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Review

Galectins - Important players of the immune response to CNS parasitic infection

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ABSTRACT

Galectins are a family of proteins that bind β-galactosides and play key roles in a variety of cellular processes including host defense and entry of parasites into the host cells. They have been well studied in hosts but less so in parasites. As both host and parasite galectins are highly upregulated proteins following infection, galectins are an area of increasing interest and their role in immune modulation has only recently become clear. Correlation of CNS parasitic diseases with mental disorders as a result of direct or indirect interaction has been observed. Therefore, galectins produced by the parasite should be taken into consideration as potential therapeutic agents.

1. Introduction

1.1. Galectins are important, multifunctional and widespread

Galectins are glycan binding proteins (GBPs) and include soluble type lectins (S-type lectins). They bind specifically to beta-galactoside sugars, such as N-acetyllactosamine which arise from N-linked or O-linked glycosylation. Galectins are evolutionary ancient proteins found in vertebrates and invertebrates and are located in the cytoplasm or extracellularly. They are unconventionally secreted as they do not possess a signal sequence. A total of 17 galectins have been identified, and 14 of these occur in humans, some with tissue-specific distribution. Binding to carbohydrates makes galectins key players in several intra- and extracellular processes. They are involved in many cell processes, including control of the cell cycle, cell division and pre-mRNA splicing (Liu et al., 2002). They are also important in hemostasis, angiogenesis and tissue repair (Arthur et al., 2015). In addition, galectins are strongly involved in immune responses via regulatory as well as inflammatory pathways and the function of galectins varies with their tissue and subcellular locations.

Galectins are expressed by various populations of immune cells such as activated T and B cells, regulatory T cells, dendritic cells, mast cells, eosinophils, monocytes/macrophages, and neutrophils. Because of the many different functions of galectins, aberrant expression results in the development of various diseases including cancer, HIV, autoimmune diseases, chronic inflammation, allergies and diabetes (Fortuna-Costa et al., 2014; Chou et al., 2018; Pugliese et al., 2014; Radosavljevic et al., 2012; Mensah-Brown et al., 2009; Ohshima et al., 2003). Galectins bind to glycosylated proteins and lipids and they regulate inflammation. Consequently, galectins also influence the central nervous system (CNS) and contribute to the pathogenesis in CNS disorders provoked by parasitic infection. Parasites are an abundant group of single cell and multicellular pathogens. However, the role of galectins in CNS pathology caused by parasites is insufficiently known.

The aim of this paper is to critically review the function of galectins in CNS parasitic diseases and identify areas where research is needed.

1.2. Role of galectins in the central nervous system

Galectins influence many CNS processes such as neuronal myelination, neuronal stem cell and microglia proliferation and apical vesicle transport in neuronal cells. The most important galectins are galectins 1 and 3 (Ramírez Hernández et al., 2020) but galectins 4, 8 and 9 also contribute (Stancic et al., 2011, 2012).

Galectin-1 (Gal-1) has regulatory properties. Apoptosis of effector T cells is the main mechanism of immunoregulation by Gal-1 (Perillo et al., 1995). In the CNS, Gal-1 is mostly produced by neuronal cells and neural stem cells (Lerman et al., 2012) and induces neural stem cell proliferation (Sakaguchi et al., 2006). The protein also inhibits proliferation and induces differentiation of astrocytes, hence it improves astrocytic brain-derived neurotrophic factor (BDNF) production (Sasaki et al., 2004). The course of Experimental Autoimmune Encephalomyelitis (EAE), a model of human multiple sclerosis (MS), was more severe in

