Micro RNA based Novel therapeutics for the treatment of Alcoholic Liver Disease

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Technology description

Inflammatory liver disease (ILD) is rapidly becoming a major global problem and is associated with a high mortality rate. ILDs may be caused by a variety of factors including viral infections, environmental stimuli (drugs, alcohol), autoimmunity or genetic mutations. Alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH) are leading causes of ILDs, leading to chronic liver inflammation associated with overproduction of TNFa and other pro-inflammatory factors. Previous clinical trials using anti-TNF antibodies have proven unsuccessful due to significant risk of increased infection arising from complete TNF blockade. Thus, as ILDs lack specific treatment, there is an urgent requirement to develop novel alternate therapies.
MicroRNAs (miRNAs) are a class of small, non-coding RNAs that modulate various physiological processes. UMass Medical School researchers, Gyongyi Szabo & colleagues, have identified miRNA-155 (miR-155), as a key regulator of TNFα, a pro-inflammatory cytokine, which is elevated in ALD and other ILDs.In vitroandin vivostudies indicate that administration of miR-155 antagonists decreased TNFα levels, providing a novel method for regulating liver inflammation associated with ILDs, while preserving host immunity in the liver.

Up-regulation of microRNA-155 in macrophages contributes to increased tumor necrosis factor {alpha} (TNF{alpha}) production via increased mRNA half-life in alcoholic liver disease.

Abstract

Activation of Kupffer cells (KCs) by gut-derived lipopolysaccharide (LPS) and Toll-Like Receptors 4 (TLR4)-LPS-mediated increase in TNFα production has a central role in the pathogenesis of alcoholic liver disease. Micro-RNA (miR)-125b, miR-146a, and miR-155 can regulate inflammatory responses to LPS. Here we evaluated the involvement of miRs in alcohol-induced macrophage activation. Chronic alcohol treatmentin vitroresulted in a time-dependent increase in miR-155 but not miR-125b or miR-146a levels in RAW 264.7 macrophages. Furthermore, alcohol pretreatment augmented LPS-induced miR-155 expression in macrophages. We found a linear correlation between alcohol-induced increase in miR-155 and TNFα induction. In a mouse model of alcoholic liver disease, we found a significant increase in both miR-155 levels and TNFα production in isolated KCs when compared with

pair-fed controls. The mechanistic role of miR-155 in TNFα regulation was indicated by decreased TNFα levels in alcohol-treated macrophages after inhibition of miR-155 and by increased TNFα production after miR-155 overexpression, respectively. We found that miR-155 affected TNFα mRNA stability because miR-155 inhibition decreased whereas miR-155 overexpression increased TNFα mRNA half-life. Using the NF-κB inhibitors, MG-132 or Bay11-7082, we demonstrated that NF-κB activation mediated the up-regulation of miR-155 by alcohol in KCs. In conclusion, our novel data demonstrate that chronic alcohol consumption increases miR-155 in macrophages via NF-κB and the increased miR-155 contributes to alcohol-induced elevation in TNFα production via increased mRNA stability.

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