, KC from *Axl*$^{-/-}$ mice challenged with LPS showed reduced autophagy flux and increased caspase-1 cleavage and IL1β/IL18 production. Similarly, in models of hepatotoxicity, *Axl*$^{-/-}$ mice exhibited lower levels of autophagy markers in liver and higher IL1β and IL18 serum concentration, showing severe liver damage and inflammation compared with WT. Therefore, autophagy-mediated inhibition of inflammasome is a novel anti-inflammatory mechanism induced by AXL activation.

With respect to acute liver failure (ALF), an early increase of MERTK^{+} monocytes and macrophages has been detected in the blood and liver of ALF patients. These cells presented a resolution-like phenotype with high capacity of neutrophil clearance and reduced secretion of inflammatory mediators.[81] This expansion was also observed in the acetaminophen (APAP)-induced liver injury mouse model, where MERTK expression increased in resident KC (F4/80^{high} CD11b^{low}) rather than monocyte-derived macrophages (F4/80^{low} CD11b^{high}). Eight hours after APAP administration, *Mertk*$^{-/-}$ mice presented larger necrotic areas and higher infiltration and activation of neutrophils compared with WT mice.[81] These results indicate that MERTK^{+} KC promotes resolution of acute liver injury enhancing clearance of apoptotic cells and dampening inflammatory responses. On the contrary, no difference between WT and *Mertk*$^{-/-}$ was found in liver damage after 48 hours of APAP dosing by Zagórska et al, while *Axl*$^{-/-}$ exhibited severe hepatotoxicity.[65] Notably, ALT levels were higher in AXL-deficient mice who showed hemorrhagic livers with accumulation of apoptotic cells. However, no significant differences in inflammation were detected. This model clearly underscores the AXL effect on vascular integrity, endothelial proliferation, and angiogenesis. Interestingly, MMP12, expressed upon activation of the coagulation cascade in APAP model, was downregulated in *Axl*$^{-/-}$ mice.[65] MMP12 is associated with liver repair as its deficiency caused hemorrhages and aggravated APAP-induced injury.[82] Plasmin has also been related to the angiogenic potential of GAS6-AXL in renal cell carcinoma.[83] The unexpected findings in *Axl*$^{-/-}$ mice evidenced a possible cooperation of AXL signaling and the fibrinolytic system to preserve vascular integrity in liver disease that could be considered in future studies.

Two more liver injury models were tested in TAM null mice by Zagórska et al: the Jo2 model consisting in anti-FAS antibody administration and the D-galactosamine/LPS endotoxic shock model.[65] In contrast to APAP model, a major susceptibility to liver damage was observed in *Mertk*$^{-/-}$ rather than *Axl*$^{-/-}$ mice. In WT mice, non-lethal dose of Jo2 induced the phosphorylation of MERTK; consequently higher transaminase levels and a 15-fold increase in apoptotic cells were observed in *Mertk*$^{-/-}$ mice compared with WT and *Axl* $^{-/-}$ strains.[65] Similarly, treatment with LPS in D-galactosamine-sensitized mice induced severe liver damage in *Mertk*$^{-/-}$ mice and the accumulation of apoptotic bodies, demonstrating the important role of MERTK in efferocytosis and in the resolution of liver damage.[84] Again, these findings highlight the divergent function of AXL and MERTK in liver diseases.

Chronic Liver Diseases

Hepatitis C

Viral infection is characterized by a rapid immune response and strong production of type I interferon. However, a limited response has been observed in hepatitis C patients with high basal expression of interferon-stimulated genes (ISGs). Hepatitis C virus (HCV) infection promoted upregulation of AXL in cell cultures and patients, in a genotype-dependent manner and, according to Read et al, AXL may contribute to this attenuated response by downregulating IFN signaling.[85] Indeed, AXL overexpression downregulated ISGs in hepatoma cell lines.[86] These mechanisms could reflect the regulatory cycle described earlier in dendritic cells, in which AXL binding to IFNAR1 restricted IFN signaling.[12] Therefore, AXL expression in HCV-infected hepatocytes may reduce ISG expression and viral response, hampering clearance of the virus.

In 2012, a genome-wide association study (GWAS) identified in a large cohort of HCV-infected patients the SNP rs4374383, located in *MERTK* gene. The rs4374383 G allele was associated with fibrosis progression based on histological analysis of HCV patients.[87] Subsequently, a meta-analysis of different cohorts validated the effect of this variant in accelerating fibrosis.[88] In the same way, a recent longitudinal study assessed liver stiffness in 208 HCV non-cirrhotic patients during a median follow-up of 46.6 months and determined a higher risk of hepatic fibrosis progression in *MERTK* rs4374383 G carriers, associated with an increased MERTK expression, although the association with cirrhosis was not significant probably due to a limited sample size.[89] While no relationship was observed between *MERTK* rs4374383 and risk of liver fibrosis in an Eastern European cohort,[90] the association may be relevant and patients carrying this polymorphism, which is found in half of the population globally, may benefit from liver fibrosis screening.

