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Inflammatory domains modulate autism spectrum disorder susceptibility during maternal nutritional programming

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Autism spectrum disorder (ASD) is a complex neurodevelopmental disease which involves functional and structural defects in selective central nervous system (CNS) regions harming capability to process and respond to external stimuli. In addition to genetic background, etiological causes of ASD have not been fully clarified. Maternal immune activation (MIA) during pregnancy have been proposed as a potential etiological cause leading to aberrant synaptic pruning and microglia-mediated neurogenesis impairment. Several clinical studies suggest that pro-inflammatory profile during maternal obesity associates with a higher risk of having a child with autism. In this context, the effect of maternal programing by high fat diet overconsumption during pregnancy sets a pro-inflammatory profile partly dependent on an epigenetic program of immunity which promotes brain micro and macrostructural abnormalities in the offspring that might last through adulthood accompanied by phenotypic changes in ASD subjects. Of note, maternal programming of inflammation during development seems to integrate the CNS and peripheral immune system cross-talk which arrays central inflammatory domains co-ordinating ASD behavior. In this review, we discuss basic and clinical studies regarding the effects of obesity-induced MIA on peripheral immune cells and microglia priming and their relationship with brain structural alterations in ASD models. Also, we show supportive evidence stating the role of maternal programming on epigenetic gene activation in immune cells of ASD subjects. We suggest that maternal programming by hypercaloric diets during development sets a central and peripheral immune cross-talk which potentially might modulate brain macro and microstructural defects leading to autism susceptibility.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disease that harms central nervous system (CNS) function and the individual capability to process and respond to external stimuli, including impaired verbal and no-verbal communication, in addition to showing repetitive or stereotypical behaviors(Lord et al., 2018). ASD shows functional and structural defects in CNS regions, such as the prefrontal cortex, the amygdala, the hippocampus and the cerebellum(Lord et al., 2018). According to the Centers for Disease Control and Prevention (CDC), in 2012, ASD prevalence increased up to 1 in 150 births to 1 in 68 with males being the most affected group showing 23.6 cases per 1000 births, whereas females had a prevalence of 5.3 cases per 1000 births(Christensen et al., 2016; Lord et al., 2018). Etiological causes of ASD have not been fully clarified; however, environmental factors, genetics, epigenetics, exposure to teratogenic agents, xenobiotics, infections and, importantly, autoimmune diseases, might modulate ASD susceptibility(Buehler, 2011; Lord et al., 2018).

Previous studies have considered the brain as an “immunologically privileged” organ; however, current research has confirmed an intimate CNS and immune system (IS) cross-talk modulating relevant physiological processes. B and T lymphocytes, macrophages, and antibodies are able to penetrate the blood brain barrier, orchestrating central-peripheral communication by IS and brain immune resident cells, such as microglia (Maldonado-Ruiz et al., 2017; Ransohoff and Brown, 2012). For instance, peripheral immune cells might infiltrate the CNS and activate cytokine secretion by microglia and astrocytes, which turn into a pro-inflammatory state releasing cytokines and triggering a positive feedback signal coordinating a proper neural growth and development (Buehler, 2011). For instance, during development, microglia regulates neurogenesis, synaptic plasticity and synaptic striping, in addition to being the mayor antigen presenting cells (APC) in the CNS(Schafer and

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Stevens, 2015). Based on this context, IS over activation might have deleterious effects on the CNS during early stages of development, such as the embryonic stage. In this regard, several research groups have reported that MIA during pregnancy sets neuronal defects leading to behavioral anomalies in the offspring, such as epilepsy, schizophrenia (SZ), cerebral palsy, Parkinson disease (PD), Alzheimer disease (AD) and also ASD (Estes and McAllister, 2016; Knuesel et al., 2014). In this review, we will comprehensively address the potential molecular pathways during MIA leading to ASD susceptibility. We will focus on the role of maternal nutritional programming as a new selective node to promote IS over activation during pregnancy, brain structural alterations and behavioral defects in offspring.

2. Autism spectrum disorder (ASD) as an autoimmune disease

By definition, immunity is the ability of the body to recognize, neutralize or destroy harmful foreign substances in our body. During autoimmunity our body recognizes, neutralizes or destroys selective targets of the body itself. Autoimmunity was initially reported as a etiological cause of ASD susceptibility, showing a positive correlation between ASD and familiar autoimmune disorder(Edmiston et al., 2017). For instance, a positive pro-inflammatory profile including circulating antibodies targeting lymphocyte antigens was identified in serum of mothers of ASD children(Edmiston et al., 2017), which correlates with an increase in the susceptibility to ASD after birth (Chen et al., 2016). In fact, serum autoantibodies against fetal neuronal migration and neural network brain targets, including the lactate dehydrogenase A and B (LDH-A and LDH-B), the stress-induced phosphoprotein 1 (STIP1), the collapsin response mediator proteins 1 and 2 (CRMP1 and CRMP2), cypin, and the Y-box binding protein 1 (YBX1), have been identified in ASD subjects (Edmiston et al., 2017; Fox-edmiston et al., 2016). Of note, serum autoantibodies in ASD subjects have also been identified against brain targets, such as the N-methyl-D-aspartate (NMDA) receptor for glutamatergic neurotransmission (Gréa et al., 2017). Finally, immunogenetic analysis confirm the hypothesis of autoimmunity as a etiological cause of ASD by identifying a third hypervariable region (HVR-3) and the C4 complement alleles have been correlated to ASD (Gesundheit et al., 2013). Together, this evidence supports the potential role of maternal or subject selective autoimmunity leading to ASD susceptibility.

