Abnormalities of lipid metabolism, gallstone disease and gallbladder function

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Abnormalities of lipid metabolism, gallstone disease and gallbladder function

Gallstone disease is highly prevalent with a complex and multifactorial pathogenesis. Gallstones are closely related to the metabolic syndrome – associated disease conditions in which abnormal regulation of lipid metabolism secondary to insulin resistance plays a major pathogenic role. Insulin resistance increases biliary cholesterol secretion and affects gallbladder (GB) motility. Regulation of lipid metabolism and energy homeostasis is complex and the GB has been considered to have a minor regulatory role in both the intestinal absorption of lipids and metabolic homeostasis of the whole body. In fact, ablation of the GB does not affect nutrient absorption or the ability to lead a normal life. GB function regulates the cycling of bile salts through the enterohepatic circulation. Bile salts have important signaling effects that can affect whole body metabolic homeostasis. The GB and intestinal mucosa are rich in the hormone FGF15/19 and the receptor TGR5, which participate in metabolic regulation. Recent evidence supports the hypothesis that cholecystectomy may not be innocuous and that the GB has a significant role in the regulation of hepatic triglyceride metabolism. This article provides information regarding recent advances in the understanding of the interaction between regulation of lipid metabolism, insulin resistance, gallstone disease and GB function.

KEYWORDS: gallbladder function gallstone disease insulin resistance triglyceride metabolism

The prevailing views about the gallbladder (GB) are that it is a gastrointestinal organ that concentrates and stores hepatic bile for delivery into the intestinal lumen during the food intake cycles for lipid digestion and absorption, and that it is the organ where gallstones (GS) form, producing GB disease (GBD). However, recent studies on the role of bile salts (BS) as important signaling molecules that participate in metabolic regulation, have raised the question of whether the GB might also play a direct role in metabolic homeostasis of the whole body.

Cholesterol (CH) GS (defined by >50% CH content by weight) are present in approximately 80% of patients with GBD [1–3]. The remaining GS patients harbor black pigment stones, mainly composed of calcium bilirubinate, and brown pigment or mixed stones. Black pigment stones form in patients with hemolytic diseases such as thalassemia, whereas brown pigment GS are frequent in conditions associated with infections of the biliary tree [1–3].

Gallbladder disease secondary to GS is a high burden disease condition that increases mortality in the general population [4]. CH GS disease is particularly prevalent among Native Americans and Hispanics [5,6]. Cholecystectomy is the best treatment for GBD and is one of the more frequently performed surgical procedures performed worldwide. Besides gender, age and family history, a number of metabolic abnormalities included in the metabolic syndrome (abdominal obesity, insulin resistance [IR], glucose intolerance or diabetes Type 2 and high triglycerides, low HDL-C dyslipidemia) are associated with both GBD and arteriosclerotic vascular diseases. The hallmark pathogenic condition that is common to all these disease conditions is IR [7–12], however, how all these metabolic abnormalities favor GS formation is unknown. Consistent with a common epidemiological and pathogenic background, patients with atherosclerotic coronary [13,14] and carotid artery [15,16] diseases have a higher risk of developing GS compared with the general population. However, which metabolic abnormalities of lipid trafficking at the cellular and molecular levels (particularly hypertriglyceridemia and low serum HDL-C dyslipidemia
frequently found in IR) can favor the precipitation and accumulation of CH in the GB and the artery wall, respectively, is unknown.

The purposes of this article are first, to review some of the metabolic links between abnormalities of lipid metabolism commonly found in IR-associated diseases, GB functions and GBD. Second, to discuss experimental evidence supporting a new metabolic role of the GB and speculate on the hypothesis that the GB, besides its well-known role in lipid digestion and absorption, could also have important endocrine functions participating in whole body metabolic homeostasis.

**GB function & lipid metabolism**

Gallbladder function is integrated in the ‘liver–GB–intestine’ axis, responsible for maintaining the homeostasis of triglycerides (TGs), free fatty acids (FFAs) and CH of the entire organism. The GB plays a central role in the digestion and absorption of lipids present in the diet. It stores and concentrates hepatic bile secreted by the liver during periods of fasting and then sends it to the intestine during food intake, through contractions triggered by duodenal cholecystokinin. The release of the ileal hormone FGF15 (human ortholog, FGF19), due to the ileal reabsorption of biliary BS, aids GB filling and at the same time inhibits the synthesis of BS [17,18]. GB bile that is rich in BS and phospholipid mixed micelles, allows intraluminal emulsification and hydrolysis of dietary TGs in the intestine [19]. After intestinal uptake, FFAs are re-esterified into new TGs, which are incorporated with CH, phospholipid and apoB, forming chylomicrons, which are then sent to the periphery.

