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EDITORIAL

Modeling NASH and NASH-Induced Hepatocellular Carcinoma: Faster and Better

Nonalcoholic steatohepatitis (NASH), a more severe manifestation of nonalcoholic fatty liver disease, is defined by excessive liver fat accumulation, lobular inflammation, and hepatocyte ballooning with or without perisinusoidal fibrosis. Progressive liver injury in NASH can eventually lead to cirrhosis, which confers an increased risk of developing hepatocellular carcinoma (HCC). Given the increasing prevalence of NASH, NASH-induced HCC is predicted to be the leading indication for liver transplantation in the United States within a decade.[1] NASH and NASH-related HCC are becoming a significant public health concern, which is confounded further by the lack of effective treatments. Therefore, there is a pressing need for novel therapeutic strategies guided by the molecular underpinnings of disease pathogenesis and progression. Preclinical studies using animal models are essential for understanding disease pathogenesis, identifying molecular targets, and developing mechanistically based therapeutic interventions. Despite the abundance of various animal models,[2] most experts in the field would agree that there still is a necessity for improved models of NASH and, in particular, NASH-induced HCC that would be both time-efficient and closely mimic the etiology of human disease (eg, overnutrition-induced obesity and metabolic syndrome), underlying pathogenetic mechanisms (eg, pathways involved in disease onset and progression), histologic features, and disease progression from NASH to cirrhosis and NASH-associated HCC.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ganguly et al[3] characterize a novel, accelerated mouse model of Western diet–induced NASH and NASH-driven HCC, and provide insights into the cross-talk and kinetics of hepatic and extrahepatic alterations, especially in the gut, during NASH progression. To this end, Ganguly et al[3] studied mice with a loss-of-function mutation in the *Alms1* gene, also known as *fat Aussie* or *Foz/Foz* mice.[4] The exact function of the ALMS1 protein remains unknown. However, mutations in *ALMS1* in humans cause Alström syndrome, a rare genetic disorder associated with childhood obesity, insulin resistance, heart disease, and other symptoms affecting multiple organ systems of the body. The *Foz/Foz* mice are hyperphagic, have reduced physical activity, quickly become obese (within 4 months), and show multiple features of the metabolic syndrome, including insulin resistance, dyslipidemia, and hypertension.[4] *Foz/Foz* mice fed high-calorie diets have been used previously to model NASH in a couple of studies. In the present report, however, Ganguly et al[3] selected a Western diet and performed a comprehensive characterization of the model. Strikingly, *Foz/Foz* mice on the Western diet developed severe obesity and histologic features of NASH within 4 weeks of feeding, and NASH with grade 3 fibrosis after 12 weeks on the diet. A wide array of experiments, including transcriptomic profiling and microbiome analyses, illuminated the molecular and cellular alterations in hepatic and gut tissue during NASH progression as well as regression (modeled by switching from the Western diet to standard chow). Notably, the report nicely shows that the transcriptome of *Foz/Foz* NASH livers displayed a significant overlap with human NASH livers. Thus, NASH in *Foz/Foz* mice seems to faithfully mimic human disease etiology and pathobiology. Moreover, this approach represents a significantly accelerated diet-induced NASH model given that commonly used C57Bl/6 mice usually are fed a Western diet for up to 24 weeks to induce NASH with fibrosis[2,5] (Figure 1).

