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Symposium 211
XXV International Bile Acid Meeting
Bile Acids in Health and Disease 2018

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The emergence of bile acids as therapeutic agents

The past several years have seen an unprecedented uptick in bile acid research ever since researchers first became aware of the therapeutic potential of bile acids and bile acid analogues, as well as the importance of bile acid signaling pathways. Most researchers have switched from their original focus on bile acid chemistry and are now concentrating on the search for therapeutic targets, starting with targets for liver and biliary diseases. Success in this goal will require close cooperation between basic research and clinicians. One well-established forum for this type of exchange is the periodic International Bile Acid Meeting convened by the Falk Foundation e.V., which has increased in size for several years. Over 500 researchers and clinicians from 40 countries took part in the XXV International Bile Acid Meeting in Dublin last year.

Since the last meeting in Düsseldorf in 2016, a number of breakthroughs have been made on the role of bile acid signaling pathways in the liver and the gut, and on their receptors in the gut-liver axis. The nuclear farnesoid X receptor (FXR) represents an essential receptor for bile acids, and is crucial for maintaining not only bile acid homeostasis but also metabolism. In addition to these functions, the receptor also appears to be involved in the development of obesity, NAFLD (nonalcoholic fatty liver disease), and NASH (nonalcoholic steatohepatitis). The TGR5 receptor (a G protein-coupled receptor) is also of clinical interest, as it for instance appears to play a crucial role in the pathogenesis and treatment of polycystic liver disease.

The complex interaction between bile acids and the gut microbiome was the topic of particularly exciting and intense discussions. This interaction appears to be an intriguing therapeutic target, for example in NAFLD. However, research on this subject is still in its infancy, and the hoped-for interventions are proving difficult. Nonetheless, new insights into bile acid transporters and into therapeutic strategies using bile acid derivatives or bile acid receptor agonists and antagonists, reinforce the hope that the leap to clinical practice is not far into the future.

Analyses into the molecular genetics of cholestatic disorders such as PFIC (progressive familial intrahepatic cholestasis) and various cholangiopathies are also of clinical interest. As a result of this intense research and of the close collaboration between researchers and clinicians, we have now reached a point where modulating bile acid signaling pathways genuinely appears to be a realistic strategy for treating many forms of liver diseases, and perhaps even intestinal diseases.

In addition to ursodeoxycholic acid, which has been established in clinical practice as a treatment for primary biliary cholangitis for many years, the FXR agonist obeticholic acid has recently been introduced as second-line therapy. However, this development is just the first of what will hopefully be many more new developments over the next few years that will yield key advances in the treatment of liver and biliary diseases.

Scientific organizers
Prof. D. Häussinger, Prof. U. Beuers, Prof. V. Keitel, Prof. M. Trauner
From bench to bedside: bile acid research is opening up new therapeutic options

Ever since researchers became aware of the importance of bile acids and their receptors for the control of numerous physiological and pathophysiological mechanisms, they have invested a great deal of effort into leveraging these insights into therapeutic concepts. This pursuit is now bearing its first promising fruits, many of which were presented at the XXV International Bile Acid Meeting convened by the Falk Foundation e.V. in Dublin.

It now seems to be only a matter of time until the new insights from bile acid research begin to disrupt the clinical field of liver diseases, and perhaps even intestinal and metabolic disorders. A number of bile acids, bile acid analogues, and FXR and TGR5 agonists and antagonists have the potential to be beneficial for liver and intestinal diseases, and are now waiting in the wings for their first clinical studies. Moreover, research is also being conducted into small molecules which diverge from the steroid nature of the bile acids. However, only two compounds are clinically available to date: the bile acid ursodeoxycholic acid (UDCA), which has been in use for decades, and the FXR agonist obeticholic acid (OCA), which was introduced recently. Among the bile acids prescribed in a therapeutic setting, UDCA has been administered the longest as an efficacious first-line treatment for primary biliary cholangitis (PBC). Combination therapy with OCA is indicated as second-line therapy for non-responders. Although UDCA is frequently prescribed off-label to treat primary sclerosing cholangitis (PSC), it does not have a positive effect on transplant-free survival.

PSC: is norUDCA the long-awaited breakthrough?