3. Role of peripheral IS activation during neurodevelopment and CNS homeostasis

Peripheral immune cell infiltration into the CNS might be considered detrimental, nevertheless, during development a sophisticated integration of molecules involving hormones, neurotransmitters and importantly, cytokines closely interacting with neurons ensure their proper development. In this context, microglia is the CNS resident self-renewal macrophages, originating 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, assisting in modulating and coordinating neuronal maturation (Maldonado-Ruiz et al., 2017; Ransohoff and Brown, 2012). For instance, microglia activation is required to modulate neurogenesis and synaptic plasticity in addition to acting as a major antigen presenting cells (APCs) in the CNS. Active microglia release selective neurotrophic factors and cytokines that modify neuronal function and brain circuit establishment and also coordinates proper receptor expression and signaling molecules to respond to neuron derivate factors(Maldonado-Ruiz et al., 2017; Ransohoff and Brown, 2012). For instance, microglia-derived insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) are required for survival of layer V cortical neurons during the first week of postnatal life (Ueno et al., 2013), stabilizing young spines in granule cells of the olfactory bulb (OB) (Breton-Provencher et al., 2016; Parkhurst et al., 2013). In contrast, pharmacological inhibition of microglia reduces neurogenesis, whereas exposition to microglia-derived cytokines such as interleukin 1 beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), interferon gamma (IFN-γ) inhibits hippocampal neurogenesis [34, 38] and reduces plasticity-related spine formation in mature neurons of the adult motor cortex (Parkhurst et al., 2013). Neural progenitor cell (NPCs) proliferation in cell culture might also be inhibited by microglia under a positive chronic pro-inflammatory state such as interferon alpha (IFN-α) and a complement protein (C3d) stimulation in a B-cell receptor (CR2) complex-dependent pathway (Moriyama et al., 2011). Also, TGF-β activates microglia leading to phagocytosis of synapses by promoting complement expression in neurons (Bialas and Stevens, 2013) and NPCs might also modulate microglia cytokine secretion, increasing synaptic pruning and migration through vascular endothelial growth factor (VEGF) (Mosher et al., 2012). Although we might conceptualize that synaptic pruning and neuron phagocytosis by microglia seems to be detrimental for neuronal function and synaptic circuit formation during neurodevelopment, it does positively coordinate proper CNS connectome. For instance, microglia in the dorsal lateral geniculate nucleus (dLGN) prune pre-synaptic terminals of the incoming retinal ganglion cells axons, contributing to the segregation of inputs into eye-specific territories and proper synaptic formation of the OB circuitry (Derecki et al., 2012; Schafer et al., 2012). In order to perform synaptic pruning on newborn neurons the microglial CX3C receptor-1 (CX3CR1) and its neuronally-derived CX3C Ligand-1 (CX3CL1) must interact with each other, for instance, during the sensory-deprived adult animals (Denizet et al., 2017). Of note, a sophisticated recent paper by Lehrman, E. et al. (2018), identified that the Cluster of differentiation 47- regulatory protein α (CD47-SIRPα) signaling pathway regulates synaptic pruning allowing proper synaptic connectome by preventing intensive microglial phagocytosis in mice (Lehrman et al., 2018).

On the other hand, microglia activation might also prevent CNS injuries following a stressful stimulus in a T cell-dependent manner. In normal conditions, $CD4^+$ T cells are able to infiltrate the cerebral spinal fluid (CSF) from cervical lymph nodes through the choroid plexus and meningeal veins (Louveau et al., 2017). $CD4^+$ T cells are effective mediators of immunosurveillance that preserve homeostatic activities essential to normal brain function, such as learning and memory neuronal recovery after a stressful stimulus, BDNF-dependent adult hippocampal neurogenesis(Maldonado-Ruiz et al., 2017), and prevent neurodegeneration injury(Duan et al., 2018). For instance, $CD4^+$ cells promote IL-4 secretion leading to BDNF and nerve growth factor (NGF) secretion from astrocytes and microglia promoting neurogenesis and young spine stabilization (Breton-Provencher et al., 2016; Parkhurst et al., 2013). In contrast, several studies have reported that $CD4^+$ T cell depletion, either surgically (excision of cervical lymph nodes) or using a transgenic animal model (Rag $2^{-/-}$), leads to compulsive behavior, deficits in nest building, and impaired learning and memory (Derecki et al., 2010; Filiano et al., 2015; Radjavi et al., 2014; Rattazzi et al., 2013). This evidence suggests that physiological microglia activation sets time-dependent synaptic pruning leading to proper CNS connectome during neurodevelopment; however, central or T cell infiltration during peripheral IS overactivation stimulates microglia and disrupts proper synaptic plasticity.

