Review

Role of NLRP3 Inflammasomes in Disorders of the Children's Digestive System

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Review

Role of NLRP3 Inflammasomes in Disorders of the Children's Digestive System A Narrative Review

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Abstract

Background/Objectives: This review article highlights the role of NLRP3 inflammasomes in various gastrointestinal and hepatic disorders in the pediatric age group. NLRP3 inflammasomes are one of the principal intracellular innate immune sensors. During inflammation, there is production of molecules as caspase-1, and the release of IL-1β and IL-18. The NLRP3 inflammasome participated in the preservation of intestinal homeostasis and mucosal immune response. The objective is to evaluate the published articles related to the role of NLRP3 inflammasome in common pediatric gastrointestinal and hepatic disorders, to identify the future perspective regarding its possible therapeutic values. **Methods:** Search the Medline for the NLRP3 Inflammasomes and disorders of the digestive system during childhood. **Results:** Although the majority of articles were related to adults' various disorders, such as Alzheimer's disease, Parkinson's disease, and atherosclerosis, neurodevelopmental disorders such as schizophrenia. A few published data related to NLRP3 roles in the pediatric age group: autism, rheumatoid arthritis, and other autoimmune diseases, as well as inflammatory bowel diseases (IBD) and hepatic infection. Some research demonstrated that the NLRP3 inflammasome has a protective role; however, it also has a pathogenic function. **Conclusion:** This review approached the comprehensive role of inflammasome NLRP3 in the most common pediatric and neonatal gastrointestinal and hepatic diseases, including clinical and experimental studies as well as the pharmacological inhibitors for NLRP3 inflammasome, which may provide future therapy of GIT problems as IBD.

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1. Introduction

Inflammasomes

Jurg Tschopp in 2002 was the first to project the term inflammasome as he described a high molecular weight complex nucleotide-binding domain, leucine-rich repeat-containing protein (NLR) family pyrin domain. The inflammasome is a multimeric protein complex; it is composed of three key groups: pattern-recognition receptors (PRR) or NOD-like receptors (NLR) or AIM2-like receptors; (2) apoptosis-associated speck-like proteins containing caspase recruitment domains (ASCs); and (3) caspase proteases [1]. Its core role is to transfer the pro-IL-1b and pro-IL-18 to the final acting structures to implement inflammatory cell death termed pyroptosis [2].

The innate immune system acts as a shield to protect the gastrointestinal tract from pathogenic microorganisms. The inflammasomes play a role in innate immunity, recognizing bacteria, fungi, viruses, and products of cell damage-that trigger inflammatory responses through the release of pro-inflammatory factors [3]. Inflammasomes activate inflammatory mediators and induce cell death to protect against infectious agents while maintaining homeostasis.

Inflammasomes can identify the pathogenic organisms and their metabolites that cause infection and inflammation, contributing to innate immunity [3]. Thus, inflammasomes protect the host from infectious agents and support homeostasis.

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Both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) provoke the inflammasome production that regulates the secretion of caspase-1; consequently, it controls the secretion of IL-1 and IL-18; moreover, it can lead to inflammatory cell death as pyroptosis [2]. This indicates that inflammasomes play a dynamic function in innate and adaptive immunity as well as inflammatory reactions of the host [4]. Up till now, quite a lot of inflammasomes have been recognized and broadly classified: NLRP1 inflammasome, NLRP3 inflammasome, NLRC4 inflammasome, NLRP6 inflammasome, and AIM2 inflammasome [2]. This review aims to evaluate the published articles related to the role of NLRP3 inflammasome in common pediatric gastrointestinal and hepatic disorders, to identify the future perspective regarding its possible therapeutic values.