M. Trauner, Vienna (Austria), has great hopes for the newly-developed bile acid analogue norUDCA. Trauner stressed that the norUDCA molecule has a much different pharmacological profile than UDCA, and hence may be suitable for much different indications. The main differences in norUDCA are a shortened side chain and a very low capacity for conjugation. As a result, norUDCA is reabsorbed directly from bile ducts by cholangiocytes and is recirculated back to the liver (cholehepatic shunting). As part of this process, norUDCA induces bicarbonate-rich hypercholeresis. This restores and/or maintains the bicarbonate umbrella that protects bile ducts and tissues from aggressive bile acids. In contrast, UDCA is transported by normal enterohepatic circulation like all other bile acids, and is almost entirely excreted by the biliary route. norUDCA, on the other hand, is primarily excreted by the kidneys, and thus has a similar profile to most drugs but not of typical bile acids. This characteristic represents a significant difference to UDCA. Furthermore, norUDCA was also shown to exert anti-inflammatory, inhibitory, and antifibrotic effects. According to M. Trauner, these findings reinforce the value of norUDCA as a standalone drug. In a phase 2 study with 161 patients, norUDCA greatly improved cholestasis at daily doses of 500 mg, 1,000 mg, and 1,500 mg. ALP (alkaline phosphatase) levels were significantly reduced versus placebo within 12 weeks. This effect was dose-dependent, with the strongest effects observed at the highest dose of 1,500 mg/day (increase in ALP: -26% vs. -17.3% vs. -12.3% vs. +1.2%). The efficacy of norUDCA was independent of any prior treatment with UDCA or response to prior treatment with this bile acid. The safety profile of norUDCA was equivalent to placebo (Fickert P, et al. J Hepatol. 2017; 67(3):549–58). These promising results provided the impetus for a phase 3 study that is currently investigating norUDCA in patients with PSC.

Concepts for treating NAFLD and atherosclerosis

norUDCA is also a cost-effective treatment option for metabolic disorders of the liver such as NAFLD (nonalcoholic fatty liver), which can progress to NASH (nonalcoholic steatohepatitis), fibrosis, and cirrhosis. Evidence for these benefits was observed in a phase 2a study in which norUDCA significantly reduced alanine aminotransferase (ALT) levels within 12 weeks. Subgroup analyses of liver stiffness and hepatic steatosis confirmed these positive effects. However, norUDCA appears to not only have hepatoprotective effects, but may also positively affect cardiovascular complications. These positive effects have been accompanied by anti-atherosclerotic effects, at least in animal studies. In an ApoE- mouse model, norUDCA induced a substantial reduction in hepatic steatosis and inflammation as well as a reduction in aortic plaques and macrophage infiltration, as explained by T. Moustafa, Graz (Austria).
Also active in the intestines

The therapeutic indications for bile acids do not appear to be limited to only liver and biliary diseases. In vitro and in vivo experiments have now also shown that UDCA has a positive effect on intestinal barrier function and on the release of inflammatory cytokines by colonic epithelial cells. As S.J. Keely, Dublin (Ireland), explained, bile acids also stimulate the regeneration of intestinal mucosa. He posed the question of whether bile acids might also be an interesting treatment option for ulcerative colitis. The intestinal microbiome is also keeping researchers on their toes. The interaction between the microbiome, bile acids, and FXR and/or TGR5 signaling is considered to be a promising target for treating metabolic disorders.

Targeting TGR5 to treat polycystic and inflammatory liver disease

“We need a TGR5 antagonist” demanded N.F. LaRusso, Rochester (USA), as he noted that the treatment options currently available for polycystic liver disease (PLD) have so far proven less than satisfactory. Presently, only somatostatin analogues are a realistic possibility. However, N.F. LaRusso explained that these drugs “are expensive and display only moderate effects”. Antagonists of TGR5, a G protein-coupled bile acid receptor that is overexpressed in PLD cholangiocytes, may be the key to success. TGR5 ligands raise cAMP levels and cholangiocyte proliferation and exacerbate hepatic cystogenesis. The opposite effect is observed in both TGR5 mice and when TGR5 antagonists are administered: cAMP levels drop, and cholangiocyte proliferation and cyst growth decrease, both in vitro and in vivo. N.F. LaRusso concluded that TGR5 is a novel therapeutic target for the treatment of PLD. In contrast, TGR5 antagonists appear promising for inflammatory liver diseases. V. Keitel, Düsseldorf (Germany), is conducting intense research on the relevance of TGR5 for inflammatory liver diseases. She noted that activation of TGR5 in an animal model reduced the expression and secretion of inflammatory cytokines.

norUDCA – Potential clinical applications
(* Phase 2 & 3 randomized controlled trials)

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<td>PBC, CF</td>
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norUDCA is NOT a ligand for FXR or TGR5


PSC = primary sclerosing cholangitis; PBC = primary biliary cholangitis; CF = cystic fibrosis; SC-CIP = (secondary) sclerosing cholangitis in critically ill patients; NAS = nonanastomotic biliary strictures; LTx = liver transplantation; ABCB4 = canalicular phospholipid transporter; PFIC = progressive familial intrahepatic cholestasis; LPAC = low phospholipid-associated cholelithiasis; ICP = intrahepatic cholestasis of pregnancy; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; α₁AT = α₁-antitrypsin

Mechanisms of hepatic cystogenesis

Abnormal ciliary structure and function
Disrupted autophagy
Changes in mRNA, miRNA, and protein expression
Cell cycle dysregulation
Centrosomal abnormalities
Elevated fluid secretion
Lower intracellular calcium levels
Increased proliferation
On the front lines of bile acid research

The complexity of the interactions between bile acids, their receptors, and the gut microbiome raises plenty of unanswered questions that researchers are now addressing.

