Journal of Molecular Medicine (2024) 102:787–799
https://doi.org/10.1007/s00109-024-02451-7

REVIEW

Role and molecular mechanism of NOD2 in chronic non-communicable diseases

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Received: 11 September 2023 / Revised: 23 April 2024 / Accepted: 25 April 2024 / Published online: 14 May 2024

Abstract

Nucleotide-binding oligomerization domain containing 2 (NOD2), located in the cell cytoplasm, is a pattern recognition receptor belonging to the innate immune receptor family. It mediates the innate immune response by identifying conserved sequences in bacterial peptide glycans and plays an essential role in maintaining immune system homeostasis. Gene mutations of NOD2 lead to the development of autoimmune diseases such as Crohn's disease and Blau syndrome. Recently, NOD2 has been shown to be associated with the pathogenesis of diabetes, cardiac-cerebral diseases, and cancers. However, the function of NOD2 in these non-communicable diseases (CNCDs) is not well summarized in reviews. Our report mainly discusses the primary function and molecular mechanism of NOD2 as well as its potential clinical significance in CNCDs.

Keywords NOD2 · Innate immunity · Peptide glycans · Chronic non-communicable diseases (CNCDs)

Introduction

Innate immune response serves as the first-line immunological defense, in which innate immune receptors identify pathogen-associated molecular patterns (PAMPs) and rapidly activate the downstream signaling pathway to eliminate pathogens and infected cells. Remarkably, nucleotide-binding oligomerization domain containing 2 (NOD2), a well-known and initially designated innate immune receptor in nucleotide binding oligomerization domain-like receptors (NLRs) family, also functions as a pattern recognition receptor (PRR) that recognizes PAMPs and endogenous substances generated by damaged tissues in innate immune system [1]. The structural domain of NOD2 is composed of a C-terminal leucine-rich repeat (LRR) domain, a central nucleotide-binding domain (NBD), and two N-terminal caspase recruitment domains (CARD), compared to NOD1, which only has one CARD (Fig. 1). NOD2 is an intracellular protein localized in the cytoplasm and widely expressed in immune cells like macrophage, monocyte, and microglia. It is also present in endothelial, skeletal muscle, and cancer cells, as well as decidual cells, which is vital for pregnancy maintenance [2] (Fig. 2).

Muramyl dipeptide (MDP), the component structure of Gram-negative and Gram-positive bacteria, is the specific exogenous ligand of NOD2 and triggers the signaling activities mediated by NOD2 as an exogenous molecule [3]. NOD2 senses MDP via the LRR domain, recruits receptor-interacting serine/threonine-protein kinase 2 (RIP2), and mediates transcriptional activation of the nuclear factor kappa B (NF-κB) family, leading to the release of inflammatory cytokines [4]. Other signaling pathways such as mitogen-activated protein kinase (MAPK) signaling, autophagy activation via interaction with autophagy-related protein 16-1 (ATG16L1), and type I interferon (IFN) signaling are also activated by NOD2 (Fig. 3). Apart from PAMPs in the innate immune response, the intrinsic substances, known as the damage-associated molecular patterns (DAMPs), are suspected to be endogenous pathogenic factors in chronic non-infectious inflammatory diseases. DAMPs, acting as endogenous ligands, activate NOD2 by binding to different molecules in three inherent domains, thereby positively or

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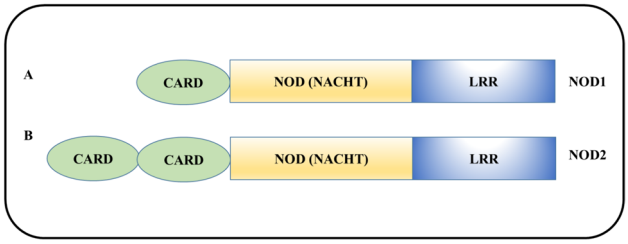

Fig. 1 Domain structures of NOD1 and NOD2. **A** NOD1 structure. **B** NOD2 structure. NACHT (NAIP (neuronal apoptosis inhibitor protein)), C2TA (MHC class 2 transcription activator), HET-E (incompatibility locus protein from *Podospora anserina*) and TP1 (telomerase-associated protein), CARD (caspase recruitment domain), LRR (leucine-rich repeat), and NOD (nucleotide-binding oligomerization domain containing)

negatively triggering the NOD2 downstream signaling pathways [5] (Table 1). Nonetheless, an abnormal innate immune response causes damage to tissues and organs. For instance, gene mutations of NOD2 can lead to Crohn's disease (CD), Blau syndrome asthma, and other immune-related inflammatory diseases [6, 7]. Therefore, NOD2 is a crucial gene associated with many inflammatory disorders. Previous reviews have mainly focused on the function of NOD2 in infectious diseases. However, perspectives on the role of NOD2 in chronic non-communicable diseases (CNCDs) remain to be systematically elaborated.

