A potential impact of *Helicobacter pylori*-related galectin-3 in neurodegeneration

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**A B S T R A C T**

Neurodegeneration represents a component of the central nervous system (CNS) diseases pathogenesis, either as a disability primary source in the frame of prototype neurodegenerative disorders, or as a secondary effect, following inflammation, hypoxia or neurotoxicity. Galectins are members of the lectin superfamily, a group of endogenous glycan-binding proteins, able to interact with glycosylated receptors expressed by several immune cell types. Glycan-lectin interactions play critical roles in the living systems by involving and mediating a variety of biologically important normal and pathological processes, including cell-cell signaling shaping cell communication, proliferation and migration, immune responses and fertilization, host-pathogen interactions and diseases such as neurodegenerative disorders and tumors. This review focuses in the role of Galectin-3 in shaping responses of the immune system against microbial agents, and concretely, *Helicobacter pylori* (Hp), thereby potentiating effect of the microbe in areas distant from the ordinary site of colonization, like the CNS. We hereby postulate that gastrointestinal Hp alterations in terms of immune cell functional phenotype, cytokine and chemokine secretion, may trigger systemic responses, thereby conferring implications for remote processes susceptible in immunity disequilibrium, namely, the CNS inflammation and/or neurodegeneration.
Neurodegeneration as the underlying mechanism of a broad spectrum of central nervous system diseases

Neurodegeneration, defined as proliferation and activation of microglia (microgliosis), and/or astrocytes (astrogliosis) (Wilkins et al., 2017) occurs as a component of a number of the central nervous system (CNS) diseases pathogenesis. Relative disorders with primary disability character include Amyotrophic Lateral Sclerosis (ALS) (Taylor et al., 2016), Alzheimer’s disease (AD) (Willem et al., 2015) and Parkinson’s disease (PD) (Scott et al., 2017). As a secondary effect, neurodegeneration may be accompanied by inflammation, metabolic disorders, including hypoxia, and neurotoxicity, stemming either from the directly accumulated neurotoxic compounds, or by degradation of damaged brain tissue, as in the case of stroke (Lima et al., 2016) and the CNS trauma (Abdul-Muneer et al., 2017); neurodegenerative disorders are owing to long-lasting pathological processes linked with the CNS abnormal toxic proteins aggregates deposition and the activation of a cascade of aberrant biochemical, metabolic, functional and structural changes (Cerami et al., 2017). Specifically, stroke and traumatic brain injury (TBI) have been linked with neurodegeneration; stroke induces a rapid and significant loss of axons in the acute phase that triggers a wave of calcium signaling, activating proteolytic mechanisms and downstream signaling cascades (Himnan, 2014). Moreover, the disruption of mutual tight crosstalk between brain and immune system is the basis of stroke pathophysiology (Brambilla et al., 2013); the immune responses can contribute to pathogenesis before the stroke onset by inducing aberrant immune response-related inflammation within and around vessel walls, leading to thrombosis, altering vascular reactivity, and promoting atherosclerosis (Fu et al., 2015). Likewise, TBI induces subtle changes in molecular signaling, alterations in cellular structure and function, primary tissue injury, and blood-brain barrier (BBB) damage and leakage, thereby allowing for increased extravasation of immune cells (i.e., increased neuro-inflammation) (Pearn et al., 2017).

Multiple Sclerosis (MS) is a typical example of the CNS inflammatory and autoimmune demyelinating disease mediated by autoreactive T-cells, activated towards various myelin antigens (Dendrou et al., 2015). In its more frequent form, relapsing-remitting MS (RRMS), episodes of the CNS inflammation lead to reversible neurological disability (Polman et al., 2011). As in the case of the TBI, BBB disruption represents the incipit to MS development by favoring the migration of pathogenic lymphocytes into the CNS. This initial step is important for the neuroinflammation establishment, responsible for neuron demyelination and the neurological manifestations of MS (Kountouras et al., 2012a, 2014a; Ullivieri and Baldari, 2017). Later, progression of disability in the absence of acute relapses signifies transition into secondary progressive MS (SPMS) (Katz Sand et al., 2014). The fact that pharmaceutical immunomodulative agents that target pathways of inflammation are effective in ameliorating disease activity in RRMS but fail to hinder disability progression once transition into SPMS has occurred (Krieger, 2011), underlines potentially different pathogenetic mechanisms between the two stages of MS (Mahad et al., 2015). In the case of SPMS, although neuropathological studies indicate that inflammation may still contribute to the CNS lesions, however, alterations in BBB permeability may render the inflammatory process inaccessible to therapeutic interventions. Although SPMS is not a primary neurodegenerative disease, evidence of increased mitochondrial disruption, oxidative stress and age-dependent iron accumulation in the diseased CNS indicate that the relative contribution of the pathogenetic mechanisms in the case of SPMS is shifted towards neurodegeneration, compared to the profound activation of inflammatory pathways evident in RRMS (Lassmann et al., 2012; Mahad et al., 2015). Neurodegeneration is also present at early stages of RRMS, contributing to cognitive defect that may accompany early MS (Calabrese et al., 2012; Pirko et al., 2007). The contribution of the B cells to MS pathophysiology has also been reassessed due to beneficial effect of B-cell-depleting therapeutic strategies (Bittner et al., 2017).

2. The pathophysiological role of galectin-lectin interactions

Galectins are the lectin superfamily members, a group of endogenous glycan-binding proteins, able to interact with glycosylated receptors expressed by several immune cells (van Kooyk and Rabinovich, 2008); they are ubiquitously expressed and distributed in mammalian tissues, including cells of the innate (dendritic cells, macrophages, mast cells, natural killer (NK) cells, gamma and delta T cells, and B cells) and adaptive (activated B and T cells) immune systems (Rabinovich et al., 2007; Stowell et al., 2008). Galectins consist of 15 different types (Ashraf et al., 2017; Rapoport and Bovin, 2015). Specifically, galectins act when secreted extracellularly and intracellularly (Liu et al., 2002; Rabinovich and Toscano, 2009); most functions of galectins are exerted extracellularly (Mansilla Pareja et al., 2017). Based on carbohydrate-recognition domains (CRD) structural organization, galectins are divided into proto-, chimera- and tandem-repeat types (Rapoport and Bovin, 2015). Prototype galectins exhibit one CRD and usually form noncovalent dimers; tandem-repeat type galectins contain two carbohydrate-recognition domains (N-CRD and C-CRD) connected by a short linker peptide; the chimera-type is presented by galectin-3 (Gal-3) which exhibits two distinct domains, i.e. C-terminal CRD and N-terminal regulatory domain that contains collagen-like repetitive regions (Rabinovich and Croci,
Gal-3 shows extracellular and intracellular actions that facilitate foreign antigen recognition by the host, with relevance to immunity (Chen et al., 2009).

