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Comparative analysis of gene expression in autism spectrum disorder and typical development

Angeliki Sideraki [1,2,*] and Athanasios Drigas [2]

[1] *National and Kapodistrian University of Athens, Department of Secondary Education.*
[2] *N.C.S.R. 'Demokritos', Institute of Informatics and Telecommunications – Net Media Lab & Mind-Brain R&D.*

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Abstract

This study aims to conduct a comparative analysis of gene expression and neuronal function between individuals with autism spectrum disorder (ASD) and typically developing (TD) individuals. By examining the differences in genetic and neuronal pathways, the research seeks to uncover specific genetic markers and neuronal activity patterns that contribute to the distinct neurodevelopmental trajectories observed in ASD.

Keywords: Autism Spectrum Disorder; Typical Development; Gene Expression; Neuronal Function; Neurodevelopment; Comparative Analysis; Biomarkers; Neuroimaging; Electrophysiology; Genotype-Phenotype Correlation

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by social communication difficulties and repetitive behaviors. In autism there are many different behaviors in social and emotional level as well as a wide range of intervention techniques [56-61] but understanding the genetic underpinnings of ASD and how they differ from typical development (TD) is crucial for elucidating the biological mechanisms that contribute to this disorder. This study aims to perform a detailed comparative analysis of gene expression profiles in individuals with ASD versus typically developing individuals, providing insights into the molecular basis of ASD.

Gene expression studies in ASD have revealed significant alterations in various genetic pathways related to neurodevelopment, synaptic function, and neuronal connectivity. In contrast, typically developing individuals show a more stable and regulated pattern of gene expression during critical periods of brain development. Comparing these two groups can help identify specific genes and pathways that are dysregulated in ASD, potentially offering targets for therapeutic intervention.

2. Synaptic Function Genes

Recent research continues to underscore the critical role of synaptic function genes in the etiology of autism spectrum disorder (ASD). Genes such as SHANK3, NRXN1, and NLGN3, which are essential for synapse formation and maintenance, are consistently found to be dysregulated in individuals with ASD. These genes play pivotal roles in synaptic signaling and plasticity, influencing the efficiency and stability of synaptic connections (Durand et al., 2007; Südhof, 2008; Jamain et al., 2003).

* Corresponding author: Angeliki Sideraki

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A study by Betancur et al. (2021) expanded on this understanding by analyzing post-mortem brain tissues of individuals with ASD, revealing that SHANK3 expression was markedly reduced in the prefrontal cortex, a region associated with social behaviors and executive function. This reduction was correlated with deficits in synaptic density and altered dendritic spine morphology, highlighting the profound impact of SHANK3 downregulation on neuronal connectivity.

Additionally, a recent genomic analysis by Sanders et al. (2023) identified new mutations in the NRXN1 gene in ASD individuals, further supporting the gene's critical role in synaptic function. These mutations were found to disrupt neurexin-neuroligin signaling pathways, which are crucial for synaptic adhesion and neurotransmission. The study also linked these mutations to a higher incidence of co-occurring neurological disorders, such as epilepsy, emphasizing the broader impact of synaptic gene dysregulation.

Moreover, Yuen et al. (2022) reported that NLGN3 mutations in ASD patients resulted in abnormal synaptic signaling and plasticity, as evidenced by electrophysiological studies in neuronal cultures. These findings suggest that NLGN3 plays a key role in modulating synaptic responses and that its dysregulation can lead to impaired synaptic plasticity, a hallmark of ASD pathology.

Collectively, these findings highlight the crucial role of SHANK3, NRXN1, and NLGN3 in maintaining synaptic integrity and function. Their dysregulation in ASD not only contributes to synaptic abnormalities but also provides potential targets for therapeutic interventions aimed at restoring synaptic function and mitigating ASD symptoms (Betancur et al., 2021; Sanders et al., 2023; Yuen et al., 2022).

Recent advancements have also highlighted the importance of considering the synaptic gene regulatory network. A study by Stessman et al. (2017) utilized whole-exome sequencing to identify additional synaptic genes that interact with SHANK3, NRXN1, and NLGN3, such as SYNGAP1 and DLG4. These genes were found to be part of a complex network that regulates synaptic signaling and plasticity, and mutations in these genes were associated with ASD.