CNCDs, which primarily include cardiovascular disorders, neuropsychiatric diseases, diabetes, cancer, and obesity, are the leading cause of poor health, disability, and death with expensive and long treatment [8]. Due to its complex pathogenesis and high healthcare expenditures, it has attracted increasing attention from researchers and government managers worldwide. To date, it has been reported that numerous factors may be associated with CNCDs, including chronic innate inflammation [9]. NOD2 has also been demonstrated to be involved in the pathological process of cardiovascular diseases like atherosclerosis [1]. Hence, in this review, we have described the opinion on functions and

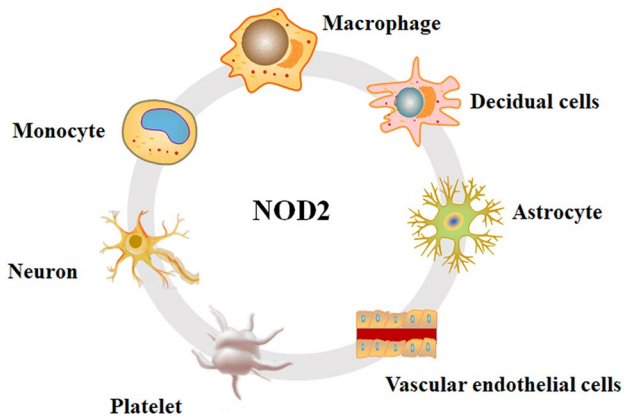

Fig. 2 NOD2 is expressed in different types of cells

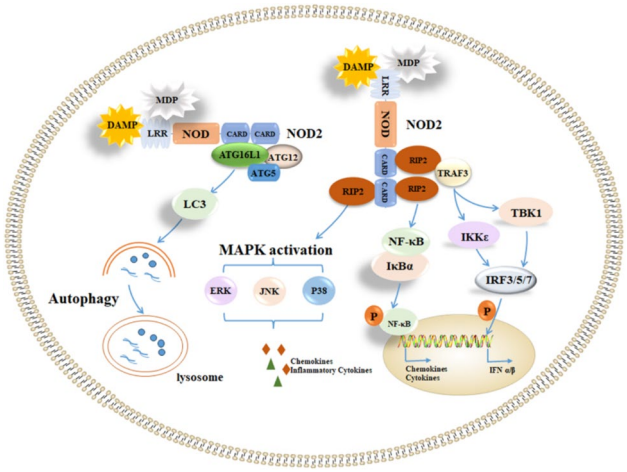

Fig. 3 Signaling pathways mediated by NOD2. NOD2 mediates NF-κB, MAPK, and IFN signaling pathways, as well as the autophagy activation. CARD (caspase recruitment domain), LRR (leucine-rich repeat), NOD (nucleotide-binding oligomerization domain containing), ATG16L1 (autophagy-related protein 16-1), LC3 (light chain 3), RIP2 (receptor-interacting serine/threonine-protein kinase 2), NF-κB (nuclear factor kappa B), DAMPs (damage-associated molecular patterns), MAPK (mitogen-activated protein kinase), IFN (type I interferon), IκBα (NF-κB inhibitor α), IKK (inhibitor of NF-κB), IRF (interferon response factor), ERK (extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinases), TRAF3 (TNF receptor-associated factor 3), and TBK1 (tank-binding-kinase 1)

molecular mechanisms of NOD2 in CNCDs, in order to provide new investigation for the highlighted areas.

NOD2 in inflammatory bowel diseases

Inflammatory bowel diseases (IBD), including ulcerative colitis and CD, are chronic, lifelong, and relapsing disorders of the gastrointestinal tract. Inflammation of CD occurs throughout the gastrointestinal tract, in contrast to ulcerative colitis which restrict inflammation to the colon. So far, IBD can only be alleviated with medication, not cured [25]. Although the etiology and pathophysiology of IBD are not yet completely understood, a number of factors, including genetic, epigenetic, environmental, microbiota, and immune system dysregulation, are implicated [26]. NOD2 is the first identified and well-documented gene in the 200 genetic risk loci associated with IBD [25]. A frameshift variant and two missense variants located in the leucine-rich repeat domain of NOD2 (Gly908Arg, Leu1007fsinsC, and Arg702Trp) have been shown to predominately increase susceptibility to CD development instead of ulcerative colitis [27]. Regardless of the homozygous or compound heterozygous types of NOD2 variants in individuals, they are apparently associated with a higher likelihood of developing CD than normal NOD2 gene type [28]. The incidence of CD is only

Table 1 Common endogenous interaction partners of NOD2

Molecule	Interaction domain	Effect	Reference
ATG16L1	CARD	Inducing autophagy	Homer et al. [10]
CARD8	NOD	Suppressing the NF-κB signaling	von Kampen et al. [11]
CARD9	NOD	Triggering the p38 signal pathway	Parkhouse et al. [12]
Caspase-1	CARD	Improving IL-1β release	Babamale and Chen [13]
FRMPD2	LRR	Activating NF-κB signaling pathway	Lipinski et al. [14]
NLRP1	CARD	Improving caspase-1-dependent IL-1β release	Hsu et al. [15]
NLRP3	CARD	Requirement of IL-1β processing	Wagner et al. [16]
NLRP12	CARD	Inhibiting the proteasome Degradation of NOD2	Normand et al. [17]
RIP2	CARD	Mediating the NF-κB signaling pathway	Maharana et al. [18]
HSP70		Enhancing the NF-κB signaling pathway	Mohanan and Grimes [19]
HSP90		Enhancing the NF-κB signaling pathway	Lee et al. [20]
PP2A		Inhibiting NOD2-dependent autophagy by PP2A phosphatase activity	Homer et al. [21]
TRIM22	NOD	Involved in the K63-linked polyubiquitination of NOD2	Zhang et al. [22]
TRIM27	NOD	Promoting NOD2 degradation via RIPK2-dependent K48 polyubiquitination	Zurek et al. [23]
TRAF4	Amino acids 260–301 of NOD2	Restricting NOD2-mediated NF-κB activation	Marinis et al. [24]

