# Neuroimmune Mechanisms of Cerebellar Development and Its Developmental Disorders: Bidirectional Link Between the Immune System and Nervous System

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**Abstract** Understanding the cross talk between the immune system and cerebellum development has noticeable implications for understanding and management of neurodevelopmental disorders. Our knowledge about cerebellar developmental maturation and remodeling is improving. Immune cells have different functions in a healthy state, but those functions are compromised during developmental stages in mammals. In this chapter, we highlight the evidence that indicates an important role of the immune system within the cerebellum and brain. We discuss the contribution of different immune responses in the development of the cerebellum and its associated disorders and highlight current understanding of the mechanisms and insights involved in these processes. Immune pathways that have a crucial role in cerebellar development are likely to become therapeutic targets for several neurodevelopmental disorders. Therefore, this information may suggest new therapeutic approaches

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to developmental disorders of the cerebellum through suppression or activation of selected immune pathways.

**Keywords** Cerebellum • Brain • Innate immunity • Adaptive immunity • Cytokines • Hypothalamic–pituitary–adrenal

## Abbreviations

| | |
|---|---|
| AICA | Anterior inferior cerebellar artery |
| ALRs | AIM2-like receptors |
| ALS | Amyotrophic lateral sclerosis |
| ANS | Autonomic nervous system |
| APCs | Antigen-presenting cells |
| BBB | Blood–brain barrier |
| CCL | C-C motif chemokine ligand |
| CNS | Central nervous system |
| Cop-1 | Copolymer 1 |
| CSF | Cerebrospinal fluid |
| DAMPs | Damage-associated molecular patterns |
| DC | Dendritic cells |
| EAE | Experimental autoimmune encephalomyelitis |
| EGL | External granule cell layer |
| FOXP3 | Forkhead box P3 |
| GAD | Glutamic acid decarboxylase antibodies |
| GIT | Gastrointestinal tract |
| HE | Hashimoto's encephalopathy |
| HSP | Heat shock proteins |
| IBS | Irritable bowel syndrome |
| IFN | Interferon |
| Ig | Immunoglobulin |
| IGL | Internal granule cell layer |
| IL | Interleukin |
| LGP2 | Laboratory of genetics and physiology 2 |
| MDA5 | Melanoma differentiation-associated gene 5 |
| MHC | Major histocompatibility |
| MIP | Macrophage inflammatory protein |
| MSA | Multiple system atrophy |
| NLRs | Nod-like receptors |
| OPCA | Olivopontocerebellar |
| P2X7R | Purinergic receptor P2X7 |
| PACA | Primary autoimmune cerebellar ataxia |
| PAMPs | Pathogen-associated molecular patterns |
| PICA | Posterior inferior cerebellar artery |

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|---|---|
| PRRs | Pattern recognition receptors |
| (RAG)-1 | Recombination activating gene |
| Rig1 | Retinoic acid-inducible gene-1 |
| RLRs | RIG-like receptors |
| Rora | Retinoic acid-related orphan receptor alpha |
| ROS | Reactive oxygen species |
| SCA | Superior cerebellar artery |
| SCID | Severe combined immunodeficiency |
| SND | Striatonigral |
| SOCS3 | Suppressor of cytokine signaling 3 |
| TGF | Tumor growth factor |
| Th | T helper |
| TLRs | Toll-like receptors |
| TNF | Tumor necrosis factor |
| Treg | Regulatory T cells |
| URL | Upper rhombic lip |

## Introduction

The cerebellum is an important motor and non-motor structure in the central nervous system (CNS), it includes more neurons than the entire cerebral cortex [1], and it is well-conserved across evolution. Despite its prominent architecture and some clear syndromes related to its malfunction, the exact role of immune regulation during cerebellum development has not been well studied. Thus, many researchers are investigating the role of the immune system within the cerebellum.

Over the past few decades, the functional autonomy of both the immune system and the CNS has been successfully challenged, and innovations in the field of neuroimmunology and psychoneuroimmunology have revealed that the immune system and the CNS are closely related and function together [2, 3]. There is a growing understanding that neurodevelopmental disorders are related to cerebellar deficits, but molecular mechanisms and underlying pathways of cerebellar defects remain poorly understood [4]. Developmental studies have revealed that the cerebellum evolves in successive waves of progenitor proliferation/migration throughout the embryonic and postnatal phases, which may identify new therapeutic options.