When kept on the Western diet for 24 weeks, the *Foz/Foz* mice developed cirrhosis and hepatocellular malignancy (75% of the mice), classified as either conventional (trabecular) HCC or steatohepatitic HCC.[3] Again, this represents very fast disease progression given that C57Bl/6 mice usually do not develop HCC even after 52 weeks of Western diet feeding. The majority of current mouse models of NASH-related HCC rely on tumor induction that has limited relevance to human NASH-HCC. Commonly used models use genetic manipulations, such as oncogene activation (eg, MYC proto-oncogene overexpression) or administration of toxins (eg, diethylnitrosamine, CCl_4, streptozotocin) to mice fed with NASH-inducing diets.[6] A recently developed inbred mouse strain, nicknamed *DIAMOND mice*, progresses to HCC within 52 weeks when fed a Western diet paired with a high-fructose, high-glucose solution, representing a clinically suitable approach.[7] Thus, most existing animal models have a rather delayed HCC onset or do not replicate the etiology and natural history of human NASH-driven HCC. Conversely, Western diet–fed *Foz/Foz* mice resemble human disease etiology and develop NASH-HCC in a reasonable time frame for preclinical research. An aspect not reported in the study by Ganguly et al[3] but worth further exploration is the in-depth molecular characterization of HCC tumors in Western diet–fed *Foz/Foz* mice. Future studies are necessary to comprehend the transcriptomic and mutational landscape of this murine HCC in comparison with human NASH-induced HCC, which will be the ultimate test of human pathophysiological relevance.

The ideal animal model of NASH should recapitulate the multifaceted mechanisms of human disease efficiently and be reproducible. Current mouse models of

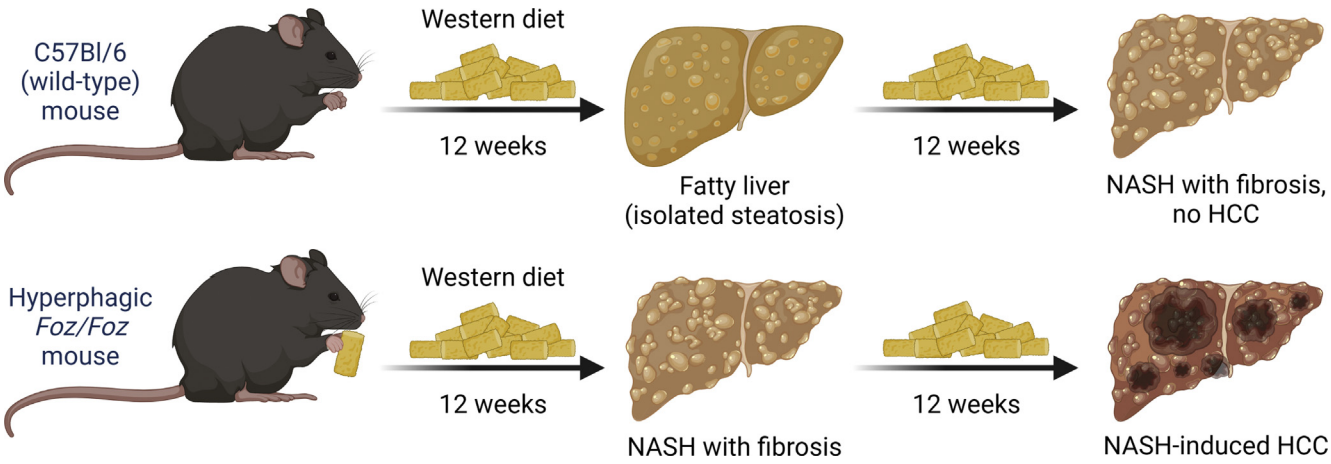

Figure 1. Accelerated murine model of NASH with fibrosis and NASH-driven HCC. Appetite-dysregulated mice lacking a functional *Alms1* gene, termed *Foz/Foz* mice, develop NASH with fibrosis and HCC on the background of cirrhosis when fed a Western diet for 12 weeks and 24 weeks, respectively. This represents a significantly accelerated onset and progression of NASH when compared with Western diet–fed wild-type mice, which commonly require up to 24 weeks of feeding to develop NASH with fibrosis.[5] Schematic was created using BioRender.com (Toronto, Canada).

NASH or NASH-HCC address only selected aspects of disease pathogenesis and have variable translational and clinical utility. The optimized model of NASH and NASH-induced HCC using Western diet–fed *Foz/Foz* mice could be well applicable for studies of disease pathogenesis and progression, as well as the development of new therapies for NASH with or without comorbid hepatocarcinogenesis.

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