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REVIEW ARTICLE

Galectin-3 in Microglia-Mediated Neuroinflammation: Implications for Central Nervous System Diseases

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Abstract: Microglial activation is one of the common hallmarks shared by various central nervous system (CNS) diseases. Based on surrounding circumstances, activated microglia play either detrimental or neuroprotective effects. Galectin-3 (Gal-3), a group of β-galactoside-binding proteins, has been cumulatively revealed to be a crucial biomarker for microglial activation after injuries or diseases. In consideration of the important role of Gal-3 in the regulation of microglial activation, it might be a potential target for the treatment of CNS diseases. Recently, Gal-3 expression has been extensively investigated in numerous pathological processes as a mediator of neuroinflammation, as well as in cell proliferation. However, the underlying mechanisms of Gal-3 involved in microglia-mediated neuroinflammation in various CNS diseases remain to be further investigated. Moreover, several clinical studies support that the levels of Gal-3 are increased in the serum or cerebrospinal fluid of patients with CNS diseases. Thus, we summarized the roles and underlying mechanisms of Gal-3 in activated microglia, thus providing a better insight into its complexity expression pattern, and contrasting functions in CNS diseases.

Keywords: Galectin-3, microglia, neuroinflammation, central nervous system diseases, chronic pain, galectin-3 inhibitor.

1. INTRODUCTION

Microglia, which comprise approximately 10-20% of glial cells, are resident immune cells present throughout the brain and spinal cord [1]. They have been regarded as the primary effectors of the innate immune response in various central nervous system (CNS) diseases [2, 3]. Microglia keep in a "resting" state under physiological conditions. In response to injuries or diseases, they turn "active" and undergo dramatic morphologic alternations [4, 5]. Activated microglia are detected in almost all kinds of CNS disorders such as neurodegenerative diseases, infectious and inflammatory diseases, chronic pain, stroke, and so on [6-8]. Ongoing controversy exists regarding whether activation of microglia has a beneficial or detrimental role on surrounding cells [9]. Indeed, microglial activation promotes the release of various proinflammatory factors such as cytokines and chemokines, thus inducing a vicious self-propagating cycle that drives the process of diseases [10]. However, others revealed the beneficial role of microglia in certain circumstances by their capacities to stimulate myelin repair, phagocytose excess synapses or neurons, as well as secret trophic factors to protect the CNS from damage or pathogens [11]. Therefore, activated microglia might serve as a double-edged sword based on surrounding circumstances [1]. Interestingly, recent studies have focused on the relationship between galectin-3 (Gal-3) and microglial activation in different pathological processes. Gal-3 is widely expressed in various inflammatory cells, especially in microglia and monocytes/macrophages [12]. Its levels have been extensively investigated in numerous pathological processes as a mediator of neuroinflammation, as well as in cell proliferation [13]. Gal-3, as a crucial tuner of various signaling pathways, is involved in the development of various CNS diseases [14]. Thus, understanding the roles and underlying signaling mechanisms of Gal-3 in microglia-mediated neuroinflammation are critical for the potential therapeutic intervention in those CNS disorders.

2. THE STRUCTURE AND DISTRIBUTION OF GALECTIN-3

Galectins, a family of glycan-binding proteins, share common highly conserved carbohydrate recognition domains (CRDs) responsible for β-galactoside residues [15]. So far, fifteen mammalian galectins (galectin1-15) have been recognized [16]. Gal-3, as one of the most widely studied

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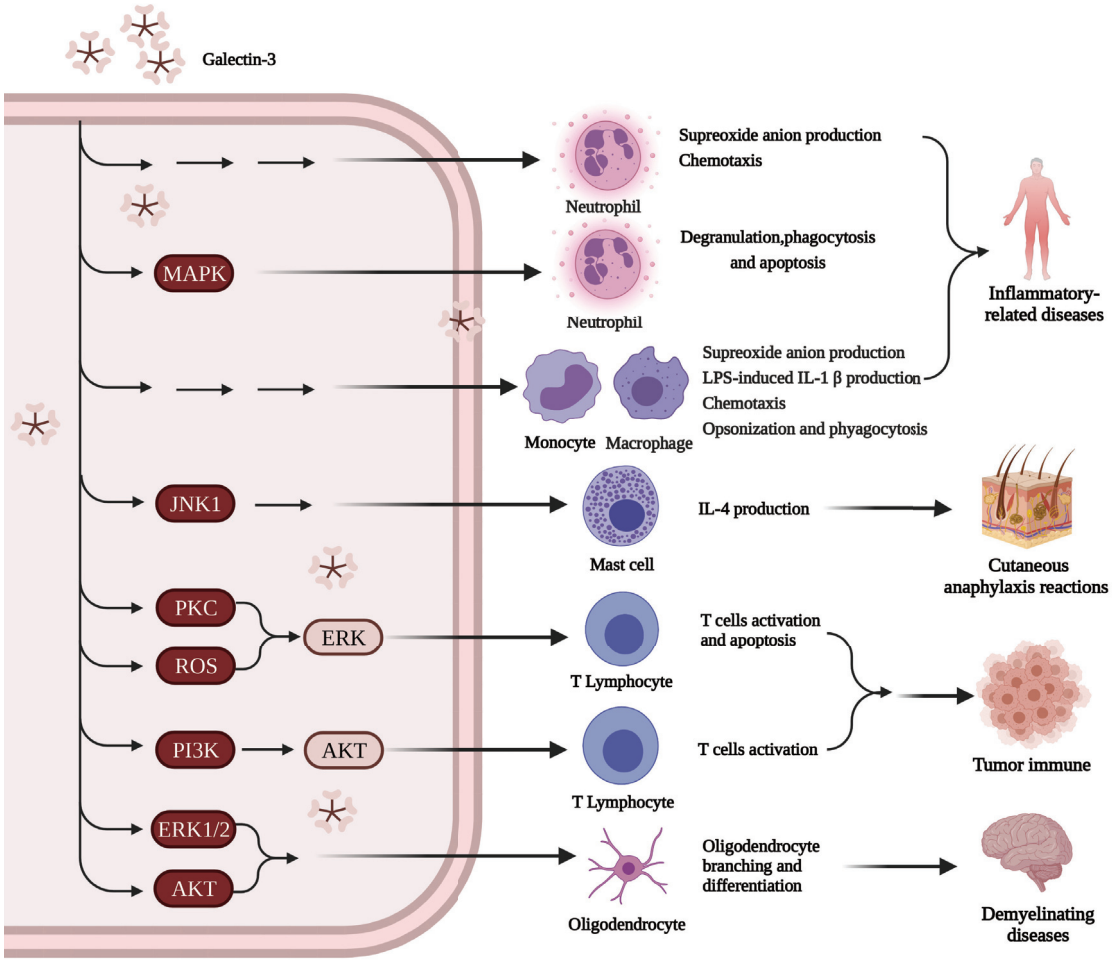

Fig. (1). The effects and underlying mechanisms of Gal-3 in the activation of immune cells in various diseases. AKT: protein kinase B; ERK: extracellular signal-regulated kinase; IL-1β: interleukin-1 beta**;** IL-4: interleukin-4**;** LPS: lipopolysaccharide; JNK1: c-Jun N-terminal kinase 1; MAPK: mitogen-activated protein kinase; PI3K: phosphatidylinositide 3-kinases; PKC: protein kinase C; ROS: reactive oxygen species. The figure was created using BioRender.com. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

molecules among all galectins, has been shown to associate with several CNS diseases. It is encoded by the LGALS3 gene and specifically binds to galactoside sugars [17]. Gal-3 is revealed to comprise two specific domains: CRD and N-terminal domain [18]. The CRD, including approximately 135 amino acid residues, is responsible for the carbohydrate-binding site [19]. In contrast, the N-terminal domain, consisting of approximately 150 amino acid residues, carries sites for phosphorylation and other determinants that participate in the regulation of Gal-3 secretion *via* a non-classical mechanism [20]. Moreover, the N-terminal domain is also responsible for the oligomerization of Gal-3 once the CRDs have bound to β-galactoside residues [19].