Liver Fibrosis and Cirrhosis

Liver fibrosis is defined as a deregulation of extracellular matrix (ECM) production and degradation. As a result, the accumulation of ECM components increases liver stiffness, reducing its function. A key driver of fibrosis development is HSC activation, defined by changes in proliferation, contractility, fibrogenesis, and inflammatory signaling.[91] Multiple pathways have been related to HSC activation, including TAM, as we review below.

First evidence of GAS6/TAM influence in liver fibrosis was observed in GAS6-deficient mice, which exhibited protection from fibrosis in the chronic CCl_4 model due to defective macrophage recruitment. Of note, the authors noticed an overexpression of AXL in *Gas6*-deficient mice; the relevance of this overexpression remains unclear. Interestingly, transgenic expression of the other TAM ligand, PROS, exacerbated liver injury and fibrosis in the CCl_4 model.[92]

Concerning HSC, AXL is crucial for HSC transdifferentiation and fibrogenesis. GAS6-AXL signaling promoted HSC activation by inducing AKT and NF-κB pathways.[93] Moreover, during activation, HSC secreted GAS6 and upregulated AXL intensifying autocrine signaling. AXL requirement for full HSC activation was proved in vitro as AXL-deficient HSC showed lower levels of α-SMA and proteins related to ECM. Consequently, *Axl*$^{-/-}$ mice exhibit reduced collagen deposition after chronic CCl_4 administration.[65,93] Similar inhibition of HSC activation and in vivo fibrogenesis were obtained

using the selective small molecule inhibitor of AXL, bemcentinib (BGB324), positioning AXL as a therapeutic target.[93] By contrast, fibrosis development in *Mertk*$^{-/-}$ mice was comparable to WT despite an increase in apoptotic debris in the CCl_4 model.[65] Overall, these findings emphasize the crucial role of AXL signaling in hepatic fibrosis that could be applicable to fibrotic diseases in other organs.[94,95]

Liver fibrosis can progress to cirrhosis, deteriorating liver function. Common complications of cirrhosis are ascites, portal hypertension, variceal bleeding, bacterial infection, and hepatocellular carcinoma (HCC). Bacterial infection in cirrhotic patients is associated with short-term mortality and can result in acute decompensation (AD) or, if organ failure occurs, in acute-on-chronic liver failure (ACLF). Susceptibility to infection may be explained by enhanced intestinal permeability and bacterial translocation as well as defective response of monocytes.[96] Actually, TAM signaling seems to be relevant in gut–liver communication, as AXL expression is decreased on gut macrophages in cirrhotic patients.[64] Besides, GAS6 secretion by intestinal macrophages, reduced in aged mice, protect from bacterial invasion and subsequent translocation to the liver.[97]

Following this line, TAM expression in monocytes of cirrhotic patients has been studied. MERTK^{+} monocytes are found at higher proportion in ACLF patients' blood compared with stable cirrhotic and control patients.[98] Moreover, MERTK expression in circulating monocytes correlated with hepatic and extrahepatic disease severity and response to systemic infection. ACLF monocytes showed a poor pro-inflammatory profile and attenuated cytokines production after LPS challenge due to the constitutive activation of MERTK. Indeed, no increase of MERTK ligands was observed in plasma of ACFL compared with cirrhotic patients. MERTK^{+} monocytes were also more prone to undergo transendothelial migration than MERTK^{-} ACLF monocytes, and consequently a significant expansion of MERTK^{high} CD163^{high} macrophages with anti-inflammatory profile was observed in the liver of ACLF patients. With similar purpose, monocytes expressing AXL were analyzed, noticing an increase of AXL^{+} monocytes in parallel with cirrhosis progression.[99] Thus, expression of AXL in monocytes correlated with disease severity, infection susceptibility, development of AD, and prognosis. AXL^{+} monocytes exhibited lower cytokine production after LPS challenge and diminished T cell activation, but enhanced efferocytosis and preserved phagocytic properties. Indeed, AXL inhibition enhanced immune responses in cirrhotic monocytes without decreasing phagocytosis, becoming a potential therapy for recurrent infections in cirrhosis. Overall, even if different expression patterns of MERTK and AXL are found in monocytes of cirrhotic patients, both receptors compromise the immune response to bacterial infection.

