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EDITED BY
Antonio Condino-Neto,
University of São Paulo, Brazil

REVIEWED BY
Anna Sediva,
University Hospital in Motol, Czechia

*CORRESPONDENCE
Daniel Kotlarz
daniel.kotlarz@med.uni-muenchen.de

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Dysregulated inflammasome activity in intestinal inflammation – Insights from patients with very early onset IBD

David Illig[1] and Daniel Kotlarz[1,2]*

[1]Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-University (LMU), Munich, Germany, [2]Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

Inflammatory bowel disease (IBD) is a multifactorial disorder triggered by imbalances of the microbiome and immune dysregulations in genetically susceptible individuals. Several mouse and human studies have demonstrated that multimeric inflammasomes are critical regulators of host defense and gut homeostasis by modulating immune responses to pathogen- or damage-associated molecular patterns. In the context of IBD, excessive production of pro-inflammatory Interleukin-1β has been detected in patient-derived intestinal tissues and correlated with the disease severity or failure to respond to anti-tumor necrosis factor therapy. Correspondingly, genome-wide association studies have suggested that single nucleotide polymorphisms in inflammasome components might be associated with risk of IBD development. The relevance of inflammasomes in controlling human intestinal homeostasis has been further exemplified by the discovery of very early onset IBD (VEO-IBD) patients with monogenic defects affecting different molecules in the complex regulatory network of inflammasome activity. This review provides an overview of known causative monogenic entities of VEO-IBD associated with altered inflammasome activity. A better understanding of the molecular mechanisms controlling inflammasomes in monogenic VEO-IBD may open novel therapeutic avenues for rare and common inflammatory diseases.

KEYWORDS

VEO-IBD, inflammasome, immunodeficiency, pediatrics, genetics, inflammation

Inflammasomes – Central coordinators of innate immunity

Inflammasomes are multimeric cytosolic protein complexes controlling immune tolerance, inflammation, host defense, cell clearance, and tissue repair (1, 2). The modal composition of inflammasomes based on common adaptors and effectors paired with cell-type specific sensors allows mounting of context-dependent responses to distinct threats (3, 4). As a first step of inflammasome activation, sensor proteins (e.g., Absent in melanoma 2 (AIM2), Nucleotide-binding oligomerization domain, Leucine rich Repeat (NLR) and Pyrin domain (PYD) containing protein (NLRP) 3, NLR family, apoptosis inhibitory protein (NAIP)/NLR family caspase activation and recruitment domain (CARD) domain-containing protein 4 (NLRC4), PYRIN) detect various danger signals including pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) (Figure 1) (1, 3, 4). Whereas some sensors are specific to distinct signals (e.g., AIM2, NLRC4), others (e.g., NLRP3) are promiscuous and can respond to a variety of stimuli (1, 4–15). Sensor proteins contain CARD or pyrin domains (PYD) mediating the interaction with adaptors and/or effectors (4, 16). Upon activation, some sensor proteins can directly recruit the effector Caspase (CASP) 1 *via* their CARD (Figure 1) (13, 16–19). In contrast, sensor proteins lacking a CARD recruit the adapter protein apoptosis-associated speck-like protein containing a CARD (ASC) *via* interaction of PYD (20–22). In turn, ASC can interact with pro-CASP1 *via* CARD resulting in oligomerization of inflammasome components and activation of pro-CASP1 by autoproteolysis (Figure 1) (3, 4, 13, 21, 23, 24). Finally, mature CASP1 cleaves the inflammasome substrates pro-Interleukin (IL)-1β, pro-IL-18 and Gasdermin D (GSDMD) (Figure 1) (1, 3, 4, 23, 25–29). While IL-1β and IL-18 trigger activation and recruitment of other immune cells contributing to inflammation and host defense, insertion of mature GSDMD into cell membranes induces pore formation and pyroptosis (Figure 1) (1, 3, 4, 25, 26).

Complex regulatory mechanisms on transcriptional and post-translational level are required to facilitate balanced inflammasome-mediated immune responses. On transcriptional level, nuclear factor κ-B (NF-κB)-mediated signaling has been shown to be critical for transcription of central inflammasome components (e.g., *NLRP3* and *IL1B*) upon Toll-like receptor (TLR)-mediated detection of PAMPs or DAMPs (30, 31). This process is often referred to as priming or signal 1 of NLRP3 inflammasomes (1, 30, 31). The subsequent triggering of sensor proteins was termed activation step or signal 2 and can involve post-translational processes. For example, NLRP3 inflammasome activation requires ATP-mediated deubiquitination of NLRP3 by BRCA1/BRCA2-Containing Complex Subunit 3 (BRRC3) but is inhibited by interferon (IFN)-γ-induced nitrosylation (1, 31–34). Furthermore, various kinases were shown to control activity of NLRC4, Pyrin (see also MEFV below), or ASC by phosphorylation (1, 35–38).