Gal-3 is located in several cell types and is widely distributed among tissues in adults [18]. In terms of cell populations, Gal-3 is primarily present in epithelial cells located in the respiratory system, digestive tract, urothelium, and skin, as well as in the myocardium, liver, *etc.* [16]. It is also revealed to express in fibroblasts, chondrocytes, osteoblasts and osteoclasts, keratinocytes, Schwann cells, and gastric mucosa, as well as in the endothelial cells among tissues [15]. Moreover, Gal-3 is known to be detected in various immune cells, including neutrophils, eosinophils, basophils and mast cells, Langerhans cells, dendritic cells, and monocytes/macrophages [12, 13]. In addition to studies on epithelial cells and monocytes/macrophages, Gal-3 has also been detected in the ependymal cells and astrocytes of the subventricular zone [21, 22]. Previous studies revealed that Gal-3 was not widely expressed in neuronal tissues in CNS. However, recent research revealed that the immunoreactivities of Gal-3 were detected in a large number of functional parts of cerebral cortex and subcortical nuclei in the hypothalamus and brainstem, as well as multiple hypothalamic nuclei associated with various biological functions [23].

3. GALECTIN-3 SECRETION AND FUNCTIONS

Gal-3 is synthesized on free ribosomes of the cytoplasm. While being primarily a cytosolic protein, this lectin is also detected on the cell surface and extracellular fluid [24, 25]. It can be released by numerous cells, including epithelial cells, as well as monocytes/macrophages [26]. This secreted protein has also been shown to function as an extracellular mol-

ecule to activate various cells, such as monocytes/macrophages, lymphocytes, mast cells, and neutrophils [27]. Due to Gal-3 having no signal sequence for the classical externalization *via* the endoplasmic reticulum (ER)/Golgi, it has been reported to be secreted by a novel non-classical pathway, probably through specific vesicles or exosomes [28]. In the proposed secretory pathway, the vesicles or exosomes with Gal-3 can be transferred outside of the cell, and the released Gal-3 might interact with components of extracellular space after their lysis [19]. This view is of great relevance for further studies, as exosomes are increasingly regarded as one of the crucial communication pathways between cells. However, the regulatory mechanisms of Gal-3 release from exosomes and into extracellular fluid remain to be further investigated.

Numerous functions have been demonstrated for Gal-3, and it is regarded as a versatile multifunctional molecule involved in several biological processes. Cytoplasm Gal-3 participates in the processes of cell proliferation and apoptosis signaling cascades [20]. In addition, cell surface Gal-3 plays a crucial role in cell-to-cell/matrix interactions, tumor proliferation, metastasis, and angiogenesis [29]. Of particular relevance to our review is the role of Gal-3 on the extracellular space in regulating inflammatory response [30]. We briefly discussed the involvement of Gal-3 in the activation of various cell types, especially those involved in inflammatory response (Fig. **1**). Gal-3 is chemoattractant to monocytes/macrophages and neutrophils, as well as potentiating lipopolysaccharide (LPS)-induced interleukin-1 beta (IL-1β) production from monocytes [27, 31, 32]. This lectin also induces phagocytosis and increases the production of superoxide anion in neutrophils and macrophages [32]. On the other hand, this protein may also regulate inflammatory response *via* suppressing apoptosis in inflammatory cells [33].

4. MOLECULAR REGULATORS AND SIGNALING MECHANISMS OF GALECTIN-3 IN MICROGLIA

4.1. Galectin-3-K-Ras-GTP Dependent PI3K Pathway

Degenerated myelin, generally presented in traumatic injury or multiple sclerosis, could suppress the process of remyelination [34]. Microglia, as primary resident immune cells in the CNS, are beneficial *via* phagocyting tissue debris [5]. Interestingly, Gal-3 proteins were found to increase in injury sites where the resident microglia or recruited macrophages phagocytosed degenerated myelin in CNS traumatic injuries and experimental autoimmune encephalomyelitis (EAE), but not in CNS Wallerian degeneration [35]. Moreover, microglia mediated-phagocytosis is significantly inhibited in Gal-3 knockdown microglia *in vitro*, suggesting that Gal-3 is indispensable in this process [4]. Further research revealed that upregulation or prolongation of K-Ras-GTP-dependent phosphatidylinositol 3-kinase (PI3K) activity could activate microglia-mediated myelin phagocytosis [36]. Consistent with this, *S-trans*, *trans*-farnesylthiosalicylic, which regulates K-Ras-GTP stabilization *via* Gal-3, could suppress PI3K activity and the process of myelin phagocytosis [4]. Consequently, previous studies indicated that Gal-3 might participate in microglia-mediated myelin phagocytosis *via* regulating K-Ras-GTP-dependent PI3K activity in traumatic injuries or multiple sclerosis.

4.2. Galectin-3-MerTK Pathway

Various studies revealed that extracellular Gal-3 could attach to the surfaces of cells and induce phagocytosis. Mer tyrosine kinase (MerTK), as a crucial phagocytic receptor expressed in microglia, is required for the process of phagocytosis [37]. Previous studies showed that Gal-3 was a ligand for MerTK and could regulate macrophage-mediated phagocytosis *via* MerTK activation [38]. Consistent with these studies, Brown *et al.* recently revealed that LPS-stimulated microglia could immediately upregulate the expression of Gal-3, as well as manifest a sialidase activity that desialylated PC12 (neuron-like) cells. Desialylation of PC12 cells could promote Gal-3 to bind and phagocytize live cells by microglia. In order to test whether the phagocytosis of activated microglia *via* Gal-3 was associated with MerTK, they first observed the colocalization of fluorescently labeled Gal-3 and MerTK both on control and LPS-stimulated microglia. Their results demonstrated that treatment with LPS increased the expression of Gal-3, bounding primarily to MerTK-positive cells. Secondly, the co-immunoprecipitation results also showed that Gal-3 was observed in the MerTK immunoprecipitated in the LPS-activated microglia. Moreover, Gal-3 induced phagocytosis of PC12 cells could be completely blocked by MerTK inhibitor UNC569 [39]. All these results demonstrated that Gal-3 could bind and activate MerTK, thus resulting in Gal-3 positive microglia-mediated phagocytosis of dying debris [14].

