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LETTER TO THE EDITOR

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Contents

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MINIREVIEWS

Immune remodulation in pediatric inherited metabolic liver diseases

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Abstract

Inherited metabolic liver diseases arise from genetic mutations that lead to disruptions in liver metabolic pathways and are predominantly observed in pediatric populations. The spectrum of genetic metabolic liver disorders is diverse, encompassing a range of conditions associated with aberrations in iron, copper, carbohydrate, lipid, protein, and amino acid metabolism. Historically, research in the domain of genetic metabolic liver diseases has predominantly concentrated on hepatic parenchymal cell alterations. Nevertheless, emerging studies suggest that inherited metabolic liver diseases exert significant influences on the immune microenvironment, both within the liver and systemically. This review endeavors to encapsulate the immunological features of genetic metabolic liver diseases, aiming to expand the horizons of researchers in this discipline, and to elucidate the underlying pathophysiological mechanisms pertinent to hereditary metabolic liver diseases and to propose innovative therapeutic approaches.

Key Words: Liver transplantation; Inherited metabolic liver diseases; Immune microenvironment; Genetic metabolic liver diseases; Immunotherapy

Core Tip: It remains unclear whether concurrent infections are connected to immunological changes beyond the established metabolic imbalances in inherited metabolic liver diseases. Previous studies often focused on changes in liver parenchyma cells, but recent studies have shown that inherited hepatic metabolic diseases also have a profound impact on the liver's immune microenvironment.

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INTRODUCTION

Hereditary metabolic liver diseases, which are caused by gene mutations leading to liver metabolic disorders, are relatively prevalent among the pediatric population[1]. These conditions can be classified as disorders related to iron, copper, carbohydrate, lipid, protein, and amino acid metabolism based on the metabolites involved. When classified by specific diagnoses, the spectrum of these diseases includes Wilson's disease (hepatolenticular degeneration), alpha-1 antitrypsin deficiency, urea cycle disorders, propionic acidemia (PA), Dubin-Johnson syndrome, tyrosinemia, and glycogen storage diseases (GSDs), among others. In addition to the well-recognized metabolic disturbances, affected individuals often present with concurrent infections that may be associated with metabolic decompensation. However, the relationship between these concurrent infections and immunological alterations, independent of the established metabolic dysregulations, remains to be elucidated.

Historically, research has concentrated on alterations within hepatic parenchymal cells. Yet, recent studies have demonstrated that inherited hepatic metabolic diseases significantly impact the liver's immune microenvironment.

In light of these developments, this review aims to encapsulate the characteristics of immune remodeling in genetic liver metabolic diseases, underscoring the importance of a comprehensive analysis of immune remodeling to foster a deeper comprehension of the underlying pathophysiology of these conditions and to propose novel therapeutic strategies informed by these insights (Figure 1).

NEUTROPHILS AND MACROPHAGES IN GSD AND WILSON DISEASE

GSDs

GSDs represent a group of rare monogenic disorders characterized by impairments in glycogen metabolism, encompassing the synthesis, breakdown (degradation of glycogen into glucose through glucose-6-phosphate [G6P]), and glycolysis (the conversion of glucose to pyruvate), as detailed in Table 1. These intricate, multi-systemic conditions display considerable heterogeneity in their clinical presentations and therapeutic strategies[2,3].

GSD type I (GSD I), also known as von Gierke disease, is a relatively prevalent autosomal recessive disorder within the spectrum of GSDs, with an incidence of approximately 1 in 100000 individuals[2]. GSD I is classified into two subtypes: GSD Ia, which arises from mutations in the *G6PC1* gene leading to glucose-6-phosphatase deficiency and represents approximately 80% of cases, and GSD Ib, which results from genetic mutations in the *SLC37A4* gene causing a deficiency in glucose-6-phosphate translocase and accounts for the remaining 20%.

Resaz *et al*[4] employed plasma-derived extracellular vesicles from LS-G6pc-/- mice, a model representative of GSD Ia, to elucidate the regulation of disease-associated microRNA expression. Their target genes were found to be significantly enriched in pathways involved in immune regulation. Cangelosi *et al*[5] conducted a liver proteomic analysis in LS-G6pc-/- mice, revealing an upregulation of proteins associated with inflammation and immune response. Notably, among these mice, six LS-G6pc-/- mice developed liver adenomas. In those with adenomatous changes, there was an observed increase in proteins involved in tissue inflammation and those influencing macrophage polarization towards the M2 phenotype. These findings suggest that immune regulation plays a pivotal role in the pathogenesis of GSD Ia and is intricately linked to the formation of adenomas and carcinomas. La Rose *et al*[6] identified a correlation between reduced circulating monocytes and disrupted platelet aggregation in L-G6pc-/- mice under fasting-induced hypoglycemic conditions, potentially relating to the bleeding diathesis observed in GSD Ia.