The role of inflammasomes in intestinal inflammation

Inflammasomes in intestinal epithelial cells

The intestinal epithelial barrier represents the first line of defense against pathogens and is critical in controlling intestinal immunity. Inflammasomes have been shown to play a central role in the defense strategy of intestinal epithelial cells (IEC), which is reflected by the expression of a diverse repertoire of inflammasome sensor proteins including NLRC4, NLRP3, and NLRP6 (39). In contrast to other epithelial cell types, IEC were shown to produce higher levels of IL-18 but less IL-1β indicating that IL-18 has a distinct role in intestinal homeostasis (39–42). For example, IL-18 has been involved in controlling infections by stimulating IFN-γ production from T and NK cells and supporting T_H1 responses (31, 43, 44). In addition, the induction of epithelial inflammasomes contributes not only to activation of immune cells *via* IL-18 but supports also viral

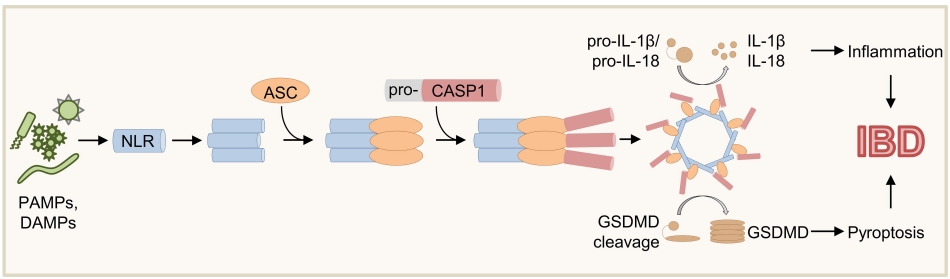

FIGURE 1
Schematic overview of inflammasome activation. Various PAMPs and DAMPs induce activation of sensor proteins resulting in oligomerization and recruitment of ASC and pro-CASP1. Upon autoproteolysis of pro-CASP1, mature CASP1 cleaves the inflammasome effector molecules pro-IL-1β, pro-IL-18, and GSDMD, which induce inflammation and pyroptosis.

clearance by inducing direct release of IFNs (16, 45). Furthermore, IEC-related inflammasomes stimulate mucus secretion, pyroptosis, or expulsion of infected epithelial cells (16, 46–48).

Inflammasomes in immune cells

Inflammasomes are primarily known for their function in innate immune cells (e.g., macrophages, granulocytes) and intestinal myeloid cells are the major source of IL-1β in the gut (31). Inflammasome activity in immune cells of the gut is critical for the detection of a wide variety of pathogens (e.g., bacteria, viruses, parasites) and the induction of appropriate host defense mechanisms (4, 16). Pathogen-induced activation of inflammasomes results in production of the pro-inflammatory cytokines IL-1β and IL-18, which induce a cascade of signaling pathways culminating in recruitment of other immune cells (e.g., neutrophils) (4, 16). Upon IL-1β sensing, immune cells produce various pro-inflammatory molecules (e.g., IL-6 and tumor necrosis factor (TNF)-α) fueling inflammation in the gut (31). In adaptive immune cells, IL-1β was shown to induce T cell survival and proliferation as well as increased immunoglobulin production by B cells (31). Furthermore, IL-1β contributes to polarization of T_H17 cells that are important mediators of intestinal inflammation (49, 50). Although immune cell-derived IL-1β can induce epithelial repair by stimulating renewal of intestinal stem cells, excess IL-1β might amplify intestinal inflammation by increasing epithelial barrier permeability and production of cytokines and chemokines (51–54). In addition to production of cytokines, inflammasome-dependent activation of pyroptosis in immune cells restrains intracellular replication of pathogens in infected immune cells (4, 16, 55). Moreover, inflammasomes were also shown to contribute to discrimination between pathogenic and commensal microbiota in the gastrointestinal tract (16, 56).

Inflammasomes in infectious diseases affecting the gastrointestinal tract

Various pattern recognition receptor families including the inflammasome sensor proteins of the NLR protein family have evolved in humans to recognize foreign and/or potentially dangerous material. Several pathogens affecting gastrointestinal health have been shown to trigger activation of inflammasomes. For example, NLRP3 inflammasomes contribute to the clearance of various bacterial (e.g., *Helicobacter pylori*, *Campylobacter jejuni*, *Yersinia enterocolitica*) and viral (e.g., adenovirus, enterovirus) species (16, 57–63). Furthermore, NAIP/NLRC4 can be triggered by components (e.g., Flagellin or type 3 secretion system) from various enteric bacterial species including *Escherichia coli, Salmonella enterica*, and *Listeria monocytogenes* (12, 14–16, 64). Moreover, *Clostridium difficile infections*, a major cause for antibiotic-related diarrhea and pseudomembranous colitis, result in toxin-mediated activation of Pyrin inflammasomes and increased IL-1β-dependent tissue damage (16, 65, 66). Mechanistically, infection-induced activation of inflammasomes contributes to pathogen clearance by cytokine-mediated recruitment and activation of immune cells (e.g, neutrophils) and pyroptosis of infected cells limiting pathogen propagation (16, 41, 46, 47, 56). Furthermore, active inflammasomes can limit further uptake of pathogens and can increase pathogen killing of professional phagocytes (16, 67). In IEC, inflammasome activation can lead to expulsion of infected cells into the gastrointestinal lumen, which may hinder pathogens to overcome the intestinal barrier (16, 41, 46, 47).