The immune system can interact with the CNS through immune mediators such as primary cytokines, CNS-derived cytokines, neurotransmitters, and neuropeptides secreted by different immune cells [5]. Bidirectional communication between immune responses and the CNS and their effect on cerebellar development has not been well studied, but direct bidirectional projections between the cerebellum and hypothalamus and the cerebellohypothalamic and hypothalamocerebellar projections have been demonstrated [6–8]. Stimulation of the cerebellar fastigial nuclei induces a postsynaptic response or an alteration in unitary activity via cerebellohypothalamic projections in the hypothalamus [9], demonstrating that the cerebellum can indirectly influence immune cell function through cerebellohypothalamic

projections. In this chapter, we will review possible direct or indirect interrelations between the immune system and cerebellum and how the immune system can affect the development of the cerebellum to maintain a homeostatic state or regulate pathological conditions such as cerebellum developmental disorders.

## Anatomy of the Cerebellum and Interconnection with Other Central Centers Implicated in Neuroimmune Regulation

The anatomical features of the cerebellum, described in chapter "The Embryology and Anatomy of the Cerebellum", are relevant to understand how immune and inflammatory responses are generated and how these immune responses could affect cerebellar development. The hypothalamus also exerts specific neuromodulation on the cerebellum, which could impact the immune response. This modulation occurs because the cerebellar cortex receives two well-identified types of afferent fibers: mossy fibers and climbing fibers. There is a third type of afferent, the neuromodulatory fiber that consists of characteristically beaded fibers, which contain amines or neuropeptides [10, 11]. For example, histamine-containing fibers originate from the tuberomammillary nucleus of the hypothalamus and broadly spread into the cerebellum [11]. Moreover, beaded fibers containing angiotensin II result from the paraventricular and supraoptic nuclei of the hypothalamus [12] and impact comprehensively upon the cerebellum.

The relationship between circulating hormones (thyroid hormones, sex hormones) and cerebellar development is well studied (see chapter "Hormonal Regulation of Cerebellar Development and Its Disorders"). These hormones have immunomodulatory effects and can shape different immune responses. Thyroid hormone and its receptor, which is a ligand-regulated transcription factor binding to a specific DNA sequence called thyroid hormone-responsive element, have a particularly vital role in brain development [13]. The receptor recruits coactivators and corepressors in a ligand-dependent manner to regulate the transcription of target genes. It may also interact with other nuclear receptors such as retinoic acid-related orphan receptor alpha (Rora), whose expression is regulated by the thyroid hormone during the first two postnatal weeks. In perinatal hypothyroidism, Purkinje cell dendrites have greatly reduced growth and branching with a reduction of synapses between granule cells and Purkinje neurons, which is associated with delayed migration of granule cells to the internal granule cell layer and deficient synaptic connectivity within the cerebellar cortex [14]. Experimentally, thyroid-deficient rats show a persistence of climbing fiber synaptic sites for a longer time along with an underdevelopment of cerebellar glomeruli [15]. These effects could be attributed to hyperthyroidism, which reduces the pro-inflammatory properties of monocytes and macrophages and promotes phagocytosis, and there may also be elevated levels of reactive oxygen species (ROS) during hypothyroidism [16]. A better understanding of the links between such hormones and immune responses could provide new insights toward clarifying the potential effects of several immune responses on the development of the cerebellum.

