Section Medical Sciences

Review Article

"GENE THERAPY FOR CHOLESTASIS: BRIDGING GENETIC DEFECTS AND LIVER FUNCTION"-A REVIEW

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Abstract

Background: Cholestatic diseases arise from dysfunction in the transporters responsible for hepatobiliary circulation. While pharmacological treatments remain the standard care, they lack curative potential, with liver transplantation being the only long-term solution for severe cholestasis, despite its associated drawbacks. Liver-directed gene therapy has emerged as a promising alternative, showing positive outcomes in clinical trials for genetic disorders and presenting a potential new therapeutic avenue for cholestatic conditions. Numerous preclinical studies have demonstrated favourable results in animal models of both acquired and genetic cholestasis. Notably, gene delivery aimed at reducing apoptosis or fibrosis and enhancing bile flow has yielded therapeutic benefits in rodent models subjected to drug-induced cholestasis or bile duct ligation. For inherited cholestatic disorders like progressive familial intrahepatic cholestasis (PFIC), research has focused on delivering a corrected version of the mutated gene to the liver using viral or non-viral vectors to facilitate the expression of the therapeutic protein. These strategies have shown promising results in treating PFIC3 in mouse models. However, significant challenges remain in translating these therapies to clinical practice and developing effective gene therapy strategies for other forms of acquired and genetic cholestasis. **Materials and Methods:** Gene therapy approaches for liver diseases utilized both viral and non-viral vectors, including AAV, Adv, and LNP. Animal models, such as bile duct ligation (BDL) and drug-induced cholestasis, were employed to study disease mechanisms. Preclinical testing involved hydrodynamic gene delivery, mitochondrial oxidative stress mitigation, and anti-fibrotic treatments using various vector types. **Results:** Cholestatic diseases encompass a wide range of disorders stemming from both acquired and inherited mechanisms. Understanding their underlying pathophysiology is crucial for developing targeted therapies and improving patient outcomes. The complexity of these diseases highlights the need for ongoing research into their molecular mechanisms and potential therapeutic interventions. **Conclusion:** Pharmacological therapies are effective for milder cholestatic diseases but show reduced efficacy in severe cases. Gene therapy emerges as a promising alternative, with preclinical studies in animal models demonstrating positive results for both inherited and induced cholestasis. Despite challenges in clinical implementation, there is optimism that these innovative therapies may soon gain approval, offering hope for patients with cholestatic disorders.

INTRODUCTION

Cholestatic diseases stem from disruptions in bile production or secretion, involving a range of enzymes and membrane transporters crucial to hepatobiliary circulation. These disorders can be broadly categorized into acquired and genetic cholestasis.

Acquired Cholestasis

Acquired cholestasis accounts for the majority of cholestatic diseases and is characterized by dysregulated hepatobiliary transporters due to an adaptive response to bile acid (BA) build up in the liver. This response involves multiple factors, including hormones, BAs, proinflammatory cytokines, and drugs, which trigger transcription factors that regulate the expression of export pumps. These pumps help reduce intracellular BA levels by

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promoting their excretion via urine, thereby protecting the liver from toxicity.[1] Common types of acquired cholestasis include primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), intrahepatic cholestasis of pregnancy (ICP), biliary atresia, drug-induced cholestasis, and inflammation-mediated cholestasis.[2]

Both PBC and PSC are classified as autoimmune disorders affecting the hepatobiliary system. These conditions are marked by the presence of antimitochondrial antibodies, portal inflammation, and immune-mediated destruction of bile ducts.[3] The disease's pathogenesis is multifactorial, driven by a combination of genetic, epigenetic, and environmental factors. Clinically, PBC and PSC may present as asymptomatic or progress to end-stage biliary cirrhosis, with significant variability in symptoms.[4]

Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatobiliary disorder occurring during pregnancy. It typically manifests in the third trimester with elevated serum BA levels, leading to intense pruritus.[5] The condition is driven by high levels of gestational hormones, particularly estrogen and progesterone, with genetic predisposition also playing a role. Although symptoms of ICP usually resolve postpartum, the disorder can recur in subsequent pregnancies.[6]

Biliary atresia is a rare but severe condition primarily affecting newborns. It results in the obliteration or malformation of bile ducts, which leads to neonatal cholestasis.[7] The etiology of biliary atresia remains unclear, though some cases are believed to result from autoimmune responses or viral infections affecting the bile duct epithelium. Early diagnosis and surgical intervention are critical for improving outcomes.[8-12]

Drug- and inflammation-induced cholestasis are interconnected and often result from the inhibition of hepatobiliary transporters. These conditions are typically immune-mediated, with proinflammatory cytokines targeting bile duct epithelium, impairing BA secretion.[10,11] Although these forms of cholestasis rarely cause severe liver damage, they underscore the liver's vulnerability to immune and chemical stressors.[13]

Inherited Cholestasis

Genetic forms of cholestasis are far less common, comprising a variety of disorders known as progressive familial intrahepatic cholestasis (PFIC). PFIC is a rare, autosomal recessive disorder, with an incidence of 1: 50,000–100,000 live births worldwide.[14] This condition accounts for about 15% of all neonatal cholestasis cases and is associated with severe clinical outcomes such as pruritus, jaundice, fat malabsorption, and hepatomegaly, which can progress to cirrhosis, portal hypertension, or liver failure.[15]