ATG16L1 autophagy-related protein 16-1, *CARD* caspase recruitment domain, *FRMPD2* FERM and PDZ domain-containing 2, *NLRP* nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3, *RIP2* receptor-interacting serine/threonine-protein kinase 2, *HSP* heat shock protein, *PP2A* phosphoprotein phosphatase-2A, *TRIM* tripartite motif-containing, *TRAF* TNF receptor-associated factor

slightly increased (2- to fourfold) in individuals with only one NOD2 variant, whereas the risk is 15- to 40-fold higher in those who carry two or more NOD2 mutations [29]. As for the three general mutations of NOD2 in CD, the risk of occurrence is much higher for Leu1007fsinsC than for Arg702Trp and Gly908Arg [28]. In addition to the three frequent variants of NOD2 gene in CD patients, pro268Ser, IVS8 + 158, and many other polymorphisms in NOD2 have also been reported to be related to CD [30–33]. Simultaneously, the prevalence of CD resulting from NOD2 mutations may exhibit variation among diverse ethnic groups [34]. A clinical trial that explored the relationship between IBD and NOD2 gene polymorphisms in the Indian population indicated that NOD2 mutations were not related to CD, but two variants (rs2066842 and rs2066843) were weakly associated with UC [35]. Actually, most NOD2 variants in the clinic do not develop CD, and there are many other factors involved in the onset of CD, such as the environment. This is verified by $NOD2^{-/-}$ and Leu1007fsinsC homozygous of NOD2 variant knock-out mice presenting no spontaneous intestinal inflammation [36].

The underlying mechanisms of action of NOD2 in IBD are still unclear. In general, the bacterial peptidoglycan (PGN)-conserved patterns in cytosol are detected by the intracellular pattern recognition receptor NOD2, which then triggers the host immunological response. However, the shortened NOD2 protein lacks its sensitivity to MDP owing to the three prevalent mutations of Leu1007fsinsC, Arg702Trp, and Gly908Arg in the LRR domain. This in turn disrupts the activation of NF-κB signaling pathways and prevents monocytes from triggering the numerous cytokine responses [37]. Concurrently, the modified protein of NOD2 loses the function of transferring to the plasma membrane to recruit ATG16L, which then hinders autophagy and bacterial clearance. Arg702Trp and Gly908Arg, in contrast to Leu1007fsinsC, interfere with MDP recognition by NOD2 without altering the intracellular location of the protein [38]. Additionally, NOD2 plays an important role in regulating the gut microbiota. Studies have shown that there are significant differences in the composition of the intestinal microbiome between $NOD2^{-/-}$ and $NOD2^{+}$ mice, in particular, NOD2-deficient mice tend to experience dysbiosis in the flora microflora of the terminal ileum [39, 40]. Consequently, NOD2 mutations result in low diversity and imbalance in the microbiome, leading to mucosal barrier dysfunction and chronic inflammation in turn, both of which increase susceptibility to developing IBD [41, 42]. Furthermore, Paneth cells localized in the small intestinal crypt are essential for the generation of antimicrobial peptides (AMPs) through secreting anti-bacterial compounds. Nevertheless, mutations of NOD2 in Paneth cells cause insufficient α-defensins in the ileum of CD patients, suppressing the elimination of internalized bacteria [43, 44]. Conversely, the intestinal flora can also influence the pathological process of CD.

Firmicutes-derived DL-endopeptidase decreases in CD patients but shows a negative association with colitis. It has been found to produce NOD2 ligands in the intestine, and its deficiency can aggravate CD pathogenesis through NOD2 signaling [45]. Different from the typical three gene mutations in NOD2, a new research found that patients with the NOD2 R444C variant in the NACHT domain are more sensitive to bacterial PGN fragments. This variant also readily activated NF-κB and proinflammatory cytokine production through its interaction with ZDHHC5 which can restrain S-palmitoylation-regulated autophagic degradation of NOD2 [46]. Therefore, the NOD2-R444C variant may be a potential target IBD therapy in the future.