Inflammasomes in IBD pathogenesis

Previous studies have indicated that inflammasomes are implicated in IBD pathogenesis, as mucosal IL-1 production is significantly enhanced during active disease (68). Furthermore, higher IL-1β levels were detected in LPS-stimulated peripheral blood mononuclear cells (PBMCs) from patients with Crohn's disease (CD) and long-standing ulcerative colitis (UC) (69). In line, expression of IL-18 was also shown to be higher in lamina propria mononuclear cells isolated from patients with CD (70, 71). Moreover, IL-1β signatures have been detected in macrophages/monocytes isolated from inflamed intestinal tissues of IBD patients by single-cell transcriptomics and deep immunoprofiling (72). Correspondingly, Liso et al. have recently demonstrated that failure to respond to anti-TNF therapy was associated with increased IL-1β in sera and colonic biopsy specimens from patients with UC (73). Genetic effects on inflammasome dysregulation in IBD susceptibility were suggested by polymorphisms in genes involved in inflammasome activity (e.g., NLRP3, IL-18) (31, 74–76). Additionally, mutations in the NLRP3 regulator CARD8 were shown to result in increased NLRP3 inflammasome activity and CD (77).

The important role of inflammasomes in controlling homeostasis of the intestinal tract has been further demonstrated by amelioration of experimental colitis through blockade of the inflammasome effector molecules IL-1β and IL-18 in different murine models (50, 73, 78, 79). Based on these studies, IL-1 blockade is considered as potential therapy for IBD and is currently being evaluated in a phase II randomized placebo-controlled double-blinded trial for patients with acute severe colitis (80).

Monogenic VEO-IBD – A powerful model to define key factors controlling inflammasome activity

IBD is a complex disease triggered by environmental factors, immune dysfunctions, epithelial barrier defects, and imbalances of the microbial flora in genetically susceptible individuals (81). In

particular, children with rare very early onset IBD (VEO-IBD) show severe and refractory inflammatory conditions different from forms observed in adults (82). Based on the early age of onset and the aggressive phenotype VEO-IBD patients are considered to have a higher genetic susceptibility. In line, >75 distinct single inherited genetic defects have been identified as molecular cause for VEO-IBD (83, 84). Notably, the majority of reported monogenic entities are underlying primary immunodeficiencies and genetic diagnosis has critical implications for the prognosis and therapy of VEO-IBD patients. For example, hematopoietic stem cell transplantation (HSCT) has been established as curative standard of care for VEO-IBD patients associated with inborn errors of immunity (85).

Notably, several studies on monogenic VEO-IBD have demonstrated that altered inflammasome activity plays a critical role in the pathogenesis of human intestinal inflammation and illustrated that inflammasome plasticity is regulated by complex networks (Figure 2). Thus, monogenic VEO-IBD represents a powerful model highlighting critical molecular nodes forming the skeleton of inflammasome regulation. A better understanding of human inflammasome biology will guide the development of personalized therapies for VEO-IBD but will also portray novel concepts for the treatment of common IBD. To stimulate research on inflammasome biology in IBD pathogenesis, we herein aim to provide an overview of genes known to cause (monogenic) IBD and influence inflammasome activity. Therefore, we screened for genetic defects reported in recent position papers (83, 86–89) related to monogenic IBD to summarize links to inflammasome-related genes and -mediated processes (Table 1).

Inflammasome dysregulation in monogenic VEO-IBD

Sensor proteins

NLRC4

The most direct link between IBD pathogenesis and dysregulated inflammasome activation has been provided by the discovery of patients carrying mutations in genes encoding for sensor proteins. In particular, *de novo* gain-of-function in *NLRC4* could be identified in patients presenting with a range of clinical manifestations of autoinflammation and macrophage activation syndrome, including severe very early onset enterocolitis (103, 104). The reported gain-of-function mutations cause spontaneous oligomerization and activation of the NAIP/NLRC4 inflammasome without the requirement of physiological triggers resulting in spontaneous cleavage of pro-CASP1 and excessive release of IL-1β and IL-18, pyroptosis of macrophages, and chronic inflammation (103, 104). In addition, Steiner et al. have recently identified an autosomal recessive NLRC4 mutation associated with increased IL-1β and IL-18 secretion in a patient with autoinflammation accompanied by diarrhea (116). Although the underlying mechanisms of biallelic NLRC4 deficiency remain elusive, IL-18 blockade was shown to be effective in treatment of NLRC4-mediated macrophage activation syndrome indicating that epithelial-derived IL-18 might be a critical pathomechanistic driver (105). Taken together, patients with germline NLRC4 mutations demonstrate that a tight regulation of NLRC4-associated inflammasomes is necessary to maintain intestinal homeostasis and physiological immune cell function.

