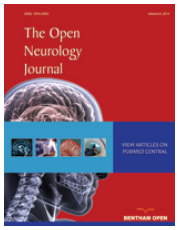

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REVIEW ARTICLE

Inflammasome-Mediated Inflammation in Neurodegenerative Diseases

Jun Young Park[1], Yeo Wool Kang[2] and Won Gil Cho[2,*]

[1]*Department of Nuclear Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea*

[2]*Department of Anatomy, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Republic of Korea*

Abstract: Inflammasomes are protein platforms consisting of multiple proteins. The biological function includes the activation of caspase-1, leading to the maturation of IL-1β and IL-18. These pro-inflammatory cytokines promote fundamental inflammatory processes in numerous infectious diseases. The inflammasome-mediated inflammation has become increasingly important in central nervous system disorders. In neurodegenerative disorders, significant contributors to disease progression include neuroinflammation and inflammatory cascades initiated by the inflammasome protein complex. This review discusses the recent progress of research on inflammasome associated with neurodegenerative disorders.

Keywords: Alzheimer's disease, Amyotrophic lateral sclerosis, Multiple sclerosis, Inflammasome, NLRP3, Neuroinflammation, Parkinson's disease.

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1. INTRODUCTION

Neurodegenerative disorders are characterized by the progressive structural and functional degeneration of nerve cells in the Central Nervous System (CNS) [1]. Most neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), and epilepsy, are associated with chronic neuroinflammation [2, 3] and increased levels of cytokines and activated immune cells [4].

Inflammasomes expressed in phagocytes, including macrophages and dendritic cells, activate caspase-1 in response to pathogenic infections and tissue damages [5]. The activation of inflammasome has been linked to different diseases including viral infections [6], diabetes [7], hypertension [8], and rheumatoid arthritis [9]. In CNS, inflammasomes play a pathogenic role in infectious conditions such as pneumococcal meningitis [10], *Toxoplasma gondii* infection [11], murine Japanese encephalitis [12], and HIV/AIDS [13]. Recently, inflammasomes have also been linked to neurodegenerative diseases. In this review, we discuss the recent research progress on the activation and function of inflammasomes in neurodegenerative disorders.

* Address correspondence to this author at the Department of Anatomy, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Republic of Korea; Tel: +82337410275; Fax: +82337411434; E-mail: wch01@yonsei.ac.kr

2. INFLAMMASOMES

Inflammasomes are multimeric protein complexes comprising of Pattern Recognition Receptor (PRR), an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) adaptor protein, and procaspase-1 [14]. The recognition of pathogen-associated molecular patterns and danger-associated molecular patterns by PRR triggers the assembly of the inflammasome complex [15]. Inflammasome oligomerization leads to self-cleavage of procaspase-1 to generate activated caspase-1, which is essential for the maturation of interleukin-1β (IL-1β) [16] and interleukin-18 (IL-18) [17]. PPRs are divided into four distinct classes: Toll-Like Receptors (TLRs), C-type Lectin Receptors (CLRs), Retinoic acid-inducible gene I-Like Receptors (RLRs), and Nucleotide-binding oligo-merization domain-Like Receptors (NLRs). It has been reported that few NLR family members including NLRP1, NLRP3, NLRC4, Pyrin, and AIM2 are able to assemble the in-flammasome complex *in vivo* [18 - 20]. Of those, NLRP3 inflammasome has been extensively studied and is linked to neurodegenerative disorders. Inflammasomes are mainly invol-ved in the innate immune response, contributing to neuro-inflammatory damage (Fig. **1**). The inflammasome mediates secretion of IL-1β and IL-18 which induces the fundamental inflammatory events in neuroinflammation [21].