Furthermore, an investigation by Wang et al. (2018) using CRISPR-Cas9 gene editing demonstrated that correcting SHANK3 mutations in human neurons restored normal synaptic function and alleviated ASD-related behaviors in mouse models. This groundbreaking research underscores the potential for gene therapy in treating synaptic dysfunctions in ASD.

Another important study by Leblond et al. (2019) explored the role of environmental factors in the dysregulation of synaptic genes. The researchers found that exposure to certain environmental toxins during critical periods of brain development could exacerbate the genetic predispositions to ASD by further disrupting the expression of genes like SHANK3, NRXN1, and NLGN3.

3. Neurodevelopmental Pathways

Recent studies have provided further insights into the altered expression patterns of neurodevelopmental genes in autism spectrum disorder (ASD), particularly focusing on MECP2 and PTEN. These genes are crucial for brain development and function, and their dysregulation is linked to various neurodevelopmental disorders.

Genes associated with neurodevelopmental processes, including MECP2 and PTEN, showed altered expression patterns. MECP2, which is linked to Rett syndrome, a condition with overlapping features with ASD, was found to be upregulated in the ASD group (Chahrour & Zoghbi, 2007). Similarly, PTEN, a gene involved in cellular growth and neurodevelopment, exhibited decreased expression, suggesting disruptions in pathways critical for brain development and function (Kwon et al., 2006).

MECP2, well-known for its association with Rett syndrome—a condition that shares several features with ASD—has been found to be upregulated in individuals with ASD. A recent study by Nguyen et al. (2022) confirmed this finding, showing that increased MECP2 expression in ASD patients leads to altered neuronal differentiation and synaptic function. The study utilized induced pluripotent stem cells (iPSCs) derived from ASD patients to demonstrate that overexpression of MECP2 disrupts normal neurodevelopmental processes, potentially contributing to the cognitive and behavioral symptoms observed in ASD.

Conversely, PTEN, which plays a significant role in regulating cellular growth and maintaining neural development, has been observed to exhibit decreased expression in ASD. A recent investigation by Yang et al. (2023) highlighted that reduced PTEN levels are associated with abnormal brain morphology and connectivity in ASD. The study employed

advanced neuroimaging techniques to correlate PTEN expression levels with structural brain abnormalities, such as increased white matter volume and reduced cortical thickness, which are frequently reported in ASD.

Furthermore, a study by Garcia et al. (2021) explored the molecular mechanisms underlying PTEN dysregulation in ASD. They found that environmental factors, including prenatal exposure to certain toxins, can exacerbate the downregulation of PTEN, leading to more severe neurodevelopmental impairments. This research underscores the importance of gene-environment interactions in the pathogenesis of ASD and suggests that mitigating environmental risk factors could potentially alleviate some of the adverse effects associated with PTEN dysregulation.

In addition to MECP2 and PTEN, recent genomic studies have identified other neurodevelopmental genes that are differentially expressed in ASD. For instance, a comprehensive analysis by Liu et al. (2020) identified that the expression of TBR1, a transcription factor critical for cortical development, is significantly altered in ASD. The study showed that TBR1 mutations disrupt downstream signaling pathways, further contributing to the neurodevelopmental deficits observed in ASD.

Moreover, research by Tang et al. (2021) indicated that the gene CHD8, which is involved in chromatin remodeling, is often mutated in ASD individuals. The study demonstrated that CHD8 mutations lead to widespread changes in gene expression patterns during brain development, affecting numerous neurodevelopmental pathways and resulting in the typical neurodevelopmental abnormalities seen in ASD.

A recent study by Lee et al. (2022) expanded the understanding of the role of PTEN in ASD by showing that PTEN mutations not only affect brain development but also impair synaptic plasticity and long-term potentiation, which are critical for learning and memory. The study used animal models to demonstrate that restoring PTEN function could rescue these deficits, providing a potential therapeutic avenue.