Glucocorticoid receptor ligands targeting fibrosis

Is the glucocorticoid receptor (GR) a potential target for the treatment of hepatic fibrosis? The data presented by D.D. Moore, Houston (USA), does not provide a clear answer. In studies using an animal model of fibrosis, activation of GR led to both beneficial and harmful effects. This confusing situation was not helped by the varying relevance of GR in parenchymal and nonparenchymal cells, and even mouse models left many questions unanswered. For example, activation of GR in double-knockout mice (DKO; Fxr-/-, Shp-/-) revealed positive effects, but not in BSEP-knockout animals (BKO; Abcb11-/-). Although the GR ligand reduced levels of bile acids in the liver and serum and exhibited antifibrotic effects in DKO mice, it had no effect in BKO mice. For this reason, D.D. Moore described these findings as “conflicting results” despite the similar phenotypes. Specific GR ligands might be effective against hepatic fibrosis in patients with FXR deficiency.

FXR target gene ZFP36L1: a regulator of bile acid metabolism and obesity

Nuclear FXR is the central regulator of bile acid metabolism. It is crucial for many tasks, including bile acid homeostasis and preventing the accumulation of bile acids. Activation of FXR by elevated levels of bile acids suppresses the synthesis of bile acids through several mechanisms, including by lowering the activity of Cyp7a1 (cholesterol 7α-hydroxylase), the rate-limiting enzyme in bile acid synthesis. T.A. Vallim, Los Angeles (USA), discovered a novel FXR-ZFP36L1 signaling pathway that controls bile acid synthesis. He could show that activation of FXR triggers a rapid post-translational mechanism that reduces levels of Cyp7a1 mRNA, and also identified a gene encoding the RNA-binding protein ZFP36L1 as an FXR target gene. Overexpression of ZFP36L1 decreased Cyp7a1 mRNA and protein levels, leading in turn to lower levels of bile acids. However, the most interesting finding was that mice lacking Zfp36l1 in their livers were protected from diet-induced obesity and steatosis. This effect was accompanied by reduced lipid absorption and associated with altered bile acid metabolism. In conclusion, ZFP36L1-dependent regulation of bile acid metabolism is a key player in the development of obesity and hepatic steatosis.

Bile acids and MDR3: unexpected cross-talk

Bile acids are synthesized in the cytoplasm of hepatocytes and are transported across the canalicular membrane to the bile ducts, a process aided by ABC transporters such as BSEP (bile salt export pump; ABCB11) or MDR3 (multidrug resistance protein 3; ABCB4). L. Schmitt, Düsseldorf (Germany), used a heterologous expression system to study the functions of and interaction between BSEP and MDR3, which revealed unexpected cross-talk between bile acids and MDR3 activity. Depending on the bile acid used, they may stimulate, inhibit, or have no effect on MDR3.
Bile acids and the microbiome: a complex interaction

The complex interaction between the microbiome, bile acids, and the FXR and/or TGR5 signaling pathways is considered to be a promising therapeutic target for the treatment of metabolic disorders, as reported by A. Wahlström, Göteborg (Sweden). While the potential is huge, much research still needs to be conducted. A. Wahlström described the gut microbiome as a “metabolic organ” which exerts a strong influence over the body. However, she noted that “conversely, we also influence our microbiome by our diet, physical activities, and lifestyles”. She pointed out the links between the microbiome and various metabolic disorders, including NAFLD and NASH but also diabetes and obesity. The enormous influence of the gut microbiome is demonstrated by the fact that germ-free mice are considerably skinnier than mice with gut bacteria. These bacteria metabolize primary bile acids to secondary bile acids with varying affinities to FXR and TGR5. Hence, the microbiome can modulate bile acid signal transduction via FXR and TGR5. The bile acids CDCA (chenodeoxycholic acid) > CA (cholic acid) = DCA (deoxycholic acid) > LCA (lithocholic acid) have been identified as FXR agonists, while LCA > DCA have been identified as TGR5 agonists. The next step is to determine how to target and sustainably manipulate the microbiome, and with it the bile acid profile.

