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The Relationship Between Maternal Immune Activation and Autism Spectrum Disorder

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Abstract

Maternal immune activation (MIA) has been linked to higher incidence of autism spectrum disorder (ASD). As maternal inflammation has been associated with viral infection and environmental stressors, much research has been dedicated to studying these connections. However, even with the research dedicated to understanding the links between MIA and ASD, how inflammation causes ASD remains unclear. This review aims to summarize the research focused on understanding the links between autism and maternal inflammation during pregnancy. We will focus on defining maternal immune inflammation, understanding how it develops, and how it can lead to ASD. Finally, we will explore new research objectives for prevention and therapeutic intervention in MIA induced ASD. Bringing these ideas into a central article will highlight common themes in MIA/ASD research as well as bring new experimental avenues to the forefront of researcher's minds.

Keywords: Behavioral and Social Sciences; Neuroscience; Inflammation; Cytokines; Autism Spectrum Disorder; Maternal Immune Activation

1. Introduction

There is no current treatment for ASD, emphasizing the importance of exploring and suggesting new avenues of work for such. As more data is collected regarding ASD, we move closer to discovering an effective treatment. Accumulating evidence suggests that maternal immune activation (MIA) while pregnant puts offspring at higher risk to develop autism spectrum disorder (ASD). If MIA, defined as the reaction of the maternal immune system of a pregnant person to a pathogen, occurs during crucial stages of neurodevelopment, the offspring is more susceptible to developing a neuropsychiatric illness, such as ASD (Boulanger-Bertolus et al., 2018). MIA has been observed in various mammals ranging from humans to mice (Boulanger-Bertolus et al., 2018) (Choi et al., 2016), demonstrating the conserved nature of the phenomenon and allowing for in depth investigation into its causes. After countless studies of these MIA models, the scientific field has gained a better understanding of how MIA relates to ASD, how modern science can be used to target MIA and how to prevent ASD in the future. Here we will summarize the main theories behind MIA!s induction and it's connection to ASD.

2. Discussion

Much of the data surrounding maternal immune activation comes from human studies. MIA occurs in humans when an expecting mother is exposed to one or more pathogens (a disease-causing organism) (Boulanger-Bertolus, et al., 2018). When a pathogen is detected, the infected space becomes inflamed in an attempt to kill the identified threat. Inflammation is the body's reaction to an irritant. Inflammation usually includes redness, swelling and aching. The goal of inflammation is to eliminate all of the foreign substance (the pathogen) and to return the body to normal

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health. However, during this process, the body scans for all possible foreign substances, which could result in the fetus being accidentally targeted by a strong immune response (Boulanger-Bertolus et al., 2018). Considering the danger inflammation can pose to developing offspring, it is important to understand the types of exposures that can lead to MIA.

One exposure that has been found to induce significant levels of inflammation is viral infection. Some viruses commonly associated with MIA are Influenza, Coronavirus and Zika (CDC, 2022) (Marteleto, 2021). These viruses can produce serious symptoms such as fevers, rashes, vomiting, ultimately resulting in inflammation throughout various parts of the body. This type of viral-induced inflammation is thought to be related to changes in neurodevelopment. For example, between 2015 and 2017, the Zika outbreak was at its peak. Interestingly, at this time there was also a spike in fetal developmental deficits. In Brazil, almost 4,000 babies were born with congenita malformations such as difficulties talking, seeing, walking and eating. This suggests that Zika, a mosquito born disease, can cause numerous birth defects if caught during pregnancy. A more recent example of a maternal viral infection is COVID-19. A few months into the pandemic, pregnancy was added to the list of at- risk health conditions by the U.S. Centers for Disease Control and Prevention (Marteleto, 2021). Finally, the flu can also be damaging for a developing fetus. Similar to Zika and Coronaviruses, the flu can induce widespread inflammation that could result in neurodevelopmental damage (CDC, 2022). The inflammation present when contracting these three viruses is deemed dangerous for the fetus because of its possibility to lead to a developmental issue, and more specifically, ASD.

While viruses have been shown to induce MIA, other types of environmental factors can also induce inflammation. For instance, exposure to stress has been shown to induce inflammation. A study conducted at University of California Irvine (UCI) focused on the environment of the expecting mother and how it might relate to psychiatric disorders in the offspring (Boulanger-Bertolus et al., 2018). Teenage mothers in particular seemed prone to elevated inflammation levels, which in turn correlated with brain structure alterations. It was hypothesized that teenage mothers may be more vulnerable to stress (e.g., due to economic instability, unplanned nature of pregnancy, stigma), which could partly explain their increased levels of inflammation. The study showed that stress exposure directly correlated with neurodevelopmental issues (Boulanger-Bertolus et al., 2018).