2. Materials and Methods

A search of the peer reviewed, full text published literature from electronic databases, including PMC and PubMed, using various combinations of keywords, including NLRP3 inflammasomes, NLRP3 inflammasome role in intestinal mucosal immunity, pathogenic roles of the NLRP3 inflammasome, protective role of the NLRP3 inflammasome, NLRP3 inflammasome in gastrointestinal diseases, and hepatic disorders in pediatric age group was done. Experimental and clinical studies were also included. The correlated articles that were published between 2000 and January 2025 were incorporated. This narrative review provides a comprehensive background of the available data and information regarding the role of NLRP3 inflammasome in pediatric digestive system disorders.

3. Results

The reviewed literature provides insights into the structural composition of the NLRP3 inflammasome, its activation mechanisms, and its involvement in immune responses and inflammation. It highlights the inflammasomes' association with various human inflammatory conditions, particularly those affecting the intestines, where it may play either a harmful or protective role. The following sections discuss the impact of NLRP3 in pediatric inflammatory bowel disease, celiac disease, intestinal infections, necrotizing enterocolitis, and liver-related disorders. Additionally, the potential use of pharmacological agents targeting the NLRP3 inflammasome in treating these conditions will be examined.

4. Discussion

4.1. Structure of NLRP3 Inflammasome

NLRP3 inflammasome has three original elements: NLRP3, ASC, and procaspase-1. These elements are a three protein, a pyrin domain, a nucleotide-binding and oligomerization domain (NOD), and a leucine-rich repeat domain [5]. The activation of the NLRP3 inflammasome could be through a two-step process: reaction to several different stimuli resulting from microorganisms and various endogenous molecules and cytokines that provoke macrophages to augment NLRP3 and pro-IL-1β extractions by generating the transcription factor NF-κB. The initial step involves priming by certain PAMPs or DAMPs, which stimulate the production of NLRP3 and the pro-form of IL-1β in affected cells. Other molecules that are connected to the regulation of NLRP3 and pro-IL-1β expressions include myeloid differentiation primary response protein 88 and TIR domain-containing adaptor-inducing interferon-β [6].

The consequent step is the oligomerization of NLRP3 by the ligands that will ensue by assembling the NLRP3, ASC, and procaspase-1. It was further described that inflammasome assembly is initiated by pyrin domain - pyrin domain interfaces involving NLRP3 and ASC, and the ATPase action of the NOD domain helps NLRP3 oligomerization. He et.al. described the canonical and noncanonical inflammasome pathways [7]. In the initial prototype, the NLRP3 inflammasome is

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primed by bacterial molecules or cytokines and is subsequently stimulated by a signal, such as ATP. It was suggested based on the detection of caspase-11-dependent pyroptosis in murine macrophages. In humans, the equivalents of caspase-11 are caspase-4 and caspase-5[8].

The production of NLRP3 could be regulated by the priming signaling through transcription-independent pathways [5] as well as by lipopolysaccharides without NLRP3 induction in an acute priming procedure. Moreover, the researchers showed that frequent signaling events at the molecular and cellular levels are activated by NLRP3 inflammasome agonists, such as ionic flux, reactive oxygen species production, and lysosomal damage [9].

Uninhibited activation of NLRP3 may be connected to diverse inflammatory diseases in humans, cryopyrin-associated periodic fever syndromes, rare hereditary auto-inflammatory diseases, involving familial cold urticaria, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease and sepsis [10–12], intestinal inflammation and ulcerative colitis [13].

4.2. NLRP3 Inflammasome Role in Intestinal Mucosal Immunity

NLRP3 plays an important function as anti-infection immunity and contributes to inflammatory conditions, including inflammatory bowel disease (IBD) and other immune-related intestinal disorders. [14]. NLRP3 participates in maintaining the homeostasis and stability of the intestine and the immune reaction of the intestinal mucosa.

Also, during bowel inflammation, it manages the innate immune responses, contributing to the support of the ongoing inflammation and the disruption of the enteric barrier through an adaptation of the tight junction proteins and cell apoptosis [15].