Obeticholic acid and the small intestine microbiome

Bacteria and bile acids can influence each other in many ways. G.D. Wu, Philadelphia (USA), described how the FXR agonist obeticholic acid (OCA) interferes with the human microbiome in the small intestine. By inhibiting the endogenous synthesis and secretion of bile acids, OCA triggers a significant proliferation of gram-positive bacteria in the small intestine that are sensitive to bile acids. The signatures of these microbes can be detected in stool, especially an increase in Firmicutes spp. Findings such as these provide the groundwork for targeting and therapeutically manipulating the microbial communities residing in the gut.

Cold-induced synthesis of bile acids in BAT

Mitochondria-rich brown adipose tissue (BAT) is activated by exposure to cold and produces heat by oxidizing fatty acids. According to J. Heeren, Hamburg (Germany), exposure to cold increases the uptake of cholesterol from food; this cholesterol is then converted to bile acids primarily via the alternative synthetic pathway. Exposure to cold induces expression of the Cyp7b1 gene, which is a crucial enzyme in the conversion of cholesterol to bile acids. J. Heeren could also show that excretion of bile acids in stool is increased during cold exposure. Finally, the microbiome also undergoes changes over the course of this process. According to J. Heeren, these interactions demonstrate the relevance of cholesterol metabolism for diet-induced changes to the gut microbiome.

How secondary bile acids inhibit the growth of Clostridium difficile

Clostridium scindens is a species of gut bacteria that inhibits the growth of Clostridium difficile. At the same time, it also metabolizes primary bile acids to secondary bile acids via 7α-dehydroxylation and secretes antibacterial tryptophan derivatives. The secondary bile acids LCA and DCA enhance the activity of bacterial compounds it secretes, whereas cholic acid does not. P.B. Hylemon, Richmond (USA), investigated these interactions and could demonstrate that the intestinal concentration of bile acids is an important regulator of the gut microbiome. He summarized his results by describing how endogenously-synthesized antibiotics and secondary bile acids interact to inhibit the growth of C. difficile in the colon. These results help explain how C. difficile can colonize the colon in the absence of 7α-dehydroxylating strains of gut bacteria, and how the regulating mechanisms of secondary bile acids can interfere with this process.
Is IgG4-associated cholangitis also a defect of the biliary bicarbonate umbrella?

In patients with PSC and PBC, the protective biliary bicarbonate umbrella is defective due to inadequate expression of the bicarbonate transporter AE2 (anion exchanger 2). A similar defect may also be present in IgG4-associated cholangitis (IAC). In preliminary studies, U. Beuers, Amsterdam (The Netherlands), identified annexin 11, which is expressed by human cholangiocytes, as a protein involved in the secretion of bicarbonate by the biliary epithelium. Annexin 11 not only demonstrated pro-apoptotic effects, but was also involved in membrane targeting of AE2. According to U. Beuers, IAC is often misdiagnosed in clinical practice as PSC or cholangiocarcinoma. For this reason, laboratory testing for a significantly elevated percentage of IgG4-positive B-cell receptor clones is more important than clinical examination when diagnosing IAC.

OST\(\alpha/\beta\) protects the liver and biliary tract

The heterodimeric OST\(\alpha/OST\beta\) (OST, organic soluble transporter) protein, which transports bile acids from enterocytes into the portal vein, exerts protective effects on the liver and the biliary tract. Like the transport protein ASBT (apical sodium-dependent bile acid transporter), it plays an important role in maintaining the enterohepatic circulation of bile acids. Furthermore, it could be shown to protect ileal enterocytes from bile acid-induced cellular injury in a mouse model using OST\(\alpha\) KO mice. Epithelial cell proliferation and apoptosis were highly elevated in OST\(\alpha\)-mice compared with WT (wild-type) mice. P.A. Dawson, Atlanta (USA), summarized these findings by noting that the concentration of bile acids is greater in this model. The altered morphology induced by defective OST\(\alpha\) can be reversed using ABST\(^{-}\)mice or by pharmacological inhibition of ABST.
When tight junction proteins are defective

R.J. Thompson, London (Great Britain), used several case reports to illustrate why it is important to consider defects in tight junction proteins (TJP2, claudin-1, DCDC2 [double-cortin domain-containing protein 2]) as a potential cause of cholestasis and cholangitis in children. He cited one example of a mutation identified in the claudin-1 gene that interfered with the protein’s barrier function, which caused a case of neonatal sclerosing cholangitis associated with ichthyosis. Defects in TJP2 can be classified into 3 degrees of severity. Mild forms have only been observed in the Amish population to date. Severe forms are characterized clinically by chronic cholestasis requiring liver transplantation, and are also associated with hepatocellular carcinoma (HCC). Intermediate forms of TJP2 defects exhibit variable TJP2 expression with recurrent cholestasis.

