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Review

Autism and IL-17 & IL-18

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ABSTRACT

Clinical trials have identified autism spectrum disorder (ASD) as a complex neurodegenerative disease. Individuals with ASD have problems with social activities and abilities, mutual communication, stereotyped behaviors, and have a propensity to and have activities and interests. The immune system and neural development are linked from fetal development to maturity, and dysfunctions in this communication impair many immune system functions. One of the most widely held beliefs about ASD is that it is a condition caused by immune system dysfunction. When a pregnant woman is exposed to an infection, an inflammatory immune response is activated, and molecules such as maternal cytokines and chemokines that can cross the placenta are produced. It has been reported that the pro-inflammatory cytokine molecules IL-17 and IL-18, which pass from the placenta to the fetus, control the ASD pathway, induce neurotoxicity as a result of inflammation, and have an impact on ASD, which is a neurodegenerative disorder.

Keywords: Autism spectrum disorder, cytokine, IL-17, IL-18, immune system, inflammation.

Autism Spectrum Disorder (ASD) is one of the most common neurodevelopmental disorders, affecting one for every 54 children worldwide.[1] Leo Kanner first used ASD in 1943,[2-4] which includes a diagnostic spectrum ranging from autistic disorder to Asperger syndrome. It is a higher-functioning type of ASD with increased intellectual abilities.[5] Clinically, ASD is a complex and heterogeneous neurological disorder that affects multiple developmental areas, including communication skills, mutual social contact, visual function, and stereotyped behavior, interests, and behaviors.[3,6] These disabilities normally appear before the age of three in early childhood, but they do not completely develop until later in life.[7] Previous studies also shown that children with ASD have altered immune functions and suffer from a chronic neuroinflammatory condition.[8-10] T cell function abnormalities have been reported in ASD patients.[11] Immune system dysfunction or disease may also increase neurological sensitivity.[12,13] Immunological disruption in ASD is complicated, and it can be related to modifications in the prenatal immune environment, which can increase the risk of ASD.[14] ASD affects children's immune systems with an early age.[12] The biological origin of ASD is uncertain, although it may provide connections between genetic responsibility and exposure to the environment.[15]

Over the last decade, the global prevalence of ASD has increased gradually, with a reported 62 million cases in 2016.[5] While the cause of ASD is still unexplained, numerous studies have identified a variety of genes and environmental factors that play a role in the disease's development.[9,16-18] Over the past decade, the contribution of genetics to the pathophysiology of ASD[19] has been comprehensively established by hundreds of different genetic polymorphisms associated with the disorder.[20,21] Studies have shown that ASD has a strong heritability component, with rates of compliance ranging from 80-90% in monozygotic twins.[22,23] Although there is a genetic component, the phenotypic heterogeneity in ASD, as well as the fact that these common functional variants are also

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seen in undiagnosed individuals, strongly suggests that these mutations alone may not be enough to cause the full spectrum.[19,24,25]

It is known that environmental factors as well as genetic factors play a role in the formation of ASD. Environmental toxins, maternal nutrition, infection and prematurity during pregnancy, other modifications other than DNA changes, and parental age at conception are only a few examples. Synapses have been proposed to be particularly vulnerable to genetic degradation and potentially related environmental impairment.[26] Recent technical advancements, such as genome-wide association studies (GWAS), bioinformatics, and big data analytical approaches, have made it possible to detect rare single point mutations and copy number variation (CNV) in patient populations of both novo and hereditary origins.[27]

As a result, the Simons foundation autism research initiative (SFARI) gene database has confirmed over 1,000 point mutations and CNV in candidate genes associated to ASD. The majority of the genetic variants are found in genes responsible for key molecular components required for neuronal synapses' development and function.[28]

A multifactorial pathogenesis has been proposed by scientists working on ASD. Various evidence, genetic and environmental factors have been included in this theory.[29] It has been discovered that central nervous system (CNS) dysfunction can lead to the development of behavioral and cognitive disorders, especially during neurodevelopment.[30] The regulation of gene expression by inducing functional variations in DNA without altering the genomic sequence is known as epigenetics. It has been shown to be a critical component of brain development, aging, and a variety of CNS disorders.[31] Indeed, epigenetics plays a major role in the plasticity stages of brain development and is therefore important for the etiology of CNS disorders.[32] Epigenetics can genetically manipulate functional genes associated to a higher risk of psychiatric or neurodegenerative disorders during prenatal brain development.[33] Therefore, epigenetic regulations are one of the mechanisms that directly affect ASD pathogenesis.