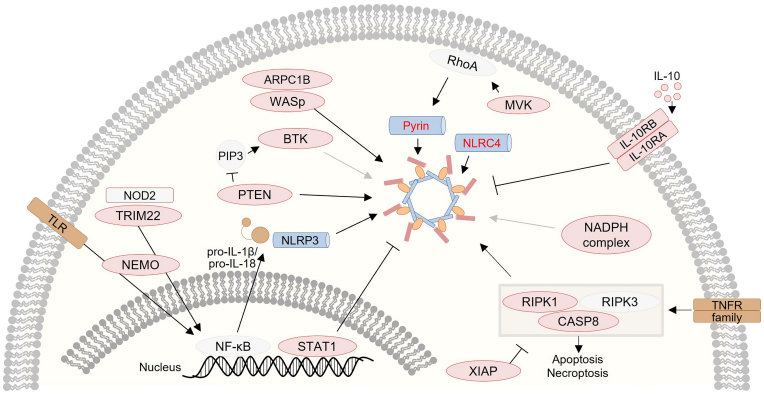

FIGURE 2
Graphical presentation of a network of inflammasome-associated monogenic defects causing VEO-IBD. Several proteins, that are several candidates for monogenic VEO-IBD (highlighted in red), have been shown to contribute to inflammasome dysregulation *via* various mechanisms.

TABLE 1 Overview of monogenic forms of IBD associated with inflammasome dysregulation.

Gene	Disease	Effect on IL-1β production	Effect of IL-1 blockade	References
ADAM17	Neonatal inflammatory skin and bowel disease	not clear	n.a.	
BTK	X-linked agammaglobulinemia 1	context-dependent	+ (mouse)	(90, 91)
CASP8	Caspase-8 deficiency	↑	n.a.	(92)
CYBA	Chronic granulomatous disease	↑	+	(78, 93)
CYBB	Chronic granulomatous disease	↑	+	(78, 93)
IKBKG	Anhidrotic X-linked ectodermal dysplasia and immunodeficiency	not clear	n.a.	
IL10/IL10RA/IL10RB	IL-10 (receptor) deficiency	↑	+	(94–96)
MEFV	Familial Mediterranean Fever	↑	+	(97–100)
MVK	Mevalonate kinase deficiency	↑	+	(38, 97, 101, 102)
NCF1	Chronic granulomatous disease	↑	+	(78, 93)
NCF2	Chronic granulomatous disease	↑	+	(78, 93)
NLRC4	Autoinflammation with infantile enterocolitis	↑	IL-18	(103–105)
PTEN	PTEN hamartoma tumor syndrome	↓	n.a.	(106)
RIPK1	RIPK1 deficiency	↑	n.a.	(107, 108)
STAT1	IPEX-like disease	not clear	n.a.	
TRIM22	TRIM22 defect	↓	n.a.	(109)
WAS	Wiskott-Aldrich syndrome	↑	+	(110–112)
XIAP	X-linked lymphoproliferative syndrome 2	↑	n.a.	(113–115)

Alphabetical list of IBD candidate genes showing effects on IL-1β production as well as the therapeutic efficacy of IL-1 blockade in the corresponding disorder. If a robust phenotype on IL-1β production has been documented the effect is indicated by arrows (up: higher IL-1β production; down: lower IL-1β production). Beneficial effects of IL-1 blockade are indicated by a plus sign. For BTK deficiency, only mouse data are available. For NLRC4 mutations, IL-18 blockade was shown to be effective. N.a., not assessed.

MEFV

Patients with mutations in the *Mediterranean fever gene* (*MEFV*, encoding for pyrin) have been shown to develop an autoinflammatory syndrome called Familial Mediterranean Fever (FMF) characterized by periodic fever attacks and associated with early-onset IBD-like phenotypes (38, 97, 117, 118). Even though mutations in MEFV are discussed rather as risk factors for VEO-IBD, underlying mechanisms in FMF provide important insights into dysregulated inflammasome activity. In steady state, pyrin molecules are phosphorylated by serine/threonine-protein kinase N (PKN)1/2 allowing binding of the chaperone protein 14-3-3 and maintenance of inactive pyrin (38, 97). In turn, activity of PKN1/2 is controlled by Rho GTPases that are critical regulators of actin cytoskeletons indicating that pyrin-mediated inflammasome activity is coupled to cytoskeleton dynamics (37, 38, 65). Various bacterial toxins (e.g., TcdB from *Clostridium difficile*) cause inhibition of Rho GTPases by post-translational modification, which results in reduced PKN1/2 activity, pyrin phosphorylation, and 14-3-3 recruitment, subsequently leading to increased pyrin activity (38, 65, 97). Similar to other inflammasomes, oligomerized pyrin recruits ASC and CASP1 resulting in inflammation and pyroptosis by inducing cleavage of pro-IL-1β, pro-IL-18 and GSDMD (119). Gain-of-function mutations in *MEFV* can cause increased IL-1β production and levels of IL-1β are indicative of disease activity in FMF patients (97, 98). As first line therapy, FMF can be successfully treated with colchicine by blocking polymerization of microtubuli and maintaining pyrin in an inactive state through subsequent activation of Rho GTPases and PKN1/2 (99, 120–122). Notably, FMF might be also treated using IL-1β antagonists demonstrating the central role of an inflammasome-mediated pathogenesis in FMF (99, 100, 120).