4.3. Galectin-3-TLRs Dependent Inflammatory Response

Neuroinflammation driven by activated microglia is an initial event related to the development of various CNS diseases [40]. Toll-like receptors (TLRs), as crucial pattern recognition receptors, have increasingly attracted particular attention in response to inflammatory agents [41]. Gal-3, as an important molecule released by activated microglia, has been known to participate in the inflammatory response upon numerous neuroinflammatory stimuli [19]. Moreover, previous studies revealed that Gal-3 could interact with TLR2, thus promoting the inflammatory response against *C. Albicans* [42]. Recent research also reported that Gal-3 released by activated microglia could act as an endogenous ligand for TLR4, thus regulating the severity of TLR4-mediated inflammatory response after injury or infection. Moreover, Gal-3 depletion significantly reversed this increased inflammatory response following global brain ischemia or LPS stimulation [43]. The findings suggested that Gal-3-dependent TLRs activation is involved in sustained microglial activation and neuroinflammatory processes, resulting in the onset or progression of various CNS disorders.

4.4. Galectin-3-TREM2–DAP12 Signaling Pathway

As a microglial surface receptor, the triggering receptor expressed on myeloid cell 2 (TREM2) is suggested to play a vital role in the immune response in Alzheimer's disease (AD) initiation and progression [44]. Thus far, studies have increasingly demonstrated that TREM2 is protective and promotes microglial progression to a fully mature disease-associated microglia (DAM) in response to amyloid pathology [45, 46]. Lee *et al.* found that upregulation of TREM2 levels enhanced the process of ramification and phagocytic marker expression in DAM, as well as improved memory

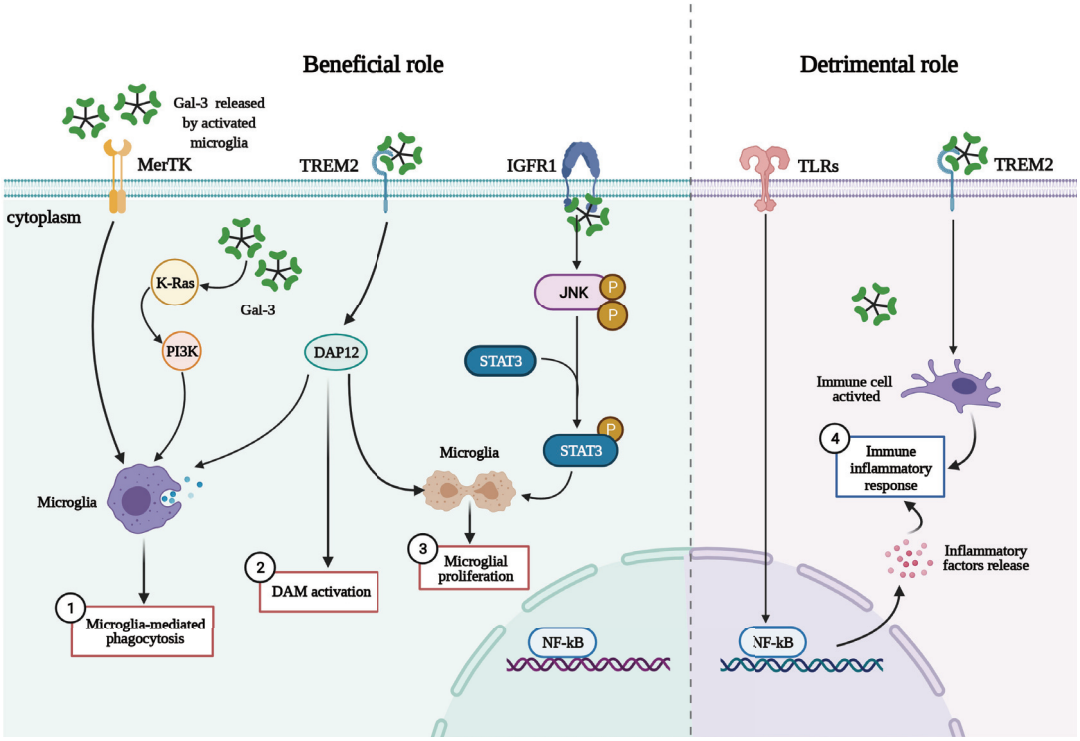

Fig. (2). Signaling mechanisms of Gal-3 involved in microglia-mediated proliferation, neuroinflammation, and phagocytosis in CNS diseases. (1) Secreted Gal-3 involved in microglia-mediated myelin phagocytosis *via* regulating K-Ras-GTP-dependent PI3K activity. Moreover, Gal-3 could also bind to MerTK or interact with TREM2/DAP12 signaling, thus regulating microglia-mediated phagocytosis. (2-3) Gal-3 could interact with TREM2/DAP12 signaling, participating in various biological processes, including DAM activation or microglial proliferation. (4) Gal-3 could also bind to IGFR and is involved in the IGF-1-mediated proliferation of microglia. (5) Gal-3 released by activated microglia could directly interact with TLRs or TREM2, thus exacerbating the release of inflammatory factors. DAM: microglia phenotype associated with neurodegenerative diseases; DAP12: DNAX-activating protein of 12 kDa; Gal-3: galectin-3; IGF-1: insulin-like growth factor 1; IGF-R1: insulin-like growth factor receptor 1; JNK: c-Jun N-terminal kinase; MerTK: Mer tyrosine kinase; NF-κB: nuclear factor-κB; PI3K: phosphatidylinositide 3-kinases; STAT3: signal transducer and activator of transcription 3; TLRs: Toll-like receptors; TREM2: triggering receptor expressed on myeloid cell 2. The figure was created using BioRender.com. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

performance in AD mice [47]. Interestingly, Gal-3, as a glycan-binding protein, is also found to be a gene strongly associated with DAM [48]. Hence, some scholars explored whether Gal-3 could interact with TREM2. The high-resolution microscopy results reported that Gal-3 was closely colocalized with TREM2 in the microglial processes, and its overexpression could be affected by the TREM2 level [49]. Indeed, current single-cell transcriptomic analyses of microglia indicated that Gal-3 was one of the most increased molecules to be TREM2-dependent [50]. Importantly, Gal-3 was demonstrated to interact with TREM2-DNAX-activating protein of 12 kDa (DAP12) signaling in a BWZ thymoma reporter cell line [49]. However, further studies remain necessary to determine the exact contribution of Gal-3/TREM2 signaling to the pathogenesis of numerous CNS diseases.

4.5. Galectin-3-IGF-R1 Signaling Pathway

Previous studies have demonstrated that a subpopulation of proliferating microglia co-expressing Gal-3 and insulin-like growth factor 1 (IGF-1) might exert a neuroprotective property after stroke [51]. Consistent with previous studies, Kriz *et al.* recently revealed that Gal-3 was up-regulated in the proliferating microglia as early as 48 h following middle cerebral artery occlusion (MACO) and that sustained Gal-3 deficiency exacerbates the size of ischemic injury [2, 52]. Interestingly, they also found a significant increase of IL-6 protein in the ischemic brains of Gal-3 knock-out mice at 72 h after MCAO, rather than other proinflammatory cytokines, such as IL-1β, or tumor necrosis factor (TNF-α). Due to recent studies suggesting a crosstalk and synergy between IL-6 and IGF receptor 1 (IGF-R1), the author further investigated whether Gal-3 might be a potential molecule involved in the IGF-R1 signaling. Moreover, the further co-immunoprecipitation experiments showed that Gal-3 could bind to IGF-R1, suggesting that the interaction between Gal-3 and IGF-R1 might be necessary for IGF-mediated proliferation of microglia after stroke [9] (Fig. **2**).