Lectin-glycan interactions are ubiquitous and critical to biological systems, not simply as the ‘glue’ between cells, but as the initiators of a functional crosstalk that modulates their physiology and homeostatic balance (Vasta, 2009). They mediate cell–cell signaling shaping cell proliferation, phenotype alterations and functional circuits (Marth and Grewal, 2008; Sato et al., 2009); they play a critical role in the living system by involving and mediating a variety of biologically important processes such as cell communication, immune responses and fertilization, pathogens immune recognition, immune cell migration, protein processing, regulation of cell-surface receptors, sperm–egg binding, and tumor development and progression (Christie et al., 2014; Kletter et al., 2013; Wang et al., 2013).

Specifically, galectins play important roles in host defense against pathogens, and they are expressed by barrier tissues and immune cells. Galectins can interact directly with bacterial surface glycans and bind to the surfaces of some pathogens and products released by the pathogens. These lead to direct effects on pathogens growth or immune responses against them. Likewise, galectins affect the process of bacteria entering the host cells, acting as bacterial sensors in host immune responses (Vasta, 2009). While galectin-mediated sensing of bacterial infection mostly takes place at the extracellular place, it can also occur at the intracellular place, by recognizing intracellular bacteria; galectins play significant roles inside the cells in response to infection by intracellular bacteria (Chen et al., 2014).

The importance of glycan signaling is depicted by the extent of intracellular glycosylation processes in the frame of post-translational protein modification (Dube and Bertozzi, 2005). Glycosylation is being conducted by the cell in Golgi apparatus (Dennis et al., 2009). Total cell glycan molecular content, namely, the “glucose”, together with the more thoroughly described genome and proteome, regulate cell interaction with the micro-environment and its fate (Campbell et al., 2017). Signaling molecules carry glycan components that interact with appropriate ligands expressed by neighboring cells. In this sense, pathogen- and danger-associated molecular patterns, PAMPs and DAMPs, respectively, expressed in the surface of microbial and viral agents, are chemically glycans recognized by pattern-recognition receptors, such as toll-like receptors (TLRs), expressed by the innate immune cells, thereby orchestrating the distinction between pathogens and the self (Varki, 2011); lectins can function as pattern-recognition receptors (PRRs), a group of soluble and membrane-associated molecules that include the mentioned TLRs, nucleotide-binding oligomerization domain (NODs) and NK cell receptors. In this respect, galectins bind glycans on the surface of viruses, bacteria, parasites and fungi, thus the potential role of galectins as PRRs has becoming an area of increased attention (Vasta, 2009). Furthermore, since galectins can form oligomers, their multivalant binding properties, including increased avidity, obviously enable galectins to participate effectively both in direct recognition of pathogens and parasites, and downstream processes resulting in innate and adaptive immune responses activation (Vasta, 2009). T-cell receptor and B-cell receptor are also examples of glycoproteins implicated in glycan-lectin signaling that determines cell’s effector phenotype and its activation towards foreign antigens (Dennis et al., 2009).

It is important to note that the abnormal production of certain glycans or glycan-binding proteins have harmful consequences (Kletter et al., 2013). In this respect, galectins play crucial role in the immune system, inflammation, wound healing, oncogenesis, atherosclerosis, cerebro-cardiovascular disease, including myocardial infarction, stroke, and other components of metabolic syndrome (MetS) (Ashraf et al., 2017; Nayor et al., 2015). Regarding the immune system, galectins have emerged as novel regulatory checkpoints that stimulate immune evasion by inducing T-cell exhaustion, limiting T-cell survival, promoting T regulatory cell expansion, de-activating NK cells and polarizing myeloid cells toward an immunosuppressive phenotype. Concomitantly, galectins can trigger vascular signaling programs, serving as bifunctional messengers that couple tumor immunity and angiogenesis (Mendez-Huergo et al., 2017). Moreover, as in the case of Helicobacter pylori (Hp) infection (Deretzi et al., 2016; Franceschi et al., 2015; Wang et al., 2015b; Zeng et al., 2015), galectins also contribute to neurological diseases pathogenesis (Mendez-Huergo et al., 2014; Parikh et al., 2015).

This review focuses on the role of galectins in shaping responses of the immune system against microbial factors, and more specifically Hp, thereby potentiating the microbial effect in areas distant from the gastric colonization ordinary site, such as in the CNS. We herein postulate that alterations caused by Hp with galectins relative involvement in the gut in terms of immune cell functional phenotype, cytokine and chemokine secretion, may trigger systemic responses, thereby conferring implication for remote processes susceptible in immunity disequilibrium, including the CNS inflammation and/or neurodegeneration.

3. Hp infection

The prevalence of Hp infection is still high in most countries; there were about 4.4 billion individuals with Hp infection worldwide in 2014, and Hp remains highly prevalent in certain ethnic populations and in migrants moving from high prevalence countries (Eusebi et al., 2014). Likewise, neurodegenerative disorders including AD, glaucoma, defined as ocular AD, and other neurological conditions are also associated with a large public health burden and are the disability prominent causes (Bourne et al., 2016; Fiest et al., 2016; Howard et al., 2016).

Hp infection is associated with a variety of gastric pathologies including peptic ulcer disease, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (Ernst and Gold, 2000). Apart from gastrointestinal tract (GIT), Hp infection is associated with a variety of extragastrointestinal disorders (Franceschi et al., 2015). As in the case of galectins, Hp is associated with functional vascular disorders caused by vascular dysregulation, atherosclerosis, hypertension, cardiovascular and/or cerebrovascular ischemia, stroke, and other MetS-related parameters (Franceschi et al., 2015; Kountouras et al., 2002, 2005, 2017a, 2017b; McColl, 1997; Mendlall et al., 1994; Nayor et al., 2015; Sawayama et al., 2005; Xu et al., 2000), all of which appear to be risk factors for AD, mainly by impairing BBB, a common denominator associated with various degrees of dementia including AD (Craft, 2006; D’Andrea, 2005; de la Torre and Stefano, 2000; Hofman et al., 1997; Mecocci et al., 1991; Pugazhenthil, 2017; Wardlaw et al., 2003); these conditions contribute to the clinical manifestations and worsening of AD (Ascher-Svanum et al., 2015; Pasquier and Leys, 1997).
practical diagnostic gold standard for active Hp infection presence (Kountouras et al., 2001b, 2006a, 2007c). Although the serologic test establishes the presence of antecedent Hp infection, it does not discriminate between current and old infections. Such a distinction is critical because only active Hp infection induces humoral and cellular immune responses that, owing to the sharing of homologous epitopes (molecular mimicry), cross-react with components of nerves, thereby contributing and possibly perpetuating neural tissue damage (Kountouras et al., 2006a). Moreover, eradicating Hp infection might delay progression of the CNS pathologies (Kountouras et al., 2006a).

Hp may access the brain mainly via the oral-nasal-olfactory pathway or the circulation, by circulating monocytes (infected with Hp due to defective autophagy) through disrupted BBB. A third pathway comprises a fast retrograde neural pathway from GIT to the brain leading to neurodegeneration (Derezi et al., 2009; Franceschi et al., 2014, 2015).