Steatohepatitis

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the major cause of liver disease worldwide, consequence of the global epidemic of obesity and metabolic syndrome.[100] MASLD refers to liver steatosis not associated with alcohol consumption and is clearly related to hypernutrition and obesity. MASLD progression to MASH (metabolic dysfunction-associated steatohepatitis), characterized by hepatocellular ballooning, inflammation, and frequently liver fibrosis, has received much attention in the last decade. Recently, the interest in TAM signaling during MASLD/MASH transition is growing with increasing literature focused on this topic[101,102] (►**Fig. 2**).

To assess TAM implications in MASH, a diet-induced model was evaluated in TAM-deficient mice. The high-fat (60%) choline-deficient methionine-restricted (0.1%) diet induces steatosis, hepatocellular damage, inflammation, and extensive liver fibrosis in 2 months, reproducing MASH features without weight loss.[103] In this model, serum levels of GAS6, sAXL, and soluble MERTK (sMERTK) were increased, demonstrating an active TAM signaling.[104] Contrary to expectations, only a slight reduction in liver fibrosis was observed in *Axl*$^{-/-}$ compared with WT mice, although the number of inflammatory foci and cytokine expression were significantly lower. However, AXL inhibition by bemcentinib resulted in a significant reduction of collagen deposition and inflammation in MASH mice. Thus, pharmacological inhibition of AXL seems to be more efficient in reducing fibrosis progression. A plausible explanation for these controversial results is the observed increase in GAS6 after bemcentinib treatment.

Moreover, severe fibrosis was observed in addition to enhanced damage and inflammation in *Mertk*$^{-/-}$ mice in this model. In fact, in vitro experiments showed that GAS6 or MERTK activating antibody evaded palmitic-induced cell death in hepatocytes demonstrating the protective role of the GAS6/MERTK axis. In addition, in KCs and bone marrow–derived macrophages, AXL activation induced inflammatory cytokines expression after LPS stimulation,[104,105] whereas no differences were found after MERTK activation.[104]

As in HCV patients, the *MERTK* rs4374383 G variant was associated with increased prevalence of fibrosis, severe steatosis, and higher *MERTK* liver expression in MASLD patients.[106,107] Focusing in HSC, the authors used a small molecule inhibitor of MERTK, UNC569, that prevented in vitro migration of HSC and decreased expression of type I procollagen after GAS6 stimulation. Although interesting, these findings need to be interpreted with caution as a high concentration of UNC569 was used, compromising HSC cell viability[108] and inhibitor specificity (10-fold selectivity for MERTK over AXL[109]). Moreover, MERTK co-localization in macrophages, and not in HSC in MASLD human liver samples,[106] may account for MERTK's role in macrophages as shown in further investigation where MERTK activation in macrophages promoted HSC proliferation and activation via soluble mediators.[110] In this line, Cai et al identified TGFβ signaling, considered the most potent fibrogenic cytokine,[91] as mediator of the crosstalk between macrophages and HSC.[111] Indeed, GAS6 promoted *Tgfb1* expression and secretion in a MERTK and ERK1/2-dependent manner in isolated liver macrophages. Using conditioned medium, TGFβ1 secreted by GAS6-stimulated macrophages was able to activate HSCs through SMAD2/3 phosphorylation. These results