GSD Ib is characterized by disruptions in glycometabolism, inflammatory bowel disease (IBD), reduced neutrophil count, and impaired neutrophil functionality[7]. Visser *et al*[7] conducted a comprehensive study encompassing all known individuals with GSD-I born between 1960 and 1995 across 12 European countries. Of the 288 individuals, 57 had GSD Ib, with 54 experiencing neutropenia, defined as an absolute neutrophil count (ANC) below 1×10^9/L. Among these patients, neutropenia was documented in 64% before the age of 1, and in 18% between the ages of 6 and 9. Persistent neutropenia was observed in five patients, while 45 experienced intermittent decreases without discernible periodicity.

Table 1 Classification of glycogen storage diseases and their mutation sites

Condition	Gene(s)	Enzyme(s) or transporter	Inheritance
GSD 0a	*GYS2*	Hepatic glycogen synthase	AR
GSD 0b	*GYS1*	Muscle glycogen synthase	AR
GSD I, Von Gierke disease	*G6PC1 (GSDIa)* and *SLC37A4 (GSD Ib)*	G6Pase (GSD Ia) and G6PT (GSD Ib)	AR
GSD II, Pompe disease	*GAA*	Acid alpha-glucosidase	AR
GSD III (Cori disease; Forbes disease)	*AGL*	Glycogen debranching enzyme	AR
GSD IV (Andersen disease)	*GBE1*	Glycogen branching enzyme	AR
GSD V (McArdle disease)	*PYGM*	Myophosphorylase	AR
GSD VI (Hers disease)	*PYGL*	Liver glycogen phosphorylase	AR
GSD VII (Tarui disease)	*PFKM*	Muscle phosphofructokinase	AR
Hepatic GSD IX	*PHKA2 (GSD IX α2), PHKB (GSD IX β), PHKG2 (GSD IX γ2)*	Liver phosphorylase kinase α2 (GSD IX α2), liver and muscle phosphorylase kinase β2 (GSD IX β), and phosphorylase kinase γ2 (hepatic and testis isoform) (GSD IX γ2)	X-linked (GSD IX α2; females can be affected depending on X inactivation), AR (GSD IX β, and GSD IX γ2)
Muscle GSD IX	*PHKA1*	Alpha subunit of muscle phosphorylase kinase (GSD IX α1)	X-linked
GSD X	*PGAM2*	Muscle phosphoglycerate mutase	AR
GSD XI	*LDHA*	Lactate dehydrogenase A	AR
GSD XII	*ALDOA*	Red blood cell fructose-1,6-bisphosphate aldolase A	AR
GSD XIII	*ENO3*	Beta-enolase	AR
GSD XV	*GYG1*	Glycogenin 1 (muscle isoform)	AR
PGM1-CDG (formerly GSD XIV)	*PGM1*	Phosphoglucomutase 1	AR
FBS (also called GSD XI), Fanconi-Bickel syndrome	*SLC2A2*	GLUT2	AR
PGK deficiency	*PGK1*	Phosphoglycerate kinase	X-linked

GSD: Glycogen storage disease.

Neutrophil function investigations in 18 patients with neutropenia revealed abnormal neutrophil function in all cases. Thirty-seven patients reported perioral infections, 27 had perianal infections, and 23 suffered from chronic diarrhea. Of the 20 patients suspected of having IBD, colonoscopic and radiographic examinations were abnormal in all 10 who underwent these procedures. Neutropenia was present in every individual with IBD, as well as in those with perioral and perianal infections[7]. Du *et al*[8] analyzed three cases of GSD Ib, observing recurrent infections and a decrease in ANC in all patients. Kaczor *et al*[9] examined 13 pediatric patients with GSD Ib (median age of 5 mo at diagnosis), with 10/13 experiencing severe infections (sepsis and/or pneumonia) as their initial symptoms during the neonatal-infant period, and 4/13 requiring long-term treatment for IBD. Wicker *et al*[10] conducted a retrospective study of nine French patients with GSD Ib, with an average age of 1.7 years at diagnosis and 3.8 years for the development of IBD. The patients experienced 0.7 acute hospitalizations per year due to infections (0.4 times/year) or digestive system-related symptoms (0.4 times/year). Those with severe clinical manifestations exhibited more pronounced digestive symptoms but also had an earlier onset of neutropenia. During follow-up, there was a declining trend in neutrophil counts in the severe group, with more frequent urgent hospitalizations (median 1.3 times per year), driven by digestive system manifestations (median 0.6 times per year) and infections (median 0.8 times per year). Shimizu *et al*[11] found that GSD type 1b (GSD1b) recipients are more susceptible to bloodstream infections compared to patients with biliary atresia following liver transplantation (LT), potentially due to lower neutrophil counts. Despite lower tacrolimus levels in the extended post-LT monitoring period for GSD 1b, there were no T-cell-mediated rejection episodes, suggesting that more personalized post-LT immunosuppressive strategies for GSD1b patients may be required. The neutropenia observed in GSD-Ib is attributed to increased neutrophil apoptosis. However, some propose that the blockade of neutrophil maturation within the bone marrow is also a contributing factor to neutropenia. Sim *et al*[12] utilized the CRISPR/Cas9 system to induce mutations in the *G6PT* gene, establishing a single-cell-derived *G6PT*-/- human myeloblastic cell line, HL-60. The *G6PT*-/- HL-60 cells

