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- Review -

Investigating the Role of Microglia in Maternal Immune Activation in Rodent Models

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Epidemiological studies suggest that maternal infection, maternal stress, and environmental risk factors during pregnancy increase the risk of brain development abnormalities associated with cognitive impairment in the offspring and increase susceptibility to schizophrenia and autism spectrum disorder. Several animal models have demonstrated that maternal immune activation (MIA) is sufficient to induce abnormal brain development and behavioral defects in the fetus. When polyinosine:polycytodylic acid (poly I:C) or lipopolysaccharide (LPS), which is commonly used in maternal immune activation animal models, was introduced into a pregnant dam, an increase in pro-inflammatory cytokines and microglial activity was observed in the offspring's brain. Microglia are brain-resident immune cells that play a mediating role in the central nervous system, and they are responsible for various functions, such as phagocytosis, synapse formation and branching, and angiogenesis. Several studies have reported that microglia are activated in MIA offspring and influence offspring behavior through interactions with various cytokines. In addition, it has been reported that they play an important role in brain circuits through interactions with neurons and astrocytes. However, there is controversy concerning whether microglia are essential to brain development or lead to behavioral defects, and the exact mechanism remains unknown. Therefore, for the potential diagnosis and treatment of brain developmental disorders, a functional study of microglia should be conducted using MIA animal models.

Key words : Autism spectrum disorder, maternal immune activation, microglia, microglial activation, neurodevelopmental disorder

Neurodevelopmental disorder

The human brain contains approximately 86 billion neurons and a similar number of glial cells such as microglia, astrocytes, and oligodendrocytes [1]. In humans, neuronal generation begins in the mid-first trimester of gestation in the ventricular zone, and cells migrate to their destination [1]. Cells of the nervous system function cooperatively through elaborate interconnections, receiving signals from the body and relaying responses to them to the body [27]. However, during nervous system development, neuronal and glia cell dysfunction from the molecular level to the circuit level, has serious consequences [3]. Neurodevelopmental disorders (NDDs) are defined as a set of conditions that occur during nervous system development and cause defects that result in a various dysfunction. Also, NDDs are known to be caused by medical or genetic conditions or environmental factors. NDDs include intellectual disability (ID), communication disorder, autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), and neurodevelopmental movement disorders, including tic disorders and specific learning disorders [34]. Although the incidence rate is increased, the diagnosis and treatment of NDDs are not known. Thus, more research is needed in various fields such as the exact cause of the disease and the development of therapeutic agents (Fig. 1).

Maternal immune activation

Numerous epidemiological studies over the past few decades have reported that maternal infection with various infectious agents during pregnancy increases the risk of NDDs. Maternal infection with rubella [11, 47], influenza virus [50], *Toxoplasma gondii* [36], and various other pathogens [10, 46] increases the incidence of complex neurologic dysfunc-

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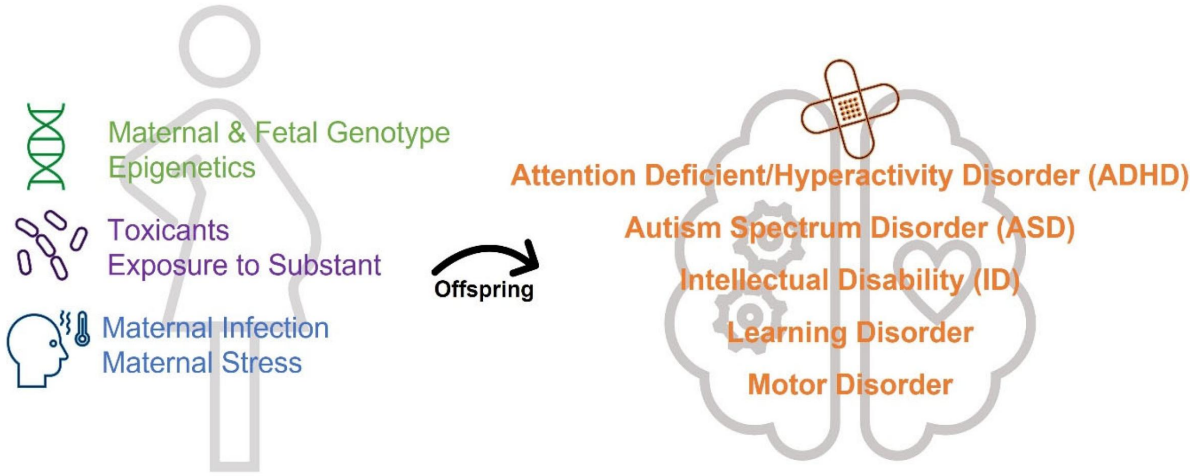