Triglycerides are key metabolites through which energy can be stored in adipose tissue and transported throughout the organism for maintaining energy homeostasis. TGs circulate in plasma incorporated in lipoproteins (preferably chylomicrons and VLDL) and are also found in fat goblets inside of cells as energy stores. There are three fundamental organs that contain TGs: adipose tissue, muscle and the liver. These organs store TGs, hydrolyze them to release FFAs, export them, and finally produce energy for cellular function. There is a continuous flow of FFAs between the three tissues via the blood. Dietary fat enters the plasma from the small intestine in the form of chylomicrons, and they then deliver FFAs from TGs to the tissues that express lipoprotein lipase. Once approximately two thirds of their TGs are unloaded in peripheral tissues, chylomicron remnants containing the remaining TGs and CH esters are quickly taken in by the liver [19]. Abnormal accumulation of hepatic lipids occurs when the amount of FFAs and CH entering the hepatocytes exceeds their exit. FFA flow between the different tissues changes according to the nutritional state of the subject. Similarly, cellular CH content will depend on the uptake from plasma lipoproteins and the level of endogenous synthesis. In the feeding stage, FFAs travel bound to albumin towards the tissues to be stored in adipose tissue. The endogenous secretion of TGs and CH to the plasma is carried out from the liver in the form of VLDL and is regulated by food intake cycles. This regulation is dependent on insulin effects that decrease the hepatic production of VLDL, which is increased in states of IR [20].

The metabolism of FFAs, TGs, CH and BS are highly interrelated processes and are regulated by genes that control synthesis, uptake of lipoproteins and their production, as well as biliary and fecal excretion of the steroidal ring in the form of neutral sterols and BS. Numerous studies have shown a close functional relationship between the regulation of BS metabolism, as well as TG and CH metabolism [21–26]. For example, hypertriglyceridemia can be observed in patients with 7α-hydroxylase deficiency [27], and in those with an increased fecal excretion of BS, as happens after removal of the distal ileum, Crohn’s disease and cholesteatomatous treatment [28–32].

A number of studies have shown that GB motility is altered, decreasing GB emptying and favoring GS formation in patients with Type 2 diabetes, IR, obesity and hypertriglyceridemia [33–35]. However, the molecular mechanism(s) responsible for this abnormality is unknown. GB motility is regulated by complex interrelated neuronal, hormonal and paracrine factors [36]. FGF15/19, produced on arrival of BS in the ileum, is also important for GB motility favoring GB filling [19].

In recent years, close relationships have been proved between the enterohepatic circulation of BS, GS, regulation of serum glucose and serum TG concentrations, presence of IR and nonalcoholic fatty liver disease (NAFLD) [21–26]. For instance, BS function as metabolic modulators through the activation of the nuclear receptor farnesoid X receptor (FXR), which acts as an intracellular sensor of the concentration of BS [26]. The activation of FXR reduces glucoseogenesis and participates indirectly in the metabolic regulation of FFAs, TGs, CH and...
Mechanisms of GS formation

The pathogenesis of CH GS formation implies abnormalities of bile secretion, CH solubility and crystal formation, and abnormal function of the GB [2,3]. Normal hepatic bile composition by weight consists of water (90%) and 10% solids: BS (72%), phospholipids (24%) and CH (4%). A number of specific ATP-binding-cassette (ABC) transport proteins expressed at the canalicular membrane are responsible for the secretion of biliary lipids into bile: ABCB11 (BS export pump) is the main BS transporter; ABCB4 (multidrug resistant p-glycoprotein MDR3) acts as a ‘flipase’ that translocates phospholipids from the inner to the outer leaflet of the canalicular membrane as unilamellar vesicles; the heterodimer ABCG5/ABCG8 is responsible for CH translocation into bile. Unilamellar phospholipid vesicles solubilize free CH, and simple BS micelles tend to dissolve them into mixed micelles in the GB, where diluted hepatic bile is concentrated. In CH supersaturated bile, vesicles persist and become enriched in CH translocated by the heterodimer ABCG5/ABCG8. When the CH:phospholipid ratio is greater than 1, CH crystals can nucleate and initiate CH GS formation [2,3].

