**Chronic liver disease- a scavenger hunt for novel therapeutic targets**

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Chronic liver disease (CLD) is a major cause of global mortality and morbidity. Recent therapeutic breakthroughs have occurred in the field of viral hepatitis, with the development of direct-acting antiviral agents (DAA) for the cure of hepatitis C virus infection1. Despite this, the incidence of liver disease continues to rise driven in particular by the increase in obesity-related fatty liver disease and the continued consequences of excess alcohol consumption2. Patients with CLD are at an increased risk of developing progressive liver fibrosis, cirrhosis and liver failure. CLD is an established risk factor for hepatocellular cancer (HCC), with 90% of cases developing on a background of CLD.

There are currently no effective therapies that can reverse advanced hepatic fibrosis3 and in patients who develop HCC the single licensed medical therapy, the multi-kinase inhibitor sorafenib, only prolongs median survival by three months4. There is therefore a clear unmet clinical need for new medical therapies for CLD.

CLD, regardless of aetiology, follows a common pathway in which persistent tissue injury and cellular death drives chronic inflammation and the activation of liver fibroblasts, known as hepatic stellate cells, which produce extracellular matrix proteins, leading to fibrosis and ultimately cirrhosis5. This fibrogenic inflammatory tissue microenvironment is associated with an increased risk of neoplastic transformation leading to HCC. Better understanding of the immune-networks that drive persistent inflammation and fibrogenesis could identify novel therapeutic targets to reduce inflammation driven fibrosis and also to boost protective immune responses that provide immune surveillance against HCC or kill it once it has developed. Thus, directed therapies will be required in the context of CLD, patients with progressive fibrosis will require inhibition of pro-inflammatory profibrogenic pathways whilst those with HCC need treatments which promote immune recognition of the cancer leading to tumour clearance.

**Scavenger Receptors as therapeutic targets in liver disease**

Scavenger receptors (SRs), are an ancient evolutionarily conserved family of molecules that are characterised by their recognition of products of chronic oxidative stress including oxidized low density lipoproteins (oxLDLs) 6. They are highly expressed in the liver and one member the Scavenger Receptor B1 (SR-B1) has been shown to recognize native and modified LDLs and also to bind the hepatitis C virus which exploits this interaction to enter hepatocytes7. Studies by our laboratory and others have demonstrated that scavenger receptors can directly influence the progression of chronic liver disease.

For example, the SR family members CD36 and macrophage scavenger receptor-1 (MSR-1) on macrophages promote inflammation and fibrosis in models of fatty liver disease8 as a consequence of the release of proinflammatory cytokines and chemokines in response to products of chronic oxidative stress generated within the liver in fatty liver disease9.

We have focused on another SR family member, stabilin-1/CLEVER-1, a multifunctional SR which binds several ligands including oxLDLs. In models of liver injury stabilin-1 recognized products of oxidative stress but in contrast to CD36 and MSR-1 played a protective role in tissue injury. The recognition and uptake of oxLDLs by stabilin-1 on macrophages suppressed the release of the chemokine CCL3 and influenced tissue remodeling as a consequence of cross talk between macrophages and hepatic fibroblasts or stellate cells10. In addition stabilin-1 functions as an atypical adhesion receptor on liver endothelium to promote the recruitment of immunosuppressive regulatory T cells11,12.

With their wide array of ligand binding, scavenger receptors were originally thought to perform silent functions with significant redundancy. Work by our group and others is calling this into question and suggests that SRs regulate the inflammatory/immune response to metabolic stress. Collectively these studies suggest that SR mediated pathways lead to distinct immune outcomes in chronic liver inury: CD36 and MSR-1 support proinflammatory pathways whereas stabilin-1 promotes an immunosuppressive tissue microenvironment (Figure 1). What implications does this have for the wider clinical field? Targeting SRs could be an effective therapeutic strategy in liver disease by on the one hand selectively inhibiting fibrosis- or cancer-promoting inflammation whilst on the other activating protective anti-cancer immunity. Although further work is required to assess the safety and efficacy of targeting SR pathways we believe they have the potential to be effective therapies for CLD in this era of precision medicine.

Figure Legend

Scavenger receptors mediate distinct immune pathways in chronic liver injury: Chronic liver injury is associated with hepatocyte damage and metabolic stress which leads to the release of danger associated molecular patterns (DAMPs) including oxLDLs and the activation of hepatic stellate cells (HSC). DAMPs are recognized by hepatic sinusoidal endothelial cells (HSEC) and liver macrophages (MACRO) through surface receptors including scavenger receptors such as stabilin-1/CLEVER-1 (STAB-1), CD36 and the Macrophage Scavenger Receptor-1 (MSR-1). In the context of chronic liver injury stabilin-1 promotes immunosuppressive pathways including suppression of the secretion of the chemokine CCL3 and recruitment of regulatory T cells whereas CD36 and MSR-1 promote pro-inflammatory immune cell recruitment. Targeting stabilin-1 or CD36 and MSR-1 with antibodies or small molecule inhibitors could block these pathways and potentially be directed therapies for hepatocellular cancer and liver fibrosis respectively.

References:

1. Chung RT, Baumert TF. Curing chronic hepatitis C--the arc of a medical triumph. *N Engl J Med* 2014; **370**(17): 1576-8.

2. Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014; **384**(9958): 1953-97.

3. Ramachandran P, Henderson NC. Antifibrotics in chronic liver disease: tractable targets and translational challenges. *Lancet Gastroenterol Hepatol* 2016; **1**(4): 328-40.

4. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**(4): 378-90.

5. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol* 2017; **14**(7): 397-411.

6. Canton J, Neculai D, Grinstein S. Scavenger receptors in homeostasis and immunity. *Nat Rev Immunol* 2013; **13**(9): 621-34.

7. Felmlee DJ, Coilly A, Chung RT, Samuel D, Baumert TF. New perspectives for preventing hepatitis C virus liver graft infection. *Lancet Infect Dis* 2016; **16**(6): 735-45.

8. Bieghs V, Wouters K, van Gorp PJ, et al. Role of scavenger receptor A and CD36 in diet-induced nonalcoholic steatohepatitis in hyperlipidemic mice. *Gastroenterology* 2010; **138**(7): 2477-86, 86 e1-3.

9. Busch CJ, Hendrikx T, Weismann D, et al. Malondialdehyde epitopes are sterile mediators of hepatic inflammation in hypercholesterolemic mice. *Hepatology* 2017; **65**(4): 1181-95.

10. Rantakari P, Patten DA, Valtonen J, et al. Stabilin-1 expression defines a subset of macrophages that mediate tissue homeostasis and prevent fibrosis in chronic liver injury. *Proc Natl Acad Sci U S A* 2016; **113**(33): 9298-303.

11. Shetty S, Weston CJ, Oo YH, et al. Common lymphatic endothelial and vascular endothelial receptor-1 mediates the transmigration of regulatory T cells across human hepatic sinusoidal endothelium. *J Immunol* 2011; **186**(7): 4147-55.

12. Patten DA, Wilson GK, Bailey D, et al. Human liver sinusoidal endothelial cells promote intracellular crawling of lymphocytes during recruitment: A new step in migration. *Hepatology* 2017; **65**(1): 294-309.