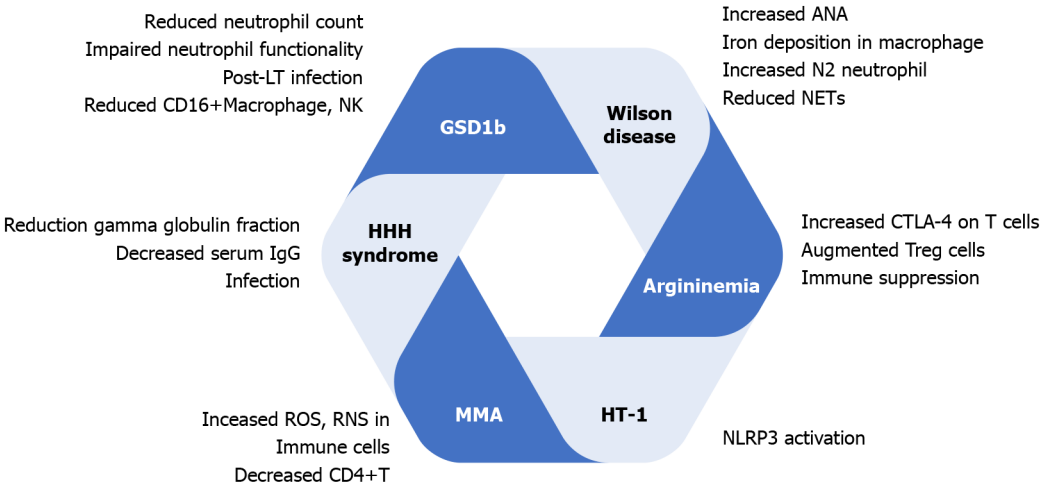

Figure 1 Immune remodulation in pediatric inherited metabolic liver diseases. GSD1b: Glycogen storage disease type 1b; ROS: Reactive oxygen species; RNS: Reactive nitrogen specie; LT: Liver transplantation; MMA: Methylmalonic acidemia.

displayed impaired neutrophil differentiation associated with two mechanisms: (1) Disrupted lipid metabolism leading to delayed metabolic reprogramming; and (2) diminished nuclear transcriptional activity of peroxisome proliferator-activated receptor-gamma, resulting in peroxisome proliferation.

The immune dysregulation in GSD1b extends beyond neutrophil deficiency, implicating both innate and adaptive immune responses. Gehlhaar *et al*[13] applied mass cytometry (CyTOF) to characterize the peripheral immune profiles in GSD1b patients, revealing a significant reduction in anti-inflammatory macrophages, CD16+ macrophages, and natural killer cells. Additionally, there was a skewed distribution towards central memory and effector memory phenotypes within various T cell subsets. This suggests that under the hypoglycemic conditions associated with GSD1b, immune cell populations may struggle to undergo the necessary metabolic shifts for proper glycolytic activity. The study also noted a general downregulation of CD123, CD14, CCR4, CD24, and CD11b across multiple cell populations, coupled with an upregulation of CXCR3, hinting at impaired immune cell migration as a feature of GSD1b pathology. Jang *et al*[14] utilized monocytes derived from *G6PT*-/- mice and human THP-1 monocytes with *G6PT* deficiency, demonstrating incomplete macrophage differentiation and altered inflammatory cytokine secretion despite increased glucose consumption under inflammatory conditions. Jeon *et al*[15] employed the CRISPR/Cas9 technique to mutate the *G6PT* gene in porcine alveolar macrophage 3D4/31 cells, which, lacking *G6PT*, showed reduced cell growth, bactericidal activity, and antiviral response. These findings of compromised immune functions in GSD1b suggest that future therapeutic interventions may need to target both neutrophils and macrophages.

Certain subtypes of GSDs have been identified to possess significant immunological features. Colonetti *et al*[16] analyzed plasma samples from treated GSD patients and observed that GSD-Ia/III/IX patients exhibited decreased levels of IL-4, CCL3, CCL22, TNF-β, and VEGF relative to controls. Among the different GSD types, GSD-Ib patients showed elevated G-CSF levels compared to GSD-Ia patients; IL-10 was higher in GSD-Ib than in GSD-Ia, while GSD-III/IX patients had increased CXCL10 levels compared to GSD-Ib individuals. When GSD-I patients were grouped and compared with GSD-III/IX patients, the latter displayed higher CXCL10 and CCL2 levels. Anemia in GSD-I patients correlated with increased IL-4 and CCL3 levels compared to non-anemic patients. Triglyceride levels in GSD-Ia patients without hepatocellular adenoma did not correlate with neutrophil counts or CCL22 levels. Overall, the cytokine profile alterations in GSD patients indicate a disruption in immune homeostasis[17].

