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Review

Bile acid receptors in the biliary tree: TGR5 in physiology and disease☆,☆☆

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ABSTRACT

Bile salts represent signalling molecules with a variety of endocrine functions. Bile salt effects are mediated by different receptor molecules, comprising ligand-activated nuclear transcription factors as well as G protein-coupled membrane-bound receptors. The farnesoid X receptor (FXR) and the plasma membrane-bound G protein-coupled receptor TGR5 (Gpbar-1) are prototypic bile salt receptors of both classes and are highly expressed in the liver including the biliary tree as well as in the intestine. In liver, TGR5 is localized in different non-parenchymal cells such as sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells and small and large cholangiocytes. Through TGR5 bile salts can mediate choleretic, cell-protective as well as proliferative effects in cholangiocytes.

A disturbance of these signalling mechanisms can contribute to the development of biliary diseases. In line with the important role of TGR5 for bile salt signalling, TGR5 knockout mice are more susceptible to cholestatic liver damage. Furthermore, in absence of TGR5 cholangiocyte proliferation in response to cholestasis is attenuated and intrahepatic and extrahepatic bile ducts show increased cell damage, underscoring the role of the receptor for biliary physiology. Decreased TGR5 expression may also contribute to the development or progression of cholangiopathies like primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) since reduced TGR5-dependent cell-protective mechanisms such as bicarbonate secretion renders cholangiocytes more vulnerable towards bile salt toxicity. Nevertheless, TGR5 overexpression or constant stimulation of the receptor can promote cholangiocyte proliferation leading to cyst growth in polycystic liver disease or even progression of cholangiocarcinoma.

Not only the stimulation of TGR5-mediated pathways by suitable TGR5 agonists but also the inhibition of TGR5 signalling by the use of antagonists represent potential therapeutic approaches for different types of biliary diseases. This article is part of a Special Issue entitled: Cholangiocytes in Health and Disease edited by Jesus Banales, Marco Marzioni, Nicholas LaRusso and Peter Jansen.

1. Introduction

Bile acids are synthesized from cholesterol in liver and are actively transported across the apical hepatocyte membrane into the bile canaliculus by the bile salt export pump (BSEP, ABCB11) [1,2]. In bile, bile salts (BSs) form mixed micelles with phosphatidylcholine, a prerequisite for the efficient digestion and absorption of dietary lipids and fat-soluble vitamins in the intestine [1]. In animals with targeted deletion of the phospholipid floppase Mdr2 (Abcb4; the human homologue is called MDR3 (ABCB4)), phospholipids are absent from bile, resulting in a lack of mixed micelles and increased BS toxicity to the biliary epithelium [1,3,4]. Despite formation of mixed micelles, cholangiocytes are constantly exposed to millimolar concentrations of free and potentially cytotoxic hydrophobic BSs. While hepatocytes undergo

Abbreviations: AC, adenylate cyclase; BS, bile salt; BSEP, bile salt export pump (ABCB11); CA, cholic acid/cholate; cAMP, cyclic AMP; CBDL, common bile duct ligation; CCA, cholangiocarcinoma; CDCA, chenodeoxycholic acid/chenodeoxycholate; CD95L, CD95 ligand; CFTR, cystic fibrosis transmembrane conductance regulator (ABCC7); DCA, deoxycholic acid/deoxycholate; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; GCDCA, glycochenodeoxycholic acid/glycochenodeoxycholate; Gpbar-1, G protein-coupled bile acid receptor 1; GPCR, G protein-coupled receptor; KC, Kupffer cells; MAPK, mitogen-activated protein kinase; Mdr2, murine multidrug resistance protein 2 (Abcb4); MDR3, human multidrug resistance protein 3 (ABCB4); MMP, matrix metalloproteinase; S1PR2, sphingosine-1-phosphate receptor 2; TCA, taurocholic acid/taurocholate; TCDCA, taurochenodeoxycholic acid/taurochenodeoxycholate; TLCA, taurolithocholic acid/taurolithocholate

