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Neuroimmune and Inflammatory Signals in Complex Disorders of the Central Nervous System

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Abstract
An extensive microglial-astrocyte-monocyte-neuronal cross talk seems to be crucial for normal brain function, development, and recovery. However, under certain conditions neuroinflammatory interactions between brain cells and neuroimmune cells influence disease outcome and brain pathology. Microglial cells express a range of functional states with dynamically pleomorphic profiles from a surveilling status of synaptic transmission to an active player in major events of development such as synaptic elimination, regeneration, and repair. Also, inflammation mediates a series of neurotoxic roles in neuropsychiatric conditions and neurodegenerative diseases. The present review discusses data on the involvement of neuroinflammatory conditions that alter neuroimmune interactions in four different pathologies. In the first section of this review, we discuss the ability of the early developing brain to respond to a focal lesion with a rapid compensatory plasticity of intact axons and the role of microglial activation and proinflammatory cytokines in brain repair. In the second section, we present data of neuroinflammation and neurodegenerative disorders and discuss the role of reactive astrocytes in motor neuron toxicity and the progression of amyotrophic lateral sclerosis. In the third section, we discuss major depressive disorders as the consequence of dysfunctional interactions between neural and immune signals that result in increased peripheral immune responses and increase proinflammatory cytokines. In the last section, we discuss autism spectrum disorders and altered brain circuitries that emerge from abnormal long-term responses of innate inflammatory cytokines and microglial phenotypic dysfunctions.

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Introduction: Cellular and Molecular Basis of Neuroinflammation in the Brain

Disturbances of the central nervous system (CNS) homeostasis (e.g., infection, trauma, ischemia, neurodegenerative diseases, and neurodevelopmental and psychiatric disorders), evoke neuroinflammatory responses in the brain. Microglial cells are designed to interpose the insult effect with the secondary activation of astrocytes that can modulate the recruitment and activation of other immunocompetent cells to the injury site. However, a persistent activation, associated with an increase of inflammatory cytokines and chemokines, followed by the recruitment of peripheral phagocytes can be deleterious to neurons and brain function [1–5].

Based on the activation stimuli and (micro)environmental factors, surveying microglia (M0) may change into two phenotypes: the proinflammatory "M1" phenotype, activated by lipopolysaccharides (LPS) and interferon-γ, corresponding to the "classical" pathway of macrophage activation; and the anti-inflammatory "M2" phenotype, activated by interleukin (IL)-4 and IL-13 through the "alternative" pathway of macrophage activation [6, 7]. Thus, the microglial population responds with a rapid morphological shift from a surveilling, ramified phenotype, to an amoeboid phenotype associated with changes in gene expression, ultimately leading to an activation state [8]. In a resting state, microglia are constantly scanning the neuropil through their highly motile processes acting on synapse maintenance, neurogenesis and growth factors secretion to keep CNS homeostasis. Under insult signals, microglia is converted into an activated mode. A short or moderate signal directs microglia toward a neuroprotective, M2 phenotype, whereas an intensive acute or chronic activation renders an M1 microglia phenotype which is potentially neurotoxic. Under such conditions, microglia fail to acquire a neuroprotective phenotype, producing reactive oxygen species, nitric oxide, proteases, and proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), all of which, may endanger neuronal population. Under severe conditions, however, M1 microglia may also recruit monocyte-derived macrophages that secrete anti-inflammatory cytokines such as IL-10 and TGF-β to restore neuroprotection and cell renewal [9]. Also, under mild microglial activation, TNF-α can stimulate the release of trophic factors related to neuroplasticity and repair [10] and increase the production of glial cell line-derived neurotrophic factor (GDNF) and nerve growth factor (NGF) by astrocytes [11]. In this way, microglial cells express a range of functional states with dynamically pleomorphic profiles [12]. Therefore, a microglial to monocyte-derived macrophage cross talk seems to be instrumental under severe lesion conditions [9]. Microglia also activates astrocytes that can modulate the recruitment and activation of additional microglial and other immunocompetent cells to the injury site closing the circle of a reactive positive feedback [13, 14]. Microglial cells express a variety of receptors for a plethora of molecules that allow them to sense environmental changes over a time scale of minutes and respond in a way that might lead to either beneficial or harmful results, according to the context [15, 16]. Two major signaling cascades, the Ca^{2+}/calcineurin/NFAT and NFκB pathways seem to be involved in microglial activation. Once in the nucleus, NFAT and NFκB interact with distinct DNA-binding elements to drive the expression of multiple cytokines [17, 18].

Several studies have shown the bidirectional interplay between the immune system activation and neuronal function. Whole-cell patch clamp experiments revealed that activation of dendritic glutamate NMDA receptors on single neurons was sufficient to trigger microglia process outgrowth [19], thereby demonstrating a direct link between neuronal activity and the dynamics of microglia dendritic-like processes. In the zebrafish larvae, neuronal activity was reduced by microglia contact while, conversely, preventing microglial processes from spontaneously contacting active neurons significantly enhanced neuronal activity, suggesting that neuronal activity itself can be altered by microglial interaction [20]. Also, microglial activation is associated with altered long-term potentiation (LTP) [21], the synaptic correlate of memory. Furthermore, calcineurin, a Ca^{2+}/calmodulin-dependent phosphatase, not only induces microglia reactivity but modulates synaptic activity through dephosphorylation of several targets required for LTP/LTD, including the modulation of NMDA receptor activity [22] and the suppression of glutamate release [23]. Microglia also responds to high concentrations of extracellular ATP through P2X7 receptors (P2X7R) [24]. Neuroinflammation and abnormal microglial activation may also play a mechanistic role in synaptopathies affecting cognition and function [25–27].

An extensive microglial-astrocyte-monocyte-neuronal cross talk seems to be crucial not only for normal brain development and function but also for the injured, severely dysfunctional, brain.

Surprisingly, in recent years, cumulative evidence has demonstrated the relevance of inflammatory mediators, immune cells, and related molecules in the development

of CNS pathologies of very diverse origin and etiologies. With the aim of highlighting differences and commonalities, we will analyze the involvement of neuroimmune interactions in four different pathologies: (a) the injured brain and its associated plasticity adaptations, (b) the brain of amyotrophic lateral sclerosis (ALS) patients as an example of neurodegenerative diseases, (c) major depression disorder (MDD), an emotional alteration of a still unknown though probably multifactorial mechanistic bases, and (d) autistic spectrum disorders (ASD) as an example of neurodevelopmental disorders.

Inflammation and Lesion-Induced Plasticity in the CNS

Brain plasticity in response to lesions is rapid and usually leads to functional recovery in the neonatal brain. However, in adults, various forms of lesions usually result in a lower recovery ratio. Inflammatory mechanisms have been involved in the modulation of reactive plasticity of intact neuronal populations in various forms of brain injury, as well as the involvement of microglial and astrocytic activation in recovery and repair of neural circuits. Then, why is the CNS so plastic during early development? Why does plasticity decrease in adulthood? Does the rapid plasticity found in infants relate to the profile and time course of glial activation? Strategies seeking the modulation of the different profiles of reactive microglia and astrocytes during early brain development may emerge as potential mechanisms to allow a more permissive milieu to plasticity and recovery in the adult brain.

Critical Periods of Development and Lesion-Induced Plasticity in the CNS

The use-dependent development of functionally organized connections in the mammalian CNS occurs over a time window known as the critical period [28]. The critical period represents a stage of development where environmental signals promote fast use-dependent rearrangements of neuronal networks, required for the acquisition of proper sensory, motor, and cognitive skills [29]. The closure of critical period affects the plasticity of the primary sensory areas of the brain, slowing down use-dependent changes of sensory-motor, as well as cognitive systems [28, 29]. However, as the critical period closes, plasticity continues, albeit at a lower speed, for both cortical and subcortical structures [30, 31]. In adults, neocortical plasticity can be reactivated by modifications of sensory inputs or sensory-motor interactions, which alter the overall level of activity in cortical circuits [29]. Therefore, brain plasticity is not uniform throughout life: plastic recovery after a brain lesion usually peaks in infancy and declines over the years [28].

Lesion-Induced Plasticity and Models

During the critical period, lesions such as contralateral eye monocular enucleation or restricted lesion to the contralateral retina trigger a series of adaptive responses of the visual system [31, 32]. In rodents, monocular enucleation leads to a massive deafferentation of subcortical visual targets of retinal axons, the dorsal lateral geniculate nucleus and superior colliculus, resulting in a remarkable plastic response of intact axons originating in the remaining eye with extensive sprouting over denervated territories [33] (Fig. 1). The plasticity of intact pathways is an important model for other forms of CNS trauma, such as traumatic brain injury, spinal cord lesions, and stroke. The functional recovery expected in those conditions relies on strategies minimizing neuronal lesion and optimizing neuronal plasticity, most of it on the regrowth of intact axonal pathways [34, 35]. Thus, uncovering the cellular and biochemical mechanisms related to plastic remodeling after CNS injury during early development might be a necessary step to improve functional recovery after brain lesions in adult individuals.

Role for Glial Cells in CNS Injury

Lesions triggered by trauma, ischemia, or infections can induce a heterogeneous and stimulus-dependent glial response known as reactive gliosis. The cross talk between microglia and astrocytes in the context of CNS injury is critical to determine intensity and time length of such glial response. During reactive gliosis, these cell types present distinct temporal activation patterns, so that while microglia is the first cell population to detect and respond to CNS homeostatic disturbances by secreting inflammatory cytokines and chemokines, astrocytes are sequentially activated by these signals [14]. On the other hand, once activated, astrocytes can modulate the recruitment and activation of microglial and other immunocompetent cells to the injury site and, later on, form a glial scar which encapsulates the lesion core from the healthy CNS areas [13].