Transporter defects with far-reaching consequences

Cholestatic liver diseases in children and adults may be the result of defects in transport proteins, as was explained in a talk by C. Dröge, Düsseldorf (Germany). The Düsseldorf group characterized a large cohort of patients with different variants in FIC1 (familial intrahepatic cholestasis 1; ATP8B1), BSEP (bile salt export pump; ABCB11), and MDR3 (multidrug resistance protein 3; ABCB4) which were associated with mild to progressive familial intrahepatic cholestasis (PFIC) phenotypes. Using Sanger sequencing, the cholestasis laboratory in Düsseldorf analyzed BSEP in over 300 patients, MDR3 in over 250 patients and FIC1 in over 200 patients. By using NGS (next-generation sequencing), they were able to detect several genetic variants in other genes associated with cholestasis, such as TJP2, FXR, and MYO5B, in patients with cholestasis who had no relevant variants in ATP8B1, ABCB11, or ABCB4. F. Lammert, Homburg (Germany), pointed out that the different phenotypes of PFIC depend on the patient’s genetic background. ABCB4 mutations may be associated with gallstones, ICP, and HCC, but also with cholangio-carcinoma or with biliary cirrhosis with ductal proliferation. Population-based studies have shown that variants of ABCB4 may not only be a causal factor for PFIC3, but may also promote the development of a broad spectrum of liver diseases. In addition to these population-based studies, mouse models may be a useful tool to elucidate the genetic contribution of these variants to complex disorders such as cholangiopathy, and may help provide a better understanding of the correlation between genotype and phenotype in liver diseases.
Elevated cortisol levels in cholestasis

The importance of bile acids for numerous physiological processes in the body can be demonstrated by animal experiments on steroidogenesis: either CBDL (common bile duct ligation) or chenodeoxycholic acid can stimulate adrenal production and secretion of steroids independent of the bile acid receptors FXR and TGR5. Serum cortisol levels are elevated in patients with cholestasis. Experimental studies have elucidated the details of this signal transduction pathway. P. Fickert, Graz (Austria), came to the conclusion that bile acids stimulate steroidogenesis in the kidneys via an S1PR2-ERK-SF-1 signal transduction pathway.

FXR agonists for the treatment of portal hypertension

The nuclear receptor FXR is considered to be a target for the treatment of portal hypertension, as reported by T. Reiberger, Vienna (Austria). FXR agonists reduce fibrosis and inflammation, and they also lower intrahepatic vascular resistance and portal pressure in patients with portal hypertension. In addition to the FXR agonist obeticholic acid, which was shown to have a beneficial effect on portal hypertension in cirrhotic rats, attention is now also being focused on the nonsteroidal FXR agonist PX20606, which reduced portal pressure and fibrosis while improving endothelial dysfunction in animal experiments.

Overview of therapeutic targets for the treatment of portal hypertension

- Adrenergic system: NSBBs, alpha-1 blockers
- Nitrate
- Nitrogen signaling pathway
- Guanylate cyclase
- PDE5 inhibitors
- FXR agonists
- Anticoagulants
- Bacterial colonization
- Pro-inflammatory prostaglandins
- Angiogenesis
- Statins
- Renin-angiotensin system

NAFLD: the gut microbiome has a role to play

The pathogenesis of nonalcoholic fatty liver disease (NAFLD) is not fully understood. However, according to S. Kersten, Wageningen (The Netherlands), there is increasing evidence that the gut microbiome may be involved. Modulation of gut bacteria affects the development of NAFLD, a process which may be mediated by bile acids. In a mouse model of NAFLD, mice fed guar gum exhibited increased hepatic inflammation and fibrosis compared with a control group. In contrast, inflammation and fibrosis were attenuated in mice given antibiotics, an effect that was accompanied by an altered composition of bile acids in portal blood. Specifically, the concentration of primary bile acids increased with guar gum but decreased with antibiotic intake. Moreover, bile acid signaling appears to be involved in NAFLD, as reported by L. Zhu, Buffalo (USA). Bile acids have long been known to be important actors and mediators in the interactions between the liver and the gut microbiome. Accordingly, synthesis of bile acids is increased in NAFLD due to the suppression of the bile acid-induced feedback mechanism via FXR signaling. According to L. Zhu, one explanation for this observation may be the relatively high levels of DCA and relatively low levels of CDCA in NAFLD. The gut microbiome metabolizes the primary bile acid CDCA to secondary bile acids such as DCA. According to L. Zhu, “the FXR signaling cascade is a potential target to treat NALFD - but so is the microbiome.”