PFIC is caused by mutations in several key genes responsible for bile transport and regulation, and is divided into six subtypes (PFIC 1-6) based on the affected gene. Mutations in ATP8B1, ABCB11, ABCB4, tight junction protein 2 (TJP2), NR1H4, and Myosin VB (MYO5B) result in the different forms of PFIC, each with unique pathological mechanisms.[16-19]

In PFIC1, mutations in ATP8B1 (also known as FIC1) disrupt the asymmetrical distribution of phospholipids in the canalicular membrane, leading to its destabilization and reduced BA transport, which causes BA accumulation in hepatocytes and subsequent cholestasis.[20] PFIC2, caused by mutations in the ABCB11 gene, leads to the absence or malfunction of the bile salt export pump (BSEP), resulting in toxic BA build-up in the liver.[21] PFIC3 arises from mutations in the ABCB4 gene, which affects multidrug resistance protein 3 (MDR3), leading to decreased phosphatidylcholine in bile and subsequent damage to bile canaliculi.[22,23]

Mutations in TJP2 cause PFIC4 by disrupting the distribution of tight junction proteins, which results in bile leakage. PFIC5 is linked to mutations in NR1H4, impairing the farnesoid X receptor (FXR), which regulates BSEP and ABCB4, leading to BA toxicity.[24,25] Finally, PFIC6 results from MYO5B gene mutations, affecting the trafficking of BSEP to the canalicular membrane, further contributing to BA accumulation in the liver.[26-29]

PFIC is associated with significant morbidity and mortality, and its clinical manifestations, such as the severity of cholestasis and liver failure, vary depending on the specific gene mutation. Additionally, less severe mutations in the ABCB11 and ABCB4 genes can lead to milder forms of cholestasis, such as benign recurrent intrahepatic cholestasis (BRIC) or other conditions like cholesterol cholelithiasis, transient neonatal cholestasis, or adult biliary cirrhosis.[30-34]

Other genetic conditions, such as cystic fibrosis and Alagille syndrome, are also associated with cholestatic disorders. Mutations in the CFTR gene, for instance, can lead to cholestasis due to bile duct complications, while Alagille syndrome results from mutations in JAG1 and NOTCH2,[35] affecting bile duct formation. Cerebrotendinous xanthomatosis (CTX) is another genetic disorder where mutations in CYP27A1 impair BA biosynthesis, leading to the accumulation of toxic metabolites that can cause cholestasis, especially in infants.

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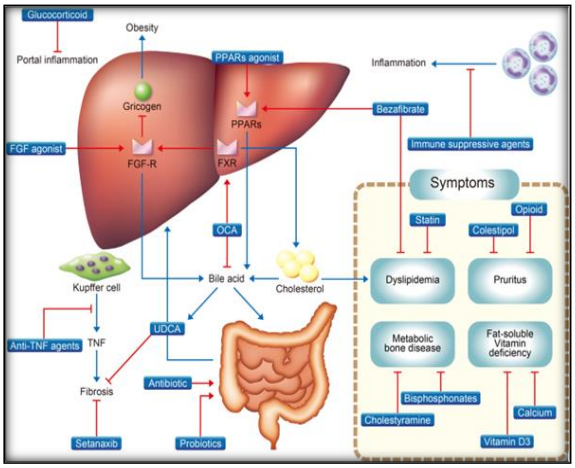

Figure 1: Biochemical and molecular mechanisms for development of Cholestosis

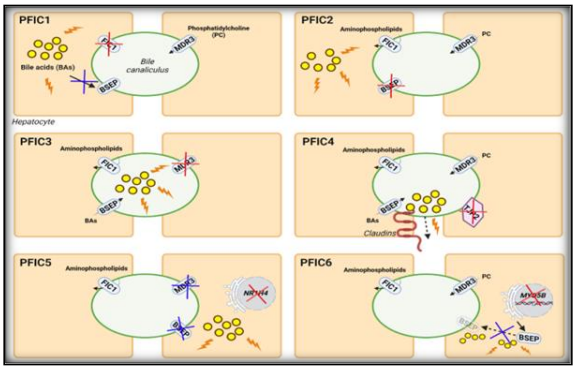

Figure 2: Progressive Familial Intrahepatic Cholestasis (PFIC). PFIC is caused by mutations in several key genes responsible for bile transport and regulation, and is divided into six subtypes (PFIC 1-6) based on the affected gene