5. GALECTIN-3: A POTENTIAL THERAPEUTIC TARGET IN CENTRAL NERVOUS SYSTEM DISEASES

5.1. Galectin-3: A Potential Therapeutic Target in Chronic Pain

Chronic neuroinflammation in the peripheral and central nervous systems is a remarkable feature shared by different

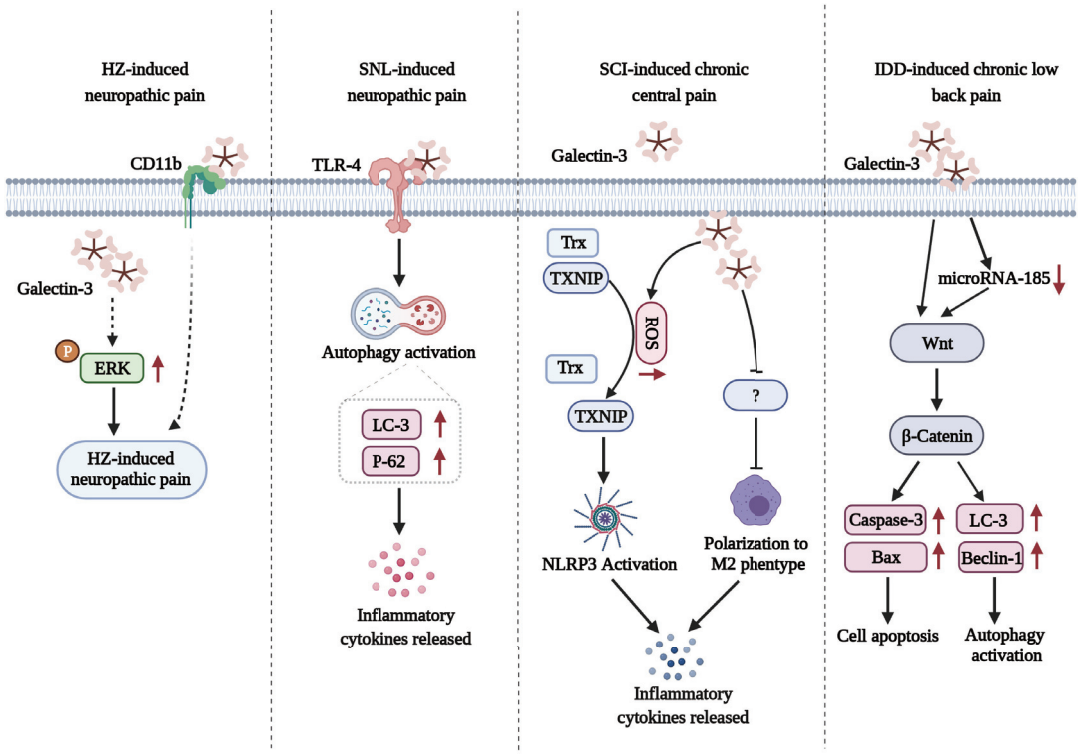

Fig. (3). The underlying mechanisms of Gal-3 that participate in the development of different types of pathological pain. (1) The possible mechanisms of Gal-3 that participate in the development of HZ-induced neuropathic pain. (2) Gal-3 inhibition could remarkably suppress SNL-induced neuroinflammation and neuropathic pain, at least in part *via* regulating autophagy activation. (3) Gal-3 plays a crucial role in aggravating the neuroinflammation of SCI rats *via* regulating the activation of the ROS/TXNIP/NLRP3 signaling pathway. Inhibition of Gal-3 improved the functional recovery of SCI rats *via* regulating the polarization of microglia towards the M2 phenotype. (4) Overexpression of miR-185 suppresses IDD-induced apoptosis and cell autophagy through suppression of the Wnt/β-catenin signaling pathway *via* regulating Gal-3. ERK: extracellular signal-regulated kinase; Gal-3: galectin-3; HZ: herpes zoster; IDD: intervertebral disc degeneration; LC-3: microtubule-associated protein 1 light chain 3; NLRP3: nod-like receptor protein 3; ROS: reactive oxygen species; SCI: spinal cord injury; SNL: spinal nerve ligation; TLR-4: Toll-like receptor-4; Trx: thioredoxin; TXNIP: thioredoxin-interacting protein. The figure was created using BioRender.com. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

chronic pain conditions [53]. Microglial activation in the spinal cord and brain is the dominating component of chronic neuroinflammation. Activated microglia under chronic pain is characterized by active proliferating potential, morphological changes, as well as inflammatory factors released [19]. Growing evidence has demonstrated that microglia have dual phenotypes (M1 proinflammatory phenotype and M2 anti-inflammatory phenotype) because of the influence of diverse circumstances [6].

Increasing studies revealed that Gal-3 plays a crucial role in activated microglia-mediated neuroinflammation [54]. However, microglia activation is regarded as a double-edged sword, and the change in either detrimental or neuroprotective effect is mediated by Gal-3 based on the disease types, stages, and severity [19]. Numerous chronic pain models have shown increased levels of Gal-3 in the spinal cord [55-57]. Additionally, a deficiency of Gal-3 or intrathecal administration of Gal-3 inhibitors could alleviate mechanical allodynia in various models of chronic pain [55]. These studies revealed the crucial role of Gal-3 in pathological pain, suggesting that targeting Gal-3 might be a potential therapeutic intervention for the treatment of chronic pain. Therefore, here we review the role and the underlying mechanisms of Gal-3, which participate in the development of pathological pain caused by herpes zoster (HZ), peripheral nerve injury, spinal cord injury (SCI), or intervertebral disc degeneration (IDD) (Fig. **3**).

5.1.1. Galectin-3 in Herpes Zoster-induced Neuropathic Pain

HZ arises from the reactivation of the varicella zoster virus in the sensory ganglion [58]. Patients with HZ are often accompanied with herpetic pain, with the hallmarks of hyperalgesia, allodynia, or spontaneous pain [59]. Delayed or ineffective treatment of herpetic pain may lead to postherpetic neuralgia (PHN) [60]. Recent studies showed that spinal herpes simplex virus type 1 (HSV-1) antigen immunoreactive cells were found approximately 5 days after varicella-zoster virus invasion [58, 59]. Interestingly, Gal-3 mRNA and protein levels were upregulated with a temporal pattern similar to that of HSV-1 invasion [55]. They also suggested that Gal-3 was mostly localized in cells positive for Iba-1 and F4/80 (markers for microglia and macrophage) in the superficial of the spinal cord 6 days after HSV-1 inoculation.