NOD2 in cardiovascular diseases

Cardiovascular diseases (CVDs), one of the most prevalent CNCDs globally, have lead to an increase in morbidity and mortality, as well as overall healthcare expenses [47]. Atherosclerosis, a chronic disease of the arteries characterized by high blood cholesterol levels and vascular inflammation, is considered a major cause of CVDs. NOD2 is involved in the development and pathological process of atherosclerosis by exacerbating vascular inflammation and enhancing the area of lipid accumulation and necrosis in mice [48]. Liu et al. found that NOD2 is abundantly expressed in atherosclerosis plaques, regulating the gene and protein expression of COX-2 and prostaglandin E2 (PGE2) in the metabolism of arachidonic acid [1]. Besides, NOD2 induces the p38 signaling pathway in MAPK upon stimulation by IL-1β or tumor necrosis factor alpha (TNF-α) in macrophages, which represent a significant cell population of the innate immune system in atherosclerotic lesions. To date, there is one report showing that plaque lipid deposition and inflammatory infiltration in atherosclerotic plaques are associated with NOD2, the deficiency of which disrupts intestinal cholesterol levels, microbiota composition, and oxLDL uptake by macrophages [49]. Kwon et al. elucidated that NOD2 is expressed in vascular smooth muscle cells (VSMCs) and involved in vascular homeostasis through regulating the proliferation, migration, and CHOP (C/EBP homologous protein) expression of VSMCs, leading to the formation of advanced atherosclerotic lesions [50]. Additionally, endothelial cells which are the primary component of the heart and the vascular system have many pivotal functions in CVDs and serve as a crucial link between the cardiovascular system and the immune system. Endothelial dysfunction contributes to the progression of diverse cardiovascular events, especially the hypertension, atherosclerosis, and myocardial ischemia [51, 52]. Although NOD2 is weakly expressed in human endothelial cells, it is rapidly overexpressed and migrates to the cytomembrane from the cytoplasm upon stimulation by MDP, then inducing NF-κB dependent transcriptional activity [53]. Our previous studies also have demonstrated that NOD2 triggers oxidative stress through the COX-2/NOX4/ROS pathway in MDP-treated human umbilical vein endothelial cells and promotes ET-1 and VCAM-1 gene expression [54, 55].

Although multiple studies have confirmed that NOD2 activation is related to the pathogenesis of heart diseases, there may be different opinions about the role of NOD2 in the myocardium. Liu et al. reported that myocardial ischemia reperfusion (I/R) damage is exacerbated by NOD2-mediated cardiomyocyte apoptosis and inflammation through JNK, p38 MAPK, and NF-κB signaling pathways [56]. NOD2 deficiency ameliorates not only the cardiac damage caused by myocardial infarction [57] but also the blood reperfusion injury via reduction of proinflammatory mediator levels and inflammatory cell infiltration after myocardial I/R [58]. However, along with research development, it has emerged different reports on NOD2 function in the heart. Zong et al. indicated that NOD2 could protect against pressure overload-induced heart disease by attenuating cardiac hypertrophy and fibrosis in the TLR4, MAPKs, NF-κB, and TGF-β/Smad signaling pathways [59]. Therefore, more research on the mechanism of NOD2 in myocardial disease should be investigated based on diverse opinions (Fig. 4).

With respect to gene polymorphism, it has been reported that the Crohn's disease-associated NOD2/CARD15 polymorphisms like Arg702Trp, Gly908Arg, and Leu1007fsinsC are not involved in the risk of cardiovascular disease in the Danish general population [60]. However, NOD2 polymorphisms may influence the occurrence and development of coronary heart disease in the Caucasian population [61]. The Leu1007fsinsC polymorphism of NOD2 increases the risk of coronary atherosclerosis and instability of coronary artery plaque, while mutations in the GLY908ARG region have a protective effect on coronary artery stenosis [61]. Based on these reports of gene polymorphism in CVDs, more fundamental experimental evidence is still required.

Role of NOD2 in neurological disease

Mutations of NOD2 (Arg702Trp and Gly908Arg) have been linked to a greater susceptibility to Guillain-Barre syndrome, an autoimmune disorder that damages the peripheral nervous system [62]. Stroke and neurodegenerative diseases are definitely essential for CNCDs. Reperfusion after cerebral ischemic stroke easily leads to more severe damage for a sudden blood supply recovery. Typically, NOD2 is expressed in inflammatory cells, like macrophages, dendritic cells, microglia, and astrocytes in the brain [63]. Currently, it has been shown that NOD2 expression is obviously increased in primary neurons of cerebral ischemia reperfusion (I/R) injury model [64]. Our research team found that NOD2 aggravates