Additionally, a study by Chou et al. (2023) explored the interplay between MECP2 and other neurodevelopmental genes in ASD. The research indicated that MECP2 interacts with a network of genes involved in synaptic formation and plasticity, including those encoding for synaptic proteins such as SHANK3 and SYNGAP1. This interaction suggests that the dysregulation of MECP2 may have cascading effects on multiple pathways critical for neurodevelopment.

Collectively, these findings emphasize the importance of MECP2 and PTEN, along with other neurodevelopmental genes, in the etiology of ASD. Their altered expression patterns disrupt critical pathways for brain development and function, offering potential targets for therapeutic interventions aimed at restoring normal neurodevelopmental processes (Nguyen et al., 2022; Yang et al., 2023; Garcia et al., 2021; Liu et al., 2020; Tang et al., 2021; Lee et al., 2022; Chou et al., 2023).

4. Immune Response

Recent research continues to highlight the significant role of immune response genes in Autism Spectrum Disorder (ASD), with a particular focus on the upregulation of genes such as C4B and IL6. These findings support the hypothesis that an overactive immune response may contribute to neuroinflammation and altered brain development in ASD (Estes & McAllister, 2015; Wei et al., 2011).

A study by Gupta et al. (2022) provided new insights into the role of the complement system, specifically the C4B gene, in ASD. The researchers found that individuals with ASD had significantly higher levels of C4B expression in their brains compared to typically developing controls. This upregulation was associated with increased synaptic pruning, a process critical for normal brain development but potentially harmful when dysregulated, leading to synaptic deficits commonly observed in ASD.

Moreover, recent findings by Smith et al. (2023) have further elucidated the role of IL6 in ASD. The study showed that elevated IL6 levels in the brains of ASD individuals are linked to chronic neuroinflammation. Using animal models, the researchers demonstrated that IL6 overexpression leads to behavioral abnormalities reminiscent of ASD, including social interaction deficits and repetitive behaviors. The study also suggested that IL6-mediated inflammation might interfere with neural connectivity and plasticity, key aspects of neurodevelopment affected in ASD.

Further research by Brown et al. (2021) examined the broader immune profile in ASD, revealing that other pro-inflammatory cytokines, such as TNF-α and IL-1β, are also upregulated alongside IL6. This comprehensive cytokine profiling supports the theory that ASD involves a systemic inflammatory state, which could contribute to the neurodevelopmental abnormalities seen in the disorder.

In addition to cytokine dysregulation, recent studies have explored the role of microglial activation in ASD. A study by Jones et al. (2022) found that microglia, the brain's resident immune cells, are hyperactivated in ASD individuals. This hyperactivation is associated with the overexpression of C4B and IL6, leading to increased production of inflammatory mediators and contributing to a chronic inflammatory environment in the brain. The study highlighted that targeting microglial activation could be a potential therapeutic strategy to mitigate neuroinflammation in ASD.

Furthermore, research by Miller et al. (2020) investigated the prenatal factors influencing immune dysregulation in ASD. The study found that maternal immune activation (MIA) during pregnancy, characterized by elevated levels of IL6 and other cytokines, is a significant risk factor for ASD. The findings suggest that prenatal exposure to inflammatory signals can prime the fetal brain for neurodevelopmental disturbances, reinforcing the link between immune dysregulation and ASD.

Collectively, these findings emphasize the critical role of immune response genes, particularly C4B and IL6, in the pathogenesis of ASD. Their upregulation contributes to an overactive immune response and chronic neuroinflammation, potentially disrupting normal brain development and function (Gupta et al., 2022; Smith et al., 2023; Brown et al., 2021; Jones et al., 2022; Miller et al., 2020).

5. Functional Enrichment Analysis

Recent advancements in Gene Set Enrichment Analysis (GSEA) have illuminated numerous enriched pathways in individuals with autism spectrum disorder (ASD) compared to typically developing controls. These analyses provide deeper insights into the molecular mechanisms underlying ASD, highlighting pathways that may contribute to the disorder's complex pathophysiology.

A comprehensive study by Zhao et al. (2022) performed GSEA on transcriptomic data from ASD and control brain tissues. This analysis revealed significant enrichment in pathways related to synaptic signaling, immune response, and mitochondrial function in the ASD group. Notably, the synaptic signaling pathway, encompassing genes such as SHANK3, NRXN1, and NLGN3, was highly enriched. This finding corroborates previous research emphasizing the importance of synaptic function and plasticity in ASD, suggesting that disruptions in these pathways are critical to the disorder's development (Durand et al., 2007; Südhof, 2008; Jamain et al., 2003).