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mice with a knockout in Gal-1 compared to wild type mice as a result of inhibited apoptosis of Th1 and Th17 cells (Toscano et al., 2007). Expression of Gal-1 increases in the acute phase of multiple sclerosis in mice models. Gal-1 regulates activation of classically activated (M1) microglia cells responsible for EAE development via p38 MAPK-, CREB-, and NF-κB pathways and inhibits proinflammatory factors: iNOS, TNF and CCL2. Adoptive transfer of astrocytes producing Gal-1 or application of recombinant Gal-1 limited EAE neuropathology (Starossom et al., 2012). In a gerbil model of focal ischemia, expression of Gal-1 is upregulated in the subventricular zone (SVZ). Introduction of human Gal-1 into the lateral ventricle of ischemic gerbils induced neurogenesis in the SVZ and sensory motor dysfunction improvement of the animals (Ishibashi et al., 2007). Increased level of Gal-1in CNS was also detected in a rat model of cerebral ischemia. In addition, administration of Gal-1 resulted in the recovery of ischemic rats (Qu et al., 2010). In a mice model of intracerebral hemorrhage, increased expression, mostly by astrocytes, of Gal-1 was observed (Bonsack and Sukumari-Ramesh, 2019). Mice without Gal-1 (Gal-1−/−) showed overlong immobility and increased compulsive-like behavior pointing to the influence of this protein on the emotional response to stress and as a result mental disorders (Sartim et al., 2020). Although Gal-1 activity and its influence on intra and extracellular pathways are not very well known, the protein has potential as a therapeutic agent (Salatino et al., 2008).

Galectin-3 (Gal-3) is mainly a product of microglia (Pasquini et al., 2011). Gal-3 is essential for microglia proliferation in aftermath of ischemic injury (Lalancette-Hébert et al., 2012). Gal-3 is important for oligodendrocyte differentiation and myelination. Knocking out the *LGALLS3* gene (LGALLS3 -/) resulted in a lack of Gal-3 and produced myelin defects, decreased g-ratio and loosely wrapped myelin. Application of extracellular Gal-3 obtained from microglia from wild type mice compensated for the deficit in endogenous production (Pasquini et al., 2011). *In vitro* stimulation of oligodendrocyte with Gal-3 involved AKt, ERK 1/2 and beta-catenin signaling pathways and produced cytoskeleton changes (Thomas and Pasquini, 2019). Gal-3 secreted by microglia is identified as a Toll-like receptor (TLR) 4 ligand and lack of Gal-3 was protective in an animal model where neuroinflammation was induced with lipopolysaccharide (LPS) (Burguillos et al., 2015). In addition, Gal-3 induced angiogenesis and migration of microglia in *in vitro* coculture of human umbilical vein endothelial (HUVEC) and BV2 microglia cells exposed to oxygen and glucose deprivation, a model of ischemic cell injury (Wesley et al., 2013).

Higher levels of Gal-3 are observed in sera from patients with Niemann-Pick disease type C1 (Cluzeau et al., 2012), amyotrophic lateral sclerosis (Yan et al., 2016), schizophrenia (Kajitani et al., 2017; Borovcanin et al., 2018) in sera and cerebrospinal fluid (CSF) with Alzheimer's Disease (AD) (Wang et al., 2015), and in plasma and brain of patients and mice with Huntington's Disease (HD). Higher levels are also correlated with disease progression and prognosis (Siew et al., 2019). In a mouse model of intracerebral hemorrhage upregulated expression of Gal-3 was observed (Bonsack and Sukumari-Ramesh, 2019).

Mice with Huntington's Disease and with suppressed Gal-3 expression had inhibited inflammatory responses, reduced mutant Huntington protein aggregation and lowered mortality (Siew et al., 2019). Previous studies have also implicated Gal-3 in the pathology of Alzheimer's Disease (AD). AD is a progressive neurodegenerative disease in which the formation of extracellular aggregates of amyloid beta (Aβ) peptide, fibrillary tangles of intraneuronal tau and microglial activation are major pathological hallmarks. Increased levels of Gal-3 were observed in the brains of AD patients and in a mouse model of AD - 5xFAD. Additionally, single-nucleotide polymorphisms associated with the Gal-3 gene increased the risk of developing AD. In the mouse 5xFAD model, inhibition of Gal-3 results in lower Aβ burden and improved cognitive behavior of animals (Boza-Serrano et al., 2019). Furthermore, Gal-3 influenced M2 macrophage development and trafficking to CNS (MacKinnon et al., 2008) which is consistent with a role for Gal-3 during CNS dysfunction and suggests that Gal-3 could be a potential target for treatment. Lack of Gal-3 in transient middle cerebral artery occlusion (tMCAO), a murine model of acute neonatal focal stroke, resulted in a worsening of injury. An increased level of proinflammatory factors cMIP1α and MIP1β and a decreased level of IL-6 cytokine as well as CD11b+/CD45$^{med\text{-}high}$ cells exacerbated disease (Chip et al., 2017).