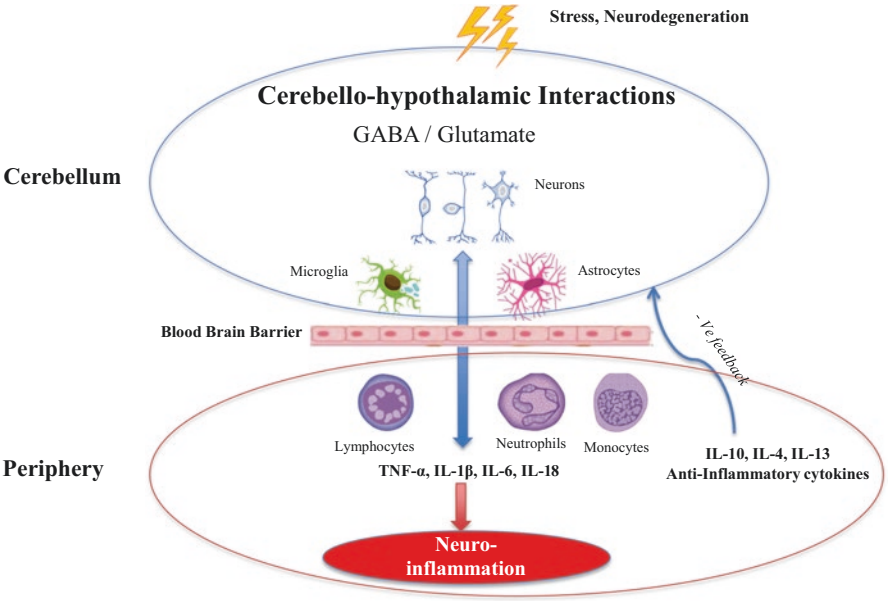


**Fig. 1** Simplified illustration shows the interaction between cerebellohypothalamic projection, neurons, astrocytes, microglia, and peripheral immune responses. In pathological conditions, there is a cerebellohypothalamic interactions via the balance between GABA and glutamate to activate neurons. Neurons deliver damage signals to glial cells and astrocytes to interrupt blood–brain barrier that lead to activate innate and adaptive immune responses and pro-inflammatory cytokine productions and end with neuro-inflammation. Anti-inflammatory cytokines result in deactivation of glial cells and astrocytes and in turn maintain homeostasis

Cerebellar immunomodulation exists, and it may be regulated by the hypothalamus, but anatomically, there is no direct connection between the cerebellum and the immune system. The cerebellum communicates with the immune system through the cerebellohypothalamic projections, which are direct projections from the cerebellum to the hypothalamus, and this pathway may serve as an important mediator in immune system modulation (Fig. 1). Moreover, many neuropeptides can be released from the CNS and can impact the immune system, which in turn affect the cerebellum, especially in the developmental stages. Thus, various immune responses can shape the development and functional consequences of the cerebellum. However, there are few direct or indirect data that demonstrate these mechanisms.

## The Immune System in the Cerebellum

Alterations in immune responses during prenatal or early postnatal development contribute to cerebellar development and disorders. The immune system is designed to reflect surrounding changes and to predict future changes as a defensive mechanism. Communication between the CNS/cerebellum and the immune system is

bidirectional, and both systems shape the other's responses through different mechanisms and mediators. As shown in Fig. 1, the CNS can mediate the innate and adaptive immune responses, which leads to the production of cytokines and which can alter cerebellar development and function. Moreover, pattern recognition receptors and innate and adaptive immune responses play a major role in regulation of the immune system.

## *Pattern Recognition Receptors*

The innate immune system senses commensal and potential antigens and detects tissue disruptions by different receptor types, which are called pattern recognition receptors (PRRs) [17]. PRRs recognize pathogens through specific pathogen-associated molecular patterns (PAMPs) that are expressed by microbes, and they play a major role in sterile inflammation response to endogenous stimuli, called damage-associated molecular patterns (DAMPs). PRRs are among the first responders to cerebellar disorders [18], and activation of these receptors on microglia, neurons, and astrocytes initiates an innate immune response [19]. Microglia, the brain's main resident immune cells, are important to the inflammatory response and can be activated by distress signals released from neighboring cells [20]. Microglia that enter a pro-inflammatory state are mostly activated by PRRs, and they are fundamental components of host innate immunity. Therefore, activation of PRRs results in inflammatory mediator release that helps to remove antigens or restore tissue homeostasis. However, chronic or continuous activation of these receptors can cause inflammatory disorders that impact cerebellar development and contribute to pathogenesis of its developmental disorders.

Toll-like receptors (TLRs) have been characterized in response to pathogens, but they also play a central role in regulating sterile inflammation [21]. TLR4 is a major route of such amplification that may occur via the purinergic receptor P2X7 (P2X7R) [22]. Interleukin-1β (IL-1β) is now counted as a master regulator of neuroinflammation; it leads to a critical contribution to cellular activation and cytokine production [23] and contributes to the pathogenesis of cerebellum disorders, as well as to other acute and chronic diseases of both the peripheral nervous system and CNS [24]. Many DAMPs such as heat shock proteins (HSP60 and HSP70), degradation products of the ECM (hyaluronic acid, fibronectin), and nucleic acids such as mRNA and miRNAs are released passively from necrotic cells after cerebellum injury [25–27]. Mitochondrial DNA and proteins are also considered to be DAMPs, particularly mtDNA and N-formyl peptides [28].

Most cells in the CNS express TLRs, but microglia express the full repertoire of TLRs, which enhance their ability to monitor the CNS and act as the first line of defense [29]. In the cerebellum, microglial activation can be partially explained by aberrant expression of TLRs in the brain regions that are involved in striatonigral

(SND) or olivopontocerebellar (OPCA) [30] and could promote neurodegenerative disorders through amplification of pro-inflammatory cytokines release via alterations in TLRs signaling, which lead to mitochondrial dysfunction that end with excessive reactive oxygen species production [30]. Astrocytes, neurons, and oligodendrocytes also express TLRs in both physiological and pathological cerebellum states [31]. Astrocytes express TLR3 under resting and activated conditions [32] and may elevate TLR2 and TLR4 upon activation [33]. Changes in TLR expression demonstrate their critical role in mediating complex and interconnected processes that are implicated in the development of the cerebellum and its developmental disorders.