Cholesterol supersaturation of bile has been considered a *sine qua non* pathogenic condition for CH GS formation. This is the result of increased hepatic secretion of CH and/or decreased secretion of BS and phospholipids into bile [1,3]. CH GS patients usually have increased relative biliary CH concentration in GB bile compared with pigment GS patients or normal subject’s bile [3]. However, it is important to note that biliary CH supersaturation is commonly found in normal subjects without GBD [41], reinforcing the concept that posthepatic events, including GB factors, are fundamental for CH GS formation.

Pathogenic GB factors include pronucleating proteins such as mucin and abnormal GB motility with impaired postprandial GB emptying, as found in obese and diabetic patients, and during pregnancy [2,3].

The pathogenesis of pigment GS is related to increased biliary concentration of unconjugated bilirubin as occurs in sickle cell disease [42] and in patients with ileal dysfunction resulting from any medical or surgical cause, such as Crohn’s disease and ileal resection [43]. Brown pigment stones are frequently found in Asian patients with bacterial infection of the biliary tract, which causes high glucuronidase activity in bile [2,3].

An intriguing finding is that patients with pigment stones as well as those with CH GS (both types of GS have very different pathogenic mechanisms) present higher than normal serum TG levels [44], a serum abnormality commonly found in IR states. This interesting epidemiological finding suggests that abnormal GB function as a consequence of GS disease could affect serum and hepatic TG metabolism.

IR, abnormal lipid metabolism & GBD

Insulin resistance is characterized by hyperinsulinemia with progressive tendency to hyperglycemia, hypertriglyceridemia and low HDL-C, and is considered the central pathogenic mechanism of the metabolic syndrome [7,8] and its clinical constituents, as shown in Figure 1. Several studies have indicated that IR predisposes to subsequent CH GBD [9–12], a link that supports the hypothesis that insulin plays a significant role in the regulation of CH and TG metabolism and the enterohepatic circulation of lipids.

Gallbladder diease is strongly associated with the metabolic syndrome [9–12], suggesting that IR could play a key pathogenic role in GS formation. Because abnormal regulation of GB function has an important pathogenic role in GBD [1–3] it is possible that IR also affects GB function. In fact, IR causes GB dysmotility in humans [34]. The two more common abnormalities of biliary lipid metabolism that induce CH supersaturated bile in CH GBD are increased biliary CH secretion and decreased BS pool and biliary secretion rate [1–3]. To understand the pathogenic mechanism leading to CH GS formation in patients with IR, it is important to know the role of insulin on biliary CH, BS and phospholipids secretion rates and GB function.

A number of experimental data support the concept that insulin plays a major role in the regulation of CH metabolism. For instance,
IR increases CH synthesis, decreases intestinal CH absorption [46], and increases VLDL production [20]. Insulin also inhibits the expression of CYP7A1, the enzyme that controls the rate-limiting step of BS synthesis [46]. The metabolic abnormality linking IR, CH-supersaturated GB bile and CH GS formation is the increase of body CH synthesis and hypersecretion of biliary CH [47]. Recent experimental studies have shown that mice with hepatic IR due to disruption of the insulin receptor (LIRKO) had increased biliary CH output and saturation [48]. These animals developed a higher incidence of GBD when exposed to a lithogenic diet compared with controls. LIRKO mice with specific hepatic IR presented hypersecretion of CH into bile as a consequence of the hepatic overexpression of CH transporters ABCG5 and ABCG8 in the canaliculi [48]. These animals have increased GB volume presumably as a consequence of increased bile flow, conditions that could also favor GS formation [49]. Interestingly, LIRKO mice also developed atherosclerosis when exposed to this lithogenic diet [50], a finding consistent with the epidemiological evidence linking CH GS with arteriosclerotic cardiovascular disease and the metabolic syndrome. Contrary to human GS patients with IR states that usually develop with higher than normal serum TG levels, LIRKO mice presented lower than normal serum TG.
levels. These observations indicate that the mechanism of hypertriglyceridemia commonly found in human GBD and IR-associated disease conditions is more complex compared with the LIRKO mouse model of hepatic IR.