In a rat model of perinatal hypoxic-ischemic brain injury, overexpression of Gal-3 by astrocytes, microglia, neurons and endotheliocytes was observed from 12 h post injury in various areas of the brain such as cortex, thalamus, corpus callosum and hippocampus (Wang et al., 2019). LGALS3−/− mice show inhibited expression of IL-6, TNF-α, GABA-1 receptor subunits and brain-derived neurotrophic factor (BDNF) in the hippocampus, however lack of Gal-3 reduced LPS-induced neuroinflammation which decreased the anxiety of animals. These opposite results show that various functions in the neurological system depend on the immunological state of the CNS (Stajic et al., 2019). In mice without Gal-3, symptoms of reduced cerebral blood flow are attenuated. Absence of Gal-3 results in preservation of retinal neurons and the lamina architecture, hence the protein can be considered as a target in therapy of retinal ischemia (Manouchehrian et al., 2015). Association of Gal-3 with cognitive function has been shown in the elderly based on variation in the LGALS3 gene coding for the Gal-3 protein (Trompet et al., 2012). In addition, there is a correlation of Gal-3 in the serum of patients with cognitive impairment and type 2 diabetes mellitus (Ma et al., 2020). Gal-3 can be a direct cause of changes leading to cognitive impairment. Moreover Gal-3 can influence behavior. Spontaneously hypertensive rats (SHR), a model of attention-deficit/hyperactivity disorder (ADHD), showed decreased levels of Galectin-3 in the brain prefrontal cortex (PFC), the most affected part of the brain in ADHD (Wu et al., 2010). Gal-3 is increased in the serum of children with ADHD and was correlated with oppositional defiant behaviors (Isık et al., 2020). This finding suggested that Gal-3 can be an etiological factor of ADHD in childhood. Studies on Gal-3 knock-out mice support the hypothesis that galectins influence development of depressive and compulsive-like behaviors (Sartim et al., 2020). Gal-3 is also correlated with depression. A higher level of Gal-3 has been reported in the blood of depressed patients with type 1 diabetes (Melin et al., 2018).

Galectin-4 (Gal-4) participates in myelination and maturation of oligodendrocytes. In a study of rat brains, expression of Gal-4 dropped just before the beginning of myelination. Moreover, stimulation of oligodendrocytes with Gal-4 delayed maturation of cells. Possibly Gal-4 partly regulates differentiation of oligodendrocytes (Stancic et al., 2012). Galectin-4 is expressed by hippocampal and cortical neurons. In addition, Gal-4 is involved in axon growth regulation, is sorted to the axon membrane and expressed in islands along the axon surface of differentiated neurons (Velasco et al., 2013). Axon segments that are unmyelinated express Gal-4 at a very low level, oligodendrocytes do not deposit myelin on surfaces covered by Gal-4 (Díez-Revuelta et al., 2017).

Galectin-8 (Gal-8) is strongly expressed in the choroid plexus and can be detected in human cerebrospinal fluid (Pardo et al., 2017). Elevated level of Gal-8 is observed in patients with Multiple Sclerosis (MS) (Stancic et al., 2011). Studies on mice with experimental autoimmune encephalomyelitis (EAE), an animal model of MS, showed that the protective role of Gal-8 is mediated by modulating Th1, Th17 and Treg immune responses (Pardo et al., 2017). Gal-8 protects hippocampal neurons cells against such unfavorable conditions as nutrient deprivation, glutamate-induced excitotoxicity, oxidative stress and β-amyloid oligomers in *in vitro* cell culture. Hippocampal neurons secreting Gal-8, lost viability during incubation with human function-blocking Gal-8 autoantibodies derived from individuals suffering from lupus (Pardo et al., 2019). Gal-8 participates in selective autophagy-dependent protection against seeded tau aggregation, which is a significant process in neurodegenerative diseases including AD (Falcon et al., 2018).

