COMMENT ON LIU ET AL.

Aberrant Expression of FBXO2 Disrupts Glucose Homeostasis Through Ubiquitin-Mediated Degradation of Insulin Receptor in Obese Mice. Diabetes 2017;66:689–698

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Diabetes 2020;69:e1 | https://doi.org/10.2337/db19-0975

F-box only protein 2 (FBXO2, or FBX2) is an E3 ubiquitin protein ligase highly expressed in the brain and cochlea but not the liver (1,2). It was reported by Liu et al. (3) that hepatic FBXO2 elevation causes hyperglycemia in obese mice. Here, we share some comments on their article.

To better understand how hepatic FBXO2 regulates hyperglycemia, we first validated the specificity of FBXO2 antibody (ab133717; Abcam) used by Liu et al. (3) by immunoblotting, using the whole-cell lysates of FBXO2 knockout mice (including heterozygous $^{+/-}$ and homozygous $^{-/-}$), with C57BL/6J (wild-type) as a control (1,2). Generally, FBXO2 is highly expressed in the brain, e.g., in the hypothalamus, and hepatic FBXO2 protein levels are very low in healthy mice (1,2). The immunoblotting results showed that the predicted single band of FBXO2 protein was shown at ~35 kDa. Multiple bands were observed in liver samples. Of importance, there was no significant difference in protein expression levels between hypothalamic and liver samples or among $^{+/+}$, $^{+/-}$, and $^{-/-}$ samples. In addition, the pattern of hepatic FBXO2 bands was inconsistent with the results reported by Liu et al. (3) in diabetic *db/db* mice (000697; The Jackson Laboratory). Our results suggested that the FBXO2 antibody from Abcam did not specifically recognize FBXO2 protein in C57BL/6J and FBXO2 knockout mice.

Further, we conducted a parallel feeding study in male wild-type and homozygous FBXO2 knockout ($^{-/-}$) mice (1,2) at 6 weeks of age for 8 weeks with the high-fat diet used by Liu et al. (3) (D12492; Research Diets, Inc.), with chow diet feeding as a control. The animals had free access to water and food throughout the study. Depletion of FBXO2 did not cause insulin resistance or elevation of the fasting blood glucose level before and/or after a chow diet feeding. However, both strains were obese and insulin resistant and had significantly elevated levels of fasting blood glucose, plasma free fatty acids, total cholesterol, and LDL cholesterol after the high-fat diet intervention. These changes did not differ by strains. The results suggested that FBXO2 depletion did not alter the glucose homeostasis in these mouse models fed the chow or high-fat diet. Thus, we conclude that FBXO2 might not mediate glucose homeostasis in obese diabetic mice.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

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