4. Gal-3 and Hp infection

Gal-3 exhibits pleiotropic biological and molecular functions via extracellular and intracellular pathways (Lu et al., 2017).

Specifically, Gal-3 exerts biological functions either as a surface molecule, or secreted in the microenvironment, in a paracrine or endocrine fashion. It recognizes β-galactoside molecules expressed by numerous bacteria, including Hp, thereby playing a role in innate immunity recruitment following bacterial infection. Gal-3 mediates macrophage (Sano et al., 2003) and neutrophil activation (Fermino et al., 2011). Experimental and clinical studies modeling infections by several bacteria show that the Gal-3-mediated host immune response is context dependent. In human leprosy, Gal-3 ligation was shown to mediate interleukin (IL)-10 production by monocytes, thus contributing into T-helper type 2 (Th2) anti-inflammatory response induction (Chung et al., 2013). Moreover, increased Gal-3 expression, as a response to microbial infection, is likely to allow the bacterium to circumvent the host’s defense mechanisms, mainly orchestrated by T-cells activated towards T-helper type 1 (Th1) effector phenotype.

Regarding Hp, Gal-3 plays a role in bacterial colonization of the gastric epithelium, and in local immune response and chronic gastric implications. Mice lacking Gal-3 exhibit more prominent colonization by Hp, extended into deep layers of the gastric wall, compared wild type mice (Park et al., 2016). This difference in the degree of mucosal invasion by Hp was partly attributed to macrophages reduced phagocytic ability in Gal-3 deficient mice, against microbial cells (Park et al., 2016). Gal-3 not only efficiently traps and aggregates Hp within the gastric surface mucus layer but also exerts a potent bactericidal activity both directly and within macrophages. Therefore, Gal-3 might be an essential host factor in keeping Hp infection and colonization at subclinical levels (Xu et al., 2000). Specifically, adhesion of Hp to the gastric lining upregulates expression and secretion of gastric epithelium Gal-3; Gal-3 was shown to bind Hp-lipopolysaccharide (LPS) (Fowler et al., 2006); its O-antigen side chain component that bears a significant structural resemblance to the human Lewis-X antigen expressed by the gastric epithelial cells (Moran, 2008). Recognition of Hp-LPS has been linked with Gal-3 gastric epithelial overexpression and recruitment of peripheral blood monocytes, namely, macrophages and neutrophils (Fowler et al., 2006), suggesting that Gal-3 plays a part in the infection host response, by promoting recruitment of phagocytic cells to the site of infection and induction of an inflammatory response, and by disrupting the interaction of the pathogen with the host cells; Gal-3 is upregulated and rapidly secreted by gastric epithelium in response to Hp infection and the Hp-related cytotoxin-associated gene A (cagA) is involved in the Gal-3 intracellular expression (Subhash et al., 2016). Moreover, in vitro infected gastric epithelial AGS (human gastric adenoma carcinoma cells) lines, galectins –3 and –1 were upregulated (Huff et al., 2004; Lim et al., 2003). Upregulation of Gal-3 is a critical endogenous event in Hp infection that interferes with various intracellular events, causing prolonged cell survival, characteristic in gastric carcinogenesis (Subhash and Ho, 2016); Gal-3 has been linked with the Hp–related gastric cancer and is considered as a factor of poor prognosis (Miyazaki et al., 2002); serum Gal-3 represents a potential diagnostic marker for gastric cancer patients and might be an adjunct to determine the individual prognosis of these patients (Cheng et al., 2015); and Gal-3 plays the key role of activating cell surface receptor through production of protease and boosts gastric cancer metastasis by further regulation of several signaling pathways, thereby having the potential to serve as a useful pharmacological target for gastric cancer metastases prevention (Cardoso et al., 2016; Kim et al., 2011). Moreover, Gal-3 is overexpressed in other Hp–related human tumors, including colorectal, prostate and lung malignancies and may also be a potential diagnostic marker for these cancers (Cheng et al., 2015; Dondoo et al., 2017; Kountouras et al., 2014c, 2017a; Kuo et al., 2016; Schoeppeper et al., 1995).

5. Gal-3 induces adverse CNS effects by promoting inflammation and neurodegeneration

Expressions of galectins are increased under neuro-inflammatory conditions, and neuroinflammation contributes to neurological diseases pathogenesis. Regarding Gal-3, its neuronal expression is observed in several functional parts of the cerebral cortex and diverse other subcortical nuclei in the hypothalamus and brainstem; strong Gal-3 immuno-signals are present in several hypothalamic nuclei related to a variety of physiological functions responsible for mediating anxiety responses, energy balance, and neuroendocrine regulation; brain Gal-3 expression is regulated by developmental cascades; and functionally and neuroanatomically related brain nuclei constitutively express Gal-3 in adulthood (Yoo et al., 2017).

Moreover, in activated neuroglia under neuroinflammation, the CNS Gal-3 expression is recognized (Yoo et al., 2017) and its expression is substantially enhanced in interferon (IFN)-γ-stimulated glia and induces high levels of proinflammatory mediators by activation of the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway. Therefore, its presence in the brain could be indicative of neuro-pathophysiology in the CNS (Jeon et al., 2010; Parikh et al., 2015).

Noteworthy, Gal-3 mediates neuronal loss in the gut, in the context of an experimental stroke model (Cheng et al., 2016). Defects in the post-stroke gastrointestinal motility have been well recognized. Interestingly, this effect was shown to be TLR4-mediated, thereby indicating a relative role for gut bacteria (Cheng et al., 2016).

Gal-3, as a promoter of immune cell recruitment in the context of inflammation, has detrimental effect in the CNS autoimmune response frequently triggered by neuroinflammation. Gal-3 mediates inflammatory infiltrations in the CNS parenchyma upon MS relapses, a response evident in the sub-ventricular zone (SVZ), a residing area for neural precursor cells and one of the rare niches of adult neurogenesis. Absence of Gal-3 in MS attenuates the CNS inflammation and restores the brain regenerative capacity by promoting neural stem cell proliferation in the SVZ (James et al., 2016). Likewise, absence of Gal-3 plays a role in the survival of retinal ganglion cells (RGC) and thus can be a potential target for RGC neuroprotective therapeutic intervention (Abreu et al., 2017). Of note, in the study of James et al.; a model of viral demyelination was
used, contrary to experimental autoimmune encephalomyelitis (EAE) mouse model for MS, induced by active immunization against a myelin antigen. What is more interesting is the possible contribution of selected TLR ligands in the Gal-mediated effect. Previous studies in active EAE indicate a detrimental role of Gal-3, by exacerbating disease through induction of pro-inflammatory IL-17 and IFN-γ, and amelioration of regulatory IL-10 (Jiang et al., 2009). Moreover, clinical evidence indicates the presence of anti-Gal-3 antibodies in sera from SPMS patients, with relevance to the integrity of BBB; it has been postulated that Gal-3 expressed by BBB may act as an immunological target molecule thus contributing to the pathogenesis of SPMS (Nishihara et al., 2017). Gal-3 exerts prominent effects mediating the CNS inflammation and subsequent neurodegeneration by directly affecting nerve cells following viral inoculation, in the absence of an autoimmune response (Kobayashi et al., 2015). Moreover, in a viral encephalitis experimental model [argentine haemorrhagic fever (AHF) caused by Junin virus (JUNV) infection], Gal-3 increased expression in activated astrocytes and glial cells was reported (Jaquenod De Giusti et al., 2011). Gal-3 production by glial cells promotes oligodendrocyte differentiation in the sites of inflammation, thereby contributing to remyelination in the context of EAE (Pasquini et al., 2011). Moreover, in a mouse model for the CNS neonatal hypoxia, Gal-3 was reported to mediate detrimental inflammatory response, whereas absence of Gal-3 attenuated macrophage phagocytic action by reducing matrix metalloproteinase-9 expression, thereby restoring the CNS homeostasis (Doverbag et al., 2010).