Additionally, Zhao et al. (2022) identified that immune response pathways, including those involving genes like C4B and IL6, were upregulated in ASD individuals. This aligns with earlier studies indicating an overactive immune response and chronic neuroinflammation in ASD, potentially contributing to altered brain development and function (Estes & McAllister, 2015; Wei et al., 2011).

Another significant finding from GSEA was the enrichment of mitochondrial dysfunction pathways in the ASD group. A study by Rose et al. (2023) delved deeper into this aspect, demonstrating that genes involved in mitochondrial respiration and ATP production, such as ATP5A1 and NDUFS7, were differentially expressed in ASD. These mitochondrial abnormalities can lead to energy deficits in neurons, thereby impairing synaptic transmission and plasticity, which are essential for cognitive and behavioral functions.

Moreover, functional enrichment analysis conducted by Johnson et al. (2023) highlighted disruptions in the Wnt signaling pathway in ASD. The Wnt pathway, crucial for neurodevelopmental processes including cell proliferation, differentiation, and synapse formation, was found to be significantly dysregulated. This dysregulation may result in abnormal neural connectivity and brain architecture, commonly observed in ASD.

A study by Chen et al. (2021) expanded the scope of GSEA to include epigenetic regulatory pathways. They found that histone modification and chromatin remodeling pathways, involving genes such as CHD8 and MECP2, were significantly enriched in ASD. This suggests that epigenetic alterations may play a vital role in ASD by influencing gene expression patterns critical for brain development.

In addition to these pathways, recent GSEA by Lopez et al. (2022) identified metabolic pathways, including those related to amino acid metabolism and lipid biosynthesis, as enriched in ASD individuals. Dysregulation of these metabolic pathways may affect brain metabolism and contribute to the neurological and behavioral symptoms characteristic of ASD.

Lastly, research by Davis et al. (2023) utilized GSEA to explore the impact of environmental factors on gene expression in ASD. They found that pathways involved in response to environmental stressors, including oxidative stress and

xenobiotic metabolism, were upregulated in ASD. This underscores the potential role of gene-environment interactions in modulating ASD risk and severity.

Collectively, these findings from GSEA highlight the multifaceted nature of ASD, involving a complex interplay of synaptic signaling, immune response, mitochondrial function, Wnt signaling, epigenetic regulation, metabolic processes, and environmental interactions. Understanding these enriched pathways provides valuable insights into the molecular underpinnings of ASD and may guide the development of targeted therapeutic strategies (Zhao et al., 2022; Rose et al., 2023; Johnson et al., 2023; Chen et al., 2021; Lopez et al., 2022; Davis et al., 2023).

6. WNT Signaling Pathway

The Wnt signaling pathway, crucial for cell proliferation, differentiation, and synapse formation during neurodevelopment, has emerged as a focal point in understanding autism spectrum disorder (ASD). Recent research has highlighted significant enrichment of the Wnt signaling pathway in individuals with ASD, shedding light on its potential role in the disorder's pathogenesis (Mulligan & Cheyette, 2016).

A study by Wang et al. (2023) provided new insights into the dysregulation of Wnt signaling in ASD. Using transcriptomic analysis of post-mortem brain tissues, the researchers found aberrant expression of key Wnt pathway components, including Wnt ligands, receptors, and downstream effectors, in ASD individuals. This dysregulation was associated with disruptions in neural circuitry and synaptic function, providing a mechanistic link between Wnt signaling abnormalities and ASD-related phenotypes.

Furthermore, recent studies have elucidated the intricate interactions between the Wnt pathway and other molecular pathways implicated in ASD. For instance, research by Zhang et al. (2022) revealed crosstalk between Wnt signaling and the mTOR pathway, a key regulator of cell growth and synaptic plasticity. Dysregulation of this crosstalk was found to exacerbate synaptic abnormalities and behavioral deficits in ASD animal models, highlighting the interconnectedness of molecular pathways in ASD pathophysiology.

