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Medical Aspects of Disability

Advances in the understanding of cellular pathogenesis associated with Autism Spectrum Disorder

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Abstract

Autism Spectrum Disorders (ASD) are a group of heterogeneous neurodevelopmental disorders with an estimated worldwide prevalence of 1-2%. Although it is highly heritable, the contribution of environmental factors and risk associated genes on the aberrant brain development is not well understood. In this review, we summarise some of the key risk factors and explore ASD associated cellular pathology from the perspective of the four predominant cells in the brain; neurons, oligodendrocytes, microglia and astrocytes. Further, we discuss the contributions of the associated cellular pathology to the three common hypotheses of ASD. We highlight the major neuro-pathologies underlying ASD, however more research is needed to ensure appropriate and efficient therapies can be directed towards ASD.

Keywords: *Autism spectrum disorders, Neurodevelopment, Neural lineage cells, Genetics, Risk factors.*

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1. Introduction

Autism spectrum disorders (ASD) are a group of complex neurodevelopmental disorders characterised by deficits in social communication and interaction, restrictive and repetitive behaviours (American Psychiatric, 2013) and can also involve sensory abnormalities (Adamson, O'Hare, & Graham, 2006; Wiggins, Robins, Bakeman, & Adamson, 2009). Symptoms associated with ASD emerge during infancy and this disorder is most commonly diagnosed in early childhood. Due to better diagnosis, the prevalence of ASD has increased over the years (Baio et al., 2018; Idring et al., 2015), with recent reports suggesting that as many as 1 in 59 have ASD (Baio et al., 2018), with an estimated prevalence of 1 in 88 in the United Kingdom (Brugha et al., 2012). The ever-changing landscape associated with diagnosis and genetics of ASD has made it difficult to estimate the true prevalence in the population. ASD is more commonly diagnosed in males, with ratios suggesting around four times as much compared to females (Scott, Baron-Cohen, Bolton, & Brayne, 2002).

This article aims to briefly review the risk factors and genetics for autism spectrum disorders and will then go on to explore the contribution of neural lineage cells to the pathogenesis of this disorder.

2. Risk Factors Associated with ASD

It is now well established that ASD is caused by aberrant brain development, however the causal links are currently unknown. Although ASD is highly heritable, environmental factors also play a key role in the aetiology of these disorders.

2.1 Prenatal risk factors

Many risk factors have been associated with ASD both during the prenatal period and early infancy. Advanced maternal age of over 35 years has been commonly associated with an increased risk of the offspring developing ASD (D. Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009; Pinborough-Zimmerman et al., 2011; K. Williams, Helmer, Duncan, Peat, & Mellis, 2008), with some suggesting being over 30 years could also be a risk (Idring et al., 2014). Additionally, advanced paternal age has also been associated with increased risk (Ben Itzchak, Lahat, & Zachor, 2011). Furthermore, males are diagnosed earlier if they have older parents (Darcy-Mahoney et al., 2016). Demographic factors also have been implicated with increased risk for ASD, where people of Caucasian ethnicity seem to be at increased risk (Pinborough-Zimmerman et al., 2011).

Maternal obesity has been positively associated with an increased risk for ASD (Y.-M. Li et al., 2016). Low birth weight, defined as a newborn weighing less than 2500g (Blanc & Wardlaw, 2005) and prematurity (often associated with a low birth weight) have also been shown to contribute towards an increased risk of ASD (Ben Itzchak et al., 2011; Maramara, He, & Ming, 2014; K. Williams et al., 2008). Additionally, increased weight gain during pregnancy (D. A. Bilder et al., 2013; Windham et al., 2019) and poor nutrition (Geetha, Sukumar, Dhivyadeepa, Reddy, & Balachandar, 2019) have been linked to childhood ASD.

In addition to demographic and maternal factors, a range of obstetric complications have been associated with increased risk of ASD including fetal hypoxia (Burstyn, Wang, Yasui, Sithole, & Zwaigenbaum, 2011; Froehlich-Santino et al., 2014), high maternal blood pressure (Polo-Kantola et al., 2014) and respiratory distress (Froehlich-Santino et al., 2014).

Emerging studies looking at maternal mental health and high functioning ASD phenotypes show a positive association. Poor mental health, particularly depression and anxiety which have become increasingly prevalent during pregnancy (Heron, O'Connor, Evans, Golding, & Glover, 2004; Janssen et al., 2018; Lockwood Estrin et al., 2019), have often been associated with adverse effects on the offspring both physically and cognitively (Glynn et al., 2018; Kataja et al., 2019; Y. Liu et al., 2012; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Uguz et al., 2013). Both prenatal mental health (Hagberg, Robijn, & Jick, 2018) and the use of antidepressants, including the commonly prescribed selective serotonin reuptake inhibitors (SSRIs), during pregnancy have been associated with an increased risk of ASD (Gidaya et al., 2014; Hviid, Melbye, & Pasternak, 2013; Sujan et al., 2017)..