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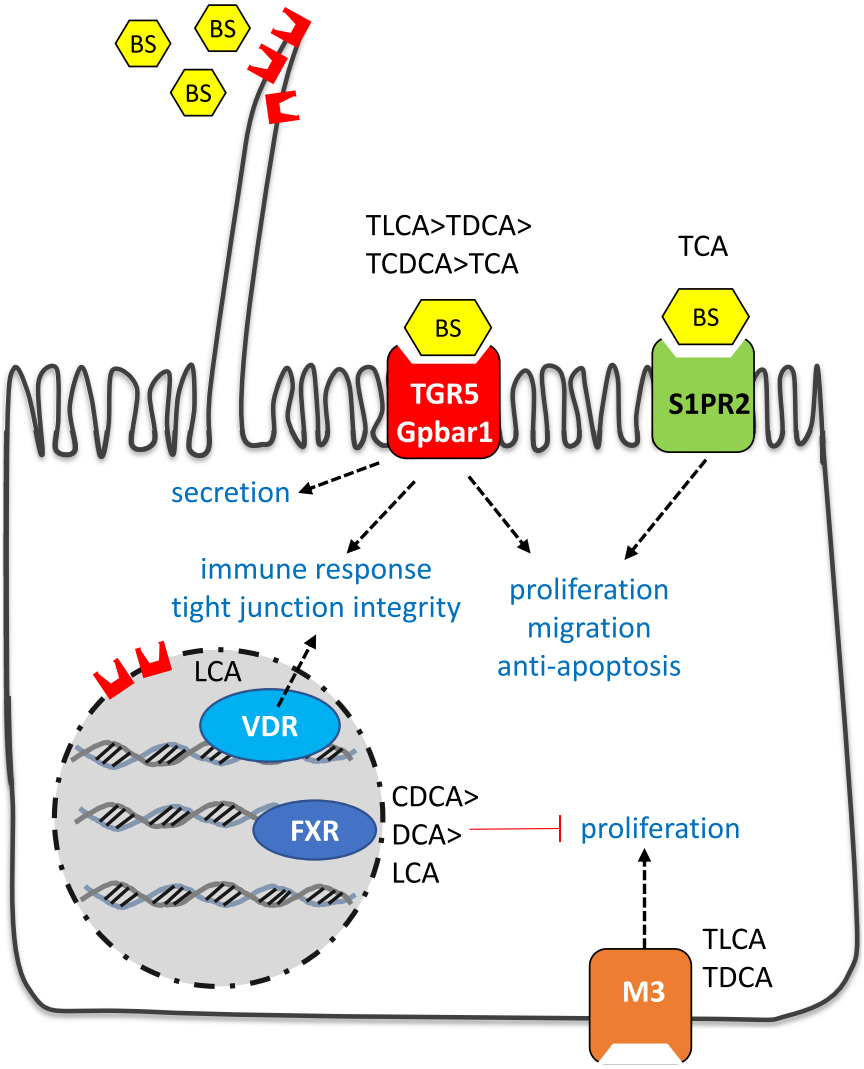

Fig. 1. Bile salt receptors expressed in cholangiocytes. Different bile salt (BS) receptors have been detected in cholangiocytes, which comprise nuclear receptors such as the farnesoid X receptor (FXR) and the vitamin D receptor (VDR) as well as several G protein-coupled receptors (GPCRs) such as TGR5 (Gpbar-1), the sphingosine-1-phosphate receptor 2 (S1PR2) as well as the subtype 3 muscarinic acetylcholine receptor (M_3). CDCA, chenodeoxycholate; DCA, deoxycholate; LCA, lithocholate; TCA, taurocholate; TCDCA, taurochenodeoxycholate; TDCA, taurodeoxycholate; TLCA, taurolithocholate.

apoptosis already in response to micromolar concentrations of hydrophobic BSs such as taurolithocholate 3-sulfate, glycodeoxycholate or glycochenodeoxycholate, cholangiocytes are vested with mechanisms that protect them from BS-induced injury [5–9]. These mechanisms comprise formation of a dense glycocalyx above the apical membrane and generation of a bicarbonate film (also known as bicarbonate umbrella), which together create an alkaline environment thereby favouring the deprotonation of glycine-conjugated bile acids to bile salts and thus minimizing free diffusion of protonated bile acids across the apical membrane into cholangiocytes [3,10–14].