Wilson disease

Wilson disease (WD) is a hereditary condition related to copper metabolism, characterized by the abnormal accumulation of copper within the body[18]. The etiology of WD is rooted in mutations affecting the *ATP7B* gene, which encodes a transmembrane copper-transporting ATPase. These mutations lead to copper accumulation in various organs, including the liver and brain. The progression of clinical symptoms in WD can vary in severity, but liver pathology is a frequently observed outcome. The dysfunction of *ATP7B* in WD results in excessive copper accumulation in the liver, leading to liver-related pathology[19-21]. Additionally, the excess copper is released into the bloodstream, causing abnormal accumulation in multiple tissues and significantly impacting the brain. This brain accumulation can lead to neurological symptoms and psychiatric disorders[22,23]. WD is most commonly diagnosed in individuals aged 5 to 35 and, despite its rarity, is estimated to affect approximately 1 in 30000 individuals[24]. Recent research has also identified a novel form of cell death dependent on copper, termed "copper-induced apoptosis" or "cuproptosis," which is distinct from all known cell death pathways. Cuproptosis is characterized by copper binding to acyl-CoA synthetase in the citric acid cycle, leading to protein aggregation, protein toxicity stress, and ultimately cell death[17]. WD is now considered to be closely associated with this process of cuproptosis.

According to recent reports, WD is closely associated with autoimmune disorders. Cases where WD was combined with autoimmune conditions have been found. Acharya *et al*[25] reported an atypical case involving an 11-year-old with WD developing IgA vasculitis nephritis. This suggests that in WD, there might be a defect in the liver's management or

clearance of IgA/IgA immune complexes, potentially leading to IgA-mediated skin and kidney damage. Pradhan *et al*[26] reported the case of a 12-year-old girl with WD combined with systemic lupus erythematosus. Ma *et al*[27] documented the case of an 11-year-old with WD combined with immune thrombocytopenic purpura. Further research is needed to clarify the fundamental pathological mechanisms linking WD with these autoimmune conditions.

The production of autoantibodies is a prevalent characteristic in systemic autoimmune diseases, and both their diversity and abundance serve as crucial diagnostic and prognostic indicators[28,29]. Additionally, autoantibodies might emerge in individuals without any apparent health issues or in conditions induced by alternative mechanisms. Antczak-Kowalska *et al*[30] found that patients with WD had a higher prevalence of autoantibodies, approximately two times than healthy participants (ANA, ANCA, NSAbs, and ONA). In patients presenting neurological symptoms, the existence of autoantibodies (ANA and ANCA) significantly increased (approximately two times) in contrast to individuals in good health. No significant variations were noted for patients presenting liver symptoms. Jańczyk *et al*'s study revealed that, among the autoantibodies, only the frequency of ANA was elevated in children with WD compared to the healthy individuals[31]. The presence of autoantibodies did not show a significant association with hepatic steatosis or liver stiffness. Nevertheless, increased liver stiffness (E > 8.2 kPa) was correlated with the production of IgA, IgG, and γ-globulins.

Immunological responses in WD have been noted to exhibit distinct characteristics, with macrophages playing a pivotal role in the development and progression of liver pathologies. In a study by Glavind *et al*[32], two cohorts comprising 175 individuals with WD were evaluated. The findings indicated that sCD163, a marker of macrophage activation, while not specific to WD, was found at elevated levels in WD patients, with more significant increases in acute cases. Notably, patients with cirrhosis demonstrated higher sCD163 levels compared to those without, which correlated with biochemical indicators of liver damage and hepatic function. These observations suggest that macrophage activation is pronounced in WD and is associated with the hepatic disease phenotype as well as biochemical markers of liver disease. Moreover, sCD163 could potentially serve as an indicator of WD severity.

The dysfunction of the ATP7B protein, as seen in WD, leads to diminished incorporation of copper into ceruloplasmin, thereby reducing the ferroxidase activity essential for intracellular iron efflux. This reduction also impacts the release of copper from hepatocytes into bile, resulting in substantial hepatic copper accumulation and iron deposition. Jończy *et al*[33] observed a decrease in plasma iron levels in tx-J mice, which carry a missense mutation in the *ATP7B* gene and serve as a model for WD, alongside iron accumulation in liver cells and hepatic macrophages. Dusek *et al*[34] reported iron deposition in brain macrophages associated with neurological symptoms in WD. Mi *et al*[35] employed *ATP7B*-/- zebrafish and mouse models, as well as *ATP7B*-knockout HepG2 cell models, to elucidate the role and mechanism of neutrophils in WD. Transcriptome analysis of neutrophils in the liver of *ATP7B*-/- zebrafish revealed a unique transcriptional signature indicative of N2-type neutrophils. Furthermore, N2-type neutrophils were identified in the liver of mice with *ATP7B* gene knockout. Interventions targeting transforming growth factor β1, DNA methyltransferases, or signal transducer and activator of transcription 3 in drug-treated *ATP7B*-knockout mice reduced hepatic N2-type neutrophils, improved liver function, and mitigated hepatic inflammation and fibrosis. The study also found that transforming growth factor β1-mediated epigenetic silencing of Socs3 facilitated N2-type polarization in bone marrow neutrophils. These findings suggest that modulating the activity of N2-type neutrophils could offer an alternative therapeutic approach to enhance liver function in WD.