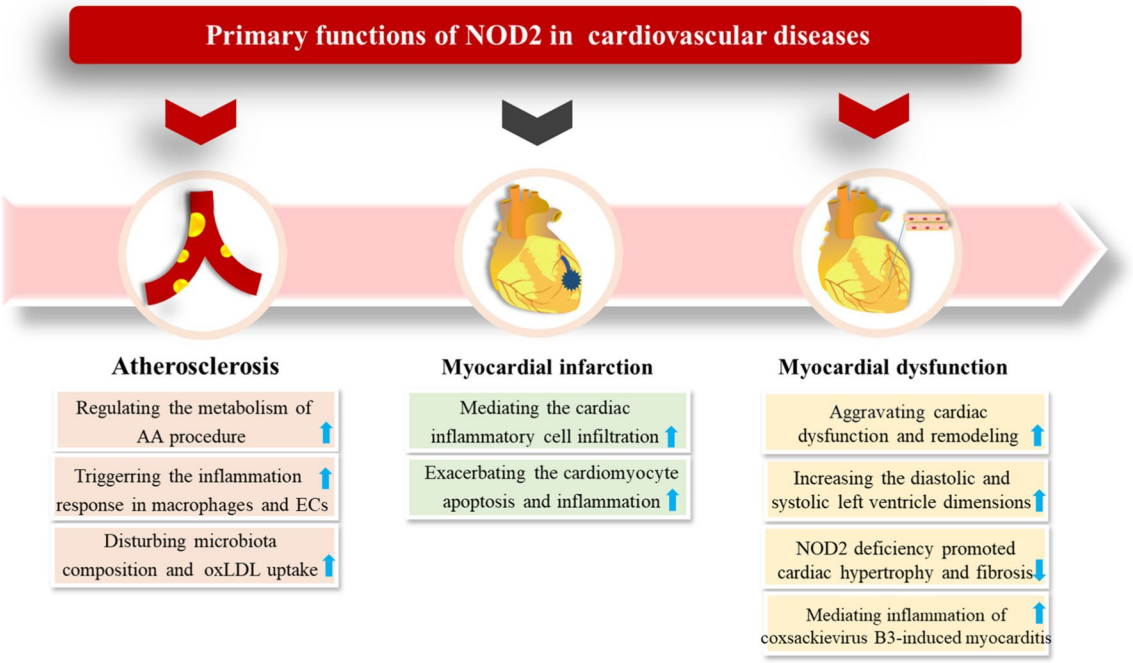

Fig. 4 Essential role of NOD2 in cardiovascular diseases (AA: arachidonic acid; ECs: endothelial cells)

the development of cerebral I/R by triggering the TRAF6/NF-κB/COX-2/MMP-9 inflammatory signaling pathway [65]. It also activates NOX2-derived oxidative stress and upregulates the levels of proinflammatory cytokines, including IL-6, IL-1β, and TNF-α after cerebral I/R injury [66]. In terms of neurodegenerative disorders, Parkinson's and Alzheimer's disease are also treated long-term, which is associated with high costs and a lot of attention. Several publications suggest that NOD2 gene variants may correlate with Parkinson's susceptibility, as exemplified by the polymorphism of c.2 857A> G p.K953E, P268S in the Chinese Han population [67]. Nonetheless, Appenzeller et al. discovered 9 SNPs of the NOD2 gene covering common variations throughout the whole sequence and announced that the NOD2 genetic mutation might not show the high susceptibility of Parkinson's disease in German patients [68]. Whether the difference is due to racial gene diversity or the other factors has not yet been identified, further research is needed. From the perspective of Parkinson's mechanism, the research is poorly implemented. Cheng et al. demonstrated that overexpression of NOD2 accelerates the pathogenesis of Parkinson's disease in mice via NOX2-mediated oxidative stress [69]. Singh et al. indicated that NOD2 acts as a substrate of parkin, which is an E3 ubiquitin ligase and a Parkinson's disease-related gene, and is degraded in a proteasome-dependent manner by parkin regulation [70]. NOD2 is involved in parkin-modulated endoplasmic reticulum (ER) stress and inflammation in astrocytes to regulate their neurotropic functions [71]. Whereas, NOD2 may be involved in the neuroinflammation related to Alzheimer's disease and benefit disease progression, as evidenced by research that showed MDP, the NOD2 receptor ligand, strongly delays cognitive decline in both sexes and protects the blood-brain barrier in a NOD2-dependent manner [72, 73]. Inflammation caused by the alteration of intestinal flora accelerates the pathological process of Alzheimer's disease, and NOD2 is a critical factor in maintaining gut microbiota homeostasis [74]. Hence, we speculate that NOD2 may play a more vital role in Alzheimer's disease. However, further studies are required to reveal the definitive and potential functions of NOD2 in neurodegenerative diseases.

NOD2 in diabetes

Along with living standard improvements, the diabetic population has skyrocketed all over the world, generating multiple complications from hyperglycemia. A multitude of studies have examined the connection between diabetes and variations in the NOD2 gene. An investigation shows that both metabolic syndrome and insulin resistance have no relationship with the NOD2 genetic polymorphism (rs2066842) in 998 Canadian population aged 20 to 29 years [75]. Consistent with this report, Ozbayer et al. described that no association could be found between the rs2066847 variant of NOD2 and the risk of type 2 diabetes mellitus (T2DM) in patients of Turkish origin [76]. On the other hand, mechanism study data have confirmed the crucial role of NOD2 in the pathological

process of diabetes. The research provides a new perspective on the unconventional role of NOD2 in the development of human metabolic diseases. It points out that glucose might be the novel stimulatory ligand of NOD2 for potential excess nutrients [77]. The NOD2 receptor is directly activated by metabolic signals such as fatty acids and glucose within cells and tissues. Following overexpression and activation of NOD2, its downstream inflammatory signals are triggered and interferes with other metabolic pathways necessary to preserve metabolic balance, including glucose uptake and insulin sensitivity [78]. The mRNA level of NOD2 is upregulated in monocytes of T2DM patients with insulin resistance or poor glycemic control [79]. NOD2 has also been confirmed to be more sensitive to T1DM development, acts as a mediator in gut microbiota alterations, and subsequently regulates the innate and adaptive immune inflammatory response [39]. Moreover, diabetes increases circulating microbial products due to disrupting the imbalance of the gut microbiome and improving intestinal permeability [80, 81]. Meanwhile, NOD2 originally regulates intestinal homeostasis by restricting bacterial translocation and transcellular permeability [7]. These studies all showed that there is a strong link between NOD2 and diabetes.