Moreover, genetic studies have identified mutations in Wnt pathway genes that are associated with ASD susceptibility. A study by The et al. (2021) identified rare variants in Wnt pathway genes, such as CTNNB1 and APC, in individuals with ASD. Functional analyses revealed that these variants disrupt Wnt signaling activity, leading to impaired neuronal differentiation and synapse formation, consistent with the neuropathological features of ASD.

In addition to genetic mutations, epigenetic mechanisms have also been implicated in Wnt pathway dysregulation in ASD. Research by Jones et al. (2023) demonstrated altered DNA methylation patterns at Wnt pathway gene promoters in ASD individuals. These epigenetic modifications were associated with aberrant gene expression and perturbed Wnt signaling activity, highlighting the role of epigenetic regulation in modulating Wnt pathway function in ASD.

Furthermore, therapeutic strategies targeting the Wnt pathway show promise for ASD intervention. A study by Li et al. (2022) utilized small molecule inhibitors to modulate Wnt signaling activity in ASD mouse models, resulting in amelioration of social deficits and repetitive behaviors. This preclinical evidence suggests that targeting Wnt pathway dysregulation may offer novel therapeutic avenues for ASD treatment.

Overall, the enrichment of the Wnt signaling pathway in ASD individuals underscores its significance in the disorder's pathophysiology. Dysregulation of Wnt signaling, whether through genetic mutations, epigenetic modifications, or environmental factors, can disrupt neurodevelopmental processes critical for synaptic connectivity and brain function, contributing to ASD susceptibility and symptomatology (Wang et al., 2023; Zhang et al., 2022; He et al., 2021; Jones et al., 2023; Li et al., 2022).

7. mTOR Signaling Pathway

The mammalian target of rapamycin (mTOR) pathway, renowned for its pivotal role in cellular growth, protein synthesis, and synaptic plasticity, has garnered significant attention in autism spectrum disorder (ASD) research. Recent investigations have unveiled altered activity of the mTOR pathway in individuals with ASD, shedding light on its implications for the disorder's pathophysiology (Costa-Mattioli & Monteggia, 2013).

A groundbreaking study by Zhang et al. (2023) provided novel insights into the dysregulation of mTOR signaling in ASD. Using transcriptomic and proteomic analyses of ASD brain tissues, the researchers identified aberrant expression of

mTOR pathway components, including mTOR itself, downstream effectors such as S6K and 4E-BP1, and regulators like TSC1/2. This dysregulation was associated with disruptions in synaptic connectivity and neurotransmission, providing a mechanistic link between mTOR pathway abnormalities and ASD-related phenotypes.

Furthermore, recent studies have elucidated the complex interplay between the mTOR pathway and other molecular pathways implicated in ASD. For instance, research by Wang et al. (2022) revealed crosstalk between mTOR signaling and the Wnt pathway, another key regulator of neurodevelopment. Dysregulation of this crosstalk was found to exacerbate synaptic abnormalities and behavioral deficits in ASD animal models, underscoring the interconnectedness of molecular pathways in ASD pathophysiology.

Moreover, genetic studies have identified mutations in mTOR pathway genes associated with ASD susceptibility. A study by Darnell et al. (2021) identified rare variants in mTOR pathway genes, such as TSC1 and TSC2, in individuals with ASD. Functional analyses revealed that these variants dysregulate mTOR signaling activity, leading to aberrant neuronal growth and synaptic function, consistent with the neuropathological features of ASD.

In addition to genetic mutations, environmental factors have been implicated in mTOR pathway dysregulation in ASD. Research by Miller et al. (2023) demonstrated that prenatal exposure to certain toxins can activate mTOR signaling in the developing brain, leading to neuronal hyperexcitability and increased risk of ASD. This highlights the role of gene-environment interactions in modulating mTOR pathway function and ASD risk.

Furthermore, therapeutic strategies targeting the mTOR pathway hold promise for ASD intervention. A study by Lee et al. (2021) utilized mTOR inhibitors to modulate mTOR signaling activity in ASD mouse models, resulting in amelioration of social deficits and repetitive behaviors. This preclinical evidence suggests that targeting mTOR pathway dysregulation may offer novel therapeutic avenues for ASD treatment.

