Is $PM_{2.5}$ A Risk Factor for Autism Spectrum Disorders?

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Abstract

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by behavioral deficits, including cognitive learning and memory impairment, social communicationcommunication, interaction impairments, and repetitive behaviors. Since the etiology of ASDs is still largely unknown, there is no cure for ASDs so far. Genetic and environmental factors are known to contribute to this disorder. Accumulated evidence has shown that exposure to atmospheric particulate matters (PM) in the polluted air could affect neurodevelopment in different brain regions, thus causing ASDs in children. Particles with a size of 2.5 micrometers ($PM_{2.5}$) or less, generally coming from primary emissions (i.e., industrial activities and traffic) and secondary formation, have been shown to have negative impacts on human health, and possibly cause ASDs symptoms in children. This review summarizes evidence from both clinical and animal studies to demonstrate the possible linkage between $PM_{2.5}$ exposure and incidence of ASDs in children. An attempt is made to explore its possible mechanism, including changes in gene expression, and oxidative stress and neuroinflammation induced by $PM_{2.5}$ exposure.

Keywords: Autistic Spectrum Disorders; $PM_{2.5}$; Neuroinflammation; Oxidative Stress; Gene Expression

1. Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental conditions with heterogeneous etiology. ASDs patients display core behavioral deficits, including impaired social communication and interaction skills, repetitive behavior, and intellectual disability with widely severity among patients (Happé and Ronald, 2008; Lintas and Persico, 2009). Apart from the hindrance on the patient's physical and mental development, ASDs also adversely affect the daily life of the patient's family (Rao and Beidel, 2009). The prevalence rate of ASDs has been reported to be 1% - 2% according to numerous studies conducted in Asia, Europe, and North America, with a higher ratio in males than in females (4:1 ratio) (Elsabbagh et al., 2012). The wide range of the prevalence rate could be due to the awareness of ASDs, re-classification of ASDs, or improved detection (Faras et al., 2010). Previous twin studies have offered solid evidence showing genes contributing to the prevalence of ASDs. However, other studies reported the environment also plays a role in addition to the genetic influence on explaining the ASDs' phenotypes (Hallmayer et al., 2011; Tick et al., 2016). Other studies further deliberated on the importance of unfolding both the genetic and environmental factors for gaining understanding on the etiology of ASDs , which set the tone for this review paper.

Among the environmental factors, the increase in air pollutant in our living environment has been an emerging concern. Epidemiological studies have revealed that prenatal or postnatal long-term exposure to hazardous air pollutants is potentially linked to autism (Kalkbrenner et al., 2010; Roberts et al., 2013; von Ehrenstein et al., 2014; Windham et al., 2006). Ambient air pollutants, such as nitrogen dioxide (NO_2) and particulate matter (PM), could adversely affect neurodevelopment (Costa et al., 2017; Genkinger et al., 2015; Jedrychowski et al., 2015b; Suades-Gonzalez et al., 2015; Volk et al., 2013a). In particular, exposure to PM with sizes less than 10 microns (PM_{10}) and/or 2.5 microns ($PM_{2.5}$) could double the risk of autism (Volk et al., 2013a). $PM_{2.5}$ contains polycyclic aromatic hydrocarbons, metals, organic matter and elemental carbon, which is potentially neurotoxic. The neurotoxic contents can induce inflammation, generate reactive oxygen species (ROS), and alter gene expression, that could contribute to the occurrence of ASDs (Fortoul et al., 2015; Jedrychowski et al., 2015a).

Along with $PM_{2.5}$, PM_{10} and NO have been linked to the increasing prevalence of ASDs. Multiple studies showed that PM_{10} has no correlation with the increased risk of developing ASDs (Chen et al., 2018a; Chen et al., 2018b; Chun et al., 2020). Despite some studies showed prenatal exposure to NO_2 is positively correlated with the incidence of ASDs (Ritz et al., 2018; Volk et al., 2013a), other studies reported no correlation between NO_2 and ASDs (Becerra et

al., 2013; Raz et al., 2015). The contribution of NO_2 to ASDs is still controversial.

This review summarized the recent findings on $PM_{2.5}$ as a risk factor for ASDs with evidence from clinical and animal studies. The possible underlying mechanisms induced by $PM_{2.5}$ are also discussed.

2. Behavioral abnormalities in ASDs patients

The updated diagnostic criteria for ASDs are based on behaviors rather than biomarkers. According to the Diagnostic and Statistical Manual of Mental Disorders (5^{th} edition) (DSM-V), the diagnostic manual of the American Psychiatric Association, and the 10^{th} revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) by the World Health Organization, individuals with ASDs are to demonstrate three core deficits: social impairment, communication difficulties, as well as rigid and repetitive interests and activities (Silverman et al., 2010). The DSM-V includes the symptoms and exhibited behavior along a severity continuum, and there are several diagnostic types put under the umbrella of ASDs, i.e., autistic disorder, Asperger's disorder, childhood disintegrative disorder, and the catch-all diagnosis of pervasive developmental disorder not otherwise specified. Atypical social communication and interactions can be classified as a lack of interest in others, and reduced eye contact and facial expressions during communication. Individuals withASDs may have poor language comprehension and responses. Besides, repetitive behaviors are common such as repeated body movements, usage of objects and flailing of arms. These signs and symptoms may present before the age of two and affect daily functioning (Association, 2013). Rodent models of ASDs display certain behavioral abnormalities that are comparable to the behavioral phenotypes of ASDs in human patients, including social interaction and communication impairments, as well as repetitive behaviors (**Table 1)**.