NLRs are primarily dedicated to sensing and detecting pathogens, but they have been shown to contribute to the inflammatory responses caused by cerebellar disorders [34]. NLRs are known for their ability to form inflammasomes. Inflammasomes are large multiprotein complexes that activate caspase-1, which is essential for maturation of pro-IL-1β and pro-IL-18 [35] and for programmed cell death [36]. Within the CNS, three different NLR inflammasomes have been described: NLRP1 [37], NLRP2 [38], and NLRP3 [39]. NLRP1 has been defined as mediating the innate immune response after brain disorders [40]. Inflammasomes are present in astrocytes [41] and microglia [42], and neuronal inflammasomes seem to contribute to cerebellum disorders [43]. IL-1β and IL-18 have a crucial role in mediating neuroinflammation and neurodegeneration in the CNS [44]. Experimentally, IL-1β is activated specifically in the cerebellum by the systemic administration of kainate, and it is involved in kainate-induced ataxia in mice. Moreover, IL-18 in the cerebellum is implicated in the recovery phase of kainate-induced ataxia by counteracting the function of IL-1β in the cerebellum [44]. IL-1β also participates in neurological processes and appears to have a role in autism as a mediator of this cerebellar developmental disorder [45]. Homeostatic levels of IL-1β and its antagonist IL-1ra are necessary for proper brain development and function.

Many PRRs that are expressed in the cerebellum can identify pathogenic microbes and are mediated through RLR and ALR [46]. RLRs are cytoplasmic PRRs that detect RNA viruses associated with the production of type I interferons (IFNs) [47]. Two ALRs have been described: IFI16 and AIM2 [48]. In neurons, AIM2 forms an inflammasome that activates pyroptosis, a novel but potentially important mode of cell death [49]. Moreover, scavenger receptors (type A and B receptors) are PRRs that are implicated in the metabolism of cholesterol and lipids and are expressed on microglia, endothelia, and astrocytes [50]. Programmed cell death plays a significant role in the cerebellum development and developmental disorders by affecting the neurons and glia during nervous system development, plasticity, and aging. Thus, defects in this mechanism can impact cerebellum development, which could result in developmental disorders. To summarize, PRRs are among the first responders in the cerebellum, and their activation will trigger an innate immune response.

## *Innate Immune Responses in the Cerebellum*

Immune responses in the cerebellum are a critical component of immune privilege in the CNS, and they are mediated by resident microglia and astrocytes without direct counterparts in the peripheral immune response. Moreover, microglia, dendritic cells (DCs), and astrocytes are also implicated in significant cross talk between CNS-infiltrating T cells, neutrophil complement, and other components of the immune system.

*DCs* play a critical role within the innate system as antigen-presenting cells (APCs) that induce adaptive immunity. However, there is no evidence that DCs with these abilities exist within the healthy cerebellum or CNS parenchyma. Additionally, some cells express DC surface markers (CD11b, CD11c) in the meningeal CNS covering and in the choroid plexus where CSF synthesis takes place [51]. The nonexistence of parenchymal DCs and the fact that no other parenchymal CNS cells correspond to the functional definition of DCs (e.g., APCs) establish the cellular basis of cerebellum immune privilege. Cerebellum immune tissue is privileged because of its robust intrathecal inflammatory reactions that can damage delicate post-mitotic cells such as neurons and oligodendrocytes. The absence of adaptive immune responses might confer a physiological advantage to the cerebellum. Because antigen entrance into the cerebellum suggests that there is a passage from a peripheral site of entry to the draining lymph nodes or spleen, it would likely be unnecessary for the cerebellum to generate a de novo adaptive immune response. However, further studies are required to support this hypothesis.

The main function of the blood–brain barrier (BBB) is to provide an accurate calibrated chemical and ionic environment to optimize neuronal function and to prevent inflammation by excluding plasma proteins and peripherally derived innate and adaptive immune responses [52, 53]. The parenchymal cerebellum environment has anti-inflammatory proprieties because of high local levels of inflammation-suppressive cytokines (TGF-β, IL-10), and it is supplied with gangliosides, which can be detrimental and lethal to T cells [54, 55]. Moreover, the absence of CNS innate immune cells activating adaptive immunity within the lymphoid organs suggests that resident innate immune cells need to interact directly with the damaged tissue [19].

