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Effect of mitochondrial dysfunction and oxidative stress on the pathogenesis of autism spectrum disorders

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ABSTRACT

There are certain aspects of autism spectrum disorder that seem to be related to the pathogenesis of mitochondrial dysfunction or the chain of events and pathways associated with mitochondrial dysfunction. In this mini-review article, we aimed to summarize these two entities separately and review how they are linked to oxidative stress pathways, genetic abnormalities, transcriptional factor changes, metabolic disorders, changes in the enteric composition of the microbiota, gene expression, and regional alterations in regulatory proteins. Some ideas on how these new findings of the current link may affect therapeutic approaches were also discussed.

Keywords: Autism spectrum disorders, electron transport chain, genetic mutations, mitochondrial dysfunction.

Autism is a complex and behaviorally diagnosed life-long condition, and individuals suffer from negative effects such as lack of self-sufficiency and mental disability.[1] Autism is not a disease but a syndrome with more than one etiology and a broad range of conditions, called autism spectrum disorder (ASD). Autism spectrum disorders are characterized by difficulties in social interaction, unusual, repetitive, and stereotypical behavioral patterns, and defects in activities and communication skills.[2] The five ASD subtypes are: autistic disorder (classic autism), Asperger's disorder, childhood disintegrative disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Rett's disorder.[3]

The word autism comes from the Greek "autos," which means "self." This term was proposed by the Swiss psychiatrist Eugen Bleuler in 1911. He used this concept to refer to a classic schizophrenic symptom.[4] Infantile autism was first described by Leo Kanner in 1943. He described 11 children (8 males and 3 females) who were unable to communicate emotionally with others but were highly concerned with the change in the environment.[5] Parents of these children referred to them as "self-sufficient," "as in a shell," "happiest left alone," and "people pretending to be absent." After Kanner, Asperger[6] described the behavior of four adolescent males with similar characteristics in 1944. In the 1960s, autism was associated with a detached and neglecting mother. Bettelheim referred to this as the "refrigerator mother."[6]

The World Health Organization (WHO) estimates the global prevalence of ASD at 0.76%; however, this only accounts for about 16% of the global child population.[7] Moreover, worldwide prevalence is estimated to be around 1 to 2% according to large-scale surveys.[8] These data show an average figure because the prevalence of ASD in many low-and middle-income countries is unknown.

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According to epidemiological studies, the prevalence of ASD is increasing every year due to increased awareness, changes in diagnostic criteria, and better diagnostic tools.[9] Autism spectrum disorders are not specific to any racial, ethnic, or socioeconomic group, although their diagnosis differs between these groups.[7]

Autism spectrum disorders occur more frequently in males than in females. The prevalence ratio of autism has been estimated as 3 to 4 males for every female diagnosed, although this ratio is varied in recent studies.[10,11] Intellectual functioning impacts this ratio, with higher functioning individuals having a higher ratio (~6:1) than lower functioning samples (~1.5:1).[12]

Autism spectrum disorders are likely to have multifactorial etiopathogenesis that includes genetic factors, environmental factors, or interactions between them.[1] These genetic and environmental factors are shown in Table 1. Environmental factors can be divided into prenatal, perinatal, and postnatal factors.[2] Individuals with ASD differ in language ability, mental retardation, and cognitive functions. This heterogeneity causes difficulties in understanding pathophysiological mechanisms.[13]

Genetic factors

Autism may be a component of a known genetic syndrome such as fragile X syndrome (FXS) and tuberous sclerosis (TS).[2] This condition, called syndromic autism, can be seen in about 10% of all ASD cases. Unlike idiopathic or primary autism, this condition presents an equal sex ratio.[22]

Fragile X syndrome is a genetic disorder caused by CGG trinucleotide expansion (>200 repeats) at the Xq27.3 locus in the fragile X mental retardation 1 (FMR1) gene and TS is caused by inactivating mutations in the tuberous sclerosis complex subunit 1 or subunit 2 genes. The underlying mechanism is the same for these