Following a monocular enucleation in rodents, microglia activation occurs quickly after denervation and precedes astrogliosis mainly in contra- but also in ipsilateral subcortical structures, including the lateral geniculate nucleus and superior colliculus [36, 37]. Both microglial cells and astrocytes are known to clean up axonal de-

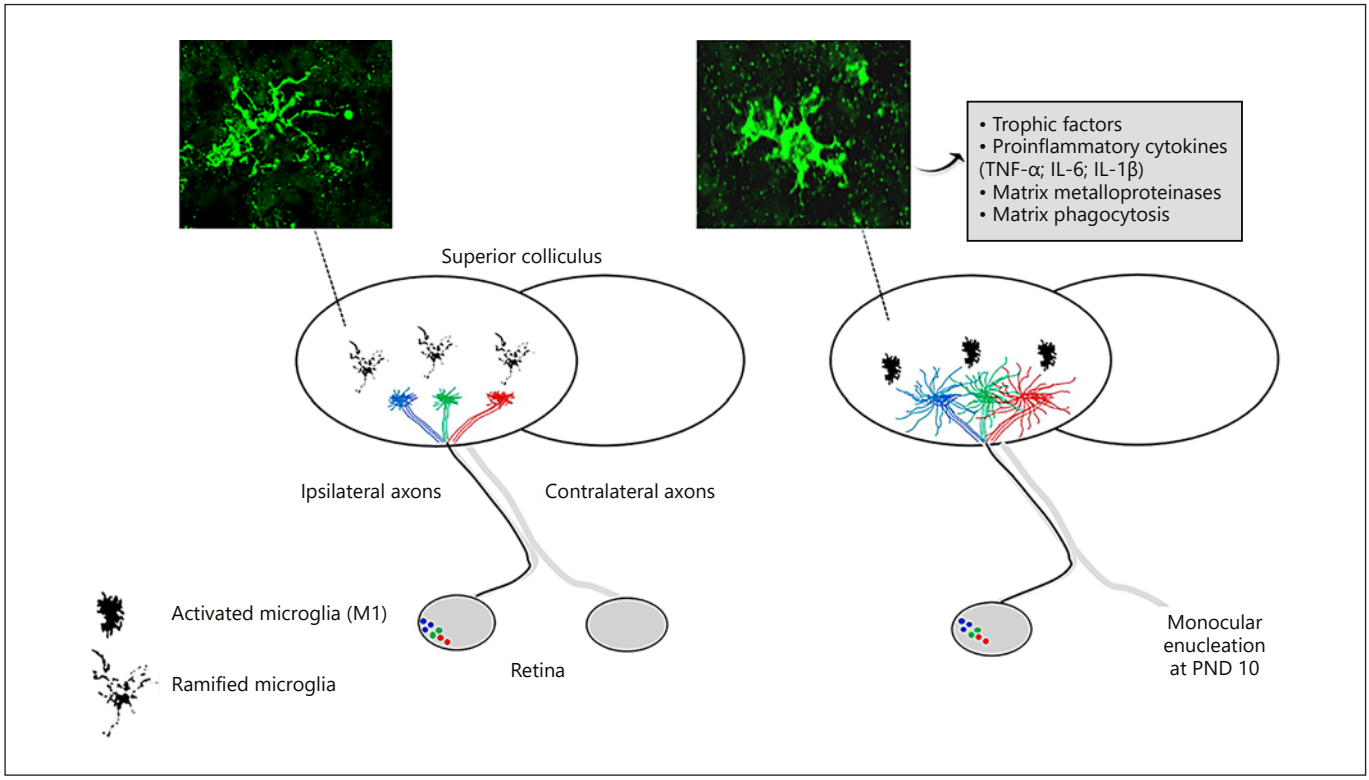

Fig. 1. Microglial activation and plasticity of the ipsilateral retinocollicular projection in a monocular enucleation model. During early postnatal development, the intact rat visual system displays a population of ramified M0 microglial cells at the time of circuitry refinement (left panel). Microglial activation is induced by a monocular enucleation at postnatal day 10 (PND10). The appearance of an M1-like phenotypic profile is co-temporal with a rapid growth of intact retinal axons from the remaining eye (right panel) [Chagas et al., manuscript in preparation]. Activated microglia seems to be necessary for neuroplastic adaptation of axons from the intact eye. Retinogeniculate projections are not displayed. Eye opening at PND14.

bris, restore tissue homeostasis and release growth factors and cytokines to stimulate neuronal sprouting [38]. Although, many studies have focused on a role of microglial cells in the mechanisms associated with a normal developmental plasticity, such as synaptic pruning [39, 40], little is still known on the influence of activated cells and the critical mechanisms mediating a reactive plasticity of nonlesioned neurons and its axonal pathways.

Microglia and Lesion-Induced Plasticity

A role for microglial cells in axonal sprouting following CNS lesions was suggested by Ngu et al. [41], in a study where they provided evidence that a full accumulation of microglia is necessary for the usual sprouting and regeneration of severed axons in the leech CNS. In the mammalian visual system, we are currently demonstrating that microglial activation plays a role in the reactive sprouting of intact axons of the retinocollicular pathway in response to a lesion in the contralateral eye. Our current data suggest that, during early postnatal development, there is a strong temporal correlation between axonal plasticity and microglial activation 24 h after a monocular enucleation in rats [Chagas et al., manuscript in preparation] (Fig. 1). Moreover, we prevented an axonal reactive sprouting with an acute systemic administration of different microglial inhibitors, cyclosporine A and minocycline. Accordingly, Bechmann and Nitsch [38] also correlate microglial activation with circuit reorganization in the hippocampus following a lesion to the entorhinal cortex. Sprouting and synaptogenesis of denervated dendrites were observed in hippocampal terminals, in such a way that both degeneration and reorganization were initially accompanied by alterations in morphology and microglial function, followed by astrocytic modifications.

Several studies correlate the role of microglia in injury-induced plasticity with the release of trophic factors. In an experimental model of acute corticospinal tract injury, immunosuppressed animals did not present a plastic re-

sponse as effective as immunocompetent animals, whose axonal growth was associated with neurotrophin-3 overexpression [42]. Similarly, Batchelor et al. [43] showed that neuronal sprouting of serotonergic and dopaminergic fibers coincides with the presence of activated microglia expressing mRNA for brain-derived neurotrophic factor (BDNF) and GDNF. In accordance, it has been demonstrated that microglia is capable of secreting trophic factors involved in neuritogenesis and, in activated state, seems to support axonal sprouting via insulin-like growth factor 1 [44].

Several lines of evidence have been ascribing a role for proinflammatory cytokines in lesion-induced plasticity. Acute lesions in the CNS promote the release of a variety of proinflammatory cytokines by microglia and astrocytes, like TNF-α, IL-1β, and IL-6. In traumatic brain injury models, some studies point to TNF-α as an important factor in its pathophysiology, while other studies demonstrate a neuroprotective role in this same model of injury [45]. TNF-α can assume opposing roles that may vary according to the region of the brain and the context of the lesion or disease, among other factors. Oshima et al. [46] observed that TNF-α contributes to axonal sprouting and functional recovery after traumatic brain injury, since in TNF-α KO animals, no regeneration in the corticospinal tract could be observed. Moreover, Kreutz et al. [47] used TNF-α neutralizing antibody to abolish axonal regrowth after optic nerve crush experiments. In addition to this, TNF-α also stimulates the release of trophic factors associated with neuroplasticity by microglia [10] and upregulates the levels of GDNF and BDNF factors in astrocyte primary cultures [11]. Indeed neurotrophic factors play a role in both normal and abnormal conditions as it has been shown that an impoverished environment delays maturation of the visual cortex [48]. On the other hand, an environmental enrichment promotes visual acuity recovery in amblyopic adult mice, and both phenomena are related to BDNF and GABAergic function [49]. Furthermore, it has been shown that either microglial depletion or a Cre-dependent removal of BDNF from microglia resulted in deficits in multiple learning tasks and a significant reduction in motor-learning-dependent synapse formation [50].

In a model of Schaffer collateral transection in organotypic hippocampal slice cultures, IL-6 induced sprouting and promoted synaptic response recovery [51]. Also, adrenergic sprouting was attenuated in IL-6 KO mice in a model of spinal nerve lesion [52]. In the monocular enucleation model, Vasques et al. [32], brought evidence that α-secretase activity is important for the axonal sprouting of ipsilateral retinocollicular projections from the intact eye, by favoring the production of sAPPα. Furthermore, it has been described that the proinflammatory cytokine IL-1β enhances α-cleavage of APP, upregulating sAPPα content in vitro [53]. Therefore, it seems that inflammation modulates extracellular proteolytic activity that in turn regulates plasticity. Indeed, it has been shown that axonal sprouting in response to a lesion in the visual system depends on the activity of MMP-9 [54].

