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Role of pattern recognition receptors and the microbiota in neurological disorders

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Abstract

In recent years, the gut microbiota has been increasingly implicated in the development of many extraintestinal disorders, including neurodevelopmental and neurodegenerative disorders. Despite this growing connection, our understanding of the precise mechanisms behind these effects is currently lacking. Pattern recognition receptors (PRRs) are important innate immune proteins expressed on the surface and within the cytoplasm of a multitude of cells, both immune and otherwise, including epithelial, endothelial and neuronal. PRRs comprise four major subfamilies: the Toll-like receptors (TLRs), the nucleotide-binding oligomerization domain leucine rich repeats-containing receptors (NLRs), the retinoic acid inducible gene 1-like receptors and the C-type lectin receptors. Recognition of commensal bacteria by PRRs is critical for maintaining host–microbe interactions and homeostasis, including behaviour. The expression of PRRs on multiple cell types makes them a highly interesting and novel target for regulation of host–microbe signalling, which may lead to gut–brain signalling. Emerging evidence indicates that two of the four known families of PRRs (the NLRs and the TLRs) are involved in the pathogenesis of neurodevelopmental and neurodegenerative disorders via the gut–brain axis. Taken together, increasing evidence supports a role for these PRRs in the development of neurological disorders, including Alzheimer's disease, Parkinson's disease and multiple sclerosis, via the microbiota–gut–brain axis.

Graphical Abstract

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Author contributions

C.E.K. and M.G.G. wrote the manuscript, K.R. designed the figures. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Competing interests

The authors declare no competing interests.

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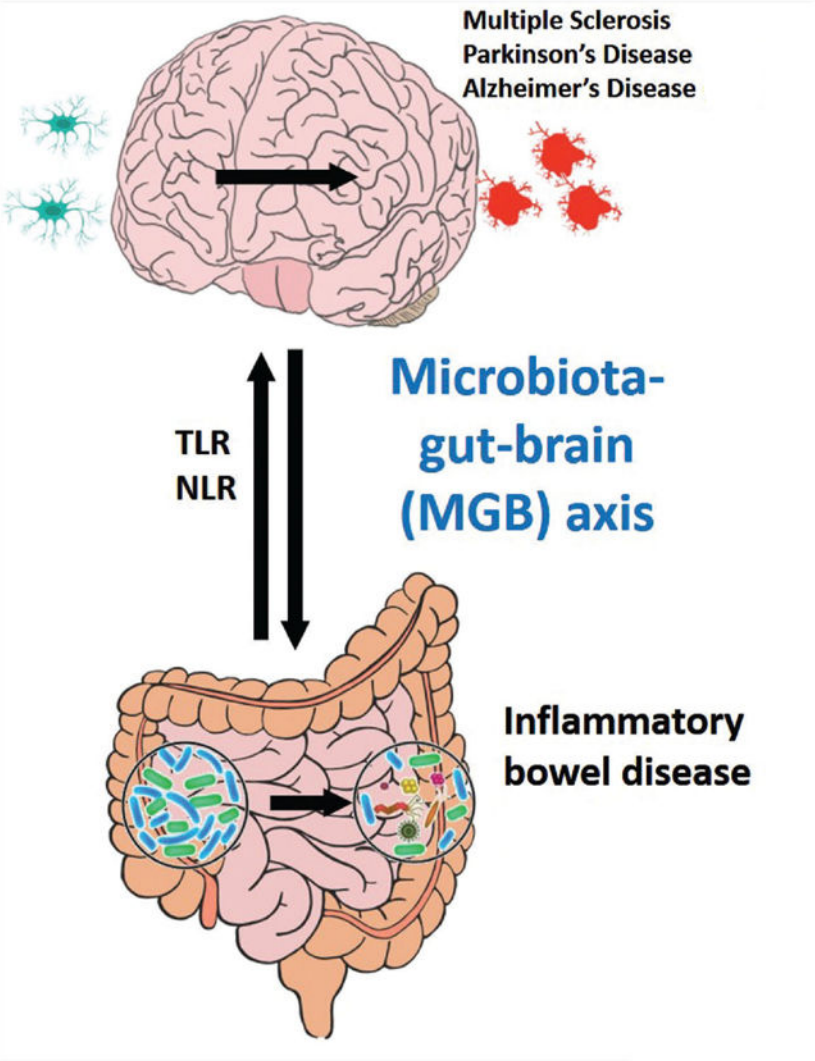

The microbiota-gut-brain (MGB) axis is involved in the pathogenesis of diseases both in the brain, including neurodevelopmental and neurodegenerative disorders, and diseases of the gut, including inflammatory bowel diseases. Pattern recognition receptors (PRRs) such as TLRs and NLRs are implicated in the development of these complex gut-brain disorders, in part via dysbiosis of the gut microbiota and alterations in the immune response.