Table 1. Multi-factorial etiopathogenesis of autism

Genetic factors	
Single gene disorders[2]	Fragile X syndrome Rett syndrome Tuberous sclerosis
Inborn errors of metabolism[14]	Phenylketonuria (PKU) Adenylosuccinate lyase deficiency
Risk alleles	-
Environmental factors	
Perinatal factors	Congenital rubella syndrome[3] Teratogen and pesticide exposure[2] Maternal and paternal age[15]
Perinatal and obstetric events	Hypoxia[16] Medication[15] Maternal and paternal smoking, alcohol usage, nutrition, and toxic exposures[1,17] Low birth weight[2] Abnormal gestational length[2] Birth asphyxia[2]
Fetal environment[17]	Imbalanced fetal sex hormone exposure Maternal obesity Diabetes Hypertension Infections Immune activity
Postnatal factors	Autoimmune disease[18] Leaky gut syndrome[19] Viral infection[1] Oxidative stress[20] Vitamin D deficiency[21]

syndromes, which is abnormal mRNA translation that increases protein synthesis associated with autism.[23-25]

In addition, some synaptic genes such as neuroligin 3 (NLGN3), neuroligin 4, X-linked (NLGN4X), and SHANK are the first mutations identified in idiopathic autism. The first identified SHANK gene mutations to affect patients were 22q13 deletion syndrome, also known as Phelan-McDermid syndrome, which is often associated with ASD.[26-28] Furthermore, comprehensive studies on patients with ASD have shown a significant number of mutations in the SHANK1 and SHANK2 genes. This is clear evidence that SHANK proteins are linked in a common molecular pathway associated with ASD.[27,29-31]

In addition, autism is a syndrome with a concordance rate of 82 to 92% in monozygotic twins and 1 to 10% in dizygotic twins.[2,32] These rates mean that this is due to shared genes rather than a shared environment. Environmental factors are thought to contribute to the development of autism since the rate of monozygotic twins is not 100%.[3]

Environmental factors

Parental age: Advanced parental age is a well-understood risk factor for chromosomal aberrations.[17] There is expanding evidence on the correlation between older parental age and the etiology of psychiatric and neurodevelopmental conditions, including bipolar disorder, schizophrenia, substance use disorders, attention deficit hyperactivity disorder, and ASD.[33,34]

Smoking and alcohol usage: It has long been known that parental lifestyle and substance use impact fetal and infant development. Due to parental smoking, the fetus is exposed to many toxic chemicals. This condition leads to oxygen deprivation and changes in neurotransmitter activity.[35,36] Ethanol consumption during pregnancy may set off forms of neurodevelopmental damage that include fetal alcohol syndrome.[37,38]

Sex steroids: In findings, it is apparent that fetal testosterone impacts autistic traits (ATs), such as differences in typical development in eye contact behaviors, vocabulary size, restricted interests, mentalizing, empathy, systemizing, and attention to detail.[39] These findings support the extreme male brain theory of autism, which claims autism can be described as an extreme variant of the male phenotype.[40] In accordance with this theory, neuroimaging studies show that fetal testosterone affects structural and functional brain development.[41-43]

Congenital rubella syndrome, infections, and immune activation: The discovery of the connection between autism and congenital rubella infection led to further debate about infections and immune activation in the etiology of autism.[44,45] Immune system and abnormal immune function, including inflammation, cytokine dysregulation, and anti-brain auto-antibodies, take a part in the etiology of autism according to the evidence.