Neutrophil extracellular traps (NETs) are directly implicated in several disease processes and are known to contribute to systemic inflammation, with significant deposition observed in hepatic sinusoids. Cichon *et al*[36] investigated the influence of copper on NETs formation in the hepatic vasculature during septicemia in a WD mouse model. They found that mutations in the *ATP7* gene resulted in reduced NETs release during systemic inflammation, where the excess copper in WD mice directly impaired the capacity to release NETs. This study has broadened our comprehension of how copper metabolism in WD influences NETs release and its subsequent pathological implications.

T CELLS IN UREA CYCLE DISORDERS

In the urea cycle, there are a total of six enzymes involved[37]. The deficiency or defect of any of these enzymes can disrupt the normal functioning of this cycle, leading to the inability to convert the metabolic product of protein, ammonia, into urea, causing its accumulation in the body[38,39]. This results in increased blood ammonia levels, leading to a range of clinical manifestations. This group of genetic metabolic disorders are commonly known as urea cycle disorders. There are several diseases classified as urea cycle disorders, such as argininemia, arginine succinate lyase deficiency, arginine succinate synthase deficiency, carbamoyl phosphate synthetase deficiency, ornithine-δ-transaminase deficiency, and ornithine transcarboxylase deficiency, among others[40].

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, an uncommon autosomal recessive disorder related to the urea cycle resulting from mutations in the *OTCD* gene, is characterized by metabolic complications and commonly presents acute hyperammonemia and cross-infections associated with metabolic imbalance. Silvera-Ruiz *et al*[41] described a case of HHH syndrome and detected a reduction in the serum gamma globulin fraction and decreased levels of serum IgG, as well as significant alterations in the phenotype and function of T and B cell immune components. This suggests that this rare metabolic genetic defect might lead to immune impairment in patients and could be associated with the high incidence of cross-infections observed in patients with urea cycle disorders.

Reports on cases of urea cycle disorders further confirm the crucial role of immune regulation in these conditions. The research findings of da Silva *et al*[42] demonstrate a significant increase in indoleamine 2,3-dioxygenase (IDO) activity (Kyn/Trp) with age. Among the metabolites most strongly associated with elevated IDO, ornithine transcarbamylase

(Orn/Arg) exhibits a robust correlation, potentially contributing to the aging of the immune system. These findings provide compelling evidence of metabolite influence on the body's immune microenvironment, advocating interventions to reduce ornithine transcarbamylase activity.

Awasthi *et al*'s study revealed that supplementing L-arginine created a favorable environment for parasite growth in mice with malaria[43]. Consequently, the infected mice supplemented with L-arginine died earlier than the control group of infected wild-type mice. Conversely, supplementation of L-citrulline inhibited parasite growth, leading to increased survival time in the mice. Flow CyTOF analysis indicated that supplementing L-arginine increased CTLA-4 in the population of T cells and augmented regulatory T cells (Treg cells), inducing immune suppression. In contrast, supplementation of L-citrulline had no impact on the population of T cells, and the number of Treg cells decreased in *P. berghei*-infected mice[43]. This suggests that metabolites have a profound influence on the biological behavior of T cells.

NAÏVE HELPER T CELLS IN ORGANIC ACIDEMIAS

Organic acidemia (OA) stems from enzyme deficiencies within the body's metabolic processes of organic acids, resulting in the accumulation of these acids and their byproducts, leading to a spectrum of disorders[44-46]. In 1966, Tanaka *et al* [47] identified the first case of isovaleric acidemia (IVA) using gas chromatographic/mass spectrometry technology, and since then, dozens of similar conditions have been progressively identified. Most OAs are inherited as autosomal recessive disorders, with common diseases within this category including methylmalonic acidemia (MMA), PA, and IVA [48].