Besides cytotoxic effects, BSs act as signalling molecules and trigger chloride and bicarbonate secretion, mediate cell proliferation and promote cell protective mechanisms in cholangiocytes and gallbladder epithelial cells. These BS effects are mediated through different BS receptors, which include intracellular, nuclear BS receptors as well as plasma membrane-bound G protein-coupled receptors (GPCRs) (Fig. 1) [15]. Nuclear BS receptors are ligand-activated transcription factors and cholangiocytes express the farnesoid X receptor (FXR, NR1H4) [16–21] and the vitamin D receptor (VDR, NR1I1) [22–24]. FXR is activated by the primary BS chenodeoxycholate (CDCA) and its conjugates (EC_{50} of approximately 5–20 μM) as well as the secondary BSs deoxycholate (DCA) and lithocholate (LCA) [16,18,20,21,25–27]. In contrast, only the secondary BS LCA acts as ligand for the VDR [22–24] (Fig. 1). While FXR is preferentially expressed in hepatocytes over cholangiocytes, mRNA levels of the VDR are significantly higher in cholangiocytes as compared to hepatocytes [22,28]. The pregnane X receptor (PXR, NR1I2) [29,30], which is also responsive towards LCA has not been detected in cholangiocytes [28–30]. Besides nuclear receptors (NRs), cholangiocytes express several GPCRs responsive to BSs such as acetylcholine receptors subtype 3 (M3) localized to the basolateral membrane [31–35] as well as the sphingosine-1-phosphate receptor 2 (S1PR2) and the Takeda G protein-coupled receptor 5 (TGR5, Gpbar-1, M-BAR) present in the apical plasma membrane [14,36–45] (Fig. 1). While S1PR2 is activated by conjugated BSs only, mainly taurocholate (TCA), both primary and secondary human BSs are ligands for TGR5, with a preference for taurine-conjugated over unconjugated or glycine-conjugated BSs [46–49]. Despite BSs, various other cholesterol metabolites and steroid hormones can activate TGR5 and may represent physiological ligands for the receptor in organs normally exposed to low BS concentrations, such as brain, adrenal glands as well as male and female reproductive organs [14,48,50,51].

In rodent and human liver, TGR5 has been detected by immunofluorescence staining not only in small and large cholangiocytes, but also in sinusoidal endothelial cells (LSEC), liver-resident macrophages (Kupffer cells, KC) and activated hepatic stellate cells (HSC) [13,40–44,52,53]. In gallbladder, TGR5 is expressed in the epithelium as well as in smooth muscle cells [54–56].

2. TGR5 localization and function in the biliary tree and the gallbladder

In cholangiocytes and gallbladder epithelial cells, TGR5 is localized in the primary cilia, which extend from the apical plasma membrane into the bile duct or gallbladder lumen, on the apical plasma membrane as well as in intracellular compartments, especially the nuclear membrane [43,44,54]. Whether intracellular TGR5 is functionally active and can be stimulated by BSs is unknown. Furthermore, TGR5 has also been detected on exosomes isolated from rat bile by electron microscopy [44].

Stimulation of TGR5 in ciliated H69 cells, which are simian virus 40-transformed human cholangiocytes, triggered colocalization of TGR5 with inhibitory $G\alpha_{(i)}$ proteins, reduced intracellular cyclic AMP (cAMP) levels and attenuated cell proliferation [44]. In contrast, ligand-activation of TGR5 in non-ciliated H69 cells, where the receptor is localized in the apical plasma membrane, promoted colocalization with stimulatory $G\alpha_{(s)}$ proteins, increased intracellular cAMP levels and induced cell proliferation [44]. In murine cholangiocytes, activation of TGR5 triggered cholangiocyte proliferation through elevation of reactive oxygen species (ROS), subsequent activation of Src kinase, matrix-metalloproteinase-dependent shedding of the epidermal growth factor (EGF), transactivation of the EGF receptor (EGFR) and subsequent phosphorylation of mitogen-activated protein kinases (MAPK) ERK1/2 [45] (Fig. 2). The TGR5-mediated cell proliferation in murine cholangiocytes was independent of adenylate cyclase activation, which contrasts the data from the human H69 cells, indicating species or cell type differences with regard to the TGR5-mediated cholangiocyte proliferative response [45].