Table 2. Clinical signs of autism that facilitate early detection

6 months	Poor attention to social interactions Lack of eye contact Lack of smiling, warm and joyful expressions
9 months	Little or no babbling Lacking in sharing sounds and facial expressions
12 months	Little interaction between infant and parent Little or no back-and-forth gestures such as pointing, showing, reaching, or waving
At any age	Restricted interests Repetitive behaviors Loss of previously acquired skills Persistent preference for solitude Difficulty in understanding other people's feelings Delayed language development Persistent and repetitive speech (echolalia) Resistance to changes in routine or environment

ASSESSMENT OF AUTISTIC TRAITS

Autistic traits are detected primarily through observation.[46] Some deficits that ease the early diagnosis of autism are shown in Table 2.

MITOCHONDRIAL DISEASES

Mitochondrial diseases (MD) form a complex cluster of disorders that arise from the various dysfunctions of the mitochondrial respiratory chain, which is a crucial common pathway for the aerobic metabolism of humankind.[47] Disorders of the respiratory chain affect tissues and organs that are relatively more dependent on aerobic metabolism compared to others.[48] The respiratory chain located on the mitochondrial membrane is made up of at least 70 different polypeptides that interact with each other; most of these are transcribed from nuclear genes, but 13 essential subunits of the respiratory chain are encoded within the mitochondrial DNA (mtDNA).[49] Seven of these genes encode mRNAs that transcribe the subunits necessary to build the complex I (NADH dehydrogenase) in the electron transport chain (ETC). One of them serves as a subunit for complex III (cytochrome b), three are subunits of complex IV (cytochrome c oxidase), and the last two help build complex V (ATP synthase). The rest of the ETC elements and subunits are encoded by nuclear genes. Mitochondrial diseases are among the most common genetic errors of the metabolism, seen at least once in every 5,000 births, and they can be the result of either mitochondrial or nuclear gene mutations.[50]

Mitochondrial diseases are best diagnosed with muscle tissue biopsies, but they also come with sensitivity and specificity limitations. Heteroplasmy analysis and mtDNA genome sequencing are also used as diagnostic tools, and they can be performed from a variety of samples like blood and urine. Urine samples contain renal epithelial cells, which express a high amount of mtDNA, that are particularly useful in the diagnostic procedure of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and its associated mitochondrially encoded tRNA leucine 1 (UUA/G) (MT-TL1) gene mutation.[51,52]

Biochemical tests are effective in evaluating the enzymatic activities of the individual components of the ETC-functional assays performed on the respiratory chain and the measurement of various protein components and the oxygen consumption of mitochondrial complexes via blue native-gel electrophoresis (Blue native polyacrylamide gel electrophoresis) and Western blot, among other techniques.[53] The “ragged red fiber” appearance of clumped up, diseased mitochondria accumulated in the subsarcolemmal region of the muscle fiber seen under modified Gomori trichrome stain or with a stain for succinate dehydrogenase (respiratory complex II) is considered highly suggestive for respiratory chain disorders and is seen in many mitochondrial diseases as well.[54]

Among some of the more common clinical features of MD include ptosis, proximal myopathy, external ophthalmoplegia, exercise intolerance, cardiomyopathies, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus.[55] The central nervous system (CNS) usually presents with fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity, but chorea and dementia are underlined as prominent features as well.[56] Loss of pregnancy at a mid-or late-stage is also common.[57]

There are non-pathognomonic biomarkers of mitochondrial dysfunction, such as lactate, pyruvate, alanine, creatine kinase, and carnitine.[23] It has also been shown that buccal swabs serve as a good alternative for muscle biopsies, which have limitations, such as the unavailability of reperforming the test after a few times for a sufficient follow-up and the requirement of anesthesia, which is especially dangerous for patients with MD.[58] The Morava criteria, designed for MD, serves as a good infrastructure for combining these ranges of biochemical test results and clinical findings to produce a scoring system for efficient diagnosis.[59] However, there have been many other systems in place in the literature to diagnose and evaluate mitochondrial dysfunction, such as the Walker criteria established in 1996,[60] the modified Walker criteria set for evaluating both adult and pediatric cases, and the consensus mitochondrial diagnostic criteria (MDC) proposed in 2002 by Wolf and Smeitink[61]

There are a huge variety of mitochondrial disorders, either inherited by the mtDNA or the nuclear genes that encode functions of mitochondrial performance, some of which are

described according to their clinical presentations in Table 3.