*Microglia* are the resident macrophages of CNS. They play critical roles during pathophysiological conditions and display different topographical morphologies across the CNS and during phases of their lifespan [56]. Microglia are implicated in brain development, including in growth of neurites, synaptic pruning, spinogenesis, and apoptosis [57, 58] in areas such as the visual cortex, hippocampus, and retinogeniculate system [59]. However, there are few studies dedicated to the role of microglia during postnatal development. In the cerebellum, microglia are dispersed in both gray and white matter across diverse species, and there is a distinct arrangement of microglial processes according to their location in the cerebellar cortex [60]. Recent findings showed a continuous process of microglial maturation and a nonuniform distribution in the cerebellar cortex, demonstrating that microglia are an essential cellular component of the cerebellum [61]. This has been confirmed in vitro, where the microglia can promote apoptosis of Purkinje neurons [62]. However, there is no information about the presence of this mechanism in vivo.

Microglia also regulate synapse formation and plasticity by phagocytosis of unwanted synapses opsonized with complement components [63]. Impaired phagocytosis leads to an increase in the buildup of cellular debris and has detrimental effects on surrounding neurons, which are suspected to play a role in several neurodegenerative and neurodevelopmental disorders [64].

*Neutrophils* are an important component of innate immunity and are also considered to be a first line of defense against bacteria, as demonstrated by life-threatening conditions that result from neutrophil deficiency [65]. Neutrophils respond to PAMPs and DAMPs through TLRs and NLRs to increase CD15, CD11b, and adhesion molecule expression, which are responsible for neutrophil recruitment [66]. Activated neutrophils release inflammatory mediators, angiogenic factors, lytic enzymes, and antimicrobial peptides [66] and play a major role in Th1 or Th17 recruitment through the production of CXCL9, CXCL10, or CCL20 [67, 68]. Neutrophil–lymphocyte interactions release survival factors that increase the lifespan of the short-lived neutrophils [19].

Chemokines and their receptors (CCL2/MCP-1, CCL5/RANTES, CXCL12/CXCR4) have an important impact on the development and maintenance of the cerebellum [69], and they are expressed in several parts of the brain including the cerebellum [70]. Moreover, chemokines may influence the cross talk between neuron and glial cell types and can function as a third communication system in the brain [71]. The cerebellum is a CNS structure whose development continues to occur in the postnatal period, leaving it susceptible to malformation events. The external granule cell layer (EGL) is formed during cerebellar development, when cerebellar granule cell progenitors produced in the upper rhombic lip (URL) migrate over the cerebellar primordium to form a secondary proliferative zone, the EGL. Formation of the internal granule cell layer (IGL) occurs during early postnatal development, when granule cell precursors in the outer zone of the EGL proliferate, migrate to the inner zone of the EGL, and exit from the cell cycle, differentiate, and radially migrate via the Purkinje cell layer to their final destination [72]. CXCL12 is a strong chemoattractant for granule cell progenitors in the URL, EGL, and dentate gyrus, also playing a critical role during neurogenesis through promotion of axonal growth and being expressed in embryonic and postnatal meninges that cover the cerebellum [73]. It is also known as a potent chemoattractant for URL cells, inhibiting CXCR4-expressing premature granule cell migration to the EGL [74]. Therefore, the irregular EGL formation could partially be attributed to defects in cell migration from URL to EGL. Focusing on a chemokine–receptor axis, CXCL12/CXCR4 could provide new therapeutic potential for cerebellum developmental disorders.

*Astrocytes* have various functions in the CNS, which support differentiation and homeostasis of neurons and influence synaptic activity. They are also responsible for the formation of the BBB [75]. The BBB constitutes an elaborate structure formed by specialized capillary endothelial cells, which, together with pericytes and perivascular glial cells, control exchanges between the CNS and the periphery. Intricate interactions between various cellular components in the BBB are crucial in establishing its function and maintaining the delicate homeostasis of the brain microenvironment [76]. Existence of numerous astrocytic end-feet near the BBB demonstrate their role in regulation of BBB permeability, which is increased by

humoral mediators that can be secreted by astrocytes as well as other glial cells, including endothelin-1, glutamate, IL-1β, IL-6, tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, and nitric oxide [77]. Astrocytes subsequently regulate neuronal differentiation and homeostasis, and evidence has shown that astrocytes interact with the immune system because they express a variety of PRRs, and both recognize danger signals and respond accordingly [78]. Following PRR activation, astrocytes produce cytokines, chemokines, and neurotrophins that target neighboring glial cells and neurons [78]. Therefore, the perception of immune privilege in the CNS can be minimized because astrocytes can reduce inflammation via releasing IL-27, and they also have constructive neuroprotective effects on the healthy brain [79]. Astrocyte activation leads to activation of damage control mechanisms such as induction of a neuroprotective effect and polarization toward Th2 profile. Conversely, IFN-γ produced by Th1 cells can suppress astrocytes that aggravate neuroinflammation [80]. Thus, astrocytes may constrain and defer neuroinflammation, but high levels of IFN-γ might promote astrocytes to become potent APCs and even promote inflammation [81].

