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Review article

NALP3 inflammasome activation in protein misfolding diseases

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ABSTRACT

Protein-misfolding diseases, such as Alzheimer's disease, type 2 diabetes, Prion diseases, and Parkinson's disease, are characterized by inflammatory reactions. In all these diseases, IL-1β (Interlukine-1β) has been shown to be an important regulator, and the misfolded proteins are proved to be triggers of the release of IL-1β. Recently, several reports demonstrated that the inflammasome activation is involved in the progress of the misfolded protein diseases, and that the inflammasome can recognize pathogenic proteins leading to the release of IL-1β. In this review, we discuss the role of inflammasome in the pathogenesis of misfolded protein diseases and the potential of inflammasome-targeting therapeutic interventions in the management of these diseases.

Contents

1. Introduction

The accumulation of misfolded proteins can cause diseases, known as protein-misfolding diseases. They have in common abnormal protein conformations leading to an irreversible change into a sticky conformation rich in beta sheets that make the protein molecules interact with each other, with an abnormal tendency to aggregate [3,5,65]. The resulting protein aggregates are organized in a cross-beta structure, with specific tinctorial properties (binding to Congo red and thioflavin S), higher resistance to proteolytic degradation and a fibrillar appearance under electron microscopy (straight, unbranched, 10 nm wide fibrils) [65].

Protein-misfolding diseases can be divided into two groups depending on the localization of protein aggregation. The first group consists of neuropathic diseases, which is characterized by protein aggregation in the central nervous system, and includes Prion diseases, Alzheimer's disease and Parkinson's disease. The second group or non-neurophathic diseases are characterized by protein aggregation in the peripheral tissues.

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At least three models have been proposed to explain the mechanisms through which protein misfolding and aggregation lead to the development of protein misfolding diseases [65]. The loss-of-function model holds that the pathological condition is caused by the loss of normal activity of the protein, which is depleted during misfolding and aggregation. The second and more widely accepted model is gain-of-toxic-activity model, according to which misfolding and aggregation results in the acquisition of a toxic function by the misfolded protein. Several mechanisms have been proposed for the toxic activity of misfolded aggregates, including activation of an apoptotic signaling pathway, recruitment of essential cellular factors, formation of ion channels and the induction of oxidative stress. The third model, the inflammation model, proposes that abnormal protein aggregates act as irritants and cause a chronic inflammatory reaction that leads to cell death [65]. A combination of these mechanisms might be involved in the pathogenesis of some protein-misfolding diseases.

In this review, we focus on the proinflammatory activity of misfolded protein through the review of the role of inflammasome activation in the pathogenesis of four protein-misfolding diseases, namely Prion disease, Alzheimer's disease, Parkinson's disease, and type 2 diabetes.

2. The inflammasome

The inflammasome is a multiprotein complex which is essential for IL-1β secretion and plays an important role in innate immunity [41]. The inflammasome comprises a germline-encoded pattern recognition receptors (PRR), the adaptor molecule apoptosis-associated speck-like protein containing a CARD (caspase activation and recruitment domains, ASC), and the caspase-1 enzyme that cleaves pro-IL-1β. Activation of inflammasome produces active caspase-1, which cleaves pro-IL-1β and pro-IL-18 into IL-1β and IL-18. However, before these proinflammatory cleaving, the mRNA expression of NALPs and IL-1β should be upregulated by specific triggers, such as the stimulation of TLR4 (Toll-like receptor 4) by LPS (lipopolysaccharide), and this step is called priming or signal 1. Following this are the assembling and activation of the inflammasome which is called signal 2 [44].