The M1 microglia phenotype has a central role in host defense against pathogens and tumor cells but also triggers damage to healthy neurons [55]. Despite that, in the range of molecules produced and secreted by M1-type microglia, we find the necessary machinery to support the mechanisms by which activated cells can mediate lesion-induced plasticity of intact circuitry, described above. These cells produce TNF-α, IL-1β, IL-6, proinflammatory cytokines that act on the regulation of specific axonal reorganization as growth factors. In parallel, the M1 type not only produces matrix metalloproteinases but also phagocyte axonal debris and extracellular matrix that can act as barriers for the sprouting fibers in the CNS [6, 38].

Reactive Astrocytes and Lesion-Induced Plasticity

A hallmark of astrocyte activation is the upregulation of the intermediate filaments glial fibrillary acid protein (GFAP) and vimentin, and the early activation of the transcription factor STAT3. Mice deficient for these filaments ($GFAP^{-}/Vim^{-}$) or under conditional deletion of STAT3 from astrocytes (STAT3-CKO) present reduced reactive gliosis and glial scar formation induced by lesions. Experiments using STAT3-CKO mice have shown pronounced functional impairment after spinal cord injury, accompanied by an increased number of reactive microglia at the lesion core and a general spread of inflammation [56, 57]. Therefore, activation of astrocytes seems to be important to gradually suppress microglia and other inflammatory players by constraining the lesion size [58]. However, a persistent astrocyte activation followed by glial scarring is consistently associated with inhibition of structural plasticity [59, 60]. Reactive astrocytes overexpress molecules like chondroitin sulfate and ephrin-A5 which block axon regeneration and outgrowth, respectively [61, 62]. In fact, $GFAP^{-}/Vim^{-}$ mice exhibit improved axon regeneration after optic nerve crush [63] and functional recovery after spinal cord trauma [64]. Thus, in a broad perspective, reactive astrocytes may play a beneficial role in the acute phase of trauma by modulating the inflammatory response. A long-term astrocytic activation, however, restricts the regenerative potential by secreting inhibitory molecules.

It has been shown that reactive astrocytes can exhibit different phenotypes depending on the nature of injury. A comparison between ischemic stroke and LPS-dependent inflammation models in mice has shown that the gene expression pattern in reactive astrocytes was stimuli-specific [65]. Based on those findings, it was recently proposed that reactive astrocytes can be classified as A1 astrocytes, which secrete proinflammatory signals that are harmful to neurons, or A2 astrocytes, which, in turn, secrete neurotrophic factors that can promote survival and modulate inflammatory response. In fact, A1 astrocytes were induced in vivo by LPS-dependent microglia activation [66]. This activation profile leads these cells to secrete toxic factors as well as losing major trophic functions like synapse support and phagocytic capacity. Interestingly, A1 astrocytes seem to be specifically induced by three simultaneous microglia-derived signals: TNF-α, IL-1α, and C1q [66]. Thus, a possibility arises that different pools of cytokines secreted from activated microglia can potentially drive distinct astroglial responses, which in turn can affect the extension and phenotype of the lesion and also of the glial scar.

Data from the literature have evidenced the role for reactive astrocytes in facilitating synaptogenesis and neurite outgrowth in a lesion environment through the release of trophic factors [67]. However, once activated, astrocytes form a glial scar which encapsulates the lesion core from the healthy CNS areas [13]. The chondroitin sulfate proteoglycan NG2, a component of the glial scar was correlated with the postlesional sprouting response in the rat fascia dentata following unilateral entorhinal deafferentation that could define boundaries for growing axons [68]. Furthermore, ablation of scar-forming astrocytes in a forebrain stab injury model resulted in increased local neurite outgrowth, revealing their role in restricting nerve fiber growth after injury [69].

Strategies seeking the modulation of the different profiles of reactive microglia and astrocytes during reactive gliosis may emerge as a potential alternative to allow a more permissive milieu to plasticity events in adulthood. The correct timing of glial activation and molecular signaling pathways must be considered as targets for CNS plasticity and repair.

Neuroinflammation in Neurodegenerative Diseases

The current increase in life expectancy results in an increase in neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, ALS, and Huntington's disease, among others. Neurodegeneration is associated with age with an estimated prevalence oscillating between 1.5 and 2.5% of the general population but rises to 50% in people with more than 85 years [70–72]. It is well accepted that the pathogenesis of neurodegenerative diseases is associated with an underlying inflammatory process in the affected areas of the CNS, which is known as "neuroinflammation" [73, 74]. Primary neuron damage likely triggers local neuroinflammation through the release of trophic factors and inflammatory mediators [75]. Damage neurons express a large variety of inflammatory mediators such as CSF1, TGF-β, IFNγ, and Fas/FasL, with the potential to elicit a localized inflammatory response [76–80]. Innate and adaptive immune responses underlie neuroinflammation, involving the complex participation of microglia, as the resident immune cell of the CNS as well as astrocytes and oligodendrocytes, which actively interact with other immune cells including T cells, monocytes, and mast cells [81–86].

When regulated and properly resolved, neuroinflammatory mechanisms can be considered as a regenerative response against damage, with glial and immune cells playing a critical adaptive role in maintaining tissue homeostasis [87]. However, if neuroinflammation is not adequately shut down, its chronic, unregulated activation becomes deleterious having the potential to be neurotoxic, compromising neuronal and progenitor survival. In addition, the blood brain barrier (BBB) and the blood spinal cord barrier make the CNS an immunologically privileged area, with limited capacity to recruit immune cells from the circulation [4, 88]. Moreover, the CNS displays a low immune surveillance and absence of specialized antigen-presenting cells, which further limit the local immune responses. Despite this immunologically privileged status, T lymphocytes and monocytes can be trafficked into the CNS parenchyma to instrument specific inflammatory responses in regions of the CNS undergoing tissue damage (Fig. 2) [89–92].

Pathogenic Role of Glial Cells in ALS

Histopathological, immunological, and biochemical evidence indicates that neuroinflammation greatly influences the progression of neurodegenerative diseases. Among them, ALS is a paradigmatic disease where inflammation develops along the motor pathway, into both the CNS and the peripheral nervous system (PNS) [81, 93, 94]. Moreover, therapeutic compounds targeting inflammation are currently being tested in a clinical trial with the aim to reduce the upper and lower motor neuron degeneration in ALS, thus delaying progressive muscle weakness [95–97].