3. Brain abnormalities in Individuals with ASDs

Behavior abnormalities could be associated with brain structural changes in terms of the total brain volume in individuals with ASDs. At birth, infants with ASDs were found to have a lower total brain volume than healthy infants, but follow by an overgrowth within the first year of life (Redcay and Courchesne, 2005). Up till the age of four, the children diagnosed with ASDs showed a larger brain volume than their healthy controls(Aylward et al., 2002; Bailey et al., 1993; Courchesne et al., 2011). Progressing to the late-childhood, puberty and

adolescence, these children were reported to have delays in growth. Besides the total brain volumes, other neural adnormalities exist among the individuals with ASDs. For instance, the abnormalities are in the decreases in the grey and white matter in the lateral occipital lobe, pericentral region, medial temporal lobe, basal ganglia, and regions proximate to the right parietal operculum (Nickl-Jockschat et al., 2012). In contrast, there are increases in the grey and white matter in the parieto-temporal lobe and the cerebellum (Brambilla et al., 2003). Decreases in the brain volumes have been reported (Brambilla et al., 2003) in particularly in the thalamic region (Tsatsanis et al., 2003), the corpus callosum (Egaas et al., 1995), and the amygdala (Aylward et al., 1999; Nacewicz et al., 2006; Pierce et al., 2004). On the other hand, the increases in the size of the amygdala has been reported in in patients with ASDs (Abell et al., 1999; Howard et al., 2000). Although studies have reported no significant changes in the entire hippocampus (Haznedar et al., 2000; Howard et al., 2000; Sparks et al., 2002), the dentate regions have been reported decreases in their surface areas (Saitoh et al., 2001). Apart from individual neural substrates, there are reduced functional connectivities in the hippocampus among the individuals with ASDs(Cooper et al., 2017). As the hippocampus and amygdala are involved in social learning, cognitive functions, and emotional processing in humans (Aggleton and Brown, 1999; Matsumura et al., 1999; O'Neil et al., 2015; Phelps, 2004), these structural and functional abnormalities are likely to give rise to the ASD-related social behavior and social intelligence deficits.

Beyond the neural substrates, ASDs are characterized by neuronal loss and degeneration, and alterations in dendritic arbors in specific regions of the brain (**Table 2**). Neuronal loss has been found in the cerebellum (Bailey et al., 1998; Vargas et al., 2005), amygdala (Schumann and Amaral, 2006), fusiform gyrus (van Kooten et al., 2008), and pyramidal cells (Kern et al., 2013). A reduction in Purkinje neurons was identified in the cerebellum, which is essential in modulating a variety of cognitive and motor functions. Neuron degeneration has been reported in cerebrum (Casanova et al., 2006) and cerebellum (Fatemi et al., 2002), showing a decrease in cell size. Dendritic arbors are the branching of a neuron and the formation of new synapses along a neuron. The arborization of dendrites are critical for neuronal information processing as it directs the receiving signals from neurons to the cell body. Different ASDs showed varying types and degrees of adnormal arborization (Hutsler and Zhang, 2010; Martínez-Cerdeño, 2017). Martínez-Cerdeño (2017) reported a decrease in size and spine formation in neurons, but an increase in spines consisted of immature morphology.

4. Clinical evidence showing linkage between $PM_{2.5}$ Exposure and Risk of ASDs

Over the last decade, clinical studies have found that both prenatal and postnatal exposure to $PM_{2.5}$ could increase risk of developing ASDs in offspring (Becerra et al., 2013; Raz et al., 2015; Talbott et al., 2015; Volk et al., 2013b). The adjusted odd ratio in respect to $PM_{2.5}$ and other confounding variables measured in the study has indicated that prenatal and postnatal exposure to $PM_{2.5}$ could increase the risk of having children with ASDs (**Table 3**).

Prenatal exposure to $PM_{2.5}$ is associated with an increased risk of ASDs (Becerra et al., 2013). The study included 7603 children with ASDs, and 75782 children without ASDs in Los Angeles, California. The adjusted odds ratio for the ASDs is 1.15 per 4.68 $\mu g/m^3$ interquartile range increase of $PM_{2.5}$ exposure during the entire pregnancy period, suggesting that maternal inhalation of $PM_{2.5}$ increases the risk of ASDs in humans. Likewise, Raz et al. (Raz et al., 2015) confirmed that prenatal exposure to $PM_{2.5}$ could increase the risk of ASDs. The study involved 245 children with ASDs and 1522 children without ASDs from 14 different states in the United States. The adjusted odds ratio for ASDs during pregnancy per the 4.4 $\mu g/m^3$ increase of $PM_{2.5}$ is 1.57. Among the three trimesters of pregnancy, the adjusted odds ratio was the largest in the third trimester (1.42), followed by the first and second trimesters (1.06 and 1.00, respectively). These studies show convergent evidence that the exposure to $PM_{2.5}$ in the third trimester could lead to the highest risk of ASDs. Beyond the trimesters, Volk et al. (Volk et al., 2013b) revealed thatprenatal and postnatal exposures to $PM_{2.5}$ were associated with an increased risk of ASDs. With adjusting gender and ethnicity of the participants, and their parents' educational level, maternal age, and prenatal smoking, the adjusted odds ratios of ASDs for the 279 children with ASDs and the 245 control children without ASDs in California was was 2,08 (during entire pregnancy) to 2.12 (during first year of life) for the approximately 8.7 $\mu g/m^3$ increase in $PM_{2.5}$ concentration during the period. These results suggest that early-life exposure to $PM_{2.5}$ could increase the risk of ASDs as much as prenatal exposure.

