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Prenatal Programming of Monocyte Chemotactic Protein-1 Signaling in Autism Susceptibility

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that involves functional and structural defects in selective central nervous system (CNS) regions, harming the individual capability to process and respond to external stimuli, including impaired verbal and non-verbal communications. Etiological causes of ASD have not been fully clarified; however, prenatal activation of the innate immune system by external stimuli might infiltrate peripheral immune cells into the fetal CNS and activate cytokine secretion by microglia and astrocytes. For instance, genomic and postmortem histological analysis has identified proinflammatory gene signatures, microglia-related expressed genes, and neuroinflammatory markers in the brain during ASD diagnosis. Active neuroinflammation might also occur during the developmental stage, promoting the establishment of a defective brain connectome and increasing susceptibility to ASD after birth. While still under investigation, we tested the hypothesis whether the monocyte chemoattractant protein-1 (MCP-1) signaling is prenatally programmed to favor peripheral immune cell infiltration and activate microglia into the fetal CNS, setting susceptibility to autism-like behavior. In this review, we will comprehensively provide the current understanding of the prenatal activation of MCP-1 signaling by external stimuli during the developmental stage as a new selective node to promote neuroinflammation, brain structural alterations, and behavioral defects associated to ASD diagnosis.

Keywords Microglia · Prenatal programming · Chemokines · Autism · Neuroinflammation

Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders that harm the central nervous system (CNS) and hinder an individual's capability to process and respond to external stimuli, including impaired verbal and non-verbal communications [1]. People diagnosed with ASD also show repetitive or stereotypical behaviors ranging from mild to severe, as described by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [1]. Based on this categorization, autism is currently considered a spectrum of deficits, where behavioral and cognitive impairments are commonly and selectively observed [2]. According to the Autism and Developmental Disabilities Monitoring (ADDM) Network 2020 of the USA, autism shows a prevalence of 23.1 per 1000 children aged 8 years in Maryland to 44.9 per 1000 in California [3]. In fact, in 2020, one in 36 children aged 8 years (approximately 4% of boys and 1% of girls) were diagnosed with ASD [3].

Etiological causes of ASD have not been fully clarified; however, environmental factors, genetics, epigenetics, exposure to teratogenic agents, xenobiotics, and, importantly, immune activation might modulate ASD susceptibility [4, 5]. Notably, dysregulation of innate and adaptive immunity contributes to ASD susceptibility. See [6]. Accordingly, in a recent breakthrough report, authors confirmed the contribution of immune-related genomic signature on ASD

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susceptibility. This study was one of the large-scale exome-sequencing experimental protocols in autism, identifying up to 102 genes strongly associated with ASD and with neurodevelopmental delay neuronal abnormalities [7]. Notably, this study pointed out that a proinflammatory gene signature and microglia-related expressed genes were enriched in people with ASD [7]. It is believed that peripheral inflammatory profiles might infiltrate the CNS and increase microglia activation, exacerbating brain inflammation during ASD occurrence. For instance, an increase in the mRNA expression for IL-1β, IL-4, and IFN-γ was found elevated in peripheral blood mononucleate cells (PBMC) of ASD individuals [8]. Also, accumulation of IL-1β and IL-6 cytokines and tumor necrosis factor alpha (TNF-α) was detected in the plasma or postmortem brain samples of people with ASD [9, 10]. Notably, proinflammatory accumulation in people with ASD might occur very early in development. A recent report identified that newborn children diagnosed with ASD showed increased levels of IL-6, IL-8, eotaxin-1, interferon-γ, and IL-12p70 [11]. This suggest that newborns with elevated levels of proinflammatory cytokines might be at risk to be subsequently diagnosed with ASD.

While still under investigation, several reports have confirmed that systemic proinflammatory profiles might infiltrate the CNS during early stages of development, such as the embryonic stage. If this is true, ASD susceptibility might be programed during prenatal stages. Prenatal programming occurs when the fetus is exposed to external positive or negative stimuli, setting normal or abnormal physiological outcomes in the newborn [12]. This hypothesis was originally raised from epidemiological data suggesting a concept referred to as the "developmental origins of health and disease," confirming that selective stimuli in utero during critical developmental periods can disrupt selective physiological pathways in the fetus that persist throughout adulthood [13]. Accordingly, during development, peripheral immune cells might infiltrate the fetal CNS and activate cytokine secretion by microglia and astrocytes, turning them into a proinflammatory state, releasing cytokines and triggering a positive feedback signal for a proper neural growth and development [14]. By itself, under physiological conditions, microglia regulate neurogenesis, synaptic plasticity, and synaptic striping, in addition to being the mayor antigen-presenting cells (APC) in the CNS [15]. However, microglia overactivation might lead to neuroinflammation during developmental stages and increase the ASD occurrence [16]. We and others have reported that immune activation during developmental stage in animal models sets neuronal defects that lead to behavioral anomalies in the newborn such as sociability defects [17], as well as depression-like [18, 19] addiction-like [20–22], and overfeeding-like behaviors [23]. This evidence supports the notion that accumulation of proinflammatory cytokines and microglia activation during prenatal stages contributes to the onset and progression of psychiatric disorders including ASD.

In this review, we will comprehensively provide a conceptual outline of our current understanding of the monocyte chemoattractant protein-1 (MCP-1), a selective chemokine that promotes neuroinflammation in the brain during ASD occurrence. We will also provide evidence of the activation of MCP-1 signaling by external stimuli during the developmental stage as a new selective node to prime neuroinflammation, brain structural alterations, and behavioral defects associated to ASD diagnosis in the newborn.