Human primary astrocytes produce Galectin-9 (Gal-9) following stimulation by IL-1β. The protein is observed in the perinuclear and membrane areas of cells (Yoshida et al., 2001). In addition, astrocytes incubated with TNF produce Gal-9 by the JNK/c-Jun pathway and Gal-9

immunoregulated neuroinflammation (Steelman et al., 2013). Galectin-9 is the ligand for Tim-3, the surface molecule of Th1 cells that regulates the inflammatory response. *In vitro,* Gal-9 induced apoptosis of Th1 cells in a Tim-3 dependent manner (Zhu et al., 2005). Gal-9 influences the interaction of astrocytes with microglia cells. In addition, Gal-9 induced production of cytokines by microglia independently of the Tim-3/galectin-9 pathway (Steelman and Li, 2014). Gal-9 seems to have potential for the treatment of neurodegeneration. Abnormal levels of Gal-9 were observed in biopsy samples from patients with MS (Stancic et al., 2011). Administration of Gal-9 cured mice with induced EAE through elimination of cells producing IFN-γ (Zhu et al., 2005).

2. Parasitic CNS infections

Parasitic CNS diseases are significant causes of morbidity and mortality all over the world. Those parasites that have a predilection for infesting the human CNS are mostly either single celled organisms (*Protozoa*) and multicellular helminths including *Nematoda*, *Trematoda* and *Cestoda*. Parasitic Protozoa that attack the brain of the host can cause lifetime chronic infection. The lack of effective therapy against protozoan parasites make it more serious. The severe course of parasitic disorders of the CNS is mainly due to the relatively large size of helminths. Moreover, helminths can evade the immune response and do not give any symptoms for a very long time after infection. Patients are often diagnosed too late. Localization of multicellular parasites in the human brain almost always involves epileptic seizures, by diffuse encephalitis or encephalopathy, or by the intracerebral position of the pathogen (Vezzani et al., 2016). Although galectins can influence the course of nervous system diseases and affect the pathogenesis of nervous tissue injury, the precise function of galectins in parasite-induced CNS pathology is uncertain.

2.1. Galectins as immunoregulators

The immunoregulatory properties of galectins are established. Until now few studies have shown a role for galectins in immunomodulation during CNS parasitic infection. The most investigated pathogen in this context is *Toxoplasma gondii*, an obligate intracellular parasite which persist as cysts in CNS for the lifetime of the host (Blanchard et al., 2015). In experimental infection with *T. gondii* of wild-type (gal3+/+) mice, Gal-3 is highly expressed in the leukocytes that infiltrate the intestine, liver, lungs, and brain. The absence of Gal-3 in *gal3*−/− mice increases IL-12 production by dendritic cells and indicates a role for host Gal-3 in controlling the parasite infection (Bernardes et al., 2006). Gal-3 influences murine neutrophils infected with *T. gondii* by decreasing the number of dead cells and degranulation following parasite infection. In addition, Gal-3 modulates the production of cytokines (IL-10, TNF-α, IL-6 and IL-12) by neutrophils. Suppression of phorbol myristate acetate-induced reactive oxygen species (ROS) in reaction to *T. gondii* infection is observed. Those observations indicate an important role for Gal-3 against *T. gondii* in the early stages of the infection (Alves et al., 2010, 2013). During ocular toxoplasmosis (OT), the levels of Gal-9 and its receptors (Tim-3 and CD137), are significantly higher in the eyes of susceptible C57BL/6 mice than in resistant BALB/c mice. Blockage of galectin–receptor interactions by α-lactose, affected neither ocular immunopathology nor parasite loads (Chen et al., 2017). Further research showed significantly higher levels of Gal-3 and Gal-9 in the brains of both C57BL/6 and BALB/c mice infected with *T. gondii* Pru strain. Since day 35 of infection, the level of galectins was higher in the brains of susceptible C57BL/6 compared to resistant BALB/c mice. Significant positive correlations existed between Gal-3 and Th1/Th2/M1/M2 cytokines as well as between Gal-9 and Th1/Th2/M2 cytokines in C57BL/6 or BALB/c mice brain tissue after *T. gondii* Pru strain infection. Significant positive correlations existed between Gal-3 and IL-4/IL-10/iNOS/Ym1 expression and between Gal-9 and IL-4/Ym1 in C57BL/6 mice; between Gal-3 and IFNγ/Arg1 and between Gal-9 and IFN-γ/Arg1 in BALB/c mice (Liu et al., 2018). These outcomes indicated substantial participation of galectins in the immune response during parasitic infections of the CNS. However, further studies on the functions and mechanisms of galectin are needed to determine their therapeutic potential.