Organic acids impact clinical manifestations of diseases by influencing the immune system. For instance, high concentrations of methylmalonic acid in the bloodstream can induce immune cells to release cytokines associated with inflammation like TNF-α and IL-6. These cytokines, along with elevated methylmalonic acid, stimulate immune cells to generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). Methylmalonic acid, cytokines, ROS, and RNS present in the serum can penetrate the blood-brain barrier, triggering cognitive impairment[49]. Medina-Torres *et al*[50] conducted a retrospective study involving 11 patients with PA and MMA, collectively known as propionate inherited metabolic disorders (PIEM), which are OAs. The results indicated that 91% of the patients exhibited immunological abnormalities. With the exception of one patient, all individuals showed decreased absolute counts of lymphocyte subsets, particularly a common reduction in CD4+ T lymphocytes. Furthermore, among the 11 participants, 9 had a low CD4/CD8 ratio. These findings suggest that monitoring immune biomarkers, such as lymphocyte subsets, may be meaningful during the follow-up of patients with PIEM. Altun *et al*[51] conducted a study involving 33 patients with OA and 32 age- and gender-matched healthy controls to evaluate the immune status of OA patients. Among the 33 patients, 21 (88%) were diagnosed with MMA, while 10 (33%) were identified with PA, and 2 (6.6%) with IVA. Sepsis was present in 18 patients (55%) among the studied group. The numbers of naïve helper T cells and recent thymic emigrants were notably reduced in OA patients ($P < 0.001$). Several anomalies affecting humoral immunity were also observed, including memory B cells and immunoglobulins. These findings suggest that OA patients might exhibit adaptive immune deficiencies, making them more susceptible to infections. Organic acids can trigger immune-related conditions in diseases. Aydin Köker *et al*[52] reported a case where hemophagocytic lymphohistiocytosis developed as a consequence of PA. Zhu *et al*[53] reported the case of a 5.5-year-old girl who simultaneously suffered from MMA, acute lymphoblastic leukemia, and congenital heart disease. However, it is currently unclear how organic acids induce other disorders in the context of the disease.

OTHER INHERITED METABOLIC LIVER DISEASES

Abnormal tyrosine metabolism is a genetic disorder affecting the liver and kidneys due to reduced activity of fumarylacetoacetate hydrolase, the ultimate enzyme in tyrosine breakdown. Succinylacetone in urine or blood is a characteristic feature of this disorder. High tyrosine levels comprise various types; among them, tyrosinemia type I (or hepatorenal tyrosinemia, HT1) exhibits the broadest clinical and pathological manifestations. Nitisinone (NTBC) is a drug used to treat tyrosinemia type I (Figure 2). Wei *et al*[54] employed NTBC as a means to explore the potential role of the Phe/Tyr degradation pathway in inflammatory responses. They discovered that NTBC exhibited efficacy in alleviating lipopolysaccharide-induced septic shock in mice. Mechanistically, this protective effect was associated with the accumulation of 4-hydroxyphenylpyruvic acid (4-HPP), an intermediate product induced by NTBC treatment in the Phe/Tyr degradation pathway. 4-HPP inhibited the initiation and activation of the NLRP3 inflammasome, thereby reducing the release of IL-1β, as shown in Figure 2. Similar to NTBC, 4-HPP was also effective in alleviating endotoxin shock in mice. These findings suggest that the Tyr degradation pathway might serve as a plausible center for immunoregulation and could be used as a therapeutic approach to mitigate inflammation.

Liver genetic metabolic diseases encompass a wide range of conditions, and their pathophysiological mechanisms are somewhat linked to the immune microenvironment. However, most of these conditions are rare diseases with few cases and limited related reports, so a detailed enumeration is not feasible here.