The Monocyte Chemoattractant Protein-1 (MCP-1)/CC Chemokine Ligand-2 (CCL2) Chemokine Signaling

The chemokines are small molecular–weight proteins of 8–14 kDa that are secreted in response to proinflammatory microenvironment cytokines and displaying chemotactic signaling for cellular migration to the site of inflammation. The structure of all the chemokines includes three main chemical domains: an α-helix that projects and two antiparallel β-pleated sheets linked to a third β-pleated sheet. The α-helix and the antiparallel β-pleated sheets are stabilized by cysteine links from the N-terminal region [24]. According to the chemical structure of cysteine residues, chemokines are divided into four subfamilies: CC (C–C motif chemokine ligands—CCL), CXC (C-X-C motif chemokine ligands—CXCL), CX3C (C-X3-C motif chemokine ligands—CX3CL), and C (C motif ligands—XCL) chemokines [25]. Chemokines bind to chemokine G protein-coupled heptahelical receptors, normally expressed in the cell surface of white blood immune cells such as monocytes, neutrophils, and lymphocytes [24]. As expected, G protein-coupled receptors are transmembrane proteins composed of a short N-terminal extracellular domain linked to seven hydrophobic transmembrane domains and by three intracellular and extracellular loops and a serine/threonine-rich C-terminal intracellular region. The latter couples to a heterotrimeric G-protein complex modulating intracellular signaling. Chemokine receptors are divided into two families of heptahelical surface molecules that bind to chemokines: conventional chemokine receptors (cCKRs) and atypical chemokine receptors (ACKRs) all of which are sensitive to chemokine gradient concentrations [26].

The MCP-1/CC chemokine ligand-2 (CCL2) belongs to the CC subfamily that integrates cysteine residues just closely adjoined to the N-terminus [24]. Also, other MCPs found in humans include the MCP-2 (CCL8), MCP-3 (CCL7), and MCP-4 (CCL13) which share about ~ 60% homology each other [24]. During a physiological scenario, MCP-1 is produced by many cell types in the peripheral and

central systems, including fibroblasts, endothelial, smooth muscle, and monocytes and also astrocytes and microglia [17, 27–29]. Mechanistically, MCP-1 mainly binds to the protein G-coupled–receptor CCR2, which according to its terminal carboxyl domain is divided into CCR2A and CCR2B displaying target cell selectivity. For instance, CCR2B is abundantly expressed at the cell surface whereas the CCR2A is detected predominantly in the cytoplasm,in fact, the CCR2B is the predominant isoform of the CCR2 able to be activated by MCP-1. As expected, CCR2A and CCR2B display selective signaling downstream pathways followed MCP-1 binding [30, 31]. CCR2 signaling integrates significant redundancy and promiscuity when activated. Accordingly, CCR2 might be activated by different ligands, such as MCP-2, MCP-3, MCP-4, MCP-5, or C–C motif chemokine ligand 16,however: MCP-1 shows significant higher activity for CCR2 [32]. In addition, MCP-1 also binds to the atypical chemokine receptor that lacks G protein binding motif (ACKR1 and ACKR2).

Activation of CCR2 receptors favors chemotactic activity whereas ACKR1 and ACKR2 activation associates to phagocytic activity [33]. MCP-1 binding to various G protein-mediated signaling cascades on the p38 mitogen-activated protein kinase (MAPK) and Janus kinase (JAK)/STAT3, MAPK and on the phosphatidylinositol 3-kinase (PI3K)/AKT cell migration-sensitive site [34]. Several reports have confirmed that after CCL2R activation, MCP-1 signaling regulates the migration and infiltration of monocytes, T lymphocytes, and natural killer (NK) cells to specific inflammatory response sites and plays a vital role in antiapoptosis, angiogenesis, and cell migration [34].

MCP-1 Disrupts Brain Functionality in ASD

Preclinical evidence has confirmed the role of MCP-1 on brain functionality by modulating neuronal survival and differentiation (Fig. 1). In the brain, MCP-1 is expressed in astrocytes, neurons, or oligodendrocyte-precursor cells in various structures, such as the cerebral cortex, basal ganglia, hippocampus, hypothalamus, substantia nigra, pons, cerebellum, and in the spinal cord [35], and mainly expressed in the developing mouse midbrain [36–38]. Accordingly, MCP-1 exposure to rat embryonic cells promoted differentiation of neurons toward the dopaminergic lineage [36] and favored an increase in neuritogenesis [36]. Similarly, CCR2-MCP1 signaling activates the migration of neuronal progenitor cells to the site of inflammatory microdomains [39].

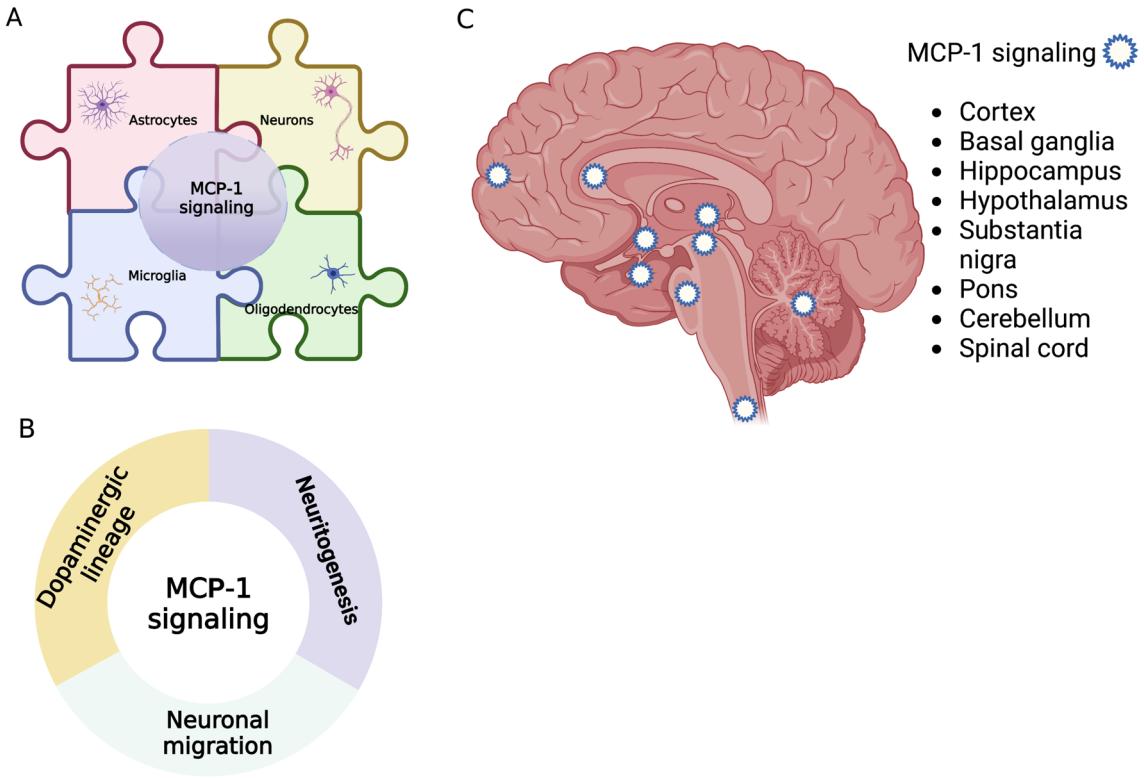

Fig. 1 MCP-1 signaling modulates brain function. **A** MCP-1 signaling is expressed in astrocytes, neurons, microglia, and oligodendrocytes. **B** MCP-1 signaling modulates neuritogenesis and neuronal migration to several microdomains and also incentivizes the dopaminergic lineage. **C** MCP-1 signaling is physiologically expressed in the cortex, basal ganglia, hippocampus, hypothalamus, substantia nigra, pons, cerebellum, and spinal cord. Created by Biorender