Up to now, several inflammasomes have been identified, including NALP1, NALP3, AIM2 and IPAF inflammasomes. The NALP1 inflammasome contains a CARD domain which can interact directly with pro-caspase-5 [40] or pro-caspase-1 [16] without recruitment of ASC. However, ASC has been reported to enhance NALP1 mediated caspase-1 activation ex vivo [16]. Unlike NALP1, the NALP3 protein contains a PYD (Pyrin domain) which can interact with ASC. The ASC harbors PYD and CARD domain, after interacting NALP3 via PYD, the CARD domain recruits the CARD of pro-caspase-1, which makes the NALP3 inflammasome (NALP3-ASC-pro-caspase-1) [58]. Similar to NALP1, the IPAF protein only contains a CARD domain which can interact directly with pro-caspase-1 without the recruitment of ASC [54]. All of the three mentioned inflammasomes belong to the NOD-like receptor family (NLR). The AIM2 inflammasome is the first identified non-NLR family member which can form an inflammasome [39,58]. The AIM2 inflammasome can recognize cytosolic DNA via its C-terminal HIN200 domain, furthermore, the AIM2 protein can interact with ASC and mediate caspase-1 activation. Among these inflammasomes, the NALP3 inflammasome is the most-studied, and is involved with a number of diseases such as metabolic disease [12] and inflammatory disease [42,73]. Studies reported that misfolded proteins, such as Aβ (amyloid β) [21], IAPP (islet amyloid polypeptide) [43], prion fibrils [61] and alpha-synuclein [4] can lead to the activation of NALP3 inflammsome (Table 1).

Several studies have focused on the molecular mechanism of inflammasome assembly and activation, especially the mechanism of NALP3 inflammasome activation. The NALP3 inflammasome can recognize a diversity of stimuli and lead to inflammatory responses. Three models have been put forward to explain the mechanisms lying behind NALP3 inflammasome activation [59]. The first model holds that ion fluxes, particularly potassium (K^+) efflux, act as a signal for NALP3 inflammasome activation. Inhibition K^+ efflux by a high concentration of K^+ in the cell culture can abolish NALP3 inflammasome activation in response to most inflammasome activators [25]. It is proposed that ATP stimulates K^+ efflux via purinergic P2X7 receptor, and leads to the decrease of intracellular K^+, which can be sensed by NALP3 [28]. A recent study has suggested that K^+ efflux is the common trigger of NALP3 inflammasome activation by particulate matter [48]. In the second model, the generation of reactive oxygen species (ROS) is believed to play an important role in the inflammasome activation. Almost all NALP3 activators, including particulate matter, increase intracellular ROS production. Moreover, inhibition of ROS with specific scavengers abolishes inflammasome activation in response to a range of NALP3 activators [11]. Another research has revealed that thioredoxin-interacting protein can bind to NALP3 in a ROS-dependent manner, further indicating the crucial role of ROS in inflammasome activation [79]. In the third model, cathepsin B is considered to be a trigger of inflammasome activation. Particulate activators such as Aβ can destabilize lysosomal intact, leading to release of cathepsin B, which can be recognized by NALP3 inflammasome. In addition, the cathepsin B inhibitor CA-074Me could disrupt NALP3 activation induced by silica, MSU (monosodium urate) and Aβ [1,13,21]. However, the function of cathepsin B may be through an unidentified target, since NALP3 inflammasome activation was not affected in cathepsin B deficient macrophages upon particulate stimulation [11]. Up to now, no direct link between NALP3 and cathepsin B has been reported.

3. Neuropathic diseases

3.1. The inflammasome in Prion diseases

Prion diseases, also known as transmissible spongiform encephalopathies, are fatal neurodegenerative disorders, characterized by brain vaculation, neuronal cell death and microgliosis [60]. This group of diseases can affect human and other mammalian species including bovine spongiform encephalopathy in cow, scrapie in sheep, chronic wasting disease in elk and Creutzfeldt–Jakob disease (CJD) in human. They are caused by the misfolding of cellular prion protein (PrP^C) into the pathological isoform (PrP^{Sc}). Studies have shown that the misfolded protein leads to activation of microglia, and these in turn produce proinflammatory cytokines and neurotoxic factors, including IL-1β, TNF-α and chemokine (C–C motif) ligand 3 (CCL3) [71]. Our research demonstrated that the misfolded PrP fibrils could activate NALP3 inflammasome,

Table 1
NALP3 inflammasome in protein misfolding diseases.