4. Peripheral IS activation and microglia cross-talk modulate ASD susceptibility

Seminal reports have demonstrated the substantial role of peripheral IS and microglia interaction during development of ASD susceptibility in offspring. Initial reports in humans identified that peripheral IS activation by virus leads to aberrant behavior. For instance, herpes simplex virus 2 (HSV-2) infection leads to active IS increasing SZ risk by 1.43% in humans (Estes and McAllister, 2016; Ransohoff and Brown, 2012). This correlates with previous reports showing positive maternal

TNF-α and IL-8 inflammatory markers and schizophrenia risk in offspring(Estes and McAllister, 2016). A high antibody title against HSV-2 has also been reported to increase ASD risk by 2.07% (Mahic et al., 2017). MIA by influenza virus during the first-trimester of pregnancy also increases bipolar disorder (BD) and SZ risk nearly 4-fold in human offspring(Parboosing et al., 2013) and an up to 12% increase of ASD (Jiang et al., 2016). Also, genitourinary infections during pregnancy decrease the anti-inflammatory profile and potentiate an increase of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α in the brain of both the fetus and mother(Edmiston et al., 2017). High plasma levels of IL-1β, IL-6, IL-8 and IL-12p40 correlate with impaired communication and aberrant behaviors in ASD children (ages 4–8 years), as well as an increased number of B and natural killer (NK) cells in ASD adult patients. Peripheral IS activation and microglia cross-talk in ASD subjects is confirmed in ASD patients showing a significant increase of TNF-α, IL-6 and granulocyte-macrophage-colony stimulating factor (GM-CSF), Th1 cytokine (IFN-γ) and chemokine (IL-8) in brain biopsies (Li et al., 2009). A marked increase of monocyte chemoattractant protein-1 (MCP-1) in the cerebrospinal fluid (CSF) of ASD subjects, which correlates with positive microglia activation and gliosis in the granular cell layer and white matter of the cerebellum(Tetreault et al., 2012) and CPF (Fatemi et al., 2012) has been identified. Of note, microglia appeared markedly activated in up to 5 out of 13 cases with autism, which seems to be located at the dorsolateral prefrontal cortex (Gesundheit et al., 2013). Recent evidence shows that primed microglia correlates with a high expression of the major histocompatibility complex (MHC) class II protein, human leukocyte antigen (HLA-DR) in the cerebellum of ASD patients (Lee et al., 2017), supporting intimate peripheral IS-microglia cross-talk.

Peripheral IS activation and its role on brain plasticity during ASD have been also demonstrated in murine models using maternal pharmacologic administration of polyinosinic:polycytidylic acid (poly I:C), lipopolysaccharide (LPS), endotoxin A and virus-associated infections. For instance, pharmacological prenatal MIA promotes Toll like receptor stimulation which correlates with a positive pro-inflammatory profile in serum including IL-2, IFN-γ, IL-6, IL-4, IL-17A and TNF-α (Careaga et al., 2017; Kim et al., 2017). A MIA pro-inflammatory profile which correlates with autism-like behavior in mice and non-human primates, is also identified in the amniotic fluid, placenta, and fetal and mother brains (Shin Yim et al., 2017). Of note, MIA also activates chemokines such as MCP-1 and cytokines including IL-2, IL-5, IL-7 and IL-13, leading to lymphocyte proliferation and maturation (Careaga et al., 2017). Despite the robust scientific evidence linking MIA and ASD, most maternal infections in humans do not lead to ASD in offspring (Selten and Morgan, 2010). In fact, basic research addressing the role of MIA in murine models supports the notion that behavioral and immunological effects during MIA are selectively depending on the animal's strain (Schwartzer et al., 2013) and selective pro-inflammatory trigger (Glass et al., 2018).

Finally, it is clear that a positive pro inflammatory profile as a potential node to modulate ASD susceptibility has been proposed in several reports, however, there is still under investigation if classical pro inflammatory cytokines are intricately related to ASD. For instance, higher levels of IL-8 were associated with increased ASD severity in females, whereas increased IL-15 and reduced IL-8, IL-1β and macrophage inflammatory protein-1α (MIP-1β) levels were associated with increasing age in males (Masi et al., 2017). Of note, additional studies have not find correlation between cytokines, TLR-4 and NF-κB profiles with ASD severity (Nadeem et al., 2018, 2017). Also, high IL-8 levels and no changes in plasma IL-1β or TNF-α have been found in ASD subjects (Tonhajzerova et al., 2015), which are also found in a murine model of ASD (Vogel Ciernia et al., 2018). The authors on these papers suggest that IL-8 might inhibits IL-1β and TNF-α synthesis in the same manner as IL-6, which both closely depend on the NF-κB. An unclear positive and selective pro inflammatory profile leading to ASD susceptibility in these studies rises the fact that even though 95% ASD cases show inflammation, there are subject dependent profiles playing a role on ASD generation (Doenyas, 2018). For example, MIA leads to oxidative stress activation even without triggering an immune response in the fetus (Oskvig et al., 2012), which shows a time-dependent profile between subjects (Pardo et al., 2017) contributing to ASD pathology for certain subgroups of individuals (Doenyas, 2018).

In summary, despite the lack of evidence regarding the effect of inflammation on selective cytokines profile leading to ASD generation, it is clear that MIA does set a "disease primer" making an individual more susceptible to the effects of genetic mutations and potential environmental exposures triggering disease-related symptoms such as ASD later in life. In any case, based on this evidence a question is still on the table if so, how does MIA alter brain function in the offspring leading to ASD susceptibility?