Fig. 1. Fetal outcomes according to maternal health. The offspring exposed to maternal immune activation during pregnancy encounter lifelong health issues. Viral infections, maternal stress, and environmental factors during pregnancy can cause schizophrenia, autism spectrum disorder, ADHD, movement disorders, and other neurodevelopmental disorders.

tion. Factors that can lead to abnormal immune system activation during pregnancy, such as diabetes [30, 43] and certain genetic risk mutations [23, 48], also reportedly to cause maternal immune activation, which is associated with neurological dysfunction in offspring. It was recently reported that maternal stress during pregnancy [8], maternal obesity [9, 30], and environmental damage that can induce inflammation, such as pesticides [19] and exposure to pollutants [40], act as additional risk factors for neuropathology in the offspring (Fig. 1).

In general, NDDs studies with maternal immune activation (MIA) use different rodent models, including immunogen type, timing, and dose. For the induction of MIA, it uses two of the most widely used immune stimulants, the virus-mimetic polyinosine:polycytodylic acid (poly I:C) and the bacterial-mimetic endotoxin lipopolysaccharide (LPS), which inhibits the activation of toll-like receptors (TLRs) 3 and 4, respectively, releasing inflammatory cytokines such as interleukin -6 (IL-6) and tumor necrosis factor-α (TNF-α) [12, 21, 37, 41]. The offspring with MIA show behavioral abnormalities such as communication deficits, sociability impairment, and repetitive behaviors [15]. Furthermore, abnormal maternal immune activity can reportedly lead to fetal immune system dysfunction [44]. Abnormal immune activity during development may interfere with neurodevelopmental processes by influencing microglial development [24, 49]. Recently, several studies have identified the role and function of microglia in MIA rodent models, however, the exact mechanism of microglia's function in MIA is still lacking. This review examines the functions of microglia that have been identified to date so far and the need for accurate functional verification of microglia in MIA.

Microglia

Microglia are immune cells that reside in the central nervous system (CNS). Microglial precursors derived from the yolk sac invade the brain parenchyma, differentiate into immature microglia, and migrate throughout the brain in a synchronized time- and region-dependent pattern [17]. Microglial colonization occurs concurrently with neurogenesis and has the unique ability to assist and direct prenatal neurodevelopment.

Microglial activation includes the expression of activation markers, increased production and secretion of pro- and anti-inflammatory cytokines and chemokines, changes in morphological appearance, and non-immunological functions including the regulation of neurogenesis, myelination, and synaptic remodeling. Thus, microglia thus play important roles in neurodevelopmental processes, including proper neural connectivity and the establishment of brain homeostasis [32].

Abnormal microglial activity can alter neurodevelopment by contributing to behavioral and neural deficits observed in NDDs [2, 7, 20, 45]. However, although many MIA studies provide insight into the role of microglia in neuroinflammation, some studies have reported heterogeneity depending on study design, microglial markers, and detection methods. Therefore, it is necessary to understand the function of microglia in order to identify the function and role of microglia in NDDs using MIA animal models. This review pro-