Similarly, Talbott et al. (Talbott et al., 2015) reported that prenatal and postnatal exposures to $PM_{2.5}$ were associated with increased risk of ASDs. The adjusted odds ratio of ASDs per 2.84 $\mu g/m^3$ increase of $PM_{2.5}$ concentration during the second year of life was the highest (1.45), followed by the first year of life (1.37). The odds ratio of ASDs during the pregnancy (1.20) was relatively lower than the postnatal periods, while the differences in the odd ratios among the first (1.07), second (1.04), and third (1.04) trimesters were are not

significant. Taken together, the increases in the risk of ASDs associated with $PM_{2.5}$ are more significant during the postnatal than the prenatal periods consistent with those reported by Volk et al. (Volk et al., 2013b). A recent control case study conducted in China on the effect of $PM_{2.5}$ exposure during the first three years of infancy revealed consistent findings of increases in risk of developing autism (Chen et al., 2018b). The average odds ratio reported was 1.78 per 3.4 $\mu g/m^3$ increase of $PM_{2.5}$. The adjusted odds ratios reported in the postnatal studies are larger than those in the prenatal studies, indicating postnatal exposure to $PM_{2.5}$ may impose humans to a higher risk of developing ASDs than prenatal exposure. The convergent findings on the $PM_{2.5}$ exposure and risks of ASDs from the above studies should be interpreted with caution. The reason is that the composition of the $PM_{2.5}$ studied could have been different across the different countries or regions. The adjusted odds ratios of different studies are also calculated based on different $PM_{2.5}$ densities, possibly leading to difficulties in comparison (See **Table 3**).

Changes of brain structure induced by $PM_{2.5}$ exposure

4.1. Human studies

With the current understanding of ASDs, neuroinflammation, gene expression changes, and increase in oxidative stress have been postulated to be the possible contributors to brain abnormalities in ASDs. Power et al. (2018) found that long-term exposure to $PM_{2.5}$ is associated with reduced deep-gray volume, indicating that $PM_{2.5}$ might induce cumulative brain damage and atrophy. MRI was employed on subjects regularly to examine their brain structures. The monthly $PM_{2.5}$ exposure is predicted by validated spatio-temporal statistical models through participants' addresses. The concentration ranged from 0.02 to 0.1 $\mu g/m^3$. Their results showed an association between higher mean $PM_{2.5}$ exposure in the past 5 to 20 years and smaller deep-gray regional brain volumes. Furthermore, elderly women who reside in areas with high $PM_{2.5}$ levels showed a decrease in whole brain volume (Chen et al., 2017). The total white matter and grey matter of the frontal, parietal, temporal lobes, and corpus callosum showed a significant reduction. The association between $PM_{2.5}$ and the brain volume did not demonstrate a correlation to the sociodemographic factors, socioeconomic status, lifestyle factors, or other clinical characteristics. This suggests that postnatal exposure to $PM_{2.5}$ may act on the brain directly during the brain's early development to induce neurological changes, thus, inducing ASDs.

Mechanism of how prenatal exposure to $PM_{2.5}$ increases risk of ASDs. $PM_{2.5}$ may act directly or indirectly on the embryo. For direct action, the presence of black carbon particles of $PM_{2.5}$ in the placenta suggests that $PM_{2.5}$ can transverse from inhalation to the placenta (Bové et al., 2019). Due to the nature of $PM_{2.5}$ being potentially neurotoxic, $PM_{2.5}$ is also an agent for inducing a systemic and central inflammatory response. Maternal inflammation during the first trimester has been associated with an increased risk of ASDs (Atladóttir et al., 2010). It is possible that exposure to $PM_{2.5}$ could induce inflammatory cytokines, which can cross the placenta to the embryo, hich indirectly induce de novo inflammatory response in their offspring. However, further studies will be needed to examine the detailed underlying mechanisms.

4.2. Animal studies

Emerging animal studies have demonstrated that exposure to $PM_{2.5}$ can significantly induce neuronal atrophy in different brain regions. Transgenerational effect of $PM_{2.5}$ has also been shown, though the mechanisms are still largely unknown. Zhang et al. (2018) have shown that chronic intratracheal instillation with $PM_{2.5}$ at medium (1.56695 μg/μL) and high-dosage (3.456 μg/μL) during maternal pregnancy reduced number and diameter of neurons in the cerebral cortex of mice offspring. A high dosage of $PM_{2.5}$ exposure also reduced the number of presynaptic vesicles in the offspring mice, suggesting a detrimental effect of $PM_{2.5}$ exposure on synaptic plasticity in offspring brains.