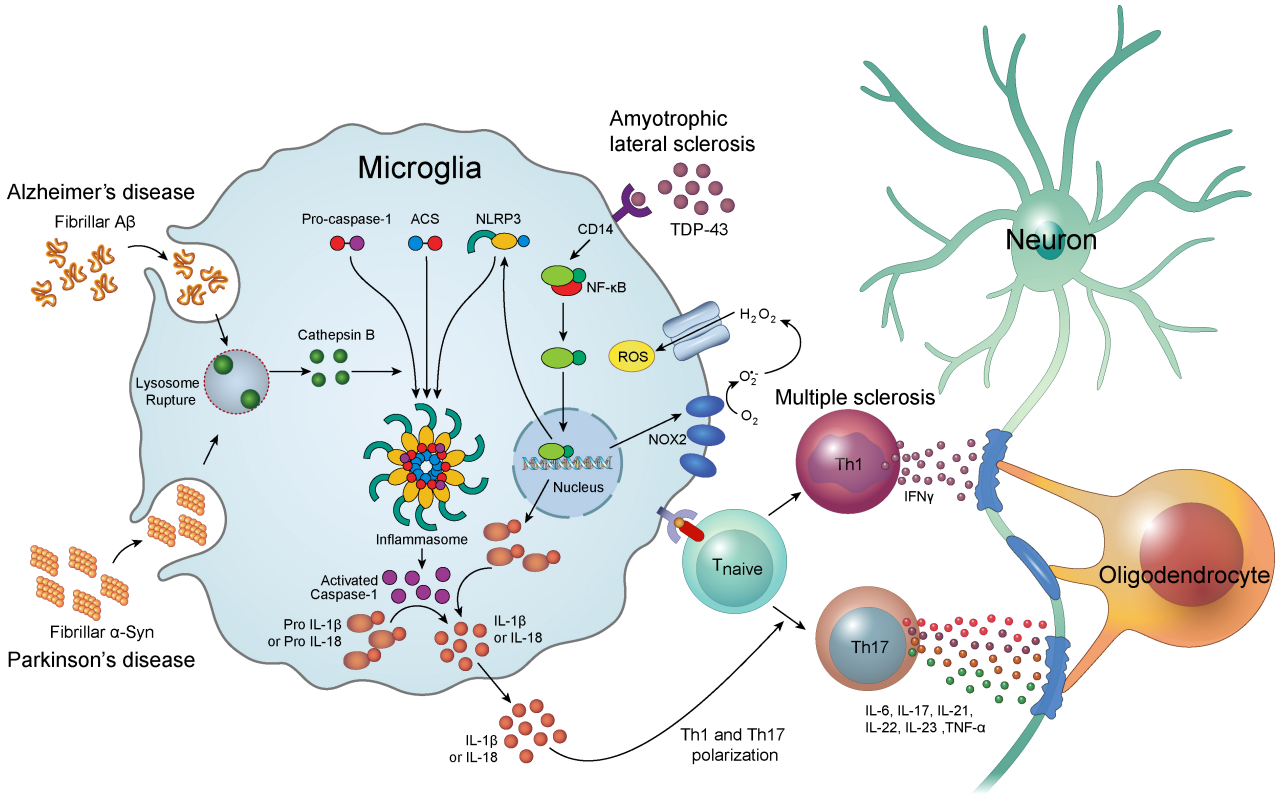

Fig. (1). Schematic description of inflammasome activation pathways in neurodegenerative disorders. The assembly of the NLRP3 inflammasome in CNS inflammatory cells can be induced by fibrillar amyloid β (Aβ) in Alzheimer's disease or fibrillar α-synuclein (α-Syn) in Parkinson's disease. Phagocytosis of fibrillar Aβ induces lysosomal rupture, resulting in the leakage of cathepsin B. Phagocytosis of fibrillar α-Syn also leads to the release of cathepsin B. Cytoplasmic cathepsin B activate the NLRP3 inflammasome. IL-1β and IL-18 can promote polarization of helper T (Th) cells. Cytokines released by both Th1 and Th17 induce the inflammatory reactions, which promote demyelination and axonal damage in the multiple sclerosis. In amyotrophic lateral sclerosis, the interaction of TAR DNA binding protein (TDP-43) with CD14 receptor promotes the activation of nuclear factor κB (NF-κB) pathways, leading to the increased expression of NLRP3 mRNA and production of caspase-1 and IL-1β.