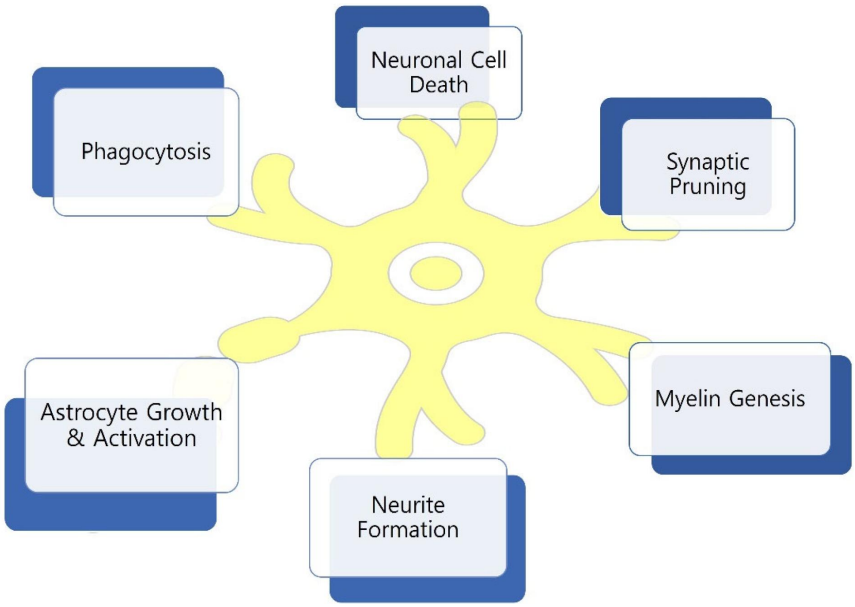

Fig. 2. The role of microglia in the brain. Microglia, which function as immune cells in the brain, play an important role in brain development through various roles such as phagocytosis, synaptic pruning, and myelin genesis.

vides only a local overview of the major role of microglia in recent rodent models of MIA, thereby contributing to future studies of microglial function in MIA models (Fig. 2).

Transcriptional analysis of microglia in MIA

It was pathophysiological observed that 2-3 years old ASD patients showed more primary microglia than branched microglia, and gray matter, while significant microglial activation was observed in the white matter [35]. Single-nuclear RNA sequencing studies revealed the increased activity of genes involved in microglial activation, along with transcription factors that regulate the developmental process of microglia in patients with ASD [29].

Virally induced MIA significantly perturbed the fetal microglia transcriptome and functional profiles, resulting in different phenotypes according to brain region and sex. These temporal disturbances disrupt neural circuit formation and/or function, resulting in abnormal social behavior. The transcriptional analysis of microglia in several MIA mice showed transient elevations in cellular and inflammatory CNS markers, as well as microglial density and amoebic morphology, however, contradictory findings were immediately resolved by postnatal expression despite a lack of microglia priming [18, 31, 45]. Therefore, the microglial activation in brain development diseases through the MIA rodent model should be verified.

Microglial pruning

Synapse formation begins during development and is responsible for the formation and strengthening of synapses between neurons [20, 52]. Early synapses that form in the developing brain are overproduced, which regulate the proper formation and function of many circuits through synaptic pruning. Less active synapses are actively eliminated whereas more active synapses are preserved and strengthened. The microglia contribute to synaptic pruning and are involved in neural circuit formation. Several studies have characterized various feeding signals on dendritic spines and axon terminals that are recognized by the microglia and induce the swallowing of weak or unnecessary neural processes, as well as the functional role of microglia in synaptic refinement and plasticity [13, 25, 39]. This suggests the ability of microglia to sculpt neural circuits, but it has not yet been directly demonstrated.

An incorrect number of synapses in certain regions of the CNS can alter proper circuit function. The network dysfunction and abnormal behaviors seen in ASD can reportedly be overproduced in cortical neurons, altering the balance between excitatory and inhibitory neurons [14, 53]. Therefore, synaptic pruning by microglia has been reported in some MIA, but the exact mechanism has not been identified. Future *in vivo* studies using microglia-specific manipulations in MIA animal models, conditional knockout/animal experiments, and circuit analysis of circuit function are needed to strengthen the support for the concept of microglial fragmented neural

circuits.

Microglia in angiogenesis

Microglia are found near blood vessels in the developing brain, suggesting that they contribute to angiogenesis during neurodevelopment. Factors released from microglia stimulate vascular sprouting and branching *in vitro*. Nestin labeling has been observed in cells of the vascular system indicating vascular plasticity in the auditory cortex of ASD patient. Moreover, neovascularization was observed throughout the superior temporal lobe (primary auditory cortex), fusiform cortex (face recognition center), pons/midbrain and cerebellum in postmortem brains of patients with ASD [5, 38]. However, significant increases in both nestin and CD34, markers of angiogenesis, were confined to pericytes and endothelial cells, respectively. As a result of examining the transcriptional profiles of MIA, genes related to hypoxia and angiogenesis are reportedly induced, and involved in neovascularization blood vessel formation in the brain [4]. However, whether microglial activation supports angiogenesis, which microglia-releasing factors can stimulate angiogenesis, and whether additional signaling mechanisms are at play during neuronal development remain unknown.