Even though some mitochondrial disorders affect a single organ (as in the cases of optic neuropathy and hearing loss), most involve multiple organ systems with accompanying muscle dysfunctions and neural impairment while being able to present themselves at any age.[47] Mitochondrial disorders that stem from nuclear gene defects can be inherited in an autosomal recessive or an autosomal dominant manner, but the ones that concern mtDNA are only inherited down a maternal line, which means that a male does not transmit the pathologic variant of mtDNA to the offspring. A female with a heteroplasmic mtDNA single-nucleotide variant, can transmit a variable amount of mutated mtDNA to her children which may result in clinical variability among siblings.[47]

There are thousands of copies of mtDNA in each human cell. In a newborn, these are all usually identical (homoplasmy), and there is generally a case of heteroplasmy in individuals with mitochondrial disorders, where these individuals have a mixture of healthy (wild-type) and mutated mtDNA in their cells.[71] Some studies

Table 3. Clinical syndromes and disorders associated with various degrees of mitochondrial dysfunction and mitochondrial gene mutation

Mitochondrial disorders	Clinical features
Diabetes mellitus and deafness (DAD)[62]	A subtype of diabetes inherited maternally in a mitochondrial manner via a point mutation in the mitochondrial DNA; develops in early ages
Leber's hereditary optic neuropathy (LHON)[63]	A mitochondrially inherited degeneration of retinal ganglion cells and their axons characterized by progressive loss of central vision.
Leigh syndrome[64]	Subacute Sclerosing Encephalopathy; onset occurs approximately a year after birth or later in adult life with a rapid loss of functions, seizures, mental instabilities, a failure to thrive, and ventilatory failure. It is thought to be undertaken by the blockage of the thiamine-diphosphate kinase enzyme.
Neuropathy, ataxia, retinitis pigmentosa & ptosis (NARP)[65]	Presents with peripheral neuropathy, ataxia, and pigmentary retinopathy in late childhood or in adult life. Clinical findings include lucencies of the basal ganglia and abnormal results in an electroretinogram.
Myoneurogenic gastrointestinal encephalopathy (MNGIE)[66]	Presents with neuropathy and pseudo-obstruction of the gastrointestinal system. The genetic defect is nuclear (TYMP) but the loss of function affects mitochondrial DNA and functions.
Myoclonic epilepsy with ragged red fibers (MERRF)[67]	Characterized by progressive myoclonic epilepsy together with short stature, hearing loss, and lactic acidosis.
Mitochondrial encephalomyopathy, lactic acidosis & stroke-like episodes (MELAS)[68]	The symptoms usually come up between 2 to 10 years of age and present with growth retardation and a progressive loss of function regarding muscle strength, sight and cortical function on top of the clinical signs mentioned in its abbreviation. NADH Dehydrogenase enzyme is usually lost due to MTND1 or MTND5 mitochondrial gene mutations.
Alpers-Huttenlocher Syndrome[69]	Presents with hypotonia, seizures, liver failure, and renal tubulopathy with depletion of mtDNA or multiple deletions. It is mainly related to a family of disorders characterized by damage to the POLG gene.
Ataxia Neuropathy syndromes[69]	Epilepsy, dysarthria, and myopathies are among its common clinical features. Includes a spectrum of disorders like MEMSA, SANDO, MIRAS, and SCAE.
Pearson syndrome[70]	Presents with sideroblastic anemia of childhood, pancytopenia, exocrine pancreatic failure, and renal tubular defects.
Kearns-Sayer syndrome (KSS)[70]	Presents with progressive external ophthalmoplegia (PEO) at an age of less than 20 years; progresses with pigmentary retinopathy, dysphagia, DM, hypoparathyroidism, and many other symptoms.
Chronic progressive external ophthalmoplegia (CPEO)[70]	Presents with ptosis, mild proximal myopathy, and external ophthalmoplegia, as the name suggests.