Cerebral malaria is a well-known complication of severe malaria and is defined as an unarousable state of unconsciousness, accompanied by the presence of asexual parasitemia mostly due to *Plasmodium falciparum*. C57BL/6 mice exhibiting symptoms of experimental cerebral malaria (ECM) overexpressed Gal-3 protein and deletion of the Gal-3 gene conferred protection from ECM caused by *Plasmodium berghei* (Oakley et al., 2009). Results obtained on *Plasmodium yoelii* 17XNL, *P. berghei* ANKA and *Plasmodium chabaudi* AS infection reflected the complexity and singularity of host-pathogen interactions, indicating a species-specific role for endogenous Gal-3 (Toscano et al., 2012). Gal-9 was released from infected or damaged cells, during acute malaria under *P. falciparum* infection, and reflected the status of inflammation indicated by pro-inflammatory cytokines such as TNF-α, IL-6, IFN-α2, IFN-γ, and IL-1Ra (Dembele et al., 2016).

A protective role for Gal-3 and Gal-7 in the neuropathology of brain parasitic infection was recently postulated in a preclinical model of neurocysticercosis. Infection of mice with the tapeworm *Mesocestoides corti* is a model of cysticercosis in humans caused by *Taenia solium*. Mice infected with *M. corti* express more Gal-7 in brain endothelial cells. Lower numbers of M2 macrophages in the brain of Galectin-7 −/− NCC mice infected with the tapeworm were observed. Possibly, Gal-7 plays a crucial role in controlling M2 macrophage migration into the central nervous system (Zangbede et al., 2018). Gal-7 was predominantly expressed by keratinocytes (Gendronneau et al., 2008) with overexpression observed in the stratum corneum of atopic dermatitis patients (Sakabe et al., 2014). Hence most studies on protein function have been focused on skin diseases and carcinomas (Advedissian et al., 2017). Gal-7 influenced keratinocyte apoptosis, proliferation, and migration in skin repair processes (Gendronneau et al., 2008) and showed immunomodulatory properties against Langerhans cells (Umayahara et al., 2017). Influence of Gal-7 on CNS has not been the aim of recent studies, however Gal-7 is involved in other brain diseases and a therapeutical potential in CNS disorders is possible. Further research by the same group showed that M2 macrophages infiltrated the brain with abundant Gal-3 expression in the CNS of mice infected with the tapeworm *M. corti*. In Galectin-3−/− mice there were increased numbers of neurological defects, augmented cell death, as well as increased accumulation of neutrophils and M2 macrophages in the CNS. Adoptive transfer of those M2 macrophages from galectin-3-sufficient WT mice was able to reduce neutrophilia in the CNS and ameliorated disease severity in parasite-infected Galectin-3−/− mice (Zangbede et al., 2018). Interestingly the studies clearly suggested a cytosolic, but not extracellular, presence of Gal-3 in parasite-infected brains; Gal-3 was not detected on the surface of macrophages and neutrophils which suggests Gal-3 influences cytoskeleton rearrangements in macrophages. These mechanisms could explain the ambiguous results of galectin treatments.

There are few studies on the immunoregulatory role of galectins during parasitic CNS infection. Other closely related parasites can illuminate the mechanisms of galectin.

During *Trypanosoma cruzi* infection, a protozoan parasite of blood present in Central and Latin America, an immunomodulatory role for Gal-1 has been recently shown. Upregulation of Gal-1 favours the establishment of *T. cruzi* as it is able to downregulate IFN-γ expression by T cells in Chagas disease. Moreover, the immunomodulatory effect of Gal-1 in parasite replication and macrophage viability of *T. cruzi*-infected mice was dose-dependent. Low concentrations of this protein increased parasite replication and inhibited macrophage activity, high concentrations of Gal-1 increased macrophage apoptosis and inhibited parasite replication (Zúñiga et al., 2001). The key to understand the mechanisms of action of galectin seems to be the dose dependent manner of galectin treatment and target cell development and/or activation.