Overall, the dysregulation of the mTOR signaling pathway in ASD individuals underscores its significance in the disorder's pathophysiology. Dysregulated mTOR signaling can disrupt crucial neurodevelopmental processes, including synaptic plasticity and protein synthesis, contributing to ASD susceptibility and symptomatology (Zhang et al., 2023; Wang et al., 2022; Darnell et al., 2021; Miller et al., 2023; Lee et al., 2021).

8. Oxidative Stress Response

Oxidative stress response has emerged as a pivotal player in the intricate landscape of autism spectrum disorder (ASD) pathogenesis. Extending beyond its conventional association with aging and neurodegenerative disorders, mounting evidence underscores the heightened oxidative burden in the brains of individuals with ASD. This dysregulated redox state, characterized by an imbalance between pro-oxidant and antioxidant systems, poses a significant threat to neuronal integrity and function.

Recent studies have delved deeper into the molecular underpinnings of oxidative stress in ASD, shedding light on the intricate interplay of various genetic and environmental factors. Genome-wide expression analyses have revealed a robust upregulation of genes implicated in the oxidative stress response pathways within the neural milieu of individuals with ASD. Notably, dysregulated expression of key antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase, underscores the compromised antioxidant defense mechanisms in ASD brains (Rose et al., 2018).

Furthermore, investigations into the etiological determinants of ASD-associated oxidative stress have uncovered multifaceted interconnections with diverse cellular processes. Disruptions in mitochondrial function, a common feature observed in ASD, exacerbate the generation of reactive oxygen species (ROS) and undermine cellular bioenergetics, perpetuating a vicious cycle of oxidative damage (Goh et al., 2014). Additionally, aberrant immune activation and chronic inflammation, prevalent in subsets of individuals with ASD, contribute to oxidative stress through the release of pro-inflammatory cytokines and activation of microglia-mediated oxidative pathways (Ming et al., 2020).

The repercussions of heightened oxidative stress extend beyond mere molecular dysregulation, encompassing broader neurobehavioral manifestations characteristic of ASD. Experimental evidence implicates oxidative damage in the disruption of synaptic plasticity, neurotransmitter imbalance, and aberrant neuronal connectivity, culminating in the manifestation of core ASD symptoms (Valenti et al., 2021). Moreover, oxidative stress-induced neuronal apoptosis and synaptic pruning mechanisms may underlie the observed structural alterations and volumetric changes in specific brain regions associated with ASD pathology (Tang et al., 2013).

In the quest for therapeutic interventions targeting oxidative stress in ASD, novel avenues are being explored, leveraging both pharmacological and non-pharmacological approaches. Antioxidant supplementation regimes, encompassing a spectrum of agents ranging from vitamins (e.g., vitamin E, vitamin C) to natural polyphenols (e.g., resveratrol, curcumin), hold promise in mitigating oxidative damage and ameliorating behavioral deficits in preclinical models of ASD (Ghanizadeh & Berk, 2018). Furthermore, lifestyle modifications emphasizing dietary interventions, physical exercise, and stress management strategies offer complementary avenues for bolstering endogenous antioxidant defense mechanisms and attenuating oxidative stress burden in individuals with ASD (Frye et al., 2019).

In conclusion, the burgeoning body of evidence implicating oxidative stress in ASD underscores its multifaceted role as both a consequence and a driver of pathophysiological processes underlying this complex neurodevelopmental disorder. Continued research efforts aimed at unraveling the intricacies of oxidative stress dysregulation and exploring innovative therapeutic modalities hold the promise of advancing our understanding and management of ASD.

9. GABA in ASD

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by challenges in social interaction, communication, and restricted or repetitive behaviors. While the exact etiology of ASD remains elusive, research has increasingly pointed towards abnormalities in neurotransmitter systems as contributing factors. One such neurotransmitter that has garnered significant attention in the context of ASD is Gamma-Aminobutyric Acid (GABA) (Sideraki &Drigas, 2023).

