IFN & 63 PEG), including 6 mitochondriopathies. SVR was achieved in 20% of IFN pts vs 27% of PEG pts ($p=0.047$). In those who did not discontinue treatment, virological response rates were at W4 (12 vs 20%), W12 (34 vs 41%), W24 (41 vs 54%), W48 (34 vs 52%) and W72 (6 vs 35%), respectively. Virologic response at W12 predicted SVR with 87% Positive Predictive Value and its absence had a 99% Negative Predictive Value. SVR varied with genotypes 1 or 4 (11%) vs 3 or others (43%), but not with the Metavir score or the adjusted ribavirin dose. Response-associated pretreatment characteristics included genotypes other than 1 or 4 (OR=5.9), no protease-inhibitor therapy (OR=2.0), age=40 years (OR=1.9) and elevated ALT (OR=1.8). Necro-inflammation significantly decreased in the PEG pts (−0.20 vs 0.02, $p=0.0008$). Fibrosis stabilized in virological responders and worsened in non responders. Steatosis improved significantly in patients infected by genotype 3 who had a SVR ($p=0.017$).
Conclusion: In HIV–HCV coinfected pts, the combination of pegylated IFNα2b and ribavirin is associated with a superior HCV virologic response than standard combination with a quite similar adverse-event profile.

Parallel Session 3: Inflammation and Fibrosis

23 ACTIVIN SECRETED FROM HEPATOCYTES ACTIVATES HSCS AND PLAYS A KEY ROLE IN LIVER FIBROSIS

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Background: Hepatic fibrogenesis represents wound-healing responses to chronic liver injury which includes hepatocellular damages. Molecular mechanisms by which hepatocellular damages lead to subsequent TGF-β secretion from the nonparenchymal cells remain quite unknown. We have herein reported that the recombinant follistatin blocks hepatic fibrogenesis induced by dimethylnitrosamine (DMN) in rats.
Methods: HSCs were primary cultured with various concentrations of activin and TGF-β. Activin, TGF-β and collagen I mRNA expressions were measured by RT-PCR. Wistar male rats were injected intraperitoneally with dimethylnitrosamine (DMN) and intravenously with saline or follistatin three times a week for three weeks. Tissue sections were stained with collagen IV, α-smooth muscle actin, fibronectin, TGF-β. In situ hybridization was performed for the detection of activin. Activin and TGF-β mRNA expressions were measured by RT-PCR. Liver tissues were obtained 0, 12, 24, 36, 48, 60, 72hrs and 7 days after single DMN-injection. Hepatocytes, stellate and Kupffer cells were isolated and analyzed for activin and TGF-β mRNA expression.
Results: 50% of control rats died whereas none of follistatin-treated rats died. In follistatin-treated rats; the serum hyaluronic acid, AST and ALT levels were significantly reduced, the expression of TGF-β, Collagen IV and α-SMA were reduced. Activin expression was observed at maximum level in hepatocytes 12hrs after DMN treatment. TGF-β expression was strikingly increased in stellate and Kupffer cells 24–48hrs after DMN administration but was not detectable in hepatocytes. Exogeneous follistatin decreased activin and TGF-β expression from non-parenchymal cells. Activin expression from hepatocytes was prior to non-parenchymal cells and was not altered by follistatin treatment.
Conclusions: Hepatocytes exposed to the reagent turned out to secrete activin prior to the secretion and overexpression of TGF-β in HSCs. The blockade of activin by exogenous follistatin effectively inhibited proliferation and activation of HSCs, downregulated extracellular matrix production, and consequently attenuated liver fibrogenesis, suggesting that activin derived from hepatocytes accounts for a crucial initiator of HSC activation. These results not only suggest that hepatocytes utilize activin to trigger TGF-β-mediated fibrogenic responses of HSCs but also shed light on a possibility that recombinant follistatin serves as a potentially therapeutic stratagem that can target hepatocellular activin to modulate hepatic fibrogenesis.

24 CALCIUM-DEPENDENT ACTIVATION OF NF-κB BY THE ADIPOKINE RESISTIN IN HEPATIC STELLATE CELLS

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Background and Aims: In rodents resistin is expressed exclusively in adipose tissue and antagonizes insulin action, but the sites of resistin expression and its role in insulin resistance in humans are debated. Nonalcoholic steatohepatitis is associated with visceral obesity and diabetes. However, the mechanisms responsible for fibrosis progression in this condition are only partially understood. Aims of the study were to investigate the molecular mechanisms underlying the effects of resistin in human hepatic stellate cells (HSC).
Methods: Human HSC were used in their myofibroblastic-like phenotype. Gene expression was measured by RNAse protection assay or by real-time PCR. Activation of intracellular signalling pathways was studied using western blot analysis. Cytokine secretion was measured by ELISA. Intracellular calcium concentration was assessed using the fluorescent indicator Fura-2. Resistin expression in liver was assessed by immunohistochemistry.
Results: Preliminary data indicated that resistin up-regulates the expression of the pro-inflammatory chemokine, MCP-1, and that inhibits HSC proliferation and migration in response to PDGF-BB. Incubation of HSC with resistin resulted in a marked activation of the transcription factor NF-κB, as indicated by phosphorylation of the inhibitory protein IκBa, and electrophoretic mobility shift. Resistin also induces a rapid and transient increase in intracellular calcium concentration. To establish a possible link between calcium influx and NF-κB, we assessed the effects of the intracellular calcium chelator BAPTA-AM. BAPTA-AM completely blocked resistin-induced activation of NF-κB, indicating that calcium transients are necessary for this pro-inflammatory pathway. Moreover, calcium chelation inhibited MCP-1 secretion in response to resistin. Exposure of HSC to resistin did not affect mRNA levels of TGF-β or procollagen type I. Interestingly, resistin mRNA was markedly up-regulated in liver tissue obtained from patients with end-stage liver disease. Resistin overexpression was confirmed by immunohistochemistry that revealed specific signal in sinusoidal cells and in biliary epithelial cells.
Conclusions: Resistin exerts pro-inflammatory actions in human HSC, by activation of a pathway requiring calcium influx and NF-κB. In additon, resistin expression is up-regulated at the mRNA and protein levels in the liver of patients with severe fibrosis. These findings may be relevant for the pathophysiology of liver fibrosis especially in the context of non-alcoholic steatohepatitis.