Diseases	Cytokine	Inflammasome trigger	Activated cell type	References
Prion disease	IL-1β	Fibril PrP	Microglia	Shi et al. [61] Hafner-Bratkovič et al. [20]
Alzheimer's disease	IL-1β	Beta amyloid	Microglia	Halle et al. [21] Trendelenburg [70]
Type 2 diabetes	IL-1β, IL-18	IAPP	Macrophage	Masters et al. [43] Donath et al. (2011)
Parkinson's disease	IL-1	Alpha-synuclein	Microglia	Codolo et al. [4]

leading to caspase-1 activation and IL-1β release. Besides, the released IL-1β could upregulate TNF-α and CCL3 expression after NALP3 inflammasome activation [61]. Similar findings were later reported by other researchers [20]. Our work also identified the molecular mechanisms at play in NALP3 inflammasome activation in response to PrP fibril stimulation (Fig. 1). First, hyperosmotic extracellular K^+ significantly decreases PrP fibril-induced release of IL-1β through downregulation of NALP3 expression, but K^+ has no effect on regulation of ASC expression. This result is consistent with previous findings which demonstrated that IL-1β processing in microglia is regulated by multiple pathways that differentially regulate NALP3 and ASC [33]. Secondly, generation of ROS in response to PrP fibril stimulation also seems to play a key role in NALP3 inflammasome activation, and ROS inhibitor NAC was shown to significantly reduce the release of IL-1β, and block NALP3 and ASC upregulation after exposure to PrP fibrils. Lastly, phagocytosis of PrP fibrils leads to lysosome destabilization, resulting in NALP3 inflammasome activation. Inhibition phagocytosis and lysosomal acidification suppressed NALP3 inflammasome activation in PrP fibril stimulated microglia [63]. It remains unclear whether these mechanisms act in concert or independently.

We also found that NF-κB activation acts upstream of NALP3, as inhibition of NF-κB activation abrogates PrP fibril-induced NALP3 mRNA upregulation. This is consistent with the role of NF-κB as the key regulator of pro-IL-1β synthesis. Recently, a research has demonstrated that A20 negatively regulates NALP3 inflammasome by suppressing NF-κB-dependent production of NALP3 and pro-IL-1β [74]. It would be therefore of interest to investigate the relationship between A20 and NALP3 inflammasome in the context of Prion diseases.

3.2. The inflammasome in Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative, progressive and chronic disease characterized by dementia, memory loss and cognitive impairment. Deposition of misfolded protein amyloid-β (Aβ) in the brain is supposed to be a principal event in AD pathogenesis. Mounting evidences show that multiple inflammatory cytokines, such as TNF-α, IFN-γ and interleukins, are elevated in the brain of Alzheimer patients [26]. In addition, inflammatory cytokines are also increased in the peripheral blood and cerebrospinal fluid of Alzheimer patients. Studies also indicate that interleukins, in particular IL-1β and IL-18, are the main cause of the inflammatory process in the central nervous system (CNS), both of which mediating the expression of other inflammatory genes [56]. IL-1β can be released from many cell types including macrophages, microglia and neurons [8] and many types of inflammasome, including NALP1, NLRC4 and NALP3 inflammasome, were shown to be involved in the inflammasome-mediated release of IL-1β in the CNS [70]. Aβ was the first misfolded protein to be shown to activate inflammasome in the CNS. Specifically, Aβ activated caspase-1 of LPS-primed microglia, leading to the release of IL-1β, and this response was dependent on NALP3 inflammasome activation [21]. The phagocytosis of fibril Aβ can cause endosomal rupture and the release of cathepsin B in the cytosol, and this endosomal rupture was proved to be an important endogenous signal for NALP3 inflammasome activation.