The extracellular protozoan parasite *Trichomonas vaginalis* colonizes

the human cervico-vaginal mucosa. The parasite is one of the most common non-viral, sexually transmitted vaginal infections. Presence of the protozoa is typically asymptomatic, however it can cause complications in pregnancy (Kissinger, 2015). During *T. vaginalis* infection, Gal-1 decreased the level of IL-8 which recruits phagocytes, cells that eliminate the parasite (Fichorova et al., 2016).

2.2. Galectins facilitate the entry into host cells

Galectins can be also useful for parasites as a crosslink to enter host cells. Gal-3 enhanced ligation of *Trypanosoma cruzi* trypomastigotes transmitted by insect vectors, or in blood infected with trypomastigotes during blood transfusion, by ligation to laminin (Moody et al., 2000). Host Gal-3 and -9 recognise surface lipophosphoglycans of *Leishmania major*, an obligate intracellular protozoan parasite. However, this association leads to the cleavage of Gal-3, resulting in impaired oligomerisation rendering it functionally inactive and disrupted galectin antiparasitic effects (Pelletier and Sato, 2002). In addition, Gal-9 promoted parasite binding to macrophages, assisted parasite invasion and promoted the interaction between *L. major* and macrophages (Pelletier et al., 2003). Gal-1 can bind to *T. vaginalis* in a carbohydrate-dependent manner through abundant lipophosphoglycans (LPG) on the surface of the parasite. Gal-1 may play a crucial role in the host cell-parasite interaction, as adherence to epithelial cells is necessary for survival of *T. vaginalis* (Okumura et al., 2008). Results obtained from various protozoa parasites show a crucial role of galectins in immunomodulation of immune response of the host as well as in host-pathogen interactions. Therefore, more studies need to be conducted to evaluate similar processes during protozoan infection of the CNS.

Although not much is known about the involvement of galectins in nervous system function, the importance of galectins on immunity is well established. Host galectins immunomodulate during parasitic infection and parasites manipulate the recognition of surface glycoconjugates by galectins to facilitate and enhance their survival. Galectin-3 is involved in parasite invasion and immunomodulation. Gal-3 is a unique member of the galectin family with unusual tandem repeats of proline- and glycine-rich regions and it is found on the surface of mammalian cells, secreted and known to interact with extracellular matrix proteins. It has been widely investigated in intracellular parasite adhesion to the extracellular matrix. Several parasites are able to induce cerebral disease. Host Gal-3, Gal-7 and Gal-9 significantly alter the pathogenic course of these infections. The main role of Gal-3, -7, -9 may be immunomodulation of parasite-specific immune responses. Besides, Gal-1 shows strong immunomodulatory properties in protozoan infections of other tissues. Therefore, the role of Gal-1 should be investigated in CNS parasitic infection.

2.3. Potential involvement of galectins in association of parasitic infections with mental diseases

The aetiology of mental disorders is not fully understood. However, many factors influence the development of those diseases including concurrent infections (Müller et al., 2015). As some neurotropic parasitic diseases can be chronic, sometimes lifelong, their impact on mental disorders needs to be investigated.

Most studies have been focused on *Toxoplasma gondii*. Based on epidemiological studies, about 25–30% of the human population is infected. Routes of infection include eating practices, contact with cats (definitive hosts of the parasite) which contaminate the environment with parasite oocysts (Robert-Gangneux and Dardé, 2012). Chronic infection with *T. gondii* is untreatable and a plethora of studies indicates that cerebral toxoplasmosis influences the host behaviour including psychomotor performance, cognitive capacities as well as human personality profiles (reviewed in Kamerkar and Davis 2012; Parlog et al., 2015). *T. gondii* is a known modulator of host behavior. Cerebral toxoplasmosis is linked with the prevalence of psychiatric disorders such as mood disorders, psychosis, and self-directed violence, obsessive-compulsive disorder or schizophrenia (Kamerkar and Davis 2012; Parlog et al., 2015). Interestingly, recent studies show an increased level of Gal-3 in patients with schizophrenia (Kajitani et al., 2017; Borovcanin et al., 2018). Similarly, *Toxoplasma* infection elevated Gal-3 in susceptible C57BL/6 mice (Liu et al., 2018). The similarity may not be accidental. Based on meta-analysis of epidemiological data, toxoplasmosis cases are corelated with schizophrenia prevalence (Daré et al., 2019). Hence those changes in Gal-3 levels in patients with psychosis could be directly or indirectly caused by parasitic infection. However, the studies did not consider chronic toxoplasmosis as a factor.