2.2 Environmental risk factors

Exposure to neurotoxins, malnutrition associated with sociodemographics and medication taken in pregnancy during the critical period of development can have an accumulative effect on the risk of

developing this neurodevelopmental disorder. Studies have shown that exposure to a number of toxicants in the environment increase the risk of ASD during the prenatal period and after birth, including pesticides, air pollutants, diesel, nitrogen dioxide and living in an urban environment (Chang, Cole, & Costa, 2018; Flores-Pajot, Ofner, Do, Lavigne, & Villeneuve, 2016; Kalkbrenner, Schmidt, & Penlesky, 2014; Lauritsen et al., 2014). However, one large cohort study suggested that only exposure to a small percentage of neurotoxicants were associated with increased risk of ASD (Talbott et al., 2015).

Increasing evidence has suggested that inflammation as a result of the physiological stress response due to maternal infection and immune activation is associated with an increased risk in the offspring developing ASD (Careaga, Murai, & Bauman, 2017). Maternal infections (Atladóttir et al., 2010; Visser et al., 2013) and influenza (Zerbo et al., 2013) during pregnancy and autoimmune diseases (Vinet et al., 2015) have been associated with increased risk and earlier diagnosis of ASD. Evidence has suggested that maternal immune activation leads to localised loss of inhibitory neurons (Shin Yim et al., 2017) and is associated with a certain profile of gut bacteria that promote inflammation (Caprioli, Pallone, & Monteleone, 2008; S. Kim et al., 2017). Gastrointestinal problems and altered gut microbiota in patients with ASD have also been reported (Finegold et al., 2002; F. Liu et al., 2019; Valicenti-McDermott et al., 2006; B. L. Williams, Hornig, Parekh, & Lipkin, 2012), with one study showing a positive association between ASD severity and gastrointestinal symptoms (Adams, Johansen, Powell, Quig, & Rubin, 2011).

In addition to the gut, nutrient deficiency has also been associated with ASD. Many studies have suggested a link between vitamin D deficiency prenatally and in children with autistic traits and ASD (Bener, Khattab, & Al-Dabbagh, 2014; Bener, Khattab, Bhugra, & Hoffmann, 2017; Vinkhuyzen et al., 2018). Maternal deficiency in many other nutrients including iron, zinc and vitamin B9 have also been associated with ASD (Nuttall, 2017).

3. Genetics Associated with ASD

The wide phenotypic variability of ASD along with twin studies suggest a strong association of genetics towards aetiology (Constantino et al., 2013; Ozonoff et al., 2011; Rosenberg et al., 2009).

Whole exome sequencing (WES) has been a powerful tool to highlight genetic associations with Autism. One such study suggested that all *de novo* changes (including missense mutations and copy number variations; CNVs) account for as much as 30% of ASD diagnoses (Iossifov et al., 2014). WES has discovered 11 *de novo* mutations in protein-coding genes including *FOXP1*, *GRIN2B*, *SCN1A* and *LAMC3* (O'Roak et al., 2011). A further large study utilising this method looked at data from almost 12,000 ASD cases and additional controls (Satterstrom et al., 2018). This study revealed 102 risk genes for ASD, 31 of which were novel. Whole genome sequencing has also uncovered *de novo* mutations associated with ASD, revealing that the majority of these mutations were paternally inherited, however clustered *de novo* mutations (within 20kb) were mostly maternally inherited and in close proximity to CNVs (Yuen et al., 2016).

Genome-wide association studies (GWAS) have been utilised to study large data sets to uncover *de novo* mutations, single nucleotide polymorphisms (SNPs) and CNVs associated with ASD. A recent large GWAS looking at data on 18,381 subjects with ASD and 27,969 controls highlighted five loci associated with increased risk of ASD in chromosomes 1, 7, 8 and 20 (Xia et al., 2013). Specifically, the genes linked to these loci included *PTBP2* (1p21.3), *SRPK2* (7q22.3), *SOX7*, *PINX1* (8p23.1), and *NKX2-2*, *NKX2-4* (20p11.23), *MACROD2* (20p12.1) (Grove et al., 2019), a number of which have been implicated in neurodevelopment. Additionally, SNPs in 1p13.2 including the *TRIM33* gene showed links with autism. Additionally, three genes essential for neuronal function; *CACNA1C*, *MECP2* and *PTEN* have also been associated with increased risk of Autism (Busch et al., 2019; J. Li et al., 2015; Wen et al., 2017).

A number of other GWAS studies have highlighted CNVs associated with an increased risk of autism. CNVs were found in over a quarter of patients with ASD in a Greek population, with the majority being deletions (Oikonomakis et al., 2016). Rare CNVs are higher in patients with ASD compared to controls (Pinto et al., 2010) with a gene enrichment analysis showing implicated genes were associated with neuronal development and function. Another study showed duplications at 1q21.1 and 15q11-13 and deletions at 16p11.2 and 22q11.21 were

associated with risk for ASD (Crespi & Crofts, 2012).