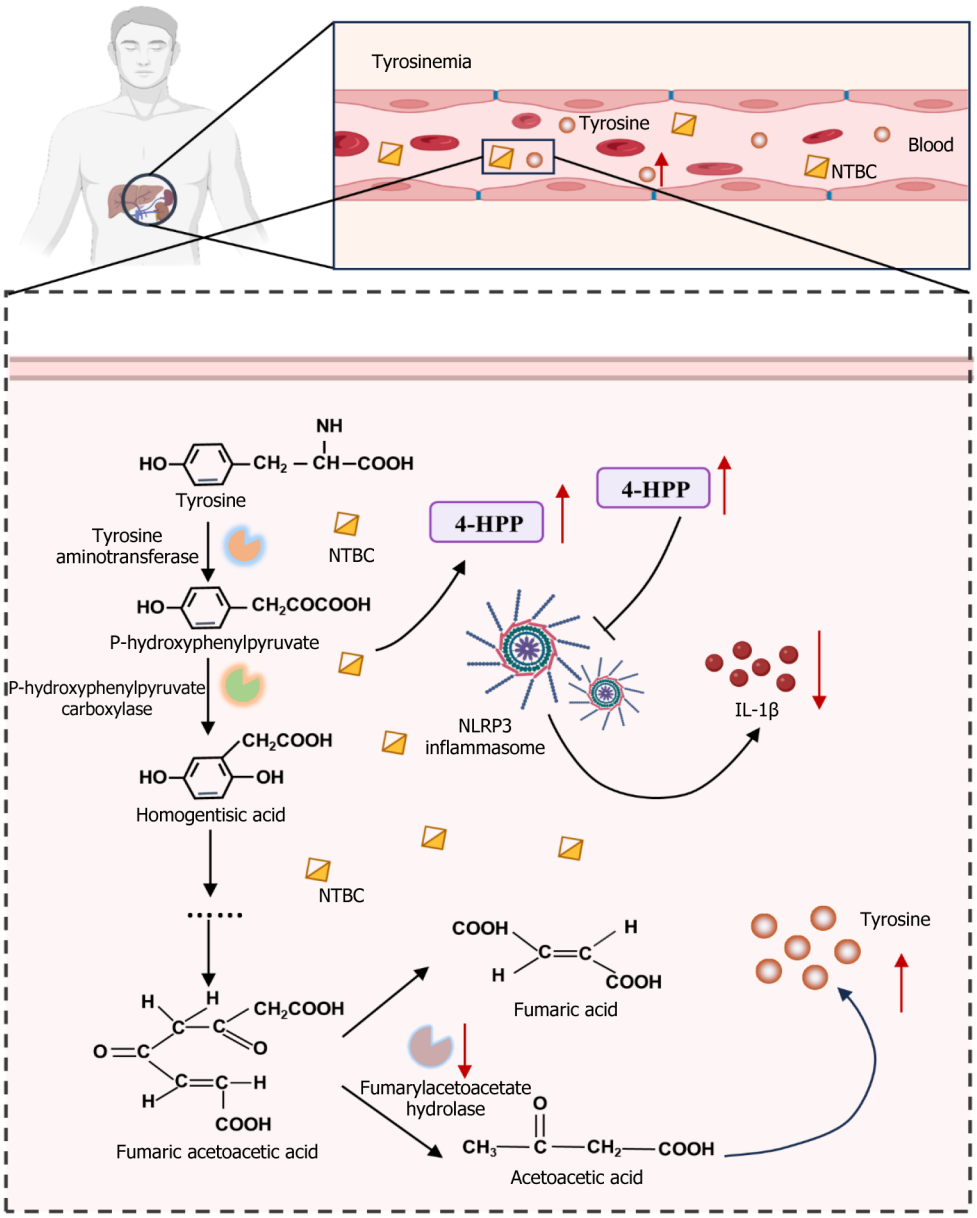

Figure 2 Mechanism of nitisinone in treating tyrosinemia. 4-HPP: 4-hydroxyphenylpyruvic acid.

GENE THERAPY FOR INHERITED METABOLIC DISORDERS OF THE LIVER: IMMUNOLOGICAL CHALLENGES

Gene therapy is increasingly recognized as a promising therapeutic strategy for a variety of genetic disorders, particularly for rare metabolic diseases with limited treatment options, such as those affecting liver function. LT currently stands as the only definitive cure for these conditions. The liver's capacity, representing 10%-15% of the body's total blood volume, positions it as an optimal site for protein secretion into the circulatory system[55]. Traditionally, viral vectors including lentiviruses, adenoviruses, retroviruses, and adeno-associated viruses (AAVs) have been the mainstays for liver cell targeting. However, over recent decades, an array of non-viral vectors, such as naked DNA, liposomes, and nanocarriers, have risen as effective alternatives for genetic material delivery[56]. Gene therapy approaches can be broadly categorized into two types based on administration methods: *Ex vivo* and *in vivo*. *Ex vivo* gene therapy involves the extraction, culture, amplification, and vector-mediated modification of a patient's cells, followed by their reintroduction into the patient. *In vivo* gene therapy, on the other hand, entails the direct administration of therapeutic agents to the patient *via* various systemic or localized routes. For liver diseases, *in vivo* gene therapy is often more appropriate given the complexities associated with *ex vivo* manipulation and amplification of liver cells[57]. A multitude of studies have attested to the efficacy of liver-directed gene therapy. However, the translation of these methods into clinical practice is encumbered by numerous challenges, chief among them being the innate and adaptive immune responses elicited by gene therapy products. While adenoviruses have garnered considerable clinical experience in oncology, their application in the treatment of genetic metabolic liver diseases has been constrained by potential inflammatory reactions. In contrast, AAVs have seen broader application in liver-targeted gene therapy[58].

