Review of experimental animal models of biliary acute pancreatitis and recent advances in basic research

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Abstract
Acute pancreatitis (AP) is a formidable disease, which, in severe forms, causes significant mortality. Biliary AP, or gallstone obstruction-associated AP, accounts for 30–50% of all clinical cases of AP. In biliary AP, pancreatic acinar cell (PAC) death (the initiating event in the disease) is believed to occur as acinar cells make contact with bile salts when bile refluxes into the pancreatic duct. Recent advances have revealed an important receptor responsible for the major function of bile acids on acinar cells, namely, the cell surface G-protein-coupled bile acid receptor-1 (Gpbar1), located in the apical pole of the PAC. High concentrations of bile acids induce cytosolic Ca2+ overload and inhibit mitochondrial adenosine triphosphate (ATP) production, resulting in cell injury to both PACs and pancreatic ductal epithelial cells. Various bile salts are employed to induce experimental AP, most commonly sodium taurocholate. Recent characterization of tauroliotholic acid 3-sulphate on PACs has led researchers to focus on this bile salt because of its potency in causing acinar cell injury at relatively low, sub-detergent concentrations, which strongly implicates action via the receptor Gpbar1. Improved surgical techniques have enabled the infusion of bile salts into the pancreatic duct to induce experimental biliary AP in mice, which allows the use of these transgenic animals as powerful tools. This review summarizes recent findings using transgenic mice in experimental biliary AP.

Keywords
biliary acute pancreatitis, bile acids, pancreatic acinar cells, pancreatic ductal cells, Gpbar1, animal model

Introduction
Biliary acute pancreatitis (BAP) refers to acute pancreatitis (AP) caused by biliary calcific diseases. It is the most common cause of AP and is associated with significant morbidity and mortality. Obstruction of the common biliopancreatic duct (CBPD) by gallstones blocks the efflux of pancreatic zymogens, creates elevated pressure in the pancreas and leads to bile reflux into the pancreatic duct. A number of experimental models have been designed to recreate this condition. The purely surgical models of BAP, such as closed duodenal loop-induced pancreatitis and CBPD or pancreatic duct ligation-induced pancreatitis have been reviewed in detail previously and thus are beyond the scope of the current review. Cannulation of the pancreatic duct has enabled researchers to apply the bile components into the pancreas of experimental animals in a more controlled way. One of the most significant recent advances involves the adaptation of this technique to a mouse model, which opens the door to transgenic studies of BAP. Another significant development refers to observations of a variety of bile salts that induce pathological responses in single acinar cells in vitro, elucidating some molecular mechanisms of the detrimental action of pancreatic bile. In addition, some
important knowledge on the role of pancreatic duct epithelial cells (PDECs) in the pathogenesis of BAP has recently emerged. Finally, this review summarizes recent advances in basic research and highlights further research prospects in the pursuit of effective clinical interventions in BAP.

**Bile acids and their targets**

Bile acids, in addition to their known functions in dietary fat absorption and cholesterol metabolism through nuclear receptors, also induce cellular signalling through the recently described cell surface G-protein-coupled bile acid receptor-1 (Gpbar1), found in brown adipose tissue, intestine and gallbladder in mammals. When Gpbar1 receptor is activated by bile acids, it can modulate energy homeostasis, lipid homeostasis and glucose homeostasis, and stimulate gallbladder filling. In hepatocytes, choleric and cholestatic bile acids activate and inhibit store-operated Ca\(^{2+}\) channels, respectively, through mechanisms which involve reversible redistribution of stromal interaction molecule 1. In pancreatic acinar cells (PACs), bile acid transporters, namely, the Na\(^{+}\)-dependent Na\(^{+}\) taurocholate co-transporting polypeptide (NTCP), located at the apex of the cell, and HCO\(_3\)-dependent organic anion transporting polypeptide-1 (OATP1), located on the basolateral portion of the cell membrane, have recently been identified. The bile receptor Gpbar1 is also located in the apical region of the cell and is positioned to respond to bile in the lumen of the duct. The bile acid transporters and receptor constitute the molecular machinery responsible for the pathological action of refluxed or circulated bile acids on PACs. Detailed bile acid uptake and targets in PACs have been reviewed recently by Lerch and Aghdassi.