Pathological MCP-1 overexpression disrupts brain function and favors ASD susceptibility (Fig. 2). Clinical studies reported that people with ASD exhibited an increase in MCP-1 immunostaining in the anterior cingulate gyrus, cerebellum, and brain tissue homogenates, as well as up to 12-fold MCP-1 increase in the CSF [40] and in the amniotic fluid [41] when compared with controls. A recent transcriptomic and modeling study closely identified the MCP-1-CCR2 pathway as one of the innate immune responses found in ASD individuals [42]. Biological assessment of behavior outcomes reported that accumulation of MCP-1 in plasma was correlated with more impaired behavior in people with ASD such as visual reception, fine motor skills, expressive language, and daily living skills [9] according to the Adaptive Behavior Scale in Autism [43] or to the Autism Diagnostic Observation Schedule-second edition (ADOS-2) [44], while a recent clinical report showed significant decrease of MCP-1 levels in the CSF of adult patients with ASD [45]. In any case, it seems that MCP-1 signaling regulates brain function in humans and when uncontrolled is found in ASD individuals.

Several preclinical studies have provided some clues of the role of MCP-1 signaling which affects brain function and prime defective behavior in ASD individuals by assisting three molecular mechanisms: (1) disruption of neuronal activity and synaptic plasticity, (2) disruption of integrity of the blood–brain barrier (BBB), and (3) microglia activation. Accordingly, experimental studies have demonstrated that exposure to elevated levels of MCP-1 leads to increased excitatory synaptic transmission, creating an imbalance between inhibitory and excitatory signals within the brain [46, 47]. This disruption in synaptic homeostasis can impair the normal functioning of neural circuits involved in social cognition, language processing, and sensory integration [46], [47], which are known to be potentially affected in individuals with ASD.

Furthermore, MCP-1 can also disrupt the integrity of the blood–brain barrier (BBB) and impact the susceptibility to ASD occurrence. The BBB is a highly specialized barrier that regulates the exchange of molecules between the bloodstream and the brain. Disruption of the BBB allows immune cells and inflammatory mediators to infiltrate the brain, leading to neuroinflammation and subsequent neuronal damage. MCP-1 has been shown to increase the permeability of the

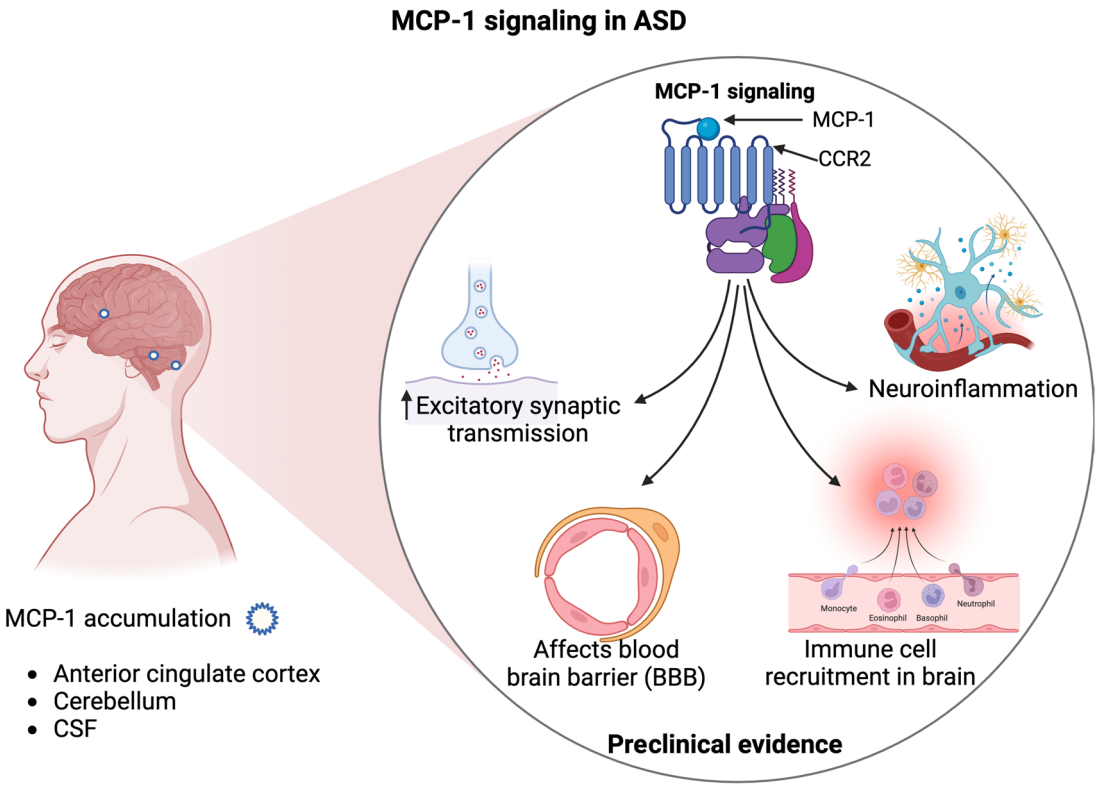

Fig. 2 MCP-1 signaling potentially affects brain function in ASD subjects. MCP-1 is found accumulated in anterior cingulate cortex, cerebellum, and cerebrospinal fluid (CSF) of ASD individuals. MCP-1 binds to a G protein-mediated signaling cascade on the CCR2 to activate the p38 mitogen-activated protein kinase (MAPK) and Janus kinase (JAK)/STAT3. Preclinical evidence documented that MCP-1 signaling is associated to an increase of excitatory synaptic transmission, neuroinflammation, disruption of blood–brain barrier, and immune cell recruitment into the brain of autism-like related animal models. Created by Biorender

BBB by promoting the adhesion and transmigration of monocytes and other immune cells across the barrier [48, 49]. This breach in the BBB further exacerbates the inflammatory response within the brain, contributing to the neurodevelopmental abnormalities seen in ASD [50].

