aLMF (CD90, -SMA) and extracellular matrix (ECM). Increased VAP-1 levels also correlated with the accumulation of advanced glycation end products in the scar, suggestive of a link between amine oxidase activity and modification of ECM. Cultured human aHSC and aLMF expressed VAP-1 mRNA and produced enzymatically active VAP-1 protein. Purified, soluble VAP-1 was a potent promigratory signal for lymphocytes and aHSC in vitro, possibly through amine oxidase activity. Soluble VAP-1 did not induce aHSC apoptosis or proliferation but was associated with an increase in cell spreading.

A role for VAP-1 in CCl4-induced liver fibrosis was confirmed in vivo. Both wild-type mice treated with a blocking anti-VAP-1 antibody and VAP-1null mice showed significantly reduced fibrosis after 8 weeks CCL4 compared with wild-type, and had accelerated resolution of fibrosis after cessation of CCl4. Wild-type mice receiving CCl4 also showed a significant increase in VAP-1 and elastin mRNA levels, mature macrophages, CD45-positive infiltrate and serum VAP-1 levels above that observed for VAP-1 null animals or those receiving antibody.

Conclusion These data suggest a multifunctional role for VAP-1 in liver disease in which VAP-1 not only supports lymphocyte and HSC recruitment but also modulates ECM remodelling and fibrogenesis.

P55 SYNGENIC BONE MARROW TRANSFER STIMULATES HEPATIC PROGENITOR CELL EXPANSION VIA TWEAK/FN14 SIGNALLING: IMPLICATIONS FOR HUMAN AUTOLOGOUS CELL THERAPY

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Introduction Autologous bone marrow cell (BMC) therapy for liver disease has shown increased liver regeneration in animal studies and in phase 1 clinical studies. As yet no clear mechanism accounts for these observations. BMCs do not directly form into hepatocytes but can improve liver regeneration and function. In chronic liver disease hepatic progenitor cells (HPCs) are a potential source of parenchymal regeneration. Whilst the transplantation of human HPCs is not currently a practical therapeutic option, manipulating endogenous HPCs in vivo represents a potential approach. HPCs exist in a specialised niche of leukocytes and mesenchymal cells, which secrete cytokines that are capable of regulating HPC behaviour. We therefore hypothesised that infusion of BMC into the liver may induce HPC expansion via paracrine signalling.

Aim To investigate the effect of autologous BMC infusion upon regeneration by hepatic progenitor cells.

Method 107 syngenic BMCs were infused into healthy mice by tail vein, we examined intrahepatic donor cell engraftment, cytokine expression, liver function tests, and HPC activation. Cell tracking utilised either GFP+ or male cells delivered into female wild type mice. Whole liver and specific cell fractions were analysed by immunocytochemistry, in-situ hybridisation, FACS, and qRT-PCR.

Results Following BMC transfer, a progressive and sustained expansion of HPCs was observed (mean±SEM 41.9±2.1 cells per field vs PBS control 23.5±4.1 at 21 days post infusion, p=0.003) with associated increase in liver/body weight ratio (BMC 0.0513±0.001 vs PBS control 0.0470±0.001, p=0.022). BMCs engrafted the liver adjacent to HPCs for up to 3 weeks and were mostly F4/80+ macrophages (81%). Transfer of F4/80+ macrophages alone into healthy mice recapitulated the HPC expansion. Cytokine gene expression analysis revealed one soluble signal in particular, TWEAK, increased in the recipient's liver following donor BMC engraftment (5.20-fold induction vs control at Day 3). Extracted donor derived BMCs expressed TWEAK, as do macrophages. TWEAK is known to be a direct mitogen to HPCs via the Fn14 receptor. When Fn14-/- mice were used as recipients to wild type BMC infusions the expansion of HPCs was entirely lost (mean±SEM 27.2±1.4 vs negative PBS control 30.6±2.4, p=0.128 vs positive wild-type control 42.7±2.3, p=0.0002), demonstrating that the HPC expansion is dependent on TWEAK-Fn14 paracrine signalling between BMCs and HPCs.

Conclusion These data describe a hitherto unknown mechanism by which infused autologous macrophages signal in a paracrine manner to HPCs via TWEAK. These observations suggest potential for the development of novel therapies to promote human liver regeneration.

P56 FACTOR XA INHIBITION SUPPRESSES THIOACETAMIDE INDUCED LIVER FIBROSIS

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Introduction In addition to its role in activating fibrinogen, thrombin mediates cellular activation of macrophages, platelets and hepatic stellate cells via the protease-activated receptor, PAR-1. Thrombin antagonists demonstrate anti-fibrotic properties. Factor Xa (FXa), a protease which is activated earlier in the coagulation cascade, promotes connective tissue growth factor, and activates fibroblasts via PAR receptors. Direct FXa inhibition has recently been shown to significantly reduce lung fibrosis, a paradigm for hepatic fibrosis, in a bleomycin mouse model. Specific inhibition of FXa may offer additional efficacy as an anti-fibrotic in models of chronic liver injury.

Aim To evaluate the impact of FXa inhibition and thrombin antagonism on hepatic fibrosis using a thioacetamide (TAA) mouse model.

Method 45 C57BL/6J mice were administered TAA (300 mg/l) via drinking water for a period of 8 weeks to induce liver fibrosis. A subset of these animals were given Rivaroxaban, a direct FXa inhibitor (n=15), or Dagibatran, a direct thrombin antagonist (n=15). Both drugs were administered daily by oral gavage at doses to achieve prolongation of the prothrombin time. The remaining animals (n=15) received no anticoagulation, and acted as the control group. At 8 weeks livers were extracted and liver sections stained with picorsirus red and visually scored for fibrosis using an adapted Ishak Modified Histology Activity Index by a blinded histopathologist. Digital image analysis was performed to calculate the mean percentage area of fibrosis per section.

Results In control mice the mean fibrosis score was 4.08 and the mean percentage area of fibrosis was 3.76%. In comparison mice treated with FXa inhibition had a mean fibrosis score of 2.46 (p=0.008) and mean percentage area of fibrosis of 2.02% (p=0.012). In contrast mice treated with thrombin inhibition had a mean fibrosis score of 3.25 (p=0.68 vs controls), and mean percentage area of fibrosis of 3.70% (p=0.68 vs controls). Factor Xa inhibition was significantly more effective than thrombin in reducing percentage area of fibrosis (p=0.031).

Conclusion FXa inhibition significantly decreased the rate of hepatic fibrosis in a TAA model of liver fibrosis. It is likely that direct thrombin inhibition is less effective than FXa inhibition because thrombin inhibitors fail to block PAR-mediated stellate cell activation by FXa. FXa inhibition is a potential novel anti-fibrotic approach and warrants further investigation in human studies.