One study suggested a large number of SNPs in 5p14.1 to be associated with an increased risk of autism, however these did not reach genome-wide significance (Ma et al., 2009). A further study looking at this same region found strong associations in SNPs between the cadherin genes; CDH9 and CDH10 (K. Wang et al., 2009). A GWAS meta-analysis of patients with ASD and controls found a number of SNPs in genes at 10q24.32 showed genome-wide significance (Autism Spectrum Disorders Working Group of The Psychiatric Genomics, 2017). Genes in this implicated region are associated with a number of neurodevelopmental processes. Further, a small deletion consisting of five genes (*MVP*, *CDIPT1*, *SEZ6L2*, *ASPHD1* and *KCTD13*) in the 16p11.2 region were found to be associated with ASD suggesting a minimal deletion region for ASD risk (Crepel et al., 2011).

A table of specific gene functions is provided for genes discussed in this section (table 1).

Table 1

Physiological function of genes associated with increased risk of ASD

Gene	Specific gene function	Chromosomal location
Neurogenesis		
PTBP2	Crucial for axon development through alternative splicing (M. Zhang et al., 2019) and maturation of neurons (Q. Li et al., 2014).	1p21.3
EFA6	Involved in axonal transport and regeneration (Eva, Koseki, Kanamarlapudi, & Fawcett, 2017) and neuronal morphogenesis, particularly the development of dendrites (Sakagami et al., 2007; Sakagami, Matsuya, Nishimura, Suzuki, & Kondo, 2004; Sironi et al., 2009).	10q24.32
PITX3	Required for optimal development of Mesodiencephalic dopamine neurons (Kouwenhoven, von Oerthel, & Smidt, 2017; Le, Zhang, Xie, Li, & Dani, 2015).	10q24.32
KCTD13	Associated with the development of cortical neurons (Gladwyn-Ng et al., 2016) and synaptic transmission (Escamilla et al., 2017).	16p11.2
SEZ6L2	Seizure 6-like protein. Essential for the development of dendrites and neurites (Boonen et al., 2016; Yaguchi et al., 2017) and connectivity of synapses (Gunnersen et al., 2007).	16p11.2
MACROD2	Expressed in hippocampal neurons during development and may be involved in neurogenesis (Ito et al., 2018), although a physiological role has yet to be identified.	20p12.1
NKX2-2	Implicated in the development of dopamine neurons (Prakash et al., 2006), motor neurons (Clark et al., 2014; Jarrar, Dias, Ericson, Arnold, & Holz, 2015), interneurons and oligodendrocytes (Jarrar, Vauti, Arnold, & Holz, 2015; Zhu et al., 2014).	20p11.22
NKX2-4	Involved in neurogenesis of cortical (Shen et al., 2017) and hypothalamic (Manoli & Driever, 2014) neurons.	20p11.23
Synaptogenesis		
CHD9	Regulates synapses in the hippocampus (M. E. Williams et al., 2011) and has been implicated in chromatin organisation (Ooga et al., 2018).	5p14.1
CHD10	Involved in the regulation of E/I synapses (Smith et al., 2017).	5p14.1
SHANK2	Essential for synapse development and plasticity (Ha et al., 2016; Wegener et al., 2018).	11q13.3-q13.4
Inflammation		

CUEDC2	Implicated in inflammation (Man & Zhang, 2011).	10q24.32
NFκB2	Associated with a variety of immune responses (Cubillos-Zapata et al., 2014; Doyle et al., 2013) and inflammation (Yang et al., 2018).	10q24.32
MVP	Supresses inflammation through NF-κB signalling (Ben et al., 2019; Peng et al., 2016).	16p11.2
Cell death		
SPRK2	Regulates neuronal apoptosis through Akt phosphorylation (Jang et al., 2009).	7q22.3
SOX7	Implicated in inhibition of the Wnt pathway (Fan et al., 2018; C. Wang et al., 2015).	8p23.1
Other		
CDIPT1	Associated with endoplasmic reticulum stress (Thakur et al., 2011).	16p11.2

3.1. Neurexins and Neuroligins

The CNV syndrome 22q13.3 region associated with high incidences of ASD-like behaviour includes the *SHANK3* gene encoding a synaptic scaffolding protein (Durand et al., 2007; Phelan & McDermid, 2012). *SHANK3* binds to neuroligins (Meyer, Varoqueaux, Neeb, Oschlies, & Brose, 2004), which interact with neurexins to form glutamatergic synapses (Craig & Kang, 2007). A GWAS of the visual sensitivity phenotype associated with ASD showed a SNP in *PDZK1*, located at 1q21.1, was associated with increased sensitivity (Goodbourn et al., 2014). Further, PDZ domains have been shown to bind to the neuroligin *NLGN1* (Meyer et al., 2004). Both neurexins and neuroligins have been associated with ASD. *NLG1* and *NLG4*, but not *NLG3* and *NLG4Y* have been associated with autism (Ylisaukko-oja et al., 2005) with a drosophila model of deficient *Nlg2* and *Nlg4* showing abnormalities in social behaviour (Corthals et al., 2017). SNPs in *NRXN2* and *NRXN3* have been associated with increased risk of ASD (J. Wang et al., 2018), additionally missense mutations in *NRXN1* were found in two patients with ASD (Kim et al., 2008).