**Effects of bile acids on acinar cells**

In 2002, Voronina et al. demonstrated the effect of tauroliothrocholic acid 3-sulphate (TLC-S) on isolated murine PACs. TLC-S induced Ca\(^{2+}\) oscillations at concentrations as low as 25 \(\mu\)M and triggered responses in almost all cells at 200 \(\mu\)M. At higher concentrations of 300–500 \(\mu\)M, TLC-S caused longlasting Ca\(^{2+}\) rises comprised of initial release from intracellular Ca\(^{2+}\) stores and followed by the influx of extracellular Ca\(^{2+}\). The study found that other bile salts, taurodeoxycholate (TDC) and taurocholate (TC), also triggered local and global Ca\(^{2+}\) oscillations, although at much higher concentrations (1 mm and 5 mm, respectively). These data highlight the role of TLC-S not only as the most potent Ca\(^{2+}\) releaser among bile acids tested on PACs so far, but also as the most effective bile acid in inducing Ca\(^{2+}\)-independent current, even at 10 \(\mu\)M. This concentration is close to the concentrations of sulphated lithocholic acid conjugates detected in serum in different pathological conditions. Indeed, in patients with severe extrahepatic duct obstruction, concentrations of bile acids of \(-200 \mu\)M have been detected in peripheral circulation.

Subsequently, Voronina et al. and other groups revealed that bile acids mediated intracellular Ca\(^{2+}\) release from both endoplasmic reticulum and acidic intracellular Ca\(^{2+}\) stores through the activation of inositol triphosphate receptors (IP\(_3\)) and ryanodine receptors, the inhibition of sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase pumps and the activation of store-operated Ca\(^{2+}\) entry, and also reduced mitochondrial membrane potential and depleted both cytosolic and mitochondrial adenosine triphosphate (ATP), leading to cellular injury.

**Effects of bile acids on pancreatic duct cells**

Although PACs have been extensively characterized, it is surprising that few studies have addressed issues of pancreatic duct cells under stressful conditions such as bile acid stimulation. Encouragingly, the work carried out by Venglovecz et al. investigated the effects of bile acids on cells of the pancreatic duct. This study has shed some light on the role of pathological agents in the function of the ductal system.

Pancreatic duct epithelial cells and PACs have mutual communication and share similar responses to bile acids. Pancreatic duct epithelial cells play a fundamental role in secreting fluid rich in HCO\(_3\) to wash out harmful digestive enzymes secreted by PACs and in neutralizing acid chyme in the duodenum. Therefore, PDECs represent the first line of defence against bile acid reflux. Venglovecz et al. found that a low concentration (100 \(\mu\)M) of unconjugated bile acid chenodeoxycholate (CDC) stimulated HCO\(_3\) secretion via phospholipase C- and IP\(_3\)-mediated Ca\(^{2+}\) signalling in PDECs. By contrast, high-concentration (1 mm) CDC inhibited HCO\(_3\) secretion, suppressed the glycolytic metabolism of PDECs and depleted mitochondrial ATP, causing mitochondrial damage. However, conjugated bile salt glycochenodeoxycholate (GCDC)-elevated intracellular Ca\(^{2+}\) signals failed to stimulate or inhibit HCO\(_3\) secretion at various concentrations and caused no morphological change in mitochondria. Further work in guinea pigs identified Ca\(^{2+}\)-activated large conductance K \(-\) channels expressed at the apical membrane of PDECs, which play a crucial role in regulating bile acid-stimulated or -inhibited HCO\(_3\) secretion.

**Induction of AP by bile salts**

The first experimental BAP model was established in 1856 by Bernard, who developed a method of retrograde injection of bile and olive oil into a canine pancreas through the ampulla of Vater. Since then, various bile salts such as sodium CDC (Na-CDC), sodium TC (Na-TC), sodium glycodeoxycholic acid (Na-GDC), TDC (Na-TDC) and TLC-S have been reported to induce AP in different species.