Microglial phagocytosis

Microglia directly phagocytose live neural progenitor cells, and actively induce apoptosis or cell survival by secreting reactive oxygen species (ROS), nerve growth factor (NGF), and cytokines [6, 16, 22]. However, the functional consequences of these actions remain unknown. The behavioral and neuropathological phenotypes of the offspring were reportedly alleviated by the administration of minocycline, an inhibitor of microglial activation, in MIA offspring [33]. However, it is unclear whether the therapeutic effect of minocycline is primarily due to its direct effect on microglial activation. Therefore, further research is needed to identify the definite therapeutic effects of ASD through microglial phagocytosis.

Microglia and IL-17A

The induction of maternal IL-17A by infection during pregnancy with certain microbes residing in the maternal gut reportedly interferes with the brain and immune development of MIA offspring [15, 28]. When E14.5 embryos were injected with recombinant IL-17A (rIL-17A), distinct clustering of microglia and an increase in the number of CD68-expressing microglia in the subventricular medial cortex were observed [42]. These results suggest the possibility of modifying the ability of microglia to support phagocytosis and cortical genesis in response to IL-17A stimulation. Furthermore, a specific receptor on microglia (G protein-coupled receptor 56, GPR56) is reportedly a molecular target of MIA, affected by IL-17A signaling [52]. However, studies of the effect of IL-17A signaling on microglial function are lacking.

Other functions of microglia

In addition, numerous studies have investigated microglial phenotype in MIA models to correlate microglia activity with brain and behavioral abnormalities. However, studies have inconsistently detected microglia with altered phenotypes, and others did not detect changes in microglial biology in prenatal MIA-exposed offspring. Additionally, according to on study, colony stimulating factor 1 receptor (CSF1R) ablation of microglia by targeted disruption of key macrophage survival factors has no apparent effect on other CNS cell populations. Moreover, these macrophage conditional knockout mice did not demonstrate vision or hearing deficits, suggesting that key neural network formation and function were not affected by microglial loss in the brain [26]. This study demonstrated that microglia could accomplish a variety of essential neurodevelopmental processes (i.e., angiogenesis, phagocytosis of cells and debris, synaptic pruning, etc.), but in their absence, other cell types are equally competent and effective. This presents an achievable concept. Nonetheless, this does not negate the essential role of microglia during normal neurodevelopment in which these cells normally exist and function.

Conclusions

Microglia constitute a significant proportion of brain cells throughout life and are important in both healthy and pathological conditions. It is necessary to identify their roles in brain development and functioning. Many studies have highlighted the diversity of microglial functions in the developing brain and their potential roles in understanding and treating brain developmental disorders. Therefore, as it is necessary to present suggestions/guidelines to improve the consistency of the field of microglia research in MIA, to identify their function.

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The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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역학 연구에 따르면 임신 중 산모의 감염, 산모의 스트레스, 환경적 위험 요인이 태아의 인지 장애와 관련된 뇌 발달 이상 위험을 증가시키고 정신분열증 및 자폐 스펙트럼 장애에 대한 감수성을 증가시키는 것으로 나타났다. 여러 동물 모델은 모체 면역 활성화(MIA)가 태아와 자손의 비정상적인 뇌 발달 및 행동 결함을 유발하기에 충분하다는 것이 입증되었다. 모체 면역활성화 동물 모델에는 흔히 바이러스 모방 Poly I:C 또는 박테리아 유래물질 LPS 등을 임신한 어미에 도입시킴으로서 모체 면역이 활성화되며, 친염증성 사이토카인이 증가하고 자손의 뇌에서 미세아교세포 활성이 관찰되었다. 미세아교세포는 중추신경계에서 중재 역할을 하는 뇌 상주 면역 세포이다. 미세아교세포는 식균 작용, 시냅스 형성 및 분지, 혈관 신생과 같은 다양한 기능을 담당하는 것으로 알려져 있다. 여러 연구에서 미세아교세포가 모체면역활성화 자손에서 활성화되어 있고, 다양한 사이토카인과의 상호작용을 통해 자손 행동에 영향을 미침이 보고되었다. 또한 신경세포와 별아교세포와의 상호작용을 통해 뇌회로에서도 중요한 역할을 담당한다. 그러나 미세아교세포가 뇌 발달 및 행동 결함에 필수적인지에 대해서는 논란이 있으며 정확한 메커니즘은 아직 알려지지 않다. 따라서 뇌 발달 장애의 잠재적 진단 및 치료를 위해서는 모체면역활성화 동물 모델에서 미세아교세포 기능 연구의 필요성이 더욱 요구되고 있다.