The body's initial reaction to a detected foreign substance is called innate immunity. To initiate an antiviral immune response, the pathogens need to be detected and considered a threat (Lim, 2013). Toll-like receptors (TLRs) are a type of pattern recognition receptor (PRRs) whose primary purpose is to identify pathogen-associated molecular patterns (PAMPs) and trigger a defense response (Lim, 2013) (Sameer and Nissar, 2021). After identifying the pathogens, these membrane proteins induce inflammatory cytokines that will recruit immune cells to try to kill the virus (Lim, 2013). During pregnancy, a strong immune system is especially important because without it, the pathogen can destroy the fetus. A one study demonstrates, mice lacking TLR-4, a key PRR, were much significantly more susceptible to fetal loss and cognitive defects (Chan et al., 2021). These data suggest that TLR4 is essential for fetal development because without it, the fetus has lost an important mechanism of immune protection and becomes more exposed to various pathogens. However, as the immune system proceeds to attack the pathogens, the fetus may be affected because it might be mistakenly identified as a foreign substance in the body.

Despite inflammation being beneficial in infected regions, inflammation can also have long-term negative impacts on the brain of the offspring. Damien Fair and his research team conducted a study connecting inflammation to an increased risk of neurodevelopmental and psychiatric disorders (Brawley, 2018). The study included assessments of the memory and executive functioning skills in two-year old children that had been exposed to MIA in utero. Throughout each trimester of the pregnancy, Fair collected blood samples from each of the exacting mothers from which they measured the quantity of an inflammatory marker (Brawley, 2018). The results showed that less inflammation correlated with better memory scores and brain communication. This suggests that inflammation directly affected the neurodevelopment in the fetus.

While general inflammation has been found to be detrimental to neurodevelopment, this effect is primarily driven by cytokines. A cytokine is a protein that either triggers the immune system or slows it down, with each variation possessing a different job (Vinicius et al., 2018). To illustrate this, Fair's study highlighted the importance of IL-6 in negative inflammatory responses in the brain (Gabay, 2006). IL-6 is an interleukin cytokine released by macrophages, a cell type commonly associated with MIA. Interleukin cytokines specifically work to stimulate the immune system

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when necessary. Because of this, interleukins are commonly investigated in studies of MIA.

Another aspect of MIA and inflammatory responses that is under investigation is the environments that lead to IL-6 production. IL-6 is associated with both increased stress and neurodevelopmental problems. This was demonstrated in both Fair's study and the study examining teenage mothers. In both of these works, elevated IL-6 levels were associated with higher levels of stress exposure (Boulanger-Bertolus et al., 2018). The teenage mothers were shown to possess both higher psychosocial stress levels and IL-6 levels (Boulanger-Bertolus et al., 2018).

Thus, as mentioned above, the mothers with the most IL-6 exposure (mostly the teenage mothers) corresponded with the fetuses with more neurodevelopmental issues (Boulanger-Bertolus et al., 2018).

Another cytokine commonly associated with MIA is Interleukin-17 (IL-17), a cytokine released by Th17 cells. Similar to IL-6, this cytokine induces inflammation in response to invading pathogens. Neuroscientist Gloria Choi conducted a study on MIA in mice that examined how different exposures to pathogens and inflammation in utero impacted the developing offspring (Choi et al., 2016). Choi's study consisted of two groups of pregnant mice: a group injected with IL-17 inhibitors or a control group without IL-17 inhibitors (Choi, et al., 2016). The inflammatory levels present in each mouse was also recorded (Choi et al., 2016). After birth, the offspring of both groups were tested for behavioral changes that mimic symptoms of ASD such as abnormal communication, repetitive behaviors and social deficits (Choi et al., 2016). It was found that the pups born from mice injected with displayed in the mice without the IL-17 inhibitor injection, rather than with it (Choi et al., 2016). These results suggest that, like IL-6, IL-17 can also induce inflammation in a way that impacts ASD in offspring.