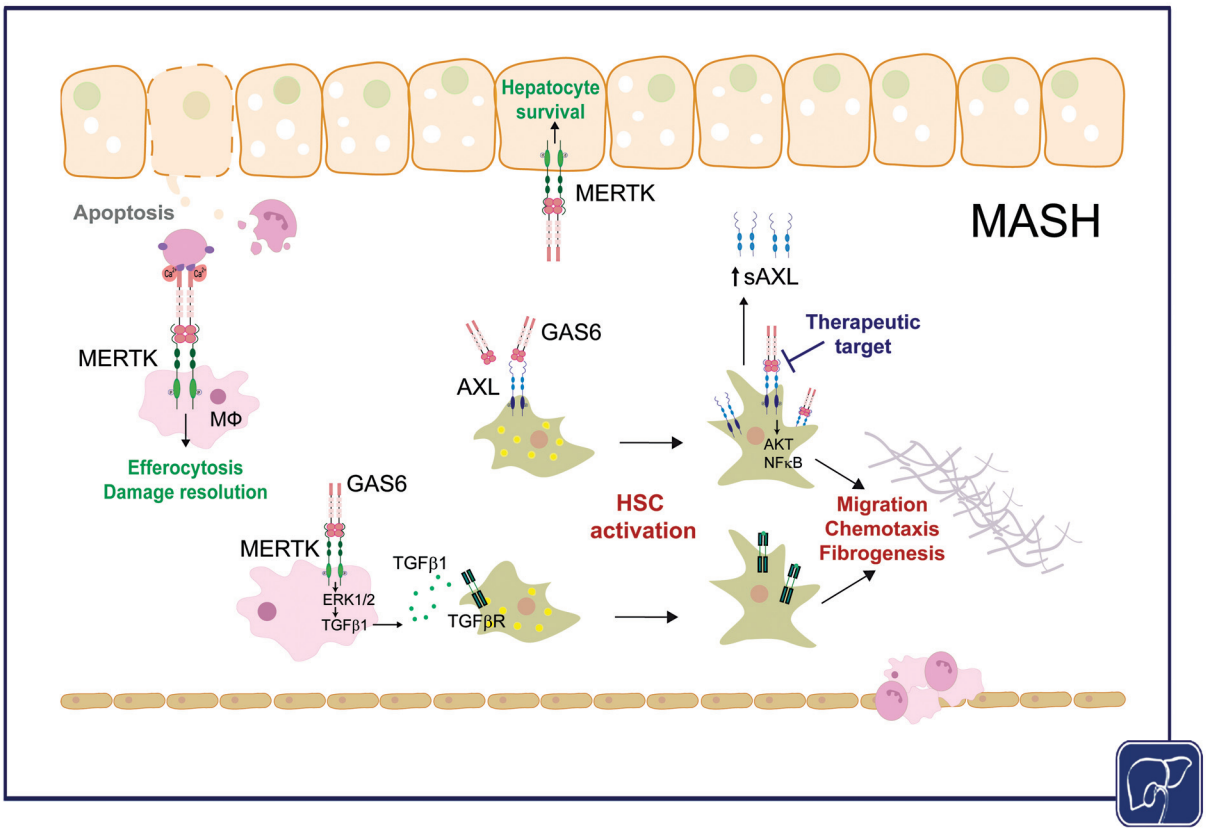

Fig. 2 Role of the TAM system in metabolic associated steatohepatitis (MASH). Different mechanisms implicating TAM receptors have been proposed in the pathogenesis of MASH. In hepatocytes, GAS6 signaling promotes hepatocyte survival by reducing lipotoxicity in the liver. Moreover, AXL activation by GAS6 in hepatic stellate cells (HSC) induces transdifferentiation into myofibroblasts, increasing motility, inflammatory signaling, chemotaxis, and deposition of extracellular matrix components. Therefore, due to AXL significance for liver fibrosis, its therapeutic inhibition has been postulated as a potential treatment for MASH. Of note, increased serum levels of sAXL are observed in MASH and fibrotic patients. On the other hand, MERTK in liver macrophages (MΦ) seems to play a complex and paradoxical role. As in other liver diseases, MERTK-expressing macrophages promote damage resolution through clearance of dead cells and attenuation of inflammation during MASH. However, a maladaptive restorative profile can lead to HSC activation due to MERTK-dependent secretion of transforming growth factor β (TGFβ).

support transcellular communication caused by a MERTK–TGFβ axis.[112]

Furthermore, the high fructose, palmitic acid, and cholesterol MASH model (FPC)[113] was used in *Mertk* $^{-/-}$ and myeloid-specific MERTK-deficient mice (*Mertk*$^{fl/fl}$ *Lyz2cre*$^{+/-}$). Both mice showed similar outcomes in weight, fasting blood glucose, and steatosis compared with WT mice, but less fibrosis and reduced expression of genes related to ECM and HSC, particularly *Tgfb1*. Of note, a lower proportion of apoptotic cells was detected in both MERTK-deficient animals and no changes in inflammatory cytokines were noticed among the groups. Moreover, transgenic mice resistant to MERTK cleavage (*Mertk*^{CR}) showed increased *Tgfb1* expression and fibrosis development of diet compared with WT. The authors determined that MERTK cleavage protects against fibrosis in early MASLD, as levels of sMERTK in WT liver were higher after 8 weeks of diet, when only steatosis is present, rather than after 16 weeks, when fibrosis is already established. Validating these findings, co-localization of MERTK and CD68 is reduced in human liver with steatosis in contrast to healthy or fibrotic livers.