**Model of pancreatitis induced by Na-CDC**

Very few studies have employed the non-conjugated bile salt, Na-CDC, to study the pathogenesis of AP or the effects of treatment regimens. This procedure sometimes requires simultaneous
ligation of the pancreatic duct and was found to cause necrotizing pancreatitis and associated lung injury in rats (5%, 2 mL/kg) and rabbits.33,34

Model of pancreatitis induced by Na-GDC
An early study demonstrated that ductal infusion of 100 μL of the glycine-conjugated bile salt, Na-GDC, at concentrations of 8.5 mM, 17 mM and 34 mM, caused progressive, severe but non-lethal AP in rats.33 Na-GDC infusions of 17 mM and 34 mM caused oedematous and necrotizing pancreatitis, respectively.34–36 When 200 ng enterokinase was administered with 34 mM Na-GDC infusate, necrotic pancreatitis with systemic disturbance and rapid lethality was produced.37

In 1992, Schmidt et al.37 established a new model in rats using the combined actions of very low concentrations of ductal infusion of Na-GDC (5 mM or 10 mM) and i.v. caerulein injection (5 μg/kg/h for 6 h). This model features a moderate onset of homogeneous moderate pancreatic injury that lasts ≥24 h and provides the potential for modulating severity, as well as clinical relevance. Therefore, this model is particularly suitable for use in the evaluation of new therapeutic modalities and has been used frequently in subsequent studies.38–41

Model of pancreatitis induced by Na-TDC
The Na-TDC model was initially used in the 1980s,42,43 both with and without ductal infusion of various concentrations of trypsin. Thereafter, the model was employed frequently to explore the pathogenesis of AP with a commonly adopted regimen of 200 μL of 5% Na-TDC in the rat. Common findings included the perturbation of energy metabolism in the intestinal wall,44 impaired intestinal permeability,45 bacterial translocation,46,47 formation of platelet-activating factor,48 pulmonary endothelial barrier dysfunction,49 microvascular endothelial barrier dysfunction,50 activation of mast cells,51–53 induction of nitric oxide synthase,54 over-induced polyamine catabolism,55–57 increased high-mobility group box,58 increased catalytic activity of phospholipase A2,59 upgraded cytokine levels60,61 and increased myeloperoxidase (MPO) activity.61

Models of pancreatitis induced by Na-TC and TLC-S
Among these bile salts, the taurine-conjugated bile salt Na-TC is the most widely used and best characterized to date in inducing AP. The Na-TC ductal infusion model has been shown to induce pancreatic oedema, haemorrhage and necrosis in large animals, such as rabbits,62 swans,63 dogs64 and pigs.65,66 However, the pancreatic injury in these large animals is not sufficient to produce multiple organ dysfunction syndromes (MODS). Instead, the rat model of Na-TC infusion serves as a well-defined tool to research MODS in severe AP, as evidenced by lung,67,68 liver,69,70 gastric,71,72 intestinal,73–75 kidney,76,77 and brain78,79 impairments, which mirror events in the human condition. Once infusion pressure and speed have been fixed by a pump, the severity of pancreatitis is determined by the concentration and volume of Na-TC infused. The regimen of Na-TC infusion was later standardized by Aho et al.74–77 in a series of studies in rats. The volume of 0.2 mL/kg at concentrations of 3.0%, 4.5% or 5.0% induced acute haemorrhage pancreatitis with 72-h mortality rates of 24%, 71% and 100%, respectively. Like the caerulein/lipopolysaccharide (LPS) model, this model is suitable for the study of bacterial translocation when combined with LPS,80 which has a dose-dependent effect on lethality in rats,79 and results in more severe MODS when trypsin is superimposed on the Na-TC/LPS model.81 In a recent study, Zhou et al.82 reported a model of infected severe AP induced by ductal infusion of Na-TC and Escherichia coli in rats.

Experimental pancreatitis induced by Na-TC in the rat may have represented the reference standard of BAP for many years. However, the technique has recently been extended to the mouse model,83 thereby enabling the increased utility of genetic approaches.84 TLC-S, which has now been extensively characterized, is favourably over Na-TC in the induction of AP. Table 1 summarizes the characteristics of pancreatitis induced by Na-TC in different species.