In an additional experimental model of TBI, Gal-3 was shown to mediate inflammation developing at the lesion site within 24 h of the trauma induction. Furthermore, blocking of the Gal-3-lectin signaling pathway by administering an anti-Gal-3 blocking antibody, or in Gal-3 knock-out (KO) mice, was shown to ameliorate the CNS trauma-related inflammatory response exerting neuroprotective effect (Yip et al., 2017), a TLR4-mediated result.

In a model of scrapie (zoonotic prion disease), Gal-3 was expressed in cells of the CNS innate immunity, such as microglia and macrophages, and its expression correlated with neurodegenerative cell death extent (Jin et al., 2007); Gal-3 by activated microglia/macrophages correlated with abnormal prion protein accumulation, thereby suggesting a possible Gal-3 involvement in the process of neurodegeneration (Jin et al., 2007).

These studies provide evidence of implication of Gal-3 signaling in model neurodegenerative diseases with a role of inflammation in the pathogenetic process. It is therefore reasonable to assume that the overall effect of Gal-3 in cells of innate immunity would modulate the CNS inflammation and neurodegeneration, with a prominent effect in the disease progression.

A case-control trial reported increased serum Gal-3 levels in AD patients than in controls (Wang et al., 2015a); high plasma Gal-3 levels were reported in ALS patients positively correlated with the disease duration; and high Gal-3 expressions were identified in the end stage ALS patients. Immune reactivity and inflammatory mechanisms play a role in ALS pathogenesis (Yan et al., 2016).

Conversely, experimental evidence stemming from a mouse model of ALS, indicates a presumably protective effect of Gal-3 overexpression in macrophages. Gal-3 upregulation is regarded as a secondary effect by which the CNS attempts to restore axonal loss. It is postulated that neurodegeneration leads to neural tissue by-products accumulation, resulting in macrophages recruitment and the secondary inflammation development (Lerman et al., 2012). These studies suggest a tissue-specific galectin effect, in addition to the trigger eliciting its production, such as the responsible microorganism.

AD and other neurodegenerative disorders such as PD or glaucoma should be regarded as degenerative metabolic diseases associated with MetS-related brain features (de la Monte, 2017; Kim et al., 2016b; Motamedi et al., 2017; Pistollato et al., 2015). MetS is related to insulin resistance (IR), the key component responsible for MetS, and its related morbidity including abdominal obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) (Franceschi et al., 2015). In this respect, recent data indicate that, apart from Hp infection, galectins play the mentioned crucial role in atherosclerosis, cerebro-cardiovascular disease, including myocardial infarction and stroke, and other components of MetS (Ashraf et al., 2017; Nayor et al., 2015). Relative studies reported circulating Gal-3 association with MetS components including abdominal adiposity, dyslipidemia, hypertension, and increased incidence of atrial fibrillation, heart failure, chronic kidney disease, and mortality (Nayor et al., 2015). Gal-3 binds directly to the insulin receptor (IRr) and inhibit downstream IRr signaling, thereby signifying its role in IR and its association with diabetes mellitus which is a risk for brain injury (Darrow and Shohet, 2015; Hamed, 2017; Li et al., 2016). Regarding NAFLD, recent data suggest a protective role for the IL-33/IL-33R (ST2) signaling pathway in obesity, adipose tissue inflammation and atherosclerosis, but a profibrotic role in nonalcoholic steatohepatitis (NASH) development. The link between Gal-3 and soluble ST2 in myocardial fibrosis and heart failure progression has been demonstrated and Gal-3 and the IL-33/ST2 pathway interact and both have a profibrotic role in diet-induced NASH, which is sufficient to induce neurodegeneration (Kim et al., 2016a; Pejnovic et al., 2016). Moreover, Gal-3, is connected with large artery atherosclerotic stroke with concomitant unfavourable outcome and its ligand Gal-3BP levels are associated with carotid artery lesions (He et al., 2017). All aforementioned data indicate the multifatorial involvement of Ga-3 in neurodegenerative diseases pathophysiology.

In association with their role in the proliferating capacity of cells, galectins also mediate vascular proliferation and neo-vascularization in the CNS tumors, such as glioblastomas (Bresalier et al., 1997) reviewed in (D’Haene et al., 2014). Also in primary CNS lymphoma, Gal-3 expression correlates with vascular hyperplasia and is a marker of poor prognosis (D’Haene et al., 2008).

6. Gut microbiota and Hp infection as independent factors regulating gut-brain axis interaction

The gut microbiota can communicate with the CNS through neuroimmune, neuroendocrine, and neural pathways comprising the GIT-brain microbiota axis (Kelly et al., 2016). The human CNS is targeted by different pathogens that, apart from trafficking into the brain through infected blood cells, may use a distinct pathway to bypass the BBB by retrograde axonal transport through sensory or motor fibres. Although, it is clear that the vagus nerve, immune signaling, and bioactive metabolites production are strongly implicated in communication across the microbiota–GIT–brain axis (Cryan and Dinan, 2015), vagal afferents appear to mediate at least partially the neural activation of the brainstem, hypothalamus and limbic structures in response to peripherally administered LPS and IL-1 (Dantzer et al., 2000).

Several hormones and neuropeptides mediate signaling between gut and the brain, under the regulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system (Tsigos and Chrousos, 2002). The importance of the gut-brain interaction has been recognized since disruption in neuroendocrine balance may result in neurodevelopmental, behavioural and cognitive disorders (Adams et al., 2011; Rhee et al., 2009). Neuroendocrine dysregulation contributes to GIT diseases pathology, including irritable bowel syndrome (Stasi et al., 2017) and inflammatory bowel disease (Glymenaki et al., 2017). Intestinal microbiota have been
recently recognized as an independent factor, shaping gut-brain interactions. The term “metagenomics” (Handelsman et al., 1998) refers to the genomic analysis of the microbiome present in biological samples without prior culture and by directly cloning extracted DNA. Thus, metagenome studies offer direct and thorough insight into diverse microbial niches from humans and other species.