A third molecular mechanism supporting the role of MCP-1 signaling on defective behavior in ASD individuals is by microglia activation. Initial research has highlighted the interplay between genetic in microglial dysfunction and MCP-1 dysregulation in ASD. For instance, genetic variations in genes associated with microglial function and immune response have also been identified in individuals with ASD [51]. Preclinical studies confirmed that MCP-1 modulates the function of microglia, the resident immune cells in the central nervous system. Microglia play a crucial role in brain development, immune surveillance, and synaptic remodeling. They constantly survey the brain environment, ensuring its proper functioning [52]. While preclinical or clinical studies have not totally defined the role MCP-1 on microglia signaling, some preclinical evidence has reported that MCP-1 is primarily secreted by activated microglia and astrocytes, acting as a chemoattractant, recruiting immune cells to sites of inflammation. In addition, it seems that might induce MCP-1 expression suggesting a crosstalk interplay between microglia and MCP-1. For instance, microglia rapidly induce MCP-1 expression in response to harmful stresses via NF-κB and p38 MAPK signaling pathways which by themselves are also involved in microglial activation [53]. In ASD, elevated levels of MCP-1 have been observed in the brains of affected individuals, suggesting its potential involvement in neuroinflammatory processes [54]. In fact, microglia in individuals with ASD exhibit an aberrant phenotype characterized by increased activation and proinflammatory responses [55]. This dysregulated immune response can contribute to the neuroinflammation observed in ASD, which has been implicated in the pathophysiology of the disorder [40]. It is expected that an increased activation in microglia can lead to the release of proinflammatory cytokines, chemokines, and reactive oxygen species, resulting in synaptic dysfunction and impaired neural circuitry [56]. These changes in neural connectivity and communication have been associated with the core symptoms of ASD, including social communication deficits and repetitive behaviors [57].

In conclusion, MCP-1, a chemokine involved in the inflammatory response, appears to disrupt brain functionality in individuals with ASD. Elevated levels of MCP-1 in the autistic brain can directly impact neuronal activity, modulate microglial function, and compromise the integrity of the blood–brain barrier. These mechanisms might contribute to the synaptic deficits, neuronal dysfunction, and neurodevelopmental abnormalities observed in ASD. Further research is needed to fully understand the intricate interactions between MCP-1 and molecular factors involved in ASD pathogenesis, which could potentially open new avenues for therapeutic interventions targeting neuroinflammation in this complex disorder.

Obesity or Maternal Exposure to High-Energy Diets Activates MCP-1-Dependent Neuroinflammation in ASD

As commented, ASD susceptibility is modulated by several stimuli including environmental factors, genetics, epigenetics, exposure to teratogenic agents, xenobiotics, infections, and diet [4, 5]. Clinical studies have confirmed crosstalk between maternal obesity or maternal exposure to high-energy diets on immune system activation and ASD susceptibility [4, 5]. It is believed that a chronic low-grade proinflammatory profile is in part promoted by the interaction of fatty acids released from adipose tissue expandability in obese mothers or from mothers exposed to high-energy diets with toll-like receptors, a pathological process known as metabolic inflammation [58].

While several authors have proposed metabolic inflammation as a major trigger of ASD, some reports have confirmed that some ASD individuals display a genetic susceptibility for physiological immune activation. Recent genome-wide association studies confirmed that people with ASD integrated common genomic variations affecting immune pathway activation and responses [59, 60] and confirming enriched proinflammatory and microglia-related genes [6, 7]. For instance, mRNA expression for IL-1β, IL-4, and IFN-γ was found elevated in peripheral blood mononucleate cells (PBMC) of ASD individuals [8]. Also, accumulation of IL-1β and IL-6 cytokines and tumor necrosis factor alpha (TNF-α) was detected in the plasma or postmortem brain samples of people with ASD [9, 10]. Also, active microglia have been found in several brain-associated areas of the mesocorticolimbic circuit, including cerebellum, PFC [55, 61], ACG, and OFC [61].

Mechanistically, it is believed that activation of the proinflammatory profile is linked to the toll-like receptor 4 (TLR4)/IKK/NF-κB pathway in microglia [62]. In fact, we reported that obese murine models show upregulation of the TBK1-related IKK marker [63, 64], a downstream target of TLR4 activation [65]. A potential scenario sets that the TLR4/IKK/NF-κB pathway allows IL-1β secretion, astrocyte activation in the choroid plexus, integrating peripheral B and T cells and a macrophage response by secreting chemoattractant molecules such as MCP-1 [5, 17]. In fact, selective depletion of TLR2 and TLR4 reestablishes social interaction in a mouse model of repeated social defeat stress by decreasing microglial activation in the PFC [66].

While this evidence supports the notion that active microglia leads to proinflammatory cytokine release, recent reports suggest that it is unclear whether individual microglia states or combinations of states of activation are protective or detrimental (or both) in the context of disease progression [52, 67]. Accordingly, a decrease in microglia number disrupts circuit establishment in humans [68]. Authors reported that a homozygous mutation in the colony-stimulating-factor 1 receptor promotes a major decrease in microglia and leukoencephalopathy [68]. Individuals with leukoencephalopathy displayed an absence of myelin-rich tracts in the corpus callosum and cingulate sulcus and dystrophic basal ganglia, thalamus, and hippocampus [68], suggesting a defective myelin turnover associated to colony-stimulating-factor 1 signaling. Accordingly, microglia actively modulates proper neurodevelopment by regulating neurogenesis, synaptic plasticity, and synaptic striping and also myelin conformation [56, 69, 70], suggesting that the colony-stimulating factor 1 receptor signaling coordinates microglial maturation during embryonic development [71]. In fact, a recent preclinical report confirmed that prenatal microglia are less responsive to immune challenges by secreting proinflammatory cytokines compared to the adult microglia [72]. Authors did not analyze the contribution of colony-stimulating factor 1 receptor signaling on behavioral traits of individuals, in part because individuals carrying the colony-stimulating factor 1 receptor mutation died at 10 months of age from streptococcal bacteremia. Based on the inaccessibility of living human brains for molecular characterization and ethical and technological limitations to test microglial function in human brains, it is still unknown whether microglial transition states during prenatal stages set behavioral traits found in people with ASD. Also, it is still unknown whether ASD behavioral outcomes are related to MCP-1 released from microglia in obesity or in response to high-energy diets.