Keywords

gastrointestinal tract; microbiota; neurodegenerative; pattern recognition receptor

Introduction

The understanding of the importance of the gut microbiota and its role in regulation of the physiology of the brain has grown exponentially in recent years. Humans are home to millions of microorganisms that reside both on the body (on the surface of the skin) and

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inside the body (gastrointestinal (GI) tract, nose and lungs). In fact, given this complex role, the gut microbiota is now considered to be a virtual organ in and of itself (Baquero & Nombela, 2012). Colonization of the microbiota begins at birth (Davis, 2016), with the early neonatal microbiome being dynamic and continuously modified as the child develops (Zhuang *et al*. 2019*b*). For example, breast-fed infants are host to species involved in the metabolism of colostrum present in breast milk, most notably *Bifidobacteria infantis* (Jiang *et al*. 2018). Upon the introduction of solid food, the infant microbiome shifts towards a more adult-like composition, increasing in its diversity and complexity (Ku *et al*. 2020). Additionally, studies have found that the gut microbiota is essential for the correct development of both the brain (Braniste *et al*. 2014; Lu *et al*. 2018) and the immune system (Schwarzer *et al*. 2019) beginning in early life. Therefore, recognition of commensal bacteria by the innate immune system is critical for maintaining host–microbe interactions and homeostasis, including behaviour.

Pattern recognition receptors

Pattern recognition receptors (PRRs) are part of the first line of innate immune defence following a pathological insult. They are expressed on multiple immune (leukocytes, macrophages, etc.) and non-immune cells (epithelial cells, endothelial cells and neurons) and respond to a variety of bacterial and viral ligands, including peptidoglycan (PGN), lipopolysaccharide (LPS), double stranded RNA, and CpG DNA, for example. PRRs comprise four major subfamilies: the Toll-like receptors (TLRs), the nucleotide-binding oligomerization domain leucin rich repeats-containing receptors (NLRs), the retinoic acid inducible gene 1-like receptors (RLRs), and the C-type lectin receptors (Walsh *et al*. 2013). In response to a pathological insult, the innate immune response is initiated by PRRs through binding of pathogen-associated molecular patterns (PAMPs), in turn triggering multiple intracellular signalling pathways, such as nuclear factor-κB (NF-κB), interferon regulatory factors and mitogen-activated protein kinase, resulting in production of cytokines and chemokines (Fawkner-Corbett *et al*. 2017). For the purposes of this review, we will focus on the TLR and the NLR families.

Despite continuous exposure to PAMPs in the lumen of the GI tract, intestinal epithelial cells (IECs) do not typically respond to commensal bacteria (Round & Mazmanian, 2009). This is due in part to PRR expression restricted to intracellular compartments, or basolateral expression in IECs, limiting their exposure to luminal PAMPs. In fact, commensal bacteria have been shown to be beneficial to the host (LeBlanc *et al*. 2017; Hiippala *et al*. 2018; Balakrishnan *et al*. 2019) by helping maintain immune surveillance. PRRs are crucial in maintaining these homeostatic interactions between the gut and the commensal microbiota, able to distinguish between pathogenic and commensal organisms. For example, distinct molecular signatures of the bacterial cell wall component PGN can elicit a variety of host immune gene patterns (Bersch *et al*. 2020). Commensal bacteria can drive myeloid differentiation primary response protein 88 (MyD88) signalling through TLR stimulation, inducing anti-microbial peptide production by Paneth cells that restrict bacterial colonization on the surface of the intestine, thereby limiting pro-inflammatory immune responses (Vaishnava *et al*. 2011). While other innate immune receptors also help maintain the balance

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between the host and the microbiota, these studies highlight a critical role for PRRs in this function.

Dysbiosis, or the disruption of the composition of the gut microbiota, has been implicated in numerous diseases not only those that impact the GI tract (e.g. inflammatory bowel diseases (IBD); Lupp *et al.* 2007; Kang *et al.* 2010) but also in diseases of the brain (e.g. neurodevelopmental and neurodegenerative diseases; Sampson *et al.* 2016; Hughes *et al.* 2018; Sun & Shen, 2018), lung (e.g. asthma; Liu *et al.* 2019; Zhuang *et al.* 2019*a*) and immune system (e.g. rheumatoid arthritis (Liu *et al.* 2013) and multiple sclerosis (MS; Cantarel *et al.* 2015)). While it remains unclear whether dysbiosis is causative or correlative in many cases, its impact on GI mucosal barrier function and host–microbe interactions can disrupt immune homeostasis in the rest of the body. Consequently, altered host–microbe interactions and subsequent GI pathophysiology could allow the commensal microbiota to gain access to the surrounding tissue, potentially leading to inflammation and damage (Garrett *et al.* 2010). Here we discuss the role of two PRR families, NLRs and TLRs, that are implicated in the development of neurological disorders and the intersection of the microbiota and the innate immune system (Fig. 1).