Inflammasome regulators

MVK

Mevalonate kinase (MVK) catalyzes the phosphorylation of mevalonate, which is a critical step in the biosynthesis of cholesterol as well as isopentenyl diphosphate and other polyisoprenoid metabolites (97, 123). Furthermore, the mevalonate pathway also produces precursors of geranylgeranyl pyrophosphate required for prenylation of proteins (101). Notably, prenylation is a critical post-translational modification of small Rho GTPases, which are important for the regulation of the pyrin inflammasome (see also *MEFV*) (38, 65, 97, 101). In patients with MVK deficiency, loss-of-function mutations impair production of mevalonate metabolites resulting in accumulation of metabolic precursors and lack of products like geranylgeranyl pyrophosphate (38, 65, 97, 101). The underlying mechanisms of enhanced inflammasome activity in MVK deficiency are not fully understood, but defective protein prenylation of small GTPases causes reduced pyrin phosphorylation and thereby

induces spontaneous activation of pyrin inflammasomes (38, 65, 97, 101). Similar to MEFV, patients with MVK deficiency suffer from an autoinflammatory syndrome characterized by recurrent episodes of fever, arthralgia, lymphadenopathy, and splenomegaly (38, 124, 125). Of note, MVK-deficient patients can also present with very-early onset diarrhea and abdominal pain reminiscent of IBD (38, 124, 125). Interestingly, the disease severity of MVK deficiency is dependent on the residual activity of mutated MVK (38, 124). Severe forms of MVD present as mevalonic aciduria associated with developmental delay and severe systemic inflammation (126). Analogous to FMF patients, MVK-deficient patients with VEO-IBD have been successfully treated by biologics blocking IL-1β signaling leading to improved endoscopic, histologic and laboratory parameters of inflammation (102).

IKBKG

NF-κB signaling is a critical cellular signaling pathway in human cells controlling pleiotropic functions such as inflammatory responses, cell stress, cell survival, and cell growth (127–129). Several studies have demonstrated that NF-κB signaling is critical for the expression of NLRP3 inflammasome components (e.g., *NLRP3, IL1B*) in response to various danger signals (priming step) (30, 31). In unstimulated conditions, NF-κB is inhibited by binding to the inhibitor of κB (IκB) (130–132). Upon cellular activation, IκB proteins are phosphorylated by the IκB kinase (IKK) complex (IKKα, IKKβ, IKKγ/NF-κB essential modulator (NEMO)) releasing IκB and enabling NF-κB-mediated signaling (132–136). In males, hypomorphic mutations in *NEMO*, a gene with X-linked inheritance encoding a regulatory subunit of the IKK complex, cause immunodeficiency and hypohidrotic ectodermal dysplasia associated with severe bacterial, viral, and fungal infections (137–139). Many NEMO-deficient patients further present with VEO-IBD characterized by intractable diarrhea and failure-to-thrive (137, 138). On a molecular level, NEMO deficiency causes aberrant TLR-, TNFR-, and IL-1R-mediated signaling impairing critical immune cell functions in response to infection (137). Of note, HSCT was shown to cure immunodeficiency and susceptibility to infections in patients with NEMO deficiency, but failed to cure intestinal inflammation indicating an important role of NEMO and NF-κB signaling in controlling intestinal epithelial cell homeostasis (138). In fact, NEMO was shown to be a critical regulator of TNF-mediated and RIPK1-dependent cell death in intestinal epithelium and NEMO-deficient epithelial cells displayed increased cell death as well as reduced production of antimicrobial molecules leading to increased permeability of the intestinal barrier for luminal microbiota and to intestinal inflammation (140, 141).

Genetic variants disturbing NF-κB signaling are obvious candidates causing inflammasome activation defects. In line, Greten et al. could show that inhibition or deletion of IKKβ results in reduced expression of IL-1β mRNA and immature protein upon LPS stimulation in mouse macrophages (142). However, they could also detect higher levels of mature IL-1β secreted by IKKβ-deficient macrophages, which might be a result of increased CASP1 activation due to enhanced apoptosis (142). Similar to these studies on IKKβ, Zhao. et al. reported that pharmacological suppression of NEMO ubiquitination resulted in reduced *Il1b* and *Nlrp3* expression in LPS-stimulated mouse macrophages (143). Despite scarce evidence, it is tempting to speculate that NEMO deficiency might also result in aberrant NLRP3 inflammasome activation similar to IKKβ. However, since NF-κB signaling controls various central (non-)immune functions, it is hard to differentiate the effects on single effector mechanisms such as inflammasome activation.

