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EDITORIAL

Lamin Deficiency in the Liver Sets the Stage for Nonalcoholic Steatohepatitis Development in Males

Nuclear lamins are type V intermediate filament proteins that play important roles in maintaining nuclear shape and in transcriptional regulation. Moreover, they serve as signaling scaffolds at the inner nuclear membrane.[1] Nuclear lamins fall into 2 separate classes, A-type and B-type, which are encoded by distinct genes. Mutations in their genes lead to tissue-selective disease phenotypes, termed *laminopathies*, which can affect muscle, adipose tissue, bone, liver, or multiple tissues depending on the site of the mutation.[2] Mutations in LMNA, encoding nuclear intermediate filament proteins lamins A and C in humans, cause multiple laminopathies including muscular dystrophy, dilated cardiomyopathy, and Dunnigan-type familial partial lipodystrophy (FPLD2).[3] Interestingly, LMNA variants, particularly those associated with FPLD2, can cause hepatic steatosis,[4] and missense mutations in LMNA are believed to contribute to metabolic syndrome.[5,6] To date, the mechanism by which lipodystrophy-associated lamin mutations promote hepatic steatosis and metabolic syndrome remains unclear.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Kwan et al[7] elegantly address the role of lamin A/C specifically in the liver. The authors generated mice carrying a hepatocyte-specific deletion of *Lmna* and demonstrated that hepatic *Lmna* deficiency induces spontaneous steatosis and liver injury in a gender-specific manner.

To begin with, lamin A/C knockout (KO) hepatocytes showed abnormal nuclear morphology, as indicated by electron microscopy findings of misshapen nuclei as compared with wild-type (WT) hepatocytes. To assess the effect of lamin A/C deficiency on liver injury, Kwan and et al[7] fed WT and KO mice a normal diet (ND) or high-fat diet (HFD) supplemented with sucrose-fructose in the drinking water for 14 weeks. Male lamin A/C–deficient mice fed an ND spontaneously developed liver injury and steatosis that progressed with age, whereas female KO mice did not. Importantly, HFD feeding resulted in even more pronounced differences between WT and KO male and female mice, with inflammatory infiltrates present in livers of male KO mice. Notably, there were no changes in serum triglycerides between WT and KO mice under either dietary condition. Livers from hepatocyte lamin A/C–deficient males had upregulated expression of genes important in fatty acid metabolism, immunity, and interferon-related genes under ND and HFD conditions. Consistent with the histologic findings, HFD-fed KO mice showed increased expression of fibrosis-related genes.

The authors further investigated the underlying mechanism for the male-specific phenotype observed in hepatocyte lamin A/C–deficient mice. Because growth hormone (GH) signaling is known to regulate male-specific gene expression in hepatocytes[8] and *Hsd3b5*, a male-specific hepatic gene that is Stat5ab-dependent, was the most highly downregulated gene in male KO livers, the authors hypothesized that the GH/Stat5 signaling pathway is disturbed during hepatocyte lamin A/C deficiency. Through various well-designed cell culture experiments in primary hepatocytes, they showed that GH/Stat5 signaling is altered in *Lmna* KO livers, as indicated by reduced induction of Stat5 phosphorylation on GH stimulation. Moreover, phosphorylation of Stat5, Jak2, and Erk was reduced in male KO livers after GH administration. Taken together, these data indicate that hepatic *Lmna* deficiency dysregulates hepatic GH signaling, thereby affecting male-specific gene expression in the liver. The exact mechanism of how lamin A/C deficiency modulates Stat5 signaling deserves future investigation.

As concluded by the investigators, lamin A/C acts cell-autonomously to maintain hepatocyte homeostasis and nuclear shape and protects against male-selective steatohepatitis via GH signaling. Although no direct causative evidence has been reported, hepatic steatosis has been previously associated with genetic variants in LMNA[4] and is a common feature of FPLD2 patients, together with other signs of metabolic syndrome.[9] Further support comes from the study by Lüdtke et al[10] in which hepatic steatosis was studied in 6 FPLD2 families carrying either the LMNA R482W or R482Q mutations. In line with the current results, patients with the specific LMNA variant (rs57920071) had signs of hepatic steatosis by ultrasound and elevated serum liver enzyme activities, consistent with nonalcoholic steatohepatitis (NASH). Because of the outcome of the current study, fatty liver development in FPLD2 patients might be the result of hepatocyte-specific LMNA deficiency as opposed to a secondary effect of the presence of metabolic syndrome. Larger clinical genetic studies are required to determine the relevance of lamin polymorphisms for the development of NASH in male patients in particular.

These data provide new insight into the mechanisms by which lipodystrophy-associated lamin mutations can cause hepatic steatosis. Hepatocyte-specific lamin A/C in males represses hepatocyte storage of excess fatty acids, with consequent induction of hepatic inflammation and fibrosis leading to NASH.

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Conflicts of interest
The authors disclose no conflicts.

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