Nod-like receptors

The NLR receptor family can be divided into three different sub-groups: (1) inflammasome-forming NLRs (i.e. NLRP1, NLRP3), (2) positive regulatory NLRs (i.e. Nod1, Nod2) and (3) negative regulatory NLRs (i.e. NLRx1, NLRC3), each with a separate and distinct signalling pathway and downstream effect (Coutermarsh-Ott *et al.* 2016) (Fig. 2). The inflammasome forming group of NLRs consists of NLRP1, NLRP3, NLRP6, NLRP4 and NLRC5, which form multiprotein complexes. These NLR proteins multiplex with, for example, apoptosis-associated speck like protein and procaspase-1, to initiate proinflammatory cytokine expression.

Inflammasome complexes, including NLRP1 and NLRP3, have been implicated in the development of many neurological disorders, for example, several single nucleotide polymorphisms of NLRP1 have been associated with Alzheimer's disease (AD). Additionally, NLRP1 mRNA is upregulated in neurons of AD patients (Pontillo *et al.* 2012). Furthermore, amyloid-β plaques have been shown to stimulate purinergic receptors initiating activation of the inflammasome, in turn contributing to late-stage AD (Tan *et al.* 2014). In a mouse model of chronic constriction injury-induced neuropathic pain, the NLRP1 inflammasome was significantly activated in the hippocampus. Inhibition of the downstream product of NLRP1 attenuated the observed depression-like behaviour in these mice (Li *et al.* 2019). Dysbiosis has been observed in AD patients, suggesting a possible avenue of further research in order to fully elucidate the mechanisms and interconnectivity of NLRP1 in the brain with the host microbiota. In line with these findings, NLRP3 signalling has also been implicated in the development of major depressive disorder via the hypothalamic–pituitary–adrenal axis (Inserra *et al.* 2018). In Parkinson's disease (PD) patients, NLRP3 levels were found to be upregulated in the serum, correlating with α-synuclein levels, a hallmark of disease severity (Chatterjee *et al.* 2020). Additionally, in mice it was found that α-synuclein activates NLRP3 via microglial endocytosis (Zhou *et al.* 2016). Deficiency in caspase-1, a

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member of the NLRP3 inflammasome complex, significantly reduced microglial activation indicating a possible role for the NLRP3 inflammasome in PD pathogenesis (Zhou *et al.* 2016; Gordon *et al.* 2018). Taken together, this suggests that intestinal dysbiosis may trigger altered NLRP signalling both in the gut and in the brain, leading to neurodegeneration in the brain.

The nucleotide-binding oligomerization domain (NOD) proteins are a family of positive regulatory NLRs that detect fragments within the cell wall of many bacteria, activating signalling pathways driving pro-inflammatory and anti-microbial responses. The two best characterized members of the NLR family are Nod1 and Nod2. They are unique in their function in that they sense bacterial PGN in the host cytosol as opposed to microbial ligands at the cell surface or within endosomes. Nod1 and Nod2 regulate activation of NF-κB transcription via a receptor-interacting serine/threonine-protein kinase 2-dependent mechanism in response to unique PGN fragments leading to the expression of pro-inflammatory cytokines (Caruso *et al.* 2014). Nod1 is ubiquitously expressed in many cell types, primarily in immune cells (Uhlen *et al.* 2015), neurons, endothelial cells and epithelial cells of many organs (Caruso *et al.* 2014). While Nod2 expression is slightly more restricted, it has been identified in lymphocytes, Paneth cells and IECs (Franchi *et al.* 2009). Importantly, studies have shown that both Nod1 and Nod2 receptors are also expressed in the brain, including within the hippocampus on multiple cell types such as neurons, astrocytes and microglia (Ogura *et al.* 2003; Arentsen *et al.* 2017) suggesting that they play an important role within the central nervous system.

Nod1 and Nod2 serve a critical role in responding to specific bacterial pathogens. For example, the enteric mouse pathogen *Citrobacter rodentium* induces an IL-17 response via a Nod1- and Nod2-dependent pathway (Rubino *et al.* 2013). Mice deficient in Nod1 and Nod2 are highly susceptible to infection with *Listeria* when they are first exposed to LPS or *E. coli*. The results of this study implicate that cells consistently exposed to microbial stimuli, such as in the GI tract, are characterized by low TLR expression and can become re-sensitized to commensal bacteria in the absence of Nod1 and Nod2 (Kim *et al.* 2008). Several studies have indicated that the recognition of pathogenic bacteria in intestinal cells lacking TLRs relies on Nod1 (Girardin *et al.* 2001; Zilbauer *et al.* 2007).