Besides proliferation, stimulation of TGR5 promotes biliary chloride and bicarbonate secretion thus enhancing choleresis [13,56]. In detail, ligand binding to TGR5 through coupling to a $G\alpha_{(s)}$ protein activates adenylate cyclase, increases intracellular cAMP concentrations and triggers chloride secretion via the cystic fibrosis transmembrane conductance regulator (CFTR, ABCC7) [13,42,54]. Subsequently, the anion exchanger 2 (AE2, SLC4A2) mediates exchange of chloride and bicarbonate across the apical plasma membrane (Fig. 2). This not only leads to bicarbonate-rich choleresis but also to the formation of a protective bicarbonate film known as the bicarbonate umbrella [3,10–14,42,54,56,57]. Transport activity as well as apical plasma membrane localization of both CFTR and AE2 are dependent on cAMP, therefore stimulation of TGR5 further increases biliary secretion indirectly through enhanced insertion of CFTR and AE2 from intracellular vesicles into the apical plasma membrane [13,42,54]. In line with an essential role of TGR5 in the formation of the protective bicarbonate umbrella, cholangiocytes from TGR5 knockout mice are more

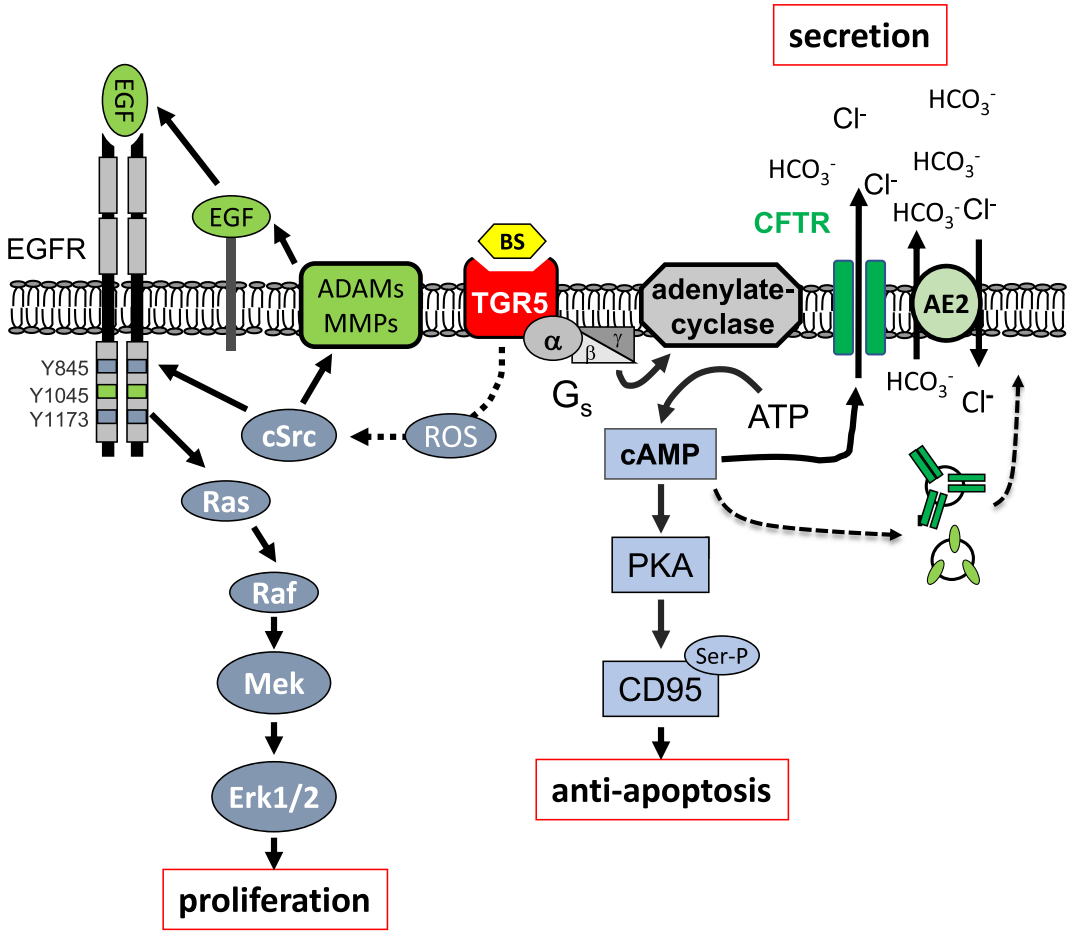

Fig. 2. TGR5-dependent signalling in cholangiocytes. Ligand binding to TGR5 triggers chloride secretion, serine phosphorylation of the CD95 receptor as well as transactivation of the EGFR, which promotes cell proliferation. TGR5 stimulation by bile salts (BSs) results in an activation of a stimulatory G-protein (Gs) and adenylate cyclase leading to increased intracellular cyclic AMP levels. cAMP in turn activates the chloride channel CFTR, which triggers chloride secretion. The anion exchanger 2 (AE2) mediates chloride/bicarbonate exchange across the apical membrane leading to the formation a protective bicarbonate film. TGR5 can also trigger protein kinase A (PKA) activation resulting in serine/threonine phosphorylation (Ser-P) of the CD95 receptor, which promotes anti-apoptotic signalling.