The controversial results in the different MASH models illustrate the difficulties in interpreting TAM biological functions in complex inflammation-related diseases. Heterogeneity and plasticity are crucial features of macrophages, switching from pro-inflammatory to restorative profiles during tissue damage and repair processes. For instance, depletion of macrophages during liver injury reduces fibrosis development, whereas macrophage depletion during repair delays recovery, leading to persistent fibrosis in mouse models.[114,115]

Usually, MERTK is associated with a restorative profile and damage repair in different pathologies through its regulation of efferocytosis and inflammation.[116,117] Indeed, injection of MERTK^{hi} M2c macrophage improved liver inflammation and fibrosis in atherogenic diet mice model.[118] On the other hand, dysregulation of pro-resolving responses appears to contribute to fibrosis in MASH.[119,120] More studies are needed to understand TAM role in macrophage diversity and plasticity during MASH development.[121]

In addition, TAM receptors expression in other immune cells should not be ignored. For example, in vitro liver NKTs

were activated by PROS apparently through MERTK. In a model of ethanol-induced steatohepatitis, mice overexpressing PROS exhibited less apoptosis and more activation (FasL expression) of NKT compared with WT exacerbating lipid deposition, liver damage, and inflammatory cytokines.[122] In vitro ethanol treatment induced CD1d expression in hepatocytes enhancing activation of NKT. Moreover, sex-dependent protective role of NKT has been described in a murine diet-induced steatohepatitis.[123] Whether the survival of activated NKTs depends on PROS/MERTK is an aspect that may deserve further research in liver diseases.

Liver Cancer

Hepatocellular cancer (HCC) is the most common primary liver cancer and the fourth most common cause of cancer-related death worldwide.[124] Very related to cirrhosis and chronic liver disease, HCC is often diagnosed at advanced stage when treatment options are limited. Among TAM receptors, AXL is the most investigated in cancer because of its relation with EMT. Therefore, AXL activation is frequently associated with tumor invasion and metastasis as well as poor clinical outcomes.[125,126] In HCC, high expression of AXL (54/246 of the cohort analyzed) has also been related to advanced disease stage, correlating with microvascular invasion and lower overall survival.[127] Other studies showed a strong AXL expression in 60% of the HCC samples analyzed and validated the strong correlation between AXL and advanced stages,[128] as well as microvascular invasion.[129] The diagnostic potential of sAXL levels will be addressed in the following section.

Few studies define the tumorigenic properties of AXL in HCC. First, AXL was described as a downstream target of YAP, a transcriptional regulator of the Hippo pathway. In a non-neoplastic hepatocyte cell, overexpression of YAP induced oncogenic transformation. In these cells, YAP binds the *AXL* promoter and induces its transcription, increasing proliferation, migration, and invasion.[130] Later, other studies related AXL to EMT and invasion in HCC. As in human tumor samples, AXL expression was found in mesenchymal HCC cell lines in contrast to epithelial cell lines, in which AXL was almost undetectable.[129,131] Reinforcing a role of AXL in EMT, only mice bearing AXL-overexpressing tumors showed metastasis in xenograft models. Moreover, AXL induced pro-oncogenic TGFβ signaling enhancing expression of pro-metastatic targets such as PAI1, MMP9, or SNAI1.[129] AXL–TGFβ axis is not restricted to invasion since expression of CXCL5, a neutrophil chemoattractant, is regulated by both AXL and TGFβ.[132] CXCL5 and neutrophil infiltration promoted an immunosuppressive microenvironment, favoring tumor progression[133] and linking AXL with tumor growth and poor prognosis (►**Fig. 3**). The role of AXL in HCC metastatic potential could be influenced by alternative splicing of exon 10, with the shorter isoform associated with increased invasive potential for hepatoma cells.[134]

In 2008, sorafenib approval for advanced HCC treatment changed HCC management.[135] This multikinase inhibitor exhibits a potent anti-angiogenic effect and limits tumor growth; however, some tumors acquire resistance. Several mechanisms of drug resistance have been described, including EMT and in consequence AXL activation.[136] In the mesenchymal cell line SKHep-1, acquired resistance to sorafenib increased migration capacity and expression of EMT-related proteins as well as overactivation of AXL. Reduced motility and migration were observed in sorafenib-resistant cells after AXL inhibition with bemcentinib (BGB324) or shRNA silencing, validating AXL-dependent resistance mechanism. Moreover, combination of sorafenib with AXL inhibition increased apoptosis in parental and resistant SKHep-1 cells.[128] Although these data should be interpreted with caution due to the endothelial origin of SKHep-1 cells,[137] they are in agreement with the observed mechanism of pharmacological resistance due to AXL overexpression in breast, lung, and other cancers.[138] Recently, synergism between AXL and Erb-B receptors has been observed in regorafenib-resistant cells, suggesting a novel target for patients who progressed on therapy.[139]