Neurocysticercosis caused by the tapeworm *Taenia solium* results in severe damage of brain. Hence mental disease such as cognitive and behaviour dysfunction or dementia was observed in patients with diagnosed neurocysticercosis (Verma et al., 2018; Ciampi de Andrade et al., 2010). Also, depression is frequently noticed (Forlenza et al., 1997). Mechanisms of influence of neurocysticercosis on development of mental disorders of the host remain unknown. A significant contribution of galectins in neuropathology during cysticercosis has been shown in mice as described above (Zangbede et al., 2018), Furthermore, mental illness accompanying infection of the brain with *T. solium* was correlated with Gal-3.

Schizophrenic patients are frequently seropositive for *Toxocara canis*. Almost half of patients with schizophrenia from Turkey had antibodies in their blood against this nematode, in comparison to the control group with only 2% of positive cases (Kaplan et al., 2008). A study conducted in Mexico did not show a similar correlation (Alvarado-Esquivel et al., 2014). However meta-analysis of the data indicated that toxocariasis is associated with an increased risk of schizophrenia (Daré et al., 2019). *Toxocara* species are cosmopolitan parasites. Humans can be infected by ingestion of *Toxocara* eggs by direct contact with animals or by contaminated food or soil. Humans are an accidental host of the parasite, larvae can migrate to the various organs including CNS and cause neurotoxocarosis. CNS infection with *Toxocara* species can cause eosinophilic meningoencephalitis manifested with meningitis, myelitis, encephalitis (Eberhardt et al., 2005). There are no studies showing the participation of galectins in the pathogenesis of neurotoxocarosis.

Beside parasites with a predilection for infesting the CNS, there are parasites attacking other tissues. In this context intestinal parasites are worthy of notice. Despite the location, investigations conducted on animal models indicated an influence of intestinal parasitic infection on behaviour of the host (Kavaliers and Colwell, 1995a, 1995b; Dobson 1988; Barnard et al., 1998). Soil transmitted helminth infections, which persist in the intestine of the host, influence cognitive function in children (Eberhardt et al., 2005; Kvalsvig et al., 1991; Nokes et al., 1992). In contrast, multicellular parasites of the intestine were able to inhibit development of CNS diseases such as MS in animal models and during clinical studies (Tanasescu and Constantinescu, 2014). Hence a peripheral immunomodulatory effect is observed, as there is no direct connection of parasite and CNS during infection. This effect can be a result of the existence of a microbiota–gut–brain axis, which is responsible for communication between the gastrointestinal tract and CNS. Functionality of the microbiota-gut-brain axis is influenced by neural, hormonal and immunological signalling (Martin et al., 2018). Association of dysbiosis of the microbiome and mental diseases such autism, schizophrenia, anxiety, depression and bipolar disease has been already reported (Meyer et al., 2011; Foster and McVey Neufeld 2013; Flowers et al., 2020). Moreover, parasitic gut infection alters the composition of microflora (Loke and Lim 2015). The relation of helminth infection with cognition and behaviour via gut microbiota has been discussed already (Guernier et al., 2017).

A correlation of depression with Chagas disease, caused by *Trypanosoma cruzi* has been shown. Interestingly, the highest level of depressive symptoms was noticed in patients with the digestive form of chagas (Ozaki et al., 2011). Microbiota–gut–brain axis can be an alternative explanation, especially as the microbiota composition in the colon is