*The complement system* includes nearly 40 soluble and membrane-bound proteins that play a critical role in host defense against pathogens and initiation of inflammation [82, 83]. The liver is the main source of complement production, but it can be produced by many types of resident cells in the CNS [84]. Complement receptor expression (C3a and C5a) has been shown on glial cells and neurons [85]. The complement system contributes to modulating CNS development and inflammation [86]. Complement components C1q and C3 are expressed on neurons throughout the CNS where they opsonize synapses to highlight them for phagocytosis by microglia [87]. Their expression peaks during crucial stages of neurodevelopment such as synapse formation and activity-dependent refinement [88]. MHC1 expression is also spread across the brain including cerebellar neurons and neuronal synaptic membranes, and MHC1 is thought to be fundamental for synapse formation and plasticity; potentially any defect in MHC1 could, thus, lead to cerebellar developmental disorders such as autism [89]. Systemic complement depletion diminishes perihematomal brain edema and TNF-α release following experimental intracerebral hemorrhage [90]. The core mechanism involving complement components in immune cells recruited into the brain and cerebellum parenchyma through the BBB remains unclear. Some therapeutic approaches using large recombinant molecules may work only when the BBB is compromised, while small molecule drugs, such as known receptor antagonists and low molecular weight heparin, could be potential therapeutics for treating patients with chronic disorders who have a non-compromised BBB. Blocking or preventing complement activation is a successful approach to decrease leukocyte recruitment and endothelial activation during CNS inflammation [78]. Therefore, specificity and balance challenges of various coincident cascades need to be highlighted; approaches that both promote beneficial effects and prevent detrimental activities are attractive goals for better understanding of human neurological disorders.

## *Adaptive Immune T and B Cells in the Cerebellum*

*Adaptive immunity is orchestrated by T-helper (Th)* cell subsets, through secretion of lineage-specific cytokines. T cells enter the CNS and cerebellum parenchyma in several autoimmune, infectious, and degenerative neurological diseases. Therefore, T cells can be directly responsible for neuronal damage in many neurological diseases via different mechanisms of neuronal damage that are mediated through different T-cell subsets. For example, lesions of the vestibulocerebellum decrease the secretion of hematopoietic cytokines in the bone marrow and thymus tissue culture and decrease peripheral blood leukocyte concentration, neutrophil myeloperoxidase activity, and antibody response [91]. Conversely, the suppressive influence of vestibulocerebellar lesions on immune function demonstrate that induced lymphocyte proliferation is significantly enhanced on days 8, 16, and 32 following the effective kainic acid lesions in the bilateral cerebellar fastigial nuclei in rats [92]. Subsequently, cerebellar fastigial nuclei contribute to the modulation of lymphocyte function but not to the hypothalamic–pituitary–adrenal axis [92].

Although T cells within the CNS and cerebellum have been reported to be pathogenic cells, recent findings have demonstrated important functions for T cells in the healthy CNS [93]. Immunization of rats with copolymer (Cop-1), which mimics the myelin basic protein in the CNS and polarizes lymphocyte activation toward the Th2 profile, protects the injured optic nerve from secondary degeneration [94]. Moreover, regulatory T cells (Treg cells) reduce microglial activation after inflammation develops, and astrocytes promote Treg cell transcription factor expression [95]. Therefore, T cells are key players and might have a beneficial role in the development of CNS adaptive immunity.

The balance between Treg and inflammatory T cells (IFN-γ-producing Th1 and IL-17-producing Th17) is critical in neuroinflammatory diseases and contributes to the pathogenesis [96, 97]. Children with cerebellar developmental disorders such as autism displayed impaired immune profiles and function, which is characterized by a systemic deficit of $Foxp3^{+}$-(Treg) cells and increased expression of some transcription factors ($ROR\gamma t^{+}$, $T\text{-}bet^{+}$, $GATA\text{-}3^{+}$) [98]. This suggests the importance of transcription factor signaling, which results in an immunological imbalance in cerebellar developmental disorders. The balance between Treg cells and other T-cell subsets (Th1, Th2, Th17) seems to be important for cerebellum homeostasis, neurogenesis, and neuroinflammation. The immune system plays a crucial role in the recovery process of cerebellum development and disorders [99]. Researchers working on new therapeutic strategies have a cutting-edge understanding of the pathogenesis of many diseases and disorders, but there is no specific central therapy targeting Treg cells or suppressing Th1 or Th17 cells. It is currently unknown whether Treg cells can be selectively targeted. By better understanding the regulation of harmful effects compared with beneficial homeostasis promoting T-cell responses at the immune and central nervous systems, it is believed that novel potential therapeutic strategies will be identified, which could also avoid side effects of currently available immunosuppressive treatments.