Considering the chronic complications of diabetic mellitus, Shen et al. found that NOD2 exacerbates the process of diabetes-induced cardiomyocyte apoptosis and cardiac fibrosis [82]. NOD2 silencing significantly upregulates B cell CLL/lymphoma-2 (BCL-2) expression in diabetic mice and inhibits TNF-α, IL-1β, and IL-6 levels in cardiomyocytes [82]. NOD2 is likewise found to be overexpressed in the kidney of diabetic patients. Mechanismly, renal injury is ameliorated in diabetic mice after NOD2 gene knocking down. NOD2 deletion decreases mesangial expansion, podocyte injury, and typical proinflammatory cytokines in diabetic mice [77]. Another research showed that NOD2 contributes to the pathogenesis of diabetic nephropathy via activation of MEK/ERK in glomerular vascular endothelial cells (GEnCs) [83]. On the basis of numerous evidence, NOD2 definitely accelerates the development and pathological process of diabetes. Conversely, one study suggested that NOD2 could benefit type 2 diabetes in the murine model via balancing intestinal meta inflammation [84]. Thus, the role and mechanism of NOD2 in diabetes still need to be further investigated.

NOD2 activation in cancer

With the advancement of medical technology, cancer has already been classified as a chronic disease by the WHO [85]. Numerous studies implicate a significant correlation between NOD2 gene polymorphisms and different types of cancer, including hematomas or solid tumors [86–89]. Significant progress has been made in studying the mechanisms of NOD2-mediated signal pathways in diverse cancers (Table 2), especially the colorectal carcinoma [22, 90–96]. NOD2 deletion, which is closely related to colitis, controls the regulation of inflammatory signaling pathways and ultimately increases the risk of colorectal cancer [91]. This is consistent with the conclusion of Udden et al. who found NOD2-mediated protection against colorectal tumorigenesis via suppressing TLR-mediated activation of NF-κB pathways [90]. Beside its role in the inflammatory response, NOD2 potentially protects against colorectal cancer by maintaining intestinal homeostasis. A study has shown that knocking out the NOD2 gene breaks the balance of gut microbiota, enhances intestinal pathology, and aggravates colorectal tumor growth [91]. Given that NOD2 benefits intestinal tumors through NF-κB inhibition, Zhang et al. showed that NOD2 directly binds to TRIM22, reduces the phosphorylation of NF-κB and I-κBα, and suppresses NF-κB activity in endometrial cancer [22]. Nevertheless, the effects of NOD2 reported in studies may be inconsistent even within the same type of cancer. Regarding liver cancer, NOD2 has been indicated as both a tumor suppressor and a chemotherapeutic regulator in hepatocellular carcinoma (HCC) cells by directly activating the AMPK pathway [92]. Aside from the classical NF-κB, JAK2/STAT3, and MAPK signaling pathways, NOD2 has also been found to mediate a nucleus autophagy pathway to promote hepatocarcinogenesis. It transports into the nucleus and binds directly to lamin A/C to accelerate its degradation, thereby impairing the repair of damaged DNA and promoting genomic instability [93]. NOD2 is also overexpressed in squamous cervical cancer and contributes to carcinogenesis by activating NF-κB and ERK signaling pathways as well as increasing IL-8 secretion [94]. Furthermore, according to proteome profiling analysis, NOD2 may modulate tumorigenesis of triple-negative breast cancer by disrupting proliferation through MAPK, TNF, and p53 pathways [95]. Despite extensive research on the involvement of NOD2 in tumor initiation and development, the benefit or deleterious role of NOD2 in cancer is still elusive.

Discussion

CNCDs represent the greatest health challenge worldwide as they have a long-lasting condition and are inextricably linked to the cause of premature deaths [97]. Thereafter, they bring a large economic and therapeutic burden on the family and society in China [98]. For prophylaxis and treatment, it is extremely meaningful to gain the pathogenesis insights of chronic illnesses. Chronic illnesses are always accompanied by chronic inflammation. And NOD2 receptor plays a fundamental role in the host immune response via mediating various inflammatory signaling pathways. Therefore, understanding the molecular mechanism of NOD2 in CNCDs is significant for the development of effective therapeutic targets in the long-term diseases.