We next described major findings supporting the role of prenatal programming on microglia phenotypes and microglia-MCP-1 release associated to ASD susceptibility after birth.

Prenatal Programming by External Stimuli Regulates MCP-1-Dependent Inflammation and Autism-Related Behavior

Several epidemiological reports have confirmed that prenatal programming favors a proinflammatory profile program in people with ASD, which might occur very early in development (Fig. 3). For instance, prenatal programming potentially might explain genomic signatures of active immune and inflammatory responses in postmortem brains of people with ASD [73, 74]. Maternal inflammation leads to elevated proinflammatory cytokines such as IFN gamma, and IL-4, IL-5, and IL-6 might affect the fetal brain development and subsequent cognitive disease outcomes [75]. Accordingly, authors identified that the intellectual disability in ASD was associated with an increase in GM-CSF, IFN-γ, IL-1α, and IL-6 plasma levels and lower plasma levels of IL-8 and MCP-1 during mid-gestation of mothers [76]. Under this

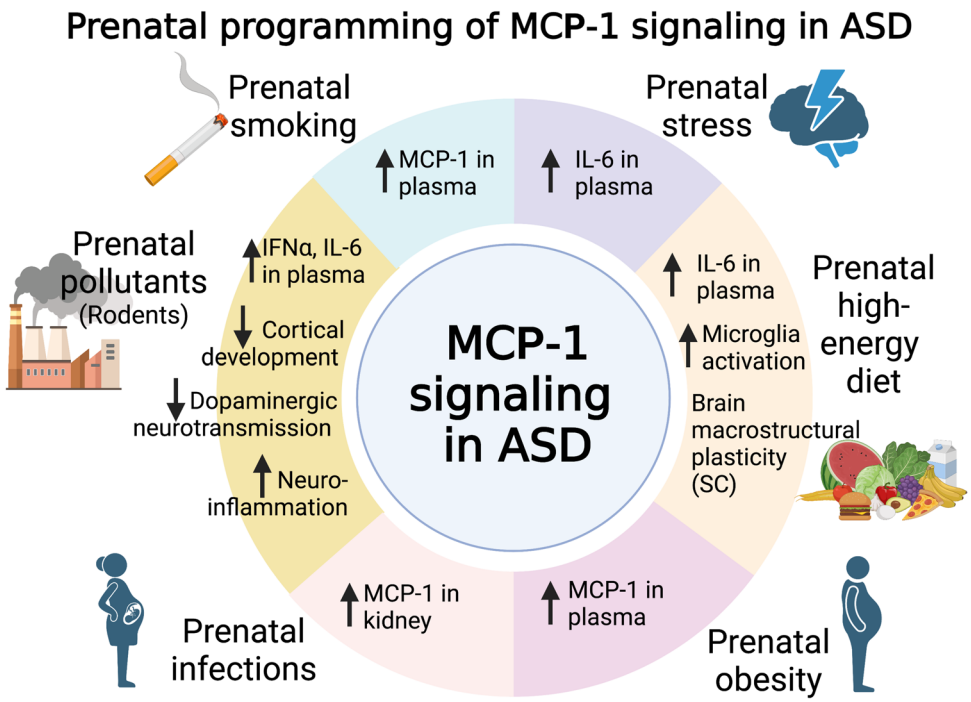

Fig. 3 Prenatal programming by external stimuli primes MCP-1 signaling in ASD subjects. Several external stimuli during prenatal stages prime the MCP-1 signaling in the brain of animal models diagnosed with autism-like behavior. Prenatal exposure to stress, high-energy diet, and pollutants increases IL-6 in plasma. Prenatal exposure to tobacco, obesity, or infections accumulated MCP-1 in plasma or kidney, respectively. Also, prenatal exposure to high-energy diets and pollutants affected cortical development and promoted neuroinflammation and microglia activation. Prenatal exposure to pollutants also decreases dopaminergic neurotransmission. Created by Biorender

scenario, it is expected that plasma proinflammatory profile infiltrates the fetal brain allowing microglia activation and neuroinflammation during prenatal stages. While still under investigation, initial reports identified accumulation of IL-6 and C-X-C motif chemokine ligand 10 (CXCL-10), also known as interferon-γ-inducible protein 10 (IP-10) in the amniotic fluid of mothers during the mid-trimester of pregnancy [77]. Notably, authors documented that IL-6 and CXCL-10 accumulation is associated to preterm delivery before or after 32 weeks of gestation, respectively [77]. While the authors did not determine the association of IL-6 and CXCL-10 on ASD susceptibility, this report confirmed the deleterious role of prenatal inflammation on newborn health. A recent report also identified that newborn children diagnosed with ASD showed increased levels of IL-6, IL-8, eotaxin-1, interferon-γ, and IL-12p70 [11]. This suggest that elevated levels of proinflammatory cytokines in the newborn might be a risk factor in the development of some behavioral traits found in ASD individuals.

We propose that MCP-1 signaling orchestrates brain neuroinflammation during prenatal stages, modulating behavioral traits in ASD after birth [17]. For major experimental evidence of immune dysregulation in ASD, see [6]. Here, we tested whether MCP-1 signaling is prenatally programmed in the newborn, favoring inflammatory profiles, microglia activity, and susceptibility to autism-like behavior. We focus our hypothesis on the role of prenatal programming of MCP-1 signaling by infections, maternal obesity, diet, stress, smoking, and pollution.