Moreover, herpetic pain was significantly reversed by a deficiency of Gal-3 or intrathecal administration of anti-Gal-3 antibodies. Conversely, intrathecal administration of Gal-3 could lead to reversible pain hypersensitivity in naïve mice

[55]. All these results suggested that Gal-3 might play a crucial role in herpetic pain. However, the mechanisms by which Gal-3 participates in herpetic pain remain unknow. Previous research demonstrated that Gal-3 could upregulate spinal extracellular signal-regulated kinase 1/2 (ERK1/2) mRNA expression and its phosphorylation level [60, 61]. ERK1/2 are widely verified to be implicated in the development of neuropathic pain [62]. Hence, it is conceivable that activation of spinal Gal-3 and ERK1/2 may participate in the development of herpetic pain. Another possible mechanism may be the action of Gal-3 on microglia. Gal-3, as a strong binding affinity for members of the integrin family such as CD11b, is widely expressed on microglia and macrophages. Since targeting Gal-3 is promising to inhibit herpetic pain, the underlying mechanisms of activated Gal-3 involved in herpetic pain should be explored in-depth, both in HSV-1 induced mice models, and most importantly, in patients with HZ.

5.1.2. Galectin-3 in Peripheral Nerve Injury Induced Neuropathic Pain

Peripheral neuropathic pain is associated with peripheral nerve injury-induced hyperexcitability of nociceptive sensory neurons [63, 64]. Activation of microglia is the crucial component of the inflammatory response, which serves as the first line of defense after nerve injury [1]. Previous evidence has demonstrated that microglial activation and the accumulated inflammatory mediators contribute to the development of peripheral nerve injury-induced neuropathic pain [7]. Gal-3, as a crucial molecule, participates in the regulation of microglia mediated-neuroinflammation. Its protein levels are increased in various diseases, including AD and ischemic injury [9, 43]. Therefore, it might be interesting to investigate whether Gal-3-mediated microglial activation is involved in the development of peripheral nerve injury-induced mechanical allodynia. Zheng *et al.* revealed that both the mRNA and protein levels of spinal Gal-3 were upregulated in rats model of L5 spinal nerve ligation (SNL) [56]. Moreover, modified citrus pectin (MCP), a Gal-3 inhibitor, significantly suppressed SNL-induced proinflammatory factors (*e.g.*, IL-1β, TNF-α, and IL-6) release in the spinal microglia, thus reversing the mechanical and cold allodynia following SNL. In order to investigate the underlying mechanisms of the anti-inflammatory effect of MCP, primary microglial cells were used. They demonstrated that MCP treatment could significantly suppress LPS-induced activation of autophagy *in vitro*. Rapamycin (a classical inducer of autophagy) treatment partially suppressed the actin of MCP on reducing the release of proinflammatory factors [56]. Based on the above findings, Gal-3 might be a potential target for treatment of peripheral nerve injury-induced neuropathic pain *via* regulating microglia-mediated inflammatory response.

5.1.3. Galectin-3 in Spinal Cord Injury-induced Central Neuropathic Pain

SCI results in devastating motor, sensory dysfunction, and neurogenic bladder dysfunction [65, 66]. In many clinical cases, patients with SCI are commonly accompanied by chronic central neuropathic pain [67]. The prognosis of SCI is strongly associated with secondary injuries, principally driven by inflammatory response [68]. Massive inflammatory mediators are released following SCI, resulting in functional alternations of surrounding nerve cells [69]. Gal-3, a potent inflammatory signaling molecule, has been revealed to regulate the process of microglia-mediated neuroinflammation [43]. In a recent manuscript, Ren *et al.* manifested that Gal-3 levels were remarkably increased in SCI rats *in vivo* and PC12 cells induced by LPS *in vitro*. They also found that Gal-3 inhibition suppressed inflammatory response and reactive oxygen species (ROS) production by regulating ROS/thioredoxin-interacting protein (TXNIP)/nod-like receptor protein 3 (NLRP3) signaling pathway following SCI [57]. In another study, they demonstrated that Gal-3 knockout mice manifested a significant decrease in CD11b (a marker of M1 macrophage) level and a more dominant arginase 1 (a marker of M2 macrophage) staining on day 7 after SCI, as well as a better functional outcome during the observation period [65]. All these studies suggested that the lack of Gal-3 could improve the functional outcome of SCI rats *via* suppressing inflammatory response and promoting microglia polarization towards the M2 phenotype.

5.1.4. Galectin-3 in intervertebral disc degeneration-induced chronic back pain

Chronic back pain is generally defined as continuous pain lasting longer than 7-12 weeks [70]. IDD is one of the dominating contributors to chronic back pain [71]. Since galectins are reported to be involved in arthritis/osteoarthritis pathogenesis by regulating inflammatory genes expression signature, a similar functional involvement of galectins in IDD has been widely investigated [72]. Gal-3, a group of β-galactoside-binding proteins, has been reported to be involved in the processes of cell apoptosis [30]. However, the underlying mechanisms by which Gal-3 participated in chronic back pain caused by IDD remain unclear. Recently, Gao *et al.* found a high level of Gal-3 accompanied by a downregulation of microRNA-185 in nucleus pulposus cells in IDD rats, suggesting that microRNA-185 might be closely associated with Gal-3 [73]. Moreover, the bioinformatics prediction and dual-luciferase reporter assay results showed that microRNA-185 could specifically bind to and inhibit Gal-3 levels [73]. In this study, they also testified that microRNA-185 overexpression inhibited cell apoptosis and autophagy *via* Wnt/β-catenin signaling axis suppression, thus alleviating IDD [73].

5.2. Galectin-3: A Potential Therapeutic Target in Other Neurodegenerative Diseases

5.2.1. Galectin-3 in Alzheimer's Disease

AD is one of the most common progressive neurodegenerative disorders characterized by amyloid-beta (Aβ) peptide aggregation, abnormal hyperphosphorylation of tau, as well as activation of microglia [49]. The role of Gal-3 in AD remains controversial because of its multifunctional property. Some scholars identified that Gal-3 was one of the crucial molecules involved in microglial activation in 5xFAD mice (an experimental model of familial AD). Its deletion could attenuate Aβ aggregation-mediated inflammatory response, especially those relevant to TLRs or TREM2 signaling, as well as improved cognitive behavior in 5xFAD mice [49]. Interestingly, they also observed that a single intrahippocampal administration of Gal-3 and Aβ monomers in wild

mice could induce a long-lasting Aβ aggregation, and this effect was suppressed when Gal-3 was lacking, suggesting that Gal-3 is indispensable in the process of Aβ aggregation [49]. Consistent with this, Lee *et al.* recently revealed that overexpression of Gal-3 could induce Aβ oligomerization and toxicity after injection of Aβ in the hippocampi [74]. In contrast, another study demonstrated that Gal-3, released by human umbilical cord blood-derived mesenchymal stem cells, could inhibit the abnormal accumulation of tau *via* downregulating its hyperphosphorylation [75]. They also analyzed the possible reasons for the conflicting functions of Gal-3 in AD mice, which might be the difference of cell types or different reactions to the stimulating environment.

5.2.2. Galectin-3 in Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disease with the hallmarks of α-synuclein formation, glia activation, neuroinflammation, and progressive loss of dopaminergic neurons [76, 77]. A more recent report has identified that Gal-3 was involved in the α-synuclein-induced microglial activation *in vitro*. Boza-Serrano *et al.* revealed that pharmacological inhibition of Gal-3 significantly reversed the increase of proinflammatory cytokines such as inducible nitric oxide synthase (iNOS), IL-1β, IL-12 induced by α-synuclein, suggesting the potential therapeutic target of Gal-3 inhibition in the treatment of PD [78].

