THE LINK BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND INSULIN RESISTANCE BY HEPATOCYTE-DERIVED FIBRINOGEN-RELATED PROTEIN 1

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OBJECTIVE Non-alcoholic fatty liver disease (NAFLD) is highly correlated with insulin resistance (IR); however, the link between these two diseases was still obscure. It was known that hepatocyte-derived fibrinogen-related protein 1 (HFREP-1) is a hepatokine that plays an important role in hepatogenesis in embryonic stage, whereas the role of this protein in NAFLD and IR was unknown. Thus, the aim of this study was to clarify the role of HFREP-1 in these two diseases.

MATERIAL AND METHODS A total of 200 healthy and diabetic patients with or without NAFLD was enrolled for the determination of plasma HFREP-1 concentrations by commercial assay kits. Lentiviral vectors containing HFREP-1 or short hairpin RNA targeted to HFREP-1 were injected through portal vein in mice to overexpress or knockdown HFREP-1. Glucose and insulin tolerance tests, as well as hyperinsulinemic-euglycemic clamp were used to evaluate insulin sensitivity. HepG2 hepatocellular carcinoma cell line was used for the investigation of mechanisms in detail.

RESULT In this study, we found that plasma HFREP-1 concentrations were significantly increased in subjects with prediabetes, including impaired fasting glucose and impaired glucose tolerance, and gradually increased in diabetic patients. In addition, plasma HFREP-1 concentrations were significantly increased in subjects with NAFLD than those without it. Hepatic overexpression of HFREP-1 induced lipid accumulation in liver and systemic IR through an ERK1/2-dependent pathway. On the other hand, knockdown of hepatic HFREP-1 improved high fat diet-induced NAFLD and IR.

CONCLUSION HFREP-1 is a novel therapeutic candidate to combat NAFLD and IR.