The role of immune system activation during specific time periods in the expectant mother as a risk factor for ASD is confirmed by a body of evidence.[34] Recent research suggests that immune system abnormalities and zinc homeostasis may have an effect on synaptic transmission. Understanding how genetic and environmental risk factors in ASD interact at synapses may be a useful starting point for future research into ASD patho-mechanisms.[26] Several studies have found that Zn2+ deficiency affects various brain functions and inhibits neuronal maturation during early development by disrupting Zn2+ dependent processes, resulting in severe brain dysfunction like irreversible learning and memory impairment.[35] However, Zn2+ deficiency is not only a biomarker for ASD, but can also be a risk factor. Zn2+ deficiency is common in autistic children.[36-38] A recent study investigated hair Zn2+ concentrations in 1,967 children with ASD and found that %43.5 of men and % 52.5 of women aged 0-3 years have Zn2+ deficiency. These findings suggest that infantile Zn2+ deficiency can play a role in ASD pathogenesis.[39]

AUTISM SPECTRUM DISORDER AND IMMUNOLOGICAL DYSFUNCTION

One of the most commonly known theories surrounding ASD, according to the science community, is immune system dysfunction.[40] The immune system's innate and adaptive branches can also impact neural development, cognitive function, and behavioral model.[41] The immune system and the CNS interact from fetal development to adulthood, affecting both the systemic immune response (peripheral immune system) and local CNS immune regulation (called "neuroimmunity").[41] Early activation of innate immunity during pregnancy, mainly due to an infectious disease, has been shown to significantly increase the risk of ASD.[42]

Activation of the maternal immune system during fetal development can cause differences in neuronal development and is a risk factor for ASD.[41] The maternal immune system may be dysregulated due to a number of interconnected factors. Zerbo et al.[43] Found that maternal infectious diseases diagnosed on hospitalization, particularly bacterial ones, were associated with an increased risk of ASD. Infections such as rubella or influenza virus during pregnancy can cause maternal cytokine and chemokine release, which not only affect the placenta directly but can also cross the placenta, entering the fetal compartment and affecting fetal development.[41] These effects can also be achieved through a generalized inflammatory response or

loss of immune regulation in the absence of active infection.[44] Inflammation is managed by the immune system through a number of signaling pathways, including pro- and anti-inflammatory mediators, as well as long-term molecular/cellular effects, and this may have consequences on development, eventually driving behavioral and cognitive symptoms of ASD.[45,46] Immunocompetent cells and their cellular mediators may become unbalanced as a result of changes in genomic, epigenetic, and environmental processes, causing inflammation and dysregulated immune function. T cells, B cells, NK (natural killer) cells, and monocyte/macrophages have all been shown to have abnormalities in ASD patients, and it should be noted that the heterogeneity of ASD may reflect different pathophysiologies and possibly ASD subtypes.[47,48]

MATERNAL IMMUNE ACTIVATION (MIA)

MIA is an ASD animal model that is based on the presence of ASD-like symptoms in the offspring of mice that were activated by an immunogen such as polyinosinic: polycytidylic acid (polyl: C) during the gestation. These are usually inserted on embryonic day 12, as this corresponds to the first trimester of pregnancy in humans, as maternal viral infections have been associated to an increased risk of ASD.[49] Using this model, he demonstrated that dams who were infected with HIV (Human immunodeficiency virus) intranasally during pregnancy had less exploratory activity, sociability, and anxiety, all of which are essential features of ASD.[50] During pregnancy, the maternal immune system provides IgG antibodies to the fetus in a tightly regulated process.[51] However, by manipulating the prenatal environment, variations in these transplacental antibody changes may alter the developing fetus's susceptibility to neurodevelopmental disorders including ASD.[18] Since the Rubella epidemic in the 1960s, when the prevalence of ASD among children born to infected mothers increased significantly, this correlation between the maternal immune system and ASD was first suggested.[34] MIA has been shown to have permanent impacts on T cell functions, as well as permanent neurodevelopmental and behavioral changes in offspring.[52-54] Perinatal stresses that cause the immune response, such as maternal infection during pregnancy, have also been associated with the pathogenesis of ASD and other neuropsychiatric disorders.[55,56] The MIA model is based on the induction of sterile immune activation by non-specific stimuli of innate immunity.[57] A tolerogenic state is reached, which is regulated by maternal immune cells in the placenta and affects the cytokine profile to increase the production of "pregnancy protective" cytokines.[58,59] External environmental factors such as maternal viral or bacterial infections, on the other hand, may disrupt this balance and trigger transient up regulation of pro-inflammatory cytokines, which can damage acute immune activation and fetal neurodevelopment.[41,60,61]