5.2.3. Galectin-3 in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized clinically by progressive muscle paralysis due to the degeneration of the function of motoneurons [79]. Sporadic and familial cases of ALS share common pathophysiology features such as glial activation and marked neuroinflammatory responses [80]. Recent studies further explored the exact role of Gal-3 in activated microglia in ALS pathology. Interestingly, in contrast with its detrimental role in PD, some scholars revealed that Gal-3 might manifest an anti-inflammatory signaling induction, thus exerting a protective role in the development of ALS. Increased spinal Gal-3 levels have been detected in the $SOD1^{G93A}$ mice model of ALS and patients with ALS at disease end-stage [79, 81]. In agreement with this study, Knoblach *et al.* revealed that deletion of Gal-3 could lead to rapid disease progression approximately 25 days earlier than their $SOD1^{G93A}$/$Gal\text{-}3^{+/+}$ cohorts. Moreover, TNF-α level and oxidative stress were increased in $SOD1^{G93A}$/$Gal\text{-}3^{-/-}$ mice [80].

5.3. Galectin-3: a Potential Therapeutic Target in Ischemic/Stroke

Stroke is a common condition with the ischemic of CNS among the elderly, accompanied by the characteristics of peripheral monocytes/macrophages infiltration, abundant production of inflammatory cytokines, as well as resident microglial activation [5]. A massive expansion of the resident microglia is the representative feature of stroke-induced microglial activation [82]. Interestingly, Kriz *et al.* detected that Gal-3 and IGF-1 levels were upregulated, and most of them were colocalized in the proliferating microglia as early as 48 h following MACO [2]. Conversely, Gal-3 KO mice represented a significant decrease in the proliferation of microglia, as well as a remarkable increase of ischemic lesions [9]. These results suggest that Gal-3 positive proliferating microglia might exert a neuroprotective effect in the early stage of stroke. Recently, Kriz *et al.* further explored the underlying molecular mechanisms of Gal-3 action in the ischemia lesion. They demonstrated that a single intracerebroventricular administration of recombinant Gal-3 could induce an IL-4-dependent morphological transformation of microglia, as well as upregulate anti-inflammatory cytokines (IL-4, IL-10) and downregulate proinflammatory cytokines (iNOS, TNF-α) 24 h after stroke [52]. However, a contradictory study suggested that Gal-3 overexpression could contribute to neonatal hypoxic-ischemic brain injury *via* promoting the release of inflammatory factors [32]. Consistent with this study, Hara *et al.* also detected a transient upregulation of Gal-3 positive microglia in the hippocampal CA1 following neuronal cell damage. Moreover, Gal-3 and Iba-1 levels were significantly suppressed after hypothermia treatment, which is regarded as cytoprotectant [83]. All these studies revealed the complex and potentially time-dependent effect of Gal-3 in the regulation of microglia-mediated neuroinflammation. Further research is greatly encouraged to investigate the exact role of Gal-3 in ischemic/stroke.

5.4. Galectin-3: A Potential Therapeutic Target in Psychiatric Diseases

Psychiatric diseases, such as schizophrenia, depression, bipolar disorder, anxiety, autism, and attention-deficit/hyperactivity disorder, affect approximately 80 million individuals worldwide [84, 85]. Despite considerable progress in studies on psychiatric disorders in past decades, the exact etiologies and pathophysiology of these diseases are far from being completely elucidated [84]. Recently, chronic inflammatory states of some specific brain areas, which are characterized by excessive infiltration of immune cells, have been implicated in the etiopathophysiologies of psychiatric disorders [86, 87]. All above findings open possible scenarios for microglia alternations where Gal-3 might have a role. Consistent with this, Rosic *et al.* revealed that Gal-3 deficiency could attenuate the anxiogenic effect in LPS-treated mice *via* downregulating the expression of IL-6, as well as upregulating brain-derived neurotrophic factor (BDNF) and GABA-A receptor subunits 2 levels [88]. In contrast, a contradictory study observed a lower Gal-3 expression in the brain prefrontal cortex (PFC) in spontaneously hypertensive rats (a currently accepted model for attention deficit hyperactivity disorder (ADHD)) [89]. Further studies are encouraged to better understand if Gal-3 may be a potential target for a novel therapeutic strategy in psychiatric disorders. The above studies suggest that Gal-3 may be a crucial factor involved in the development of various CNS diseases, including chronic pain, neurodegenerative diseases, ischemia/stroke, and psychiatric diseases (Table **1**).

6. GALECTIN-3: IMPLICATION FOR DIAGNOSIS OR PROGNOSIS OF CENTRAL NERVOUS SYSTEM DISEASES

Given its visible biological fluids concentrations, Gal-3 may act as a potential diagnostic or prognostic biomarker for various CNS diseases [24, 30, 90] (Table **2**). A more recent study revealed that the plasma Gal-3 levels and Gal-3

Table 1. Galectin-3 functions in central nervous system diseases.

-	Diseases	Experimental Methods	Primary Experimental Findings	Gal-3 Function	Refs.
Chronic pain	HZ-induced neuropathic pain	C57BL/6J mice with HSV-1 inoculation	Gal-3 level was increased, and the formation of herpetic allodynia	Detrimental	[55]
	SNL-induced neuropathic pain	Injection of MCP in L5 SNL rats	Suppression of the expression of Gal-3 and SNL-induced inflammatory process	Detrimental	[56]
	SCI-induced central neuropathic pain	Gal-3 deficiency in SCI rats	Attenuation of neuroinflammation *via* downregulation of ROS/TXNIP/NLRP3 signaling pathway	Detrimental	[57]
	SCI-induced central neuropathic pain	Gal-3$^{-/-}$mice after SCI	Improvement in functional outcomes by suppression of the inflammatory response	Detrimental	[65]
	IDD-induced chronic pain	Overexpression of microRNA-185 in rats with IDD	Downregulation of Gal-3 and inactivation of Wnt/β-catenin signaling pathway	Detrimental	[73]
Neuro degenerative disease	Alzheimer's disease	5xFAD and APP/PS1 mice with BAC-TREM2 transgene	Overexpression of TREM2, switching of homeostatic microglia to DAM, amelioration of behavioral deficit	Beneficial	[46, 47]
	Alzheimer's disease	5xFAD–Gal-3 KO transgenic mice	Decrease in the Aβ burden and improvement of cognitive behavior	Detrimental	[49]
	Alzheimer's disease	Gal-3 KO mice with Aβ injection	Decrease in Aβ oligomerization and toxicity	Detrimental	[74]
	Alzheimer's disease	Overexpression of Gal-3 by hUCB-MSC in 5xFAD mice	Reduction in aberrant Tau hyperphosphorylation	Beneficial	[75]
	Parkinson's disease	Gal-3 KO in BV2 cells with α-synuclein addition	Prevention of iNOS expression and reduction of proinflammatory cytokines release	Detrimental	[78]
	Amyotrophic lateral sclerosis	SOD1^{G93A}/Gal-3$^{-/-}$ transgenic mice	Exacerbation of inflammatory response and acceleration of ALS progression	Beneficial	[80]
Ischemic/ stroke	Cerebral ischemia	Gal-3 KO mice with ischemic injury	Decrease in microglial proliferation and a remarkable increase in ischemic lesion	Beneficial	[2, 9]
	Stroke	Intracerebroventricular injection of Gal-3 in stroke mice	Shifting of microglia polarization towards M2 phenotype and exertion of a neuroprotective role	Beneficial	[52]
	Transient forebrain ischemia	Ischemic damage in the hippocampal CA1	An increase of Gal-3 expression in CA1 region following neuronal cell damage	Detrimental	[83]
Psychiatric diseases	Anxiety	Gal-3 deficiency mice with LPS-treated	Attenuation of the anxiogenic effect caused by LPS-induced neuroinflammation	Detrimental	[88]
	Attention-deficit/hyperactivity disorder	Spontaneously hypertensive rat	A decrease in Gal-3 expression in brain PFC	Beneficial	[89]