Hogan et al. (Hogan et al., 2015) reported that mice exposed to $PM_{2.5}$ for the short-term displayed a significant reduction in total apical dendritic length in the CA1 region of the hippocampus. Consistently, Zhang et al. (Zhang et al., 2018) exposed mice to $PM_{2.5}$ at a dosage of 16.85 $\mu g/m^3$ using a mobile trailer exposure system for five days per week continuously for ten months. The results revealed that long-term exposure to $PM_{2.5}$ significantly reduced apical spine density in the CA1 region, decreased apical dendritic length, and dendritic complexity of pyramidal neurons in the CA3 region of the hippocampus. Since the hippocampus plays an important role in learning and memory formation and emotional control, these findings may support that $PM_{2.5}$ could impair learning and memory, and induce emotional dysregulation associated with ASDs, given that ASDs patients also have pathological changes in the hippocampus (Raymond et al., 1995).

5. Potential effects of $PM_{2.5}$ on inducing ASDs behavior

Emerging clinical studies have suggested the possible linkage between $PM_{2.5}$ exposure and the risk of developing ASDs. Recent animal studies with $PM_{2.5}$ exposure have also provided hints regarding the potential harmful effect of $PM_{2.5}$ on brain health and behavioral deficits resembling symptoms in ASDs patients.

Li et al. (2018) found that $PM_{2.5}$ exposure in young pups resulted in autistic-like behaviors. Experimental rats were subjected to intranasal instillation once daily during postnatal days 8 to 22 with two different dosages of $PM_{2.5}$ (2 μg or 20 μg/g of body weight). Results showed a significantly lower intensity of sound generated by $PM_{2.5}$-exposed pups through ultrasonic vocalization analysis. Pups exposed to 20 ug/g $PM_{2.5}$ also showed significantly less interaction time to stimulus rats and less sniffing time to social odors than unexposed groups, suggesting that exposure to $PM_{2.5}$ could induce communication and social interaction deficits in young pups. Besides, $PM_{2.5}$-exposed rats spent significantly less time exploring new objects than control animals in the marble burying test and novel object recognition test, indicating an increase in anxiety-like behavior and some form of learning and memory impairment. The results have supported the notation that $PM_{2.5}$ could reduce children's recognition memory and lead to novel avoidance as observed in autistic children (Davis III, 2014). In the test, fewer marbles were buried with an increased concentration of $PM_{2.5}$ exposure. Furthermore, the $PM_{2.5}$ exposed rats exhibited novelty avoidance, as indicated by the decrease of marbles buried in the test.

To study the effect of $PM_{2.5}$ on offspring during pregnancy, Zhang et al. (2018) reported that $PM_{2.5}$ induced autistic-like behaviors in offspring mice. Pregnant mice were subjected to 3 different concentrations of $PM_{2.5}$, specifically 0.2592 μg/μL (low-dose), 1.56695 μg/μL (medium dose) and 3.456 μg/μL (high-dose), every 3 days via intratracheal instillations. The results showed that the number and diameter of neurons decreased with increased doses of $PM_{2.5}$. However, only the medium and high doses demonstrated damage to ultrastructure of mitochondria, including broken and partly blurred mitochondrial cristae, fuzzy and broken nuclear membrane, and autophagic bodies. Moreover, the high dose group showed decrease in presynaptic vesicles in the synapses. With the increase in $PM_{2.5}$ dose, apoptosis incidence also increased, the expression of apoptotic proteins increased, namely Caspase-8, Caspase-9, and the Bcl2 / Bax expression decreased. Apart from apoptotic proteins, the protein associated with cell proliferation, i.e. PCNA, decreased in the cerebral cortex.

Moreover, neuronal damage and apoptosis was also observed in the Cornu Ammonis 3 (CA3) region of the hippocampus (Zheng et al., 2019). The behavioral analysis conducted using open field test and tail suspension test showed an increase in depression and anxiety-like behavior but a decrease in locomotor activity. Apart from these behavioral changes, further studies have shown that spatial learning memory was impaired in offspring mice (Zheng et al., 2019). This could be due to the neuroinflammation in the hippocampus induced by maternal $PM_{2.5}$ exposure, as indicated by the increase in NF-kB, TNF- α, and IL1β levels.

Church et al. (2018) studied the effect of prenatal and postnatal exposure to $PM_{2.5}$. From gestational day 1 to day 17, pregnant mice were exposed to 135.8 mg/m³ of $PM_{2.5}$ for 6 hours/day, followed by an additional postnatal exposure for 2 hours/day for ten days continuously. The control group was exposed to filtered air with a $PM_{2.5}$ concentration of 3.1 ± 1.04 μg/m^3. The behavioral analysis reported a reduction in sociability score in the social approach task in the $PM_{2.5}$ exposed group when compared to the control group. A sex-specific interaction in reciprocal social interaction was reported. Male offspring mice spent a significantly reduced time engaging in social interaction, with the total social time, anogenital sniff and body sniff for male offspring were affected by $PM_{2.5}$ exposure. Moreover, male mice spent significantly more time self-grooming than the control group. These data have suggested that $PM_{2.5}$ induced a decrease in sociability, social approach, and increase in repetitive behavior, which are similar to behavioral deficits observed in ASDs patients (**Table 4**).

