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INHIBITION OF THE FAS PATHWAY OF APOPTOSIS WITH RNA INTERFERENCE DURING LIVER MACHINE PERFUSION PRESERVATION REDUCES ISCHEMIA REPERFUSION INJURY AFTER LIVER TRANSPLANTATION

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Background: Severe ischemia reperfusion injury (IRI), which is associated with hepatocyte apoptosis, limits the use of extended criteria donors (ECD) in liver transplantation (LT). Machine perfusion (MP) is a promising technology for administering specific therapies to improve graft function. Inhibition of genes associated with apoptosis during MP could decrease the intensity of IRI post-LT.

Aim: We attempted to investigate whether inhibition of an apoptosis-associated gene (FAS) using a small interference RNA approach could alleviate the IRI in a rat LT model.

Methods: In two sets of syngeneic rat liver transplant experiments FAS-siRNA (500ug) was administered either to rat donors 2hs before organ procurement followed by a static cold storage (SCS) period of 22hs to intensity IRI effects or was added to the perfusate during 1h of ex situ hypothermic oxygenated perfusion (HOPE) to livers previously preserved for 4hs in SCS. Liver tissue and serum samples were collected at 24hs post-LT.

Results: Post-LT transaminases levels (AST) were lower in the siRNA-SCS (979±117 x 1914±229IU/L p=0.0005)(Fig. 1) and siRNA-HOPE (Fig. 2) (810±72 x 1041±262IU/L p=NS) groups. Inflammatory cytokines (IL2, IL6, IP10, TNFα, and IFNγ) were significantly decreased in siRNA-SCS group. In addition, anti-inflammatory cytokines (IL4, IL10) were increased in the siRNA-HOPE group. Apoptosis index (TUNEL+ cells) was lower in siRNA-SCS (13±3.7 x 44±15IU/L p=0.023) and siRNA-HOPE (47±10 x 74±12IU/L p=0.056) groups, which was associated with less necrosis in histological analyses. Hepatocyte siRNA uptake was confirmed by confocal microscopy (Fig. 3). Finally, FAS-protein expression was decreased in siRNA-treated groups.

Conclusions: Our results suggest that inhibition of FAS through siRNA therapy decreases apoptosis, inflammation and the severity of IRI. In addition, treatment with FAS siRNA during MP seems to induce anti-inflammatory pathways. This approach can be used to optimize ECD liver grafts function and has the potential to improve outcomes and increase the pool of transplantable livers.

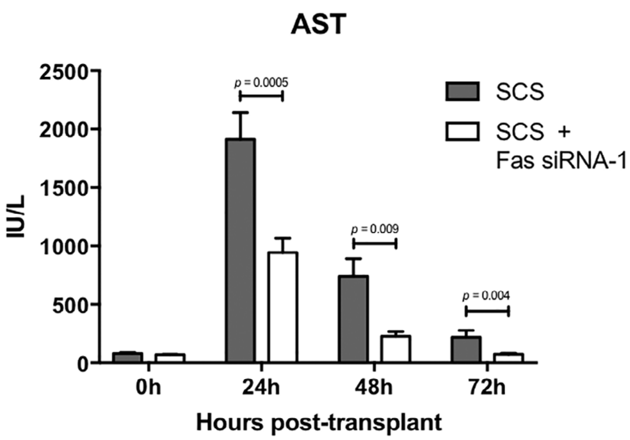

Fig. 1.

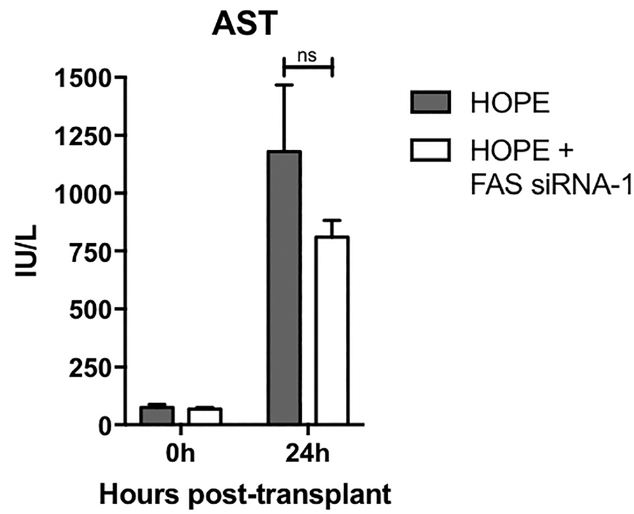

Fig. 2.

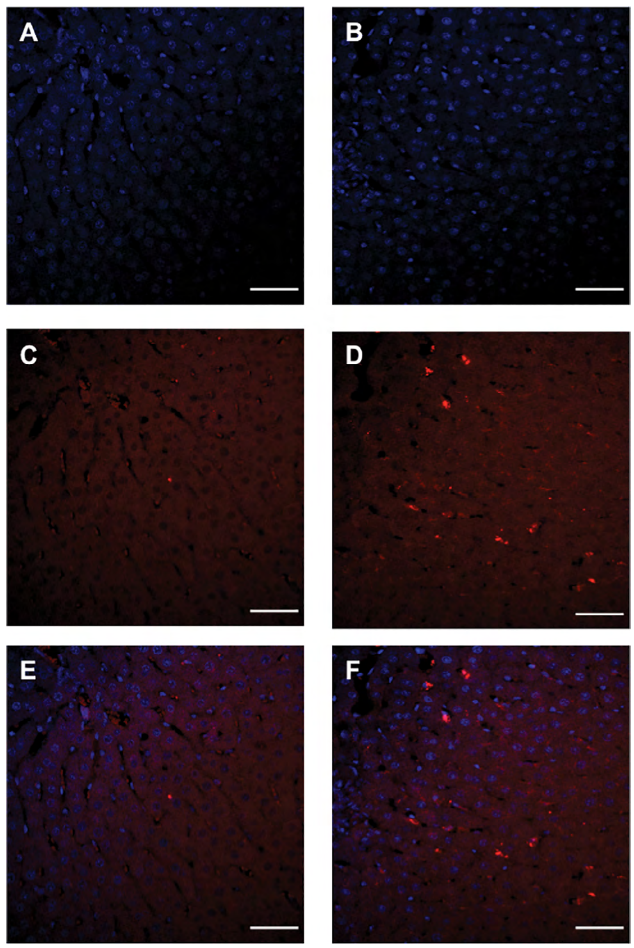

Fig. 3.