Prenatal Programing of MCP-1 Signaling by Infections

Preclinical reports have confirmed that fetal exposure to infections during pregnancy modulates the susceptibility to mental illnesses in the newborn. Authors reported that prenatal programming by maternal immune activation after rubella virus exposure [78–80] was associated to ASD susceptibility in the offspring. Accordingly, maternal immune activation appearing in the first 3 months of embryonic development has been involved in the disruption of neurodevelopment and potentially affects behaviors in the newborn [81]. Prenatal programming of inflammation and ASD behavior in the offspring was initially reported to be primed by pharmacologic activation of the toll-like-receptor 3 signaling [82]. In an elegant preclinical report, Kim et al. demonstrated that prenatal exposure to Poly I:C in mice favors IL-17A increase and alteration in cortical microstructures, which correlates with autism-like behavior in the mouse offspring [82], as well as in non-human and human primates [83]. Notably, defects in sociability correlates with an increase of proinflammatory cytokines INF-γ, IL-6, IL-17a, and TNF-α in plasma [82, 83] and high expression of IL-6, tool-like receptor 4 (TLR4), and MCP-1 on the fetal brain [84]. Also, the toll-like receptor signaling integrates a potential signaling pathway associated to MCP-1 secretion. For instance, pharmacologic activation of the toll-like-receptor 7/8 during maternal programming increased plasma MCP-1 in maternal and fetal brains, which correlates with microglia activation [85].

Experimental data also confirmed that a microglia activation shows a time-dependent response to a proinflammatory profile in the brain after a maternal immune activation by Poly(I:C) inoculation in mice [86]. Authors reported that maternal immune activation promoted changes in microglia motility in the brain as early as E18 and are sustained through to adolescence in mice (postnatal day 42) [86]. Notably, maternal immune activation induced earlier (at E12) caused sustained alterations in the patterns of microglial process motility and asocial behavior in the offspring, which is associated to increased IL-6 expression in prenatal microglia [86].

Prenatal Programing of MCP-1 Signaling by Obesity

As commented, several reports confirmed that maternal obesity predisposes ASD appearance in the offspring. Preclinical data reported that obese mice showed increased microglial activity that correlates with phagocytosis and diminished dendritic spine density in the PFC and hippocampus [87–89]. As expected, obesity disrupts offspring connectome found in the dopaminergic circuitry of the substantia nigra and the nigrostriatal tract [90]. Also, in a recent study, authors confirmed that maternal weight gain during pregnancy increases the risk of ASD after birth [91]. In fact, weight gain during pregnancy was suggested as an important risk factor for ASD compared to pre-pregnancy obesity [92]. Accordingly, insufficient rates of weight gain during the second trimester and excessive rates of weight gain during the third trimester were associated with a higher risk of neurodevelopmental disorders in offspring including ASD [93, 94]. For instance, maternal obesity is linked to up to 1.39% and 1.59% of ASD cases and a greater likelihood of having a child with ASD compared with their leaner counterparts [95–98]. Physiologically, adipose tissue accumulation and expansion has been associated to MCP-1 release, favoring macrophage infiltration into the adipose tissue and setting a proinflammatory cytokine profile [99]. Humans showing failure in adipose tissue expansion experienced a major increase in the proinflammatory profile in plasma including accumulation of MCP-1 [100]. This evidence supports the notion that adipose tissue expansion during maternal obesity promotes MCP-1 accumulation and immune cell infiltration, exacerbating the proinflammatory profile. Although the association of MCP-1 signaling in obesity programming ASD susceptibility has not been firmly established, this data

provides evidence of the deleterious effect linked to maternal/fetal adipose tissue accumulation.

Prenatal Programming of MCP-1 Signaling by Diet

Maternal exposure to high-energy diets favors defective social novelty [101] and suppresses social interactions in the newborn [5, 102]. Experimental studies by our group and others have reported that prenatal exposure to high-energy diets sets a systemic and central proinflammatory profile in the male offspring diagnosed with asocial behavior [17]. Maternal exposure to high-energy diets during fetal development substantially increases the MCP-1 plasma levels [17, 103, 104] and also favors microglia activation in the hypothalamus [105] and gliosis in the hippocampus of the offspring [19]. As commented, active microglia have been found in several brain-associated areas of the mesocorticolimbic circuit, including cerebellum, PFC [55, 61], ACG, and OFC [61]. It is expected that active microglia and astrocytes underlie neuroinflammation and synaptic degradation in ASD [106]. Accordingly, exposure to high-energy diets activates microglia [107] and promotes excessive synaptic stripping, affecting hippocampal plasticity [108]. We reported that maternal exposure to high-energy diets during pregnancy promoted structural brain abnormalities showing a decrease in hippocampal and nucleus accumbens volume in the offspring [19]. Also, maternal exposure to high-energy diets decreased the total volume of the brain as well as the volume of the medial amygdala and basal forebrain of the offspring [109]. In fact, a decrease of the synaptophysin marker in the hippocampus was found in mice exposed to high-energy diets during programming [19]. Also, a decrease in dendritic spines and synaptic maturation were found in the primary somatosensory cortex of offspring exposed to high-energy diets [110]. We and others reported a priming phenotype of microglia after prenatal exposure to high-energy diets, demonstrated by exacerbated IL-6 upon an LPS-induced immune challenge [103, 105]. While the authors did not analyze MCP-1 release after prenatal exposure to high-energy diets, we reported that administration of MCP-1 antibody in mice decreased plasma IL-6 levels, reduced microglia complexity, and improved social behavior [17]. These studies suggest that prenatal exposure to high-energy diets primes MCP-1 signaling pathways modulating microglia plasticity and cytokine release that assist social behavior in the offspring.

Prenatal Programing of MCP-1 Signaling by Stress

Stress is frequently referred to experiences in life that might be beneficial or negative and even traumatic, but all of them affect our daily lives [111]. Stress can cause an imbalance of neural circuitry affecting cognitive and motor behavior and, also, the systemic physiology via neuroendocrine, autonomic, metabolic, and immune disruptions [111]. Also, maternal exposure to high-energy diet or maternal obesity, maternal infection, or maternal smoking/pollutants might be also considered as prenatal stressors. Accordingly, authors reported that prenatal stress caused fetal MCP-1 secretion in mice, promoting brain inflammation leading to defective sociability [84]. Notably, prenatal stress increases fetal brain IL-6 in a CCL2-dependent manner [84]. In fact, MCP-1 expression was detected in placenta and fetal brain [84], suggesting that MCP-1 signaling integrates prenatal stimuli, coding for IL-6 expression in the intrauterine environment, potentially leading to defective behavior after birth [112], [92]. This resembles what we found in prenatal programing of MCP-1 signaling by diet: prenatal programming by stress promotes MCP-1 plasma accumulation leading to IL-6 secretion and defective behavior in the newborn. If this is true, MCP-1-IL-6 signaling might provide a context-dependent pathway that defines a proinflammatory profile and sets defective behavioral outcomes in the newborn.