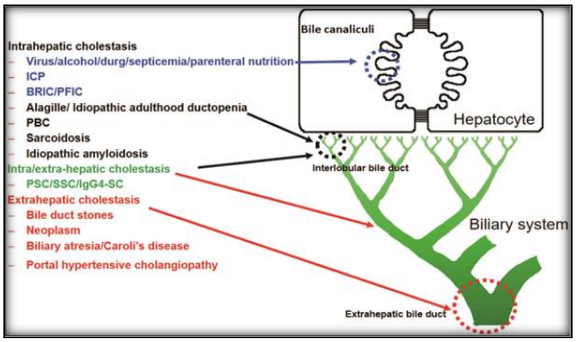

Figure 3: Schematic depiction of the diseases associated with the biliary tree

Present Modalities of Treatment of Cholestatic Disorders

1. Surgical manoeuvres:

Therapeutic options for cholestatic disorders remain limited, with liver transplantation being the sole curative intervention for severe cases. However, this approach is fraught with numerous challenges, including organ failure, a shortage of available donors, limited organ viability, the necessity for lifelong immunosuppression, and the risk of immunological rejection. For inherited conditions such as certain types of Progressive Familial Intrahepatic Cholestasis (PFIC),[36] liver transplantation is reserved for end-stage patients experiencing severe complications like hepatocellular carcinoma (HCC), hepatic steatosis, and liver cirrhosis.[37-42] While orthotopic transplantation can effectively alleviate cholestasis and associated symptoms within 3 to 5 years, it has been linked to the development of circulating anti-Bile Salt Export Pump (BSEP) antibodies in a minority of PFIC2 patients, leading to transplant rejection.[39,40] Furthermore, this method is only partially effective for cholestatic diseases that exhibit extrahepatic manifestations, such as PFIC1.As an alternative to liver transplantation, surgical interventions aim to disrupt the enterohepatic circulation. Procedures like partial internal biliary diversion (PIBD), ileal exclusion, and partial external biliary diversion (PEBD) have been shown to lower bile acid (BA) levels and reduce pruritus while potentially reversing hepatic fibrosis.[41,43-47] However, these surgeries are not without complications; issues related to stoma bags—such as dehydration and leakage—have been reported. Biliary diversion has proven more effective in PFIC2 patients with residual BSEP activity but is often performed late in the disease course for PFIC3 patients, making it challenging to halt disease progression.[48-50] Thus, there is an urgent need for alternative therapeutic strategies beyond liver transplantation and surgical approaches. Fortunately, advancements in understanding the mechanisms underlying genetic and acquired cholestatic diseases have opened avenues for developing new drug and gene therapies.[48]

Drug Based Therapies

Pharmacological treatments are typically the first-line options for managing cholestatic diseases. Current strategies under investigation focus on Farnesoid X Receptor (FXR) agonists and inhibitors targeting BA uptake transporters within the enterohepatic circulation.[49]

FXR Agonists[51]

In recent years, selective FXR agonists like ursodeoxycholic acid (UDCA) have emerged as primary treatments for cholestatic disorders.[50,52] UDCA is a hydrophilic BA that reduces the toxic hydrophobic BA pool within hepatocytes and diminishes the detergent properties of bile in the bile canaliculi. Clinical benefits of UDCA have been observed in patients with Intrahepatic Cholestasis of Pregnancy (ICP), Primary Biliary Cholangitis (PBC), and PFIC3, particularly in early disease stages.[54] However, approximately 50% of PFIC3 and PBC patients exhibit either no response or an incomplete response to this treatment. Notably, PFIC3 patients with milder ABCB4 deficiency tend to respond more favourably to UDCA therapy.[53] In contrast, UDCA fails to provide symptomatic relief for most PFIC2 or Primary Sclerosing Cholangitis (PSC) patients. Other UDCA-derived BAs such as 24-norursodeoxycholic acid (Nor-UDCA) and its taurine conjugate (TUDCA) have also shown promise as therapeutic

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agents; Nor-UDCA has demonstrated improvements in serum biomarkers like transaminases and alkaline phosphatase levels in PSC patients, although larger studies are necessary to confirm its efficacy. Obeticholic acid (OCA),[55,56] a semi-synthetic BA acting as an FXR agonist, has shown safety and efficacy in reducing serum alkaline phosphatase levels in PBC and PSC patients through two Phase II studies. OCA has been approved as an alternative treatment for PBC patients who do not respond adequately to UDCA.[57,58] Recent research indicates that OCA may also reduce liver damage in mouse models of PFIC2; however, its use has been associated with severe pruritus—a significant concern given that pruritus is a primary symptom in cholestatic diseases.[59,60] Similarly, cilofexor, another non-steroidal FXR agonist, has demonstrated significant improvements in cholestasis markers among PSC patients but may also induce pruritus in a dose-dependent manner, limiting its application in specific cholestatic disorders.[61-64]