3. ALZHEIMER'S DISEASE

Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterized by dementia and memory loss [22]. The pathological hallmarks of AD are the extracellular deposits of amyloid plaques and intracellular accumulation of Neurofibrillary Tangles (NFTs) [23]. Although there are numerous possible etiologies for AD, the exact mechanisms for the onset remain unclear. Recently, neuroinflammation has emerged as an important risk factor in the development of AD. In CNS, microglia play a pivotal role in the inflammatory reaction [24]. In an AD patient's brain, the microglia are seen gathered around the amyloid β (Aβ) plaques [25] and induce massive neuronal cell death through secretion of tissue necrosis factor α (TNF-α) [26].

Helle *et al*. first reported that NLRP3 inflammasomes can be activated by fibrillar Aβ. Phagocytosis of fibrillar Aβ by activated microglia induces lysosomal damage, resulting in the leakage of cathepsin B. This study revealed that cytoplasmic cathepsin B activates NLRP3 inflammasome and induces the release of IL-1β by microglia [27]. The study by Heneka *et al*. reported that knockdown of NLRP3 decreases the accumulation of Aβ, and prevents the behavioral and cognitive dysfunction in the aged APP/Presenilin-1 (PS1) transgenic mice model of AD. APP/PS1/NLRP3$^{-/-}$ mice also showed decreased accumulation of Aβ plaque in the hippocampus [28]. Other evidence has suggested that activation of the nuclear factor-kappa B (NF-κB) pathway has a critical role in the activation of NLRP3 inflammasome [29]. Shi *et al*. showed that artemisinin, a known antimalarial drug, significantly inhibited the activation of NF-κB and NALP3 inflammasome, and reduced the amyloid plaque deposition in the cortex and hippocampus in APPswe/PS1dE9 transgenic mice [30].

It has also been reported that NLRP1 contributes to the age-related neuronal loss. The expression of NLRP1 was observed to increase after 6 months in APP/PS1 mice; however, knockdown of NLRP1 decreases the neuronal cell death and rescues early cognitive deficits [31]. Kaushal *et al*. showed that NLRP1 inflammasome activates caspase-1, which subsequently activated caspase-6, in human primary neurons treated with serum deprivation and benzylated ATP [32]. Caspase-6 is known as a key effector of apoptosis. Numerous other evidences reveal that caspase-6 activity is strongly associated with AD pathologies. LeBlanc *et al*. reported that caspase-6 is responsible for the increased levels of Aβ in primary cultures of human neurons [33]. It was also reported that the activated caspase-6 is exceedingly observed in the brain of both sporadic and familial AD [34, 35].

Tau protein can be cleaved by caspase-3 at Asp^{421} [36] and this truncated tau (TauΔCasp3) induces cell death in the primary hippocampal neurons [37]. Caspase-6 also cleaves the tau at Asp^{402} [38] and Asp^{13} [39] *in vitro*. Another study showed that the activated caspase-6 and TauΔCasp6 were highly observed in neuropil threads, NFTs, and neuritic plaques of end-stage AD brain [38].

4. PARKINSON'S DISEASE

Parkinson's Disease (PD) is the second most common neurodegenerative disorder, characterized by progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) located in the midbrain [40]. The pathological hallmark of PD is Lewy bodies composed of misfolded α-synuclein (α-Syn) aggregates [41]. Pathogenesis of PD is still unclear, but accumulating evidence indicates that neuroinflammation may act as a risk factor for the development of PD. Significantly increased levels of pro-inflammatory cytokines, including IL-1, IL-2, IL-6, and TNF-α, were detected in the serum and Cerebrospinal Fluid (CSF) of PD patients [42]. It was reported that the use of non-steroidal anti-inflammatory drugs reduces the risk of PD onset [43, 44].