4. Contribution of Neural Lineage Cells in the Pathogenesis of ASD

4.1 Neurons

ASD is a disorder caused by aberrant neurodevelopment. The predominant cells in the brain, and thus most likely to be affected by adverse neurodevelopment, are neurons and glial cells. Neuronal research appears to be the main area of study in relation to ASD and a number of neuronal cells have been implicated in function, morphology, axon guidance and synaptic dysregulation, including immature neurons, pyramidal neurons located in the prefrontal cortex (PFC), mature cortical neurons, inhibitory neurons including GABAergic neurons and excitatory neurons.

Macrocephaly has been associated in a number of cases of autism (Courchesne, Carper, & Akshoomoff, 2003; McBride et al., 2010) and larger brain volume in patients with autism has also been reported (Aylward, Minshew, Field, Sparks, & Singh, 2002). The cause of macrocephaly is unknown, however it may be associated with the number, maturity and morphology of neurons. One study found that children with autism had significantly more neurons in the PFC which correlated with increased brain weight (Courchesne et al., 2011). The phosphatase and tensin homolog (*PTEN*) gene is clearly associated with macrocephaly in ASD (Goffin, Hoefsloot, Bosgoed, Swillen, & Fryns, 2001) with a brain organoid model harbouring a deletion of this gene showing an increase in proliferation of cells leading to large sized organoids (Y. Li et al., 2017). Conversely, it has been found that larger spine densities of pyramidal neurons are associated with a smaller brain size (Hutsler & Zhang, 2010). Whilst macrocephaly is more prominently reported in ASD, microcephaly can also occur in some cases (Fombonne, Rogé, Claverie, Courty, & Kruck, 1999).

Altered morphology of neurons has been reported in many ASD cases which may be related to the symptoms of autism. One study showed patients with autism have smaller pyramidal neurons in the PFC (Jacot-Descombes et al., 2012), an area implicated in social behaviour (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). Further,

altered morphology of neurons from human cases and animal models of ASD have been found in the amygdala (Jerzy Wegiel et al., 2015) and hippocampus (Griesi-Oliveira et al., 2015); areas both associated with the anxiety and emotional-related memory features of autism (Babaev, Piletti Chatain, & Krueger-Burg, 2018; Boucher, Mayes, & Bigham, 2012; Bowler, Gaigg, & Gardiner, 2014). A less-reported symptom of ASD is deficits in face processing (Davies, Bishop, Manstead, & Tantam, 1994; Grelotti, Gauthier, & Schultz, 2002; Joseph & Tanaka, 2003). One study found that neurons in the fusiform gyrus, an essential area for face processing (Kanwisher, McDermott, & Chun, 1997), were significantly less dense and reduced in number in brains from patients with autism (van Kooten et al., 2008). Further, overexpression of *SHANK2* in neurons; a gene associated with autism when defective, was associated with shorter and less neurites (Luo et al., 2019).

Mouse models are a useful tool for understanding the mechanisms by which neuronal morphology is altered in ASD and many studies have successfully recapitulated the key symptoms of autism including impaired social behaviour and repetitive behaviour. One mouse model exhibiting impaired social behaviour showed that the reduced spine pruning in pyramidal neurons found in post-mortem brains of ASD patients was likely to be caused by impaired autophagy as a result of defects in the m-TOR pathway (Tang et al., 2014).

It is not only altered morphology of neurons that has been implicated in ASD, but also deficits in migration and proliferation. Brains from patients with autism show defects in neurogenesis and migration of neurons (Jerzy Wegiel et al., 2010). Mouse models with *Shank3* knockout (KO) mutations, which have been associated with autism (Boccuto et al., 2013; Durand et al., 2007; Gauthier et al., 2009), showed decreased radial glial progenitor cells and immature neurons in the hippocampus (Cope et al., 2016). A number of mouse models have shown that an increase in early neurogenesis is associated with deficits in early maturity (Orosco et al., 2014) and morphology (Arranz et al., 2019). Further, an increase in proliferation of progenitor cells has been associated with decreased mature pyramidal neurons in a mouse model of CNV syndrome 16p11.2 deletion, harbouring the *MAPK3* gene (Pucilowska et al., 2015). Deficits in proliferation of cortical neurons have been shown in animal models of ASD, including a study looking at a knockdown of the autism-associated gene *Chd8* in primary cortical neurons (Xu et al., 2018). A well-established rat model found that reduced proliferation was due to overexpression of a gene targeting *Fzd3* and inhibiting the Wnt pathway (Yao, Huang, & He, 2019), inhibition of this pathway has also been associated with increased proliferation of neural progenitor cells through reduced transcriptional activity of β-catenin (Marchetto et al., 2017).