The NLRP3 inflammasome resides in epithelial and immune cells. Its molecular structure regulates the biological activity and detects microbial-derived ligands. The inflammatory response in the intestine is mediated by activation of the NLRP3 inflammasome by bacterial toxins, ATP, reactive oxygen species, and other danger signals, initiating caspase-1 effector proteins to trigger provocative elements such as IL-1 and IL-18. Moreover, caspase-1 triggers the gasdermin D protein. which is considered to be a crucial regulator of innate immunity [16]. It is assumed that proper activation of the NLRP3 inflammasome in intestinal epithelial cells supports intestinal stability and barrier integrity by inducing IL-18, which is essential for promoting epithelial cell production and the proliferation of intestinal endothelial cells.[17].

4.3. Pathogenic Roles of the NLRP3 Inflammasome

Abnormal levels of the NLRP3 inflammasome and pro-inflammatory cytokines are linked to several gastrointestinal disorders, such as IBD [18]. Consequently, inflammasomes are thought to be a risk factor for IBD. NLRP3 inflammasome causes abolition of IL-1β production. Liu et al. [18] observed that patients with colitis had high levels of the NLRP3 inflammasome. NLRP3 inflammasome activity progressively increased as the disease progressed, and this situation was amplified in the IL-10$^{-/-}$ mice. The NLRP3 dysfunction is due to the loss of IL-10 signaling due to accumulated mTOR-induced mitochondrial damage [19].

4.4. Protective Roles of the NLRP3 Inflammasome

The NLRP3 inflammasome pathway is reportedly an indispensable part of promoting gut epithelial integrity and stability. Zaki et al. [20] suggested that the NLRP3 inflammasome may exert a protective effect on intestinal homeostasis; furthermore, they observed that the lack of the downstream inflammasome aggravated pathological injury in gene-deficient mice. The regulation of IL-1 β and IL-18 secretion by the NLRP3 inflammasome is beneficial in colitis. Initiation of the NLRP3 inflammasome can accelerate a compensatory reaction for epithelial cell proliferation to preserve barrier integrity. Therefore, inflammasome deficiency causes an increase in the permeability of the intestinal barrier. The antimicrobial capacity of the inflammasome NLRP3-deficient mice was impaired as there was a change in their gut microflora, thus resulting in intestinal disorders [21].

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4.5. The Causes of Contradictory Results for the role of NLRP3 Inflammasome

The opposing results of several studies on the role of the NLRP3 inflammasome may be attributed to alterations in laboratory and experimental circumstances, research types, or disease stages [22]. This contradictory role is seen in diseases such as IBD.

5. NLRP3 Inflammasome in Gastrointestinal Diseases Concerning the Pediatric Age Group

Several studies have shown the role of NLRP3 inflammasome in the pathogenesis of digestive diseases. The stimulation of the NLRP3 inflammasome impacts gut homeostasis. The NLRP3 inflammasome is involved in stomach, intestine, liver, and even pancreatic disorders. In stomach disease, it is involved with the persistent infection of Helicobacter pylori-related gastritis and gastric cancer. NLRP3 inflammasome is also involved in inflammatory bowel disease, colorectal cancer, changes of the gut microbiome, and colitis and enteritis [23]. It is associated with liver diseases such as viral hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease, cholestatic liver injury, drug-induced liver injury, autoimmune hepatitis, hepatic fibrosis, hepatocellular carcinoma, NLRP3 inflammasome and pancreatic disease, chronic pancreatitis, acute pancreatitis, severe acute pancreatitis, and pancreatic ductal adenocarcinoma.

5.1. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic, recurrent intestinal disease. It results from an abnormal immune reaction to the intestinal microflora of the host and is marked by symptoms such as abdominal pain, bloating, and changes in bowel habits. Inflammatory Bowel Disease is influenced by multiple contributing factors such as environmental causes, infection-related mediators, as well as genetic vulnerability. IBD includes two major types: ulcerative colitis (UC) and Crohn's disease (CD) [23], which can affect any segment of the gastrointestinal tract from the mouth to the anus. Evidence of genetic tendency among IBD patients is suggested, as well as malignancy.