Several studies have shown that α-Syn activates microglia *in vitro* and *in vivo* [45 - 47]. The exposure of monocytes to fibrillar α-Syn induced the secretion of IL-1β *via* caspase-1 activation and the up-regulation of NLRP3 [48]. This study also showed that phagocytosis of fibrillar α-Syn by monocytes leads to the release of cathepsin B and production of Reactive Oxygen Species (ROS), which are known activators of NLRP3 inflammasomes. A recent study reported that α-Syn can be cleaved directly by caspase-1 *in vitro* [49]. The level of cytotoxicity in neuronal cells correlated with the level of truncated α-Syn, but inhibition of caspase-1 activity rescued the α-Syn-induced cytotoxicity.

MicroRNA-7 (miR-7) is a direct regulator of α-Syn in post-translational modification. Li *et al*. reported that miR-7 has a neuroprotective effect in the 1-methyl-4-phenylpyridinium (MPP^+) mediated PD model [50]. In this study, the MPP^+-elicited apoptotic effects on neurons were significantly reduced by miR-7. Another study showed that NLRP3 inflammasomes are activated in the midbrain of α-Syn-overexpressed A53T transgenic mice, but subsequent transfection of miR-7 significantly inhibited the A53T α-Syn-induced the upregulation of NLRP3 [51].

ATP13A2 gene, also called Park9, encodes a transmembrane lysosomal p5-type ATPase (ATP13A2) which is involved in the stabilization of lysosome membrane structure. It has been reported that ATP13A2 is highly expressed in the SNc [52]. Other studies reported that deficiency of ATP13A2 leads to the accumulation of α-Syn in neuronal cells [53], and the mutation of ATP13A2 gene causes an early-onset PD [54]. The study by Qiao *et al*. reported that knockdown of ATP13A2 in primary astrocytes causes increased secretion of pro-inflammatory cytokines (TNF-α and IL-6), and decreased the production of anti-inflammatory cytokines (IL-4 and IL-10). In addition, the downregulation of ATP13A2 increased the expression of as-trocytic cathepsin B, which subsequently induces the activation of NLRP3 inflammasome [55].

5. MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is an autoimmune disease characterized by the progressive loss of myelin sheaths of neurons. T lymphocytes play a pivotal role in the pathogenesis of MS [56]. It has been reported that high numbers of T cells, especially myelin-specific autoreactive T cells, are present in the peripheral blood of MS patient [57]. Immune cell infiltration into the CNS is tightly controlled by the Blood-Brain Barrier (BBB). Nevertheless, many immune cells are able to cross the BBB in neuroinflammatory diseases. The etiology of MS is still not known, but it is thought that the activated myelin-specific T cells cross the BBB and trigger the recruitment of other in-flammatory cells, which consequently lead to the destruction of the myelin sheath [58].

T helper type 1 (Th1) cells are the main effector cells, which activate the macrophages *via* interferon-gamma (IFN-γ). Activated macrophages promote neuroinflammatory events by releasing inflammatory mediators including cytokines, ROS, nitric oxide and glutamate, which then induce tissue damage [59]. IL-17-producing effector T helper cells, called Th17 cells, have emerged as key mediators of MS. Th17 cells produce the effector cytokines including IL-6, IL-17, IL-21, IL-22, IL-23 and TNF-α, which induce the inflammatory reactions [60].

Previous studies have shown that NLRP3 inflammasome contributes to the development of MS. It was observed that the expression of caspase-1 is significantly increased in the Peripheral Blood Mononuclear Cells (PBMC) of MS patients [61]. Another study reported that the mRNA expression of inflammasome associated molecules, including NLRP3, caspase-1, IL-1β, is increased in the PBMC of MS patients as compared to the healthy control group [62]. In active demyelinating lesions of MS, reactive astrocytes and infiltrated perivascular macrophages express IL-1β and NLRP3 inflammasome components including NLRP3, ASC, and CASP1 [63].