*Humoral immune responses controlled by B lymphocytes* have been implicated in CNS and cerebellar diseases and disorders [99]. Recently, it was reported that the association of maternal autoimmune disorders with cerebellar developmental disorders in offspring may be regulated by the passive transfer to the fetus of maternal immunoglobulin G (IgG) antibodies that show reactivity to self-proteins in the mother or child [100]. Thus, pregnant women who have immune disorders or autoimmune reactions, even at a clinically undetectable level, may be linked with the production of maternal antibodies that can enter the fetal brain and potentially perturb fetal brain development. Collectively, immune responses are critical in cerebellum development, and balance of these responses is required to avoid cerebellar developmental diseases/disorders.

Purkinje cells are a class of GABAergic neurons located in the cerebellum that could shape adaptive immunity. Immunoglobulin plays a role in many neuro-disorders. Antibodies to cytoplasmic components of cerebellar Purkinje cells have frequently been labeled in serum and CSF [101]. However, the roles of such antibodies in the pathogenesis of neuronal injury are undefined. Intact neurons are thought to be essentially impermeable to IgG, and antibodies to cytoplasmic or nuclear neuronal antigens cannot enter neurons and bind to their intracellular targeted antigens [102]. The cerebellar Purkinje cell is a possible exception. Experimentally, Purkinje cells showed a high endocytic activity for a wide range of substances that originate from the ventricular CSF [103], and they can also incorporate IgG and S100 [101]. Therefore, the aptitude of Purkinje cells and related neurons to engulf antibodies is vital because of the possible role of autoantibodies in disease pathogenesis and because cerebellar injuries and Purkinje cell damage have been demonstrated in animals and human patients receiving IgG-conjugated immunotoxins [101].

## Cerebellum and Immune Response Interactions in Cerebellar Diseases

Cerebellum and cerebellar Purkinje cells seem to be a common immunological target in some neurological disorders. This may be because the cerebellum is one of the largest, oldest, and most conserved structures in the nervous system and/or because Purkinje cells have good and various antigenic targets.

The immune system mediates the pathophysiology of cerebellar diseases via different immune responses. Evidence suggests that the cerebellum is a CNS target of autoimmunity, as shown by the high prevalence of paraneoplastic cerebellar degeneration (PCD) within paraneoplastic neurological syndromes [104]. Immune-mediated cerebellar ataxia, according to the associated autoantibodies, includes gluten ataxia, paraneoplastic cerebellar degeneration, anti-glutamic acid decarboxylase antibodies (GAD) antibody associated with cerebellar ataxia, and Hashimoto's encephalopathy (HE) [105]. Many of these autoantibodies distinguish cerebellar-specific antigens traced in the Purkinje cell soma to dendrites resulting in a Medusa-head immunohistochemical staining pattern [106]. There is a large amount of

evidence to suggest that the cerebellum can be a primary target for organ-specific autoimmune disease, and thus, the proposed term of primary autoimmune cerebellar ataxia (PACA) suggests that there is no known trigger factor for the development of immune-mediated damage to the cerebellum, but that it is more likely attributed to a hormonal imbalance, which impairs various immune responses such as in hypothyroidism, type 1 diabetes mellitus, and vitiligo. Therefore, humoral mechanisms, cell-mediated immunity, inflammation, and vascular injuries could contribute to the cerebellar discrepancies in immune-mediated cerebellar ataxia.