Hepatic TG content and VLDL production are increased in normal weight GS patients with normal liver histology, compared with individuals without GS, suggesting that GS formation, or altered GB function could affect hepatic TG metabolism [51]. NAFLD usually presents higher than normal serum TG levels and GBD [9,35,52] and it would appear that IR is the principal pathogenic factor [33,54]. NAFLD is the main cause of cryptogenic cirrhosis with a major impact on healthcare systems [55,56]. Cirrhosis is also associated with GBD [57–59].

The cause of the increase of hepatic and serum TGs in GBD has not been completely deduced. However, it is known that IR is a fundamental factor that can alter each of the processes that regulate the concentration of TGs in blood and liver as well as CH secretion into bile. IR increases lipolysis from adipocytes, liberating FFAs, which are quickly taken up by the liver. In the IR state, the activity of the peripheral lipoprotein lipase is diminished, producing an increase of chylomicrons and VLDL remnants, which are also taken up by the liver, thus increasing TGs and CH mass in the organ and increasing the availability of hepatic free CH for secretion into bile.

Genetics of GBD & abnormalities of lipid metabolism

The genetics of GS disease is complex and GS disease is polygenic, as are obesity, diabetes and arteriosclerosis. It is well known that an important component of GBD depends on genetic factors [60–64] giving an estimate that a number of genes could contribute approximately 25% of the development of symptomatic GBD in populations with a relatively low prevalence of GBD [64]. However, in populations with a high prevalence of GBD the genetic contribution could be as high as 60% [65]. Genetic factors play an important role not only in CH GS pathogenesis, but also in pigment GS formation [66].

Candidate genes for GBD, the so-called Lith genes, have long been known in mice. Quantitative trait locus mapping was employed to identify more than 40 candidate genes for susceptibility to GS [67]. Most of these genes are involved in lipid metabolism and traffic, as well as in GB function. However, in contrast to the plentiful information on mouse Lith genes, information in humans is more scarce. However, more than ten candidate genes have been described with an attractive mechanistic hypothesis [68,69]. Through studies of genome-wide association and linkage in affected sibling pairs the ABCG8 D19H variant was identified as a common genetic factor contributing approximately 10% of the total risk for the development of GS [70]. Confirming these results, a recent study in Swedish twins has shown that heterozygous or homozygous twins carrying the ABCG8 D19H genotype have a significantly increased risk of GS disease [70]. Genetic variants in the ABCG8 and ABCG5 genes have also been found to be associated with CH metabolism and individual responsiveness of plasma CH to dietary and pharmaceutical interventions for hypercholesterolemia [71].

Other attractive candidates as genetic factors linking lipid metabolism, IR and GBD are the nuclear receptors that control the expression of transporters and key enzymes of lipid metabolism. The nuclear receptor FXR acts as an intracellular BS sensor [72,73] and induces the expression of Abcb11 and Abcb4 and represses BS synthesis by SHP-mediated CYP7A1 inhibition. Results obtained by Moschetta et al. confirmed the relevance of FXR in CH GD development in mouse models. FXR-deficient mice fed with a lithogenic diet showed decreased biliary phospholipid and BS concentrations and increased CH GS formation. In contrast, treatment of wild-type mice with an agonist of FXR decreased CH GS susceptibility [74]. In addition, FXR regulates lipogenesis, plasma VLDL-TG and plasma TG export and turnover [25,26]. Moreover, FXR is also involved in the regulation of hepatic gluconeogenesis, glycogen synthesis and insulin sensitivity [26]. Interestingly, a common polymorphism in the FXR gene was associated with decreased hepatic lipid gene expression of some FXR-target genes, suggesting that genetic FXR modulation could affect the susceptibility to conditions such as GBD, arteriosclerosis and diabetes.

The liver X receptor (LXR), which is an oxysterol intracellular sensor, regulates master genes related to sterols, lipids and BS homeostasis. LXR are also known to induce the expression of CH and phospholipid efflux transporters such as ABCG5 and ABCG8, as well as ABCA1, a basolateral ABC transporter that effluxes both CH and phospholipids [75]. Although increased expression in LXR as well as ABCG5 and ABCG8 has been found in
nonobese Chinese GS patients, no correlations were found between SREBP1c and LXR [76]. Interestingly, activation of LXR augmented mice susceptibility to a lithogenic diet, increasing the CH saturation index in bile and CH GS formation [77]. Further studies are required to establish whether nuclear receptors are relevant as genetic link factors between GBD, lipid abnormalities and IR in humans. Some well-documented monogenic mutations that occur very rarely in the general population clearly predispose to CH GBD [78]. These monogenic diseases mainly include monogenic deficiency of Abcb4, responsible for the secretion of phospholipids into the canaliculi, and deficiency of Cyp7A1 [27], the rate-limiting step of BS synthesis that determines familiar early-onset GBD associated with hyperlipidemia.