have shown that for a mitochondrial disorder to perform biochemical abnormalities and clinical findings, the proportion of mutated mtDNA must exceed a certain threshold.[72]

Some disorders of mtDNA maintenance, mitochondrial protein synthesis, coenzyme Q10 biosynthesis, and the formation of respiratory chains may be due to nuclear gene mutations since there are more than a thousand nuclear genes encoding mitochondrial proteins.

Mitochondria are unique cytoplasmic organelles engaged in the production of ATP through oxidative phosphorylation, generation of reactive oxygen species (ROS), metabolic homeostasis, and the execution of apoptosis in the human cell. The mtDNA that encodes all these functions is sensitive to oxidative damage, even more so than nuclear DNA, due to the lack of histone proteins and a sufficient repair system.[73] Dysfunctions of mitochondria contribute to the pathogenesis of many neurological disorders, such as Alzheimer's, Parkinson's, and Huntington's disease, as well as amyotrophic lateral sclerosis and Rett syndrome.[74] There is also a significant body of evidence suggesting that mitochondrial disorders play a role in certain stages of cancer progression and development since mutations, polymorphisms, and some variants of mtDNA have been described in certain tumors.[73]

CONNECTION BETWEEN MITOCHONDRIAL DISORDERS AND AUTISM SPECTRUM DISORDER

Knowing that autism is a multifactorial disorder involving many systems of the human body, there have been many indicators that demonstrate mitochondrial dysfunction as a factor in its pathophysiology.[75] This idea was described by Frye and Rossignol,[76] who pointed out the overlap between the characteristics of children with ASD and the Morava criteria set for diagnosing mitochondrial dysfunction. Weissman et al.[77] managed to assemble one of the first clinical series of patients who were diagnosed with both autism and mitochondrial dysfunction, exhibiting an array of non-neurological symptoms like gastrointestinal dysfunction, exercise intolerance, and gross motor delay.

GENETIC MUTATIONS

Deletions of the IMMP2L gene, which helps process cytochromes inside mitochondria and encode an inner mitochondrial membrane protease-like protein, is implicated in ASD as well.[78] Many mitochondrial gene mutations and deletions are demonstrated to be associated with ASD.[79] Gene mutations observed in Leber hereditary optic neuropathy and MELAS are some other examples of this phenomenon.[80]

Mutations in nuclear genes, such as NDUFA5, NDUFS4, POLG, and SCO2, shown to cause dysfunction in mitochondria, were also associated with ASD as with SLC25A12 and SLC6A8 genes.[81,82] Mutations in the WD45 gene cause increased mitochondrial respiration and a significant elevation in ETC complex expression, while DEPDC5 mutations cause an increased rate of proton-leak respiration and a reduction in ATP-linked respiration, and both are associated with ASD.[83]

INVOLVEMENT OF THE ELECTRON TRANSPORT CHAIN (ETC)

In 1985, ASD was proposed to be a disorder of the carbohydrate metabolism, and deficits in mitochondrial function are found in %80 of patients with ASD.[84,85] Muscle biopsies and buccal swabs were employed to examine the ETC in patients with ASD to propose a groundwork for this intricate connection between the two conditions, which resulted in many significant findings.

