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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Rebuttal to: The Benevolent Bile: Bile Acids as Stimulants of Liver Regeneration

See Point-Counterpoint articles on pages 1474 and 1478.

Bhushan and Apte[1] highlight the beneficial effects of bile acids (BAs), such that increasing BA levels stimulate regeneration and recovery after partial hepatectomy (PH) or drug-induced acute liver injury. Although we agree with the protective role of BAs in liver regeneration, increasing evidence points to the fact that the composition of the BA pool is crucial for downstream signaling.

Hydrophobic BAs induce cytotoxicity while hydrophilic BAs alleviate liver injury, and the ratio of BAs in the pool determines the hydrophobic index. Deletion of small heterodimer partner[2] and a lithocholic acid–enriched diet[3] both can increase the hydrophobic BA pool, causing bile infarcts, bile duct obstruction, and liver injury. Moreover, altered BA composition after PH has been noted with a particular increase in cholic acid and a reduction in chenodeoxycholic acid, resulting in a more hydrophilic BA pool during regeneration. Mechanistically, the membrane Takeda G-protein–coupled receptor activation modulates BA composition to become more hydrophilic, and thus protects against cytotoxic BA accumulation.[4]

However, if the BA composition became more hydrophobic, it correlates with increased liver injury after PH in human beings and mice.[4] Mouse models with hydrophobic BA composition, including *Cyp2c70* knockout and *Cyp2a12/Cyp2c70* double-knockout mice, show inflammation and injury in the liver despite having a reduced overall BA concentration.[5] In addition, increasing evidence has shown that changes in BA composition can modulate immune responses in the liver and contribute to the pathogenesis of inflammatory diseases.[6]

BAs also activate cell death and survival pathways, and the balance between these signals determines the beneficial or toxic effects of specific BAs in the liver. For example, hydrophilic ursodeoxycholic acid induces hepatocyte apoptosis to clear them from inherent BA toxicity, whereas taurine conjugate of a slightly hydrophobic BA, chenodeoxycholic acid, facilitates survival pathways and hepatocyte proliferation.[7]

Apart from receptor-based cellular signaling, more recent data have uncovered the role of the gut microbiota–BA axis in several liver diseases. In fact, gut microbiota can facilitate the production of novel phenylalanine- and tyrosine-conjugated cholic acids that are enriched in disease conditions in human beings.[8] Furthermore, in patients with intrahepatic cholangiocarcinoma, gut microbiota correlate with BA levels and composition along with inflammatory cytokines.[9]

Therefore, appropriate regulation of BA composition, hydrophobic index, and overall concentration will influence if the outcome in the liver will be harmful or beneficial.

"Light. Darkness. A balance." -The Last Jedi

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