**GB function & hepatic TG metabolism**

It is generally accepted that cholecystectomy is the best treatment for GBD without any negative impact on metabolic regulation or on normal life. In fact, the digestion and absorption of liposoluble vitamins and dietary fats is normal after a cholecystectomy, due to the fact that the BS pool size remains normal and the bile is stored in the proximal portion of the small intestine during fasting periods [79]. Cholecystectomy determines an increase in the number of times the pool of BS travels the enterohepatic circulation, exposing the mucosa of the distal ileum and hepatocytes and biliary tree to an increase in the mass flux of BS per day. Due to hormonal connections between the distal ileum, the liver and the GB it is important to explore the possibility of an inter-relationship between the regulation of hepatic metabolism of lipids, energy balance and predisposition to the development of the metabolic syndrome, associated diseases and the presence or absence of the GB in the enterohepatic circuit.

Recent studies from our group have found increased serum and hepatic TG levels, increased hepatic VLDL production, and increased activity of hepatic microsomal TG transfer protein after ablation of the GB in mice [80]. In these experiments, BS pool size, composition and synthesis remained unchanged after cholecystectomy. This observation indicated that the mechanisms responsible for the metabolic changes of TG metabolism after ablation of the GB were different from those observed in conditions that determine altered BS metabolism, as occurs in patients with CYP7A1 deficiency [27], ileal resection and Crohn’s disease [28–30], and in subjects receiving cholestyramine treatment [31,32].

Bile salts, which circulate faster through the enterohepatic circulation after cholecystectomy, are signaling molecules for a number of receptors that control important metabolic pathways, including FXR and TGR5 [21,22,24,25]. For example, feeding BS prevents hepatic TG accumulation and VLDL production in mouse models of hypertriglycerideremia through reduction of Srebp1c and its target lipogenic genes [81]. The FXR–SHP–SREBP1c pathway was normally expressed in cholecystectomized mice, therefore if the changes observed in TG metabolism in cholecystectomized mice were also BS-dependent, other unknown target(s) and signaling factors for BS molecules should be responsible for the accumulation of TGs in the liver and the increase in hepatic VLDL production [80]. It is plausible that metabolic effects mediated by the hormone FGF15/19 [21,22,82] or by the membrane-bound TGR5 receptor [21,22,39,83,84], which are both expressed in the GB mucosa [84,85], could be affected after ablation of the GB. We postulate that changes in FGF15/19 secretion or altered function of the membrane-bound TGR5 due to increased enterohepatic cycling of BS after cholecystectomy, may be critical mechanisms underly- ing the metabolic phenotype observed after surgical removal of the GB. Cholecystectomy could decrease the serum levels of FGF15/19, favoring the increase in serum and hepatic TG concentrations, as found in cholecystectomized mice or overstimulation of TGR5 secondary to increased enterohepatic cycling of BS (Figure 2). Supporting this hypothesis, for example, are the observations that FGF19 transgenic mice have reduced serum TG concentration and adiposity [37] and administration of recombinant FGF19 to mice induces important metabolic changes in the whole animal, including a reduction in serum TG levels, body weight, adiposity and insulin sensitivity, and an increase in energy expenditure [38].

It is remarkable that findings in cholecystectomized mice are consistent with a number of studies in humans. The majority of epidemiological studies aimed at the identification of associated risk factors of GBD show that higher than normal serum TG concentration is associated with GBD [1–3], a finding that has been interpreted as a marker of the underlying metabolic abnormality that favors the production of lithogenic
bile during CH GS formation. However, Thijs et al. demonstrated that higher than normal serum TG concentration was an associated risk factor related to both pigmented and CH GS, diseases that have different pathogeneses [44]. This finding is not consistent with the prevailing view that higher than normal serum TG levels represents a metabolic marker of GS formation, or a risk factor of CH GS formation. In contrast, it suggests that the presence of GS and GB inflammation could alter a GB-derived regulatory factor(s) of whole body metabolism. Experiments in mice showing increased hepatic VLDL production, serum and hepatic TG concentration in cholecystectomized mice [80], are consistent with the study by Juvonen et al. showing increased serum VLDL-apoB and IDL-apoB, 3 years after cholecystectomy in GS patients [86]. We have also demonstrated that Chilean patients with normal weight and symptomatic GBD disease have increased serum apoB, and TG-VLDL levels and increased hepatic TG concentration.
Conclusion & future perspective