There is a relationship between neuroinflammation and the progress of AD. Higher IL-1β in the CNS can exacerbate AD pathogenesis and affect synaptic plasticity and long-term potentiation [52]. Besides, inhibition of IL-1β signaling has proved beneficial effects on AD mouse model. NALP3 inflammasome activation by Aβ in CNS is necessary for caspase-1 cleavage and IL-1β release and subsequent inflammatory response; however, the role of NALP3 inflammasome activation in AD in vivo is still unclear. A recent study conducted on APP/PS1 mice, which develop similar symptoms of AD, indicates that NALP3 inflammasome activation has a critical role in the pathogenesis of AD [22]. The study showed that APP/PS1/NALP3$^{-/-}$ and APP/PS1/caspase-1$^{-/-}$ mice were largely protected from loss of spatial memory and other sequelae compared to APP/PS1 mice. The deficiency of NALP3 reduced caspase-1 activation and IL-1β secretion and enhanced Aβ clearance. Furthermore, NALP3 or caspase-1 deficiency resulted in a skew of microglia activation towards an M-2 like activated state, as markers of alternative activation of microglia of the M2 type such as "found in inflammatory zone 1 (FIZZ1)" and arginase-1 are upregulated, and hallmark of classical activation M1 type-NOS2 are downregulated [22]. This is consistent with our previous study which demonstrated that inhibition of NALP3 inflammasome by Cytochalasin D reduced classical activation of microglia upon exposure to Aβ and PrP fibrils [61,62]. It has been proved that activation of NALP3 inflammasome induced M1 type

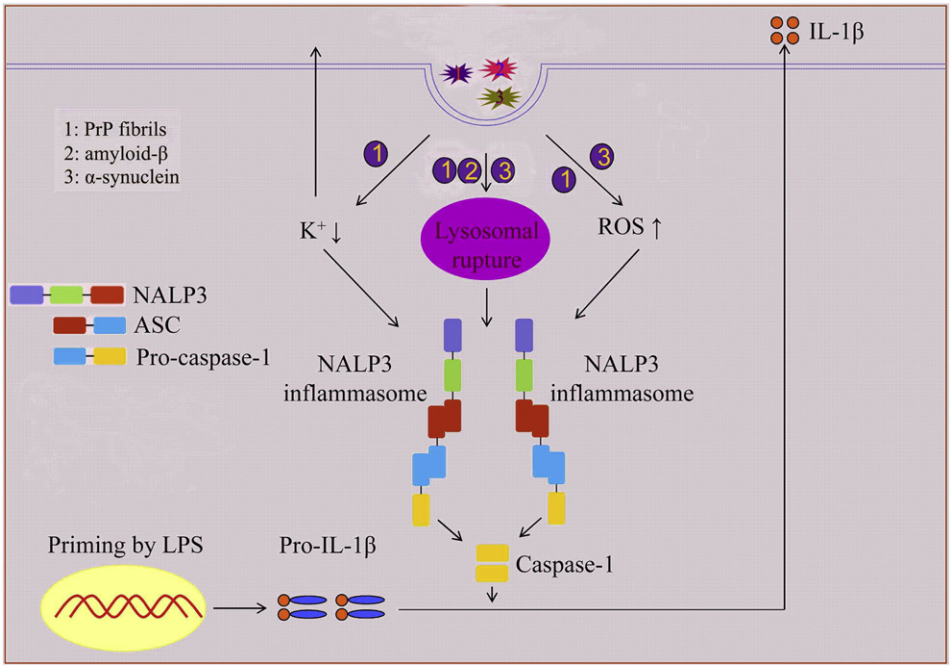

Fig. 1. Schematic model of NALP3 inflammasome activation in response to misfolded protein stimulation. The misfolded proteins can set fire to microglial NALP3 inflammasome via K^+ efflux, lysosomal destabilization and ROS increase. Then, the activation of NALP3 inflammasome leads to caspase-1 activation and IL-1β release.

activation of microglia and resulted in the clearance of Aβ, but activation of M2 type of microglia could ultimately reduce Aβ deposition and protect against synaptic dysfunction [62].