5. Central microglia activation during MIA regulates micro and macro structural brain changes leading to ASD susceptibility

Recent research using murine models has contributed to initially understand the role of MIA during development on brain function leading to ASD susceptibility in offspring, suggesting that microglia might promote brain micro and macro structural alterations related to aberrant plasticity changes (Fig. 1). Basal functional brain connectivity integrates the left and right CA1 hippocampal region, exchanging information bidirectionally to the amygdala. CX3CR1 receptor deletion in microglia leads to a decrease in the functional connectivity between the PFC, CA1 of hippocampus, nucleus accumbens (NAc), and the temporal association cortex (TEa) (Zhan et al., 2014) (Fig. 1A and B). Also, MIA

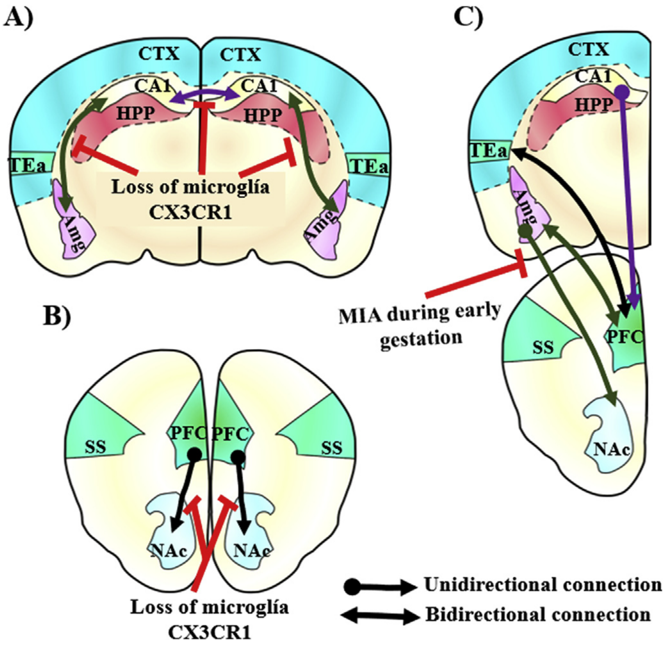

Fig. 1. Defects in brain connectivity in ASD induced by MIA during pregnancy. ***A)*** Under normal circumstances, both left and right CA1 hippocampal region sustain a functional connectivity, integrating bidirectional connections (purple arrows) between hippocampal CA1 (HPP), amygdala (Amg) and nucleus accumbens (NAc) at both hemispheres (green arrows). ***B)*** Loss of microglia receptors leads to reduction in brain specific functional integration. Normal input signals from prefrontal cortex (PFC) to NAc (black arrows), decrease when CX3CR1 gene is absent in microglia. ***C)*** PFC maintains an unilateral connection with the CA1 hippocampal region (purple arrow), and a bidirectional connection with the temporal association cortex (TEa) and Amg (black and green arrow, respectively), Amg has an unidirectional connection with NAc (green arrow). Maternal immune activation reduces synaptic inputs from one of these regions to other in the offspring, propitiating the development of neurologic diseases.

disrupts the Amg - NAc unidirectional connection (Fig. 1C). Also, MIA is able to mediate microstructural defects related to synaptic and dendrites morphology. For instance, immune activation during pregnancy leads to MHCI-synaptic pruning in neurons by promoting long lasting changes in immune molecule expression (Careaga et al., 2017).

MIA increases the number of dendritic spines in the hippocampus of male mice, while decreasing the microglia receptor CX3CR1 (Fernández de Cossío et al., 2017), a key receptor in the regulation of phagocytosis (Keren-shaul et al., 2017). In this regard, C3 protein ablation decrease synaptic pruning in the PFC (Fagan et al., 2017), which correlates with C2, C5 and mannose-associated serine protease 1 (MASP1) down-regulation in the PFC of ASD patients (Fagan et al., 2017). Reduced CX3CR1 expression in MIA models has also been reported to promote an increase in the number of spines on hippocampal granulate cells in male offspring (Fernández de Cossío et al., 2017). Recent reports have also identified that subexpression of the receptor expressed on myeloid cells 2 (TREM2) correlates with aberrant synapse elimination and defects in brain connectivity in ASD subjects and in a murine model displaying repetitive behavior and altered sociability (Filipello et al., 2018). Together, we propose that reduce expression of TREM2 and CX3CR1 genes in microglia or neurons lacking FMR1 gen impair synaptic pruning resulting in immature neurons showing high dendritic density in the hippocampal region CA1 (Fig. 2A and B). Under this scenario, immature neurons are less responsive to glutamate influx allowing mature neurons overactive and secreting large amounts of glutamate which reaches other brain regions exacerbating firing of neighboring synapses, whereas far away brain regions show reduced synaptic input specificity (Fig. 2B). These cellular and neuro connectome changes might contribute to impaired social behavior found in ASD subjects. Finally, MIA also decreases neuronal migration to the somatosensory cortex (SS) in mice by down regulating SATB2 expression which correlates with defective social behavior (Shin Yim et al., 2017) (Fig. 2C).