The human microbiota consists of 100 trillion microorganisms that provide essential metabolic and biological functions benefitting the host. There are more than 2000 species of bacteria within the adult human gut. The density of bacterial cells increases generally from stomach to colon (Ley et al., 2006), exhibiting remarkable individual compositional stability (Faith et al., 2013). “Intestinal dysbiosis” refers to a relative microbial composition diversity in the presence of disease, compared to healthy individuals. Gut dysbiosis is a well-characterized condition (Baumgart and Carding, 2007) correlated with extra-gastric diseases including diabetes (Qin et al., 2012), IBD (Manichanh et al., 2006), rheumatoid arthritis (Zhang et al., 2015), cardiovascular diseases (Tang et al., 2017), AD (Jiang et al., 2012), IBD (Manichanh et al., 2006), rheumatoid arthritis (Zhang et al., 2015), cardiovascular diseases (Izzotti et al., 2009a, 2009b; Kountouras, 2009). Furthermore, bloodstream Hp antibodies may enter the aqueous circulation due to BOB disruption possibly contributing to glaucoma pathophysiology; when serum specific antibodies access brain, they are capable of killing retinal cells, thereby contributing to glaucoma pathologies (Izzotti et al., 2009a; Kountouras, 2009). In addition, the mentioned activated monocytes (possibly infected with Hp due to defective autophagy resulting in Hp replication in autophagic vesicles) might access brain (“Trojan horse” theory), via BBB/BOB disruption, thereby triggering the brain neurodegenerative diseases development and progression (Kountouras et al., 2014a). Other bacterial pathogens also access CNS, via the “Trojan horse” mechanism, and infect the brain (Dando et al., 2014).

The mentioned fast retrograde vagal pathway from GIT to the brain has been demonstrated for the prion protein PrPSc and several neuropeptides. Prions induce a devastating subacute neurodegeneration human Creutzfeldt-Jakob disease (CJD) when they successfully reach the CNS (Shearin and Bessen, 2014); in the case of contaminated tissue human consumption, the infectious agent, after replication in lymphoid tissues, uses the parasympathetic nervous system (e.g., from the vagus nerve to the dorsal motor nucleus of the vagus) and the sympathetic nervous system (e.g., from the splanchnic nerve to the intermediolateral cell column of the spinal cord) to access the CNS (Haik et al., 2004); (McBride et al., 2001). In this regard, Hp infection may promote uptake and propagation of alimentary prions from the GIT by gastric PrPSc expression upregulation (Deretzi et al., 2009); Hp creates a milieu for increased prions’ propagation in the GIT (Konturek et al., 2005). Axonal transport of several other neuropeptides in the vagus nerve has also been demonstrated, e.g. somatostatin (SST), substance P (SP), cholecystokinin octapeptide (CCK-8) and vasoactive intestinal polypeptide (VIP) (Brimijoin et al., 1980; Gilbert et al., 1980). It appears that the synthesized neuropeptides are transported toward the CNS and influence brain function. All aforementioned neuropeptides are involved in the pathophysiology of GIT infections induced by Hp or other pathogens (Bercik et al., 2002; El Karim et al., 2008; Robinson et al., 2003; Tomoh et al., 2001; Wang et al., 1996; Yamamoto et al., 2001). For instance, Hp infected mice exhibit high density of SP and VIP immunoreactivity nerves in the stomach and of SP in the spinal cord (Yamamoto et al., 2001); Hp correlates with gastric SST regulation; SST and/or octreotide exerting GIT inhibitory effects promote bacterial translocation (El Karim et al., 2008; Low, 2004; Tomoh et al., 2001); VIP displays GIT antimicrobial activity (El Karim et al., 2008); SP plays a role in diarrhea mediation in HIV patients with naturally occurring chronic cryptosporidiosis; and CCK by stimulating intestinal transit time prevents the GIT bacterial overgrowth and translocation. These neuropeptides also contribute to MS pathophysiology (Barker and Larner, 1992; Reink et al., 2006; Staines et al., 2008); grade 3 acute EAE disrupts the striatal neuropeptide SST receptor-effector system, thereby contributing to a better understanding of MS molecular basis in human; vasoactive neuropeptides (VNs) including VIP, have crucial roles in the CNS as neurotransmitters, vasodilators, immune and nociception modulators and autoimmunity VNs or VN receptors may affect BBB and Virchow-Robin spaces functions, thereby contributing to neurological-related diseases pathophysiology including MS (Barker and Larner, 1992); the occurrence of SP immunoreactive astrocytes in MS suggests that SP may play a role in plaque development and in governing MS natural history (Reineke et al., 2006); and CCK-8 augmented amounts are released together with enhanced aminopeptidase activity in MS (Bryd et al., 1987). Of note, MetS characteristics may associated with CJD (Rosenbloom et al., 2017).
pathogens’ trafficking into the brain through infected blood cells, the faster GIT-associated retrograde axonal transport pathway appears to play a crucial role in Hp metabolic-related neurodegenerative disorders pathophysiology.

Hp-induced chronic gastritis and gastric atrophy predispose for defective nutrient absorbance; by causing reduction in serum vitamin B12 and folate and subsequent increase in serum homocysteine (Hcy), all these factors are implicated in CNS neurodegenerative disorders pathogenesis (Kountouras et al., 2007a). Specifically, Hp-induced chronic gastritis can lead to vitamins B12 and folate malabsorption, leading to methylation by 5-methyltetrahydrofolinic acid failure and, hence, in Hcy accumulation (Kountouras et al., 2007b). Elevated Hcy, in turn, triggers endothelial damage resulting in atherothrombotic disorders and AD (Kountouras et al., 2007a). Considering these data, we speculate that Hp infection might further contribute to MCI, AD and other neurological disorders pathogenesis through induction of chronic atrophic gastritis-vitamin B12–folate deficiency-Hcy sequence; Hp positive MCI patients accompanied by increased Hcy are more likely to AD progress (Kountouras et al., 2015a).

In this respect, Hp eradication is likely to confer a significant delay in the CNS disease physical history (Kountouras et al., 2002, 2009a, 2010a, 2011). Hp infection recruits the host mechanisms of innate and acquired immunity, as indicated by increase in cytokine production by gastric epithelial cells, infiltration of gastric mucosa by neutrophils, macrophages and lymphocytes and induction of antigen-specific humoral immune response (Lindholm et al., 2001; Rossi et al., 2000). Hp neutrophil activating protein (NAP) activates cells of innate immunity viaTLR2 signaling and induces infiltration by monocytes (Del Giudice et al., 2001; Kountouras et al., 2006b, 2014b; Lepper et al., 2005); NAP (+) Hp strains show increased capacity to absorb iron, thus contributing in the pathogenesis of iron-deficiency anemia (Liao et al., 2013; Yokota et al., 2013); and NAP implicates in mechanisms underlying MS and NMO by inducing oxidative damage to neurons, mediated by inflammation (Kountouras et al., 2001a, 2009b, 2010b, 2012a; Li et al., 2009).