The mammalian ETC, as one of the most important mechanisms of ASD-related mitochondrial dysfunction, functions on four complexes and two electron transporters, cytochrome c and ubiquinone. Complex V of the chain employs the proton gradient created in the intermembrane space by the electron flow from the chain complexes to produce ATP to be used in cellular functions.[86]

Buccal swabs have revealed throughout many studies that abnormal ETC activity is a prominent finding in children with ASD, especially concerning the complexes I and IV and citrate synthase.[87] In more severe cases of ASD, a higher complex I to complex IV ratio is seen.[88] The Vineland Adaptive Behaviour

Scale (VABS) yields scores dependent both on complex I and complex IV, and complex IV in this case has an inverted u-shape association curve with the VABS results such that both lower and higher levels are found to be problematic.[87] However, complex I is in a direct ratio with VABS and citrate synthase activity is found to be more effective on the Social Responsiveness Scale.[87]

Hypotonia, epilepsy, autism, and developmental delay (HEADD syndrome) associated with hypotonia, epilepsy, autism, and developmental delay was one of the first clinical platforms in which mitochondrial dysfunction (namely complex III deficiency) was found side by side with ASD.[89] A study conducted in 2010 discovered compromised activities of complex I, III, and IV, consistent with previous findings.[90]

These disturbances of mitochondrial respiratory chain complexes are expressed regionally in different physiologic processes to cause the changes seen in ASD. Studies demonstrated decreased expression of ETC genes in the occipital and the cerebellar areas of the brain[91] and decreased activity of complexes I, II, and IV in lymphocytes,[85] and these sites become a hotspot for the research on the topic. There are many studies conducted to underline the involvement of mitochondrial complex changes and impairments in the brain[91,92] and in some other systems in patients with ASD.[85]

Lymphoblastoid cell lines (LCLs) have become especially pronounced for studying mitochondrial dysfunction since they display an increased vulnerability to ROS and highly active mitochondria.[75] They also present with a decreased mitochondrial membrane potential, decreased activities of complexes I and III, and an increased production of ROS in patients with ASD.[93] Rose et al.[23] examined the effect of oxidative stress with the LCLs obtained from ASD patients treated with 1,4-naphthoquinone to increase oxidative stress *in vitro* and a control group. In high concentrations of 1,4-naphthoquinone, the LCLs of ASD patients show a serious decline in respiratory capacity of their mitochondria, which is consistent with the propagation of mitochondrial exhaustion and collapse of cellular physiology.

However, in a study in children with Phelan-McDermid syndrome, higher levels of complex I were observed more in coherence with findings of ASD, while lower levels displayed a more classic presentation of mitochondrial diseases.[94] This suggests that the disorders of the respiratory chain are not, by themselves, enough to establish a definite connection between ASD and mitochondria. Through a considerable amount of research, it has become evident that the primary pathway in which mitochondria are involved in ASD is oxidative stress.[95-97] Damaged mitochondria produce ROS-like hydrogen peroxide, and they cripple the ability of the cell to mitigate the damage of ROS such that the reduced form of GSH is usually found deficient in patients with ASD.[98]

REACTIVE OXYGEN SPECIES

The term ROS describes a series of molecules derived from oxygen that contain an unpaired electron and can cause oxidative stress in the cell, a deleterious process in which proteins, lipids, and polysaccharides essential for cellular function can get damaged. Mitochondrial ETC elements produce these reactive species by leaking electrons to molecular oxygen and reducing it to a superoxide anion. Dismutation of these anions via superoxide dismutase produces hydrogen peroxide (H_2O_2), which is either reduced into water molecules or hydroxyl radicals (OH^-).[99]

As mentioned before in this review, the mechanisms of oxidative stress seem to stand out regarding the contribution of mitochondrial dysfunction to the pathogenesis of ASD. The same mechanism is employed in the immune system as well, such as during a Salmonella infection, where macrophages employ mitochondria for the formation of phagosomes.[100] Activated Toll-like receptors lead to the translocation of tumor necrosis factor receptor-associated factor 6 into mitochondria, where it ubiquitinates evolutionarily conserved signaling intermediate in Toll pathways, a protein involved in the production of ETC complex I, which finally increases mitochondrial ROS production - a process vital for clearing out the infection.[101]