Table 2 Summary of reports on the functions of NOD2 in cancer

Authors	Types of cancer	Research topic	Molecule mechanism	Effect
Udden et al. [90]	Colorectal cancer	NOD2 suppresses colorectal tumorigenesis	NOD2 downregulates TLR-mediated NF-κB and MAPK signalings, as well as the IRF4, suppressing inflammation, and tumorigenesis in colon.	Positive
Couturier-Maillard et al. [91]	Colorectal cancer	NOD2 protects the balance of intestinal bacterial communities	NOD2 deficiency breaks the intestinal microecology, increases intestinal pathology, and aggravates transmissible colitis and colorectal tumor growth in mice	Positive
Ma et al. [92]	Liver cancer	NOD2 functions as a tumor inhibitor and a chemotherapeutic regulator in HCC cells	NOD2 restricts hepatocarcinogenesis and improves the sensitivity of HCC cells to chemotherapeutic drugs through AMPK pathway and subsequently suppressing the mTORC1 pathway	Positive
Zhou et al. [93]	Liver cancer	NOD2 promotes hepatocarcinogenesis	NOD2 is overexpressed and activated in HCC. It aggravates liver carcinogenesis in a RIP2-dependent manner and interaction with lamin A/C to promote its degradation by nuclear autophagy	Negative
Zhang et al. [94]	Cervical cancer	Upregulation of NOD2 exacerbates cancer progression	NOD2 enhances the tumorigenic and metastatic potential of CSCC cells through NF-κB and ERK signaling pathways in human squamous cervical cancer	Negative
Velloso et al. [95]	Breast cancer	NOD2 overexpresses in the proteome profile and contributes to triple-negative breast cancer	NOD2 overexpression interferes with immune signaling pathways involving NF-κB and MAPK, leading to decreased proliferation through modulation of TNF and p53 pathways	Positive
Dong et al. [96]	Lung carcinoma	NOD2 antagonist is a potential adjunct in treating non-small-cell lung cancer	NOD2 decreases the chemotherapeutic sensitivity of tumor cells to paclitaxel and disturbs the formation of an inflammatory tumor microenvironment to facilitate tumor metastasis	Negative
Zhang et al. [22]	Endometrial cancer	The NOD2/NF-κB signaling pathway is involved in TRIM22-inhibited endometrial cancer progression	TRIM22 upregulates and directly interacts with NOD2 to inhibit endometrial cancer proliferation and metastasis	Positive

NOD nucleotide-binding oligomerization domain containing, TLR Toll-like receptor, MAPK mitogen-activated protein kinase, *IRF4* interferon-regulatory factor, AMPK AMP-activated protein kinase, *mTORC1* mechanistic target of rapamycin complex 1, *HCC* hepatocellular carcinoma, *CSCC* cervical squamous cell carcinoma, *NF-κB* nuclear factor kappa B, RIP2 receptor-interacting serine/threonine-protein kinase 2, *ERK* extracellular signal-regulated kinase, TNF tumor necrosis factor, *TRIM22* tripartite motif-containing 22

Table 3 NOD2 genetic mutations which may lead to CNCDs

Diseases	Genetic mutations of NOD2
Crohn's disease	L1007fsinsC [27], R702W [27], G908R [27], R311W [31], S431L [31], R703C [31], N852S [31], M863 [31], R138Q [32], R38M [32], L248R [32], W355stop [32], L550V [32], N825K [32], L1007P [32], R1019stop [32], R138Q [33], W157R [33], N289S [33], D291N [33], L348V [33], 558delLG [33], A612T [33], A612V [33], R713C [33], E843K231 [33]
Cardiovascular diseases	L1007fsins [61], G908R [61]
Cancer	L1007fsins [86], R702W [86], G908R [86], P268S [85], rs7205423 [87]
Parkinson	P268S [64], K953E [64]
Guillain-Barré syndrome	R702W [62], G908R [62]

Genetically, NOD2 mutations are associated with an increased susceptibility to considerable CNCDs (Table 3). In mechanism, it mediates the production of various proinflammatory cytokines, oxidative stress, and apoptosis through MAPK and the canonical NF-κB signaling pathway, which depends on the scaffolding kinase RIP2 [99, 100]. Nowadays, it is recognized as an autophagy inducer that straightly initiates autophagy by recruiting the host ATG16L1 [101]. Particularly, the upstream event of NOD2 activation in CNCDs remains to be discussed. NOD2 is a special detector for the stimulation of PAMPs and DAMPs in innate immune response. Actually, there is a report suggesting that the peptidoglycan component, which abundantly exists in vulnerable plaques of atherosclerotic, is in accordance with the DNA phylotypes of the gut microbiota [48]. The gut microbiota does contribute to the development of CVDs such as atherosclerosis, hypertension, and myocardial infarction via induction of an inflammatory response, or regulation of host lipid metabolism [102]. It functions as a "metabolic organ" to modulate glucose and protein metabolism [103]. Further, diabetes increases the possibility of microbial products entering the circulation system, then improving intestinal permeability [77]. Therefore, we speculate that the peptidoglycan component that activates NOD2 in CNDCs may originate from the intestinal flora. In turn, CNDCs perhaps increase the probability of bacteria transferring into the circulatory system. Parallelly, bacteria belonging to the oral cavity are also observed in the atherosclerotic plaques [102], indicating that periodontal disease or poor dental hygiene increases the occurrence of CVDs [104]. Lately, metabolic diseases that excess nutrients like glucose and fatty acids are supposed to be the endogenous ligands as DAMPs to stimulate NOD2 [40]. Moreover, Dong et al. surmised that DAMPs generated from the chemotherapy straightly activated NOD2-mediated inflammatory signaling pathways in anti-tumor treatment [96].

As our advanced understanding of NOD2 in CNCDs, it has emerged as a potential therapeutic drug target for diseases. Daillere et al. showed that NOD2-mediated inflammatory response reduces the anticancer efficacy of cyclophosphamide and inhibits the cancer immunosurveillance, suggesting that NOD2 may be recognized as a new immune checkpoint [105]. In addition, NOD2 disrupts the TME remodeling following paclitaxel chemotherapy by promoting the production of inflammatory factors, chemokines, and the recruitment of myeloid suppressor cells (MDSCs). This further impairs the therapeutic effect of chemotherapy drugs and then accelerates tumor invasion and metastasis [96]. Dong et al. also proposed a NOD2 antagonist as an antitumor drug to inhibit tumor growth and metastasis in combination with chemotherapeutic agents, providing a new idea and strategy for tumor immunotherapy. Presently, Zhong et al. found that NOD2 is expressed in platelets [106]. Activation of NOD2 releases numerous inflammatory factors to activate platelets through the MAPK pathway. The expression of P2Y12, which plays a central role in the process of platelet agglutination, is upregulated by NOD2 to promote platelet aggregation [106]. This mechanism further explains the essential role of NOD2 in cardiovascular and cerebrovascular disorders, as well as other CNCDs, in which NOD2 may serve as a new target for antiplatelet drugs.