TYRO3 is barely expressed in the liver but seems to have a role in HCC. Significant overexpression of *TYRO3* was detected in tumor samples of 42% of patients analyzed (23/55) as well as in HCC cell lines. In Hep3B cells, silencing of *TYRO3* reduced phosphorylation of ERK and cell viability.[140] Recently, the analysis of RTK expression in human HCC samples identified *TYRO3* as 1 of the 11 genes upregulated in tumor compared with adjacent tissue. Gain and loss-of-function experiments in HCC cell lines confirmed the tumor-promoting role of TYRO3 in tumor-sphere formation assays and in xenograph mice models.[141] Moreover, upregulation of *TYRO3* was found in 28% of a large HCC cohort and strongly associated with cirrhosis, HCV, liver inflammation, necrosis, and advanced stages. In fact, linking inflammation and cell damage with *TYRO3* expression, IL6 was able to induce *TYRO3* upregulation in HCC cell lines through the transcription factor STAT3. In addition, apoptotic cells via GAS6-activated TYRO3, further increasing STAT3 signaling. Moreover, HCC development was detected only in thioacetamide-treated mice injected with *TYRO3* expressing cells. Other factors might regulate TYRO3 expression in HCC such as the RAS family member RAB10[142] or the miR-7.[143] Downregulation of *TYRO3* by this microRNA not only reduced tumor growth but also overcame sorafenib resistance,[143] providing another link between TAM receptors and drug resistance.

Overall, TAMs emerge as therapeutic targets in advanced HCC and the identification of target patients or the combination with other drugs could lead to new treatment options. Actually, cabozantinib, which inhibits MET, VEGF1–3, and AXL, demonstrated longer overall survival in patients who failed to respond to sorafenib treatment[144] and is approved as second-line option. Furthermore, in the era of immunotherapy, TAMs have been proposed as therapeutic targets and TAM modulators are administered in clinical trials in combination with check-point inhibitors. However, more data on TAM-induced immunosuppression are required to decipher TAMs immunological role in HCC progression and