BRAIN INVOLVEMENT

Anitha et al.[102] demonstrated brain region-specific gene expression changes of metaxin 2 (MTX2), neurofilament light peptide (NEFL), and SLC25A27, which were down-regulated to cause a clinical presentation seen in autism. Genes that have a role in calcium homeostasis are up-or down-regulated in certain parts of the brain in ASD patients, which is associated with mitochondrial function itself.[103] In postmortem studies, ETC markers and non-ETC mitochondrial markers, such as aconitase and pyruvate dehydrogenase, are found depressed in frontal, temporal[104] and cerebellar[92] cortices.[105] Studies with magnetic resonance spectroscopy revealed abnormal energy metabolites in the frontal cortex of the brain of ASD patients[106] and a reduction in N-acetylaspartate[107] as a marker in the global white and gray matters, as well as in the cingulate cortex and cerebellum. Lin-Hendel et al.[108] conducted a study in 2016 to block oxidative phosphorylation in medial ganglionic eminence of the brain with either oligomycin (ATP-synthase inhibitor) or bongkrekic acid, and they found that GABAergic interneuron migration was especially affected by the change, suggesting that these mitochondrial gene abnormalities have an impact on neural development. Cerebral folate deficiency has also been shown to contribute to ASD pathogenesis through the lack of folate in the cerebrospinal fluid of ASD patients, thought to be propagated by a dysfunction in the folate receptor alpha in the CNS.[109] Hypoplasia of the corpus callosum, cerebellar hypoplasia, failure of dendritic sprouting, and axonal branching are also among some of the issues of neural development seen in ASD patients, and these are also viewed to be related to mitochondrial dysfunction.[77]

THE GUT-BRAIN AXIS

The connection between the human gastrointestinal system and brain function has been a topic of focus for neuropsychiatry for more than 20 years.[110] New information has been brought to light to show just how this relationship can exert an effect on the mitochondria and the propagation of ASD.

There are around a thousand species and 104 cells in the human microbiome, and a majority live in the intestines.[111] The enteric microbiota, mostly made up of the phyla Bacteroidetes and Firmicutes, help us digest many substances crucial for our bodily functions, such as vitamin B and essential amino acids.[112] They also produce short-chain fatty acids to modulate the synthesis of neurotransmitters,[113] stimulate neural development and inflammation,[114] initiate neural migration,[115] and even affect mitochondrial membrane composition.[116] Short-chain fatty acids can lead to carnitine deficiency,[115] increased release of ROS, and reduced glutathione production.[117] In addition, hydrogen sulfide released by mitochondria contributes to oxidative stress as well,[118] while the lipopolysaccharides of pathogenic bacteria are recognized as pathogen associated molecular patterns (PAMPs) to drive inflammatory responses.[119] Inflammation can epigenetically damage mitochondria and mitochondrial gene expression, further establishing the importance of the mentioned pathways in ASD pathogenesis. Accordingly, many ASD patients are known to present with a history of gastrointestinal episodes, multiple exposures to antibiotics, and a greater incidence of diarrhea and constipation.[120] Two studies demonstrated that treatment options such as fecal transplants[121] and supplementation of folate, cobalamin, fatty acids, and antioxidants[122] help with some aspects of ASD. However, further research is needed to develop a consensus of treatment strategies to improve the life quality and prognoses of patients with ASD.

In conclusion, mitochondria contribute to ASD in terms of oxidative stress, inflammatory responses, and disturbances in neural development and adult brain function. The complicated metabolic pathways of mitochondria contribute in various ways to ASD pathogenesis, and the regional expression of these mitochondrial abnormalities (as in the brain and the immune system) specifies the ways in which the association is built. Disorders in oxidative phosphorylation cripple neural development, the changes in ETC affect behavioral presentations, and the alterations in enteric microbiota further aggravate both impairments. However, the development of techniques such as buccal swabs

helps researchers uncover more information on ASD, and newly found connections, such as the role of microbiota in the mitochondrial disturbances seen in ASD, are helping new treatment approaches to come to light, as with fecal transplants.

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