Active IS and/or MIA seems to last beyond the gestational stage in order to maintain a pro-inflammatory profile. For instance, in an elegant recent paper, Duan et al. (2018) identified that active IS primes neuroinflammation by platelet-derived growth factor receptor betta (PDGFRb) mural cells of blood vessels which secrete the chemokine CCL2 and disrupts synaptic activity brain regions implicated in ASD (Duan et al., 2018). Also, single nucleotide variant in the PTPN4 gen, a specific inhibitor of Toll like receptor 4/TIR domain-containing adapter -inducing interferon β (TLR4/TRIF) dependent IRF3 activation and IFN-β production (Huai et al., 2015), is sufficient to reduce dendritic spine density on the hippocampal neurons in ASD subjects (Szczałuba et al., 2018). Recent evidence has shown that immunity also bidirectionally targets metabolism by mitochondria function regulating micro structural brain changes and ASD susceptibility. For instance, serum of ASD subjects have high levels of extracellular vesicles (EV) containing mitochondrial DNA (mtDNA) which promote high secretion of IL-1β *in vitro* at later stages (Tsilioni and Theoharides, 2018). Of note, serum from young autistic children have elevated mtDNA levels and an anti-mitochondrial antibody, anti-mt antibody Type 2 (AMA-M2), which potentially might exacerbate the pro-inflammatory profile (Zhang et al., 2010). Also, human mast cells (MCs) stimulated with IgE immunoglobulin secrete EV containing mtDNA and ATP (Zhang et al., 2012), which might act as autocrine and paracrine signals promoting degranulation and IL-8, TNF, and IL-1β cytokines release (Zhang et al., 2012) simulating “innate pathogens” leading to ASD (Theoharides et al., 2013). In fact, the pathological contribution of extracellular mtDNA could be even more relevant in ASD patients showing mitochondrial dysfunction (Rossignol and Frye, 2012). In this regard, our research group has found that positive inflammatory profile during maternal programming by caloric diets exposure induces hypothalamic mitochondria fusion, metabolic dysfunction and fat accumulation in male offspring (Cardenas-Perez et al., 2018). Additionally, candidates for micro structural synaptic plasticity changes modulating the ASD phenotype have been identified, for instance, Jawaid et al., showed that the Fragile X Mental Retardation Protein (FMR1) ablation in mice display an increase in the CA1 dendritic spines contributing to hippocampal dysfunction by reducing synaptic input specificity (Jawaid et al., 2018). Here, we propose that damaged mitochondria due to harm stimuli such as hyperlipidemia, oxidative stress or MIA might compromise mitochondria function, promoting secretion of extracellular vesicles (EV) packaged with mtDNA, favoring microglia and T cell activation. M1 microglia leads to IL-1β secretion, whereas B cells activation synthetizes the pathological antibody AntiAMA-M2 Ab.

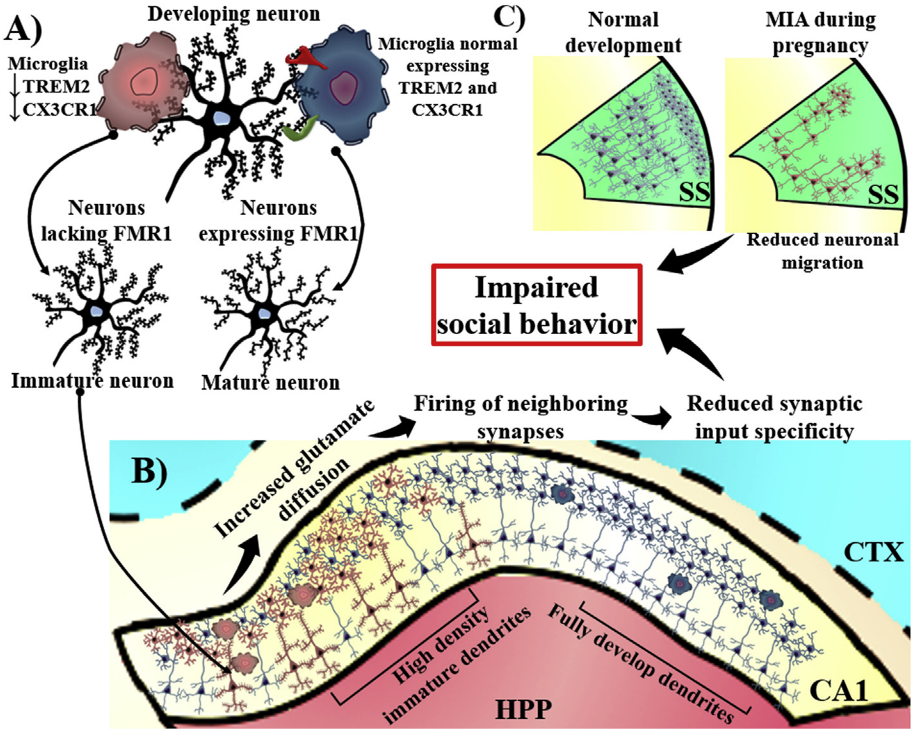

Fig. 2. Microstructural brain alterations related to ASD following by MIA during pregnancy. *A)* Double deletion of CX3CR1 and TREM in microglia (red microglia) and neurons lacking FMR1 gen impairs synaptic pruning resulting in immature neurons showing high density of immature dendritic spines. Correct expression of these genes (blue microglia) results in a fully mature and functional neuron. ***B)*** High density of neurons with immature dendritic spines in the hippocampal region CA1, result in neurons incapable of transduce proper glutamatergic synaptic signals. In order to compensate this, fully mature neurons increased glutamate influx, which diffuses beyond its target site firing neighboring synapses and reducing synaptic input specificity. ***C)*** MIA by exposure to an inflammatory stimulus by 12.5 gestational day in mice results in decreased migration of neurons into the somatosensory cortex (SS) leading to defective social behavior.