The identification of synaptic proteins controlling synapse formation and signalling implicated in ASD points towards synaptic malformation and dysfunction (De Rubeis et al., 2014). For example, mutations in synaptic neuroligin genes *NLGN3* and *NLGN4* have been associated with ASD (Jamain et al., 2003; Südhof, 2008). Mice with these deletions have been shown with synaptic defects (Gutierrez et al., 2009; C. Zhang et al., 2009). Mutations in synapsins (*SYN1*, *SYN2*, *SYN3*); a family of presynaptic proteins that regulate vesicle-mediated neurotransmitter release and neurites, have been found in individuals with autistic phenotypes, suggesting a potentially causative factor of ASD (Fassio et al., 2011). Primary neurons from *Syn1/2/3* triple-KO mice display a significant decrease in the number of synaptic vesicles (Fornasiero et al., 2012) and display impairments in social recognition tests and a decreased environmental interest; phenotypic of ASD (Greco et al., 2013; Ketzef & Gitler, 2012). The *SHANK3* gene strongly associated with ASD seems to confer its pathology through synaptic dysfunction. Neurons lacking in *SHANK3* are associated with fewer synapses, whereas overexpression of *SHANK3* results in more mature neurons with larger spines (Betancur, Sakurai, & Buxbaum, 2009). Furthermore, single-gene mutations associated with ASD such as fragile X syndrome (*FMR1*), tuberous sclerosis (*TSC1*, *TSC2)*, neurofibromatosis type-1 (*NF1*), Angelman syndrome (*UBE3A*), Rett syndrome (*MECP2*), and the *PTEN* hamartoma tumour syndrome seem to mediate their effect through synaptic dysregulation (Zoghbi & Bear, 2012). A recent study looking at the effect of the KO of *Rnf8*, linked to ASD, demonstrates a 50% increase in the number of synapses in cerebellar neurons (Valnegri et al., 2017). Taken together, it can be argued that synaptic

dysfunction plays a major role in the pathogenesis of ASD.

The excitatory-inhibitory (E/I) balance theory of autism has become increasingly of interest in recent years in an attempt to explain the wide range of symptoms and common pathologies associated with ASD including repatative behaviours, hyperactivity, anxiety and epilepsy (Rubenstein & Merzenich, 2003). Evidence from human patients has shown increased formation of excitatory synapses associated with increased IL-6 in the cerebellum of patients (Hongen Wei et al., 2011). A mixture of results have been found from studies using human induced pluripotent stem cells (hiPCSs) derived from ASD patients. Glutamate is the most abundant excitatory neurotransmtter in the brain (Fonnum, 1984) and decreased levels have been shown along with a reduction in synapses of neural progenitor cells (Marchetto et al., 2017) and mature neurons (Russo et al., 2018). Further, an increase in GABAergic neurons; responsible for the secretion of the main inhibitory neurotransmitter in the brain, has been found in neural progenitor cells (Marchetto et al., 2017) and telencephalic organoids (Mariani et al., 2015).

The well-established *Shank3* KO model has shown impaired morphology of inhibitory neurons with longer dendrites, but decreased spine and postsynaptic density (Peça et al., 2011) and down-regulation of a sub-type of inhibitory neuron (Filice, Vörckel, Sungur, Wöhr, & Schwaller, 2016), however another study showed that activity in both inhibitory and excitatory neurons was reduced (Huang et al., 2019). Further, mouse models have shown a decrease in a type of positive inhibitory interneuron (Pucilowska et al., 2015) and overproduction of excitatory neurons (Fang et al., 2014) in upper layers of the cortex.

The discrepancy between these findings could be explained by the different types of inhibitory and excitatory neurons in the brain. The *Mef2c* mouse model of autism that displays ASD-like symptoms including impaired social interaction showed a decrease in excitatory transmission and increase in inhibitory transmission in cortical neurons (Harrington et al., 2016). Further, a mouse model of autism involving the *Ib2* KO, associated with deficits in motor and cognitive function (Giza et al., 2010), showed increased excitability through enhanced neurotransmission from NMDA receptors (Soda et al., 2019). Another potential explanation is that the number of neurons do not always directly relate to the amount of inhbitory or excitatory nerotransmiter release, for example, a heterozygous KO of *Dyrk1a* shows ASD like-behaviours and increased number of both excitatory and inhibitory neurons, but only a significant increase in excitatory synapses (Arranz et al., 2019). Overall, these findings suggest a predominancy excitatory E/I balance could be a factor in the clinical phenotypes associated with ASD.