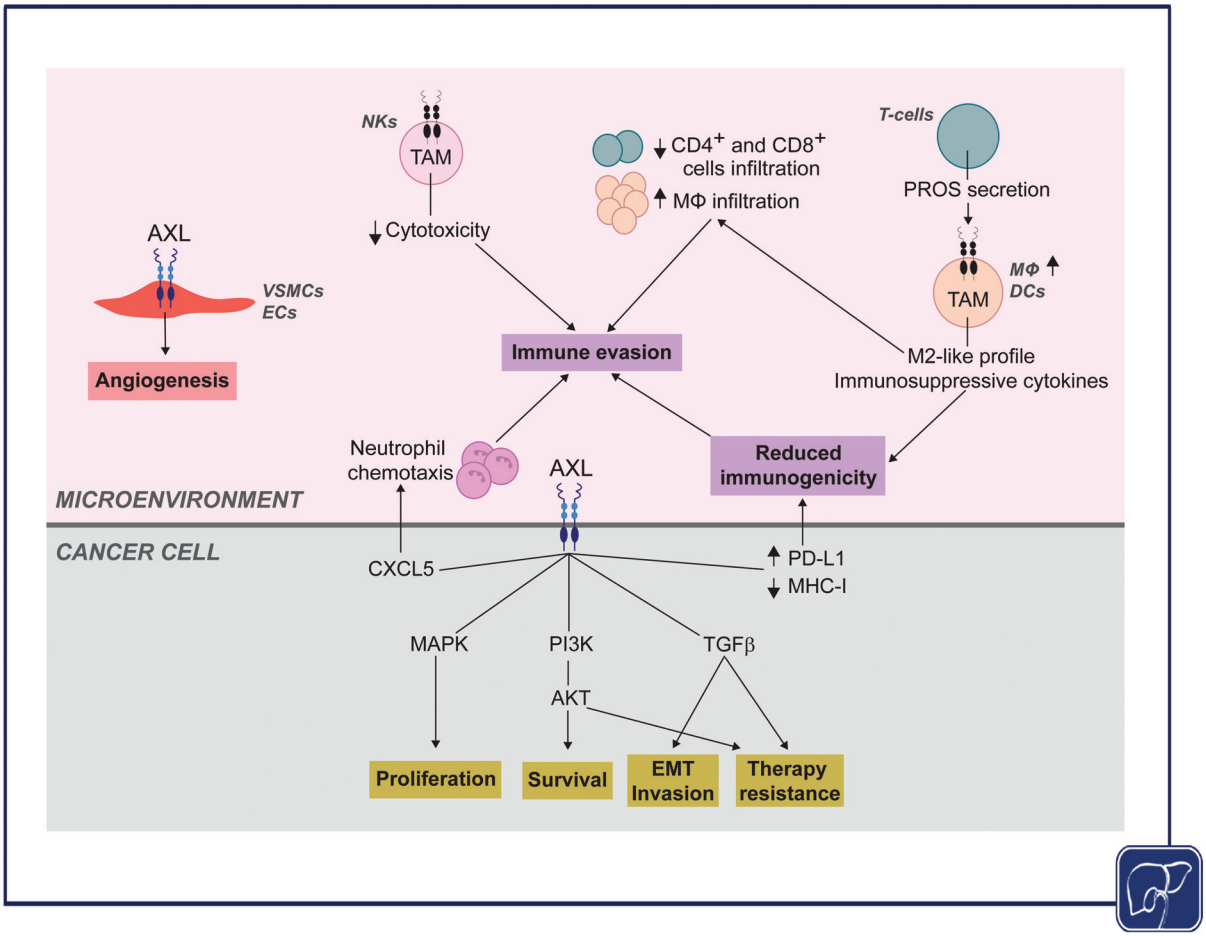

Fig. 3 AXL in cancer and hepatocellular carcinoma (HCC). In cancer cells, AXL stimulation triggers different intracellular pathways to promote cell survival, proliferation, epithelial–mesenchymal transition, invasion, and resistance to therapy. Moreover, AXL expression has been linked to higher PD-L1 and lower MCH-I surface levels, reducing tumor immunogenicity and therefore escaping immune surveillance. In HCC cells, AXL signaling also induces secretion of chemokine CXCL5, a neutrophil chemoattractant, which contributes to the immunosuppressive microenvironment. Indeed, immune evasion is an expected function of TAM in cancer and HCC attributed to its expression in different immune cells. In macrophages (MΦ) and dendritic cells (DCs), TAM induces an immunosuppressive profile which may prevent triggering of adaptive immunity and alter infiltration of lymphocytes and macrophages. Besides, PROS secretion by activated T cell contributes to these effects. In natural killer cells (NKs), TAM activation reduces their cytotoxic activity, hindering anticancer responses. Finally, AXL, expressed in blood vessel cells, promotes neovascularization, stimulating angiogenesis and tumor progression.

to support TAM inhibitors as future players in HCC treatment.

TAM Shedding and Its Usefulness as Biomarkers in Liver Disease

A remarkable feature of TAM receptors is the release of the extracellular region after its cleavage. As a consequence, soluble TAM receptors can be detected in serum in humans and mice.[15,16,145] GAS6 and PROS are also found in blood. Their detection in serum has been reported in SLE and cancer patients and evaluated in liver diseases due to the need for noninvasive techniques for diagnosis and patient follow-up.[146]

Bárcena et al identified GAS6 and sAXL as serum biomarkers of liver fibrosis.[93] Samples of alcoholic liver disease patients were analyzed detecting higher levels of sAXL and GAS6 in cirrhotic rather than fibrotic or healthy patients. Moreover, serum levels correlated with the liver functionality score MELD. To better explore fibrotic stages, serum of HCV patients at different stages of liver fibrosis (F0–F3/4) were analyzed. Significant differences were obtained in GAS6 levels between initial stages (F0 and F1) and more advanced fibrosis (F2 and F3/4), while sAXL increase was robust only in advanced fibrosis. Although in an early study Reichl et al did not found differences between healthy and cirrhotic patients,[147] the subsequent analysis of a larger cohort confirmed sAXL as an accurate biomarker of cirrhosis and advanced liver fibrosis of different etiology.[148,149] Similar results concerning GAS6 were obtained in a cohort with a great proportion of HCV-infected patients. The authors established a direct correlation between GAS6 levels and liver fibrosis denoted by liver stiffness (as measured by transient elastography) but also by fibrosis staging after biopsy.[150] Later, increased GAS6 plasma concentrations were also associated with esophageal varices in cirrhotic patients.[151] Similarly, GAS6/albumin showed high accuracy to detect significant (≥F2) to advanced fibrosis and

cirrhosis but failed to discriminate between HCC in cirrhosis and cirrhosis only.[152]

These candidate biomarkers have also been assessed in MASLD. In cirrhotic MASH patients, GAS6, sAXL, and sMERTK serum levels were increased in agreement with previous data. In non-cirrhotic patients, only higher sAXL was observed in early MASLD, increasing in parallel with disease progression. Of note, no relationship with arterial hypertension was detected in this cohort, but high sAXL values were observed in diabetic patients of all groups.[104]

TAM shedding is supposed to occur after receptor activation as a regulatory mechanism of the system.[16] Two metalloproteinases have been proposed as responsible for AXL and MERTK cleavage: ADAM10 and ADAM17.[15,153] Due to their wide range of targets, including cytokines and their receptors, growth factors, and components of the NOTCH signaling pathway, these "sheddases" have a complex role in inflammation and liver homeostasis.[154,155] For instance, ADAM10 deficiency in hepatocytes induces necrosis and concomitant liver fibrosis in mice because of impaired regulation of c-MET and NOTCH-2.[156] Besides, TNF, target of ADAM17 (also known as TACE), is a potent pro-inflammatory cytokine, playing a crucial role in hepatotoxicity[155] and autoimmune hepatitis.[157]