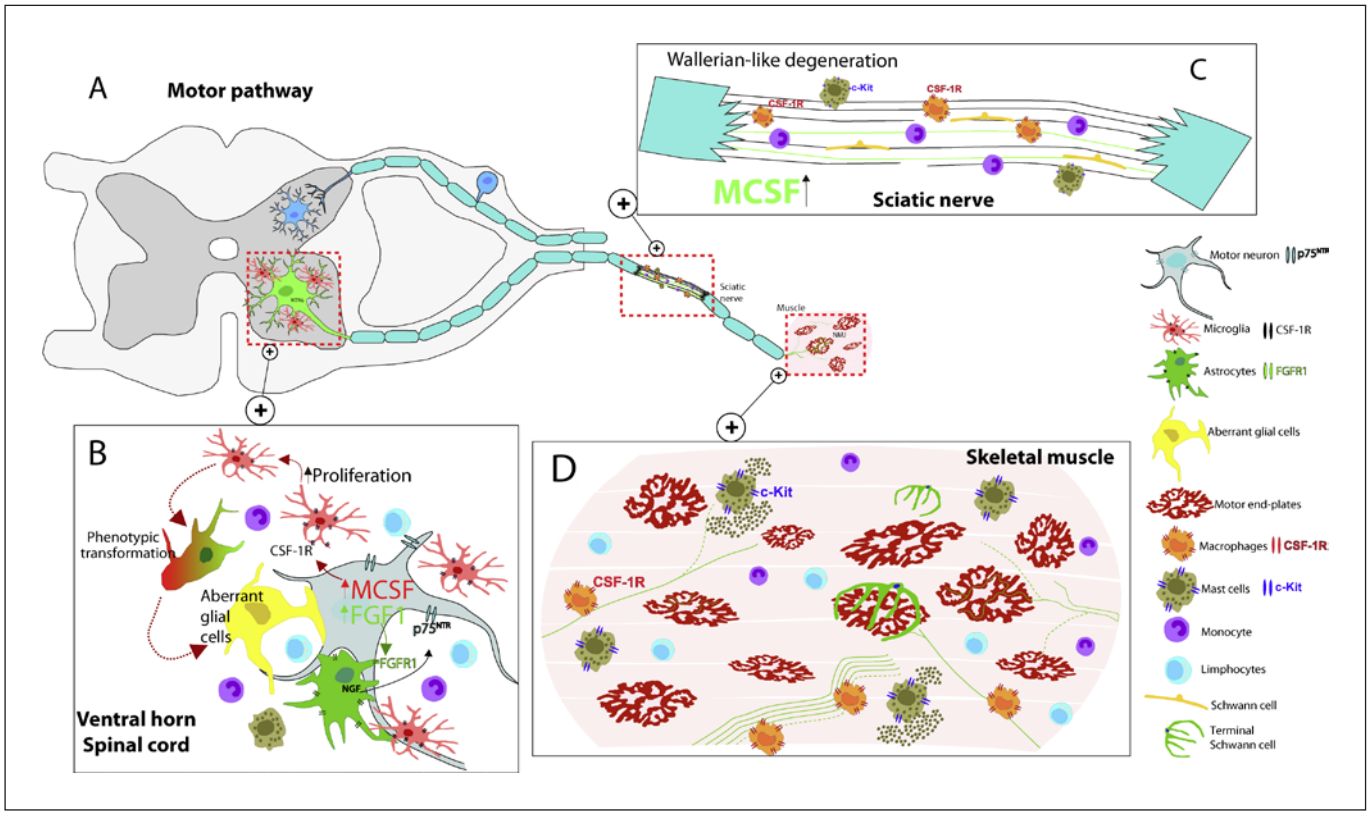

Fig. 2. Neuroinflammatory mechanisms influencing lower motor neuron degeneration in ALS. **A**, **B** Representative drawing showing how neuroinflammation orchestrates a neurodegenerative microenvironment along the motor pathway during disease progression in ALS. In the ventral spinal cord, glial cells, astrocytes, and microglia proliferate and surround degenerating motor neurons after disease onset. Such neuroinflammatory scenario promotes the emergence of a subpopulation of aberrant glial cells that actively proliferate and likely are highly toxic to motor neurons. The constitution of this neurodegenerative microenvironment contributes to the acceleration of paralysis progression. Dying motor neurons can release several factors that stimulate glial cell proliferation and activation, including FGF-1 and MCSF. FGF-1 stimulates surrounding astrocytes to express and release NGF which in turn can induce motor neuron death through $p75^{NTR}$. MCSF is an agonist of CSF-1R, thus stimulating microglia proliferation and activation. Other immune cells such as monocytes, mast cells, and lymphocytes infiltrate the spinal cord of ALS during the symptomatic phase of the disease. **C**, **D** The degeneration of peripheral motor axons in ALS also triggers a potent inflammatory response, both in peripheral motor axons and in skeletal muscles. Motor axon degeneration is characterized by Schwann cell proliferation and immune cell infiltration such as macrophages, monocytes, lymphocytes, and mast cells. **C** Degenerating motor axons can express and release MCSF, which induces macrophage infiltration through CSF-1R activation. Neuromuscular junction (NMJ) denervation constitutes one of the first pathological events of ALS, taking place even before spinal cord and peripheral nerves become compromised and symptoms appear. NMJ denervation and terminal Schwann cell dissociation from the motor end-plates is accompanied by significant mast cell infiltration and degranulation after disease onset. Macrophages also infiltrate skeletal muscle during disease progression.

Astrocytes contribute to orchestrate chronic neuroinflammation in ALS, displaying a variety of phenotypic changes, with the potential to induce motor neuron apoptosis [66, 82, 98, 99]. Astrocytes are in direct contact with neurons, providing structural, metabolic, and trophic support, while actively participating in the modulation of neuronal excitability and neurotransmission [100]. However, in pathological conditions astrocytes become hypertrophic and overexpress a number of cytoskeletal and inflammatory markers. In ALS patients and murine models expressing SOD1 mutations, astrocyte activation positively correlates with the degree of motor neuron loss, vacuolization of mitochondria, and focal loss of the GLT-1 glutamate transporter in the ventral horn of the spinal cord [101–104]. Inflammatory mediators released by damaged motor neurons are able to trigger an inflamma-

tory phenotype in surrounding astrocytes [105, 106]. For example, FGF-1 is strongly upregulated in motor neurons after sublethal damage and, once released, induces the activation of astrocyte through activation of its cognate receptor FGF-1R [105]. FGF-1R activation in astrocytes strongly induces transcription factor nuclear factor erythroid 2-related factor-2 (Nrf2), which likely mediates cytoprotective effects [107, 108]. In addition, FGF-1 strongly induces nerve NGF expression in astrocytes, which upon secretion can activate the proapoptotic neurotrophin receptor $p75^{NTR}$ [109]. Because postnatal motor neurons can express p75NTR following nerve injury or during neurodegeneration [110–112], the NGF/p75NTR pathway might modulate the elimination of neurons in ALS. Such NGF-mediated motor neuron apoptosis is further stimulated by nitric oxide and peroxynitrite, a mechanism linking oxidative stress and mitochondria failure in astrocytes to motor neuron cell death [98]. The finding that astrocytes from ALS patients and animal models are neurotoxic to motor neurons, suggests a pathogenic pathway based on a defective function of glial cells that surround the motor neuron cell bodies, implying loss- and gain-of-function mechanisms associated with inflammation [113–115].

Activated microglia also drive neuroinflammation in ALS, being a fundamental part of the innate immune response in the CNS [116]. Pathological microglia can present diverse states of activation depending on the induction trigger by the microenvironment [117, 118]. During the symptomatic phase of ALS, microglia are characterized by proliferation and transformation into phagocytic cells, displaying a morphology similar to that of macrophages in the periphery [118, 119]. They can form clusters of proliferating microglia adjacent to the damaged motor neurons [120, 121], thus playing a preponderant pathogenic role during the progression of ALS [122, 123]. In a mouse model of ALS expressing mutant SOD1, genetic excision of the mutated protein only in myeloid cells and microglia results in a slower paralysis progression as compared with mice expressing the mutant protein in microglia [124]. Microglia from mice expressing ALS-linked SOD1 mutations cause neurotoxicity to motor neurons in culture conditions [122, 125]. These results suggest activated microglia actively contribute to motor neuron damage through the induction of local detrimental inflammation.

Relevant for the understanding of the pathogenic role of microglia in ALS is the fact that following activation, microglia display different phenotypes depending on the induction exerted by the microenvironment [117, 118]. While some phenotypes can be deleterious for neuronal survival, other coexisting phenotypes can be neuroprotective. Therefore, pharmacological targeting of microglia could only have beneficial effects if restricted to those pathological phenotypes. For example, in ALS mouse models, the drug minocycline is able to inhibit microgliosis and decrease inflammation in the CNS, delaying paralysis onset and progression of symptoms [126]. However, minocycline failed to improve survival when tested in ALS patients [127].

In ALS paralytic rats expressing the $SOD1^{G93A}$ mutation, overactivated microglia in the spinal cord originate an aberrant cell phenotype displaying both microglia and astrocyte markers in the ventral horn of the spinal cord [120, 128]. Moreover, such aberrant glial cells actively proliferate after the onset of paralysis and make intimate contact with degenerating motor neurons, suggesting they contribute to spread motor neuron pathology [120, 128]. Accordingly, aberrant glial cells isolated in culture are highly toxic to motor neurons, suggesting they are key neurotoxic effectors in ALS [128]. Based upon these observations, Trias et al. [129] investigated whether ALS progression might be ameliorated by masitinib, a drug that potently targets aberrant glial cells through the inhibition of the tyrosine kinase receptor CSF-1R. ALS rats treated with masitinib after paralysis onset displayed decreased inflammation in the CNS and PNS [129], and in parallel the treatment prevented motor neuron loss and denervation of neuromuscular junctions [81, 129].

Inflammation along the Peripheral Motor Pathway in ALS

Neuroinflammation in ALS also involves the participation of blood-borne immune cells such as lymphocytes, monocytes, mast cells, and neutrophils, among others [92, 130–132]. These cells are known to permeate the BBB in specific regions and actively interact with the degenerative cellular microenvironment surrounding motor neurons and motor axons [81, 131, 133, 134]. It is also possible that chronic neuroinflammation restricted to the CNS can extend to skeletal muscles and then to other organs, becoming a systemic inflammation [135, 136]. Evidence indicates that these cells can exert both neuroprotective and neurotoxic influence on motor pathways [137]. Thus, proinflammatory $Ly6C^{hi}$CCR2+ monocytes from the blood have been shown to infiltrate mice spinal cord, contributing to the death of the motor neurons. The genetic attenuation of these neurotoxic monocytes is sufficient to significantly slow the course of the disease [130].

Along this line, ALS patients display higher levels of circulating monocytes, neutrophils, and CD4 lympho-

cytes, with the increased number positively correlating with a more rapid progression of the disease [132, 138]. Mouse models as well as ALS patients also have high levels of cytotoxic CD8 lymphocytes and circulating natural killer cells [133, 139, 140]. Patients also show dysfunctional regulatory T cells (Treg), which correlate with the progression and severity of symptoms [135, 141, 142]. This finding is currently under evaluation as a potential therapeutic strategy in ALS [135]. Finally, it has been shown that mast cells can infiltrate the spinal cord of patients with ALS during the symptomatic phase of the disease, and through dialogue with the microglia, they could contribute to the degeneration of motor neurons [131, 133].

Using a transgenic rat model of ALS, Trias et al. [81] reported histopathological evidence for mast cells favoring neuromuscular junctions (NMJs) pathology and paralysis progression in ALS, representing a previously unknown and significant inflammatory pathogenic mechanism. Interestingly, massive mast cell infiltration into skeletal muscle correlates with paralysis progression, with a clustering of inflammatory cells around denervated NMJs. Downregulation of infiltrating mast cells by therapeutic doses of the tyrosine kinase inhibitor drug masitinib that inhibit the c-Kit receptor resulted in a significant delay of muscle denervation [81]. This study further supports a role of inflammation in the PNS. The deeper understanding of the inflammatory mechanisms that underlie this fulminant neurodegenerative disease, will allow a more specific search for novel therapeutic strategies that seek to slow its progression.