Almost twenty percent of patients begin at less than 20 years old. Four percent of cases with IBD started less than 5 years old, and 18% of cases started before age 10 years. The peak onset is during adolescence [24].

Over the past 20 years, growing evidence has suggested that Crohn's disease and ulcerative colitis may be triggered by defective innate immune responses, leading to impaired clearance of antigens and/or pathogens and ultimately contributing to chronic inflammation and disease development.

Still, there is a dispute regarding the protective roles of the NLRP3 inflammasome in IBD. Its association with IBD has been suggested, with studies reporting upregulation of NLRP3 and IL-1β in patients with ulcerative colitis (UC) [25] and Crohn's disease (CD) [26]. Additionally, the activity and severity of the disease was perceived with increased excretion of the NLRP3 inflammasome and its effectors, such as IL-1β, in the mucosa of IBD patients. Elevated inflammasome gene expression and an abundance of immature intestinal macrophages have also been noted [27]. A molecular switch role of the NLRP3, endorsing an inflammatory phenotype in intestinal immune cells via IL-1β.

The progression of IBD is enhanced by the uncontrolled activation of the NLRP3 inflammasome and its key cytokines [18,28]. Mice genetically deficient in miR-223 exhibit significantly worsened experimental colitis, characterized by heightened immune infiltration of neutrophils and monocytes, hyperactivation of NLRP3, and increased IL-1β release. Conversely, nanoparticle-mediated delivery of miR-223 mimetics can mitigate NLRP3 activation, provide early intervention, regulate cytokine-driven immune imbalances, and reduce the severity of experimental IBD [29].

The early stimulation of NLRP3 in intestinal epithelial cells limits pathogen colonization and averts additional inflammation of the intestine [30]. IL-1β and IL-18, produced through NLRP3 inflammasome activation, play a protective role against colitis and colitis-associated tumorigenesis [20,31]. Research indicates that a deficiency in the NLRP3 inflammasome increases susceptibility to

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experimental colitis in mice [21,31]. Furthermore, NLRP3 has a beneficial role in probiotic-centered treatment for colitis [32].

The conflicting findings regarding the role of NLRP3 in IBD may stem from variations in experimental protocols, available resources, differences in microbiota composition, and the genetic backgrounds of the mice used in the studies. The NLRP1 and NLRP3 inflammasome signaling pathways may regulate the immune mechanism of IBD in children by upregulating the expression of Caspase-1 and IL-1β. The study of Wang and Ma included 126 children with IBD: 32 children with Crohn's disease, and 94 children with ulcerative colitis. They found significantly higher mRNA expression of NLRP1, NLRP3, Caspase-1, and IL-1β in CD or UC cases, which correlated with the severity of the disease. There was a significant positive correlation in the children with UC or CD between the mRNA expression levels of NLRP1, NLRP3, Caspase-1, and IL-1β with serum IgM and IgG levels. A positive correlation of the mRNA secretion of NLRP1 and NLRP3 inflammasomes with Caspase-1 and IL-1β was detected [33].

Genetic factors affect IBD by regulating the activation of inflammasomes; the CARD8 gene inhibits NLRP3 inflammasome assembly, interacts with NLRP3, and inhibits NLRP3 oligomerization caused by variant V44I that exacerbates colitis and Crohn's disease [34].

Deficiency of the IL-10R gene inhibits NLRP3 inflammasome activation and inhibits expression of NLRP3 and IL-1β, which cause spontaneous colitis in mice and infant-onset IBD in humans/Mouse spontaneous colitis and human IBD [28]. Also, the deficiency of the receptor-interacting protein kinase 1 (RIPK1) gene inhibits NLRP3 inflammasome activation upon lipopolysaccharide stimulation, participating in human colitis [35].