In liver fibrosis, where metalloproteinases are crucial for ECM remodeling, ADAM10 and ADAM17 may regulate TAM shedding. In human samples, higher mRNA expression of both proteins was observed in fibrotic liver and their expression was significant in HSC.[158] Indeed, ADAM17 regulated shedding of different proteins in HSC.[158,159] In HFD-induced MASH model, while no increment of active ADAM10 was detected, ADAM17 expression and activity were upregulated in liver. This concurred with increased sAXL in mice serum even after 2 weeks of HFD feeding when fibrosis is not yet detected.[104] In the FPC diet model, ADAM17 activity was also induced in MASH mice compared with control, although a more potent induction was observed in steatotic rather than fibrotic liver.[112] Indeed, ADAM17 activity was triggered in different cell types by palmitic acid, LPS, high glucose, insulin, and all-trans retinoic acid.[112,160] Then, increased fatty acids, diabetes, and bacterial translocation may contribute to activation of ADAM17 in MASLD and MASH, enhancing TAM cleavage in early MASLD and in fibrosis.

To date, the specific sources of soluble TAM and GAS6 in liver disease remain unclear. GAS6 is likely to be secreted by KCs and infiltrating macrophages after inflammation induction, as well as by activated HSC.[93] Regarding MERTK, cleavage by ADAM17 has been described in KC.[112] AXL shedding in HSC cell line has been validated and was dependent on ADAM10 and ADAM17 activity.[104] However, as AXL is expressed in HSC, KC, monocyte-derived macrophages, and endothelial cells in liver disease,[65,66,93,104] cleaved receptor probably comes from multiple cell sources. Moreover, sAXL in cirrhotic patients strongly correlated with AXL^+ monocytes[99]; thus, cleavage in these circulating monocytes could contribute to higher levels of sAXL in cirrhotic serum.

Interestingly, enhanced levels of sAXL were also described in HCC patients[147] and associated with poor prognosis. Other cancer types, even liver metastasis from colon and cholangiocarcinoma, did not show changes in sAXL levels,[147,149] indicating that a specific mechanism was involved. Recently, this cleaved protein has been associated with melanoma progression[161] or early detection of pancreatic ductal adenocarcinoma and differential diagnosis from chronic pancreatitis[162]; so, combination of sAXL with other parameters might be required for specific HCC detection.[147,163] Regarding prediction of treatment efficacy, in sorafenib-treated HCC patients, those with high pre-treatment sAXL levels exhibited poor overall survival (3 vs. 16.5 months).[128] Since the identification of noninvasive biomarkers is a medical need for liver disease diagnosis and management, sAXL and related proteins should be further evaluated as potential candidates for diagnosing or monitoring at-risk population.

Table 2 Therapeutic modulation of GAS6-TAM signaling in liver diseases

Therapeutics	Disease	Model	Effects	Ref.
BGB324 (AXL inhibitor)	Fibrosis	CCl_4 mice model Diet-induced MAFLD mice model	Decreased fibrogenesis and inflammation	Bárcena et al[93] Tutusaus et al[104]
BGB324 (AXL inhibitor)	HCC	HCC cell lines	Reduced motility, migration and increased apoptosis in pharmacological resistant cell	Pinato et al[128] Breitenecker et al[139]
Cabozantinib (tyrosine kinase inhibitor including AXL)	HCC	HCC patients	Increased overall survival in patients who failed to respond to sorafenib	Abou-Alfa et al[144]
BGB324 (AXL inhibitor)	Recurrent infections in cirrhosis	Patients-derived monocytes	Enhanced immune responses in cirrhotic monocytes	Brenig et al[99]
Recombinant GAS6	Hepatic ischemia	Ischemia reperfusion mice models	Attenuated ischemic damage and increased survival	Llacuna et al[75] Wang et al[76]

Conclusion

TAM ligands and receptors have arrived relatively late to the hepatology arena, but their continuity is guaranteed according to recent publications that reveal the prominent role of TAMs in the development of liver diseases. AXL and MERTK regulate pathophysiological processes, especially in the response to hepatic injury and during liver healing, including controlling the clearance of damaged cells, recruitment and activation of inflammatory cells, as well as ECM remodeling. Furthermore, the TAM family offers interesting plasma biomarkers to track liver disease progression by providing early clues of fibrosis and inflammation advance. As a consequence, drugs regulating TAM activity and its ligands are being actively sought to treat various liver diseases (►**Table 2**). Research in this field is an opportunity not to be missed.

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Conflict of Interest
None declared.

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