Hp infection might be further involved in neurodegenerative disorders pathophysiology by: a) promoting in Mef5-related platelet–leukocyte aggregation proposed to play pathophysiological roles in MCI and AD. Amyloid precursor protein (APP) accumulation has been reported in platelets of patients with AD and MCI, with amnestic type of MCI regarded as an AD preclinical type. APP cleavage by secretases leads to amyloid-β (Aβ) peptide formation, the brain amyloid plaques key component of AD and the pathological “hallmark” of the disease (Selkoe, 1994). Increased APP accumulation by platelets of patients with MCI correlates with higher risk of progression towards AD (Padovani et al., 2002); b) like galectins, producing reactive oxygen species (ROS) and circulating lipid peroxides involved in AD pathogenesis; c) causing cross mimicry development between endothelial and the CNS cells (Kountouras et al., 2005); d) increasing the aforementioned Hcy, a risk factor for MCI, dementia and AD, implicated in endothelial damage and neurodegeneration via oxidative injury; and e) like galectins, influencing the apoptotic process, an important form of cell death in neurodegenerative diseases including AD (Bauer et al., 2016; Fan et al., 2016; Fernandes Bertocchi et al., 2008; Hsu et al., 2015; Kountouras et al., 2006a, 2007c, 2017a; Pejnovic et al., 2016; Smith and Refsum, 2016; Sreckovic et al., 2017).

7. Hp via Gal3-mediated signaling may trigger inflammation and neurodegeneration in the CNS

Variable suggested Gal3-mediated mechanisms may be involved in Hp-related neurodegeneration (Fig. 1). Hp cells or Hp epitopes stemming from pathogen phagocytosis and processing may potentially directly access the CNS via BBB disruption, intra-nasal inoculation, or fast retrograde vagal pathways (Deretzi et al., 2009, 2011) (Table 1). The assumption of Hp protein CNS presence is supported by anti-Hp IgG antibodies occurrence in glaucoma aqueous humor, the titer of which correlated with the glaucomatous damage severity, and by Hp bacteria presence in eye biopsies of glaucoma patients (Kountouras et al., 2003; Zavos and Kountouras, 2006).

Gal-1 stabilizes the BBB, thereby contributing to neuroprotective effect. This effect is mediated by molecules with increased expression that are implicated in BBB formation, including tight-junctional proteins zonula occludens-1 (ZO-1), Claudin-3, and adhesion molecule intercellular adhesion molecule-1 (ICAM-1) (Parikh et al., 2015). Limited evidence exists regarding the Gal-3 role in BBB integrity. Gal-3 is expressed by CNS cells, such as innate immunity cells, namely, brain resident macrophages referred as microglia, oligodendrocytes, astrocytes and endothelial cells (Filiano et al., 2013; Shin, 2013); likewise the BBB microenvironment contains several cell types, including endothelial cells, astrocytes, macrophages, pericytes, microglia as well as extracellular matrix (Zhao et al., 2017).

Serum anti-Gal3 antibodies of MS patients recognize BBB structures. The serum levels of these antibodies in SPMS but not in RRMS patients denotes a pathogenetic link of these antibodies with the specific disease type. Gal-3 expressed by BBB may act as an immunological target molecule thus contributing to the pathogenesis of SPMS (Nishibara et al., 2017).

Thus, we can speculate that circulating Hp-infected monocytes through disrupted BBB might access brain, thereby possibly leading to Glal-3-related neurodegeneration; however it is important to declare, that there is, yet at least, no direct evidence proving this logical postulation. It is reasonable also to assume that altered BBB homeostasis potentially mediates the CNS direct effect of Hp, and this effect may be Gal-3 mediated. BBB disruption permits blood macrophages to transmigrate towards the CNS, as a response to molecular signals stemming from tissue damage, as in the case of neurodegeneration. Such mechanism may be responsible for the inflammatory compound in the pathogenesis of neurodegenerative disease including ALS and the long-term sequelae of cerebrovascular stroke and TBI. Effective tissue debris clearance is critical for tissue regeneration: by a study on retinal ganglion crush mouse model, upon which Gal-3 overexpression was found to interfere with regenerative processes (Abreu et al., 2017).

Conversely, Hp-infection affects the gastric mucosa macrophages functionally; following Hp colonization, macrophages exhibited reduced phagocytic activity rendered less effective towards microbe clearance, thereby resulting in persistent bacterium deep gastric mucosa colonization. Gal-3 overexpression correlates with microbe extensive presence and increased resistance against the host’s innate immune defense mechanism; Gal-3-mediated alterations in macrophage phagocytic activity, induced by Hp, may confer important implication for systemic innate immunity reactions in distant organs; and BBB disruption, mediated in part by increased Gal-3 expression, may facilitate macrophages with reduced phagocytic capacity entry in the otherwise immunoprivileged CNS. The sequence constitutes steps in a mechanism presumably mediating a Hp effect in the innate immunity and the homeostasis regulation in the CNS upon neurodegenerative disease. Gal-3 may facilitate such interactions by regulating the macrophage activation degree and their infiltrating capacity towards the CNS through the BBB.

Furthermore, Hp might be further involved in the BBB breakdown, by releasing defensins, particularly those that display unique distribution at BBB sites (Kountouras et al., 2016). Hp can activate granulocytes and induce defensin release from granulocytes;
consequently, defensins, secreted by activated granulocytes, penetrate the BBB, gain access to the brain, thereby possibly contributing to neurodegeneration (Kountouras et al., 2014a). In the brain, human β defensin-1 (hBD-1) expression acts as activator and modulator of innate and adaptive immunity within microglia and astrocytes, cerebral cells critical to the brain neuroinflammatory responses. HBD-1 mRNA expression is significantly increased in the choroid plexus and hippocampus of the
neurodegenerative brain; and HBD-1 might be of considerable importance early in the neurodegenerative process (Kountouras et al., 2014a). In this respect, a quantitative proteomics analysis of the macular Bruch membrane/chorioid complex was pursued for insights into the molecular mechanisms of age-related macular degeneration (AMD), an important cause of blindness worldwide and is approaching epidemic proportions in the United States. A total of 901 proteins was quantified, including 556 proteins from ≥3 AMD samples. Around 60% of the elevated proteins are implicated in immune response and host defense, including complement proteins and damage-associated molecular pattern proteins such as α-defensins 1–3 and Gal-3. Interestingly, Gal-3 was the most significantly elevated protein in advanced dry AMD, supporting a role for advanced glycation end products in dry AMD progression. Uniquely elevated proteins such as Gal-3 in advanced dry AMD and α-defensins 1–3 in neovascular AMD might not only contribute to

