News Release

Title

The sodium-glucose cotransporter-2 inhibitor Tofogliflozin prevents the progression of nonalcoholic steatohepatitis–associated liver tumors in a novel murine model

Key Points

- Genetically obese melanocortin 4 receptor (*Mc4r*)-deficient mice fed Western diet developed hepatic steatosis, NASH, and multiple liver tumors sequentially up to 1 year.
- *Mc4r*-deficient mice fed Western diet receiving a chemical procarcinogen developed multiple liver tumors together with obesity, diabetes, and NASH within a relatively short period (approximately three months).
- The sodium glucose cotransporter 2 inhibitor Tofogliflozin prevented the development of NASH-like liver phenotypes and the progression of liver tumors in the accelerated model.
- This study provides a unique animal model of NASH-associated liver tumors, which is applicable for assessing drug efficacy to prevent or treat NASH-associated liver tumors.

Summary

Diabetes and obesity contribute to the pathogenesis of nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). However, how diabetes and obesity accelerate liver tumorigenesis remains to be fully understood. Moreover, to verify the therapeutic potential of anti-diabetic drugs, there exists a strong need for appropriate animal models that recapitulate human pathophysiology of NASH and HCC. We previously reported that genetically obese melanocortin 4 receptor (*Mc4r*)-deficient mice fed Western diet develop hepatic steatosis, NASH, and multiple liver tumors sequentially up to 1 year. In this study, we established a novel murine model of NASH-associated liver tumors in combination with *Mc4r*-deficient mice fed on Western diet and a chemical procarcinogen. Our model developed multiple liver tumors together with obesity, diabetes, and NASH within a relatively short period (approximately 3 months). Using this model, we demonstrated that sodium glucose cotransporter 2 inhibitor Tofogliflozin prevented the development of NASH-like liver phenotypes and the progression of liver tumors. In terms of the underlying mechanism, our data suggest that Tofogliflozin treatment attenuates cellular senescence of hepatocytes under obese and diabetic conditions. This study provides a unique animal model of NASH-associated liver tumors, which is applicable for assessing drug efficacy to prevent or treat NASH-associated HCC.

Research Background

Diabetes and obesity contribute to the pathogenesis of nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). However, how diabetes and obesity accelerate liver tumorigenesis remains to be fully understood. Moreover, to verify the therapeutic potential of anti-diabetic drugs, there exists a strong need for appropriate animal models that recapitulate human pathophysiology of NASH and HCC.

Research Results

We established a novel murine model of NASH-associated liver tumors using genetically obese melanocortin 4 receptor-deficient mice fed on Western diet in combination with a chemical procarcinogen, and verified the validity of our model in evaluating drug efficacy. Our model developed multiple liver tumors together with obesity, diabetes, and NASH within a relatively short period (approximately three months). In this model, sodium glucose cotransporter 2 inhibitor Tofogliflozin prevented the development of NASH-like liver phenotypes and the progression of liver tumors. Tofogliflozin attenuated p21 expression of hepatocytes in non-tumorous lesions in the liver.

Research Summary and Future Perspective

This study provides a unique animal model of NASH-associated liver tumors within a relatively short period, which is applicable for assessing drug efficacy. Using this model, we demonstrated that the SGLT2 inhibitor Tofogliflozin prevented the development of NASH-like liver phenotypes and the progression of liver tumors. In terms of the underlying mechanism, our data suggest that Tofogliflozin treatment attenuates cellular senescence of hepatocytes under obese and diabetic conditions.

Publication

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