Neuroimmune Basis of the Mechanisms of Depression

Depression, an Epidemiological Burden with Elusive Causal Mechanisms

MDD is a main contributor to the global burden of disease with a lifetime prevalence of 14.6 and 11% in high-income and low/middle-income countries, respectively [143]. Along this line, MDD and anxiety are the leading cause of years lived with disability [144], and approximately 30–50% of these patients are not responsive to standard antidepressant medication [145, 146]. Despite the cost for the national systems of health, the epidemiological relevance, and the billionaire investments in R&D both in the academy and industry, the underlying basis of MDD remains unknown. Although genetic signatures impose some heritable risk for developing depressive symptoms, it seems so far evident that depression is a rather syndromic, multifactorial disorder that involves the interplay of genetic predispositions and environmental factors out of which maladaptive responses to traumatic or psychosocial chronic-stress arguably are amongst the most frequent [147–150]. Over the past 35 years, numerous studies revealed the existence of a complex but robust bidirectional communication between immune, endocrine, and neural systems [151–157]. In this context, a multiplicity of studies have been reported suggesting a role of immune and inflammatory signals in MDD [158–160].

MDD: The Consequence of a Dysfunctional Interaction between Neural and Immune Signals?

One of the most indicative clinical suggestions of the association of inflammation and MDD is the elevated prevalence of depression comorbidity with inflammatory-related diseases such as diabetes, metabolic syndrome, asthma, multiple sclerosis, and rheumatoid arthritis [159, 161]. More specifically, a series of clinical correlative studies carried out by Maes et al. [162–164] in the early 1990s revealed the association between depressive symptoms and increased peripheral immune responses and inflammatory biomarkers including acute-phase proteins as well as inflammatory cells and cytokines. In the following years, these results have been vastly replicated and extended [159], and further meta-analyses have shown that while natural killer and T-activity are moderately reduced, several hallmarks of inflammation such as IL-6, TNF-α, IL-1β, and the acute-phase C-reactive protein (CRP) are the markers most reliably associated with depression [165–167].

Recently, a study conducted by Felger et al. [79] using resting-state functional magnetic resonance imaging in MDD unmedicated patients, showed a negative association between blood levels of CRP and inflammatory markers (IL-1β, IL-6, and IL-1RA) and connectivity of reward-related brain circuits such as ventral striatum and ventromedial prefrontal cortex. These findings suggest that inflammatory mediators might directly target reward circuits in depression.

Interestingly, the link between inflammation and depressive symptoms might also have predictive value since patients with lower baseline inflammatory markers are more likely to respond to antidepressant treatment [168–170]. Other studies however, reported no changes in the plasma levels of IL-1β, IL-6, and transferrin receptor in fluoxetine-treated patients [171, 172]. These contradictory findings may be attributable to differences in age,

gender, and treatment duration but could also be indicative that the influence of inflammation in MDD occurs only in a subset of so far poorly defined patients. In any case, when analyzing association studies in humans, it is always relevant to underline that correlative phenomena do not imply causation but co-occurrence. Even though many studies on animal models suggest a causal relationship between immune-related molecules and depressive-like behaviors, this causality has not been proven beyond doubt in humans yet. Future studies in preclinical animal models and humans will help understand whether depression and chronic inflammatory diseases are mechanistically linked or if chronic peripheral inflammation influences the course of MDD via independent mechanistically unrelated events.

Peripheral Immune Cells and Cytokines in Chronic Stress and Depression

Both environmental and systemic stress rapidly activates hypothalamic pituitary adrenal axis (HPA) and the efferent autonomic pathways [173–175]. Noradrenaline is directly released on peripheral organs by sympathetic terminals and the endocrine release of adrenaline increases heart rate and blood pressure and favors glucose availability. At the immunological level, these catecholamine mediators lead to the expansion and mobilization of hematopoietic phagocytes in the bone marrow [176, 177]. In parallel, the synthesis and release of glucocorticoid (GC) by the adrenal cortex first promote immune cell mobilization to injured tissues and primes immune cells for subsequent inflammatory challenges [107, 178, 179]. Later on, if the stress challenge persists, the sustained elevation of GC homeostatically suppresses inflammation and acquired immunity, thus preventing overactivity of innate inflammatory responses and preserving the specificity of immune reactions [180–182]. In his original description, Tausk [183] actually assigned to GC a broad shutdown function in the general stress response and exemplified stress to a fire and the role of GC to that of preventing water damage caused by the firefighters.

At the central level, chronic or repetitive stress induces a desensitization of corticosteroid receptor-mediated feedback mechanisms that result in high and-long lasting production of corticotropin-releasing factor and vasopressin, and this dysregulation sustains a higher basal activation of the HPA axis and favors stress vulnerability to new traumatic episodes [147, 184–187]. The GC receptor (GR) desensitization seems to be pleiotropic and takes place in peripheral immune cells too. Multiple and eventually coincident mechanisms such as epigenetics marks, increased expression of GRβ isoforms, microRNA-mediated instability, or posttranslational modifications might help explain the long-lasting changes in GR feedback sensitivity [188–190]. Recent findings suggest that epigenetics mechanisms might be particularly relevant to understand the dysregulation of stress-related pathways.

In rats, low levels of maternal care induce a long-lasting decrease in central GR transcription, a phenomenon mediated by increased levels of histone 3 lysine 9 acetylation (H3K9) and decreased DNA methylation of exon I7 of the GR promoter [191]. Interestingly, similar epigenetics marks have been found in the human orthologous site of the GR promoter (GR 1F) in the hippocampus of suicide victims with early exposition to child abuse [192]. These environmental effects on the epigenetic regulation of gene expression might be influenced by genetic variation giving rise to the concept of *gene × environment interaction*. Klengel et al. [193] showed for the first time a significant gene × early trauma interaction based on the epigenetic regulation of an MDD-associated polymorphism of FKBP5, a GR-induced co-chaperone that restricts GR transactivation in an ultrashort feedback [194, 195]. Risk-allele carriers show an increased GR-mediated induction of FKBP5 which would lead to GR resistance and HPA hyperactivation. Prolonged high-cortisol levels and GR activation as a result of chronic abuse or maltreatment during childhood induces a long-lasting demethylation of GC response elements and further transcriptional depression of FKBP5 [18] perpetuating the GR resistance and stress dysregulation specially in risk allele carriers with a history of childhood trauma. The dysregulation of the negative feedback mechanism favors an increase in the basal proinflammatory status, which additionally contributes with the GR resistance (Fig. 3). Mechanistically, cytokine-induced repression of GR might be mediated by the activation of NF-κB and AP-1 transcription factors that reduce GR transactivation either by inhibiting GR nuclear translocation or by blocking accessibility to chromatin remodelers or transcriptional cofactors [157, 196–199]. Along this line, chronic stress or prolonged exposure to GCs in rodents reduces the sensitivity of immune cells to the anti-inflammatory feedback of this hormone and increases production of bone marrow-derived phagocytes that display GC resistance (Fig. 3) [200, 201]. This is consistent with the fact that the elevated blood levels of GCs induce a general expansion of the granulocyte lineages in the bone marrow [202]. Likewise, in humans, genome-wide expression microarrays of peripheral blood monocytes from chronical-