Cholangiocyte proliferation is induced by TGR5 through elevation of reactive oxygen species (ROS), subsequent Src kinase activation, matrix-metalloproteinase (MMP)-dependent shedding of the epidermal growth factor (EGF), transactivation of the EGF receptor (EGFR), followed by phosphorylation of MAP kinase ERK1/2. Dotted lines represent indirect effects. Modified from [13,45].

susceptible towards BS toxicity as compared to wildtype cells [45]. Furthermore, TGR5 activation triggers anti-apoptotic signalling thereby protecting cholangiocytes from BS- and CD95 ligand-induced apoptosis (Fig. 2) [45].

In human and rodent gallbladder TGR5 is expressed both in the epithelium as well as in smooth muscle cells [54–56]. Gallbladder volume in mice fed control chow diet or BS (cholate 0.2%)-enriched diet is significantly smaller in absence of TGR5 [14,55,56], which is explained by attenuated TGR5-dependent biliary secretion as well as by impaired smooth muscle cell relaxation [55,56]. Administration of different synthetic TGR5 ligands (6α-ethyl-23(*S*)-methyl-cholic acid (INT-777), a 4-phenoxypyrimidine-5-carboxamide derivative (compound 18) or a 4-phenoxynicotinamide derivative (compound 23 g)) increased gallbladder volume substantially in wildtype mice [56,58,59]. Interestingly, TGR5 knockout mice are protected from cholesterol gallstone formation when fed a lithogenic diet, despite the impaired gallbladder motility [56,60].

3. Role of TGR5 in the biliary tree in cholestatic liver diseases

TGR5 knockout mice are more susceptible towards cholestatic liver damage inflicted by feeding a BS-enriched diet (cholate 0.5–1% for 5–7 days) or by common bile duct ligation (CBDL) as demonstrated by more pronounced elevation of aspartate (AST) and alanine aminotransferases (ALT) and/or more severe liver injury on histopathology [14,45,61]. In line with the important role of TGR5 for BS-dependent cholangiocyte proliferation, targeted deletion of TGR5 almost completely attenuated biliary proliferation in response to BS-feeding or CBDL [45]. Furthermore, feeding a diet enriched with the cytotoxic secondary BS lithocholate (1%, 3–4 days) resulted in a more severe injury of both intrahepatic and extrahepatic bile ducts in TGR5 knockout mice as compared to wildtype littermates, which was also reflected in higher serum levels of alkaline phosphatase.