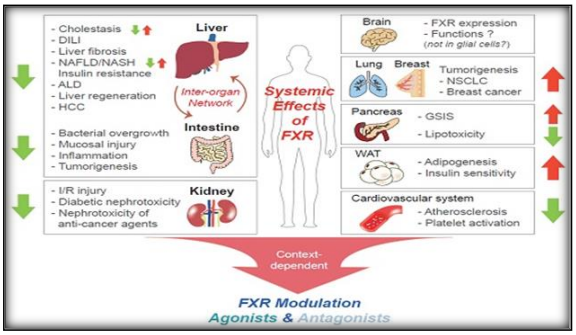

Figure 4: FXR modulators – Agonists and Antagonists

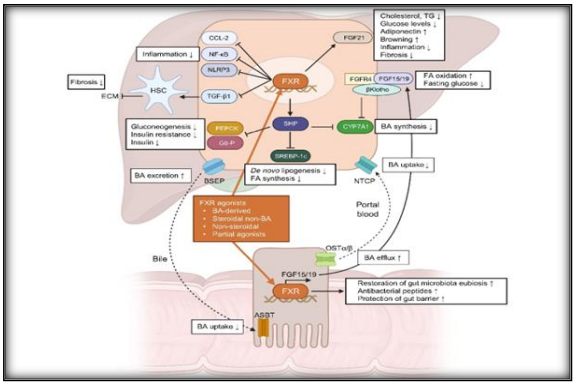

Figure 5: Biochemical metabolic reactions and the effects of different substances including FXR agonists on the hepatocyte.

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Table 1: Table summarizes the drug therapies currently in clinical trials for cholestatic diseases, including their indications, current status, and sponsor

Drug Name	Indication	Current Status	Clinical Trial Sponsor
FXR Agonists			
UDCA (Actigall/Ursodiol/Ursofalk)	ICP, PBC, PFIC3	Phase III, Approved	Turku University Hospital, Sanofi-Synthelabo
Nor-UDCA	PSC	Phase II	Pharma GmbH
TUDCA (Taurolite)	PBC	Phase III	Beijing Friendship Hospital
OCA (INT-747/Ocaliva)	PBC, PSC	Phase II, Phase III	Intercept Pharmaceuticals
Non-bile Acids			
Cilofexor (CILO)	PSC	Phase I/II	Gilead Sciences
Tropifexor (LJN452)	PBC	Phase II	Novartis Pharmaceuticals
EDP-305	PBC	Phase II	Enanta Pharmaceuticals
ASBT Inhibitors			
Odevixibat (A4250)	ALGS, PFIC	Phase III, Approved	Albireo
Maralixibat (LUM001)	ALGS, PFIC	Approved, Phase III	Mirum Pharmaceuticals
Linerixibat (GSK2330672)	PBC	Phase III	GlaxoSmithKline
Volixibat (SHP626)	ICP, PBC, PSC	Phase II	Mirum Pharmaceuticals
Other Pharmacotherapeutic Agents			
Aldafermin (NGM282)	PBC, PSC	Phase II	NGM Biopharmaceuticals
Bezafibrate	PBC	Phase III	Hôpitaux de Paris
Elafibranor	PBC	Phase II	Genfit
Seladelpar (MBX-8025)	PBC	Phase III	CymaBay Therapeutics

Recent advancements in the development of pharmacological agents targeting bile acid (BA) uptake transporters have garnered significant attention for managing cholestatic disorders. The enterohepatic circulation of BAs is facilitated by four key transporters: the apical bile salt transporter,[65] (ASBT, also known as IBAT), BSEP, the sodium-taurocholate cotransporter polypeptide (NTCP), and the basolateral organic solute transporter (OST) 166 Inhibiting BSEP and OST is not viable due to the risk of toxic BA accumulation in hepatocytes and enterocytes, respectively. Conversely, NTCP inhibition has been shown to be well-tolerated, leading to an increase in plasma BAs while decreasing liver BA levels, thereby providing hepatoprotection and alleviating cholestasis.[66-70] ASBT inhibitors disrupt BA reabsorption in enterocytes, promoting their excretion through feces. Clinical trials are currently evaluating several ASBT antagonists, including odevixibat (A4250, Albireo), maralixibat (LUM001, Mirum Pharmaceuticals), elobixibat (A3309, Albireo), linerixibat

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(GSK2330672, GlaxoSmithKline), and volixibat (SHP626, Mirum Pharmaceuticals).[71-75] These compounds have demonstrated favorable safety profiles with minimal adverse effects outside the gastrointestinal tract and high specificity for ASBT when administered orally.[72] Therapeutic outcomes observed include reduced BA levels in both liver and serum, along with improvements in pruritus, liver inflammation, and fibrosis.[74]

In 2021, odevixibat received approval from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in patients with progressive familial intrahepatic cholestasis (PFIC).[73,76] Its efficacy for other cholestatic conditions such as Alagille syndrome (ALGS) is under investigation. Although maralixibat was initially assessed for primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), clinical trials were halted because it did not significantly alleviate pruritus compared to placebo. However, maralixibat has been approved for ALGS patients by the FDA, with ongoing evaluations for its effectiveness in PFIC1-4 by the EMA.[77-80]

Other Pharmacotherapeutic Approaches

Additional therapeutic strategies for cholestatic disorders include the exploration of peroxisome proliferator-activated receptor (PPAR) agonists and fibroblast growth factor (FGF) analogues,[81,82] which have shown efficacy in treating PBC and PSC. FXR transcriptional regulators like sirtuin 1 have also demonstrated potential in mitigating cholestatic liver injury by altering hepatic BA composition and reducing plasma BA levels.[83] Furthermore, antifibrogenic and anti-inflammatory agents such as histone deacetylase inhibitors and phosphodiesterase 5 inhibitors have been effective in reducing fibrosis and liver damage in PFIC3 mouse models.[84,85] ABC transporter enhancers like ivacaftor may restore functionality to canalicular membrane transporters implicated in cholestatic disorders, offering potential benefits for PFIC2 patients. Fibrates such as bezafibrate may also aid PBC patients who do not respond to ursodeoxycholic acid (UDCA) treatment.[86-88]

Despite these advancements improving patient outcomes and quality of life, they do not provide a definitive cure for hepatobiliary dysfunction. Therefore, there is a pressing need for innovative strategies such as gene therapy that could offer long-term solutions for these conditions. The following section will delve into gene therapy approaches currently being tested in preclinical models of cholestatic diseases.