Abbreviations: ALS: Amyotrophic Lateral Sclerosis; Aβ: Amyloid-beta; DAM: Microglia Phenotype Associated with Neurodegenerative Diseases; Gal-3: Galectin-3; HZ: Herpes zoster; HSV-1: Herpes Simplex Virus Type 1; IDD: Intervertebral Disc Degeneration; iNOS: Inducible Nitric Oxide Synthase; MCP: Modified Citrus Pectin; NLRP3: Nod-like Receptor Protein 3; PFC: Prefrontal Cortex; ROS: Reactive Oxygen Species; SCI: Spinal Cord Injury; SNL: Spinal Nerve Ligation; TREM2: Triggering Receptor Expressed on Myeloid cell 2; TXNIP: Thioredoxin-Interacting Protein.

Table 2. Galectin-3 levels in central nervous system disorders and potential use as clinical biomarkers.

-	Diseases	Usage of Biomarker	Primary Experimental Findings	Refs
Neurodegenerative diseases	Huntington's disease	Plasma and post-mortem caudate putamen levels	A biomarker correlates with disease severity	[91]
	Amyotrophic lateral sclerosis	The spinal cord, brainstem sections, and spinal fluid levels	A biomarker correlates with ALS progression	[81]
	Amyotrophic lateral sclerosis	Serum and cerebrospinal fluid levels	A potential biomarker for ALS	[92]
	Amyotrophic lateral sclerosis	Plasma level	Positively correlate with the duration of ALS	[93]
	Idiopathic Parkinson's disease	Serum level	A biomarker for detection of PD and advanced stages	[94, 95]
	Alzheimer's disease	Serum and cerebrospinal fluid levels	A biomarker and therapeutic agent for AD diagnosis	[92, 96, 97]
Pain	Herpes zoster neuralgia or postherpetic neuralgia	Serum level	A potential risk factor of HZN and PHN	[60]
Ischemic/ stroke	Acute ischemic stroke	Serum level	Combination with HDL-C identifies the poor outcomes of acute stroke	[98]
	Acute ischemic stroke	Serum level	A prognostic biomarker in poor outcomes of acute stroke	[99]
psychiatric disorders	Depression	Serum level	A potential novel indicator for depression	[103, 104]
	ADHD	Serum level	Indication of potential neuroinflammation in ADHD	[105]

Abbreviations: AD: Alzheimer's Disease; ADHD: Attention-Deficit Hyperactivity Disorder; ALS: Amyotrophic Lateral Sclerosis; HDL-C: High-Density Lipoprotein Cholesterol; HZN: Herpes Zoster Neuralgia; PD: Parkinson's Disease; PHN: Postherpetic Neuralgia.

transcripts in the post-mortem caudate-putamen of Huntington's disease (HD) patients were higher than those in normal individuals using ELISA analysis and real-time polymerase chain reaction [91]. Moreover, an increased level of Gal-3 has also been demonstrated to be a potential biomarker for ALS [81, 92, 93]. Importantly, some scholars found that the expression of serum Gal-3 was relevant to idiopathic PD activities [94, 95]. Recent studies have been widely concerned about the importance of Gal-3 in AD. Some scholars found a remarkable overexpression of serum Gal-3 in AD patients compared to healthy controls [96, 97]. They also demonstrated that the elevated levels of serum Gal-3 might be a crucial biomarker for potential inflammatory response, proapoptotic activation, and impaired neurodegeneration in AD patients [97]. However, there are fewer studies about the expression patterns of Gal-3 in patients with pain. More recently, Huang *et al.* aimed to investigate the role of Gal-3 in patients with herpes zoster neuralgia (HZN) and PHN. Their results demonstrated that serum Gal-3 and IL-6 levels were significantly increased in HZN patients compared to those of non-PHN patients. Furthermore, the logistic regression analysis revealed that Gal-3 had a remarkable predictive effect on PHZ, suggesting that serum Gal-3 might be regarded as a potential biomarker for the initiation of PHN [60]. With respect to stroke, several clinical studies have suggested that high levels of Gal-3 are positively relevant to poor clinical outcomes in patients with acute ischemic stroke [98, 99]. Although Gal-3 has been recently reported in relation to psychiatric disorders, it is still controversial whether Gal-3 could be regarded as a potential diagnostic or prognostic biomarker for those diseases. Kajitani *et al.* revealed that serum Gal-3 levels were increased in patients with schizophrenia [100]. In contrast, Borovcanin *et al.* found lower serum concentrations of Gal-3 in first-episode psychosis and schizophrenia in relapse than those in control [101]. Interestingly, they reported higher Gal-3 levels in patients with schizophrenia in remission [101]. Consistent with their results, Yüksel *et al.* demonstrated that Gal-3 levels were elevated in the unaffected siblings relative to the patients [102]. Their results suggested that Gal-3 might serve as a protective agent against the inflammation. However, the recent studies on the serum levels of Gal-3 in patients with depression are relatively consistent. Their findings demonstrated that Gal-3 levels were higher in depressed patients, suggesting that Gal-3 may be a novel indicator for depression [103, 104]. Moreover, Is¸ık *et al.* also reported the changes in serum Gal-3 levels in children with ADHD [105]. Their results also supported that elevated serum Gal-3 levels may indicate potential neuroinflammation in patients with ADHD. More importantly, further prospective cohorts with larger samples are needed to study the diagnostic or prognostic roles of Gal-3 in CNS diseases.

7. GALECTIN-3 INHIBITORS AND THEIR THERAPEUTIC USE FOR CNS DISEASES

As Gal-3 specifically recognizes and binds to β-galactoside residues *via* the CRDs, pharmacological inhibition of Gal-3 is mostly mediated *via* CRDs for inhibiting the activity of this protein [17]. Recently, the widely used inhibitors against Gal-3 are generally divided into carbohydrate-based and peptide-based compounds [19]. Carbohydrate-based compounds cause Gal-3 to be incapable of binding to its ligands through competing for the binding sites or allosterically regulating it. Recently, peptide-based inhibitors such as NH2 terminally truncated Gal-3 (Gal-3C) and G3-C12 have only been studied in the treatment of Gal-3 related tumors [17, 106]. Here, we have briefly discussed the therapeutic potential of carbohydrate-based Gal-3 inhibitors in Gal-3 related pathologies.