It is apparent that the pathogenesis of CH GS is very complex and frequently associated with the metabolic syndrome. Abnormalities of lipid metabolism in GBD are related to both primary abnormalities in the regulation of biliary lipid secretion and GB function, and abnormalities of whole body lipid metabolism commonly found in IR states, particularly obesity, Type 2 diabetes and NAFLD. The series of studies in humans and mice showing increased serum VLDL-apoB and serum TG concentrations after ablation of the GB, suggest that cholecystectomy and GBD disease may impact negatively on the metabolic homeostasis of the whole body. These observations indicate that GB function has an important role in regulating systemic TG metabolism and energy balance. Thus, cholecystectomy, one of the most frequently performed surgical procedures worldwide, may indeed favor the development of the metabolic syndrome and associated highly prevalent chronic disease conditions. These considerations raise the important question as to whether cholecystectomy might have a serious negative impact on public health [80,87]. Future prospective epidemiological and intervention studies should help to address the actual cause–effect relationship between abnormalities of serum lipids, hepatic TG metabolism, cholecystectomy and GB function that emerge from epidemiological surveys in humans and experimental data in mice. Another important issue for further study is defining whether GB-derived FGF15/19 and/or altered TGR5 receptor activity in the enterohepatic organs and adipose tissue induce systemic effects on energy balance and metabolic regulation.

Financial & competing interests disclosure

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Executive summary

Gallbladder function & lipid metabolism

- Gallbladder (GB) filling and contraction depends on fed–fasting cycling and regulates the dynamics of the enterohepatic circulation of bile salts (BS).
- After feeding, the GB contracts and delivers concentrated bile into the intestine for digestion and absorption of lipids.
- Cholecystectomy does not affect lipid absorption.

Mechanisms of gallstone formation

- The primary pathogenic event is cholesterol (CH) supersaturation of bile. This occurs by increased hepatic secretion of CH and/or decreased secretion of BS into bile.
- Pigment gallstones are related to an increased biliary concentration of unconjugated bilirubin.
- Pronucleating biliary proteins (mucins) facilitate CH crystal formation.
- Abnormal GB motility (frequent in obesity and diabetes) facilitates gallstone growth.

Insulin resistance, abnormal lipid metabolism & GB disease

- GB disease is more frequent in insulin resistance states.
- Insulin resistance increases biliary CH secretion and decreases GB motility.

Genetics of GB disease & abnormalities of lipid metabolism

- Lith genes have been identified in mice. GB disease is associated with polygenic factors.
- Genes could contribute 25% to the development of symptomatic GB disease in humans.
- Altered function of nuclear receptors (Farnesoid X receptor, liver X receptor) could favor the production of both dyslipidemia and biliary CH supersaturation.

GB function & hepatic triglyceride metabolism

- In mice, ablation of GB increases VLDL production serum and hepatic triglyceride content.

Conclusion & future perspective

- Studies in humans could confirm the relevance of a GB factor(s) in the regulation of hepatic triglyceride metabolism.
- Cholecystectomy might not be innocuous and could favor metabolic syndrome-associated abnormalities.
- A GB-dependent factor could have a major role in the regulation of whole body metabolic homeostasis.
Disclosure of hormonal-mediated relaxation of the gallbladder (GB) by FGF15/19.


First evidence that the ileal hormone FGF15/19 regulates bile salt (BS) synthesis.


* Demonstration that FGR15/19 influences triglyceride (TG) metabolism and energy balance.


** Disclosure of the molecular mechanism of the BS-mediated increase of basal metabolic rate.
Reports the mechanism of BS-mediated regulation of glucose metabolism.


** Epidemiological study that shows increased serum TG levels in GB disease patients with pigment or cholesterol gallstones.


Liver-specific ablation of the insulin receptor induces expression of canalicular cholesterol transporters ABCG5/8.


Molecular mechanism through which BS influence TG metabolism.

First evidence that GB mucosa is rich in FGF19.