Gene Therapy: Gene therapy entails the addition, removal, or alteration of an individual's genetic material to treat diseases. Its success hinges on effective delivery to target cells, utilizing both viral and non-viral vectors. Viral vectors are derived from modified viruses, including adenoviruses (Adv), adeno-associated viruses (AAV), retroviruses, and lentiviruses, which have demonstrated high efficacy in gene delivery but come with challenges such as immunogenicity and size limitations for the genetic material.[89] In contrast, non-viral vectors, like polymeric or lipid nanoparticles (LNP), do not facilitate delivery to the cell nucleus and result in more transient expression of the transgene; however, they offer a superior safety profile, lack packaging constraints, and provide various advantages in terms of manufacturability and shelf-life. Recently, non-viral vectors have shown significant efficacy, as evidenced by the COVID-19 vaccines that utilize mRNA encapsulated in LNPs.[90,91]

Gene therapy has emerged as a promising strategy for achieving safe, stable, and efficient long-term correction of various genetic disorders, including monogenic liver diseases where liver transplantation is currently the sole curative option, as well as acquired liver diseases. Both viral and non-viral vectors have yielded encouraging therapeutic outcomes in numerous relevant animal models and a multitude of clinical trials.[92,93] The approval of over a dozen gene therapy products by regulatory bodies like the FDA and EMA—albeit only three specifically for liver gene therapy—signals a hopeful future for this technology in treating liver disorders.[94,95]

Gene Therapy for Acquired Cholestasis

With no definitive treatments available for certain acquired hepatic cholestatic conditions such as Primary Biliary Cholangitis (PBC) and Primary Sclerosing Cholangitis (PSC),[96] there is a pressing need to discover new therapeutic options that can diminish fibrogenesis and potentially avert chronic liver injury. Genetic-based therapies represent an appealing approach to achieve sustained long-term therapeutic effects. Animal models of acquired cholestatic disorders have been developed using methods such as bile duct ligation (BDL) and drug-induced cholestasis through agents like estrogens and carbon tetrachloride (CCL4).[97-100] The progression of cholestasis involves multiple processes including cellular apoptosis, proinflammatory cytokine production, and fibrogenesis leading to biliary dysfunction. Gene therapy strategies targeting acquired cholestasis aim to alleviate liver damage by reducing apoptosis and fibrosis while enhancing bile formation.[101]

Apoptosis Reduction

A primary focus of gene therapy for acquired liver disorders is minimizing hepatocyte apoptosis. Hydrodynamic gene delivery of an insulin-like growth factor 1 (IGF-1)-expressing plasmid has shown promise in reducing hepatocellular apoptosis and liver injury in BDL rats. 102IGF-1 facilitates improvement in cholestatic disease through activation of the phosphatidylinositol-3-kinase pathway, inhibition of glycogen synthase kinase-3 beta, and prevention of caspase-9 cleavage.[103,104] Additionally, the inactivation of hepatic stellate cells has been noted, potentially explaining significant improvements in liver fibrosis.[105]

Mitochondrial Oxidative Stress Mitigation

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Targeting oxidative stress has emerged as a therapeutic goal for acquired liver cholestasis. For instance, Adv-mediated delivery of mitochondrial superoxide dismutase (SOD) genes has been effective in reducing liver injury by preventing the formation of oxygen free radicals from accumulating hydrophobic bile acids and inhibiting proinflammatory cytokines like TNFα and TGF-β in BDL mice.[106-110] Similarly, Adv vectors expressing an inhibitor gene for proinflammatory cytokine signalling such as collagen triple helix repeat containing-1 (Cthrc-1) have been successful in decreasing liver fibrosis through TGF-β signalling inhibition.[111,112]

Anti-Fibrotic Treatments

Anti-fibrotic strategies for cholestatic disorders focus on reducing pro-inflammatory factors that promote collagen degradation to lessen liver fibrosis. Adv vectors expressing urokinase-plasminogen activator (uPA) have led to slight reductions in liver fibrosis and partial histological improvements in BDL rats through metalloproteinase activation that triggers collagen degradation.[113,114] Furthermore, AAV vectors facilitating hepatic expression of angiotensin-converting enzyme (ACE2) have demonstrated sustained anti-fibrotic effects across various animal models.