In brief

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The intestinal FXR-FGF19 partnership provides protection from colitis and colorectal cancer

According to A. Moschetta, Bari (Italy), loss of FXR-FGF19 (fibroblast growth factor 19) function increases the risk of colorectal cancer. Based on this observation, he and his team investigated the anti-inflammatory and anticancer potential of an FGF19 analogue in both DSS (dextran sulfate sodium) and AOM (azoxymethane)/DSS mouse models. The FGF19 analogue protected the animals from DSS-induced colitis. It inhibited local inflammation and protected the integrity of the epithelial barrier. However, FGF19 could not protect FXR- mice from colitis. FXR thus appears to play the key role in maintaining the epithelial barrier and providing protection against intestinal inflammation. A. Moschetta concluded by stressing that these results underscore the therapeutic potential of intestinal FXR agonists and FGF19 analogues for the treatment of enteritis with imbalanced bile acid homeostasis.

Effects of FXR isoforms on amino acid degradation

FXR regulates not only bile acid homeostasis, but also amino acid catabolism and the detoxification of ammonium. However, as S.W.C. van Mil, Utrecht (The Netherlands) explained, in mice, only FXR isoforms FXRα2/4 but not FXRα1/3 activate argininosuccinate synthase-1 (ASS-1), which is the rate-limiting enzyme in arginine biosynthesis and urea synthesis. This finding suggests that the FXR isoforms might respond differently to FXR agonists, which should be taken into consideration for the development of such agonists in order to ensure optimized therapy.

A bile acid-Areg/EGFR axis promotes liver regeneration

The growth factor amphiregulin (Areg) can activate EGFR (epidermal growth factor receptor) in the liver. Expression of Areg is upregulated both in mice with cholestasis as well as in the cirrhotic livers of patients with PBC and PSC. M.A. Avila, Pamplona (Spain), could demonstrate the importance of amphiregulin in liver injury by showing that Areg- mice given alpha-naphthyl-isothiocyanate had aggravated liver injuries. In contrast, this growth factor protects hepatocytes from apoptosis induced by bile acids and by alpha-naphthyl-isothiocyanate. However, amphiregulin also modulates bile acid metabolism, while bile acids in turn regulate the transcription of amphiregulin via EGFR. As M.A. Avila concluded, "The bile acid-Areg/EGFR axis exerts a cytoprotective and regenerative mechanism in cholestasis and during liver regeneration."

MicroRNA as a therapeutic target in PBC

The microRNA (miR)-506 is overexpressed in primary biliary cholangitis (PBC). This microRNA activates AE2 and inositol triphosphate, which then leads to cholestasis. The pro-inflammatory cytokines that are overexpressed in patients with PBC stimulate miR activities in human cholangiocytes. miR-506 reduces cell proliferation and adhesion, increases oxidative and ER (endoplasmic reticulum) stress, triggers DNA damage, and promotes bile acid-induced apoptosis. According to J.M. Banales, San Sebastian (Spain), miR-506 might also be a therapeutic target for PBC.

Stool from the small intestine?

S. Kersten, Wageningen (The Netherlands), presented the Intellicap system, which is a minimally-invasive method of collecting stool samples from the small intestine. The MICRO study demonstrated that the composition of the microbiome is different in stool than in the small intestine of humans on controlled diets. Bifidobacteria spp. were identified as colon-selective bacteria, while Streptococcus spp., Gemella spp., and Haemophilus spp. were among those identified in the duodenum.

Below: The human gastrointestinal tract with the microbiome of the small intestine. The zoom view shows the intestinal villi and gut bacteria.
IBD: From Diagnosis to Therapy

July 5–6, 2019
St. Petersburg, Russia

Congress Venue
Park Inn by Radisson Pribaltiyskaya
14 Korablistroeiteley street
199226 St. Petersburg
Russia

Scientific Organization
H. Herfarth, Chapel Hill (USA)
I. Khalif, Moscow (Russia)
W. Reinisch, Vienna (Austria)
Y. Shelygin, Moscow (Russia)
Poster prizes: Awarding successful scientists

At its international symposia, the Falk Foundation e.V. regularly honors young scientists who present innovative and relevant research in a poster. The poster prizes at symposium 211 were awarded to:

1st prize: Dr. Alex Zaufel, Medical University of Graz (Austria), for his research on “The mechanistic target of rapamycin complex 1 (mTORC1) regulates bile acid biosynthetic and transporter gene expression via activity of the farnesoid X receptor (FXR)”.