Recent advances in experimental BAP in mice
Recently, Laukkarinen et al.84 established a non-lethal BAP model in mice using a retrograde ductal infusion of 50 μL 2% Na-TC and published a detailed methodology.85 This protocol produced necrotizing pancreatitis in the head of the pancreas, but did not elicit associated lung injury. These authors’ parallel in vitro findings confirmed that Na-TC induced pathological Ca2+-dependent trypsinogen activation and cell death in isolated PACs. This model in mice has been further validated.86,87 Ductal infusions at 2 mL/kg of 4% and 5% Na-TC resulted in necrotizing pancreatitis, lung injury and increased cytokines, causing mortality rates of 10% and 60% at 24 h, respectively.85 These new developments allow for coherent, coordinated studies of pancreatic pathological stimuli on many layers of scale from isolated mitochondria90 to whole animals,85 especially genetically manipulated mice.

Gpbar1
The presence of Gpbar1 on the apical pole of PACs was first identified by Perides et al.13 using C57BL/6 mice deleted for Gpbar1. These authors infused 50 μL of 3 mM TLC-S or Na-TC into the pancreatic duct and found that, whereas TLC-S injection caused pancreatitis, Na-TC failed to do so. Gpbar1 knockout mice were completely protected against pancreatitis induced by TLC-S. In their parallel in vitro study, they found that 500 μM TLC-S elicited pathological Ca2+-dependent signals, intrapancreatic trypsinogen activation and cell death in isolated PACs.13 Again, these effects were mostly absent in PACs from Gpbar1−/− mice. Interestingly, 500 μM TLC-S was still able to induce amylase secretion in isolated PACs from Gpbar1−/− mice, an event that was Ca2+-dependent. When the concentration of TLC-S was increased to 1 mM, the induced amylase secretion seemed to be neither Gpbar1- nor
Ca\textsuperscript{2+}-dependent. These findings suggest that: (i) the mechanism by which TLC-S acts on PACs is independent of bile acid co-transporters and exchangers, and occurs specifically through luminal surface Gpbar1; (ii) as amylase secretion seems to be independent of Gpbar1 and, at higher concentrations, even independent of Ca\textsuperscript{2+}, non-receptor-mediated mechanisms may also account for complicated effects of bile acids on PACs, and (iii) unlike caerulein, TLC-S does not block pancreatic secretion, which suggests that the early damage to the pancreas during AP, at least in the case of TLC-S, can occur independently of the inhibition of zymogen secretion and intracellular trypsin activation.

**Cathepsin L**

Cathepsins are proteases that break down other proteins. They are found in all animals in many types of cell and are classified according to structure and catalytic type into serine, aspartic and cysteine families, the last of which includes cathepsin B and cathepsin L.\textsuperscript{89} Cathepsin B inhibitors or gene knockout have been found to block trypsinogen activation \textit{in vitro}\textsuperscript{90} and to protect against AP \textit{in vivo}.\textsuperscript{91-93} Cathepsin B demonstrates enzymatic properties similar to those of cathepsin B, and is widely expressed and exhibits much stronger endopeptidolytic activity than cathepsin B.\textsuperscript{94}

The role of cathepsin L in AP was recently investigated by Wartmann \textit{et al.}\textsuperscript{95} using Ctsl\textsuperscript{-/-} mice\textsuperscript{96} in models of pancreatitis induced by Na-TC (2%, 50 \textmu l) and caerulein, respectively. They found that, in the early stages of AP, circulating genomic DNA was markedly increased, but serum mitochondria appeared to be unaltered. This suggests that mitochondrial DAMPs may be largely restricted to the injury site.\textsuperscript{101} Deletion of TLR9 or application of its antagonist IRS954, as well as deletion of inflammasome components NLRP3-ASC and P2X7 receptor or application of P2X7 receptor antagonist A-439079, were all shown to reduce the severity of AP induced by caerulein.\textsuperscript{102} Moreover, pancreatic pro-interleukin-1\beta (pro-IL-1\beta) mRNA was reduced in TLR9\textsuperscript{-/-} or