Crigler-Najjar syndrome, a recessive hereditary disorder of liver metabolism attributable to mutations in the *UGT1A1* gene, currently has LT as its sole definitive treatment. D'Antiga *et al*[59] reported on a phase 1-2 clinical trial of gene therapy for Crigler-Najjar syndrome, wherein patients administered a higher dose of adeno-associated virus serotype 8 vector encoding UGT1A1 (GNT0003) showed a reduction in bilirubin levels and remained free from phototherapy requirements for at least 78 wk post-vector infusion. During follow-up, ALT levels increased in four patients, associated with a T-cell-mediated response to the vector. However, T-cell-mediated immune responses against UGT1A1 and AAV8 were challenging to detect owing to the concurrent use of immunosuppressive drugs. In all five patients, IgG and IgM antibody levels against AAV8 peaked concurrently before returning to baseline levels, with sustained high titers of neutralizing antibodies observed[58]. Hordeaux *et al*[60] developed the AAVhu68 vector for Pompe disease (GSD II) treatment, a type F adenovirus closely related to AAV9, carrying an engineered human acid alpha-glucosidase (hGAA) with an insulin-like growth factor 2 variant (vIGF2) peptide tag. Eleven cynomolgus monkeys treated with intravenous AAVhu68.vIGF2.hGAA exhibited a spectrum of severe anti-hGAA responses, from absent to severe cell-mediated myocarditis with elevated cardiac troponin I levels, resulting in cardiac toxicity in five monkeys. Eggers *et al*'s study similarly illustrated that while the adenovirus vector AT845 is efficacious for gene therapy in Pompe disease, high doses can trigger anti-acid alpha-glucosidase (GAA) immune responses, inflammation, and cardiac abnormalities[61]. In contrast, a vector expressing cynomolgus monkey GAA did not induce detectable pathological changes, suggesting that AT845's toxicity may stem from an anti-GAA heterologous immune response. In a gene therapy trial, Somanathan *et al*[62] administered arterial delivery using adenovirus type 5 (Ad5) as a vector to a patient with ornithine transcarbamylase deficiency, which regrettably led to fatal systemic inflammation. Further investigation indicated that neutralizing antibodies against Ad5 may enhance transduction and activation of dendritic cells (DCs) by Ad5, potentially post-formation of Ig-Ad5 immune complexes binding to DCs. This finding may shed light on the mechanisms behind systemic inflammatory reactions induced by adenovirus-based gene therapy.

To surmount the immune challenges associated with gene therapy for hepatic genetic metabolic diseases, various strategies have been explored. For instance, the use of viral vectors with lower immunogenicity in their capsids has been investigated, alongside the combination of gene therapy with immunosuppressive treatments. Chandler *et al*[63] examined the potential of AAV44.9 as a vector for gene therapy in MMA. AAV44.9, initially isolated as a contaminant in the rhesus adenovirus SV15 monkey kidney cell culture system, shares the highest homology with AAVrh.8 and features a novel capsid. In human trials, AAV44.9 has demonstrated low immunogenicity, reducing the risk of neutralizing antibodies and enhancing safety. Tissue distribution in treated MMA mice indicates that AAV44.9 possesses efficient transduction in the liver and heart, also reducing mortality and disease-related metabolic products, positioning it as a promising vector for clinical applications. Choi *et al*[64] discovered that the combination of bortezomib and mouse-specific CD20 monoclonal antibody as immunosuppressive therapy can effectively mitigate the production of neutralizing antibodies against AAV. This strategy holds potential for the elimination or amelioration of immune responses triggered by neutralizing antibodies.

CONCLUSION

The field of immunology related to genetic metabolic liver diseases is replete with promising prospects. Approaches such as immune modulation, immunocellular therapy, and immune suppression may improve disease progression and symptom severity. Interventions targeting immune responses could mitigate inflammation and immune-related tissue damage, thereby protecting affected liver tissues. Additionally, the deployment of immunocellular therapies, including stem cells or immune-regulatory cells, may foster repair or replacement of damaged liver tissues, offering more enduring therapeutic benefits for patients.

As we delve deeper into immunological research, a clearer understanding of the interplay between genetic metabolic liver diseases and the immune system will emerge. This knowledge could pave the way for more precise, personalized treatment strategies, thereby enhancing therapeutic outcomes and improving patients' quality of life. Although this domain remains in its exploratory phase, the relentless advancements in immunology herald a new era of potential treatments for genetic metabolic liver diseases.

FOOTNOTES

Author contributions: Wu YC, Xiang XL, Yong JK, and Li M conceived, designed, and refined the study protocol; Li LM, Zhang ZJ, Tong H, and He XY were involved in the data collection; Lv ZC, Zhou Y, and Sun XC analyzed the data; Wu YC and Feng H drafted the manuscript. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Wu YC and Xiang XL contributed equally to this work as co-first authors. Xia Q and Feng H contributed equally to this work as co-corresponding authors, which accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the review. Both authors have contributed equally to the conception and design of the research. They have collaboratively developed the hypothesis and outlined the experimental approach. Both authors have been involved in the comprehensive review of the existing literature to establish the research context, identify gaps in knowledge, and support the rationale for the study. They have engaged in intellectual discussions and debates that have shaped the direction of the research, leading to the refinement of ideas and the development of innovative approaches. Both co-corresponding authors have been actively involved in drafting the manuscript, ensuring that the writing reflects their collective thoughts, interpretations, and conclusions drawn from the research.

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