Genome-wide association studies (GWAS) in patients with primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) identified a disease susceptibility locus at the chromosomal region 2q35, which comprises the TGR5 gene [13,62–64]. However, resequencing of Norwegian PSC patients and healthy controls revealed that non-synonymous mutations within the coding sequence of TGR5 were rare and may not play an important role for PSC disease susceptibility. However, the study also identified a common single nucleotide polymorphism (SNP) in the untranslated exon 1 (rs11554825), which was significantly associated with both PSC and UC [13,63,64]. It has been suggested that this rs11554825 SNP reduces TGR5 mRNA expression [64]. Based on the animal studies described above, low TGR5 expression levels may render cholangiocytes more susceptible towards BS toxicity and cholestatic injury and thus predispose towards the development of cholangiopathies such as PSC and primary biliary cholangitis (PBC).

This hypothesis is underscored by the finding that a decrease in TGR5 immunofluorescence staining intensity was found in cholangiocytes of livers from PSC patients as well as in livers from Abcb4 (Mdr2) knockout mice, which serve as an animal model for PSC [13,14,45,65]. The mechanisms as well as the timing (early or late) underlying the reduction of TGR5 protein levels in cholangiocytes needs further investigation [13,14].

4. TGR5 and polycystic liver disease

Cholangiocyte-derived liver cysts are the hallmark of polycystic liver disease (PLD). The second messenger cAMP can trigger proliferation and secretion of cystic cholangiocytes [66,67]. Furthermore, elevated BS levels have been detected in cystic fluid as well as in livers from PLD animal models, suggesting a role for BS signalling in hepatic cyst formation [68]. A significant, about 2–3 fold overexpression of TGR5 as well as of $G\alpha_{(s)}$ proteins has been described in cystic cholangiocytes [65]. Stimulation of TGR5 in cystic cholangiocytes triggered cAMP production which in turn induced cell proliferation and cyst growth. Treatment of cystic cholangiocytes with a novel TGR5 antagonist (SBI-115) or downregulation of TGR5 by shRNA or targeted deletion attenuated the proliferative response as well as cyst growth [67]. Therefore, TGR5 antagonists may represent a promising therapeutic strategy for PLD [14,67].

5. TGR5 and cholangiocarcinoma

Bile salts have been reported to facilitate cholangiocarcinoma (CCA) development not directly, but indirectly via induction of biliary proliferation, promotion of hepatic inflammation as well as downregulation of FXR [69–71]. Similar to PLD, TGR5 protein levels were about 3-fold increased in human CCA tissue as compared to cholangiocytes from the nontumorous resection margin [13,45]. Similarly, TGR5 is expressed in EGI-1 and TFK-1 cells, which are derived from an intrahepatic, low-differentiated and an extrahepatic, well-differentiated CCA, respectively [72]. Stimulation of TGR5 in both CCA cell lines induced cell proliferation using the same ROS-cSrc-MMP-EGFR-ERK1/2 signalling pathway as in cultured murine cholangiocytes. This finding was further supported by increased levels of ERK1/2 phosphorylation in CCA tissue [45]. Cell proliferation in response to a synthetic TGR5 agonist or TLCA was abolished in TFK-1 cells after knockdown of TGR5 using siRNA [45]. Furthermore, ligand activation of TGR5 by a synthetic agonist or TLCA triggered cell migration and invasion of CCA cell lines, supporting a role for BSs and TGR5 in progression of CCA (Fig. 3).

Similar to TGR5, S1PR2 has also been detected in human CCA tissue and CCA cell lines [39]. Stimulation of S1PR2 with TCA induced proliferation, migration and invasion of CCA-derived cell lines [39], indicating that BSs use redundant signalling pathways in CCA to promote disease progression. In contrast to the plasma membrane-bound G protein-coupled BS receptors, expression of the nuclear receptor FXR is downregulated in CCA tissue [71].

6. Beyond TGR5: other BS receptors in cholangiocytes

Besides TGR5 cholangiocytes express M3 acetylcholine receptors, S1PR2, VDR and FXR. Binding of conjugated BSs to S1PR2 results in activation of ERK1/2 and protein kinase B (AKT) and cell proliferation [36]. Similar to TGR5 knockout mice, S1PR2-deficient mice have significantly reduced cholangiocyte proliferation in response to CBDL [36]. However, while liver injury is more severe in TGR5 knockout mice following CBDL, S1PR2 knockout mice have lower BS levels and reduced liver inflammation and fibrosis as compared to wildtype controls [36,45]. All three BS-responsive GPCRs have been detected in human CCA tissue and CCA-derived cell lines. Stimulation of TGR5, S1PR2 and M3R promotes proliferation of CCA cell lines and activation of TGR5 and S1PR2 also enhances cell migration and invasion [39,45,73].