AUTISM SPECTRUM DISORDER AND IMMUNE SYSTEM CELLS

In ASD patients, the number of NK cells is 40 percent higher than in healthy individuals. Increased gene expression of NK cell-related cellular receptors and effector molecules has been detected in granzyme, perforin, and interferon gamma (IFNγ) cells. Reduced responsiveness of NK cells to in vitro stimulation and an imbalance between inhibitory and activating NK cells were also found in ASD patients' NK cells. Furthermore, NK cells from people with ASD are more active.[47,62-66]

NK CELLS

The innate immune system heavily relies on NK cells, which make up about 15% of circulating lymphocytes.[67] They have cytolytic activity and interact with dendritic cells to mediate cellular cytotoxicity and immune surveillance. In autoimmune disorders, imbalances between activation and inhibitory states may play a role; however, the specific underlying mechanisms still are uncertain. The roles of NK cells in the pathogenesis of neurological disorders such as multiple sclerosis, schizophrenia, Tourette syndrome, and Rett syndrome have also been defined. In fact, autistic folk's peripheral blood has been shown to include higher total numbers of NK cells (161 cells µL versus 117 cells/µL).[68-73]

MICROGLIA

Microglia, the brain's resident innate immune cells, are CNS tissue macrophages that keep track of brain homeostasis. They are known to play a role in the pathogenesis of neuropsychiatric disorders, such as ASD. Microglia plays a role in synaptic and neuronal development, as well as stem cell proliferation regulation during brain development. Microglia become more involved in various parts of the brain, particularly the cerebellum, in

autistic children.[17,74-78] The role of microglia in the pathophysiology of ASD includes changes in the activity, density, and morphology of microglia cells verified by in vivo neuro-visual tests of the human brain, neuropathological studies on postmortem tissue, and various experimental mouse models.[79,80]

AUTO-ANTIBODIES

According to some studies, ASD is triggered by a wide number and variety of antibodies. Glial filament proteins, serotonin receptors, nerve growth factor, brain peptides, brain neurotrophic factor, brain endothelial cells, serotonin receptors, and mitochondria are among the targets of these antibodies. During the inflammatory process, autoantibodies to CNS proteins can cross the blood-brain barrier and disrupt the neuronal stimulant/inhibitor balance, resulting in behavioral changes.[14,81-93] The presence of maternal IgG antibodies against fetal brain proteins has been associated to ASD and low language scores.[94] Autoantibodies were detected in approximately 10-12% of children with ASD, compared to none in the control group.[87] Animal models support the role of maternal IgG antibodies in ASD-like pathogenesis.[95]

CYTOKINES

One of the immune hallmarks of ASD is an increase in pro inflammatory cytokines and a decrease in anti-inflammatory cytokines (TGF-, IL-10). In fact, it's important because it regulates the balance of pro inflammatory and anti-inflammatory cytokines. ASD is related to abnormal levels of these molecules in a variety of complex disorders.[44,47,61,96-103] Cytokines have been shown to impact neuronal and glial cell development as well as behavioral phenotypes. Multiple members of the broad cytokine family are required for proper brain development, synaptic flexibility, and injury responses, according to various articles. Neurons, astrocytes, and microglia all produce cytokines, and abnormalities in their levels have been associated to neurodevelopmental disorders. Increased IL-6 levels in the brain due to glia activation are related to impaired neuroanatomical processes and altered synaptic plasticity. Some cytokines such as IL-1β and tumor necrosis factor-a (TNF-α) induce neurotoxicity through increased glutamate synthesis resulting in neuronal excitotoxic death.[16,104] IL-5, IL-8, IL-13, IL-17, IL-12, IL-21, and IL-22 were all reported to have significant levels.[105]

THE EFFECT OF IL-17 ON ASD MECHANISM

The inflammatory cytokine IL-17 is the first member of a new family of cytokines. Although IL17's proinflammatory properties are essential for the host's ability to protect itself, unrestricted IL-17 signaling has been linked to immunopathology, autoimmune disease, and cancer progression.[106] CTLA-8 was discovered in a screening of genes specifically expressed by murine T cells in 1993, making it the first member of the IL-17 family. In 1995, it was known as Cytokine and given the name IL-17. In fact, the cytokines in this family are not classical interleukin, but they show some similarity to neurotrophin, a protein class belong to a unique cysteine knot family.[107-111]