| Table 1 Clinical and experimental evidence of Galectin-3 implication in neurodegenerative disease and relevance with Helicobacter pylori infection. |
|-----------------------------------|-----------------|-----------------|
| **Clinical evidence**            | **Gal-3 implication** | **Hp potential implication** |
| SPMS                             | persistent BBB disruption | anti-Gal-3 antibodies in sera from patients with SPMS | BBB disruption (Dereti et al., 2009; Dereti et al., 2011) |
| AD                               | neurodegeneration     | increased Gal-3 levels in the serum of patients with AD (Wang et al., 2015a) | Hp and/or Hp-antigen possible presence in the CNS promoting neurodegeneration (Dereti et al., 2009; Franceschi et al., 2014; Franceschi et al., 2015; Kountouras et al., 2003; Wang et al., 2015b; Zavos and Kountouras, 2006; Zeng et al., 2015) |
| ALS                              | neurodegeneration     | high plasma Gal-3 levels in ALS patients (Yan et al., 2016) | Hp and/or Hp-antigen possible presence in the CNS promoting neurodegeneration (Dereti et al., 2009; Franceschi et al., 2014; Franceschi et al., 2015; Kountouras et al., 2003; Zavos and Kountouras, 2006). |

<table>
<thead>
<tr>
<th><strong>Experimental evidence</strong></th>
<th><strong>Underlying pathology</strong></th>
<th><strong>Gal-3 implication</strong></th>
<th><strong>Hp potential implication</strong></th>
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<tbody>
<tr>
<td>mouse model of ALS</td>
<td>secondary inflammation</td>
<td>protective effect of overexpression of Gal-3 in macrophages (Kerman et al., 2012)</td>
<td>Hp-mediated cytokine production of the pro-inflammatory milieu, locally at the gastric mucosa and systemically (Kountouras et al., 2006a)</td>
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<td>EAE</td>
<td>CNS Inflammation</td>
<td>increased Gal-3 expression by activated microglia (Yoo et al., 2017)</td>
<td>Hp-mediated cytokine production of the pro-inflammatory milieu, locally at the gastric mucosa and systemically (Kountouras et al., 2006a)</td>
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<td>Post-stroke paralytic ileus</td>
<td>Neuronal loss in the gut</td>
<td>Gal-3- and TLR4-mediated mediated neuronal loss in the gut (Cheng et al., 2016)</td>
<td>IL-8 production from Hp-activated T-cells is mediated also by TLR molecules (Delaby et al., 2015; Hirata et al., 2006; Watanabe et al., 2010)</td>
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<td>retinal ganglion trauma</td>
<td>Gal-3- and TLR4-mediated mediated retinal ganglion cell degeneration</td>
<td>(Jiang et al., 2009) systemic response</td>
<td>Hp and/or Hp-antigen possible presence in the CNS promoting neurodegeneration (Dereti et al., 2009; Franceschi et al., 2014; Franceschi et al., 2015; Kountouras et al., 2003; Wang et al., 2015b; Zavos and Kountouras, 2006; Zeng et al., 2015)</td>
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<td>viral encephalitis</td>
<td>direct Gal-3-mediated neurodegenerative effect on neurons (Kobayashi et al., 2015)</td>
<td>increased expression of Gal-3 in activated astrocytes and glial cells (Jaquenod De Giusti et al., 2011)</td>
<td>Hp and/or Hp-antigen possible presence in the CNS promoting neurodegeneration (Dereti et al., 2009; Franceschi et al., 2014; Franceschi et al., 2015; Kountouras et al., 2003; Zavos and Kountouras, 2006)</td>
</tr>
<tr>
<td>neonatal hypoxia</td>
<td>inflammatory response</td>
<td>Gal-3 promotes macrophage phagocytic action through matrix metalloproteinase-9 signaling (Doverhag et al., 2010)</td>
<td>reduced phagocytic activity of macrophages following Hp colonization, rendering microbe clearance less effective (Dereti et al., 2009; Kountouras et al., 2006a, 2007a,b,c,d; Park et al., 2016; Xu et al., 2000)</td>
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<tr>
<td>TBI</td>
<td>inflammation</td>
<td>TLR4-mediated result (Yip et al., 2017)</td>
<td>reduced phagocytic activity of macrophages following Hp colonization, rendering microbe clearance less effective (Dereti et al., 2009; Kountouras et al., 2006a, 2007a,b,c,d; Park et al., 2016; Xu et al., 2000)</td>
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<tr>
<td>scrapie</td>
<td>neurodegeneration</td>
<td>Gal-3 by activated microglia/macrophages correlates with abnormal PiPc protein accumulation (Jin et al., 2007)</td>
<td>Hp induces MetS-related platelet–leukocyte aggregation; produces reactive oxygen species and circulating lipid peroxides; causes cross mimicry between endothelial and Hp antigens;</td>
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<td>cecebro-cardiovascular disease</td>
<td>MetS components including abdominal adiposity, dyslipidemia, hypertension</td>
<td>Gal-3-mediated insulin receptor (IR) signaling inhibition leading in insulin resistance (Darrow and Shohet, 2015; Hamed, 2017; Li et al., 2016)</td>
<td>Increases homocysteine implicated in endothelial damage and neurodegeneration via oxidative injury; influences apoptotic process (Bauer et al., 2016; Fan et al., 2018; Fernandes Bertocchi et al., 2008; Hsu et al., 2015; Kountouras et al., 2005, 2006a, 2007a,b,c,d; Park et al., 2016; Xu et al., 2000)</td>
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<td>glioblastoma</td>
<td>neovascularization</td>
<td>Galectin-mediated vascular proliferation (Bresalier et al., 1997)</td>
<td>Hp-mediated cytokine production of the pro-inflammatory milieu, locally at the gastric mucosa and systemically (Kountouras et al., 2006a)</td>
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<tr>
<td>primary CNS lymphoma</td>
<td>vascular hyperplasia</td>
<td>Galectin-mediated vascular proliferation (D’haene et al., 2008)</td>
<td>Hp-mediated cytokine production of the pro-inflammatory milieu, locally at the gastric mucosa and systemically (Kountouras et al., 2006a)</td>
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SPMS, secondary progressive multiple sclerosis; AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; EAE, experimental autoimmune encephalomyelitis; Gal-3, galectin-3; BBB, blood-brain barrier; Hp, Helicobacter pylori; CNS, central nervous system; IL, interleukin; IFN, interferon; TLR, toll-like receptors; TBI, traumatic brain injury; MetS, metabolic syndrome; PiPc, prion protein.
disease progression, but they may also be useful as AMD biomarkers (Yuan et al., 2010).

Moreover, although, in the presence of Hp some, macrophages engulf gastric mucosa microbial cells, they exhibit reduced capacity to process microbial components, thus contributing to the circulation of Hp cells via the blood stream towards various remote extra-gastric organs. This mechanism has been proposed to the aforementioned CNS Hp entry, thereby exerting direct effect in the residing innate immunity cells (Trojan horse theory) (Dereti et al., 2009; Gavalas et al., 2007; Kountouras et al., 2006a).