5.2. NLRP3 Inflammasome in Gut–Lung Interaction

Distinct connection concerning the pathology of IBD and pulmonary diseases. The use of advanced technology improved the accuracy of diagnosis of the link between gut and lung as microbiome sequencing, and modern imaging like high-resolution computed tomography. Mansi et al. reported that up to71%of children and adolescents with Crohn's disease had abnormal bronchial hyperreactivity [36].

5.3. Celiac Disease

Celiac disease is an autoimmune disorder characterized by chronic inflammation that essentially affects the small intestine and is caused by eating gluten-containing foods, in a study done by Al-Assaf et al., they showed that gene expression of NLRP3 Inflammasome in the peripheral blood of Iraqi children with Celiac disease was down-regulated in the present samples, and it was accompanied by a decreased serum level of IL-1β [37].

6. NLRP3 Inflammasome and Gastrointestinal Tract Infection

It has been declared that the NLRP3 inflammasome is activated by several pathogenic organisms that invade the gastrointestinal tract, bacteria such as Helicobacter pylori, Campylobacter jejuni, Yersinia enterocolitica, and Clostridium difficile infections. Also, it is prompted by viral as adenovirus; and enterovirus species [38,39] as well as protozoal infections such as Entamoeba histolytica and Giardia [40].

6.1. Infectious Enteritis and Colitis

NLRP3 inflammasome also has an important role in infectious enteritis and colitis, and protection from intestinal pathogens. NLRP3 inflammasome induces the secretion of pro-inflammatory cytokines and controls the majority of immune mechanisms necessary to resist infections, such as acidification of the phagosome [41]. Augmentation of inflammation of the intestine is due to the activation of the NLRP3 inflammasome and IL-1β. There is evidence that induction of

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NLRP3 inflammasome damages the intestinal barrier via the prevention of goblet cell maturation [42].

The pathogens residing in the intestine can activate the NLRP3 inflammasome by several molecules, including Hemolysin A generated by Proteus mirabilis. The stimulation of NLRP3 by *P. mirabilis* plays a crucial role in exacerbating colitis.[43]. Toxin Clostridium difficile A and Clostridium difficile B toxin produced by Clostridium difficile [44], and Yersinia enterocolitis adhesin invasin postulate ''signal I'' for NLRP3 inflammasome activation, while the bacterial type three secretion system translocon constitutes ''signal II''that initiates IL-18 maturation and secretion [45]. Clostridium difficile infections are linked to antibiotic-associated diarrhea and pseudomembranous colitis, with toxins that trigger the Pyrin inflammasomes and subsequent elevation of IL-1b-dependent tissue damage [46].

A study showed contradictory data on the protective role of NLRP3, as in the mice deficient in NLRP3 or mice receiving a pharmacological inhibitor of NLRP3, those mice had increased survival and amplified bacterial clearance compared with untreated mice due to decreased autophagy and increased phagocytosis by neutrophils [47]. The role of NLRP3 in Salmonella typhimurium infection is still intangible [48].

Ectopic colonization of Klebsiella aerogenes, activate the NLRP3 inflammasome in intestinal macrophages, which, caused periodontitis in mice through a robust release of IL-1b by macrophages [49]. The absence of NLRP3 or the inhibition of IL-1 eliminates the colitogenic effect of *Klebsiella aerogenes* in mice, highlighting the crucial role of the NLRP3–IL-1β axis in the development of oral commensal pathobiont-driven colitis [49].

Pathogen-induced inflammasome-mediated IL-1β secretion helps suppress pathogens by activating the host's innate immune response, such as neutrophil recruitment through the production of adhesion molecules in endothelial cells. Some studies suggest that the NLRP3 inflammasome regulates the intestinal microbiota [20,21].