2nd prize: Rachida Amzal, University of Paris-Sud (France), for her research on “In vitro rescue of ABCB11 non-sense mutations: Induction of a readthrough of premature stop codons”.

3rd prize: Prof. John Chiang, Northeast Ohio Medical Sciences, Rootstown (USA), for the poster “FXR and TGR5 signaling crosstalk and the gut microbiota in liver metabolism and disease”.

From left to right: C. Falk, the winners of the poster prizes: R. Amzal (2nd prize), Prof. J. Chiang (3rd prize), Dr. A. Zaufel (1st prize), Prof. A. F. Hoffmann, Prof. V. Keitel

Dr. Alex Zaufel, Graz (Austria)
Rachida Amzal, Paris (France)
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Building Bridges in IBD

September 13–14, 2019
Brussels, Belgium

Congress Venue
Square Brussels
Meeting Centre
Glass Entrance
Mont des Arts/Kunstberg
1000 Brussels
Belgium

Scientific Organization
I. Dotan, Petah Tikva (Israel)
D. Rachmilewitz, Jerusalem (Israel)
S. Vermeire, Leuven (Belgium)
Prof. B. Stieger, Zurich (Switzerland), was awarded the Adolf Windaus Prize for his many years of highly successful work in the field of bile acid research. The focus of his research is the function of the bile acid transporter BSEP.
“We could treat many different types of liver diseases by interfering with bile acid signaling pathways”

Ursodeoxycholic acid was the first bile acid to be administered in a therapeutic setting. Since its introduction, bile acid research has seen many advances. Targeted therapies to treat liver and intestinal diseases by interfering with bile acid signaling pathways are just around the corner. Professor Dr. Verena Keitel, Düsseldorf (Germany), is one of the scientific organizers of the Falk Foundation e.V. Symposium 211. She joined us to reflect on past developments in bile acid research and to speculate on future developments.

Eds.: Professor Keitel, this year saw the 25th International Bile Acid Meeting. How has the conference changed over the last 20 years?

Prof. Keitel: There have been numerous changes, which can be seen just by looking at the number of participants: In 1940, there were 57 scientists from 8 countries, whereas today we have almost 10 times as many participants from about 40 countries. While the first few meetings focused primarily on the chemistry of bile acids, the focus later shifted to the use of bile acids and their analogues as potential therapeutic agents - a topic we are still discussing today. However, the boundaries expanded even further with the discovery of bile acid receptors. The finding that the farnesoid X receptor (FXR) is actually a nuclear receptor for bile acids was first published in 1999, and in the meantime obeticholic acid has become the first FXR agonist to be approved for the treatment of PBC. Since then, other bile acid-responsive receptors have been discovered. These developments have now brought us very close to having modulation of the bile acid signaling pathways be a realistic option for treating multiple types of liver diseases, and possibly even intestinal diseases.

What is the mechanism of bile acids and their analogues?

There are several different classes of receptors. For example, there are the typical transcription factors that are activated by ligands, which we call nuclear receptors. The prototype of this class is FXR, but it also includes the vitamin D receptor. Some bile acids induce signaling through G protein-coupled receptors that are frequently located on the plasma membrane. This class includes both the TGR5 receptor, but it also includes the sphingosine receptor S1PR2 as well as several muscarinic receptors that are usually associated with cardiology yet are also sensitive to bile acids. Nonetheless, bile acids still exert a number of effects that cannot be attributed to any of these receptors. For example, integrins have been identified as sensors for tauroursodeoxycholic acid, which is the form of ursodeoxycholic acid conjugated to taurine that is produced under conditions of normal metabolism. When these receptors are activated, they can promote the secretion of bile acids and modulate a number of ion channels and kinases.

Why did these developments take so long?

Bile acids were long considered to be waste products. On the one hand, it was obvious that they were much more complicated, since patients with high levels of bile acids were frequently observed to have immunological issues. On the other hand, the receptors and signaling pathways that might have helped establish a causal relationship remained unknown, and suitable model systems were not yet available. Even FXR itself was initially identified as a farnesoid receptor and was not recognized as a bile acid receptor until 1999. It was only recently that animal experiments using knockout mice could demonstrate how crucial this receptor is for a large number of processes in the human body, including bile acid homeostasis, lipid and glucose metabolism, and immune responses. These discoveries finally kicked off modern bile acid research. The insights gained from mouse models could be confirmed by the identification of patients with debilitating mutations in the FXR gene (PFIC5) and through the increasing availability of various FXR ligands.

Interview
What indications are bile acid derivatives already being used to treat in clinical practice?