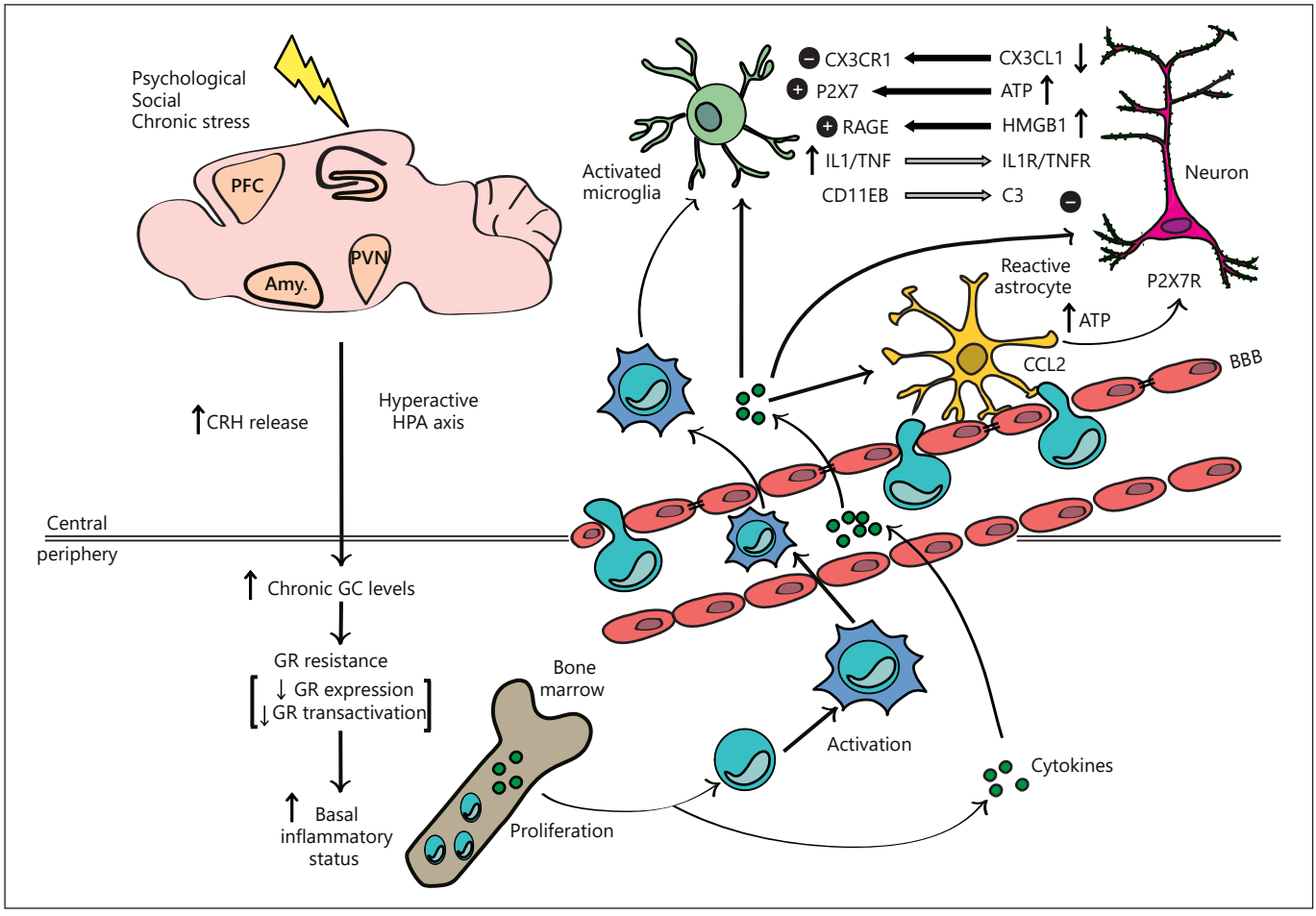

Fig. 3. The role of glucocorticoids and the microglia-neuron-astrocyte interactions in the chronic stressed brain. Stressful stimuli activate the adrenal cortex to release glucocorticoids (GCs). With prolonged exposure, GC release increases, leading to GC resistance that triggers an increase in the inflammatory status. Activated monocytes and cytokines traffic to the brain where they affect neuronal plasticity. Changes in neuronal synapsis such as the inhibition of CX3CL1 (fractalkine) expression are detected by microglia favoring cytokine release and monocyte recruitment. In turn, monocytes can acquire microglial properties. Sustained increased levels of cytokines cross the blood brain barrier (BBB) and activate microglia cells inducing persistent synaptic remodeling. Microglial activation and proinflammatory cytokine release contribute to the inhibition of astrocyte activity. Psychosocial stress also leads to the switch of microglia to a proinflammatory phenotype, which releases CC-chemokine ligand 2 (CCL2) that in turn attracts activated myeloid cells to the brain. Perturbations of the microglia/neuron interaction, have been reported in animal models of depression. These include the reduction in CX3CL1 and its receptor CX3CR1, and induction of high-mobility group box 1 (HMGB1) and ATP from reactive astrocytes. Many of these microglial activation pathways converge on the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome. The release of the proinflammatory cytokines IL-1β and TNF-α also elicits molecular changes in neurons. Astrocytes engulf synapses regulating synapse transmission, but at the same time they control BBB permeability and integrity. Upon activation, astrocytes express high levels of the chemokine CCL2 which, acting on its receptor (CCR2) on peripheral phagocytes, promotes the extravasation and infiltration of monocytes into the brain. A main activator of CCL2 expression is the P2X7 receptor which is activated upon ATP release. P2X7R activation also promotes IL-1β release and inflammasome activation to trigger depression-like behavior. Exposure to chronic stress reduces the expression of CX3CL1 and CX3CR1. Another important effector molecule is the C3 complement protein, which triggers synaptic pruning by tagging targeted synapses to be phagocytosed by microglia. RAGE, receptor for advanced glycation end products.

ly stressed individuals show increased stress-induced proinflammatory markers and diminished expression of transcripts bearing response elements for GCs [203].

Adult neurogenesis has also been hypothesized as a relevant mechanism in depression. It is clear that in rodents, chronic stress decreases proliferation and maturation of newborn neurons, and antidepressants exert opposite effects [204]. Seemingly, adult hippocampal neurogenesis would not be a major contributor to the development of depression but might contribute in a more restricted manner to specific anxiety-related symptoms [205]. On the other hand, ongoing adult neurogenesis in the hippocampus is necessary for the behavioral effects of antidepressant drugs in rodents [206]. However, its relevance and even its actual occurrence in the human brain have recently been put under debate [207–209], and therefore the actual potential role of the newborn neurons in the dentate gyrus in depression and antidepressant mechanism of action remain unclear.

In addition to the influence on adult neurogenesis, chronic stress paradigms also reduce dendritic arborization of CA1 pyramidal cells in the hippocampus, a phenomenon plausibly associated to a reduction in local BDNF levels [210–212]. Interestingly, early maternal separation paradigms also trigger long-lasting reduction in BDNF levels in the rat hippocampus [213].

Several studies have found that hippocampal BDNF expression is directly downregulated by GCs [214, 215] and antidepressant treatments can prevent stress-induced reduction of BDNF [216] as well as corticosterone-mediated decrease in BDNF expression [217]. Mechanistically, antidepressants may exert their function by inducing acetylation of histone subunits around the BDNF gene promoter, thus leading to an increase in BDNF expression and production [216]. BDNF function is mediated by its binding to high-affinity receptor TrkB (tyrosine kinase B). However, a deficiency of BDNF or the Trk receptor does not induce depressed-like behaviors, suggesting that BDNF reduction per se is not sufficient to alter mood and that other concurrent factors are necessary to trigger depression [218, 219]. Nevertheless, the antidepressant response does require an increase in BDNF activity and the associated structural recovery of the neuronal network [220–222].

Several in vivo studies demonstrated that inflammation causes a reduction of BDNF gene expression [223–225]. These findings support the possibility that a cross talk between inflammatory mediators and neurotrophins contributes to the development of mood disorders by reducing BDNF-related neuroplasticity.

The stress response can influence peripheral immune responses not only by means of humoral pathways but also through the fast actions of the autonomic nervous system. Sympathetic terminals profusely innervate primary and secondary lymphoid organs, and many immune cells express adrenergic receptors [157, 226]. Increased catecholamine release leads to the proliferation and mobilization of hematopoietic cells in the bone marrow, and therefore regulating the influx of myeloid lineage immune cells [176, 177]. When chronic social stress models are applied in rodents, this process contributes to an increase in circulating immature proinflammatory monocytes and granulocytes [227, 228] (Fig. 3).

Early life traumatic experiences in humans strongly influence the appearance of depressive symptoms later in life [148, 229]. Interestingly these long-lasting changes have also been verified at immune level suggesting that chronic stress-induced dysregulation of immunological parameters might be instrumental in the development of depression. Clinical studies have revealed that proinflammatory profile states are typically associated with low socioeconomic status but, remarkably, human individuals who experienced high levels of maternal warmth were protected from these long-lasting immunological changes [230]. Moreover, maltreated children showed a significant clinically relevant increase in plasma CRP levels 20 years later [231], and MDD patients with antecedents of early life stress show transcriptional changes in peripheral mononuclear cells that underlie susceptibility to hyperinflammatory responses [232]. Remarkably, a recent report from Khandaker et al. [233] described that high levels of IL-6 in childhood are associated with 10% higher risks of developing depression by 18 years in young adults. This longitudinal study shows for the first time that peripheral inflammation precedes depressive symptoms in at least a subpopulation of patients.

A still open but relevant question is as to how peripheral inflammation can impact brain circuits. A series of preclinical studies have addressed this relevant question. Different reports from Sheridan's group indicate that chronic social stress-induced anxiety is promoted by a direct recruitment of mononuclear cells to the brain mostly mediated by β-adrenergic inputs and facilitated by an IL-1-mediated leakage of the BBB [234–236]. On the other hand, blood-borne IL-1β, IL-6, and TNF-α have been shown to cross the BBB via saturable transporters to enter cerebrospinal fluid and interstitial spaces of the brain [1] (Fig. 3). In a recent report, Hodes and coworkers [159] showed that irradiated mice transplanted with he-

matopoietic stem cells from mice previously subjected to repeated social defeat stress (RSCD) model displayed increased susceptibility to RSCD, whereas IL-6 KO bone marrow chimaeras remain resistant to stress. Interestingly from the clinical perspective, increased macrophage recruitment to the brain has been described in depressive suicides compared to controls [237].

Hence, both direct actions of cytokines and innate immune cells might help explain the detrimental influence of abnormal activation of peripheral immune cells on brain circuits and emotional behavior.

Central Immune Signals in MDD and Animal Models of Depression

Glial cells exert a multiplicity of functions in the healthy and diseased brain defining key developmental brain steps, and are involved in neuronal metabolism, synaptic transmission, repair, and survival [2]. Astrocytes, which actively respond to cytokines, engulf synapses sustaining and regulating synapse transmission, but at the same time their end feet control BBB permeability and integrity. Upon activation, astrocytes express and release high levels of the chemokine CCL2 which, acting on its receptor (CCR2) on peripheral phagocytes, promotes the extravasation and infiltration of monocytes into the brain [238]. Likewise increased CCL2 expression has been found in the anterior cingular cortex of postmortem samples of MDD patients who committed suicide [237].

The strategic location of astrocytes lining on brain capillaries and the high expression levels of the chemokine CCL2 help explain its role in stress-induced recruitment of peripheral phagocytes. A main activator of CCL2 expression is the purinergic multimeric P2X7R channel which is activated upon ATP release [239]. Interestingly, recent studies showed that the heterozygous expression of the genetic variant P2X7R-Gln460Arg is associated with mood disorders [240, 241], and only the coexpression of both WT and 460 variants compromises the receptor function [242]. Recently, a humanized mouse model of this mutation has been developed [243], and mice that harbor both P2X7R variants showed alterations in their sleep quality resembling signs of a prodromal stage of depression. Besides CCL2, P2X7R activation also promotes IL-1β release and inflammasome activation to trigger depression-like behavior (Fig. 3) [244].

