

EDITORIAL

Staging NAFLD: Diagnostic and Therapeutic Value of TAM Signaling



A sedentary lifestyle and the overconsumption of calorie-dense refined meals reflect today's modern society. These factors undoubtedly explain the global epidemic of overweight and metabolic syndrome, whose hepatic consequence is the so-called *nonalcoholic fatty liver disease* (NAFLD). This spectrum of liver disease ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), the latter characterized by inflammation, injury, and hepatic fibrosis. However, because of the limitations of the current clinical diagnosis of liver fibrosis, there is an urgent unmet need for novel potential biomarkers.

It was not until 1995 that the family of receptor tyrosine kinases (RTKs), TYRO3, AXL, and MERTK (TAM) was no longer considered orphan receptors.¹ In that year, their vitamin K-dependent ligands, protein S and the growth arrest-specific protein 6 (GAS6) were identified. The TAM RTKs together with their ligands constitute the TAM system, a major regulator of cell death and the innate immune response. Deficient or aberrant TAM signaling has been associated with a wide range of diseases ranging from chronic inflammation to cancer development.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Tutusaus et al² expand the current knowledge of the contribution of GAS6/TAM RTKs in chronic liver disease (CLD). However, where exactly are the GAS6/TAM RTKs expressed in the liver? TAM receptors differ in their physiological expression. AXL is expressed mainly in quiescent hepatic stellate cells (HSCs), endothelial and immune cells (monocytes, macrophages, platelets, and dendritic cells), whereas MERTK and TYRO3 expression is confined to inflammatory cells. Interestingly, each receptor can be produced in a soluble form as well (sAXL, sMERTK, and soluble TYRO3). In turn, GAS6, the predominant ligand that binds all 3 TAM RTKs, is produced in Kupffer cells in

basal conditions, while GAS6 overexpression in macrophages, HSCs, and liver progenitor cells has been reported in experimental models of injury and regeneration.³⁻⁷

Nonetheless, the functional relevance of the TAM system during hepatic fibrogenesis was unknown. Several investigators^{4,6} have shown that global GAS6 deficiency reduced the inflammatory response by limiting Kupffer cell activation and macrophage infiltration, and improving hepatic fibrogenesis. Intriguingly, GAS6-deficient mice show overexpression of AXL. The functional relevance of AXL overexpression remains unclear but alarming because TAM RTK overexpression can drive conventional oncogenic signaling.^{1,5} In fact, AXL protein expression is observed in patients with hepatocellular carcinoma.⁸

Thus, AXL as a theranostic target for CLD needed to be examined thoroughly. Constitutive-deleted AXL mice challenged chronically with CCl₄ showed decreased HSC activation in vitro and liver fibrogenesis.⁸ In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Tutusaus et al² challenged global AXL and MERTK knockout mice with experimental models of NASH. The same research group previously tested the pharmacologic use of an AXL inhibitor in experimental murine CCl₄-derived periportal fibrosis.⁸ Bemcentinib, a selective small-molecule inhibitor of AXL (BGB324), also was successful in preventing murine experimental NASH. Specifically, bemcentinib blocked HSC transdifferentiation and macrophage activation, greatly diminishing hepatic inflammation and fibrosis. Therefore, GAS6 signaling through the AXL receptor contributed to the progression of NASH, while experimental inhibition of AXL showed enormous therapeutic potential.

In contrast, MERTK-ablated mice showed aggravated liver damage,² most likely owing to the anti-inflammatory role of GAS6 in macrophages via MERTK. Thus, the role of

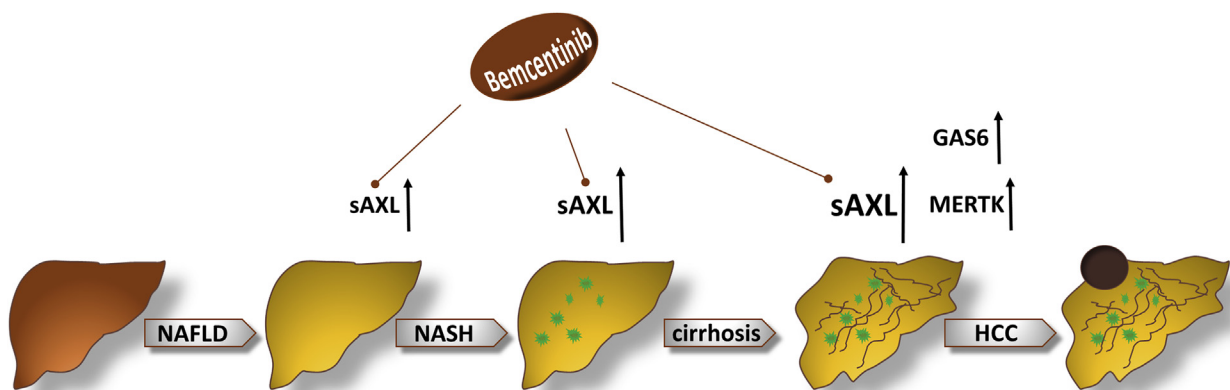


Figure 1. NAFLD staging.

MERKT seems to be more important in macrophages than in HSCs, where it would modulate viability.

The next obvious question is whether hepatic injury and inflammation could be diagnosed using markers of the TAM system. Barcena et al⁸ analyzed data from patients at different stages of alcoholic liver disease and hepatitis C virus infection and showed correlation between GAS6/AXL serum levels and liver dysfunction. Later, Petta et al⁹ reported a link between MERKT messenger RNA and the severity of liver fibrosis in NAFLD patients. Tutusaus et al² found increased levels of GAS6, sAXL, and sMERTK in cirrhotic NASH patients, compared with control individuals or patients with simple steatosis. Importantly, only sAXL was increased in early stages of NAFLD. Indeed, it also could act as a novel biomarker of metabolic syndrome (eg, diabetes) when liver fibrosis still was absent and with increasing values directly proportional to the stage of NAFLD (Figure 1). However, GAS6 and sMERTK were increased only in cirrhotic NASH patients, and thus its measurement would be more appropriate for later stages, reinforcing the therapeutic value of AXL inhibition even for end-stage hepatocellular carcinoma (Figure 1). Unfortunately, the current scientific evidence is preliminary and, in vivo validation studies, using large cohorts of patients, still are missing, but, undoubtedly, the relevance of the TAM system in CLD merits further investigation.

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Conflicts of interest

The author discloses no conflicts.

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