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Role of Bone Marrow in Pathophysiology of Hepatic Fibrosis and Regeneration

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Objective: It is recently reported that bone marrow (BM)-derived cells participate in either progression or regression of liver fibrosis by expressing collagen and matrix metalloproteinases (MMPs) [1], respectively. Here we examined the functional role of BM in hepatic fibrosis and regeneration.

Methods: BM of wild type mice was replaced by cells obtained from transgenic mice harboring a promoter of alpha2(I) collagen gene (COL1A2) linked to enhanced green fluorescent protein (EGFP) gene. Liver fibrosis was introduced into those mice or their BM recipients by repeated carbon tetrachloride (CCI4) injections. To examine the effects of MMPs on migration and function of BM cells, MMP-13 knockout (KO) mice and recombinant adenoviruses overexpressing MMP-13 were used in the CCI4-induced liver fibrosis model.

Results: A large number of EGFP-expressing cells were observed in fibrotic liver of transgenic COL1A2/EGFP mice. In contrast, there were few, if any, EGFP-expressing cells detected in the fibrotic liver of COL1A2/EGFP recipients. Experiments using MMP-13 KO mice indicated that BM cells-derived MMP-13 certainly contributes to the regression of liver fibrosis. Overexpression of MMP-13 remarkably enhanced the migration of BM-derived cells into the parenchyma of fibrotic liver, and some of which exhibited the phenotype of sinusoidal endothelial cells.

Conclusions: By using a specific experimental system which detects exclusively BM-derived collagen-producing cells, the role of BM-derived cells was very limited in collagen production during hepatic fibrosis. On the other hand, overexpression of MMP-13 enhanced the migration of BM-derived cells and their differentiation, which suggests the therapeutic implications in the repair and regeneration of fibrotic liver.

REFERENCES

S6-4
Resolution of Tissue Fibrosis by siRNA HSP47 encapsulated in Vitamin A bound Liposome.

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There are currently no approved antifibrotic therapies for liver cirrhosis. We used vitamin A-coupled liposomes to deliver small interfering RNA (siRNA) against gp46, the rat homolog of human heat shock protein 47, to hepatic stellate cells.

Our approach exploits the key roles of these cells in both fibrogenesis as well as uptake and storage of vitamin A. Five treatments with the siRNA-bearing vitamin A-coupled liposomes almost completely resolved liver fibrosis and prolonged survival in rats with otherwise lethal dimethylnitrosamine-induced liver cirrhosis in a dose- and duration-dependent manner.

Rescue was not related to off-target effects or associated with recruitment of innate immunity. Receptor-specific siRNA delivery was similarly effective in suppressing collagen secretion and treating fibrosis induced by CCl4 or bile duct ligation. The efficacy of the approach using both acute and chronic models of liver fibrosis suggests its therapeutic potential for reversing human liver cirrhosis.

Because recent investigations suggest wide distribution of stellate cells in other tissues, we then extended our exploration to examine if our approach is also valid for other organ fibrosis including lung fibrosis, chronic pancreatitis and myelofibrosis. Results so far obtained indicate promise of our approach in application to these fibroses.

Mechanisms underlying such dramatic effect involved 1) inhibition of collagen secretion from stellate cells by siRNAHSP47, 2) resolution of predeposited collagen fiber by metalloproteinase in the fibrosis tissue and 3) apoptosis of stellate cells caused by removal of collagen matrix which triggers survival signal (PI3K/AKT/1KB) for stellate cells.

We are currently developing a new complex consisted of VA, biodegradable polymer and siRNAHSP47 for future clinical application of our modality.