On the contrary, some studies report contradictory findings. They found that activation of the NLRP3 inflammasome in epithelial cells by G protein-coupled receptor signaling protects against Dextran sodium sulfate-induced colitis [50]. Mice lacking NLRP3 are more prone to Dextran sodium sulfate-induced colitis [20,21,31]. These studies observed that NLRP3 activation leads to IL-18 secretion, which guards against colitis. IL-18 signaling helps maintain homeostasis in the commensal microbiota by inhibiting the growth of pathobionts [20]. This contradiction could be due to the variances in the gut microbiota among the different studies. The stimulation of the NLRP3 inflammasome by precise pathobionts could play a critical role in either triggering or exacerbating intestinal inflammation.

6.2. Helicobacter Pylori

Helicobacter pylori (HP) is a damaging bacterium that is located in the gastric mucosa. The WHO classifies *HP* as a Group 1 carcinogen. [38]. The NLRP3 inflammasome and HP infection augment each other in an endless circle. The amount of NLRP3 and gasdermin D protein was considerably elevated in the stomach of HP patients. It was proven that during the initial phases of *HP* infection, the NLRP3 inflammasome is activated through the release of hsamiR-223-3p and IL-10 [51]. *HP* also imparts a secondary signal mandatory for NLRP3 inflammasome activation, including K+ efflux and reactive oxygen species release, which control the increase in IL-1β secretion. Elevated levels of mature IL-1β during *HP* infection can contribute to the development of atrophic gastritis and cancer [52].

6.3. Protozoan Infections

NLRP3 has also been involved in protozoan infections, as it was found critical in identifying the Entamoeba histolytica invasion and in escalating a vigorous inflammatory reaction. *Giardia duodenalis* is a frequent cause of diarrhea among children in developing countries. Manko-Prykhoda et al. stated that a new NLRP3-modulatory mechanism regulates the severity of enteric diseases

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during co-infections with *Giardia* spp. and A/E enteropathogens; they reported a decrease in colitis, bloody soft stool, bacterial invasion, and weight loss in co-infected mice [40].

6.4. Viral

The involvement of NLRP3 in the COVID-19 gastrointestinal affection was shown by a study by Masir and Shirvaliloo. NLRP3 comprises Caspase-1, IL-1β, and GSDMD production. The downstream effects of NLRP3 activation are triggered by the SARS-CoV-2 ORF3a, N, and/or E proteins.[53].

The NLRP3 inflammasome may be stimulated by several elements of SARS-CoV-2. The S protein is associated with angiotensin-converting enzyme 2, which leads to NLRP3 inflammasome activation [54]. Remarkably, the SARS-CoV-2 viral proteins Viroporin 3a and ORF8b were suggested to activate NLRP3, and genetic modification of these viral proteins was related to variation in the severity of clinical pictures [55].

MIS-C children have gastrointestinal symptoms, higher levels of markers of myocardial injury, elevated ferritin, and frequently manifest with shock. Furthermore, there is evidence of inflammasome over-activation in MIS-C with marked elevation of IL-6 and IL-18 [56].

7. Inflammasome and Neonatal Gastrointestinal Disorders

Necrotizing Enterocolitis

One of the emergencies in the NICU is necrotizing enterocolitis (NEC) [57]. NLRP3 inflammasome plays a significant role in the pathogenesis of NEC. It has been assumed that the restraint of stimulation of NLRP3 could have protective consequences on NEC [58]. The inflammasome acts as a microbial sensor, and its activation by the commensal microbiota may be a factor in the pathophysiological outcomes of NEC.NLRP3 inflammasome activation was reported to be an important regulator in the development of NEC. Yin et al. 2020 found that NLRP3 inflammasome and downstream inflammatory factors, such as IL-1β and IL-18, were increased in NEC human and mouse intestinal tissues. There was an elevation of NLRP3, pro-Caspase-1, and Caspase-1 p10 in the mice with NEC. In neonates, NLRP3 and Caspase-1 were increased in NEC, and they were expressed both in the epithelium and lamina propria. These data demonstrated that NLRP3 inflammasome enzymatic protein caspase-1, as well as their downstream IL-1b and IL-18, were increased in NEC [59].