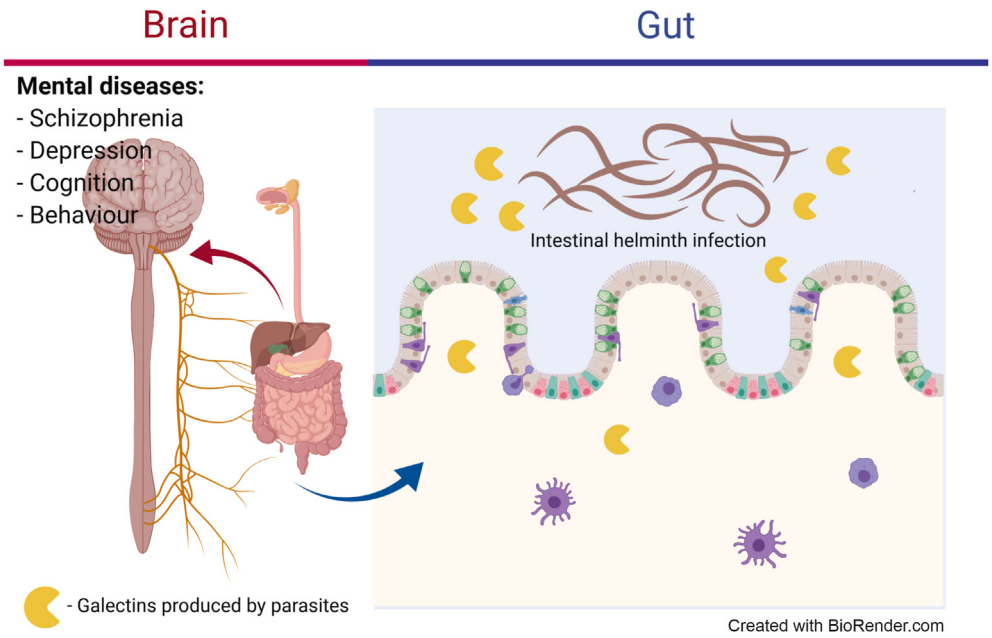

Fig. 1. Proposed pathway of parasitic galectins effect on CNS diseases via the parasite-microbiota-brain axis.

altered in Chagas chronic gastrointestinal disease (Guimarães Quintanilha et al., 2000).

Parasites produce their own galectins (reviewed in Shi et al., 2018). The role of nematode galectins is not firmly established. However, they are crucial for parasite viability (Young and Meeusen, 2004). Galectins from parasitic nematodes are extraordinarily interesting as they are closely associated with host disorders.

Toxascaris leonina is a parasite of predatory mammals including domestic and wild canines and felines. *T. leonina* galectin (Tl-gal) identified in adult worms is similar to human Gal-9 (Cho et al., 2009). Administration of Tl-gal inhibits inflammation of the colon in a DSS-induced mice model of colitis through increasing IL-10 and TGF-β production in splenic T cells (Kim et al., 2010). However, the same protein exacerbates the course of EAE. Administration of Tl-gal to EAE mice increased the number of CD45R/B2201 B cells and production of autoantibody [anti-myelin oligodendrocyte glycoprotein (MOG)35–55] in serum at the chronic stage with changes in cytokine TNF-α and IFN-γ in spleen cells. Unexpectedly, despite the similarly of parasitic Tl-gal to human Gal-9, the proteins exhibit dissimilar influences on EAE course, which can indicate different functions of nematode and host galectin (Bing et al., 2015) or possibly their competitive effects.

Galectins can be important players in CNS parasitic infections. In addition, parasitic infections of other tissues, especially the intestine, probably influence CNS with galectins involvement via the parasite-microbiota-brain axis (Fig. 1). Therefore, host galectins as well as galectins produced by the parasite should be taken into consideration as therapeutic agents or diagnostic factors. Analyses of correlations between galectins and the presence of parasite-specific antibodies in patients with mental disorders such schizophrenia, depression or cognitive impairment could give new insight into CNS-galectin-parasite association.

3. Conclusion

Some members of the galectin family play an essential role in the initiation and amplification of the inflammatory response, whereas other members exert a suppressive role. To date, no one has clearly demonstrated how galectins can influence both innate and adaptive immune responses. More studies are needed to identify the mechanisms involved and to determine at which stage of cell development, galectin is a key regulator. As galectins are involved in entry of parasites into the host cells, deeper exploration could identify galectins as new targets for therapy of CNS parasitic diseases. Correlation of CNS parasitic diseases with mental disorders has also been observed. Galectins could be the connection between those two groups but more research is needed to confirm this.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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