NOD2 and TRIM22

Nucleotide-binding oligomerization domain 2 (NOD2) is an intracellular pattern recognition receptor (PRR) of the NLR protein family detecting muramyl dipeptide (MDP), which is a component of the bacterial cell wall (81, 144–146). Upon activation, NOD2 signaling induces expression of pro-inflammatory cytokines *via* RIPK2- and NF-κB-mediated signaling and contributes to clearance of different pathogens (144, 146, 147). Of note, genome-wide association studies demonstrated that single nucleotide polymorphisms (SNPs) in *NOD2* represent the strongest genetic risk factor for the development of CD (81, 148, 149). However, mono- or biallelic *NOD2* mutations are not considered as a monogenic cause for IBD, as they can be also frequently found in the genome of healthy humans (81, 150). In contrast, mutations in the NOD2 regulator *tripartite motif containing 22 gene* (*TRIM22*) were shown to cause severe refractory VEO-IBD associated with diarrhea, failure-to-thrive, and multiple infections (151). TRIM22 is a RING finger E3 ubiquitin ligase that catalyzes K63 polyubiquitination of NOD2 and thereby controls NOD2 signaling function (151). Since NOD2 can regulate NF-κB signaling, it is likely that NOD2 signaling may also influence expression of important inflammasome components (i.e., *NLRP3, IL1B, IL18*). Indeed, studies in a mouse model of MDP-induced eye inflammation could demonstrate NOD2-mediated production of IL-1β and IL-18 *in vivo* (152). In the human setting, macrophages from CD patients expressing homozygous *NOD2* frameshift mutations fail to induce *IL1B* expression upon MDP stimulation demonstrating a critical role for NOD2 in regulating *IL1B* expression (153). Furthermore, PBMCs from NOD2-deficient CD patients demonstrated a reduced IL-1β secretion in response to MDP/TNF-α co-stimulation indicating that NOD2 signaling also regulates post-translational mechanisms influencing inflammasome activity (153). In line, Hsu et al. demonstrated that MDP and Anthrax toxin stimulation induces formation of the NOD2/NLRP1/CASP1 complex catalyzing IL-1β maturation in mouse macrophages (154). Contrary to MDP stimulation, NOD2 was shown to negatively regulate TLR1/2-mediated

induction of *Il1b* expression indicating the complex signaling mechanisms controlled by NOD2 and NF-κB (155). Interestingly, TRIM22 was also shown to support NLRP3 inflammasome responses upon oxygen-glucose deprivation in a neuronal cell line substantiating a potential role of NOD2-mediated signaling on inflammasome activation (109). Similar to the expressivity of NOD2-deficient patients, the role of NOD2 in inflammasome activation and intestinal inflammation models is not completely understood (156, 157). For example, Umiker et al. showed that colitis in *Nod2* knock-out (KO) mice was driven by NLRP3 inflammasome activity, but the underlying mechanisms of increased NLRP3 activity are still unclear (157).

Cell death regulators

CASP8, RIPK1, and XIAP

Patients with X-linked inhibitor of apoptosis (XIAP) deficiency present with a primary immunodeficiency characterized by hemophagocytic lymphohistiocytosis, severe infections, splenomegaly, and cytopenia (113, 158, 159). However, XIAP deficiency was also shown to often manifest with VEO-IBD (113, 158–161). Up to 4% of pediatric IBD has been associated with mutations in XIAP (113, 160, 161). As proposed by its name, XIAP can block apoptosis by inhibiting CASP-3, -7, and -9 *via* baculovirus IAP repeat (BIR) domains (113, 162–164). Furthermore, XIAP was shown to be essential for propagation of NOD2-mediated NF-κB signaling downstream of NOD2 and expression of important NLRP3 inflammasome components (113, 165, 166). In line, cells deficient for XIAP-related signaling components [receptor-interacting protein kinase (RIPK)2, BIRC2, and BIRC3] fail to induce expression of *IL1B* upon exposure to the NOD2 agonist MDP (113, 165, 166). However, loss of XIAP resulted in increased IL-1β secretion and cell death in response to various TLR agonists providing a rationale for autoinflammatory symptoms observed in XIAP deficiency (113–115). Aberrant inflammasome and cell death responses upon loss of XIAP in myeloid cells were shown to be dependent on TNF-, RIPK3-, and CASP8-mediated signaling processes (113–115). In the absence of XIAP, TLR- and TNFR-mediated signaling induces ubiquitination of RIPK1 causing activation of RIPK1 and RIPK3, which results in formation of a complex called ripoptosome that recruits and activates CASP8 (113, 115, 167, 168). Mature CASP8 can induce apoptosis, NLRP3 inflammasome activation, and cleavage of IL-1β demonstrating a direct XIAP-RIPK-CASP8-inflammasome axis (113, 114). Of note, TLR- or TNFR-mediated RIPK3 activation in the absence of CASP8 has been shown to induce NLRP3 inflammasomes and necroptotic cell death (113, 114).