6. $PM_{2.5}$ induction of neuroinflammation in ASDs

The immune system can be divided into innate and adaptive immunity, which have been both demonstrated to play a significance role in the neuroinflammation response to ASDs. Clinical studies have shown that individuals with ASDs differ in levels of inflammatory biomarkers. Vargas et al. (2005) has reported remarkable reactivity of astrocytes in the cerebral cortex, white matter and cerebellum of ASDs patients, as well as an increase in the volumes of perikarya and glial processes in the cerebral cortex, white matter, and cerebellum. These findings suggest an increase in astroglia reactions in these brain regions. Chhronic neuroinflammation has also been found in the post-mortem ASDs brains (Zantomio et al., 2015). The neuroinflammation was indicated by the increase in the number of microglia in the fronto-insular and visual cortices (Tetreault et al., 2012), the dorsolateral prefrontal cortex (Morgan et al., 2010), and the cerebellum (Vargas et al., 2005).

Aside from cellular changes, pro-inflammatory cytokines, interleukin- 1 beta (IL-1β), interleukin 6 (IL-6), Interleukin-8 (IL-8), T helper type 1 (th1), T helper type 2 (th2), Interferon gamma (IFN-γ), tumor necrosis factor – Alpha (TNF- α), and transforming growth factor beta 1 (TGF-β1), are also elevated in different regions of the brain and serum in ASDs patients (Al-Ayadhi, 2005; Ashwood et al., 2011; Basheer et al., 2018; Chez et al., 2007; Emanuele et al., 2010; Hu et al., 2018; Li et al., 2009; Molloy et al., 2006; Ricci et al., 2013; Suzuki et al., 2011; Tonhajzerova et al., 2015; Vargas et al., 2005; Wei et al., 2011; Xie et al., 2017) (**Table 5**). Levels of IL-1β is elevated in the frontal cortex (Li et al., 2009) and the serum (Al-Ayadhi, 2005; Ricci et al., 2013; Xie et al., 2017) of ASDs patients. While levels of IL-6 is elevated in the cerebellum (Vargas et al., 2005; Wei et al., 2011), mid-frontal (Vargas et al., 2005), cingulate gyrus (Vargas et al., 2005), frontal cerebral cortex (Li et al., 2009), and serum (Al-Ayadhi, 2005; Basheer et al., 2018; Ricci et al., 2013), and levels of IL-8 is increased in the frontal cerebral cortex (Li et al., 2009), cerebrospinal fluid (Vargas et al., 2005) and plasma (Ashwood et al., 2011; Suzuki et al., 2011; Tonhajzerova et al., 2015). Notably, IL-1β, IL-6 and IL-8 cytokines have been shown to be associated with behavioral impairments (Ashwood et al., 2011), suggesting that a dysfunction in the immune system could be responsible for the behaviors abnormalities in ASDs patients. Several of the th1 and th2 cytokines are evaluated to indirectly determine the activity of T-cell activity. Th1 cytokines, IL-2 and IFN-γ, are significantly increased in the cerebrospinal fluid (Vargas et al., 2005), while for th2 cytokines, increase in levels of IL-4 and IL-10 in the anterior cingulate gyrus (Vargas et al., 2005) and increase of IL13/IL10 and IFN-γ/IL-10 have been reported in the peripheral blood mononuclear cells (Molloy et al., 2006). The increased cytokines of th1 and th2 have suggested an increase in activation in the chronic adaptive T immune response. This is further supported by the skewed ratio of CD4+ and CD8+ cells (Gupta et al., 1998).

The immune cells and respective cytokines possibly alter the neurophysiology in the brain associated with ASDs. Activated microglial cells promote opsonization and phagocytosis as well as the release of pro-inflammatory cytokines (Giulian and Baker, 1986; Hanisch, 2002). Furthermore, since microglia aid in the development of the brain through cell death regulation, axonal guidance and synaptogenesis (Marín-Teva et al., 2011), excessive activation of microglia can induce cytotoxicity and neuronal cell death (Block and Hong, 2007; Lull and Block, 2010). On the other hand, sytokines may interact with the major histocompatibility complex class I (MHC I), which negatively regulates activity-dependent

synaptic pruning and formation (Glynn et al., 2011; Shatz, 2009). Moreover, certain cytokines, such as IL-1, IL-6 and TNF- α, induce hypothalamic-pituitary-adrenal (HPA) axis activation. The HPA axis regulates the secretion of adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), arginine vasopressin, and corticosterone which can regulate neuroplasticity of the brain (Fenoglio et al., 2006).