Plausibly, a mechanistic convergence between ATP/P2X7R and CCL2-mediated monocyte recruitment might also take part in the development of MDD.

Reduced numbers of astrocytes have been found in brain regions controlling emotion in suicide victims [245], and both reduced number of astrocytes as well as decreased expression of GFAP have been found in rodent chronic stress models [245–247]. This suggests that after a first wave of astroglial activation, probably due to peripheral cytokines, chronic activation might impair astrocytic function, further affecting BBB permeability and support of neuronal metabolism.

Microglial cells are also reactive to psychological stress, and rodents subjected to chronic stress models display an increased number of activated microglial cells in limbic brain regions [234, 248]. Interestingly, HPA axis activation prime microglial proinflammatory response and both GC and glutamate signaling promote microglia proliferation upon restraint stress [179, 249]. Employing an inescapable stress model in rats, Weber et al. [250] recently showed that stress increases the high-mobility group box 1 (HMGB1) protein which further triggers proinflammatory cytokine secretion in microglia upon membrane-bound RAGE (receptor for advanced glycation end products).

Recent preclinical studies also provide evidence for a causal role of microglial activation in depressive states. The administration of minocycline, a well-known inhibitor of microglial activation, rescues the stress-induced depression-like behaviors [251]. On the other hand, recent studies suggest that the chemokine system CX3CL1-CX3CR1 might also play a role in depressive-like behavior. Exposure to chronic social defeat stress reduces the expression of CX3CL1 and CX3CR1 [236]. Most importantly, mice lacking CX3CR1 are resilient to chronic unpredictable stress-induced anhedonia [252] and do not develop social stress-induced anxiety-like behaviors [236]. Another important effector molecule in microglial cells is the C3 complement protein, which triggers synaptic pruning during development by tagging targeted synapses to be further phagocytosed by microglia [253]. Further studies will surely address this issue in order to define the participation of this interesting mechanism in the development of mood disorders and depression.

Finally, postmortem analyses of brains from depressive patients show morphological changes compatible with microglial activation [254], and a recent positron emission tomography-based study shows greater microglial activation in prefrontal, insular, and anterior cingulate cortices [255].

Towards a Neuroimmune-Based Therapeutics of MDD

Modern antidepressants have not substantially improved their efficacy compared to old drugs: they still require several weeks to exert their effects, side effects are still a significant problem, and a substantial proportion of patients respond only partially or remain completely resistant to medication [145, 147, 148]. The therapeutic role of anti-inflammatory drugs is still a matter of debate with studies showing either beneficial or detrimental effects of nonsteroidal anti-inflammatory drugs (NSAID) in patients treated with antidepressants [256, 257]. A large meta-analysis concludes that NSAID, but particularly the Cox-2 inhibitor celecoxib, have clinically relevant antidepressant effects with and without concomitant antidepressant medication [258], although the authors claim that conclusions should be taken with caution due to the high risk of bias and high heterogeneity of the studies. A large and ideally prospective study with a more homogenous group of patients will be necessary to solve this still open question.

Strategies directly targeting cytokines are under investigation. A double-blind placebo-controlled clinical trial showed that infliximab, a chimeric monoclonal anti-TNF-α antibody, improves depressive symptoms in patients with high basal levels of inflammation [259]. Besides, two clinical trials will investigate the antidepressant actions of two different antibodies targeting IL-6, sirukumab (NCT02473289), and tocilizumab (NCT02660528) (www.clinicaltrials.gov).

Finally, new therapeutic opportunities might be related to P2X7R antagonists. Several compounds blocking these receptors have been patented in recent years [260] and might be interesting candidates to be tested in future clinical trials.

Neural and Immune Networks Underlying Autism

ASD are a group of neurological conditions in which affected individuals have compromised cognition related to social and communication skills, restriction or rigidity of interests, and present obsessive and repetitive behaviors. Clinically, immune comorbidities are commonly described in these disorders, while immune events during development increase autism incidence pointing both to an environmental component of ASD, as well as to a neuroimmune cross talk (Fig. 4). Evidence suggests that immune deregulation at prenatal or early postnatal development may result in specific brain circuitries that typify autistic behavior as well as a characteristic immunological profile. Finally, a corollary of the fact that ASD is established during development is that immune cells and molecules are probably involved in CNS ontogenesis and functioning since, for example, IL-6 and its receptor mRNAs were described in neonatal rat brain neurons [261]. Neuronal expression of MHC molecules seem to affect regulation of synaptic densities and neural connectivity during development [262, 263], sensory and social cognition [264, 265], and, together with TNF-α, affect homeostatic synaptic plasticity, a phenomenon by which neurons avoid neural network damage caused by chronic inactivity or hyperactivity [266].

Social interaction emerges in postnatal life and relies on a morphological scaffold that is structured in early intrauterine developmental stages and depends on intrinsic and extrinsic factors that properly form brain structure to function normally [267–274]. Mutations or biological imbalance disrupts this morphological assembly and produces mild or severe cognitive impairments [275, 276]. In this sense, genetic [277–279] and environmental [280, 281] risk factors are described for ASD, and it is possible that they interact in some cases or at some level [262, 263, 282] to generate the heterogeneous spectrum of disorders that comprise ASD. This interaction constitutes a third etiology that arises from two aspects: (1) autism risk genes establish a complex canonical network in which a mutation of a single component could disrupt many other related molecular pathways; (2) immune activation events during brain development are known to be a relevant environmental factor that induces gene expression changes in the developing brain and later CNS disorders [243].

The fetal and maternal organism interaction is vital but opens a vulnerability window for the developing fetus [266]. An increased frequency of autism cases after the rubella outbreak in the 1960s was the first clue that ASD and the immune system might be connected [283]. Still today, several studies have been unraveling this correlation with 3 perspectives: (1) outcomes of maternal immunological perturbation in offspring immunity, brain morphology, function, and behavior; (2) the abnormal humoral and cellular innate immune responses in autistic patients; (3) the participation of immune cells and molecules in CNS ontogenesis [284–287]. Here, we update clinical and research data that correlate immune system with ASD and brain development (Fig. 4).

Evidence of Immunological ASD Etiology

Experimental maternal immune activation (MIA) by viral, bacterial or proinflammatory insults showed that all