Beyond that, NOD1, another earliest identified receptor in NLRs in the intracellular cytosol, has similar domains and functions to NOD2 in maintaining immune homeostasis. Compared to the NOD2 structure, it is encoded by CARD4 genes and includes only a single CARD domain. NOD1 regularly serves as a sensor for Gram-negative bacteria and specifically distinguishes diaminopimelic acid, a specific muropeptide (G-D-glutamyl-meso-diaminopimelic acid, iE-DAP) derived from bacterial peptidoglycans [107], while NOD2 responds to MDP from all bacterial peptidoglycans [3]. Although NOD1 has a ubiquitous distribution, NOD2 is predominantly expressed in innate immune cells. Due to the functional similarities between NOD1 and NOD2, NOD1 generally recognizes the iE-DAP and binds this ligand directly to the LRR domain. Subsequently, it also undertakes oligomerization and recruits the downstream interacting protein RIP2 to activate the NF-κB and MAPK pathways, leading to the secretion of proinflammatory cytokines and chemokines. Similar in function to

NOD2, NOD1 is involved in the occurence and progression of inflammatory disorders, such as Crohn's disease and atherosclerosis [49, 108]. In contrary to NOD2, previous studies have not found an association between NOD1 gene mutations and susceptibility to IBD. In terms of mechanisms, NOD1 is extensively expressed by a variety of cell types, including intestinal epithelial cells, and is important for regulating the balance of normal gut microbiota and intestinal pathogens in cells. When NOD1 is stimulated by pathogenic bacteria, it induces the production of inflammatory chemokines and initiates autophagy in both epithelial cells and murine macrophages [109]. NOD1 knock-out mice exhibit aggravating intestinal inflammation compared to wild-type mice, in part because of rising intestinal permeability [110]. NOD1 is also expressed in heart, fibroblasts, and cardiomyocytes and has been found to be involved in cardiac function, including atherosclerosis, dilated cardiomyopathy, and I/R injury. iE-DAP or DAMP stimulation triggers the NOD1-mediated inflammatory response that impairs cardiomyocytes and vascular endothelial cells, hastening cardiac failure. NOD1 activation also interferes with Ca^{2+} homeostasis through the NF-κB pathway in cardiomyocytes, which further contributes to the development of heart disorders [111]. In light of NOD1 in diabetes, it not only promotes metabolic inflammation but also influences regular endocrine function, both of which can lead to insulin resistance [112, 113]. Additionally, the role of NOD1 in different types of cancer is controversial. It is far from being elucidated that whether NOD1 activation protects the host from these invasive microorganisms or it indeed promotes carcinogenesis. Plenty of research indicate that NOD1 activation enhances tumor proliferation and migration, as well as metastasis by promoting macrophage M2 polarization and producing an immunosuppressive microenvironment [114, 115]. However, NOD1 knockout mice appear to have a high susceptibility to the inflammation-related colon tumorigenesis [116]. In support of this conclusion, overexpression of NOD1 markedly suppresses tumorigenesis in hepatocellular carcinoma and is consistent with much lower NOD1 expression in tissue. It is said that NOD1 exerts an antitumor effect by inhibiting the SRC-MAPK axis and improving the chemosensitivity of hepatocellular carcinoma cells to chemotherapy agents [117].

To a large extent, NOD1 and NOD2 play comparable roles in chronic diseases and collaborate with each other to maintain immune system balance. However, because of variations in distribution, expression, and binding structure, the concrete mechanisms of NOD1 and NOD2 are distinguished. For instance, there is a close correlation between Crohn's disease and mutations in NOD2, but not in NOD1. Thereby, more studies are required to reveal the exact mechanism of difference between NOD1 and NOD2. Collectively, NOD2 is a fundamental member of the innate immune family and performs as the first line of defense against external invasions. On the contrary, the excessive inflammatory response can cause damage to the body. Unlike previous reports on the role of NOD2 in infectious disorders, we have mainly reviewed the contributions of NOD2 to CNCDs and aim to provide new perspectives on therapeutic target for CNCDs. Although NOD2 activation triggers the specific innate inflammatory or metabolic signaling pathways in CNCDs, the positives and negatives of NOD2 in CNCDs are still controversial. Therefore, further studies on the mechanism of NOD2 need to be explored in the future.

Author contribution Dr. Lingjun Kong designed and performed the review article. Analysis from a clinical perspective was under the guidance of Professor Yahui Zhang. Ms. Yanhua Cao and Yanan He participated in part of the discussion and reviewed the manuscript. All co-authors approve the final version of the manuscript.

Funding This work is supported by the Natural Science Foundation of Shandong Province (ZR2021QH158).

Availability of data and material Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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