Enhancing Bile Flow

Adv-mediated delivery of aquaporin-1 (AQP1) has been shown to improve bile flow in estrogen-induced cholestatic rats by significantly lowering serum alkaline phosphatase levels and enhancing biliary output via increased bile salt export pump activity.[115]

Gene Therapy for Inherited Cholestasis

Gene therapy targeting inherited hepatic diseases has gained considerable attention following successful applications where AAV vectors expressing human coagulation factors IX and VIII provided sustained therapeutic effects for over three years in patients with haemophilia B and A respectively.[116,117] Numerous gene therapy products have shown promising results in clinically relevant animal models leading to clinical trials for inherited liver disorders such as phenylketonuria, familial hypercholesterolemia, ornithine transcarbamylase deficiency, acute intermittent porphyria, methylmalonic acidemia, and Wilson's disease.[118-121]

Genetic Disorders with Associated Cholestasis

Preclinical studies have yielded positive outcomes in animal models for conditions like Cerebrotendinous xanthomatosis (CTX) and Crigler-Najjar syndrome type 1. In CTX cases, administering an AAV8 vector expressing CYP27A successfully restored bile acid metabolism while normalizing plasma concentrations with only 20% transduced hepatocytes required—facilitating potential clinical translation.[122] For Crigler-Najjar syndrome type 1 treatment with an AAV8 vector expressing UDP-glucuronosyltransferase family 1-member A1 (UGT1A), normalization of total serum bilirubin levels was achieved across two animal models.[123,124]

Gene Therapy for PFIC Diseases

Gene therapy strategies for Progressive Familial Intrahepatic Cholestasis (PFIC) can involve either gene supplementation or editing techniques aimed at modifying affected genes. Implementing gene therapy across different PFIC types presents challenges; achieving stable long-term efficacy may necessitate transducing most hepatocytes which could require high viral vector doses raising safety concerns. Additionally, some PFIC types exhibit extrahepatic clinical manifestations complicating targeted treatment approaches.

The decision to pursue gene therapy for PFIC will likely depend on the specific mutations within the affected gene; patients with missense mutations that decrease protein activity may respond more favourably than those with complete deficiencies. Notably, ABCB4 deficiency causing PFIC3 offers certain advantages over other PFIC types regarding liver gene therapy due to previous findings indicating that engrafting just 12% healthy hepatocytes suffices for therapeutic effectiveness.

Recent studies involving AAV8 vectors expressing ABCB4 demonstrated long-term efficacy in preventing serum transaminase increases after bile acid challenges in mouse models with varying phenotypes associated with PFIC3.125 Additionally, a preclinical study utilizing LNP-encapsulated mRNA therapy showed temporary reversal of disease phenotypes in BALB/c Abcb4-/- mice.

However, non-integrative vector-based strategies face significant limitations such as loss of transgene expression due to hepatocyte division or the short half-life of mRNA necessitating frequent administration. An alternative approach using integrative vectors has shown promise; hybrid vectors combining piggy Bac transposase expression with AAV8 containing ABCB4 expression cassettes demonstrated recovery of biliary phosphatidylcholine levels along with normalization of serum biomarkers post-treatment while preventing biliary cirrhosis.

These preclinical findings have led to orphan drug designation for an AAV vector harboring a codon optimized version of ABCB4 developed by Vivet Therapeutics, paving a hopeful path forward for treating patients with this cholestatic disorder.[126]

Gene Therapy Strategies for PFIC3: Mechanisms and Approaches

Gene therapy for Progressive Familial Intrahepatic Cholestasis type 3 (PFIC3) primarily focuses on gene supplementation or correction of the mutated gene, specifically the ATP-binding cassette subfamily B member 4 (ABCB4) gene.[127] However, emerging studies indicate that alternative strategies targeting the expression of other genes involved in the disease's pathology may also be effective.

Gene Supplementation and Correction

The most direct approach for PFIC3 treatment involves the delivery of vectors that express the

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functional ABCB4 protein. Recent research has demonstrated that an AAV8 vector expressing ABCB4 can significantly improve disease markers in preclinical models, such as FVB Abcb4-/- mice, which exhibit symptoms analogous to human PFIC3.[128] This method has shown promise in restoring biliary phosphatidylcholine levels and normalizing serum biomarkers, effectively preventing liver fibrosis and other complications associated with the disease.

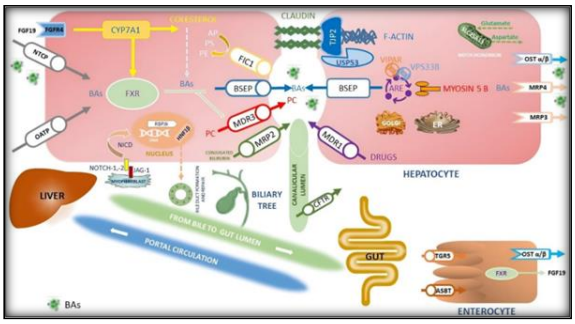

Figure 6: Molecular integration between hepatocyte and enterocyte –a synergy

Alternative Gene Targeting Approaches

1. Modulating Liver Fibrosis

Several studies have explored the potential of gene therapy to modulate liver fibrosis in PFIC3. For instance, an AAV8 vector expressing Angiotensin-Converting Enzyme 2 (ACE2) has been shown to reduce liver fibrosis in both early- and late-stage FVB Abcb4-/- mice. Similarly, administration of HNF4A mRNA encapsulated in biodegradable lipids restored metabolic activity in hepatocytes, leading to a significant inhibition of fibrogenesis.[129]