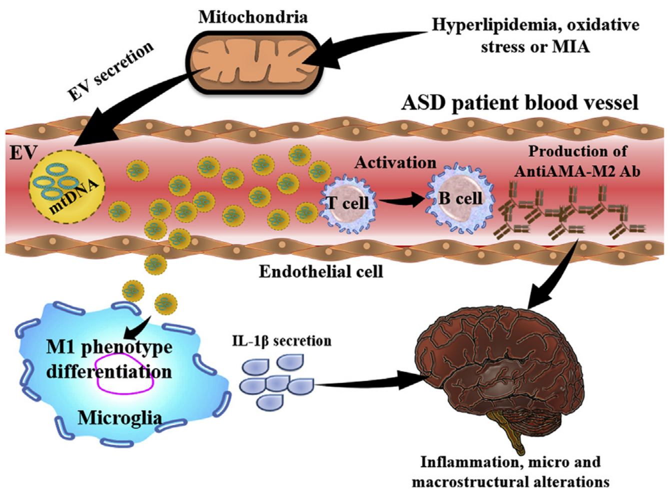

Fig. 3. Extracellular vesicles (EV) containing mitochondrial DNA (mtDNA) promotes inflammation in ASD children. Hyperlipidemia, oxidative stress or MIA lead to mitochondria dysfunction and EV leading to secretion of IL-1β secretion in autistic children. Also, plasma from ASD subjects show pathological antibody (AntiAMA-M2 Ab) over production by plasma T cell and by microglia, which together contribute to micro and macrostructural alterations on brain regions associated with ASD.

Together, these changes contribute to micro and macrostructural alterations on brain regions associated with ASD. (Fig. 3). By contrast, deletion of the transcription factor Tcf4 gene in mice leads to a reduction in the number and microstructural changes of cortical and hippocampal CA1 dendritic spines which correlate with ASD-like behavior (Crux et al., 2018). Of note, as we will address later, tcf4 has to be involved with ASD syndrome (Pitt-Hopkins syndrome) progression through a neuroepigenetic mechanism, altering CNS plasticity and the major subdomains of cognitive function, including memory, social interactions, and auditory communication (Kennedy et al., 2016) and B cell differentiation (Zhuang et al., 1996). Whether FMR1 and Tcf4 are regulating by MIA during development is an open question to be addressed in future studies.

Active IS during MIA also promotes macrostructural brain defects leading to ASD behavioral alterations including grip, righting reflex and geotaxis. For instance, MIA leads to structural cortical defects mediated by Th17 lymphocyte-dependent production of IL-17a(Kim et al., 2017). Of note, recent research shows that MIA phenotypes in offspring require maternal intestinal bacteria that promote TH17 cell differentiation(Kim et al., 2017). Of note, in a recent paper it was identified that positive maternal IL-6 correlates with defective functional architecture of the brain and decrease in working memory in the offspring at 2 years of age (Rudolph et al., 2018). Interestingly, the midgestational maternal cytokine profile of elevated IL-6 and IL-2 was associated with having a child sharing other developmental disorders, but not ASD, whereas elevated serum IFN-γ, IL-4 and IL-5 in women correlate with an ASD child (Goines et al., 2011; Jones et al., 2017), suggests a differential role for cytokine profile during development. At least in murine models, social interaction defects has been related with prefrontal microglial TLR2/4-dependent activation during MIA (Nie et al., 2018).

This evidence proposes that active IS by T-cell-mediated MIA and central microglia cross-talk selectively coordinate positive pro-inflammatory plasma and neurodevelopmental and behavioral alterations in offspring such as ASD. Long lasting microglia activation promotes micro and macrostructural brain alterations that might potentially be modulated through epigenetic changes synerging with genetic and/or environmental risk factors at different stages of life and culminating in ASD susceptibility(Estes and McAllister, 2016)· In brief, we will address the role of MIA by nutrition on epigenetic pro-inflammatory profile modulation during pregnancy leading to active IS and microglia activation in ASD susceptibility in the offspring.

6. Implications of epigenetic dysregulation of immune genes in the etiology of ASD

ASD is a neurodevelopmental complex disease linked to up to 800 specific mutations in single or multiple genes; however, mutations do not totally match with autistic phenotype, making it difficult to find a common genetic signature (Vorstman et al., 2017). Of note, most of the risky genes for ASD are involved in the regulation of chromatin and transcription, such as chromodomain-helicase-DNA-binding protein 8 (CHD8) and FMR1. For instance, mutations in the methylated DNA binding protein MeCP2 leads to Rett Syndrome and dysregulated DNA methylation signatures in the autism-related genes RELN, EN-2 and Shank 3 gene have been reported (Vorstman et al., 2017). Given the sophisticated role of imprinted genes on the normal development and function of the human brain (Banik et al., 2017), selective environmental alterations might potentially modulate the epigenetic program linked to complex neurodevelopmental disorders such as schizophrenia (Dempster et al., 2011), addiction-like behavior (Montalvo-Martínez et al., 2018) and ASD (Wong et al., 2014), which might be potentially implicated in active IS and central inflammation. For instance, microglia from the offspring of dams with allergic asthma displays hypermethylation of pro-inflammatory genes which correlates with autism (Vogel Ciernia et al., 2018). Also, cortical regions of ASD subjects showed a hypomethylated CpGs genomic landscape responsible for immune functions, such as C1Q, C3, ITGB2, (C3R), TNF-α, IRF8 and SPI1 (Nardone et al., 2014), which are importantly implicated in synaptic pruning and microglial cell specification (Paolicelli et al., 2011; Schafer et al., 2012). Despite the large amount of scientific evidence proposing the positive effect of MIA on ASD susceptibility, selective potential molecular pathways modulating this scenario have not been totally dissected. In this context, in recent years, obesity as a chronic pro-inflammatory state has emerged as a risk factor for the development of neurologic diseases and altered behavior such as addiction-like behavior, SZ, Down syndrome, Prader-Willi syndrome and ASD (Zheng et al., 2017), and which potentially might sets a selective epigenetic program in offspring. We will address this in the next section.