As Nod1 and Nod2 are activated by PGN, they are also important in maintaining gut homeostasis by priming the immune system in the absence of infection, employing the gut microbiota as its stimulus (Clarke *et al.* 2010; Claes *et al.* 2015). Mice deficient in both Nod1 and Nod2 (NodDKO) display stress-induced anxiety-like behaviour, cognitive impairment and depression (Pusceddu *et al.* 2019). In the hippocampus, NodDKO mice displayed decreased 5-HT at baseline and following acute stress. In particular, Nod1 expression on IECs was identified as a specific factor in regulating the stress response and serotonergic signalling, but the precise signalling mechanisms behind this effect have yet to be fully elucidated (Pusceddu *et al.* 2019). Numerous studies have implicated the NLR family as important PRRs in the development of neurological diseases mediated by the gut microbiota. However, much is still unclear about the mechanism of action of these effects. Given these findings, the NLR family, in particular Nod1 and Nod2, remain attractive targets

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for the development of therapeutics for treatment of many of the aforementioned neurological disorders.

PGN derived from commensal gut bacteria can cross the blood–brain barrier into the central nervous system (CNS), with levels of PGN within the brain increasing with age (Arentsen *et al.* 2017). Several PGN-sensing molecules, such as the peptidoglycan recognition protein (PGRP) PRRs and NLRs, are highly expressed in the neonatal brain during early development and are highly susceptible to changes in the gut microbiota (Arentsen *et al.* 2017). Knockout of PGN recognition molecule 2 (Pglyrp2) induces behavioural changes and alterations in the autism spectrum disorder risk gene *c-Met* in a sex-specific manner (Arentsen *et al.* 2017). Taken together, these findings highlight a novel role for PRRs in maintaining behaviour and CNS function.

Toll-like receptors

TLRs are a highly expressed family of transmembrane PRRs responsible for initiating downstream signal transduction in response to PAMPs and tissue damage. Localization of each TLR allows classification into two groups, those expressed on the plasma membrane (TLR1, TLR2, TLR4, TLR5, TLR6, TLR11) and those expressed within the cytoplasm and organelles (TLR3, TLR7, TLR8, TLR9) (Fig. 3). To date, 11 human and 13 mouse TLRs have been characterized (Akira & Takeda, 2004). Activation of each TLR, following specific PAMP recognition, causes a conformational change in the receptor allowing recruitment of the appropriate downstream signalling adaptor, in turn activating specific transcription factors, and subsequent innate immune responses (Takeuchi & Akira, 2001). Four adaptor proteins have been identified, each one responsible for a specific immune response. For example, the universal adaptor protein MyD88 is known to induce activation of NF-κB and activator protein 1 (AP-1) triggering the expression of inflammatory cytokines such as tumour necrosis factor-α (TNFα). Alternatively, TLR3 and TLR4 can signal through the adaptor protein Toll/IL-1 receptor domain-containing adapter inducing interferon-β (TRIF) in order to activate type-I interferon (IFN) (Fitzgerald *et al.* 2003). The regulation of these responses is tightly controlled via post-translational modifications such as glycosylation (Weber *et al.* 2004; Sun *et al.* 2006; Abdulkhalek *et al.* 2011; Iavarone *et al.* 2011) and ubiquitination (Boone *et al.* 2004; Chuang & Ulevitch, 2004; Shembade *et al.* 2010; Guedes *et al.* 2014; Kinsella *et al.* 2018) and through negative feedback (Scott *et al.* 1993; Renner & Schmitz, 2009). Disruption of TLR activation or maturation can lead to dysregulation of the immune response (Barrat *et al.* 2005; Reynolds *et al.* 2010; Ziegler *et al.* 2011; Suarez-Farinas *et al.* 2013; Cavalcante *et al.* 2018). Despite continuous exposure to TLR ligands in the gut lumen, IECs express low levels of TLRs. Introduction of pathogenic bacteria causes upregulation of some TLRs, namely TLR2, TLR4, TLR5 and TLR9 (Muzio *et al.* 2000; Gewirtz *et al.* 2001; Ewaschuk *et al.* 2007), while others are differentially expressed in response to pathogenic bacteria. TLRs play an important role in maintaining host–microbe interactions and mucosal immunity in the GI tract.