2. Regulation of Bile Acid Synthesis

Another innovative approach involves regulating bile acid (BA) synthesis and homeostasis. The expression of Limb expression 1-like protein (LIX1L) is elevated in cholestatic liver conditions. Normalizing LIX1L expression has been linked to alleviating cholestatic liver injury in various mouse models, including FVB Abcb4-/- mice. An AAV vector overexpressing miR-191-3p was shown to ameliorate cholestasis by directly repressing liver receptor homolog-1 (LRH-1), which subsequently reduced the synthesis of BAs.

3. Targeting Inflammatory Pathways

Additionally, targeting the neurokinin 1 receptor (NK1R) axis and transforming growth factor-beta 1 (TGF-β1)/miR-31 signalling pathways presents another potential strategy for reducing liver fibrosis. In FVB Abcb4-/- mice, knockout of NK1R led to decreased levels of miR-31 and pro-inflammatory mediators like TGF-β1, resulting in diminished liver inflammation and fibrosis.[130]

Challenges in Gene Therapy for Other Types of PFIC: While gene supplementation remains a viable option for PFIC3, other types of PFIC (such as PFIC1, PFIC4, PFIC5, and PFIC6) present unique challenges. These include extrahepatic manifestations that cannot be addressed through liver-targeted therapies and the necessity to correct a higher percentage of hepatocytes due to toxicity occurring within these cells. Moreover, the absence of suitable animal models for certain types of PFIC complicates the development of targeted therapies.

Future Directions in Liver-Targeted Gene Therapy for Cholestatic Diseases

The increasing success of liver-targeted gene therapies, particularly in preclinical studies addressing cholestatic diseases like progressive familial intrahepatic cholestasis type 3 (PFIC3), highlights the urgent need to navigate the challenges associated with translating these therapies from laboratory settings to clinical applications.[131]

Challenges in Pediatric Gene Therapy

One significant challenge is the potential loss of therapeutic efficacy in pediatric patients. This issue may arise from a reduction in viral genomes due to hepatocyte proliferation during liver growth, particularly with adeno-associated virus (AAV)-based therapies, or from the transient expression associated with non-viral vector-mediated mRNA delivery.[132] Other hurdles include immune responses to the treatment—either against the vector or the transgene—and vector-mediated toxicities, especially when high vector doses are employed. Addressing these challenges will be crucial for guiding both current and future research efforts.

Strategies for Overcoming Challenges

1. Repeated Vector Administration:

Administering repeated doses of vectors could help sustain therapeutic effects. This approach is more feasible for non-viral vectors like mRNA-loaded nanoparticles, although it significantly increases treatment costs.[133] For viral vectors such as AAVs, the development of neutralizing antibodies post-initial administration complicates re-administration. Proposed strategies to mitigate this include using alternative AAV serotypes that do not exhibit cross-reactivity, employing IgG-degrading endopeptidases to eliminate neutralizing antibodies, and co-administering vectors with rapamycin encapsulated in lipid nanoparticles to suppress immune responses.

2. Combination Therapies:

Combining gene therapy vectors with pharmacological treatments, such as ursodeoxycholic acid (UDCA), may yield synergistic effects, particularly for PFIC3 patients exhibiting severe pathology unresponsive to UDCA alone.[134] This pharmacological support could enhance liver health and improve vector transduction efficiency, potentially allowing gene therapy administration at a later age when vector genomes can be maintained more effectively.

3. Sequential Therapy Approaches:

Utilizing non-viral vectors like mRNA-loaded nanoparticles initially in pediatric patients with developing livers, followed by viral vectors for stable long-term transgene expression later, represents another promising strategy. This sequential approach may also involve combining different vectors that

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reduce liver injury and enhance long-term gene therapy efficacy.

4. Vector Optimization:

Enhancing gene therapy vectors through codon optimization or the incorporation of potent promoters could reduce the required viral dose, thereby minimizing toxicity risks associated with high doses. Additionally, employing inducible promoters could facilitate controlled transgene expression, mitigating adverse effects related to overexpression such as silencing or exacerbated immune responses that might lead to hepatocyte elimination.

5. Gene Editing Techniques:

For cholestatic disorders where long-term correction of most hepatocytes is necessary—such as certain PFIC subtypes—CRISPR/Cas9 technology offers a compelling alternative for specific gene correction via various mechanisms including non-homologous end-joining and prime editing. The liver's high efficiency in gene delivery makes it an ideal target for these gene editing strategies; however, challenges remain regarding specificity and safety concerns associated with targeted integration.[135,136]

DISCUSSION

Cholestatic diseases arise from disruptions in bile production or secretion, significantly impacting hepatobiliary circulation. These disorders can be categorized into acquired and genetic cholestasis, each with distinct pathophysiological mechanisms and clinical implications.