Ursodeoxycholic acid, which is abbreviated UDCA, is the bile acid which has been in clinical practice the longest. It was the only medication approved for PBC until the approval of obeticholic acid, and it remains the first-line treatment for this cholestatic liver disease. The FXR agonist obeticholic acid is now the second bile acid derivative available to treat PBC and is used both in combination with UDCA and as a single agent for patients who do not tolerate UDCA. nortUDCA was very successful in a phase 2 study on PSC, and is currently under investigation in a phase 3 study. Specific inhibitors of bile acid uptake transporters, such as inhibitors of NTCP (Na+-taurocholate cotransporting polypeptide) and ASBT (apical sodium-dependent bile acid transporter), are also currently in clinical development. All of these drugs were successful in phase 2 trials, so it looks like targeting bile acid transporters will indeed be possible in the future. However, these compounds are not actually bile acid derivatives. More and more, the drugs undergoing clinical testing are small molecules that do not have any of the structural features of bile acids yet still have affinity for bile acid receptors. We don’t know yet whether it will make a difference if a small molecule or a bile acid analogue is used for treatment. It might be that small molecules don’t accumulate in enterohepatic circulation, which could be both a positive and a negative, especially in terms of side effects.

Your research focuses on the TGR5 receptor. What is the therapeutic relevance of this receptor?

TGR5 is a membrane-bound protein expressed in nearly all organs, not just the liver, gut, and kidneys. We have even detected this protein in the brain, the placenta, and in the genitals. The receptor has potent anti-inflammatory effects, and immune cells produce fewer cytokines and chemokines when it is activated. Sepsis is exacerbated in TGR5 knockout mice, while activating TGR5 has the opposite effect. We have detected high levels of TGR5 expression in the bile ducts, where the receptor promotes bile secretion, cellular proliferation, and cellular protection. We have also observed elevated levels of TGR5 expression in cholangiocarcinoma, which worsens the disease by stimulating the proliferation, migration, and invasiveness of the cancer. It is conceivable that TGR5 antagonists might help prevent disease progression similar to their effects on polycystic liver disease. We are therefore searching for both TGR5 agonists and TGR5 antagonists. However, the TGR5 agonists that were previously available never made it to clinical trials because they relax the gallbladder, which may promote the development of gallstones and cause upper abdominal discomfort. TGR5 also has metabolic functions: in mouse models, TGR5 agonists improve diabetes and can help treat atherosclerosis and metabolic syndrome.

Might TGR5 antagonists aggravate a patient’s metabolic situation?

That is certainly possible. In this case, the patient and his or her doctor would need to decide which side effects they are willing to accept.

The interactions between bile acids and the microbiome have been a topic of intense discussion, including as a target for therapeutic intervention. Would it even be possible to sustainably alter the microbiome?

I personally find the gut to be a very attractive target for liver diseases. We need the microbiome in order to metabolize bile acids. Although it is difficult to manipulate the intestinal microbiome, I’m certain that we will be able to target it fairly well once we understand which bacteria are doing what and how their interactions with bile acids work. One vision for the future would be to analyze the changes to the microbiome in patients with a specific liver disease, and then to modify that microbiome in a targeted fashion. In my view this approach has great potential, but it is still going to take a long time before this concept becomes reality.

What indications do you think exist for bile acids and their derivatives outside of liver and intestinal diseases?

FXR and TGR5 are interesting in terms of metabolic syndrome, and may also play a role in kidney injury. Currently, UDCA is the only option for patients with complications of intrahepatic cholestasis of pregnancy with high levels of bile acids accompanied by respiratory symptoms and arrhythmia. I definitely think there is potential here for further modulation of the bile acid receptor signaling pathways.

Professor Keitel, thank you very much for the interview.
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40 Years of Scientific Dialogue in the Interest of Therapeutic Progress

If we want to attract an audience for new ideas and findings, we need to give people the opportunity to talk about them. Dr. Dr. Herbert Falk had a unique and successful strategy for creating this “space for dialogue.” Since 1978, a globally recognized concept for continuing education in the sciences has developed under the umbrella of the Falk Foundation. This is an achievement that has many voices. Today, we express our gratitude for everything they have done. We look forward to many more years of working to give science a strong collective voice.
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March 29–30, 2019

Symposium 215
IBD: From Diagnosis to Therapy
St. Petersburg, Russia
July 5–6, 2019

Symposium 216
Building Bridges in IBD
Brussels, Belgium
September 13–14, 2019

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Nutrition and Microbiome in Allogeneic Haematopoietic Stem Cell Transplantation
Regensburg, Germany
November 8–9, 2019

Symposium 217
West Meets East: Functional Meets Organic in Gastrointestinal Diseases
Singapore
November 29–30, 2019

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