**Therapeutic potential of microRNAs and stem cell-derived factors in treating liver disease**

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Liver fibrosis, a major characteristic of chronic liver diseases, is regulated by a complex network of signaling pathways. Hedgehog (Hh) signaling regulates hepatic fibrogenesis. MicroRNAs (miRNAs) mediate various cellular processes; however, their role in liver fibrosis is unclear. Here we investigate regulation of miRNAs in chronically damaged fibrotic liver. MiRNA profiling shows that expression of miR-378 family members (miR-378a-3p, miR-378b, and miR-378d) declines in carbon tetrachloride (CCl4)-treated compared with corn-oil-treated mice. Overexpression of miR-378a-3p, directly targeting Gli3 in activated hepatic stellate cells (HSCs), reduces expression of Gli3 and profibrotic genes but elevates the inactivation marker, *gfap*, of HSCs in CCl4-treated liver. Smo blocks transcriptional expression of miR-378a-3p by activating the p65 subunit of nuclear factor kappa B (NF-κB). The hepatic level of miR-378a-3p is inversely correlated with expression of Gli3 in tumor and non-tumor tissue in human hepatocellular carcinoma. Our results demonstrate that miR-378a-3p suppresses activation of HSCs by targeting Gli3, and its expression is regulated by Smo-dependent NF-κB signaling, suggesting miR-378-3p has therapeutic potential for liver fibrosis.

Therapeutic effects of Mesenchymal stem cells (MSCs) in the treatment of liver disease are known to be mediated by secreting tropic and immunomodulatory molecules. Since these factors secreted from MSCs were known to create a favorable micro-environment for liver regeneration, it is necessary to identify and characterize such biologically active soluble factors. Tumor necrosis factor-inducible gene 6 protein (TSG-6), one of the cytokines released by human MSC, has an anti-inflammatory effect and alleviates several pathological conditions; however, the hepatoprotective potential of TSG-6 remains unclear. Hence, it was examined whether TSG-6 promoted liver regeneration in liver failure. First, we investigated the effect of TSG-6 in hepatocytes of chronically damaged liver, and demonstrated that TSG-6 contributed to the liver regeneration by enhancing the autophagy influx in hepatocytes in mice with NASH. In second, we have investigated the biological effect of TSG-6 on hepatic stellate cells (HSCs). Liver fibrosis is a major characteristic of liver disease. When the liver is damaged, quiescent HSCs transdifferentiate into proliferative myofibroblastic/activated HSCs, which are the main contributors to liver fibrosis. Hence, a strategy for regulating HSC activation is important in the treatment of liver disease. TSG-6 decreased HSC activation markers and increased senescence markers with upregulation of stem cell markers. TSG-6 also promoted these cells to form spherical organoids, which exhibited elevated expression of stemness-related genes. These organoids differentiated into functional hepatocytic cells under specific culture conditions. Organoids derived from TSG-6-treated HSCs regenerated livers in organoid transplant mice subjected to CCl4 treatment (which induces liver fibrosis). These findings demonstrate that TSG-6 induces the conversion of HSCs into stem cell-like cells in vitro and that organoids derived from TSG-6-treated HSCs can restore fibrotic liver.

Taken together, these results suggest that TSG-6 has therapeutic potential for the treatment of liver diseases.