Studies are emerging highlighting a novel connection between TLRs and neurodegenerative diseases, including AD, PD and MS. A link between gut microbiota-associated inflammation and brain amyloidosis in AD has been shown, with bacterial amyloids able to

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initiate expression of inflammatory cytokines (Nishimori *et al.* 2012). In AD brains, a higher bacterial LPS load was observed (Zhan *et al.* 2016) and administration of LPS in mice led to prolonged elevation of amyloid-β and cognitive deficits (Kahn *et al.* 2012). Further studies have observed increases in amyloid-β in mouse brains alongside alterations in the gut microbiota (Kaji *et al.* 2010). LPS-dependent TLR4 signalling is reduced in AD mice, suggesting TLR4 may play a role in disease manifestation (Go *et al.* 2016). In PD patients, misfolded α-synuclein protein activates microglia via TLR2, activating MyD88-dependent NF-κB signalling, in turn increasing the expression of TLRs. TLR4 also has an observable interaction with α-synuclein and a genetic knockout of TLR4 protected mice from neurodegeneration (Stefanova *et al.* 2011). Increased gut permeability and bacterial translocation leading to TLR4 activation in the pre-frontal cortex has been observed in mice with depressive behaviour (Martin-Hernandez *et al.* 2016). Finally, TLR2 expression is upregulated in both MS patients and, in the mouse model, experimental autoimmune encephalomyelitis (EAE) (Fujiwara *et al.* 2018). While the signalling pathways involved are not well understood, TLR2 knock-out mice develop attenuated EAE, suggesting a role for TLR2 (Fujiwara *et al.* 2018). Studies have found that the microbiota in MS patients is directly responsible for the dysregulation of TLR2 and its subsequent role in pathology (Wasko *et al.* 2020). Taken together, these studies indicate the importance of TLR signalling in development of multiple neurological disorders and present novel therapeutic strategies with which to treat them.

Our understanding of neurological disorders and the importance of the gut microbiota in their development is continually expanding, with new targets for treatment being identified. PRRs in particular can make attractive targets due to their function as the first line of defence against pathogens and their dysregulation in many disease pathologies (Mullen *et al.* 2015). Targeting of TLR2 signalling by increased TLR2 tolerance in a mouse model of MS significantly enhanced CNS remyelination (Wasko *et al.* 2019). A loss-of-function mutation in the TLR4 gene was shown to suppress the activation of microglia and monocytes by Alzheimer's amyloid peptides in *in vitro* studies (Walter *et al.* 2007). Melatonin treatment was beneficial in attenuating NLRP3 inflammasome activation following LPS-induced depressive-like behaviours, in part via reduced microglia activation (Arioz *et al.* 2019). Further studies of the mechanisms these PRRs regulate are needed to identify more targets in the treatment and prevention of many neurodegenerative and neurodevelopmental disorders.

PRRs in other diseases

As well as their role in neurological disorders, PRRs have been implicated in the development of other disorders, including autoimmune diseases. Polymorphisms of both Nod1 and Nod2 have been associated with an increased susceptibility to Guillain–Barre syndrome, an autoimmune disorder that attacks the peripheral nervous system (Kharwar *et al.* 2016). Furthermore, increased expression of Nod1 and Nod2 has been noted in the pathogenesis of Vogt–Koyanagi–Harada syndrome, a rare autoimmune disorder (Deng *et al.* 2016). Additionally, polymorphisms in the NLR family increase the risk of developing IBD, with Nod1 and Nod2 deficient mice displaying an increase in DSS-induced colitis severity (Natividad *et al.* 2012) and Nod2 mutations correlating with dysbiosis in IBD patients (Aschard *et al.* 2019). A single nucleotide polymorphism (SNP) located on chromosome

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1q44 downstream of NLRP3 has previously been implicated in increased susceptibility to Crohn's disease (CD) (Villani *et al.* 2009), but more recent studies in a Chinese Han patient population (Zhang *et al.* 2014) and a panel of patients in the UK (Lewis *et al.* 2011) indicate that SNPs in the NLRP3 gene are more closely associated with ulcerative colitis (UC) than with CD. Despite this, loss-of-function CARD8 mutation in CD patients leads to increased NLRP3 activation, indicating that there may be a role for NRLP3 in CD pathogenesis (Schoultz *et al.* 2009; Mao *et al.* 2018). NLRP3$^{-/-}$ mice displayed higher sensitivity to oxazolone-induced colitis, indicating a protective role for the inflammasome in UC (Itani *et al.* 2016).

In the case of the TLRs, receptor activation and subsequent NF-κB signalling in the gut is important for the survival of enteric neurons responsible for gut motility. Knockout mouse models indicate that TLR4 is important for gut motility, with delayed GI motility associated with decreased numbers of nitrergic neurons (Anitha *et al.* 2012). Preliminary studies suggest a role for TLR4 in the development of multiple system atrophy (MSA), where, similar to PD, MSA patients were found to have disrupted tight junction proteins and a higher expression of TLR4 in their colonic sigmoid mucosa when compared to healthy controls (Engen *et al.* 2017). Taken together, these findings demonstrate the critical role NLRs play in multiple disease pathways, highlighting their potential in maintaining normal physiology.