IL-17 is the most frequently studied member of the IL-17 family of cytokines, containing six members, named IL-17A through IL-17F. IL-17E is an inhibitor of IL-17 function and has very little homology with IL-17. T-helper 17 (TH17) cells are known for producing IL-17, but other innate and adaptive immune cells, such as CD8+ T cells, γδ T cells, innate lymphoid cells, and NK cells, can also produce it. There are five subtypes of the IL-17 receptor (IL-17R) family, varying from IL-17RA to IL-17RE. Since the multi-chain receptors IL-17RA and IL-17RC are expressed in nearly all cell types, IL-17 mediates a variety of local and systemic effects. Activation of IL-17RA and/or IL-17RC signal up regulates many inflammatory genes, including pro-inflammatory cytokines or neutrophil-specific chemokines. IL-17 has an important function in host defense against extracellular pathogens, including fungi and bacteria, as well as in the development and chronicity of inflammatory diseases. Although IL-17 is only generally active on its own, it cooperates with other mediators such as TNF, IL-1β, IFN-γ, and granulocyte-macrophage colonization factor (GM-CSF) to generate additive or synergistic effects. The molecular mechanisms of these synergistic interactions with IL-17 seem to differ depending on cell target. As a result, the cytokine microenvironment can play a significant role in IL-17-mediated effects.[112-116]

When the predicted amino acid sequences of IL17A and other members were matched, it was discovered that IL17A and IL-17F had the highest overall amino acid sequence identity (50%), whereas IL17A and IL-17F had only 10 to 30% sequence identity. They have the greatest similarity of the C-terminal 70 amino acids and have 4 well-conserved cysteines. The crystal structure of IL-17F has been

recently determined. The 4 conserved cysteines in the C-terminal half of the IL-17F sequence have been shown to form a crystalline cysteine node, and has been seen in a variation of growth factors, such as bone morphogenic proteins, TGF, nerve growth factor, and platelet-derived growth factor. It tends to be a typical structural pattern. Furthermore, while IL-17F is assumed to form disulfide-linked homodimers, other members of the IL-17 family are expressed as dimers that are closely related.[110]

Increased oxidative inflammation of autistic children's peripheral monocytes is induced by activation of the IL-17 receptor. Various neurodevelopmental disorders affect millions of children, and ASD is one of them, with its related behavioral abnormalities, presents a significant obstacle to a normal lifestyle. The expression and release of the Th17-related cytokine IL-17A is increased in ASD, according to several reports. Through the use of the IL-17A receptor, IL-17RA, which is expressed on immune cells (such as monocytes) in autistic children, IL17A can enhance neuroinflammation. Increased oxidative stress plays a role in a number of neuropsychiatric disorders, including ASD. However, it has never been investigated if the IL-17A/IL-17RA signal contributes to oxidative inflammation in autistic children's monocytes. Furthermore, in vitro activation of the IL-17 receptor by IL-17A in ASD monocytes results in increased iNOS expression through the NF-κB pathway. In vitro, treatment with an anti-IL-17RA antibody reversed the IL-17A-induced rise in NF-κB and iNOS/nitrotyrosine expression in monocytes isolated from ASD patients. Increased IL-17A / IL-17RA signaling in ASD patients is associated with increased oxidative inflammation in monocytes, according to some indications. As a result, IL-17 receptor signaling in monocytes will enhance the effects of IL-17A released by other immune cells, exacerbating neuroinflammation in people with ASD.[117]