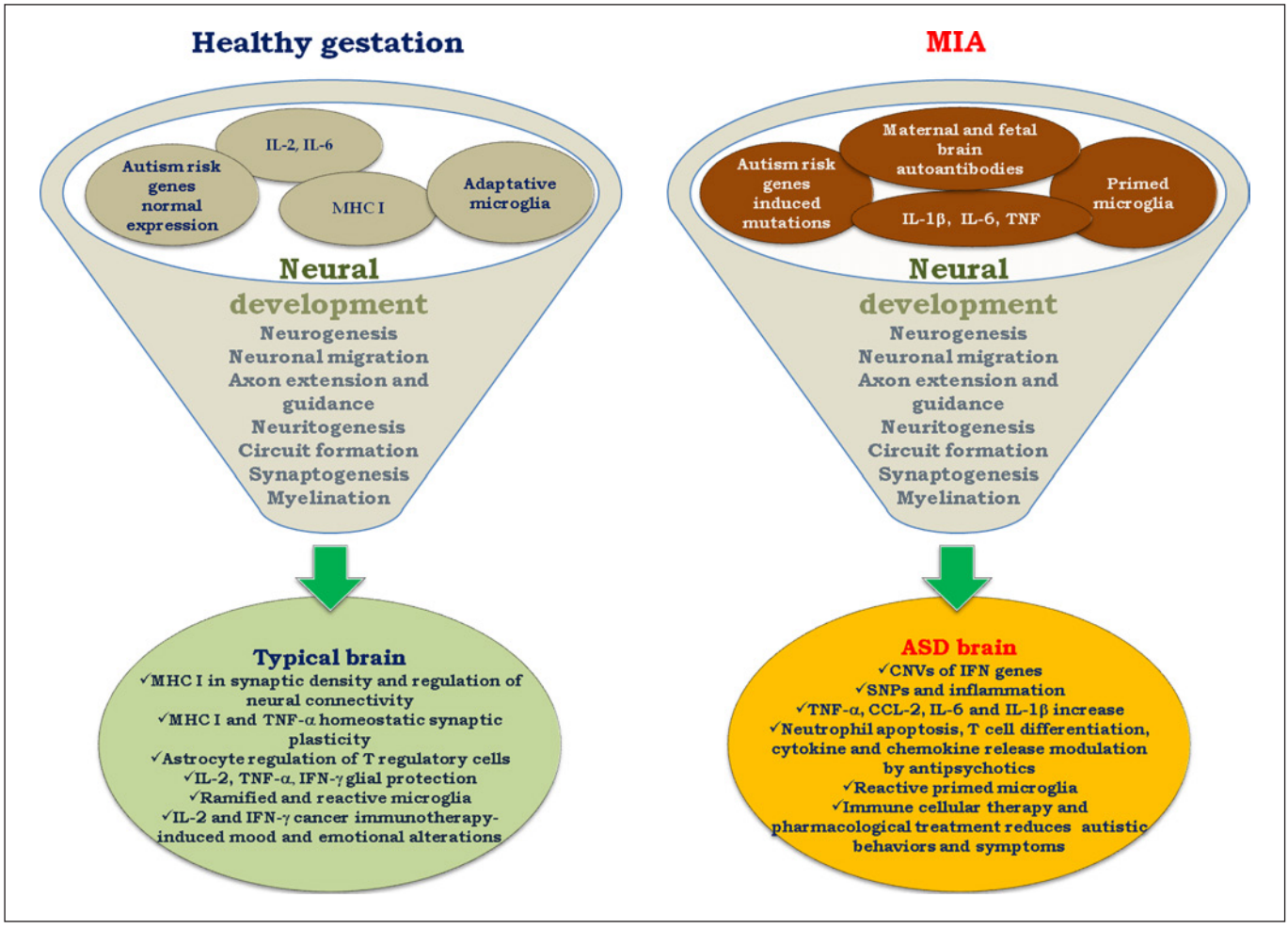

Fig. 4. Cross talk between the CNS and immune system in ASD. In the center, main ontogenic events of CNS development susceptible to immunological modulation. Immune system components normally participate in these processes in healthy gestation leading to a normal brain; therefore, immunological responses in maternal immune activation (MIA) can also interfere with neural developmental events which would lead to an ASD brain. IFN, interferon; CNV, copy number variation; SNP, single nucleotide polymorphism; TNF-α, tumor necrosis factor-α; CCL-2, chemokine (C-Cmotif) ligand 2; IL, interleukin; MHC-I, major histocompatibility factor-I.

these immunogens could change immune system gene transcripts in embryonic and postnatal brain, as well as brain and serum immune responses, with common and different features, but with specificity for CNS regions and developmental stages [288, 289]. Garbett et al. [289] suggested that MIA-elicited neuroprotective mechanisms lead to defective neural morphologies.

New data describe that MIA also deregulates, directly or indirectly, genes for general cell processes that have related functions or constitute a genetic cascade, and present high penetrance in ASD, such as the PTEN, Tsc2-mTor-Eif4e, and FMRP genes [290]. MIA transient interference on the expression of each of these genes would be small, but the co-occurrence of multiple MIA-induced gene expression regulatory events associated with the higher frequency of MIA itself could cause a devastating effect comparable to their permanent individual mutations. These results speak in favor of the ASD genetic and environmental etiological crossway.

The autistic-like behaviors generated following immune activation in pregnant women and neonates are important clues to understanding immune etiology. In non-human primates, poly I:C-LC treatment of pregnant macaques induced long-term high responses of innate inflammatory cytokines and associated autistic behaviors with abnormal immune profile in offspring [291]. An-

other recent work demonstrated that a LPS challenge in rodent neonates compromised immunity and neurochemical aspects of the prefrontal cortex, hippocampus, and hypothalamus in adolescent and adult animals [292]. Myeloperoxidase activity and IL-4 were higher, while IL-6 presented reduced levels in the LPS-challenged group. The alterations generated were not homogeneous between males and females for the 3 brain regions mentioned above in the different developmental stages evaluated since there were differences for the interactions of these 3 factors (IL-4, IL-6, and myeloperoxidase activity). Hippocampus also had higher BDNF levels in adults of both sexes and higher nitrite levels and lower parvalbumin expression in males. Depressive- and anxiety-like, repetitive and risk-taking behaviors and working memory impairments were also altered with specific sex- and age-related patterns congruent with these features in human ASD [293, 294]. The study also explored the critical aspect of the developmental time window susceptibility considering the nervous, immune, and brain-blood barrier ontogeny periods.

Immune System in Autism

The second aspect explored is the distinct immune profile detected in autistic patients and found in the different animal paradigms [291, 295]. Serum IL-1β and IL-4 at birth, is associated with higher risk of ASD diagnosis in children and symptom stringency [296]. Antibodies, monocytes, T cell responses, and natural killer cells of autistic children were also found to be altered [291].

In the CNS, there is evidence that microglial cells are also implicated in autism [284, 297–299]. An experimental genetic autism paradigm revealed a transient reduction, during the first postnatal week, of the microglial marker Iba1 in the basolateral amygdala, one of main cerebral regions executing behaviors impaired in ASD [300]. The administration of the microglial modulator minocycline reverted this morphological phenotype without an effect on the high anxiety behaviors such as the increased maternal separation-induced ultrasonic vocalizations in the mutants [301].

Another experimental cue comes from data of immune therapy attenuating ASD behaviors in rodents of an environmental paradigm of the disorder [302]. In this work, the disorder was induced by the gestational treatment with the antiepileptic, anticonvulsant, and mood stabilizer drug valproic acid (VPA), known to raise the risk of treated pregnant women to generate autistic children [302, 303]. The therapeutic target was histamine, a molecule that is active both in the immune and nervous systems [304, 305]. The therapy consisted in the application of an acute dose of ciproxifan (CPX), an antagonist of the histamine receptor 3 (H3R), 30 min before behavioral tests with young mice from mothers treated or not with VPA during gestation. CPX reduced social impairments and repetitive behavior in VPA animals [306], suggesting a potential role of the histamine-H3R system in the expression of ASD-like behaviors in rodents.

The Immune System during CNS Ontogeny

During development, neurons express class I MHC molecules which regulate synaptic density and neural connectivity [307, 308] and use other immune-related molecules to avoid neural network damage caused by chronic inactivity or hyperactivity [309]. A clear evidence that immune system directly takes part in CNS ontogenesis is the MIA putative effect in impairing microglia to properly execute its protective function in mature CNS [310].

Microglial developmental time window and novel functions described for these cells in CNS ontogenesis indicate they may also play a relevant role in triggering ASD [311–313]. Microglial cells enter the developing brain before midgestation and spread out regulating early axon guidance events, for example; although they are known to have a prominent role in later stages mainly in refinement processes [310, 314]. When present in postnatal neurogenic niches, they adopt more immature morphologies, and their detection is illusive since they do not display their typical markers [12]. In the adult brain, microglia regulates neural progenitor cell proliferation and survival after induction of neuroinflammation through the IL-1β and p53 pathway, affecting cell cycle and programmed cell death [315]. When analyzed in postmortem temporal cortex samples from typically developing and autistic individuals, the function-related morphologies of these cells showed that the primed phenotype, associated with synaptic plasticity, presented reduced density, while the ramified morphology, associated with the immune response, was increased, despite the comparable number of Iba-1-positive cells. These changes can be related to losses in sensory processing and social cognition as well as regional immunological weakening that increases dysfunction [316].

Future Perspectives

There is a vast body of clinical and experimental evidence strongly corroborating the immune system involvement in the etiology of ASD solely as an environ-

mental factor as well as in genetic cases. The variability in specific aspects matches the heterogeneous symptomatology but is a difficulty for data collection. Therefore, despite their higher frequency compared with rare point mutations, the definition of an etiological mechanism is still a challenge. The complete comprehension of neuroimmune interactions in ASD is far from being achieved, and we expect convergent data will shorten this distance.

General Conclusion

In recent years, it has become more and more evident that a multiplicity of molecules originally found in cells of the immune system are expressed in the CNS not only in astrocytes and microglial cells but even in the neurons themselves [307, 308]. It seems obvious that these molecules have been "acquired" by neurons throughout evolution to be used in new cell-specific processes unrelated to the immune response. Similar phenomena can be found in the case of proteins from other intracellular machineries, such as molecules related to DNA replication or cell cycle controllers such as cyclins [317–319] that perform new molecular functions in the context of neuronal physiology. Thus, it is likely that the CNS has not only co-opted immune molecules to carry out new functions but also employ similar strategies to interact with microglia and astrocytes, cells that resemble peripheral phagocytes in many ways.

It is following that logic that we could probably understand why similar, or even sometimes the very same, cells, cytokines, neurohormones, or inflammatory mediators, exert critical pathophysiological roles in such a diversity of complex brain diseases with completely divergent etiological bases.

Since fluent communication occurs between the endocrine, immune, and central nervous systems, an activation of the inflammatory response can influence neuro-/endocrine processes, and vice versa. Under physiological conditions, this cross talk operates as negative feedbacks to counterbalance potential overshooting of the responses and thus keeping homeostasis. It seems clear, however, that in pathological states these cross talks became misbalanced either reaching new "pathological" set points or even becoming feedbacks of positive and iterative valence.

If immune and inflammatory responses are the cause or consequence of these pathologies is a "chicken and egg" question that remains unsolved. However, it seems plausible that altered iterative loops more directly or indirectly involving immune signals lead to brain disorders upon chronicity. Under this scope, a general misbalance of these integrative communication systems per se, rather than the dysfunction of one specific molecular component, would stem on the mechanistic bases of complex brain disorders once the disease is installed. Thus, immune-based therapies might represent new avenues for pharmacological interventions that might exert both effects on direct cellular effectors and/or contribute to normalize altered neuro-endocrine-immune communication.

Probably, we have underestimated the relevance of these immune-related mechanisms in different brain disorders. From the basic research perspective, the advent of new "omics" technologies at single cell level will surely provide new insights on this topic. On the other hand, it is expected that new pharmacological studies are initiated in order to select promising compounds from the large list of drugs already designed for immunological purposes and incorporate them into new clinical trials aimed to evaluate the potential roles of these drugs on a variety of brain disorders and pathologies.

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Disclosure Statement

The authors declare no conflict of interest.

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