Cuprizone is known to cause extensive demyelination in the corpus callosum [64]. Jha *et al*. reported that the expression of Nlrp3 is increased in the cuprizone-induced demyelination model [65]. This study also showed that demyelination and microglial infiltration are significantly reduced in the cuprizone-treated $Nlrp3^{-/-}$ mice, $Casp1^{-/-}$ mice and $IL\text{-}18^{-/-}$ mice; however, no alteration was observed in $IL\text{-}1\beta^{-/-}$ mice. Experimental Autoimmune Encephalomyelitis (EAE) is a widely-used rodent model for MS [66]. It is known that macrophage and microglia were involved in the development and progression of EAE [67 - 69]. However, the study by Vainchtein *et al*. reported that the role of macrophages and microglia is different in acute EAE [70]. This study showed that infiltrated macrophages were highly immune reactive, while microglia were only weakly immune activated during acute EAE. In the EAE model, $Nlrp3^{-/-}$ mice displayed reduced severity of EAE, and significant reduction of the inflammatory cells infiltration including macrophages, dendritic cells, $CD4^+$, and $CD8^+$ T cells [71]. IFN-γ and IL-17 are key pro-inflammatory mediators in the development of EAE, and their levels were significantly reduced in the $Nlrp3^{-/-}$ mice and $IL\text{-}18^{-/-}$ mice. Another study showed that $Asc^{-/-}$ mice and $Nlrp3^{-/-}$ mice were resistant to the

development of EAE. In addition, both EAE-induced $Asc^{-/-}$ mice and $Nlrp3^{-/-}$ mice showed significantly reduced numbers of $CD4^{+}$ T cells in the spinal cord and brain [72]. These findings suggest that NLRP3 inflammasome is required for the development of EAE.

6. AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic Lateral Sclerosis (ALS) is a fetal neurodegenerative disorder characterized by progressive degeneration of the upper and lower motor neurons [73]. Astrocytes and microglia play major roles in the disease progression of ALS. The aggregation of mutant Superoxide Dismutase 1 (SOD1) is the pathologic hallmark of familial ALS (fALS) [74]. It has been reported that astrocytes expressing mutated SOD1 result in the death of primary motor neurons through the activation of a Bax-dependent pathway [75]. Another study showed that microglia in $SOD1^{G93A}$ transgenic mice carrying the human SOD1 mutant gene induced the motor neuron death *via* the NF-κB dependent mechanism [76].

There is accumulating evidence suggesting that inflammasome is involved in the progression of ALS. The expression of NLRP3 inflammasome components and IL-1β were increased in the $SOD1^{G93A}$ mouse model, as well as in spinal cord tissue of human sclerosis ALS (sALS) patients [77]. Another study showed that the IL-18 expression was increased in the cerebral tissue of sALS patients as compared to an age-matched control group [78]. Symptoms of cognitive and behavioral impairment in the later stages of ALS are believed to be the results of neurodegeneration in the subcortical areas. Massive dendritic swelling and neuronal loss were detected in $SOD1^{G93A}$ mice. In addition, the accumulation of misfolded SOD1 protein and autophagy markers was observed in the anterodorsal nucleus of the anterior thalamus [79]. This study also showed that the expression of NLRP3 and ASC was significantly up-regulated in the anterodorsal thalamic nucleus of $SOD1^{G93A}$ mice.

TAR DNA binding protein (TDP-43) is the insoluble multifunctional nucleic acid binding protein which has an important role in neuronal RNA metabolism related to neuronal development and synaptic function [80]. TDP-43 is normally located in the cell nucleus; however, enhanced deposition of TDP-43 in the cytoplasm is observed in ALS [81]. A recent study reported that the interaction of TDP-43 with CD14 receptor in microglia triggers the activation of the microglial NF-κB, AP-1 and NLRP3 inflammasome pathways, leading to the production of TNF-α and IL-1β [82]. This study showed that TDP-43 induced the up-regulation of NLRP3 mRNA and activation of caspase-1, but did not alter the mRNA expression of NLRP1, NLRP2, AIM2, and NLRC4. TDP-43 also induced the up-regulation of NADPH oxidase 2 (NOX2), which is known an important source of ROS [83, 84]. ROS have been suggested as the key triggers of NLRP3 inflammasome activation [85].