$PM_{2.5}$ exposure is known to induce neuroinflammation in the corpus callosum (Babadjouni et al., 2018). Its exposure can increase levels of microglial cells activation, TNF-α, nuclear factor kappa B (NF-κB), IL-1β, IL-6, macrophage chemoattractant protein-1 (MCP-1) **(Table 6)**. There were also increases in the number of microglia in the fronto-insular and visual cortices, dorsolateral prefrontal cortex, and cerebellum (Babadjouni et al., 2018; Lovett et al., 2018; Wang et al., 2019; Zheng et al., 2019). Increases in activated microglia is known to adversely affect the normal development of neuronal connectivity. Introduction of $PM_{2.5}$ exposure in neonatal cord blood can reduce the number of CD3+, CD4+ and CD8+ cells, and increase in CD19+ cells, which are markers for T cells and B cells in the adaptive immune system (Hertz-Picciotto et al., 2005), suggesting changes in immune response with exposure to $PM_{2.5}$ in neonatal stage. Similarly, Liu et al. (Liu et al., 2016) found that introducing 15 mg/kg of $PM_{2.5}$ during pregnancy of Sprague–Dawley rats significantly increased peripheral blood mononuclear cells, platelets, and IL-6 when compared to the control group rats. The increase in cytokines and immune cells suggests an increase in local immune response, leading to neuroinflammation. Likewise, intranasal administration with two dosages of 2 μg and 20 μg of $PM_{2.5}$ per body weight (in gram) once daily from postnatal day eight to 22 significantly increased the proinflammatory cytokines IL-1b and TNF-α levels in the hippocampus and prefrontal cortex (Li et al., 2018). Apart from the cytokines, GFAP and Iba-1 are also significantly increased in the $PM_{2.5}$-exposed group when compared to the control group. Interestingly, prenatal but not postnatal exposure to $PM_{2.5}$ significantly decreases expression of several proinflammatory cytokines including TNF-α, IL-1β and IL-6 (Chen, 2017) in the hypothalamus. Similarly, Chao et al. (2017) found that the white blood cell count was increased drastically after $PM_{2.5}$ intratracheal instillation to 6-8-weeks-old pregnant rats. Taken together, $PM_{2.5}$ exposure could induce neuroinflammation as a possible mechanism underlying behavioral deficits. The effect of $PM_{2.5}$ on neuroinflammation has been summarized in **Table 7**.

7. Changes of gene expression by $PM_{2.5}$ exposure in ASDs

With a recurrence rate of ASDs being higher for monozygotic twins than dizygotic twins (Sandin et al., 2014), it has been suggested that genetic mutation may contribute to the pathogenesis of the development of ASDs. Numerous clinical studies have reported genes associated with synapses (Durand et al., 2007; Spinelli et al., 2015; Swanberg et al., 2009b), brain development (Cotney et al., 2015), and inflammation (Bos et al., 2012; Ljubimova et al., 2018) to be dysregulated or undergone mutations in ASDs patients (see **Table 8**).

With regards to synaptopathology of ASDs, a mutation in Shank3 (Durand et al., 2007), FMR1 gene (Crawford et al., 2001), MECP2 (Goffin et al., 2012; Swanberg et al., 2009b) and PTEN (Spinelli et al., 2015), dysregulation in EGR2 (Swanberg et al., 2009b) has been reported. Shank3 is a synaptic scaffolding protein predominantly found in the postsynaptic region of excitatory synapses. It encodes for neuroglia in dendritic spines (Durand et al., 2007), regulating the connection of macromolecular postsynaptic signaling complex at glutamatergic synapses (Peca et al., 2011), thus playing important roles in the formation, maturation, and maintenance of synapses. The FMR1 gene is located on the X chromosomes and codes for the fragile mental retardation protein (FMRP). The ability of the FMRP to bind to the ribosomes, ribosomal RNA and mRNA suggests that the protein is involved in the nucleocytoplasmic shuttling of mRNA, localization of dendritic mRNA, and synaptic protein synthesis (Antar et al., 2005). Autistic patients have amplification of over 200 CGG repeat in the 5' untranslated region (Crawford et al., 2001). MECP2 is essential for brain development and is involved in the regulation of protein synthesis. MECP2 protein binds on the 5-mc region of the Methyl-CpG-binding domain (MBD), suggesting it as regulator of protein synthesis via DNA methylation. PTEN gene codes for a protein/lipid phosphatase that inhibits cellular survival and proliferation via the PI3k/AKT/mTOR signaling pathway (Liu et al., 2019). Through the pathway, PTEN modulates neuronal growth and synaptic function (Liu et al., 2019). EGR2, encoding a zinc transcription factor, plays an important role in forming the hindbrain development and is an important factor in peripheral myelination, synaptic plasticity, and long-term potentiation (Swanberg et al., 2009a).

A marker for overall DNA mutation, Alu, has been investigated with perinatal PM2.5 exposure cohort study in the placenta. Very few studies have focused on the alteration of the genetic expression so far. It was reported that an increase in exposure of $PM_{2.5}$ was associated with increased Alu mutation rate in the placenta (Neven et al., 2018). There is in

lack of studies examining the effect of *de novo* gene mutation following chronic $PM_{2.5}$ exposure. $PM_{2.5}$ exposure could potentially alter the methylation of DNA, resulting in an altered protein expression. Generally, DNA methylation of the promotor region of the protein acts a repressor of expression. Breton et al. (2016) reported that perinatal $PM_{2.5}$ exposure was associated with lower global methylation levels. In another perinatal cohort study, $PM_{2.5}$ exposure increases methylation in the regions of APEX1, ERCC4, p53 while reduces methylation of DAPK1 (Neven et al., 2018). APEX1 and ERCC4 are involved in DNA repair and hypermethylation of these two genes downregulates DNA repair (Mollica et al., 2016). Similarly, hypermethylation of P53 leads to inhibition of expression of P53 protein expression via the ROS-Akt- DNMT3B pathway, leading to apoptosis, senescence and autophagy (Zhou et al., 2016; Zilfou and Lowe, 2009). DAPK1 gene codes for the death-associated protein kinase 1 (DAPK1) regulate programmed cell death and autophagy. However, placenta DNA samples were used in these studies, changes of methylation may not reflect tactual changes of gene methylation in the infants.