GM-CT-01 and GR-MD-02 (belapectin) are two complex carbohydrate-based Gal-3 inhibitors that have been revealed to be efficacious in preclinical models of nonalcoholic steatohepatitis (NASH) and liver fibrosis [107]. GR-MD-02 treatment (60 mg/kg, twice a week for 4 weeks) resulted in a significant decrease of NASH induced-fat deposition, hepatocellular ballooning, and inflammatory infiltrate, as well as the expressions of iNOS (a TH-1 inflammatory marker), CD36 (a scavenger receptor for lipoproteins), and α-smooth muscle actin (an activated stellate cells marker) [108]. However, GM-CT-01 (120 mg/kg, twice a week for 4 weeks) has an intermediate effect between GR-MD-02 and vehicle [108]. In addition, they have also been demonstrated to have low toxicity potential due to the characteristics of non-toxic metabolites [109]. A phase 2b study has demonstrated that GR-MD-02 (2 mg/kg) for 52 weeks is safe and well-tolerated in patients with NASH, cirrhosis, and portal hypertension [109]. Although few clinical studies have been investigated to verify the therapeutic role of GM-CT-01 and GR-MD-02 in CNS diseases, they have been shown to have good safety, tolerability, and efficacy in other disorders.

MCP, a natural carbohydrate-based compound derived from citrus plants, has been extensively studied in numerous cells and animal models as a classical carbohydrate-based Gal-3 inhibitor [19]. In rat models of high-fat diet and streptozotocin (STZ)-induced diabetic, Liu *et al.* confirmed that MCP (100 mg/kg/day, oral for 6 weeks) could remarkably suppress the inflammatory response, oxidative stress, as well as cognitive impairment *in vivo* [110]. Moreover, their study *in vitro* in high glucose-induced BV-2 microglial cells further verified this effect of MCP [110]. In another study, MCP (100, 200 mg/kg/day, oral from day 14 to day 21) significantly inhibited inflammation and collagen deposition *via* suppressing the expression of Gal-3 and activation of TLR4/myeloid differentiation factor 88 (MyD88)/nuclear factor (NF)-κB signaling pathway in a rat model of isoproterenol-induced heart failure [111]. Recently, Bermu´dez-Oria *et al.* reported five novel pectoliv extracts from olives, representing a much higher potential in inhibiting Gal-3 activity with respect to commercial MCP [112]. Pectoliv extracts manifested more potent activities of agglutination inhibition in the hemagglutination assay. Moreover, these pectoliv extracts showed a higher antiproliferative effect on four different human bladder cancer cell lines [112]. They also thoroughly analyzed the different potential inhibition mechanisms for pectoliv and MCP. Commercial MCP might exert its effect *via* blocking the binding of Gal-3 to β-D-galactoside residues present on metastatic cancer cells [113]. In contrast, the agglutination inhibition effect of pectoliv may be associated with the interactions of polyphenols present in the hydrocolloid extracts with the Gal-3 protein suppressing the agglutination of lectin [112]. Therefore, further studies are encouraged to explore whether pectoliv extracts could potentially be a novel Gal-3 inhibitor.

CONCLUSION

Recent findings have widely expanded our knowledge on the crucial role of Gal-3 in the etiopathogenesis of various CNS diseases, including neurodegenerative diseases, chronic pain, stroke, and psychiatric disorders. Our review summarized the underlying signaling mechanisms of Gal-3 in microglia and demonstrated in some detail our knowledge of its role in microglia-mediated neuroinflammation. Despite unprecedented insights into the signaling mechanisms of Gal-3 in microglia, limitations in our knowledge still exist. In addition, Gal-3 is readily released into biological fluids, and it may be regarded as a potential diagnostic or prognostic biomarker for various CNS disorders. However, many questions remain to be answered.

First, the complexity of the Gal-3 expression pattern and sometimes its contrasting functions in CNS diseases were revealed [18]. Although Gal-3 is primarily distributed in the cytoplasm, it can also be found in the nucleus, extracellular environment, or even on the cell surface [20]. Various immune cells, including astrocytes, macrophages, and infiltrating monocytes, were found to express Gal-3 in different CNS disorders [114]. Moreover, Gal-3 has been revealed to participate in extensive pathological processes, such as cell-to-cell or cell-to-matrix contacts, inflammation, allergy, cell proliferation, apoptosis, and antimicrobial activity [30]. All these studies strongly support its multifunctional property. Depending on the expressed cell types of Gal-3 and the surrounding environment, it may represent different functions to exert beneficial or detrimental roles [115]. For example, Gal-3 is deemed to be one of the primary initiators of microglial proliferation and activation [18]. However, the role of activated microglia upon CNS diseases remains questionable. Therefore, the overall complexity roles of Gal-3 render it an interesting and worth-exploring target in CNS diseases.

Moreover, the studies on the roles of Gal-3 in CNS disorders remain in the nascent phase [18]. Even some preclinical studies targeting Gal-3 provide a potential target for clinical therapies of CNS disorders. Few or no therapeutic drugs specifically targeting Gal-3 are available to provide novel treatments for CNS diseases [16]. In addition, the extracellular and cell surface Gal-3 seem to be more crucial in neuropathology. Therefore, future exploratory studies or clinical trials should be developed with more selective and clinically relevant drugs targeting Gal-3.

LIST OF ABBREVIATIONS

AD = Alzheimer's Disease

ADHD = Attention Deficit Hyperactivity Disorder

AHP	=	Acute Herpetic Pain
ALS	=	Amyotrophic Lateral Sclerosis
Aβ	=	Amyloid-Beta
BDNF	=	Brain-derived Neurotrophic Factor
CNS	=	Central Nervous System
CRDs	=	Carbohydrate Recognition Domains
DAM	=	Microglia Phenotype Associated with Neurodegenerative Diseases
DAP12	=	DNAX-activating Protein of 12 kDa
EAE	=	Experimental Autoimmune Encephalomyelitis
ER	=	Endoplasmic Reticulum
ERK1/2	=	Extracellular Signal-regulated Kinase 1/2
Gal-3	=	Galectin-3
HSV-1	=	Herpes Simplex Virus Type 1
HZ	=	Herpes Zoster
HZN	=	Herpes Zoster Neuralgia
IDD	=	Intervertebral Disc Degeneration
IGF-1	=	Insulin-like Growth Factor 1
IGF-R1	=	Insulin-like Growth Factor Receptor 1
LPS	=	Lipopolysaccharide
IL-1β	=	Interleukin-1 Beta
IL-6	=	Interleukin-6
iNOS	=	Inducible Nitric Oxide Synthase
MACO	=	Middle Cerebral Artery Occlusion
MCP	=	Modified Citrus Pectin
MerTK	=	Mer Tyrosine Kinase
MyD88	=	Myeloid Differentiation Factor 88
NASH	=	Nonalcoholic Steatohepatitis
NLRP3	=	Nod-like Receptor Protein 3
NF-κB	=	Nuclear Factor-κB
PD	=	Parkinson's Disease
PFC	=	Prefrontal Cortex
PHN	=	Postherpetic Neuralgia
PI3K	=	Phosphatidylinositol 3-kinase
ROS	=	Reactive Oxygen Species
SCI	=	Spinal Cord Injury
SNL	=	Spinal Nerve Ligation
STZ	=	Streptozotocin
TNF-α	=	Tumor Necrosis Factor-α
TLRs	=	Toll-like Receptors
TREM2	=	Triggering Receptor Expressed on Myeloid Cell 2
TXNIP	=	Thioredoxin-interacting Protein

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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