Reply to Letter to the Editor HEP-20-0593

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REPLY:

We sincerely thank Dr. Javitt for his interest in and perspective on our article.[1] He indicates that aspecific effects of Myrcludex B should be considered an explanation for increased biliary cholesterol and phospholipid secretion after Myrcludex B treatment as partial hepatectomy (PH) also leads to an increased contribution of pericentral hepatocytes to bile salt uptake and secretion, but biliary cholesterol and phospholipid secretion are not affected. In our opinion, nonspecific Myrcludex B–induced activation of canalicular or sinusoidal transporters seems unlikely given the absence of Na^+-taurocholate cotransporting polypeptide (NTCP) homology with these transporters and our data from experiments with scavenger receptor class B member 1 or adenosine triphosphate binding cassette subfamily G member 8 null mice. Myrcludex B is an NTCP-specific peptide showing minimal uptake by hepatocytes.

In contrast to the situation of Myrcludex B–mediated NTCP inhibition, PH acutely leads to a higher flow per gram liver; and periportal hepatocytes thus face a large influx of bile salts, close to their maximal transport capacity. As the bile salt to cholesterol/lecithin curve tends to plateau at higher bile salt concentrations, this explains a relatively low biliary cholesterol/lecithin secretion despite increased bile salt transport.[1,2] Another major adaptation upon PH is that the liver is reprogrammed toward rapid restoration of liver mass. This includes reduced cholesterol synthesis in periportal hepatocytes. Cholesterol and phospholipids are also pivotal for membrane formation in newly generated hepatocytes. The pool of hepatic cholesterol/lecithin available for biliary secretion is thus likely decreased after PH. Finally, PH leads to activation of the nuclear bile salt receptor farnesoid X receptor (FXR), stimulating hepatic regeneration. This is in contrast to Myrcludex B–treated mice, in which hepatic FXR activation is unaffected or even reduced and expression of FXR-regulated proliferative genes is repressed.

Dr. Javitt concludes his letter by stating that the canalicular concentration of bile salts is a major determinant of biliary cholesterol and phospholipid secretion. We partially agree with this notion but note that the amount of lipid secreted per bile acid molecule is variable[2] and that the location matters. Not hampered by adaptations occurring during liver regeneration, we have directly investigated zonation-related differences in bile formation using a very specific NTCP inhibitor combined with monitoring the distribution of a fluorescent bile salt.[1] The results are in line with a shift of hepatic bile salt uptake from predominantly periportal toward more pericentral hepatocytes, leading to increased canalicular exposure and more cholesterol and phospholipid excretion in bile while total biliary bile salts are not increased or are even decreased. It is not known to what extent such a shift occurs in the regenerating liver after PH, and given the complex adaptive changes after PH, this is difficult to predict without experimental data.

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