In line with the importance of the XIAP-ripoptosome-CASP8 axis, germline loss-of-function mutations in *RIPK1* and *CASP8* were recently shown to cause VEO-IBD (92, 107, 108). Interestingly, RIPK1 and CASP8 deficiencies resulted in increased premature NLRP3 inflammasome activity characterized by higher IL-1β secretion without requirement of a second signal. Of note, enhanced inflammasome activity was associated with abnormal cell death responses (92, 107, 108). Overall, identification of causative mutations in all these three genes controlling activation of NLRP3 inflammasomes downstream of different immune signaling pathways exemplified the role of inflammasome activation and cell death regulation in IBD pathophysiology and intestinal homeostasis. The only available curative treatment option for VEO-IBD caused by XIAP deficiency is allogeneic HSCT demonstrating the urgency to find treatment alternatives (113, 159, 169). Similarly, there are no curative therapeutics available for RIPK1 or CASP8 deficiencies affecting both the immune system and intestinal epithelium. Since all three genetic defects are characterized by an increased inflammasome activity with higher IL-1β secretion, usage of therapies targeting inflammasomes and/or anti-IL-1R antibodies might represent an attractive approach for treatment.

Interleukin-10 receptor

IL-10R deficiency was the first identified monogenic cause for severe VEO-IBD accompanied by perianal disease and folliculitis, which can be only cured by allogeneic HSCT due to the underlying primary immunodeficiency (85, 170). The IL-10 receptor is a heterotetrameric protein complex consisting of two IL-10R1 and IL-10R2 subunits, which are encoded by *IL10RA* and *IL10RB* (171). The corresponding ligand IL-10 is a highly potent anti-inflammatory cytokine controlling pleiotropic functions in the immune systems (171–175). Of note, IL-10-mediated signaling was also shown to inhibit NLRP3 inflammasome activation on a transcriptional and post-translational level (94, 176). In line, IL-10-deficient mice showed increased NLRP3 inflammasome activation and IL-1β levels (94, 95, 177). Enhanced inflammasome activity manifested in mice prior to onset of colitis and the disease could be successfully treated by blockade of NLRP3 inflammasomes or IL-1β signaling demonstrating that symptoms of IL-10 deficiency are mediated by inflammasome perturbation (96, 177, 178). Analogously, cells from IL-10R-deficient patients showed increased and premature NLRP3 inflammasome activation as well as enhanced IL-1β secretion (94–96). Mechanistically, deficient IL-10 signaling was demonstrated to result in altered inflammasome activation by causing defective mitophagy (95). Interestingly, increased IL-1β production in human IL-10R-deficient macrophages can be also caused by alternative inflammasome activation, which is a CASP1-independent process mediated by CASP8 (94). Of note, IL-1β receptor blockade has been shown to ameliorate symptoms in IL-10R-deficient patients providing therapeutic windows for curative allogeneic HSCT (94).

WAS

The X-linked Wiskott-Aldrich syndrome (WAS) presents with a life-threatening immunodeficiency characterized by thrombocytopenia and recurrent infections and is caused by mutations in the homonymous gene (179–181). Upon cellular activation, autoinhibition of Wiskott-Aldrich syndrome protein (WASp) is resolved and WASp transfers G-actin to the Arp2/3 complex inducing actin filament formation and branching (181–184). Overall, WASp deficiency has been shown to disturb actin polymerization resulting in impaired chemotactic, migratory, phagocytic, and activation responses of immune cells and platelets (181, 185). Of note, WAS patients can manifest with VEO-IBD and WASp deficiency was shown to cause experimental colitis in mice (110, 186, 187). In fact, intestinal inflammation in *Was* KO mice is driven by macrophages, which develop an inflammatory phenotype characterized by higher levels of pro-inflammatory IL-1β and IL-23 as well as reduced levels of anti-inflammatory IL-10 (110). Analogously, macrophages from WAS patients showed a pro-inflammatory phenotype with higher expression of IL-1β (110). Furthermore, WASp-deficient cells exhibited an increased NLRP3 inflammasome activity, which might be caused by defective clearance of pathogens due to failure of actin assembly around phagocytosed pathogens and defective autophagy (111). Correspondingly, enteropathogen infection of myeloid cells expressing mutant WASp has been shown to enhance ASC speck formation and pyroptosis, indicative of robust inflammasome activation in WASp deficiency (111). Increased inflammasome activation might contribute to autoinflammatory symptoms observed in WAS and might be a target to bridge WAS patients for HSCT, similar to IL-10R-deficiency (110–112). In fact, anti-IL-1R therapy was shown to ameliorate symptoms in one WASp-deficient patient (112). Interestingly, increased inflammasome activation in WASp-deficient cells could be also inhibited by treatment with type I IFNs representing another potential therapeutic option prior to HSCT (111).