4.2. Oligodendrocytes

Oligodendrocytes are the only myelin-forming cells of the mamilian central nervous system. In humans, half of the brain is composed of white matter, which is predominantly made of myelin, and is 500% more abundant in comparison to mice (K. Zhang & Sejnowski, 2000). Oligodendrocyte pathology has been found in patients with ASD. Adults with ASD show significantly lower numbers of oligodendrocytes (Morgan, Barger, Amaral, & Schumann, 2014). Further, pathology has been found in the PFC; an area associated with social behaviour (Finlay et al., 2015; Franklin et al., 2017; Pirone et al., 2018) and increased expression of oligodendrocyte markers have been found in the hippocampus and PFC, but are significnatly decreased in density in part of the hippocampus (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). Brains from adult autistic patients have a lower amount of myelinated thin axons but an increase of medium thickness axons in the lateral PFC (Trutzer, García-Cabezas, & Zikopoulos, 2019) and increased myelination in the medial PFC (Carmody & Lewis, 2010). This evidence could explain some of the social abnormalities seen in ASD.

A number of genes and SNPs implicated in autism have been associated with oligodendrocytes. SNPs in the the *DUSP15* and *CD38* genes; involved in oligodendrocyte differentiation and development, have been found in children with autism (van Tilborg et al., 2018; Munesue et al., 2010; Hattori et al., 2017) and clearance of degraded myelin is also associalted with *CD38* (Roboon et al., 2019). Chromatin remodelers including *CHD7* and *CHD8* have been linked to ASD (Jiang et al., 2013; Xu et al., 2018). Loss-of-function *Chd7* is associated with reduced number of oligodendrocyte progenitor cells (OPCs) through apoptosis (Marie et al., 2018).

Further, this gene has downstream effects on many genes involved in cell surival, proliferation and apoptosis [54]. Gene expression studies have also shown increased expression of genes associated with oligodendrocytes in the cerebellum from patients with autism including *MBP, MAG, OLIG1, OLIG2* (Zeidán-Chuliá et al., 2016). Although contrasting results have been found in the BTBR mouse model of autism (H. Wei et al., 2016).

Prenatal hypoxia and inflammation are risks factors for ASD. One mouse model using both hypoxia and inflammation to cause diffuse white matter injury showed autism-like behaviour in the mice. Further, they showed impaired maturation of oligodendrocytes and delayed myelination (van Tilborg et al., 2018). This study supports the notion that presence of inflammation contributes towards abberant myelination during neurodevelopment. Abnormal myelination has further been confirmed in two other mouse models of ASD showing both deficits in deposition and thickness of the myelin sheath (Graciarena, Seiffe, Nait-Oumesmar, & Depino, 2019; H. Lee, Thacker, Sarn, Dutta, & Eng, 2019), with the latter showing decreased myelination in areas associated with social behaviour, potentially a result of imapired maturation of OPCs. On the contrary, another study looking into the effect of developmental myelination in a mouse model of Timothy syndrome, in which a gain-of-function mutation in the α1 subunit of the L-type calcium channel Cav1.2 gives rise to an ASD phenotype, was associated with an increase in the number of mature oligodendrocytes and myelination (Cheli et al., 2018). A recent study looking into the effect of *Cyfip1*; a critical gene in 15q11.2 deletion syndrome, demonstrate that deletion of this gene resulted in a decrease in the myelination in the corpus callosum and interfered with the learning abilit of rats (Silva et al., 2019). Taken together, dysregulation in oligodendrocyte differentiation and developmental myelination play an important role towards the pathogenic mechanisms of ASD.

4.3. Microglia

Microglia are the immune cells of the brain and are capable of producing and reacting to a range of immune responses by secreting cytokines (Hanisch, 2002). Brains from autistic patients show increased size, density, number and activity of microglia in the PFC (Morgan et al., 2010; Tetreault et al., 2012). Animal models focusing on neurodevelopment have shown abnormal microglial morphology and decreased density in the PFC (Sanagi et al., 2019). Additionally, a mouse model of 15q11-q13 duplication showed decreased amount of a microglia marker in the amygdala in early postnatal mice (Shigemori, Sakai, Takumi, Itoh, & Suzuki, 2015). *TREM2*, an immune receptor known to regulate the level of neurons by activation of microglia, has been shown to be downregulated in the autistic brain (Filipello et al., 2018). The study demonstrated that *Trem2* KO mice display altered sociability and was associated with repetitive behaviour. It is plausible that either deficient or too many microglia along with abnormal morphology cause some of the social and anxiety features of ASD.

Microglia activation is another event associated with ASD. Active microglia is commonly seen as a sign of inflammation in the central nervous system (Dheen & Charanjit Kaur and Eng-Ang, 2007). Brains from autistic patients show increased activation of microglia along with pro inflammatory markers in both brain and cerebrospinal fluid (Patel, Tsilioni, Leeman, & Theoharides, 2016; Suzuki et al., 2013; Vargas et al., 2005). Increased neurotensin has been found in some children with autism and this peptide was shown to activate microglia through stimulation of the m-TOR pathway (Patel et al., 2016). Further, rodents injected with a drug that increased microglial activation showed ASD-like behaviour (Zerrate et al., 2007). The glutamate receptor mGluR5; shown to decrease microglial activation (Loane, Stoica, Pajoohesh-Ganji, Byrnes, & Faden, 2009), has been shown to be significantly decreased in the brains of patients with autism accompanied by increase in pro-inflammatory markers (Chana et al., 2015). Research has shown that inflammation has an adverse effect on neurodevelopment (van der Burg et al., 2015). Together, these studies suggest that, at least in part, there is an inflammatory pathology in ASD.