Several reports have documented the role of prenatal IL-6 signaling on defective behavior in the newborn. Clinical evidence reported that maternal IL-6 penetrates into the fetal compartment [113, 114]. Accordingly, recent studies in humans have confirmed the role of maternal IL-6 concentrations during pregnancy and defective offspring behavior [115–118]. These studies demonstrated that IL-6 accumulation during maternal immune activation is associated to defective cognitive performance coded by the cortex, amygdala, and frontolimbic circuit in the newborn. ASD shows functional and structural defects in CNS regions, such as the prefrontal cortex, the amygdala, the hippocampus, and the cerebellum [4], so the fact that IL-6–dependent maternal immune activation affects brain circuits suggests that MCP-1 signaling might be an initial contributor of the immune response. Finally, IL-6 itself might amplify leukocyte accumulation at sites of inflammation by activating STAT3 through increased local production of MCP-1 and ICAM-1 [119]. We recently proposed that physiological or pathological outcomes of IL-6 signaling are related to its pleiotropic effects and levels in the brain by microglia, astrocytes, neurons, and endothelial cells and also by peripheral infiltrating macrophages or T lymphocytes [120]. In this context, MCP-1-IL-6 signaling might mutually interplay during prenatal programming in assisting brain circuit establishment during pregnancy, coding for ASD-related behaviors after birth.

Prenatal Programing of MCP-1 Signaling by Smoking

Epidemiological studies documented that smoking during pregnancy programs brain function and behavior after birth. Women who smoked during pregnancy prime food

preferences in the offspring: infants born from mothers who smoked consumed more carbohydrates than protein [121]. Preclinical data also confirmed that exposure to tobacco smoke during pregnancy incentivizes consumption of palatable foods in the offspring [122]. For many years, nicotine has been considered the main psychoactive substance present in tobacco smoke, which promotes higher levels of anxiety [123]. Previous findings identified elevated MCP-1 levels in middle-aged smokers compared to age-matched non-smokers [124], which seem to increase with a longer smoking history (~ 15 years) [125].

Prenatal exposure to nicotine was also associated to a proinflammatory profile in the offspring. A preclinical model of maternal cigarette smoke exposure in mice documented MCP-1 accumulation in the kidney of offspring [126]. Also, humans exposed to environmental tobacco smoke developed significant elevation of inflammatory markers in plasma, including the MCP-1 [127].

Evidence on the association between maternal prenatal smoking and the likelihood for autism has been contradictory and, in some cases, conflicting, based on some studies supporting association effects and others failing to prove a real risk. A recent clinical report integrating 72 cohorts in the Environmental Influences on Child Health Outcomes consortium reported that maternal prenatal tobacco smoking is consistently associated with an increase in autism-related symptoms in the general population and modestly associated with elevated risk for a diagnosis of ASD when looking at a combined analysis from multiple studies that each included both pre- and full-term births [128]. Conversely, in a Finnish national birth cohort, authors reported that prenatal maternal levels of serum cotinine, a biomarker for tobacco exposure, were not associated with the odds of autism [129], which was also confirmed by other authors [130], [131]. In any case, despite experimental evidence supporting MCP-1 accumulation in the offspring of mothers exposed to tobacco smoke, no causality between MCP-1 signaling on neuroinflammation and autism susceptibility in the offspring has been confirmed.

Prenatal Programing of MCP-1 Signaling by Pollutants

Air pollution is known to affect neurological function and to have effects on the fetus in utero US-EPA [132]Several recent studies have reported associations between perinatal exposure to air pollution and ASD susceptibility in children, including agricultural pesticides [133] [134]. Air pollutant exposure is becoming one of the most consistent environmental risk factors for neurodevelopmental disorders. In particular, using a prospective cohort of 116,430 US female nurses recruited in 1989, authors reported that higher maternal exposure to particulate matter (< 2.5 µm) during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD [135].

Preclinical models documented that exposure to particulate matter < 2.5 µm in mice increased the infiltration of inflammatory cells TNF-α and IL-6, as well as MCP-1 gene and protein expression levels in the liver, kidney, spleen, and thymus in a dose-dependent manner [136] and during vascular dysfunction in the brain of rodents [137]. Also, prenatal exposure to a high dose of particulate matter < 2.5 µm impaired the development of the cerebral cortex in mice [138] and promoted defective dopamine neurotransmission associated to hyperactive responses in mice [139] and in rabbits [140]. Experimental evidence confirmed that air pollutants activate neuroinflammation [141]. While the molecular pathways regarding the exposure to particulate matter < 2.5 µm during exposure to air pollutants on MCP-1 levels and neuroinflammation have not been totally established, the MCP-1 chemokine actively participates in the innate immune activation, which is expected to be activated during exposure to air pollutants [141].

A recent report documented that prenatal exposure to air pollutants is exacerbated by stress. Authors designed a murine model co-exposing pregnant dams to an environmental pollutant and limited-resource stress and found that both robustly activate the maternal immune system [142]. Notably, male offspring, but not females, developed defective social interaction that correlates with diminish microglial function within the anterior cingulate cortex [142]. In fact, prenatal exposure to particulate matter < 2.5 µm affects brain structure and promotes defective socialization in the newborn [143]. This suggest that an early postnatal impairment of microglial phagocytic function is sufficient to induce social behavior impairments in male offspring.

Potential Molecular Determinates of MCP-1 Signaling in Autism-Related Behavior

As commented, MCP-1 is expressed in astrocytes, neurons, or oligodendrocyte precursor cells in the brain [35] and mainly expressed in the developing mouse midbrain [36–38]. MCP-1 signaling promotes neuronal differentiation [36] and neuritogenesis [36] and incentivizes migration of neuronal progenitor cells to the site of inflammation [39]. One hypothesis states that MCP-1 signaling recruits immune cell types into the brain during neurodevelopment promoting neuroinflammation and a defective establishment of the brain connectome.