It should be noted that the cleavage of IL-1β is just one aspect of NALP3 inflammasome activation, and that inflammasome dependent pyroptosis in AD is still at debate. A recent research has demonstrated that NALP1 inflammasome is one of the key pathways responsible for Aβ neurotoxicity. The NALP1 expression was upregulated in APP/PS1 mice, and this increase in NALP1 levels in neurons was due to Aβ accumulation. In addition, the increase in NALP1 expression activated caspase-1 signaling and led to neuronal pyroptosis and inflammation cytokine release [68]. Therefore, further studies are needed to clarify the nature of correlation between NALP3 inflammasome and other signaling pathways involved in AD.

3.3. The inflammasome in Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD) with a prevalence of 0.5–1% among people older than 65 years of age [69]. It is characterized by the death of dopaminergic neurons in the substantia nigra (SN) pars compacta [23] and presence of intraneuronal aggregated inclusions called Lewy bodies [66].

As one of the neuropathologic hallmarks of PD, Lewy body is mainly composed of an amyloid polypeptide known as α-synuclein [49], which was shown to share intriguing similarities with other amyloid polypeptides [3,49]. The accumulation of α-synuclein has also been reported in peripheral tissue in T2DM mice, suggesting a possible amyloid-based link between the two diseases.

It is established that the inflammatory process plays a crucial role in the pathogenesis and/or progression of PD. Extracellular α-synuclein has been shown to be taken up by neuronal and microglial cells in culture, although the nature of the mechanism involved is still controversial [37]. α-Synuclein is released early in the disease and, acting as an endogenous disease-related signal, it activates microglia to release pro-inflammatory molecules, such as TNF-α and IL-1β, which are detrimental to dopamine neurons [17,38].

A recent study has demonstrated the involvement of NALP3 inflammasome activation in α-synuclein-mediated microglia activation [4]. Specifically, fibrillar α-synuclein induced synthesis of IL-1β, through TLR2-dependent pathway, and its phagocytosis resulted in increased ROS production and cathepsin B release into the cytosol leading to NALP3 inflammasome activation [4].

4. Nonneurophathic diseases

Protein aggregation diseases are not exclusive to the central nervous system, and can appear in peripheral tissues as well. Examples of protein misfolding diseases that appear in peripheral tissues include type 2 diabetes, inherited cataracts, some forms of atherosclerosis, hemodialysis-related disorders, and short-chain amyloidosis. Our focus here is confined to the role of inflammasome in type 2 diabetes.

4.1. The inflammasome in type 2 diabetes

Type 2 diabetes mellitus (T2DM) is an auto-inflammatory disease induced by a metabolic disorder. It is characterized by a reduction in the ability of insulin to stimulate glucose utilization, insulin resistance and inadequate pancreatic β-cell insulin secretion in response to hyperglycemia [7,10]. Elevated level of IL-1β and limited beta-cell function are two primary predictors for the development of T2DM [75]. Pioneering studies have demonstrated the contribution of NALP3 inflammasome in the pathogenesis of T2DM. Specifically, it was shown that the genetic deletion of NALP3 and ASC in high-fat diet fed mice results in improved glucose tolerance and enhanced insulin sensitivity [67,72,76]. Lee et al. demonstrated the specificity of the NALP3 inflammasome in inducing inflammation originating from myeloid cells of drug-naïve diabetic patients [35].

Metabolic stress due to chronic hyperglycemia stimulates inflammasome mediated production of proinflammatory cytokine, IL-1β, which in turn activates signaling pathways that result in pancreatic β-cell death and dysfunction [14,18,47]. Fatty acids, glucose, and islet amyloid polypeptide (IAPP) have been put forward as metabolic danger signals that possess the capacity to activate the inflammasome and stimulate IL-1β production in T2DM patients [10].

