Fibroblast growth factor 2 conjugated superparamagnetic iron oxide nanoparticles (FGF2-SPIONs) ameliorate hepatic stellate cells activation in vitro and acute liver injury in vivo

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Abstract	Liver diseases are the growing health problem with no clinically approved therapy available. Activated hepatic stellate cells (HSCs) are the key driver cells responsible for extracellular matrix deposition, the hallmark of liver fibrosis. Fibroblast growth factor 2 (FGF2) has shown to possess anti-fibrotic effects in fibrotic diseases including liver fibosis, and promote tissue regeneration. Among the fibroblast growth factor receptors (FGFRs), FGF2 interact primarily with FGFR1, highly overexpressed on activated HSCs, and inhibit HSCs activation. However, FGF2 poses several limitations including poor systemic half-life and stability owing to enzymatic degradation. The aim of this study is to improve the stability and half-life of FGF2 thereby improving the therapuetic efficacy of FGF2 for the treatment of liver fibrosis. We found that FGFR1-3 mRNA levels were overexpressed in cirrhotic human livers, while FGFR1c, 2c, 3c, 4 and FGF2 mRNA levels were overexpressed in TGF beta-activated HSCs (LX2 cells) and FGFR1 protein expression was highly increased in TGF beta-activated HSCs. Treatment with FGF2 inhibited TGF beta-induced HSCs activation, migration and contraction in vitro. FGF2 was conjugated to superparamagnetic iron-oxide nanoparticles (SPIONs) using carbodiimide chemistry, and the resulting FGF2-SPIONs were confirmed by dynamic light scattering (DLS), zeta potential, dot-blot analysis and Prussian Blue ironstaining. In vitro, treatment with FGF2-SPIONs evidenced increased therapeutic effects (attenuated TGF beta-induced HSCs activation, migration and contraction) of FGF2 in TGF beta-activated HSCs and ameliorated early liver fibrogenesis in vivo in acute carbon tetrachloride (CCl4)-induced liver injury mouse model. In contrast, free FGF2 showed no significant effects in vivo. Altogether, this study presents a promising therapeutic approach using FGF2-SPIONs for the treatment of liver fibrosis.
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