Several reports have provided experimental data supporting the role of MCP-1 signaling during neurodevelopment on brain function and ASD susceptibility. Initially, sex-dependent neonatal immune signatures were identified in subjects diagnosed with ASD [144]. Authors reported

that male newborns diagnosed with ASD have higher levels of inflammatory 6CKINE, MPIF-1, and also MCP-1 than female newborns [144]. While still under investigation, no data is available to precisely identify the cellular source of MCP-1 in people with ASD,however, it seems to depend on the selective diagnosis of the pathological brain. Reports have traced MCP-1 release from glia, astrocytes, and microglia. For instance, Müller cell-derived MCP-1 might diffuse throughout the neural retina and photoreceptors at the onset of degeneration [145]. As expected, retinal MCP-1-CCR2 signaling recruits peripheral monocytes into the site of neurodegeneration [145]. A recent report also confirmed the production of MCP-1 from astrocytes of mice after MPTP exposure in a murine model of Parkinson disease [146]. Also, during chronic traumatic encephalopathy in humans, authors reported MCP-1 expression and microglia accumulation into the dorsolateral frontal cortex [147]. In fact, microglia response during cerebral hemorrhage seems to contribute to MCP-1 release [148]. In fact, activating the expression of the MCP-1 receptor, CCR2, in bone marrow cells improved memory capacities and decreased soluble Aβ accumulation in mice [149], confirming that the MCP-1-CCR2 signaling incentivizes cell migration toward sites of inflammation to preserve brain homeostasis [39]. This evidence confirms that MCP-1 secretion from neurons, astrocytes, and microglia supports peripheral immune cell recruitment into the brain, modulating neurodegeneration.

The contribution of MCP-1 signaling on cellular recruitment into the brain has also been reported in prenatal stages. During development, tissue-resident macrophage populations first arrive in the CNS from embryonic precursors starting from E8.5 [150]. Microglia are derived from erythromyeloid progenitors from yolk sac cells, which infiltrate the brain during early prenatal day 9 (E9) embryogenesis in mice and in the first trimester in humans [150, 151]. While still under investigation, very early in development, the initial seeding of the premacrophages partially depends on the chemokine receptor CX3CR1 signaling at E9.5 and E10.5 [152]. MCP-1-CCR2 signaling contributes to microglia recruitment in embryonic development [153]. In fact, intracerebral stimulation by low doses of MCP-1 efficiently enhanced fetal cell mobilization into the mouse brain [154]. Central immune cell infiltration in prenatal stages might also be promoted in response to inflammatory stimulus [155]. Authors reported that during prenatal inflammation the choroid plexus secretes MCP-1, recruiting peripheral macrophages into the brain by the embryonic choroid plexus-blood-cerebrospinal fluid interface [155]. In fact, postnatal (3 to 11 days) exposure to pharmacologic inflammatory stimulus in mice followed by toll-like receptors 2 agonist increased cerebral microglia density and MCP-1 levels [156]. Conversely, we reported that inhibiting the MCP-1-CCR2 signaling by systemic administration of AbMCP-1 in mice offspring decreased neuroinflammation and microglia activation [17]. This evidence supports the hypothesis that systemic and central MCP-1 signaling during prenatal stages promotes myeloid cell recruitment and microglia seeding in the brain.

Brain microglia initially originated from the yolk sac during embryogenesis have an estimated median life span of > 15 months in the mouse cortex [157–159] and of 4 years in humans, with some reports identifying a life span of 20 years [160]. This selective long-lived identity benefits microglia by preserving its embryogenic phagocytic, immune, and proinflammatory profiles,however, they also might be compromised, favoring negative outcomes in adulthood if they were negatively primed during prenatal programming such as by exposure to infections, diet, obesity, stress, smoking, or pollution. For instance, authors reported that exposure to hypercaloric diets primes an immunity phenotype by reprograming the innate cells toward an enhanced immune response at later stages [161], a molecular mechanism termed "trained immunity" [162]. Notably, the adaptive innate phenotype has also been reported in microglia [163]. Hence, if we assume that MCP-1–responsive microglia regulate a proper activity and experience-dependent refinement of brain structure, setting a mature mesocorticolimbic connectome during neurodevelopment [15], it is conceivable that, in individuals with ASD, prenatal stimuli of MCP-1 might prime microglial cells to be recruited and overresponsive, affecting the neuronal connectome and setting abnormal behavioral traits at earlier years of life. Accordingly, we reported that inhibiting the MCP-1-CCR2 signaling by systemic administration of AbMCP-1 in mouse offspring improved sociability, which associates with structural changes into the somatosensorial cortex [17]. In fact, intracerebral stimulation by low doses of MCP-1 efficiently enhanced fetal cell mobilization into the brain to reduce microglia activation and brain excitotoxic damage in postpartum mice [154]. Also, central accumulation of inflammatory monocytes in mice exhibiting anxiety-like behavior was associated with microglial priming [164]. This evidence supports the notion of the existence of MPC-1 signaling on myeloid cell recruitment, microglia responsive and microglial training, and defective behavior in the offspring.

Despite the epidemiological and preclinical evidence, one of the major challenges is still to understand the contribution of inflammation during prenatal stages on ASD susceptibility after birth. We conceive that MCP-1 signaling activates peripheral immune cell recruitment into the brain during prenatal stages, incentivizing neuroinflammation and defective brain development. Also, MCP-1 signaling might drive local cytokine synthesis by resident glia, amplifying central immune response to external challenges. If this hypothesis is true, MCP-1 signaling might participate

in two main detrimental pathways, promoting the immune cell recruitment and exacerbation of the immune response to external stimuli.

Conclusions

Individuals diagnosed with ASD have found a seminal relationship between immunity and ASD susceptibility. Prenatal programming by several stimuli, such as exposure to infections, diet, stress, smoking, pollution, or even obesity, seems to be a potential environmental trigger which sets MCP-1 signaling, allowing myeloid cell recruitment and active microglia in the newborn's brain. Primed microglia might contribute to micro and macro structural defects on several brain regions, affecting connectome establishment and favoring ASD susceptibility. A current limitation is the lack of causality of prenatal MCP-1 signaling on the myeloid cell recruitment and primed microglia in ASD individuals. A combination of postmortem tissue analysis coupled to spatial and temporal resolution neuroimaging studies, such as the recent positron emission tomography analysis of CNS-infiltrating myeloid cells in a mouse model [165], might be useful to confirm the role of MCP-1 molecule as trigger signaling to favor microglial priming and behavioral traits in people with ASD.

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