NADPH complex

Chronic granulomatous disease (CGD) leads to increased susceptibility of recurrent bacterial and fungal infections and is caused by a defective function of the NADPH oxidase complex in innate immune cells (188–190). Interestingly, up to 40% of CGD patients develop intestinal inflammation reminiscent of IBD (191, 192). The NADPH oxidase complex contains gp91-phox, p67-phox, p47-phox, and p22-phox subunits, which are encoded by the genes *CYBB, NCF2, NCF1*, and *CYBA*, respectively (190). Of note, mutations in all four genes have been shown to cause defective production of ROS in innate immune cells resulting in impaired defense against pathogens (190). Production of ROS has been identified as a common intermediate step induced by different inflammasome activators (e.g., ATP, asbestos, silica) and inhibition of ROS generation has been shown to block NLRP3 inflammasome activation (5, 193, 194). Based on these findings defective ROS production might disturb inflammasome activity, however CGD patients show an inflammatory phenotype associated with increased IL-1β release upon TLR stimulation (78, 93). As a potential mechanistic link, De Luca et al. demonstrated that peripheral blood-derived macrophages from NADPH oxidase-deficient mice and CGD patients exhibited defective autophagy resulting in increased IL-1β release (78). Correspondingly, treatment with Anakinra has been shown to enhance a rapid and sustained amelioration of colitis in CGD patients (78).

Other immune defects associated with VEO-IBD and altered inflammasome activity

Many inborn errors of immunity are known to present with VEO-IBD, which might be a consequence of the complex interplay between the microbial flora and the immune system at the intestinal barrier. For example, phosphatase and tensin homolog (PTEN) regulates phosphoinositide 3-kinase (PI3K) signaling by dephosphorylating $PI(3,4,5)P_3$ and loss-of-function mutations in *PTEN* have been shown to cause autoimmunity or immunodeficiency associated with IBD (195–197). PTEN has been also shown to interact with NLRP3 and KO of PTEN resulted in reduced NLRP3 inflammasome activation after TLR stimulation (106). In detail, PTEN was shown to remove inhibitory phosphorylation from NLRP3 at position Y32, T193, and T195, which enables interaction of NLRP3 with ASC and subsequent oligomerization allowing enhanced inflammasome activation (106). Although data from mouse studies show inflammasome dysregulation in PTEN deficiency, a role of inflammasome activation in human patients with *PTEN* mutations remains to be demonstrated.

The Bruton tyrosine kinase (BTK) is important for B cell receptor (BCR) signaling as well as B cell development and mutations in *BTK* are the most common cause for hypogammaglobulinemia (198–202). Besides its role for B cell development and function, BTK was also shown to interact with NLRP3 and modulate phosphorylation of NLRP3 in myeloid cells (90, 91, 203). Of note, *Btk* KO mice develop severe TNBS-induced colitis, which can be improved by IL-1β blockade indicating a central role of inflammasome activation in BTK-dependent colitis development (91). However, the consequence of BTK activity on human NLRP3 inflammasome activity remains controversial, as reports have shown either increased or decreased NLRP3 inflammasome activation in murine *Btk* KO cells and cells from patients with BTK deficiency (90, 91).

Signal transducer and activator of transcription 1 (STAT1) is a critical signaling molecule in interferon (IFN) responses and STAT1 deficiency causes Mendelian susceptibility to mycobacterial disease associated with severe infections (204, 205). In addition, dominant gain-of-function mutations in STAT1 have been shown to cause a severe immune deficiency associated with polyendocrinopathy and enteropathy (206). Interestingly, STAT1 is also an essential mediator of type I

IFN signaling, which can inhibit NLRP1 and NLRP3 inflammasomes (207, 208). Correspondingly, alterations in STAT1 activity and subsequently changed type I IFN responses might predispose patients to dysregulated inflammasome activity upon challenge with pathogens, which still needs to be shown in IBD patients.

Mutations in A disintegrin and metalloprotease 17 (ADAM17) can cause VEO-IBD associated with skin inflammation and susceptibility to gastrointestinal and skin infections (209). ADAM17 has been shown to cleave the pro-inflammatory cytokine TNF-α, which is produced as membrane-bound precursor after activation (210–212). In line, PBMCs from patients with ADAM17 deficiency produce reduced amounts of TNF-α upon LPS stimulation (209). TNF-α-mediated activation of NF-κB signaling has been shown to induce expression of NLRP3 inflammasome components (e.g., NLRP3, IL-1β, and IL-18) and modulate pyrin inflammasome activity (210, 213, 214). In line, targeting TNF-α in a mouse model of autoinflammation caused by NLRP3 mutations was shown to ameliorate symptoms (213). Thus, it is tempting to speculate that failure to produce mature TNF-α in ADAM17 deficiency might also result in disturbed inflammasome activation.

Conclusion

Several monogenic VEO-IBD defects have been linked to dysregulated inflammasome activity demonstrating the central role of inflammasomes in intestinal homeostasis. As perturbation of inflammasomes can be caused by various genetic entities, studies on monogenic VEO-IBD have highlighted that inflammasomes are controlled by complex regulatory networks and represent a critical common path of human intestinal inflammation. Therefore, targeting inflammasomes and regulatory molecules might be attractive strategies for the treatment of IBD patients. Further studies on the underlying mechanisms in monogenic IBD as disease model will shed light on inflammasome biology and help to identify potential therapeutic targets for rare and common IBD.

Author contributions

DI and DK wrote the manuscript and prepared the figures. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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