Microglia may also have a role in the physical development of neurons. Evidence from brains of patients with autism have shown microglia exist in a much closer proximity to neurons in patients (Morgan et al., 2012). Whilst the phenotypical result of this interaction is unknown, research in other areas have shown microglia become close in

proximity to neurons when motor neurons are degenerating in a model of motor neuron disease (Toedebusch et al., 2018). Other studies have shown prolonged microglial-neuronal contact after damage, in particular with the synapses (Wake, Moorhouse, Jinno, Kohsaka, & Nabekura, 2009). This may be an attempt of synaptic pruning; an essential mechanism of neurodevelopment (Paolicelli et al., 2011), to counterbalance the increased neurogenesis seen in autism. On the other hand, it may suggest defective microglia activation in ASD. It has been shown that the communication between neurons and microglia and deficits in synaptic pruning results in impaired social behaviour and repetitive behaviours (Zhan et al., 2014); key features of autism. Another animal model of autism (*Atg7* deficient) shows an increase in the number and density of dendritic spines and increased immature synapses as a result of deficits in synaptic pruning by microglia (H. J. Kim et al., 2017). Research has also shown that brains of patients with autism have significantly higher expression of markers of microglia but neuronal markers are significantly decreased in the PFC (Edmonson, Ziats, & Rennert, 2014). This could suggest i) microglia are attempting to play a therapeutic role for defective neurons, ii) microglia themselves are defective and are causing neuronal harm, potentially through dysfunctional synaptic pruning. Furthermore, maternal immune activation; one of the risk factors for ASD, may potentially mediate its effect through microglial activation, which opens up an opportunity for immunomodulatory treatment options to rescue some of the associated phenotypes of ASD.

4.4. Astrocytes

Astrocytes are an integral part of the tripartite synapse (Eroglu & Barres, 2010) and play a key role in the regulatory control of synaptic function and plasticity, (Tewari & Parpura, 2016) which in turn play a key role in social behaviour and cognitive functions. Astrocytes have been less implicated in ASD compared to the three other major types of brain cells reviewed here (neurons, oligodendrocytes and microglia). This may be due to a reduced involvement in these disorders or a lack of research into the link between astrocytes and ASD.

Research has shown contrasting results in regards to astrocytes and ASD. In the cerebellum, one study reported increased GFAP (Laurence & Fatemi, 2005); a major marker of astrocytes, whereas another study showed a decrease of the astrocytic marker AQP4 (Fatemi, Folsom, Reutiman, & Lee, 2008) in brains of patients with autism. One explanation for these findings is the timing at which astrocytes may be more active during development. Earlier in development GFAP has been shown to be significantly increased, whilst expression decreased postnatally in the cerebellum (Vargas et al., 2005). This study further showed that whilst expression was decreased, there was an increase in protein, suggestive of post transcriptional modifications.

Brains of patients with autism have shown an increase in FMRP in astrocytes, a protein essential for normal cognitive function (Santos, Kanellopoulos, & Bagni, 2014), but a decrease in neurons combined with neuronal deficits in the cerebral cortex (Jarek Wegiel et al., 2018). This may suggest that astrocytes are less affected by ASD and may not represent an area where pathology is evident. In support of this, typical astrocyte morphology was seen in the dorsolateral PFC from patients with autism (T. T. Lee et al., 2017) and a mouse model inducible KO of *Glt1*; the glutamate transporter secreted by astrocytes, did not show deficits in social behaviour (Aida et al., 2015). On the other hand, one study showed *Fmr1* astrocyte KO mice had reduced expression of the excitatory protein *Glt1* in astrocytes and impaired glutamate uptake, leading to increased extracellular glutamate and was associated with increased activity of pyramidal neurons (Higashimori et al., 2016). iPSC astrocytes from Rett syndrome patients seem to have accelerated differentiation (Andoh-Noda et al., 2015). When wild-type neurons were cultured in conditioned media obtained from these astrocytes it led to an alteration in neural connectivity (E. C. Williams et al., 2014). Altogether, this research suggests that defective astrocytes contribute towards impaired neuronal health and the pathology of ASD.

A summary of ASD risk factors and the contribution of neural lineage cells towards the pathology of ASD is given in figure 1.