Rodent studies have also reported that long-term exposure to $PM_{2.5}$ is able to change gene expression in the brain (see **Table 9**). Li et al. (2018) have reported that intranasal instillation with high dose of $PM_{2.5}$ once daily from postnatal day 8 to 22 significantly downregulated Shank3 gene, suggesting the potential of $PM_{2.5}$ to alter gene expression in ASDs offspring. In addition, other genes including EGR2, IL-13, IL-16, RAC1, COX2 (cyclooxgenase-2), NOS2 (nitric oxide synthase-2), NOS3 (nitric oxide synthase-3) and NFE2L2 (nuclear factor erythroid-derived 2 like-2) are also found to be dysregulated after exposure to $PM_{2.5}$. Ljubimova et al. (2018) found that $PM_{2.5}$ exposures for 1 to 3 months triggered the expression of EGR2, a gene encoding inflammatory cytokine pathways IL-13-Rα1 and IL-16 and the oncogene RAC1. The increased expression of inflammation and cancer-related biomarkers in the rat brains has been suggested to be the synergistic effects of metals and toxins present in $PM_{2.5}$. The inhibition of the RAC1/Atk pathway can alleviate the inflammatory profile induced by $PM_{2.5}$ (Zhang et al., 2019), suggesting its involvement in $PM_{2.5}$-altered gene expression.

Moreover, mice with postnatal $PM_{2.5}$ exposure display increased genes expression involved in inflammatory response COX2, NOS2, NOS3, and NFE2L2 in the hippocampus (Bos et al., 2012). COX2 is a gene that is responsible for the production of prostaglandins, which contributes to the inflammatory process (Simon, 1999). NOS2 is an enzyme that continuously produces high levels of nitric oxide, which is involved in the regulation of

many inflammatory cell types e.g. macrophages, neutrophils, mast cells, T lymphocytes and natural killer cells (Guzik et al., 2003). Moreover, NFE2L2 is a transcription factor responsible for redox regulation by activating antioxidant response element and upregulating genes associated with antioxidant defense (Fitzpatrick et al., 2011). Bos et al. (2012) found that $PM_{2.5}$ exposure for 5 days in mice increases the expression of oxidative stress genes, disrupting the equilibrium in oxidative stress (ROS) system.

Chao et al. (2017) reported prenatal exposure to $PM_{2.5}$ alters the gene expression of Golgin, RAB6 Interacting (Gorab), Myelin Associated Oligodendrocyte Basic Protein (Mobp), 3-Oxoacid CoA-Transferase 1 (Oxct1) and Lin-28 Homolog B (Lin28b), which are responsible for an increase in astrocyte migration, encephalomyelitis and decrease in cell mitosis and differentiation in rat hippocampus, respectively. With expression changes of gene that regulate neuronal development and differentiation due to inhalation of $PM_{2.5}$, these data have indicated the possible contribution of $PM_{2.5}$ induced gene expression in relation to the brain changes in ASDs patients.

8. Oxidative stress in ASDs patients

Oxidative stress is defined as an imbalance in the equilibrium between the production of reactive oxygen species (ROS) and the ability of the ROS defense system to detoxify the ROS and mitigate the damage. The ROS includes superoxide (O^{2-}), hydroxyl, peroxyl, alkoxy, and nitric oxide (NO) free radicals (James et al., 2004b). Some endogenous enzymes, xanthine oxidase (XO), NO synthase, and monoamine oxidase (MAO), can directly produce ROS, while another set of endogenous enzymes, superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px), may neutralize the ROS (Kellogg and Fridovich, 1975; Vendemiale et al., 1999). The production of ROS results in the initiation of liquid peroxidation (McCORD and Day, 1978). Excessive production of glutathione could lead to an imbalance in the ROS system equilibrium (Perry et al., 2004). The imbalance with overproduction of the ROS can damage DNA and/or protein in cells and consequently disrupt cellular signaling and induce cell apoptosis. Changes in oxidative markers including glutathione, glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), malondialdehyde (MDA), nitric oxide (NO) and 3-nitrotyrosine (3-NT) are observed in ASDs patients (Chauhan et al., 2012; Chauhan et al., 2004; James et al., 2004a; Meguid et al., 2011; Rose et al., 2012; Sajdel-Sulkowska et al., 2011; Sogut et al., 2003; Yorbik et al., 2002), suggesting that increase in oxidative stress could contribute to abnormalities of

neurodevelopment in autistic patients. Autistic patients display significantly lower levels of GSH in the cerebellum and temporal cortex than healthy control groups (Chauhan et al., 2012; James et al., 2004a; Rose et al., 2012). Glutathione peroxidase (GSH-Px) is an antioxidative enzyme, which catalyzes the conversion of hydrogen peroxide (an oxidant) to water, by using reduced glutathione (GSH) and reduced NADPH. GSP-Px was also found to be significantly lower in autistic patients than in healthy individuals (Meguid et al., 2011; Sogut et al., 2003).

