Hepatocellular Nuclear Factor 4 alpha (HNF-4 alpha) activation by saRNA rescues dyslipidemia and promotes favorable metabolic profile in a high fat diet (HFD) fed rat model.

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Abstract

Background:

Nonalcoholic fatty liver disease (NAFLD) culminates in insulin resistance and metabolic syndrome. As yet there is no approved single agent that targets steatosis or its pathological progression to hepatitis. Hepatocyte-nuclear-factor 4-alpha (HNF-4α) is at the centre of a complex transcriptional network where its disruption is directly linked to diabetes and steatosis. Re-activating HNF-4α expression in NAFLD could therefore reverse pathology.

Aim:

Small activating RNAs (saRNAs), designed synthetically for upregulating HNF-4α expression in hepatocytes, was administered intravenously (I.V) into a rat NAFLD model. These animals were sustained on a high fat diet (HFD) for 16 weeks to induce pathology. I.V. delivery (3x injections) of saRNAs (0.6mg/kg) beginning at week 16 was performed using 5-(G_5)-triethanolamine-core poly(amidoamine) dendrimers. Treatment continued for a further two weeks (1 x injection per week) whilst the animals were maintained on HFD.

Results:

saRNA treatment caused a significant increase in HNF4A transcript levels in the liver. This was also followed by a reduction in liver triglyceride; increased HDL/LDL ratio and decreased white adipose tissue/body weight ratio. Since HNF-4α is a key transcriptional factor in hepatocytes we analysed saRNA transfected liver cells for global phoshoproteomic changes driven by HNF4A upregulation. We observed significant beneficial changes in proteins regulating in sphingolipid metabolism, fatty acid β-oxidation, ketogenesis, detoxification of reactive oxygen species and lipid transport

Conclusions:

We demonstrate that HNF-4α (currently an undruggable target) can be specifically activated by saRNAs when delivered using nanoparticles with high tropism to the liver. HNF4A-saRNA treatment induced a favorable metabolic profile; thus potentially representing a single agent for the treatment of NAFLD and insulin resistance.

Keywords: Oligonucleotides; small activating RNA, nanoparticles, NAFLD, HNF4A, Fatty liver disease