As important as cytokines have been shown to be in maintaining health, it is clear that in times of pregnancy, they can increase the risk of neurodevelopmental issues in utero. Since the interleukins are the cause of inflammation, they are the considered key contributors to MIA and a risk factor for ASD. The placenta, an organ that develops to provide nutrients to the fetus, acts as a shield for the developing child, however only to an extent (Boulanger-Bertolus et al., 2018). For instance, when cytokines induce inflammation in an expecting mother (MIA), they can pass through the placenta that is protecting the fetus (Han et al., 2021). After passing through the placenta, the exposure to the cytokine can alter the neurodevelopment of the fetus. As presented in Choi's study, the inflammation can cause cortical changes in regions of the brain controlling behavioral and cognitive abilities, possibly resulting in ASD (Figure 1) (Choi et al., 2016).

Considering the strong relationship between inflammation and neurodevelopmental issues, it is reasonable to consider cytokines and inflammation as a viable target for preventative ASD therapies. One possible approach to reducing inflammation is producing pregnancy safe immunosuppressants. Immunosuppressants are commonly used for organ transplants, autoimmune diseases, and other scenarios where an active immune system is detrimental (Han et al., 2021). The immune system's job is to keep the body safe and remove anything that is foreign. However, in cases of transplants or pregnancy, the immune system can do more harm than good. In the case of MIA, taking an immunosuppressant would reduce the strength of the immune system, allowing the fetus to be more protected from inflammatory cytokines.

Although an immunosuppressant may seem like a good solution, like most medications, there are possible risk factors. The most obvious issue regarding an immunosuppressant during pregnancy is whether or not it is pregnancy safe. Expecting mothers are cautioned to consider what medications they're taking in order to ensure safety for themselves and the fetus. Current research has limited information regarding safety for pregnant women, so immunosuppressants are not commonly prescribed during pregnancy (Han et al., 2021). However, some types of this drug, such as hydroxychloroquine can cross the placenta with no

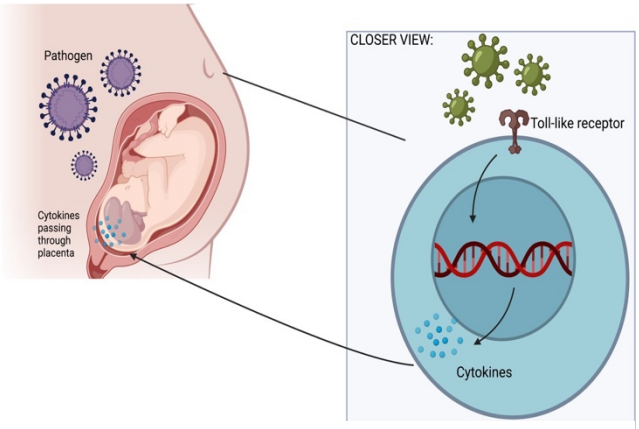

Figure 1. Graphical representation of maternal immune activation inducing cytokine expression through toll- like receptors. Figure made in Biorender.

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evidence of neurodevelopmental defects.

Even if the immunosuppressant is proven to be pregnancy safe, it might not be the best option for someone with a virus or autoimmune disease. The point of an immunosuppressant is not to lessen the strength of a specific action of the immune system, but to weaken the entirety of the immune system. This raises more health risks for the expecting mother because it also is reducing her ability to fight off any virus she may contract. A more specific approach is a cytokine inhibitor. A cytokine inhibitor can target specific cytokines and limit their ability to function. If this was directed towards an inflammatory cytokine associated with neurodevelopment impacts, such as IL-6 or IL-17, it could possibly reduce inflammation that could harm the fetus, while allowing the rest of the immune system to function properly.

3. Conclusion

Maternal immune activation in an expecting mother puts the fetus at higher risk for neurodevelopmental and neuropsychiatric disorders, such as autism. Some common MIA inducers are viral infections and stress. When these instances are detected in the body, inflammatory cytokines are released to help the body return to normal health. Although the inflammation may be helping the mother, it could also be attacking the fetus. Once MIA is induced, cytokines are capable of passing through the placenta and damaging the neurodevelopmental process of the fetus. However, MIA can be responsible for more neuropsychiatric disorders than just autism. For example, inflammation has also been associated with schizophrenia. Thus, work investigating the benefits of inhibiting detrimental inflammation during pregnancy could have a positive impact on a wide variety of disorders. Better understanding of the causes and outcomes of MIA on neuropsychiatric disorders is vital to the future of neurodevelopmental health. With the creation and utilization of new therapies targeting inflammation, science and medicine can continue to develop to better help and prevent neurodevelopmental disorders such as ASD.

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