Acquired Cholestasis

Acquired cholestasis is the most common form, primarily characterized by the dysregulation of hepatobiliary transporters due to bile acid (BA) accumulation in the liver. This accumulation triggers an adaptive response involving various factors such as hormones, proinflammatory cytokines, and drugs, which activate transcription factors that regulate the expression of export pumps. These pumps are essential for reducing intracellular BA levels by promoting their excretion, thereby protecting the liver from toxicity.

Common Types of Acquired Cholestasis

1. Primary Biliary Cholangitis (PBC): An autoimmune disorder marked by antimitochondrial antibodies and immune-mediated destruction of bile ducts. Its pathogenesis is multifactorial, involving genetic, epigenetic, and environmental factors.
2. Primary Sclerosing Cholangitis (PSC): Similar to PBC, PSC is characterized by portal inflammation and can lead to severe complications such as cirrhosis.
3. Intrahepatic Cholestasis of Pregnancy (ICP): The most prevalent hepatobiliary disorder during pregnancy, typically presenting in the third trimester with elevated serum BA levels and intense pruritus. Hormonal changes play a significant role in its development.
4. Biliary Atresia: A severe condition affecting newborns, characterized by the obliteration or malformation of bile ducts leading to neonatal cholestasis. Early diagnosis and surgical intervention are critical for improving outcomes.
5. Drug-Induced Cholestasis: Often linked to the inhibition of hepatobiliary transporters, these conditions underscore the liver's vulnerability to chemical stressors.

Inherited Cholestasis

Inherited forms of cholestasis are less common but include conditions such as Progressive Familial Intrahepatic Cholestasis (PFIC). PFIC is a rare autosomal recessive disorder with an incidence of 1 in 50,000 to 100,000 live births and accounts for about 15% of neonatal cholestasis cases.

Subtypes of PFIC

PFIC is divided into six subtypes based on specific gene mutations affecting bile transport:

- PFIC1: Caused by mutations in ATP8B1, disrupting phospholipid distribution in the canalicular membrane.
- PFIC2: Linked to mutations in ABCB11, leading to dysfunction of the bile salt export pump (BSEP).
- PFIC3: Associated with mutations in ABCB4 affecting multidrug resistance protein 3 (MDR3).
- PFIC4: Caused by TJP2 mutations disrupting tight junction proteins.
- PFIC5: Linked to NR1H4 mutations impairing farnesoid X receptor (FXR) function.
- PFIC6: Involves MYO5B mutations affecting BSEP trafficking.

Other genetic conditions associated with cholestatic disorders include cystic fibrosis and Alagille syndrome, which result from specific gene mutations that disrupt normal bile duct formation or function. Cholestatic disorders, including Progressive Familial Intrahepatic Cholestasis (PFIC), Primary Biliary Cholangitis (PBC), and Primary Sclerosing Cholangitis (PSC), present significant treatment challenges. While liver transplantation remains a potential curative option for severe cases, it is hindered by donor shortages, organ rejection, and lifelong immunosuppression. Surgical interventions like biliary diversion provide partial symptom relief but are often performed late in the disease course, particularly in PFIC3. Advancements in pharmacological treatments, such as FXR agonists (e.g., UDCA and Obeticholic acid), have shown promise, although response rates can be inconsistent, particularly in PFIC2 and PSC patients. Furthermore, ASBT inhibitors like odevixibat have demonstrated favorable outcomes in PFIC and Alagille syndrome (ALGS), promoting bile acid excretion and alleviating pruritus. Gene therapy is emerging as a potential game-changer, offering long-term solutions by targeting the genetic causes of cholestasis. Preclinical studies for inherited disorders, like PFIC3, are showing encouraging results with gene

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supplementation and editing techniques using AAV vectors. These developments, particularly for PFIC3, hold significant promise for more effective, durable treatments that address the underlying genetic defects, although challenges remain, such as the need for high viral vector doses and concerns over safety and efficacy.

Gene therapy for progressive familial intrahepatic cholestasis (PFIC) shows promising results, particularly for PFIC3, with strategies targeting liver fibrosis, bile acid synthesis, and inflammatory pathways. However, challenges persist in addressing other PFIC types with extrahepatic manifestations and the need for high hepatocyte correction. Pediatric gene therapy faces additional obstacles such as immune responses, reduced therapeutic efficacy during liver growth, and vector-associated toxicities. Future advancements may involve repeated vector administration, combination therapies, sequential approaches, and vector optimization to enhance treatment efficacy. Gene editing technologies like CRISPR/Cas9 also offer potential for long-term solutions but require further refinement for safety and specificity.

CONCLUSION

Pharmacological therapies can be effective for treating cholestatic diseases with milder phenotypes; however, their efficacy diminishes significantly in patients with more severe forms of the disease. As discussed in this review, alternative strategies such as gene therapy present a promising novel approach to address these challenges. Numerous preclinical studies utilizing liver-directed gene therapy in relevant animal models of both inherited and induced cholestasis have demonstrated encouraging outcomes. Despite the existing obstacles to the clinical implementation of these innovative treatments, it is anticipated that some of these therapies will receive approval in the near future, offering renewed hope for many patients suffering from cholestatic disorders.

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