Conclusions

PRRs, in particular the NLR and TLR families, have been implicated as novel signalling mechanisms in the development of many complex neurological disorders, likely acting in concert with numerous other signalling pathways. Their high levels of expression in many tissues, in particular the GI tract, make them an attractive target for further study of the gut microbiota and its impact on human health and development of gut–brain function.

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Biography

Ciara Keogh received her BSc in Genetics (Hons) from Dublin City University in Dublin, Ireland in 2018. During her PhD in University College Dublin, under the supervision of Dr Eoin Cummins, she worked on the effects of carbon dioxide on inflammatory signalling. She then moved to UC Davis, School of Veterinary Medicine, where she studies the role of antibiotics in the microbiota–gut–brain axis signalling in neonatal mice under the supervision of Dr Melanie Gareau.

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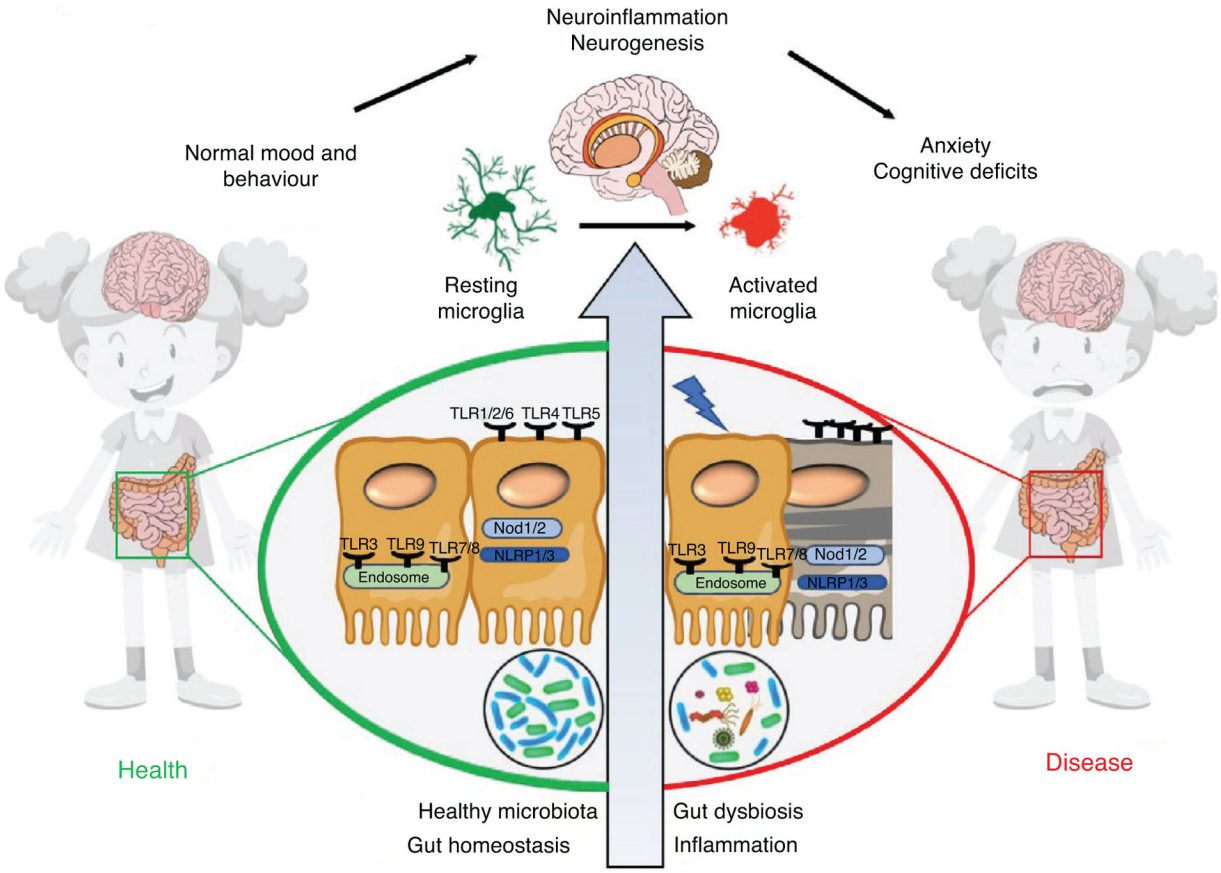

Figure 1. The role of NLRs and TLRs in gut–brain signaling

Under physiological conditions, host–microbe interactions maintain intestinal physiology via pattern recognition receptors (PRRs), including Nod-like receptors (NLRs) and Toll-like receptors (TLRs). In the brain, the PRRs regulate multiple cell types, including neurons, microglia and astrocytes. Dysbiosis, GI inflammation and neuroinflammation all contribute to diseases within the GI tract as well as in the brain. Understanding these pathways will provide new insight into disease pathogenesis and novel targets for restoration of physiology.

