Bile acids are important for bile flow, digestion, and overall liver and metabolic health. Mutations in the bile salt export pump (BSEP) cause a potentially fatal cholestasis in children (PFIC2) due to a build-up of toxic bile acids. Dr Renxue Wang at the British Columbia Cancer Research Centre discovered that a PFIC2-mutation, engineered into mice, resulted in the production of tetrahydroxylated bile acids (THBA) that protect the mice. THBA behave like common bile acids, with little toxicity. Dr Wang and his colleagues are developing THBA therapeutics for cholestatic liver disease.

Bile acids facilitate the absorption of lipid soluble vitamins and dietary fats. They make up a major component of bile and are synthesised from cholesterol in the liver. Bile acids also regulate glucose and lipid metabolism. Bile acid imbalance can cause or exacerbate a wide range of liver and gastro-intestinal diseases.

Low toxicity bile acids can be used for treating bile acid imbalance. For instance, ursodeoxycholate (UDCA), a hydrophilic low toxicity bile acid originally isolated from bear bile, has been approved by the Food and Drug Administration to treat primary biliary cirrhosis (PBC) and is widely used in many other cholestatic diseases. However, UDCA is ineffective in many cholestatic liver diseases, for which no effective therapies are available. Novel low toxicity bile acids offer great opportunities as therapeutic agents for these liver diseases.

Figure 1. Selected diseases associated with bile acid imbalance. Cholestatic diseases or genetic diseases that cause cholestasis are indicated. Bile acid imbalance can exacerbate and cause progression of many common diseases (Reproduced based on Sheps et al., 2021, Biochim Biophys Acta – Mol Cell Biol Lipids. 1866(7):158925).

Table 1. Structure of bile acids

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Bile acid</th>
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<tbody>
<tr>
<td>Cholic acid</td>
<td>Taurine conjugation</td>
</tr>
<tr>
<td>Deoxycholic</td>
<td>Glycine conjugation</td>
</tr>
<tr>
<td>Lithocholic</td>
<td>Taurine conjugation</td>
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<td>Glycine conjugation</td>
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dr. renxue wang

Dr Renxue Wang and his colleagues from Dr Victor Ling’s Laboratory at the British Columbia Cancer Research Centre are working on the development of a promising treatment for diseases with bile acid imbalance. The researchers discovered that mice engineered with the same mutation as PFIC2 were little affected by cholestasis. Instead, the mice appeared to compensate for this otherwise fatal disease by making large quantities of THBA, a novel tetrahydroxylated bile acid.

THBA was discovered to be much less toxic than normal bile acids, so that its accumulation in the liver is less harmful. Moreover, THBA was able to promote bile flow, allowing the mutant mouse to live a normal life span.

Dr Wang and his colleagues subsequently showed that a high level of THBA can also protect mice from cholestatic disease, reducing liver inflammation, formation of gallstones and liver tumours. THBA is a product of one or more hydroxylation reactions carried out by the P450 cytochrome pathways triggered in animals – and patients – experiencing cholestatic stress. Mice are able to respond well to this stress while humans only produce THBA in minimal amounts; therefore, they are more vulnerable to the effects of cholestasis. Dr Wang and his colleagues suggest that THBA may be prime candidates to be developed as therapeutic agents for cholestatic and other bile acid-associated diseases.

The development of the BSEP/sPgp knockout mouse provided a unique model for gaining new insights into therapeutic interventions for cholestasis and understanding mechanisms associated with lipid homoeostasis. The surprising findings of the 2001 paper led to the hypothesis that THBA may have a protective effect on the liver in the genetically modified rodent model, leading to the milder form of cholestasis observed in Bsep mice, compared to humans with the same mutation.

THBA PREVENTS LIVER DAMAGE IN MICE LACKING THE MDRI GENE

The knockdown of a gene known as multi-drug resistance 2 (Mdr2) in mice produced 10 times less THBA than the Bsep knockout mice, as shown in both liver and plasma. In a recent paper, published in 2019 by Dr Wang and his colleagues, the authors describe the development of a double knock-out mouse model (DKO) by crossing Bsep and Mdr2 defective mice, to test whether the production of THBA, triggered by a lack of the Bsep gene, can protect DKO mice against the severe liver damage caused by their genetic defect in Mdr2. Defects in the human analogue of Mdr2 also causes a devastating, often fatal, childhood disease due to a biliary lipid secretory deficiency in the liver and resulting highly toxic bile acids in the bile ducts. The conclusions from this study were particularly significant, as they highlighted the potential for THBA to act as therapeutics for progressive liver pathologies brought on by abnormalities of bile flow. This study also showed that, in cholestasis, the concentration of toxic bile acids is the determining factor leading to progressive liver injury.

The authors found that the DKO mice displayed a very mild cholestatic disease.
behind the research

Dr Renxue Wang

Research Objectives

Dr Wang studies tetrahydroxylated bile acids (THBA) and its potential as a therapeutic agent for cholestatic and other bile acid associated diseases.

Detail

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Bio

Dr Renxue Wang is a scientist at the BC Cancer Research Centre in Dr Victor Ling’s laboratory. He discovered THBA and is a founder and Vice president of Research and Development at Qing Bile Therapeutics Inc, a company developing the Therapeutic potential of THBA.

References


Personal Response

What will the next steps in your research be?

There is much to be learnt about the properties and therapeutic applications of THBA in different diseases. Hundreds of isomers of tetrahydroxylated bile acids, depending on the position and configurations of the hydroxyl groups, can be synthesised. These THBA isomers have diverse chemical and physiological properties and can be tested for therapeutic applications in multiple liver and gastrointestinal disorders.

Dietary feeding with synthetic THBA can protect Mdr2 defective mice from liver damage.

THE PROTECTIVE ROLE OF THBA

In another recently accepted review paper, due to be published in 2021, Dr Wang and colleagues reviewed several studies that suggest that increased hydroxylation of bile acids is a common compensatory response observed in animals, and patients, experiencing cholestatic stress. This article reviewed earlier work on highly hydroxylated bile acids in different species. The authors speculate that there might be a role for these polyhydroxylated bile acids, in particular tetrahydroxylated bile acids (THBA), as protective agents in alleviating cholestatic stress and reducing the risk for liver damage. In humans and mice, THBA normally represent only a minor component of the bile acid pool and their functional significance has not been well established yet. It was only after the discovery that THBA appear to be a major component of the bile acid pool in Bsep knock out mice, that the Ling Lab decided to investigate the potential functional role of polyhydroxylated bile acids. Bile acid hydroxylation differs significantly between mice and humans, both normally and in response to cholestatic stress, and this strongly affects the toxicity of bile acids in the liver circulation.

CONCLUDING REMARKS

Dr Wang and his collaborators observed that elevated production of THBA, in genetically engineered mice that did not express the Bsep gene, protected these mice from severe cholestatic liver injury, which is often seen in humans lacking BSEP function. THBA are more hydrophilic and less cytotoxic than the usual bile acids; they can behave like the common bile acids in the sense that they can stimulate bile flow and can participate in the circulation to and from the liver. Dr Wang has founded Qing Bile Therapeutics Inc with the goal of developing THBA as potential therapeutic agents for hepatic protection. If his research is fruitful, this has the potential to treat a wide range of liver diseases in humans with cholestatic liver injury.