7. EPILEPSY

Epilepsy is a chronic neurological disorder that is characterized by spontaneous recurrent seizures accompanied by cognitive impairment and psychiatric disturbances [86]. Accumulating evidence suggests that the unbalanced regulation of neuroinflammation plays a key role in the development of seizures and epilepsy [87]. Increased levels of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, are detected in the brain of an epilepsy model [88], and in the serum and CSF of epilepsy patients [89, 90]. In addition, the microglia activation is correlated with the increased expression of pro-inflammatory cytokines in the epileptic brain [91]. Microglia display both neurotoxic and neuroprotective effects in CNS disease [92]. Recent studies have shown that myeloid infiltrates, including monocyte and macrophages, and astrocytes exacerbate the neuroinflammatory status, whereas microglia play a protective role during early epileptogenesis [93, 94].

Several studies have reported that NLRP3 inflammasome can be up-regulated in an epilepsy model. The expression of cleaved IL-1β and hippocampal NLRP3 inflammasome components was elevated in a rat brain after Status Epilepticus (SE). On the other hand, siRNA knockdown of NLRP3 reduced the levels of IL-1β, IL-18, and caspase-1 expression, and inhibited hippocampal neuronal loss [95]. Similarly, the levels of IL-1β, NLRP3, and caspase-1 expression were up-regulated in a Kainic Acid (KA)-induced epilepsy model; however, curcumin suppressed the protein expression of IL-1β, NLRP3 and caspase-1, and reduced neuronal loss in the hippocampus [96]. NLRP3 inflammasome can be activated by oxidative stress [97]. The concentration of oxidative stress markers, including nitrite and malondialdehyde (MDA), and the expression of IL-1β, NLRP3, and caspase-1 were increased significantly in a KA-induced Temporal Lobe Epilepsy (TLE) model. In contrast, the high antioxidant activity, including glutathione (GSH), superoxide dismutase (SOD), and catalase, was decreased significantly [98]. Huperzine A (Hup-A), a natural acetylcholinesterase inhibitor, has been used for the treatment of AD because of its neuroprotective effects [99]. In the KA-induced TLE model, treatment with Hup-A reduced the nitrite and MDA concentrations, as well as the expression of IL-1β and caspase-1, while it increased the SOD and catalase activities.

Recent evidence also suggests that NLRP1 contributes to the pathogenesis of TLE. The increased expression of NLRP1 and caspase-1 was observed in the hippocampus of mesial TLE patients. In an amygdala kindling-induced TLE rat model, siRNA knockdown of NLRP1 reduced neuronal loss and caspase-1 expression and attenuated the seizure frequency and severity [100]. Similarly, the expression of inflammasome components, including NLRP1, ASC, and csapase-1, and inflammatory cytokines, including IL-1β, IL-18, IL-6, and TNF-α, increased in the brains of a pentylenetetrazole-induced epilepsy model. On the other hand, treatment with sinomenine, an anti-rheumatic alkaloid, suppressed the expression of NLRP1 inflammasome components and inflammatory cytokines [101].

CONCLUSION

In this review, we focused on the role of inflammasomes in neurodegenerative disorder. Each neurodegenerative disease has its own prognostic characteristic and symptomatic patterns.

However, the up-regulated inflammatory response is common to all diseases. Inflammasomes especially play an important role in the initiation and progress of neuroinflammation. In AD, the amyloid plaques and neurofibrillary tangles activate inflammasomes in the microglia, astrocytes and neuron itself. As a consequence, the level of IL-1β increases in the CNS of AD patients, thereby promoting neuroinflammation. In Parkinson's disease, α-synuclein aggregation activates the inflammasome complex in microglia. Enhanced NLRP3 inflammasome activation and up-regulated caspase-1 were detected in the postmortem MS brain. Increased expression of NLRP3 inflammasome components and IL-1β was observed in ALS animal models, as well as human CNS tissue. The up-regulated expression of NLRP1 and NLRP3 inflammasomes was detected in the brain tissue of an epilepsy model. As discussed in this paper, inflammasome is a major contributor to neuroinflammation in neurodegenerative disorders. However, only a few inflammasomes have been characterized. Better understanding the role of the inflammasome in neuroinflammation will provide more information to investigate the pathogenesis of neurodegenerative disorders.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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