7. Metabolic inflammation during obesity and overnutrition program epigenetic modifications leading to ASD

Obesity produces a chronic low-grade pro-inflammatory state mainly coordinated by the interaction of fatty acids from diet with TLR, known as metabolic inflammation (Cai and Liu, 2011; Milanski et al., 2009). Several clinical studies have identified that maternal obesity leads to up to 1.39% and 1.59% of ASD cases(Andersen et al., 2017; Bilder et al., 2013; Krakowiak et al., 2012; Li et al., 2016; Reynolds et al., 2014). Maternal obesity during pregnancy is associated to a greater likelihood of having a child with ASD compared with their lean counterpart controls (Bilder et al., 2013; Krakowiak et al., 2012; Li et al., 2016; Reynolds et al., 2014). In fact, diet-induced obesity in murine models has proven that metabolic inflammation leads to increased cognitive rigidity and diminished preference for social novelty in the BTBR mouse model (Zilkha et al., 2017), whereas adult mice fed with a “Western diet” exhibit suppressed social interactions and dominant-like behavior (Veniaminova et al., 2017). Mechanistically, metabolic inflammation in the CNS activates the pro-inflammatory pathway TLR4/IKK/NF-κB in microglia (De Souza et al., 2005; Milanski et al., 2009), which allows IL-1β secretion, astrocyte activation in the choroid plexus, and integrates peripheral B and T cells and a macrophage response by secreting chemo attractant molecules (Maldonado-Ruiz et al., 2017). In fact, selective depletion of TLR2 and TLR4 reestablishes social interaction in a mice model of repeated social defeat stress (Nie et al., 2018). Of note, serum polymorphonuclear cells from ASD subjects are hypersensitive to *in vitro* TLR ligands such as LPS, Poly

I:C and GpC-B(Jyonouchi et al., 2012). Metabolic inflammation following a high fat diet in mice also leads to active B cells which secrete the IgG1b antibody allowing macrophage and microglia to adopt a proinflammatory M1 phenotype (Winer et al., 2011; Yi et al., 2012), and decreasing hippocampal-dependent spatial memory (Hao et al., 2015; Keren-shaul et al., 2017; Valdearcos et al., 2014). Based on this evidence, it is tentative to propose that metabolic inflammation during maternal obesity programs set an epigenetic signature regulating fetal phagocytic aberrant synaptic pruning and IS activation increasing ASD susceptibility.

A positive energy balance linked to maternal overnutrition during pregnancy modulates the epigenome in offspring and increases ASD susceptibility (Banik et al., 2017; Montalvo-Martínez et al., 2018). Specifically, selective diet components modulate IS function through epigenetic mechanisms (Paparo et al., 2014). For instance, in a recent elegant study, Christ A et al. (Christ et al., 2018) identified that a hypercaloric diet in a murine model sets transcriptomic and epigenomic reprogramming of myeloid progenitor cells that show increased proliferation and enhanced innate immune responses at later stages. The effect of maternal hypercaloric diet exposure during pregnancy and its role on epigenetics modulation of immunity leading to ASD has not been totally elucidated; however, if so, it seems to last through adulthood accompanied by phenotypic changes (Keleher et al., 2018). In the same context, recent reports have shown that unsaturated fatty acids (FA), arachidonic acid (AA), and oleic acid (OA) might modulate DNA hypermethylation and hypomethylation, respectively, both in human and mouse cultured cells (Silva-Martínez et al., 2016). In addition, a high intake of n-6 polyunsaturated fatty acids (PUFAs) by adult zebrafish (*Danio rerio*) results in negative genetic regulation of LPS-mediated inflammation in offspring (Adam et al., 2018). Recently, MIA leads to significant DNA hypomethylation of the ASD-related gene, MECP2, in the hypothalamus of offspring (Basil et al., 2014). This is reverted following n-3-PUFA-enriched diet supplementation in the offspring (Basil et al., 2018). In this context, epigenetic modulation might also coordinate $CD4^+$ T_{reg} differentiation by changes in the expression of FOXP3 (Polansky et al., 2008) and maternal methyl donor diet supplementation modulates B and T lymphocyte activation and maturation by regulating the genomic expression of the TNF receptor, LcK, CD6, CD7 and CXCL10 (Schaible et al., 2011). Of note, in neurons of ASD subjects enriched CpGs regions for immune genes, such as TNF-like domain, complement C1q protein, a positive regulator of MyD88-dependent TLR pathway and Ig mediated immune response, and the IFN-γ signaling innate immune response to viral infection protein, OAS2, have been found (Nardone et al., 2017). Also, offspring of the autoimmune ASD murine model shown hypermethylated DNA regions in several transcription factor motifs including RUNX1, IRF8, NF-kB and MAFB, which are critical for early microglial development and immune activation, respectively, as well as the cytokines IL-6, IL4, IL-8 and Jak-STAT, TNF and mTOR signaling (Vogel Ciernia et al., 2018). In contrast, prevention of demethylation using siRNA transfection in murine models reduces IL-6 and IL-1β expression in the amygdala and juvenile social interaction (Kigar et al., 2015). This evidence supports the role of a positive energy balance in the context of obesity and maternal hypercaloric diet overnutrition in epigenetic programing of immunity in the offspring, a context potentially implicated in ASD susceptibility. We conceptualize that a selective diet formula might closely coordinate IS and central inflammation cross-talk supported in part by a "trained immunity", as was initially proposed by Christ A et al. (Christ et al., 2018).