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<th>Dose</th>
<th>Species</th>
<th>Effect</th>
<th>Reference(s)</th>
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<tr>
<td>10%, 1.0 ml/kg</td>
<td>Dog</td>
<td>Significantly increased serum and ascites amylase, lipase levels; pancreatic parenchymal oedema, inflammatory cell infiltration and necrosis; other organ injury: N/A</td>
<td>64</td>
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<tr>
<td>5%, 1.0 ml/kg</td>
<td>Rabbit</td>
<td>Pancreatic oedema, inflammatory cell infiltration, necrosis, haemorrhage and fat necrosis; other organ injury: N/A</td>
<td>62</td>
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<tr>
<td>20%, 1.0 ml/kg</td>
<td>Pig</td>
<td>Significantly increased serum lipase level, WBC counts and neutrophils; significantly decreased mean blood pressure, serum lymphocytes and platelets; pancreatic oedema, haemorrhage, necrosis and accumulation of neutrophils, lymphocytes and macrophages; other organ injury: N/A</td>
<td>65</td>
</tr>
<tr>
<td>5%, 0.5 ml/kg plus 5% trypsin</td>
<td>Pig</td>
<td>Significantly increased serum amylase and WBC counts; focal liquefactive necrosis in most of the pancreas, with neutrophil infiltration; other organ injury: N/A</td>
<td>63</td>
</tr>
<tr>
<td>3–5%, 1.0 mg/kg</td>
<td>Rat</td>
<td>Significantly increased serum amylase, lipase and proinflammatory cytokine levels; pancreatic oedema, vacuolization, inflammation, haemorrhage, acinar cell and fat necrosis; lung, liver, gastric, kidney and brain injuries</td>
<td>67–72, 74, 123–125</td>
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<tr>
<td>2%, 50 \mu l</td>
<td>Mouse</td>
<td>Increased serum amylase and IL-6; transient increase of intrapancreatic trypsin activity; pancreatic oedema, leukocyte infiltration and necrosis; no mortality</td>
<td>82</td>
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<tr>
<td>4%, 5%, 2.0 ml/kg</td>
<td>Mouse</td>
<td>Increased serum amylase, lipase and IL-6; decreased serum IL-12; pancreatic oedema, leukocyte infiltration, necrosis, haemorrhage and fat necrosis; increased pulmonary BAL fluid albumin and MPO activity; 10% and 60% mortality rates at 24 h for 4% and 5% Na-TC, respectively</td>
<td>85</td>
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Na-TC, sodium taurocholate; WBC, white blood cell; IL, interleukin; BAL, bronchoalveolar lavage; MPO, myeloperoxidase; N/A, not applicable.

\textbf{Toll-like receptor 9 and NOD-like receptor 3 inflammasome}

Zhang \textit{et al.}\textsuperscript{98} recently demonstrated that cellular injury can release into the circulation endogenous damage-associated molecular patterns (DAMPs) that activate polymorphonuclear neutrophils through formyl peptide receptor-1 and Toll-like receptor-9 (TLR9), respectively. TLR9 is expressed on the cell surface and endocytic compartment and plays an important role in detecting self molecules and DNA.\textsuperscript{99} NOD-like receptor-3 (NLR3) is expressed in cytosol and is required by uric acid and ATP for inflammasome activation via plasma membrane purinergic receptor P2X7r, which is activated by DAMPs.\textsuperscript{100,101} Hoque \textit{et al.}\textsuperscript{102} studied the roles of TLR9, NLRP3 inflammasome (NLRP3-ASC) and DAMPs in AP using models of AP induced by TSL-S (3 \textmu M, 50 \textmu l) and caerulein, respectively. They found that, in the early stages of AP, circulating genomic DNA was markedly increased, but serum mitochondria appeared to be unaltered. This suggests that mitochondrial DAMPs may be largely restricted to the injury site.\textsuperscript{103} Deletion of TLR9 or application of its antagonist IRS954, as well as deletion of inflammasome components NLRP3-ASC and P2X7 receptor or application of P2X7 receptor antagonist A-439079, were all shown to reduce the severity of AP induced by caerulein.\textsuperscript{102} Moreover, pancreatic pro-interleukin-1\beta (pro-IL-1\beta) mRNA was reduced in TLR9\textsuperscript{-/-} or
TLR9 antagonist-treated mice. In pancreatitis induced by TLR-S, pretreatment with TLR9 antagonist IRS954 significantly reduced serum amylose, pancreatic oedema, inflammation, necrosis and lung histology.102 This study highlighted new therapeutic potentials of DAMPs-receptor pathway antagonism, such as TLR9 and P2X7 receptor antagonists.