The intensified expression of NLRP3 in the hippocampus and cerebral cortex proved the role of NLRP3 inflammasome in the pathogenesis of NEC-associated brain injury. Also, high levels of caspase-1 and mature IL-1β were demonstrated in the brain of NEC animals [60]. IL-1β facilitates pro-inflammatory cytokine levels, stimulates microglia, and interrupts the blood-brain barrier, consequently participating in a diversity of neuroinflammatory diseases [58].

Zhu et al.'s study discloses a possible relation between the activation of NLRP3 inflammasome, intestinal and brain injury, and long-term intellectual dysfunction. They found a significant rise in the IL-1β levels of the intestine of the experimental NEC in mice, which is related to increased activity of the inflammasome NLRP3. IL-1β triggers damage to the intestinal mucosal barrier, leading to neutrophil recruitment to the damaged site and endorsing macrophage stimulation. They studied the effect of blockage of NLRP3 inflammasome activation to detect if it can ameliorate acute inflammatory injury, brain injury, and long-term cognitive impairment induced by necrotizing enterocolitis in mice. They showed that MCC950, which is a selective small molecule inhibitor of NLRP3, markedly reduced the overall mortality of the NEC mouse model, downregulated proinflammatory cytokine expression (mature IL-1β, IL-6, and TNF-α), and markedly improved the severity of histological damage in the intestines of NEC mice. MCC950 has a protective effect from NEC and NEC-induced acute brain damage, as well as their long-term cognitive impairment. It is a promising new therapeutic modality for infants suffering from NEC [60].

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8. Inflammasome and Hepatic Disorders

Inflammasomes are extracted in the parenchymal and non-parenchymal cells of the liver in response to harmful activators. Inflammasomes are dynamic in the hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells, and macrophages and are involved in the pathogenesis of acute liver injury, chronic liver diseases with augmented gut permeability, infectious diseases of the liver, including hepatitis C virus infection, and Schistosomiasis. It is also associated with drug-induced liver injury as acetaminophen, ischemia/reperfusion, or endotoxin.

8.1. Viral Hepatitis

Viral hepatitis is one of the most common infections associated with hepatic disorders in the pediatric age group. Hepatitis B virus (HBV) infection in infants and children is often associated with few or no symptoms but poses a high risk of developing into a chronic condition [61]. The hepatic concentration of NLRP3, apoptosis-associated speck-like CARD-domain containing protein, and IL-1b from chronic hepatitis B patients was associated with HBV-DNA intensity [62]. NLRP3, IL-18, IL-1β, and caspase-1 were significantly increased in hepatic tissues of patients with HBV-associated acute-on-chronic liver dysfunction. Likewise, hepatitis B core antigen was found to induce the expression of NLRP3 inflammasome and IL-1β [63]. Therefore, persistent infection with HBV triggers the NLRP3 signaling pathway, with afterward damage to hepatic tissues by the expression of cytokines such as IL-1β and IL-18. Patients who suffered from chronic hepatitis showed high values of IL-1β. Following Hepatitis C infection, apoptosis-associated speck-like protein containing a caspase (ASC) interacts with NLRP3 and dissociates from Golgi-resident protein immunity-related GTPase M, leading to Golgi breakup. This mechanism enhances the multiplication of HCV, which promotes hepatic chronic inflammation [64].

Also, the elements of the Hepatitis E virus strongly activate NLRP3 inflammasome in primary macrophages and macrophage cell lines. Remarkably, inflammasome activation counteracts interferon reaction to enable HEV reproduction in macrophages [65]. Future approaches to restrain the NLRP3 inflammasome or its inflammatory cytokines could offer treatment to alleviate liver inflammation alongside antiviral treatments.