IAPP is a peptide of 37 amino acids produced by pancreatic beta cells and forms amyloid deposits in the pancreas during T2DM in humans [43]. Masters et al. [43] have shown that IAPP has the ability to activate the NALP3 inflammasome in dendritic cells or macrophages primed with TLR4 agonist such as LPS or minimally modified LDL (mmLDL). Interestingly, the soluble oligomers of IAPP rather than the mature amyloid fibrils seem to be the culprit of IAPP-mediated inflammasome activation. As in amyloid-induced inflammasome activation, IAPP driven NALP3 inflammasome activation required ROS, cathepsin B, and the phagocytosis [43].

Pancreatic islets, macrophages and dendritic cells may all be sources of IL-1β in the pancreas. Although beta cells can produce IL-1β in response to IAPP stimulation, macrophage is likely to be the dominant IL-1β-producing cell in pancreatic islets. Expression of IAPP has also been reported in the gastrointestinal tract and sensory neurons [77], suggesting extra pancreatic involvement of IAPP in inflammasome activation during T2DM.

Importantly, IAPP seems to provide signal 2 for inflammasome activation in T2DM patients. Indeed, IAPP lacks the ability to drive IL-1β mRNA expression, yet robustly promotes NALP3-mediated caspase-1 activation. T2DM related metabolic stress due to elevated free fatty acids may account for priming signal 1 necessary for IL-1β mRNA upregulation.

Elevated circulating level of free fatty acids is one of the hallmarks of type 2 diabetes [30]. Owing to their ability to bind and activate members of the TLR-family in vitro [36], saturated fatty acids may provide the first signal needed for IL-1β production though induction of IL-1β gene transcription. Interestingly, expression of IAPP by the pancreatic beta cell line MIN6 cells is activated by saturated fatty acid palmitate [77], highlighting the potential contribution of fatty acids in boosting pancreatic IL-1β production.

High glucose levels may also be involved in providing the priming signal for transcription of IL-1β by activation of thioredoxin-interacting protein (TXNIP), a protein that acts as an endogenous inhibitor of the ROS scavenging protein thioredoxin [45,51]. Zhou et al. [79] have shown that, upon activation, TXNIP is able to directly interact with NALP3 in a ROS-dependent manner, leading to activation of caspase-1 and processing of IL-1β in pancreatic islets. However, the role of TXNIP was not evident in IAPP-induced NALP3 inflammasome activation [79].

5. Potential and challenges for therapeutic interventions

As shown above, there is a growing body of evidence that inflammasome activation is a key feature in the pathogenesis of protein misfolding diseases, which suggests that pharmacological strategies targeting inflammasome constituents or inhibiting its final product, may be therapeutically useful in treating or preventing protein-misfolding diseases.

As the final product of the inflammasome activation, IL-1β seems to be the most obvious target for inflammasome-targeting therapeutic approach. Inhibition of IL-1β is currently a therapeutic strategy in a broad spectrum of diseases [9]. So far, three agents directed against IL-1β have been approved for the treatment of inflammatory diseases: the IL-1 receptor antagonist anakinra, the soluble decoy receptor rilonacept (a hybrid molecule consisting of the extracellular portion of the IL-1 receptor

and the Fc domain of human immunoglobulin G1), and the neutralizing monoclonal anti-IL-1β antibody canakinumab [15,50].

The blockade of IL-1β activity with anakinra or canakinumab in patients with T2DM has shown a remarkable clinical improvement in glycemic control and beta cell function in parallel to a decrease in systemic markers of inflammation [2,31,32,55,64]. Moreover, the investigation of the effect of rilonacept on beta-cell function in animal models has shown that it prolongs survival of transplanted pancreatic islets to type 1 diabetic NOD mice [57].