Tumour necrosis factor-α and Ly-6C\textsuperscript{hi} monocytes

Recently, genetically altered mouse strains have been employed to show either the complete deletion of tumour necrosis factor-α (TNF-α) or the expression of human diphtheria toxin receptor (DTR) coupled to the CD11b promoter (CD11b-DTR).104 In CD11b-DTR mice, the severity of pancreatitis was associated with pancreatic Ly-6C\textsuperscript{hi} monocytes/macrophages,\textsuperscript{105} which are released from bone marrow to injured tissue in response to distant organ injuries.106 Prior administration of diphtheria toxin (DT) abolished Ly-6C\textsuperscript{hi} monocytes and prevented pancreatic oedema and necrosis in pancreatitis induced by either caerulein or Na-TC (37 mm, 50 μl). This protective effect by DT was reversed by adovasive transfer of purified Ly-6C\textsuperscript{hi} monocytes harvested from CD11b-DTR mice or TNF-α\textsuperscript{−/−} donors but not from TNF-α\textsuperscript{+/−} donor mice.105 These findings indicate that monocytes and macrophages regulate pancreatic oedema and necrosis through the TNF-α pathway and therefore that targeting either Ly-6C\textsuperscript{hi} monocytes or TNF-α may represent a promising strategy in the treatment of AP. Indeed, TNF-α antagonism has been evaluated as a pharmacological strategy for treating pancreatitis in response to promising results in numerous studies of various experimental AP models.107,108 However, other reports have demonstrated that TNF-α blockage was ineffective in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in canines\textsuperscript{109} and even augmented the severity of caerulein-induced pancreatitis in rats.108 Moreover, neutralization of TNF-α has failed in sepsis clinical trials.111-113 These findings indicate that the extrapolation of laboratory results into clinical trials is complex.

Rho-kinase, lymphocyte function antigen-1 and CD40 ligand

Awla et al.\textsuperscript{114,115} and Abdulla et al.\textsuperscript{116} investigated the roles of Rho-kinase, lymphocyte function antigen-1 (LFA-1) and CD40 ligand (CD40L) in experimental AP induced by Na-TC (5%, 10 μl) and/or caerulein. Rho-kinase inhibitor Y-27632 (5 mg/kg), given prior to the induction of pancreatitis, was found to dramatically reduce the severity of AP and associated lung injury.114 Moreover, pancreatitis-induced trypsinogen activation peptide levels were reduced in vivo and in vitro (caerulein) by Y-27632 treatment. However, the administration of Y-27632 after induction of pancreatitis had no significant effect on pancreatic or systemic injuries. These authors therefore postulated that Rho-kinase inhibitor may regulate trypsinogen activation in pancreatitis.\textsuperscript{114} In another study, they showed that both LFA gene deletion and anti-LFA-1 antibody were protective against AP in genetically targeted LFA-1 mice.115 The inhibition of LFA-1 function not only greatly reduced Na-TC-induced leukocyte adhesion, neutrophil accumulation in the pancreas and acinar cell necrosis, but also attenuated pulmonary neutrophil infiltration. However, trypsinogen activation induced by Na-TC was not affected.112 The authors concluded that LFA-1 may act on a downstream pathway of trypsinogen activation and that blocking LFA-1 may provide therapeutic potential.115 CD40L is a transmembrane glycoprotein that belongs to the TNF family of cell surface interaction molecules.117 Induced to express mainly on a CD4⁺ T cell subset, it has been found to activate platelets and to exert proinflammatory\textsuperscript{117-120} and procoagulant effects.121,122 Abdulla et al.\textsuperscript{1} examined responses in CD40L\textsuperscript{−/−} mice to AP induced by either Na-TC or caerulein, but observed no beneficial effects in CD40L\textsuperscript{−/−} mice compared with their littermates.116

Conclusions

The extensive research conducted over the last decade has advanced our understanding of the deleterious effects of bile acids/salts on PACs and PDECs in the pathogenesis of BAP. As BAP models mirror the aetiology of gallstone-induced pancreatitis in the clinical setting, the application of these models in mice would facilitate studies on genetic aspects of this disease, as well as allowing the scrutiny of candidate therapeutic drugs. Recent advances in basic research using this BAP model have revealed the importance of Gpbar1 and cathepsin L, and have provided potential therapeutic targets such as the DAMPs-receptor pathway, TNF-α and Ly-6C\textsuperscript{hi} monocytes. Further investigation might eventually lead to the discovery of effective treatments for AP.

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Conflicts of interest

None declared.

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