9. Pharmacological Inhibitors for NLRP3 Inflammasome

Pharmacological inhibitors that target the NLRP3 inflammasome may be a better alternative for the treatment of NLRP3-associated diseases [66]. NLRP3 inflammasome can be inhibited through direct and indirect inhibitors [67] .Inhibition of NLRP3-driven inflammation can be achieved directly or indirectly, through targeting signaling pathways, such as transcription and oligomerization, inhibition, or Gasdermin D cleavage inhibition.

Future research must benefit from new data regarding the structure of NLRP3 and develop direct inhibitors with better specificity and effectiveness. The nanobodies are recently being studied as therapeutic drugs; they have high specificity, stability, and low toxicity [68]. Moreover, there are indirect inhibitors for the inflammasome NLRP3, such as Glyburide, 16673-34-0, JC124, FC11A-2. Also, there are inhibitors for the constituents of NLRP3 inflammasome that include Parthenolide, VX-740, and VX-765, Bay 11-7082, and β-Hydroxybutyrate (BHB). Additionally, there are direct inhibitors such as A diaryl sulfonylurea-containing compound termed MCC950, 3,4-Methylenedioxy-b-nitrostyrene, CY-09, OLT1177, Tranilast, and Oridonin.

Still, none of these drugs is approved by the Food and Drug Administration or other agencies. However, IL-1β inhibitors could be utilized in clinical trials. More research is needed to develop suitable inhibitors with better pharmacokinetic properties that can reach the specific organs with no side effects, and be more cost-effective [66,69].

10. The Future Direction

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The NLRP3 inflammasome participated in multiple gastrointestinal and hepatic diseases among pediatric age group. However, exclusive research is in the initial phase. Future studies to elucidate NLRP3 inflammasome protective and or pathogenic role in intestinal disorders are needed.

Future studies may reveal what is better: direct inhibition or indirect inhibition of the NLRP3 inflammasome. More extensive research is needed for the role of the anti-inflammatory effect of BHB in inhibiting the NLRP3 inflammasome and subsequent management of the NLRP3-mediated inflammatory diseases. The relation to gut probiotics is also still not well clarified.

The NLRP3/caspase-1/IL-1β/IL-18 axis is a good target for treating inflammasome-related diseases; a potential study of this axis inhibitors, bioavailability, effectiveness, and safety may show the possibility of their therapeutic impact [69].

Precise information is required regarding the mode of action of the inflammasome inhibitors, such as the synthetic small molecules, phytochemicals, organic compounds, and probiotics, e.g., as a therapeutic alternative for IBS management. [70].

Moreover, prospective research related to BHB to confirm its effect in inhibiting NLRP3 inflammasome activation and regulating intestinal pro-inflammatory Th17 cells could be beneficial [50]. Pursuing NLRP3 using gene editing techniques, such as exosomes and miRNA may present some concepts for future direction [68].

11. Conclusion

This article consolidates previously dispersed research into a cohesive and comprehensive review. The significance of NLRP3 in pediatric gastrointestinal diseases is gaining increasing attention. Inflammasomes are important controllers of the innate and adaptive immunity. Findings from this review emphasize the essential role of NLRP3 in preserving the balance of gut microbiota and in modulating the immune function of the intestinal mucosa.

The NLRP3 inflammasome is stimulated by a variety of stimuli [67].

The activation of the NLRP3 protein engages the ASC protein, which recruits the procaspase-1, leading to initiation, maturation, and secretion of inflammatory cytokines and pyroptosis [70].

It is improper to define the NLRP3 inflammasome as a protective or injurious cause for various diseases, including diabetes, atherosclerosis, metabolic syndrome, cardiovascular diseases, neurodegenerative diseases, and gastrointestinal disorders such as IBD. Current studies have revealed various inhibitors of the NLRP3 inflammasome pathway using animal models, either through direct inhibition of the NLRP3 protein or other components and products of the inflammasome.

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