IL-1β targeting may also be a reliable target for protective therapies in neurodegenerative diseases. In a study that highlights the potential therapeutic benefit of IL-1β targeting in Alzheimer's disease, blocking IL-1 signaling with an IL-1R blocking Ab in a mouse model of Alzheimer's disease significantly altered brain inflammatory responses, rescued cognition, attenuated tau pathology, and restored neuronal β-catenin pathway function [29]. However, these results need to be interpreted with caution, as the pleiotropic functions of IL-1β make it difficult to predict the net therapeutic effect of targeting IL-1β in the brain. In a recent review of the therapeutic effect of IL-1β targeting in Parkinson disease, Leal et al. suggest that the functional effect of IL-1β depends on the duration and dose of its expression on the substantia nigra (SN) pars compacta in patients with Parkinson disease, and that an in-depth analysis to identify downstream mediators of the toxic effects of IL-1β in the SN is needed to spare the possible neuroprotective effect of these cytokines operative in the patients at the time of treatment, and to increase the probability of efficacy in a clinical setting [34].

Alternative potential therapeutic strategies consist of targeting upstream constituents of NALP3 inflammasome, including caspase 1 and ASC. Three therapeutic agents that inhibit caspase-1 have been described, namely Pralnacasan, VX-765, and parthenolide. Parthenolide is a sesquiterpene lactone isolated from the extracts of Mexican-Indian medicinal herb (*Tanacetum parthenium*), and has shown promise in the treatment of various inflammatory conditions. In addition to its anti-NF-κB activity, it inhibits the activity of multiple inflammasomes by directly inhibiting the protease activity of caspase-1 through alkylation of critical cysteine residues [27].

Pralnacasan and VX-765 are peptide based caspase-1 inhibitors [53]. Pralnacasan was shown to significantly increase insulin sensitivity in obese mice [67], and to reduce the development of cardiomyopathy in a rat model of diabetic cardiomyopathy [78], whereas VX-765 was tested for the treatment of partial epilepsy, with apparent success [9].

Although activated caspases have been detected in the brains of AD and PD patients [19,24,46], the exact role of caspase-1 in the progression of neurodegenerative diseases is still unclear, and as a result, the use of caspase inhibitors as therapeutic agents in neurodegenerative diseases will prove difficult until the mechanisms behind disease progression are elucidated.

Finally, the recent identification of ASC inhibitors provides a promising therapeutic strategy for the management of NALP3 activation-related diseases. CRID CP-456,773 (also known CRID3), is a member of the recently identified class of diarylsulfonylurea containing compounds called Cytokine Release Inhibitory Drugs (CRIDs), and was shown to inhibit NALP3 by preventing ASC oligomerization [6].

Notwithstanding the promising therapeutic perspectives the continuous advances in inflammasome research are opening, the management of misfolding protein diseases through inflammasome inhibition must be considered with caution. Indeed, inflammasome inhibition may also result in reducing the ability to fight infection, since inflammasome activation is involved in immune response to several infectious diseases.

6. Conclusion

Recent reports related to the role of inflammasome activation in the pathogenesis of protein misfolding diseases helped to elucidate the molecular mechanisms lying behind the inflammatory process associated with their progression, and paved the way for the exploration of new therapeutic targets for the management of this group of diseases.

However, many questions still need to be answered. For example, the relevance of inflammasome activation in the onset and progression of misfolding protein diseases in natural conditions still remains to be determined since most of the reported findings have been found in in-vitro experiments. More works are also still needed to elucidate the relationship between inflammasome activation and other pathological process associated with the aggregation of misfolded protein, such as cell death.

Finally, most of works have so far focused on the role of NALP3 inflammasome. It will be of interest to investigate the involvement of other types of inflammasome in misfolded protein-induced inflammation and the existence of possible redundancy between them.

Conflict of interest statement

The authors declare that there are no conflicts of interest

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