Some of the pathological damage to CNS is a result of immune-mediated mechanisms and not secondary to vitamin or nutrient deficiencies. Examination of patients with gluten ataxia revealed patchy loss of Purkinje cells in the cerebellar cortex [107]. Moreover, gluten ataxia is characterized by a diffuse infiltrate of T lymphocytes with a smaller number of B lymphocytes and macrophages in the cerebellar white matter and the posterior column of the spinal cord as well as loss of Purkinje cells [107]. Similar findings have been defined in patients with established celiac disease who then developed cerebellar ataxia [108]. Experimentally, antibody cross-reactivity between antigenic epitopes on Purkinje cells and gluten peptides has been reported [109]. Serum from patients with gluten ataxia and patients with celiac disease but with no neurological symptoms display cross-reactivity with epitopes on Purkinje cells using both human and rat cerebellum. The reactivity can be abolished after absorption of the antigliadin antibodies using crude gliadin. A study investigated the epitope responsible for cross-reaction between gliadin peptides and cerebellar peptides, by assessing the reactivity to specific peptides from the gliadin and cerebellum in serum from 50 autism patients and 50 healthy controls. Autism patients showed a significant increase in the antibodies against gliadin and the cerebellar peptides [110]. Therefore, this study suggests that a subgroup of patients with autism produce antibodies against Purkinje cells and gliadin peptides, which may be responsible for some of the neurological symptoms of autism. An antibody-mediated pathogenesis is also supported experimentally, revealing that intraventricular injection of serum from patients with gluten ataxia can induce ataxia in mice [111]. In conclusion, the brain–gut axis, the enteric nervous system, and the immune system contribute to the immune pathobiology of neurodevelopmental disorders through production of specific antibodies against cerebellum peptides to induce immune responses, which have detrimental effects on cerebellar tissues.

Communication between the gut and the brain, which is regarded as the gut–brain axis, is a well-known bidirectional neurohumoral communication system. Previous research that focused on the gut–brain axis mostly referred to its contribution in functional gastrointestinal syndromes, such as irritable bowel syndrome (IBS) [112]. It was recently reported that gut microbiota can modulate brain development and produce behavioral phenotypes via the gut–brain axis [113]. Thus, the potential effects of the microbiota–gut–brain axis in neurodevelopmental disorders are receiving much attention. The bidirectional communication in the microbiota–gut–brain axis acts mainly through both neuroendocrine and neuroimmune mechanisms. Moreover, the metabolites of microbiota can be absorbed and transported by the blood before crossing the BBB to modulate cerebral functions. The gut micro-

biota also contributes to cerebral developmental disorders by modulating the host immune response through releasing a storm of pro-inflammatory cytokines (including IL-1, IL-6, and IL-18) by intestinal epithelial cells, intestinal DCs, and macrophages [114]. Vagal afferents could be another potential mechanism by which the microbiota–gut–brain axis regulates communication, in which gut microbiota can send signals to the brain through the vagus nerve. Additionally, interruption of the microbiota–gut–brain axis in neurodevelopmental disorders such as autism is a comorbidity of neurodevelopmental deficits and intestinal symptoms. Moreover, autistic behaviors were often associated with gut microbiota dysbiosis [115]. Restoring the balance of the microbiota–gut–brain axis offers promising beneficial therapeutic effects on cerebellar developmental disorders such as autistic deficits.

Therefore, a link between the cerebellum and gastrointestinal tract might exist. Patients with gluten sensitivity and normal bowel mucosa (occasionally signified as potential celiac disease) have evidence of antibodies targeting tissue transglutaminase (TG) in the small bowel mucosa and at extraintestinal sites such as the CNS and/or cerebellum [116]. IgA deposition on the jejunal tissue transglutaminase has been reported in the jejunal tissue but also in the brain (mostly in cerebellum) of patients with gluten ataxia and in none of the controls [117]. This immune response described for gluten ataxia suggests a neural transglutaminase and results in clinical manifestations primarily in the brain or the peripheral nervous system, with minimal involvement of the gut; the gut may be involved through deposition of autoantibodies against brain transglutaminases (TG6) [107]. Thus, gluten ataxia is immune-mediated and belongs to the same spectrum of gluten sensitivity as celiac disease. Transglutaminases may play a critical role in pathogenesis of various signs seen in the context of gluten sensitivity. Thus, antibodies against TG6 may become novel markers for the neurological manifestations of gluten sensitivity. There is also cell-mediated immunopathogenesis. Most patients with celiac disease have HLA-DQ2 or HLA-DQ8 class II molecules that bind and present peptides derived from exogenous protein antigens to CD4 T cells. Thus, it has been hypothesized that T cells that react with gluten peptides play a major role in the pathophysiology of cerebellar ataxia because celiac disease is caused by an exogenous protein antigen and is linked to HLA-DQ2/HLA-DQ8 expression.

## Conclusion

Understanding the links between the immune, CNS, enteric, and endocrine systems is fundamental to understand the bidirectional communication between the immune system and cerebellum. An imbalance in the neuroimmune interaction may promote the onset of autoimmune disorders and constitute an important component of pathogenic mechanisms involved in neurodevelopmental and neurodegenerative diseases such as autism and cerebellar ataxia (Fig. 1). The eventual challenge may be to elucidate how these various mechanisms of communication interact with each other.

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