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Treatment of non-alcoholic steatohepatitis with the designer cytokine IC7Fc

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Background: Non-alcoholic fatty liver disease (NAFLD) is increasing at an alarming rate due, in part to the rising incidence of obesity worldwide. A proportion of patients with NAFLD will progress to the more seious liver disease termed non-alcoholic steatohepatitis (NASH), which is a risk factor for the development of hepatocellular carcinoma (HCC) (1). Our recently study found that, even though NASH is a liver-specific disorder, the gut-liver axis plays a key role in the disease progression as well (2). In an effort to treat metabolic disorders including NASH, we generated a chimeric cytokine, IC7Fc which improved liver steatosis and metabolic homeostasis in mice (3). In addition, activation of gp130 signalling, the downstream signalling target of IC7Fc, can protect the gut from high-fructose induced intestinal barrier deterioration and NASH(2). Accordingly, we tested the hyoyhesis that IC7Fc could be a potential treatment for NASH.

Methods: MuP-uPA transgenic mice have been shown to be a useful animal model to mimic human NASH progression(4). 24 MuP-uPA mice were randomly divided into IC7Fc-treated group (n=12) and Fc control-treated group (n=12). All the mice were fed high fat diet (HFD) from their 6 weeks to 23 weeks of age. During this diet intervention, mice underwent intraperitoneal injection of IC7Fc (1mg/kg) or Fc control weekly and body weight and body composition were monitored via magnetic resonance imaging. Liver tissues were obtained at their 12 weeks and 23 weeks of age for H&E and Sirius Red staining. Mice were anaesthetized by isoflurane inhalation and humanely killed at their 23 weeks of age, then tissues were collected immediately and colonic length was measured.

Results: Compared with Fc control-treated group, IC7Fc decreased fat body mass and slightly increase lean body mass. Liver steatosis, hepatocellular ballooning and inflammation infiltration tended (NS) to improve when comparing IC7Fc with Fc control. Consumption of a HFD decreases colonic length in mice, which is thought to contribute to the pathophysiology of such a diet. Importantly, we observed that treatment of IC7Fc prevented ($P<0.05$) the HFD-induced shortening in colonic length.

Conclusion: IC7Fc plays a positive role in NASH progression, while exerts significantly positive effects on gut protection.

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