THE EFFECT OF IL-18 ON ASD MECHANISM

IL-18 is an inflammatory cytokine produced mainly by activated microglia in the brain.[118] It belongs to the IL-1 family and is also known as IL-1 or interferon-inducing factor (IGIF). In 1989, IL-18 was first identified in the serum of mice following intraperitoneal endotoxin injection as the 'IFN inducing factor'.[119] It has a similar structure to IL-1b and utilizes IL-1 receptor system and signal transduction pathway members.[120] IL-18, a pro-inflammatory cytokine, exerts its various effects on immunity, inflammation, tumor growth and tissue repair through induction and production of interferon, chemokines, growth factors, and inducible NO (iNOS) synthase. The skin, intestines, and bone marrow are all high in IL-18. IL-18 mRNA is also detected in the brain, which is interesting. Lipopolysaccharide (LPS) stimulates IL-18 secretion from astrocytes and microglia, and IL-18 concentrations in the brain are elevated during ischemia, suggesting that IL-18 plays a role in the brain.[121-125] When IL-18 binds to its receptor in the CNS, a complex intracellular cascade activates the transcription factor NF-casB. IL-18 can stimulate both Fas and Fas-L promoter functions by NF-κB activation, suggesting that it may be one of the apoptosis-inducing factors contributing to neurodegeneration. IL-18 can also modulate neuronal excitability, and IL-18, such as IL-1β and TNF-α, inhibits long-term potentiation (LTP), a form of neuronal plasticity both believed to underlie learning and memory.[126-129] IL-18 has been attributed to the occurrence of neuropathological modifications in various neurodegenerative disorders, including Alzheimer's disease.[130] Inflammatory processes can contribute to various aspects of neurodegeneration, and IL-18 can increase the synthesis of toxic inflammatory molecules such as IFN- and IL-1, which can lead to a vicious circle in which inflammatory processes contribute to different aspects of neurodegeneration [131]

Cytokines are produced by neurons, astrocytes, and microglia, and abnormalities in levels have been reported in association with neurodevelopmental disorders.[104] ASD is a neurodevelopmental disorder characterized by repetitive and stereotypical behaviors and impaired social communication.[132] Activated microglia and astrocytes drive inflammation in the brain, leading to an overproduction of inflammatory cytokines and other inflammatory molecules, as well as an increase in reactive oxygen species (ROS).[133] As both neuroinflammatory processes and the increased immune response seen in ASD produce high levels of cytokines in the brain, these proteins may affect behavior.[134]

IL-18 is associated with several inflammatory disorders affecting both cellular and humoral immunity. The presence of a naturally occurring IL-18 binding protein with a high affinity balances the activity of IL-18 (IL-18BP). Increased disease severity in humans has been related to an imbalance of IL-18

to IL-18BP, resulting in higher levels of circulating free IL-18. The production of IL-18 has been utilized in different brain regions, especially in activated microglia. IL-18 has been shown to increase amyloid production by human neuron-like cells that affect the production of amyloid precursor protein (APP), resulting in increased A production and APP levels in autistic patients' brains.

IL-18 is produced in different parts of the brain, including the hippocampus, hypothalamus, and cerebral cortex, where several receptor isoforms have been discovered. It plays a significant role in central nervous system development, and also synaptic plasticity, glutamate release, and postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor responses, according to some theories. Previous research has suggested that high levels of IL-18 in the brain can cause motor and cognitive dysfunction, as well as a debilitation of long-term enhancement, impairing learning and memory. The increase in IL-18 levels in ASD patients was associated to previous research results and concluded. However, further research is required to determine the cause of the rise in IL-18 in the brains of ASD patients, as the number of subjects studied was small due to the difficulty of sampling postmortem tissue from autistic children, particularly autistic patients.[118,131,135-140]

Conclusion

ASD is a neurological condition caused by the degeneration of a complex neural system. As a result of the neural system's deformity, people with ASD have a variety of symptoms. These diseases manifest themselves at a young age. Individuals with ASD have been documented to have immune system dysfunction as well as a neuroinflammatory process. Since immune system dysfunction is associated to neurological dysfunction, it's possible that it's related to nervous system cell sensitivity. Although the biological cause of ASD is unclear, studies show that genetic, epigenetic, and environmental factors all play a significant role.

The disease affected by immune system dysfunction is one of the most common views and effects of ASD. In this regard, both the innate and acquired (specific) immune systems are believed to have an effect on their arms, neuronal development, behavioral patterns, and cognitive movements. There is communication between the immune system and the CNS from fetal development to adulthood, and dysfunctions in this communication affect various immune system functions. ASD was also induced by the abnormal activation of MIA by maternal auto-antibodies, according to research. It has been reported that this irregular activation during fetal development affects the CNS, and the irregularity of neural development is a risk factor for ASD. Essentially, the effects of various interrelated factors can trigger the irregular activation of MIA. When a pregnant woman is exposed to an infection, an inflammatory immunity environment is developed, and molecules such as maternal cytokines and chemokines that can cross the placenta are triggered, thus directly crossing the placenta and affecting the fetal development in the fetal section. The purpose of this study is to examine and demonstrate the impact, roles and functions of IL-17 and IL-18, which are pro-inflammatory cytokines, on ASD mechanism.

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