Summary

Non-alcoholic steatohepatitis (NASH) is a disorder characterized by simultaneous fat accumulation and chronic inflammation in the liver. In this study, Pin1 expression was revealed to be markedly increased in the livers of mice with MCDD (Methionine choline-deficient diet)-induced NASH, a rodent model of NASH. In addition, Pin1 KO mice were highly resistant to MCDD-induced NASH, based on a series of data showing simultaneous fat accumulation, chronic inflammation and fibrosis in the liver. In terms of Pin1-induced fat accumulation, it was revealed that the expression levels of PPARα and its target genes were higher in the livers of Pin1 KO mice than in controls. Thus, resistance of Pin1 KO mice to hepatic steatosis is partially attributable to lack of Pin1-induced down-regulation of PPARα, although multiple other mechanisms are apparently involved.

Another mechanism involves the enhancing effect of hematopoietic Pin1 on the expressions of inflammatory cytokines such as tumor necrosis factor and monocyte chemoattractant protein 1 through NF-κB activation, eventually leading to hepatic fibrosis.

Finally, to distinguish the roles of hematopoietic or non-hematopoietic Pin1 in NASH development, mice lacking Pin1 in either non-hematopoietic or hematopoietic cells were produced by bone marrow transplantation between wild-type and Pin1 KO mice. The mice having non-hematopoietic Pin1 exhibited fat accumulation without liver fibrosis on the MCD diet. Thus, hepatic Pin1 appears to be directly involved in the fat accumulation in hepatocytes, while Pin1 in hematopoietic cells contribute to inflammation and fibrosis.

In summary, this is the first study to demonstrate that Pin1 plays critical roles in NASH development. This report also raises the possibility that hepatic Pin1 inhibition to the appropriate level might provide a novel therapeutic strategy for NASH.