Activation of FXR in cholangiocytes triggers expression of fibroblast growth factor (FGF) 15/19 which in turn downregulates expression of sterol 27 hydroxylase (Cyp27) thereby reducing biliary bile acid synthesis [74]. In contrast to the BS-responsive GPCRs, activation of the nuclear BS receptors FXR and VDR inhibits proliferation of CCA cell lines [71,75]. This suggests, that BSs promote CCA proliferation and progression through BS-responsive GPCRs, while stimulation of BS-responsive NRs induces antiproliferative effects.

7. Summary and perspective

Effects of BS signalling can be mediated through NRs and GPCRs, several of which are expressed in cholangiocytes. TGR5 is localized in the primary cilia and the apical plasma membrane of cholangiocytes and activation of the receptor by BSs modulates cell proliferation, triggers cell protective mechanisms and promotes chloride secretion. The important role of TGR5 for biliary physiology is underscored by the

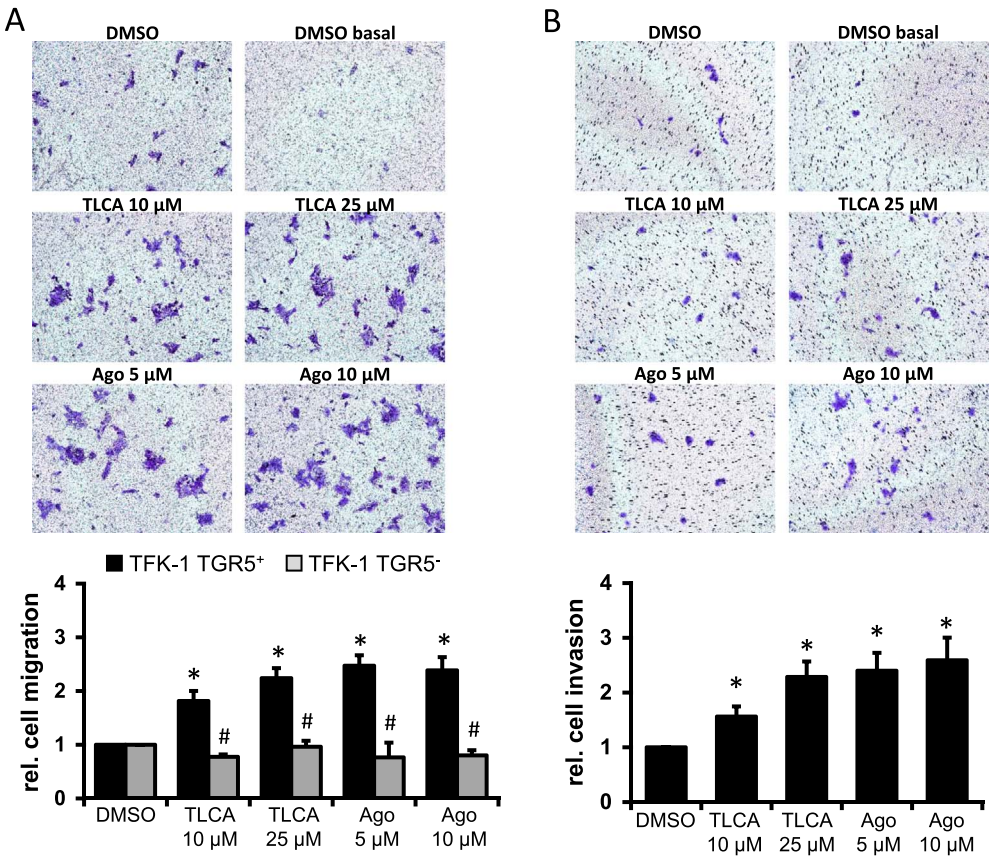

Fig. 3. TGR5 ligands trigger migration and invasion of the CCA cell line TFK-1. TFK-1 cell migration (A) and invasion (B) assays (CytoSelect™, Cellbiolabs, Heidelberg, Germany) were carried out over 24 and 48 h, respectively. Cells were seeded in the upper well of a 24-well transwell plate (Corning Inc., Tewksbury, MA, USA) in the presence of DMSO (vehicle control), taurolithocholate (TLCA) or a synthetic TGR5 agonist (RO5527239; Ago). 10% fetal bovine serum (FBS) served as chemoattractant in the lower well. Cells cultured without the chemoattractant (DMSO basal) served as negative control. Migration and invasion was measured towards the FBS gradient and was significantly enhanced in the presence of taurolithocholate (TLCA) or the synthetic TGR5 agonist RO5527239 (Ago). Upper panels show crystal violet staining of migrated cells photographed at 100 × magnification. Diagrams depict optical density normalized to DMSO treated control cells (A, n = 9), whereas TFK-1 cell invasion was measured by counting of all invaded cells per filter (B, n = 6). For TGR5-specific gene knockdown (A, grey boxes, TGR5^{-}) four single guide RNA oligo sequences were designed using the CRISPR Design Tool (http://benchling.com/crispr), cloned into the pSpCas9(BB)-2A–Puro (PX459) vector (Addgene, Cambrigde, MA, USA) [91], transfected into TFK-1 cells using the 4D–Nucleofector™ X Kit (Lonza, Cologne, Germany) and cultivated in the presence of puromycin. Subsequently clonal cells clusters were picked and expanded. Successful targeting of the TGR5 gene was verified by sequencing. Data are expressed as means + SEM, * = significantly different from DMSO treated cells ($p < 0.05$) and # = significantly different from TGR5 wildtype cells under the same treatment ($p < 0.05$) using a two-sided student *t*-test. RO5527239 was kindly provided by F-Hoffmann-La Roche Ltd. (Basel, Switzerland).

