SL02 **Bile Formation: How It Goes Right and What Can Go Wrong**

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Bile formation has two main purposes: 1. disposition of drugs, toxins and waste products and 2. excretion of bile salts to allow dissolution of lipids in the intestine. Both functions make bile a very toxic fluid. The detergent action of bile salts potentially damages the biomembranes lining the biliary tree. Normally this does not happen but deficiencies in the biliary machinery have proven that various protective mechanisms prevent membrane dissolution. This protection is mediated by transport proteins in the apical membrane of hepatocytes and cholangiocytes. Thus, bile salts are secreted from hepatocytes into bile by the apical bile salt export pump (BSEP, ABCB11). This is the main process that drives bile flow through an osmotic mechanism and as a consequence, patients with mutations in the ABCB11 gene do not secrete bile salts and suffer from cholestasis. In parallel, hepatocytes secrete substantial amounts of phospholipid into bile through the action of a homologous ABC transporter, ABCB4. The activity of this secretion process is regulated by the amount of biel salt in the canalicular lumen of the hepatocytes. Secreted phospholipids combine with bile salts into mixed micelles. The presence of phospholipids reduces the detergent activity of simple bile salt micelles. The importance of this process is proven by the severe pathology associated with (complete) ABCB4 deficiency, which usually leads to liver failure within the first decade of life. Cholesterol is also secreted into bile through the ABC transporter ABCG5/8. This secretory process is essential for the elimination of plant sterols and cholesterol, but does not contribute to protection of the liver against bile salts. Yet another transport protein, ATP8B1 from the flippase family of Type 4 P-type ATPases, also fulfils a protective role by flipping phosphatidylserine from the outer to the inner leaflet of the apical membrane of hepatocytes and cholangiocytes. This flippase activity indirectly increases the relative amount of sphingolipid and cholesterol of the outer leaflet of these membranes, which makes them more detergent resistant. Deficiencies of ATP8B1, ABCB11 and ABCB4 lead to similar (but not identical!) forms of cholestasis and are therefore have been coined “Familial Intrahepatic Cholestasis” (type 1,2 and 3, respectively).

A versatile set of drug ABC transporters ensures biliary secretion of drugs, toxins and waste products. These apical transporters in the hepatocyte include ABCB1, ABCC2 and ABCG2. In situations of cholestasis, the hepatocyte protects itself against accumulation of these compounds by overflow towards the blood. This is mediated by basolateral ABC transporters, ABCC3, ABCC4 and ABCC5. The inevitable consequence of this overflow is accumulation of cholephilic compounds in the systemic blood, which has pathological consequences. It is well established that many patients with (any form of) cholestasis suffers from itch, which can become severe and intolerable. Cholestatic itch must be (indirectly) caused by the accumulation of cholephilic compounds in the circulation, because it resolves within 24 hours upon interruption of the enterohepatic circulation (by nasobiliary drainage or extracorporeal bile diversion). We have recently shown that the occurrence of cholestatic itch is closely associated with increased levels of autotaxin in systemic blood. Autotaxin is the enzyme in the circulation that is responsible for the conversion of lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA). LPA is a potent bioactive molecule that can signal through a family of LPA-recptors and is involved in many processes like cell motility, tumor growth and metastatizing capacity, but also neuropathic pain. When injected intradermally in mice, LPA gives rise to scratch behaviour. We are currently analyzing the potential role of LPA, generated by autotaxin, in initiation or potentiation of itch during cholestasis.