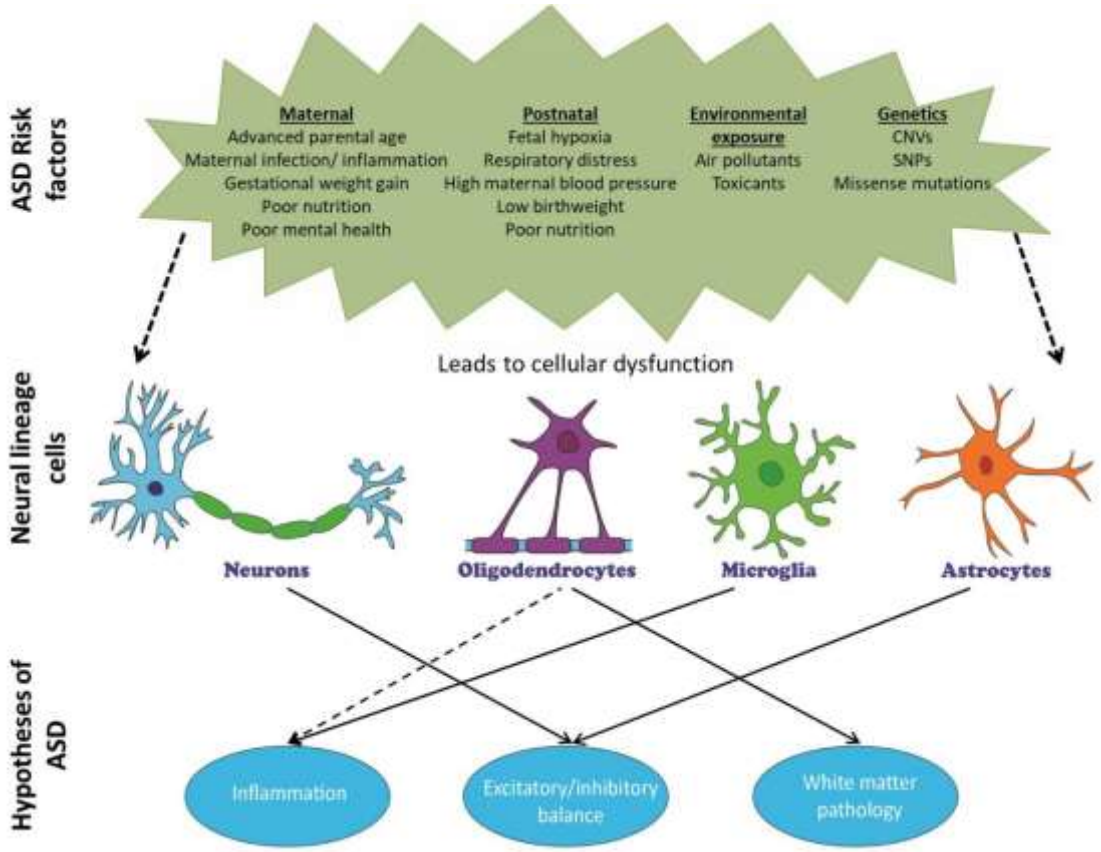

Figure 1: Contribution of the risk factors to the cellular pathologies and hypotheses associated with ASD.

Diagram of risk factors, hypotheses of ASD and which neural lineage cells may be linked to these hypotheses. The solid arrows denote hypotheses with strong links to the relevant neural lineage cells. The dotted arrow shows a potential link between the hypothesis and neural lineage cells.

4.5. Brain organoids

Organoids are becoming increasingly popular ways to study structure and function of neural cells. There are a number of advantages of using 3D cellular model organoids over the widely-used 2D neural cultures. Organoids are much better models as they are able to replicate the development of the neocortex (Camp et al., 2015) and are improved models to test drugs for treatment due to their more complex structure and organisation (Ranga, Gjorevski, & Lutolf, 2014); better to recapitulate brain pathology over 2D models. Currently, due to the relative novelty of this cellular model, very little research on cerebral organoids and ASD have been conducted. Of the research published it has been shown that heterozygous knockouts of the *CHD8* gene replicate results of 2D cell culture in regards to differentially expressed genes associated with *CHD8* and autism (P. Wang et al., 2015; P. Wang et al., 2017). One other study looking at overproduction of *FOXG1* in patient-derived organoids showed an overproduction of GABAergic inhibitory neurons (Mariani et al., 2015). Whilst this gene is not directly linked to autism, it has been associated with Rett Syndrome (Ariani et al., 2008); which involves a number of autistic-like features. Further, brain organoids are potential models to recapitulate morphological phenotypes of ASD, as discussed, the *PTEN* mutation leads to large sized organoids (Y. Li et al., 2017); consistent with the macrocephaly phenotype of this gene mutation.

5. Clinical Implications and Future Perspectives

To make a difference in the lives of subjects with ASD, it is essential to provide a better diagnosis and an effective treatment. The therapies that are available for ASD varies widely for very young children and toddlers. While social and adaptive therapies have been recommended for young children, behavioural therapies have proven to be effective for adults. Due to the complex genetics associated with ASD, it is crucial to define and

investigate the impact of genetics on brain development and cellular pathogenesis such as impaired neural maturation and neuroinflammation. This information will serve as a basis for the development of effective therapies that can alleviate some of the symptoms. Furthermore, developing and refining the human cellular models that can identify a clear neurobiological process is crucial, as to develop a platform for the screening of drugs.

Conflict of Interests

The authors declare no conflict of interest.

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