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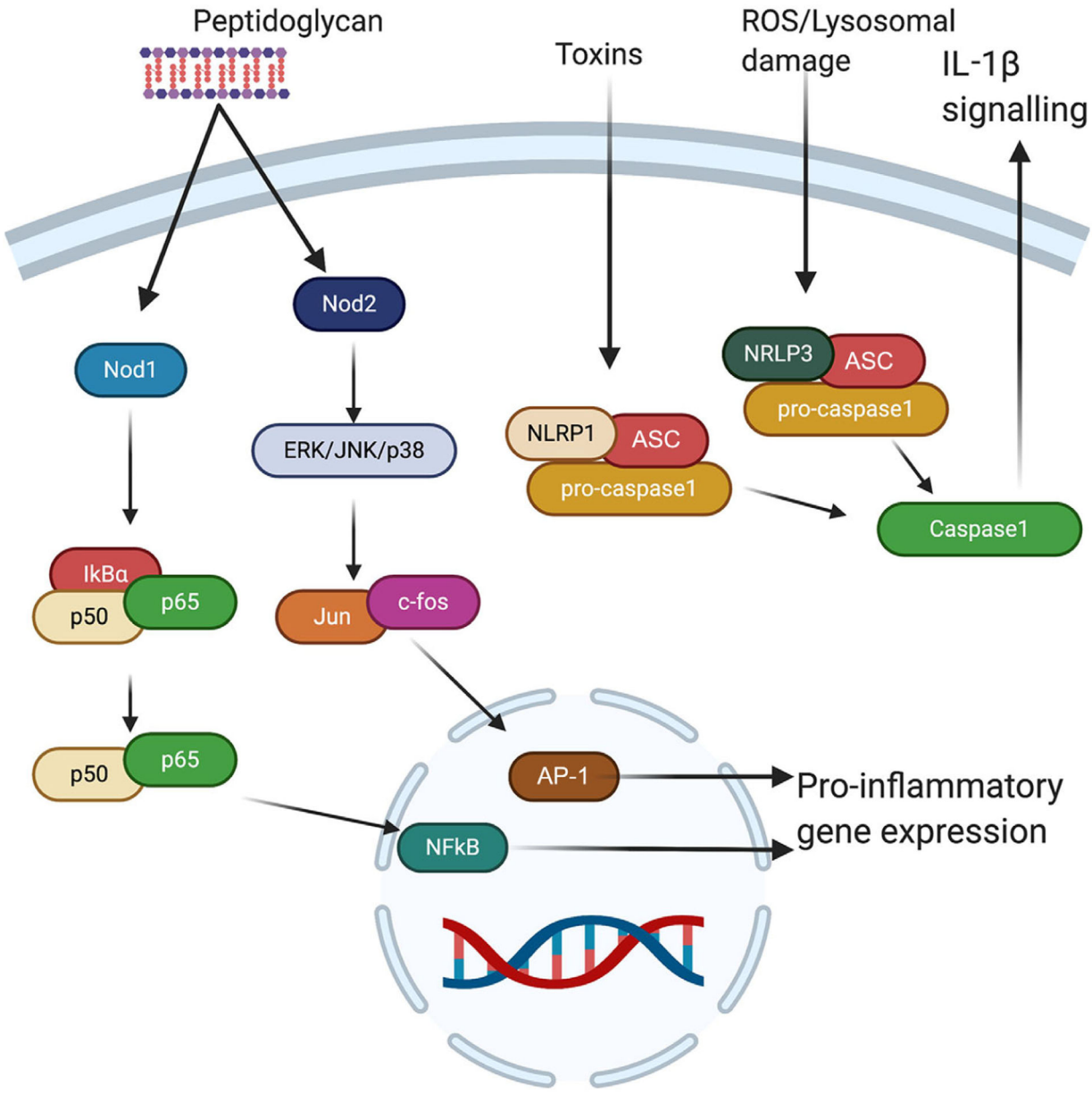

Figure 2. The NLR signalling pathway

NLRs are predominantly present in the cytosol of cells, including immune, epithelial, endothelial and neuronal cells. Both Nod1 and Nod2 respond to bacterial peptidoglycan, with Nod1 initiating NF-κB-dependent pro-inflammatory gene expression and Nod2 initiating AP1 inflammatory genes via extracellular signal-regulated kinase (ERK)/c-Jun N-terminal kinase (JNK)/p38. NLRP1 activates caspase1 signalling in response to toxins and NLRP3 activates caspase1 in response to lysosomal damage and reactive oxygen species. AP-1, activator protein 1; ASC, apoptosis-associated speck-like protein containing a CARD; IκBα, inhibitor of nuclear factor-κB α; ROS, reactive oxygen species.