Gal-3 expression and upregulation is a crucial endogenous event in Hp infection that interferes with various intracellular events (Subhash and Ho, 2016). Hp–related Gal-3 upregulation mediates gastric epithelium IL-8 production. Gastric epithelium T-cells produce IL-8 following signaling by NOD1 through activation of nuclear factor (NF)-κB and activation protein-1 (AP-1) transcription factors and mitogen–activated protein kinase (MAPK) system. IL-8 production by T-cells is a marker of Hp-induced gastric inflammation (Allison et al., 2009; Viala et al., 2004); IL-8 mediates gastric tissue damage by recruiting innate immunity cells and inducing oxidative stress response (Kountouras et al., 2004). Hp-activated T-cells IL-8 production is mediated by TLR molecules, especially the ones mediated intracellularly by the downstream molecule myeloid differentiation primary response gene 88 (MyD88) (Hirata et al., 2006); there is an alternative NOD1- and CagA-independent mechanism of IL-8 induction in Hp infection (Correll et al., 2013); NOD1 signaling triggered by Hp antigens induces C-X-C motif chemokine 10 (CCL10) and IFN-β production by gastric epithelium (Watanabe et al., 2010), leading to gastric mucosa infiltration by neutrophils and further IL-8 secretion; IL-8, an inflammatory and neurotoxic mediator in the CNS, is linked with various neurodegenerative conditions including AD (Delaby et al., 2015), ALS (Blasco et al., 2017), Huntington’s disease (Politis et al., 2015), and in neurodegenerative sequelae of CNS primary autoimmune conditions CNS (Rossi et al., 2014); Catteneo et al., reported that gut microbiota modification resulted in alterations in blood cytokine profile in brain amyloidosis patients, including IL-8, elucidating potent anti-inflammatory capacities of certain gut bacterial taxa, with implication for AD physical history (Catteneo et al., 2017); IL-8 serum levels correlate with vascular lesion burden in the context of AD, thereby having clinical application as a marker of white matter pathology in AD patients (Zhu et al., 2017); and IL-8 gene polymorphism –251T>A might contribute to AD susceptibility (Qin et al., 2016).

Therefore, Hp may be implicated in neurodegenerative disease pathogenesis by promoting pro-inflammatory cytokine IL-8 production at the site of gastric mucosa, and systemically by gastric T-cells potentially entering the blood circulation and subsequently the CNS parenchyma through disrupted BBB. Again, the aforementioned postulated mechanism, although assumable, is not, at least till now, directly evidence based. Gal-3 is likely to mediate IL-8 production by T-cells and gastric epithelium, thus being additionally implicated in the immune response that orchestrates mechanisms of the CNS tissue damage and the secondary efforts to recover homeostasis by recruiting innate immunity following signals of neuron loss.

In addition, since, Gal-3 is upregulated in gastric epithelial cells as a host response to Hp (Subhash and Ho, 2016), Hp leads to gastric PrPc upregulation (Konturek et al., 2005) and Gal-3 expression by activated microglia/macrophages correlates with abnormal prion protein accumulation in CJD (Jin et al., 2007), it is reasonable to speculate that Hp might promote prion protein PrPsc retrograde axonal transport to access brain, thereby contributing to Gal-3-related abnormal prion protein accumulation and CJD development and/or progression.

Furthermore, Hp- and Gal-3–related MetS might be involved in neurodegenerative disorders pathophysiology by several mechanisms, such as by producing reactive ROS and circulating lipid peroxides involved in the AD pathophysiology or influencing the apoptotic process, an essential form of cell death in neurodegenerative diseases including AD and other neurological disorders (Bauer et al., 2016; Fernandes Bertocchi et al., 2008; Kountouras et al., 2007c, 2017a; Nayor et al., 2015). However, further large-scale relative studies are needed to elucidate these fields.

8. Conclusion

Hp possesses a plethora of antigens or epitopes that, apart from their ability to function as virulence factors promoting microbe chronic gastric colonization, they also act as “immunogens”, eliciting cellular and the humoral immunity mechanisms. Hp shows a well-documented capacity to circumvent the host’s innate immunity response. Gastric epithelium Hp constantly triggers immune responses locally, thus contributing to sustained signaling of the systemic innate and acquired immunity cells. Galectin–glycan signaling is an excellent example of host–microbe interaction extending our knowledge beyond the traditional TLR-dependent pathway. Galectins, as particularly conserved molecules across a variety of epithelial and the immune system cells, may partly explain phenotypic and functional diversity in the otherwise well-characterized TLR-dependent signaling outcome, acting as possible modulators. Gal-3 expression was recently shown to be upregulated by gastric epithelium in Hp infection. Hp infection may confer implication for numerous primary neurodegenerative diseases and diseases with secondary neurodegenerative compound for which clinical and experimental evidence for Gal-3 implication has been documented, by the following mechanisms: a) Gal-3 upregulation and Hp mediators contribute to BBB breakdown, with potential detrimental effects in inflammatory disease with accompanying neurodegeneration, including SPMS. By promoting BBB disruption Hp may facilitate Hp epitopes CNS entry, stemming from pathogen phagocytosis and processing, thereby resulting in the brain parenchyma infiltration by the immune immunity cells, or by exerting direct effect in the CNS resident antigen-presenting cells, namely, microglia. Sustained inflammation and microglia activation in the CNS contribute to secondary neurodegeneration, as in the case of SPMS. b) Hp-induced Gal-3 overexpression, interferes with the phagocytic activity of macrophages. Hp-antigen-bearing macrophages may enter the CNS, thus delivering microbial molecules with capacity to elicit molecular mimicry towards the antigens. Because molecular mimicry between gastric epithelium Hp antigens and the host antigens has been verified, further structural similarities between Hp antigens and the CNS antigens remain to be elucidated, an assumption that has been postulated to date. c) Macrophages compromised functional integrity, following Gal-3 overexpression in the context of Hp infection, may result in reduced clearance of tissue debris, a procedure critical for tissue regeneration. Similarly to a study referred to the retinal ganglion, macrophages reduced phagocytic activity may also confer a detrimental effect in brain tissue degeneration, in the context of either primary neurodegeneration, or axonal loss following hypoxic or traumatic stress. d) Hp infection triggers IL-8 production by gastric epithelium and activated T-cells with a concomitant Gal-3 mediated IL-8 production by T-cells, a cytokine implicated in brain amyloid accumulation pathogenesis, a process underlying AD and other neurodegenerative diseases. e) Hp might promote toxic agents including prion protein PrPsc retrograde axonal transport to the brain, thereby contributing to Ga-3-related abnormal prion protein accumulation and CJD or other degenerative diseases development and/or progression. f) Hp- and Gal-3–associated MetS
might be involved in neurodegenerative disorders pathophysiology by several mechanisms. However, further studies are warranted to clarify these points.

**Conflicts of interest**

Authors declare no conflicts of interest.

**References**