7.1. *Dietary dysbiosis of gut microbiota in ASD susceptibility*

Gut microbiota refers to the complex gut microbial community that has a symbiotic relationship with their host. The gut microbiota is involved in many important biological and metabolic functions, from the synthesis of nutrients, hormones, vitamins, supply of energy from dietary sources otherwise unavailable to the host and importantly for the present review, the modulation of brain activity and behavior via the gut-brain axis (Doenyas, 2018). In addition, microbiota regulates intestinal barrier function and both immune/inflammatory responses, by changing the expression and distribution of tight junction proteins (Doenyas, 2018). Under a physiological scenario, gut microbiota coordinates both specific and nonspecific immunity in the first years of life by a beneficial and very well controlled low-grade inflammation, however, it might be deleterious for children at risk for ASD (Madore et al., 2016). For instance, microbial colonization sets signaling mechanisms that affect neuronal circuits involved in motor control and anxiety behavior (Heijtz et al., 2011). In addition, patients with autism display a higher abundance of *Lactobacillacease* and *Clostridia,* and a reduced incidence of the *Prevotella* and other fermenters. Of note, in a MIA mice model by high-fat diet (MHFD) exposure, ASD susceptibility correlates with a marked decreased in *Lactobacillus, Parabacteroides, Helicobacter*, and *Bacteroides uniformis* (Buffington et al., 2016). Also, germ-free mice show defects in social interaction over a familiar mouse (Desbonnet et al., 2014), which correlate with differential gene expression of transcriptional program leading to neuronal structure and function in the amygdala (R.M. et al., 2015). These evidences suggest that gut microbiota modulates brain functionality in ASD-related behaviors.

The role of intestinal microbiota and immune system activation on ASD susceptibility has been recently reported. Western diet exposure promotes gut microbiota dysbiosis, altered immune system and ASD development (Krajmalnik-Brown et al., 2015). However, potential molecular mechanisms regulating gut microbiota composition, immunity and their effects on neurodevelopment is no fully clarify. Nevertheless, gut microbiota ferments non-digestible compounds, such as starch, producing nutrients in the form of short chain fatty acids (SCFAs) including formate, acetate, propionate, and butyrate; which have been implicated in the training and regulation of the human immune system. For example, the digestion of complex carbohydrates into SCFAs by intestinal bacteria may play a significant role in the development of the host immune system and immune cell responses in neurodegenerative diseases (Spielman et al., 2018). Also, reduced expression of proinflammatory cytokines in stimulated T cells, increased human plasma B cell maturation and IgG production (Spielman et al., 2018). Of note, accumulation of IgG antibodies in the brain has also been identified following a high fat diet protocol (Yi et al., 2012). Thus, it is potentially plausibly that metabolism of caloric formula during maternal nutritional programming by intestinal bacteria might play a significant role in the development of behavioral pathologies such as ASD.

8. Conclusions

Worldwide multiple research groups have found a seminal relationship between immunity and ASD susceptibility. MIA induced by high-fat diet intake seems to be a potential environmental risk stimulus in our present society which sets a chronic pro-inflammatory program during fetal development allowing active microglia to negatively modulate synaptic pruning and neurogenesis by altering the expression of key phagocytic genes (HLA-DR, MHC, TREM2, CX3CR1 and C3) through the TLR2/4 pathway and also by promoting a central pathological antibody (IgG1b) response. Also, lipid and diet metabolites might modulate epigenetic programming setting microglia, T and B lymphocyte differentiation (FOXP3), activation (TNFR, LcK, CD6, CD7 and CXCL10) and migration (MCP-1), which closely impact on ASD development. Based on this evidence, we conceptualize that maternal programming by hypercaloric diets sets an epigenetic program during fetal development that closely integrates active peripheral IS and central microglia cross-talk leading to micro and macro structural defects on several brain regions such as PFC and CA1 hippocampal which confines synaptic pruning and defective neurogenesis in the fetus

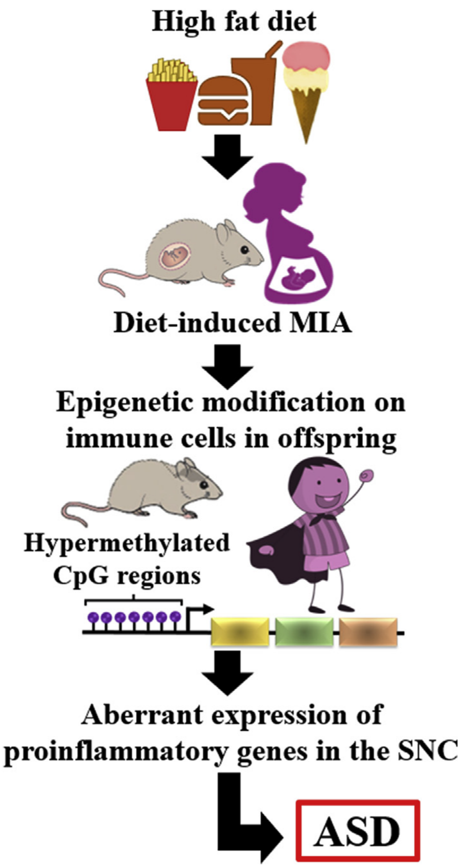

Fig. 4. High fat diet (HDF) during pregnancy programs epigenetic modifications of immune genes in the offspring leading to ASD. High consumption of fatty acid during pregnancy might induce metabolic inflammation and epigenetic rearrangement potentially inherited in the offspring. Positive immune system activation in offspring sensitizes decreased social behavior later in life.

(Fig. 4).

Conflicts of interest

The authors declare no conflict of interest.

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