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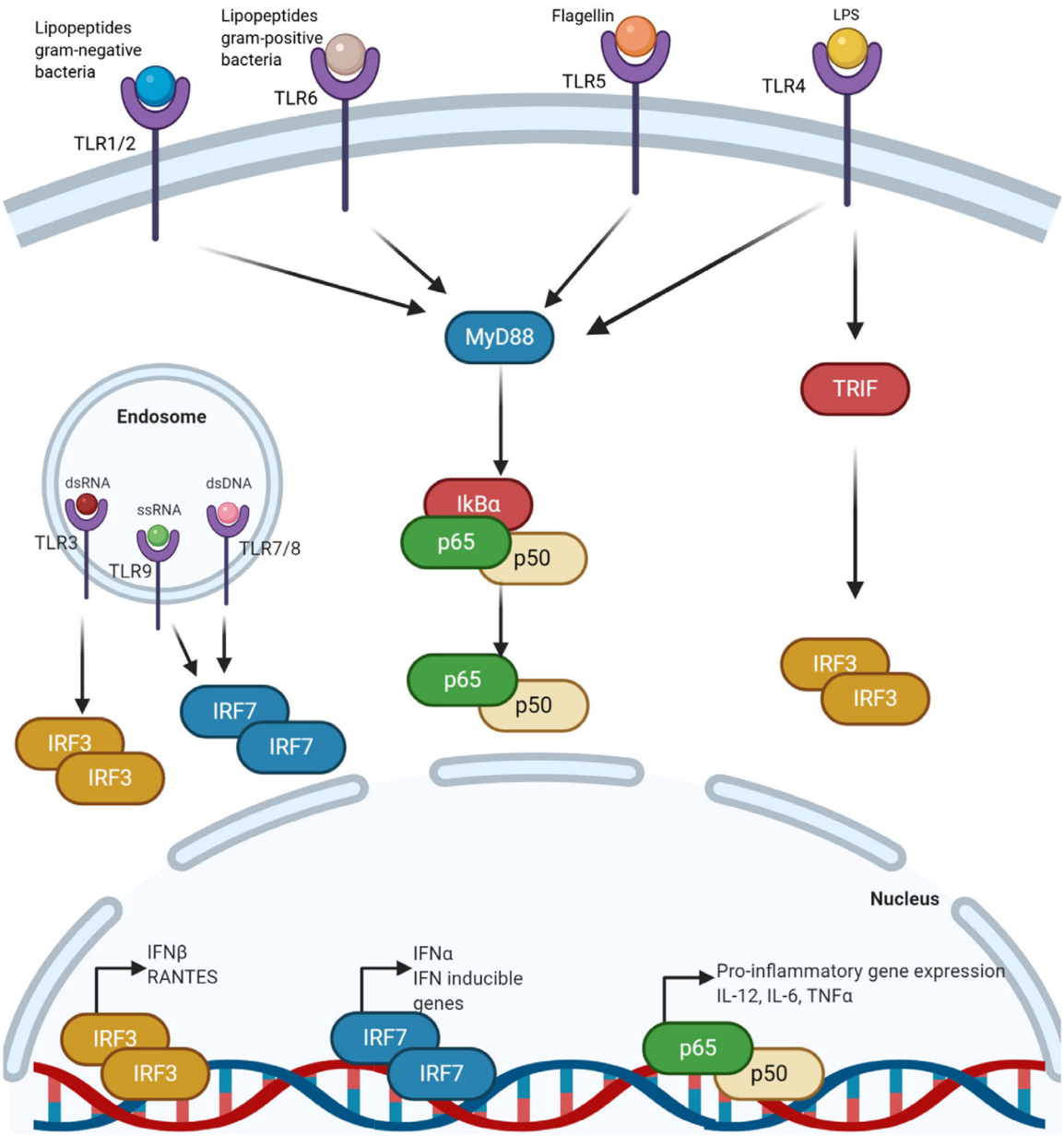

Figure 3. The TLR signalling pathway

TLRs are membrane bound or endosomally bound. Membrane bound TLRs (TLR1, 2, 6, 4 and 5) signal through MyD88 in response to a variety of stimuli, such as lipopeptides from gram-negative or gram-positive bacteria, flagellin or lipopolysaccharide, and activate NF-κB-dependent pro-inflammatory genes. TLR4 can also signal through a MyD88 independent pathway and activate interferon (IFN) signalling. Endosomally bound TLRs (TLR3, 9, 7 and 8) are activated by dsRNA, ssRNA and dsDNA and activate IFN signalling in response to these stimuli. IRF, interferon regulatory factor; TRIF, Toll/IL-1 receptor domain-containing adaptor-inducing IFN-β.