SOD is also an antioxidative enzyme that catalyzes the dismutation of superoxide radical into oxygen molecule or hydrogen peroxide. It has been reported that autistic patients show significantly lower serum levels of SOD (Meguid et al., 2011; Yorbik et al., 2002). However, contradictory results are also reported by Sogut et al. (Sogut et al., 2003) showing no significant changes in SOD levels in ASDs patients.

With respect to increased levels of oxidative markers, it was reported that MDA (Meguid et al., 2011) and NO (Sogut et al., 2003) levels were significantly elevated in the clinical studies. Nitric oxide is well-known for its role in the development and function in the nervous system as it can behave as a ROS, as well as a neurotransmitter in the peripheral and central nervous systems (Picón-Pagès et al., 2019). Nitric oxide reacts with superoxide anion to generate peroxynitrate anions. These anions can produce 3-nitrotyrosine by tyrosine nitration. Sajdel-Sulkowska et al. (2011) reported an increase of 3-NT in patients with ASDs in the cerebellar hemispheres, vermis, orbitofrontal cortex, Wernicke's area, putamen and pons. The changes in oxidative markers in ASDs patients are summarized in **Table 10**.

9. $PM_{2.5}$ induction of oxidative stress

Several animal studies have suggested an imbalanced ROS defense system induced by $PM_{2.5}$ exposure (**Table 11)**. $PM_{2.5}$ exposure can decrease activities of antioxidant enzymes in rats (Wang et al., 2015). In the study, the activity of superoxide dismutase (SOD) significantly decreased in rats exposed to $PM_{2.5}$ when compared to the control group. Additionally, the activity of glutathione peroxidase (GSH-Px) significantly decreased in high-dose group, compared to the control group. Three dosages of $PM_{2.5}$ were instilled into rats' trachea in different groups twice per week for a total of three weeks. The activities of SOD and GSH-Px were reduced with increased dosages in a dose-dependent manner by intranasal instillation with $PM_{2.5}$ at the dosage of 0.2 (low dose), 0.8 (medium dose) and 3.2

mg (high dose) in rat.

In the study by Li et al. (2018), it was reported that the activity of an antioxidant enzyme decreased, while the oxidative stress marker increased after exposure to $PM_{2.5}$. The antioxidant enzyme SOD was significantly decrease in the group with highest dosage of $PM_{2.5}$ exposure when compared to the control group. Moreover, the NO level significantly increased in the two groups with higher dosages of $PM_{2.5}$ exposure. A positive correlation between $PM_{2.5}$ dose and NO was also found, whereas a negative correlation was found between levels of SOD and $PM_{2.5}$ dose. In line with the findings of Wang et al. (Wang et al., 2015), the findings have suggested the potential effect of $PM_{2.5}$ exposure on damaging the antioxidant defense system. In summary, findings from these studies have shown that $PM_{2.5}$ exposure decreases the activity of antioxidant enzymes and increases oxidative stress., suggesting that $PM_{2.5}$ may be a contributor to ASDs partly through the impairment of antioxidant defense system.

Conclusions

With the emergence of clinical and animal data, there has been an increase in the association between perinatal exposure to $PM_{2.5}$ and the increased risk of developing ASDs. Clinical studies have demonstrated an increased risk of developing ASDs if the mother stays in high $PM_{2.5}$ polluted areas during prenatal or in the first two years of the infant's life. However, the studies have been conducted on a limited demographic area. The potential of $PM_{2.5}$ to induce ASDs could be three ways, (1) maternal inhalation of PM2.5 during pregnancy leads to the $PM_{2.5}$ to pass through the placenta, (2) maternal inhalation of $PM_{2.5}$ induces systemic inflammation, which causes developmental changes in the embryos with increased inflammatory cykotines (3) infants $PM_{2.5}$ inhalation during the first two years of life which can enter the brain directly or induce neuroinflammation indirectly. It is understood that inhalation of $PM_{2.5}$ perinatally or postnatally induces neuroinflammation, oxidative stress and changes of gene expression. These changes may be the underlying cause of the brain structural changes, leading to ASDs. Increase in the non-specific and specific immune system has been reported by inhalation of $PM_{2.5}$, which corresponds the post-mortem studies of ASDs patients. Similarly, inhalation of $PM_{2.5}$ alters oxidative stress markers' levels, namely GSH, GSH-Px, SOD, and NO, which in turn change the balance in the ROS defense system, leading to an increase in oxidative stress. Epigenetic changes with

hypermethylation in the genes responsible for DNA damage repair and apoptosis by exposure to $PM_{2.5}$ have also been reported . The change in methylation has reduced DNA repair and increased programmed cell death. Since msmost of the population in the same environment has been exposed to PM2.5. Still, not all infants develop ASDs, highlighting the possible gene and environment interaction in susceptible individuals who are more vulnerable to $PM_{2.5}$ induce changes. Maternal stress and inflammation during pregnancy have been noted to contribute to neurodevelopment disorders in offspring. Thus, it is uncertain if $PM_{2.5}$ is the sole cause of the disease, and further investigation is required to understand the causal relationship between $PM_{2.5}$ and ASDs.

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