finding, that TGR5 knockout mice develop more severe liver damage with increased biliary injury and reduced adaptive cholangiocyte proliferation in response to BS-feeding or CBDL. It is therefore not surprising that a common polymorphism in the TGR5 gene has been linked to cholangiopathies such as PSC and PBC. Furthermore, TGR5 is downregulated in cholangiocytes from livers of PSC patients and Mdr2 knockout mice, which may promote disease progression due to reduced TGR5-dependent cytoprotection.

In contrast, upregulation of TGR5 expression as well as stimulation of the receptor by agonists will trigger cholangiocyte secretion, proliferation and render the cells more resistant towards BS-induced toxicity thereby reducing cholestatic liver injury. Together with the strong anti-inflammatory function of the receptor in different immune cells [46,52,76–79], these TGR5-dependent effects make this GPCR an interesting target for biliary diseases. However, since TGR5 is expressed not only in the liver and gastrointestinal tract but also in the heart and vasculature, the peripheral and central nervous system, the male and female reproductive organs and many other tissues, systemic activation of TGR5 may have multiple adverse effects, such as inhibition of gallbladder emptying, itch, decreased systemic vascular resistance with subsequently increased heart rate and cardiac output as well as proliferation of tumor cells and thus progression of CCA, esophageal and gastric but also endometrial cancers [56,58,80–85].

Besides TGR5 other BS-responsive GPCRs are highly expressed in CCA and ligand activation of TGR5, S1PR2, and the M3R induce cell proliferation and cell migration. Through GPCR signalling BSs can contribute to CCA progression.

In summary, TGR5 has been linked to biliary diseases such as PSC and PBC, where upregulation and stimulation of the receptor may be a valuable therapeutic approach. However, in PLD and CCA inhibition of TGR5, S1PR2 and M3R signalling may diminish disease progression, thus underscoring the need for the development of TGR5 antagonists. Novel experimental models such as cholangiocytes derived from human-induced pluripotent stem cells (iPSC) as well as human biliary organoids [86–90] will not only allow further investigation of TGR5-dependent signalling pathways in normal and diseased cholangiocytes but may prove to be a valuable tool for testing novel TGR5 agonists and antagonists.

Further studies will be needed to elucidate the potential crosstalk of different BS-responsive receptors in cholangiocytes in health and disease. This may lead to novel therapeutic approaches for biliary diseases.

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