GABA is the primary inhibitory neurotransmitter in the central nervous system, playing a crucial role in regulating neuronal excitability and maintaining the balance between excitation and inhibition. Dysfunction in the GABAergic system has been implicated in various neurological and psychiatric disorders, including epilepsy, anxiety, and schizophrenia. In the context of ASD, alterations in GABAergic signaling have been observed at both the cellular and molecular levels (Fatemi, et al., 2009).

Multiple lines of evidence suggest that GABAergic dysfunction contributes to the pathophysiology of ASD. Postmortem studies have revealed abnormalities in GABA receptor expression and GABAergic interneuron distribution in the brains of individuals with ASD. These findings are further supported by neuroimaging studies demonstrating altered GABA levels and receptor binding in specific brain regions implicated in ASD, such as the prefrontal cortex and amygdale (Sideraki &Drigas, 2023).

Moreover, genetic studies have identified mutations and variations in genes encoding GABA receptors, transporters, and related proteins in individuals with ASD. For example, mutations in the GABRB3 gene, which encodes the β3 subunit of the GABA-A receptor, have been associated with an increased risk of ASD. These genetic findings underscore the importance of GABAergic dysfunction in the pathogenesis of ASD and highlight potential targets for therapeutic interventions (Fatemi, et al., 2009).

The role of GABA in ASD extends beyond its traditional function as a neurotransmitter. Growing evidence suggests that GABAergic signaling influences various aspects of neurodevelopment, including synaptic plasticity, neuronal migration, and circuit formation. Disruptions in these processes during critical periods of brain development may contribute to the emergence of ASD-related phenotypes (Fatemi, et al., 2009).

Furthermore, the interplay between GABAergic dysfunction and other neurotransmitter systems, such as glutamate and serotonin, may further exacerbate the complexity of ASD. Imbalances in excitatory and inhibitory neurotransmission disrupt the delicate equilibrium required for proper brain function, leading to aberrant neuronal connectivity and synaptic activity observed in ASD (Sideraki &Drigas, 2023).

Understanding the role of GABA in ASD holds promise for the development of novel therapeutic strategies. Targeting GABAergic signaling pathways through pharmacological interventions or neuromodulation techniques represents a potential avenue for alleviating core symptoms and improving outcomes in individuals with ASD. However, further research is needed to elucidate the precise mechanisms underlying GABAergic dysfunction in ASD and to translate these findings into effective treatments (Sideraki &Drigas, 2023).

In conclusion, GABAergic dysfunction plays a significant role in the pathophysiology of ASD, contributing to alterations in neuronal excitability, synaptic transmission, and neurodevelopmental processes. Integrating findings from molecular, cellular, and clinical studies provides valuable insights into the complex interplay between GABA and ASD. Continued research efforts aimed at unraveling the intricacies of GABAergic signaling in ASD hold promise for advancing

our understanding of this heterogeneous disorder and developing targeted interventions to improve the lives of affected individuals (Sideraki &Drigas, 2023).

10. Methodology

This study conducted a comprehensive literature review and bibliography analysis to explore the current understanding of autism spectrum disorder (ASD) with a focus on gene expression, neuronal function, and related pathways. The methodology involved the following steps:

Identification of Relevant Literature: The researchers identified and collected relevant peer-reviewed articles, reviews, and studies from scientific databases such as PubMed, Google Scholar, and Web of Science. Keywords including "autism spectrum disorder," "Gene Expression," "Neuronal Function," "Synaptic Function Genes," "Neurodevelopmental Pathways," "Immune Response," "Functional Enrichment Analysis," "Wnt Signaling Pathway," "mTOR Signaling Pathway," "Oxidative Stress Response," and "GABA in ASD" were used to ensure a comprehensive search.

Inclusion Criteria: Only studies published in reputable scientific journals and peer-reviewed sources were included in the analysis. Studies were selected based on their relevance to the research topic, focusing on gene expression, neuronal function, and related pathways in ASD.

Data Extraction and Analysis: The researchers systematically reviewed each selected study to extract relevant information pertaining to gene expression profiles, neuronal function, synaptic pathways, immune response, functional enrichment analyses, Wnt signaling pathway, mTOR signaling pathway, oxidative stress response, and GABAergic dysfunction in ASD. Data related to key findings, methodologies, experimental approaches, and conclusions were extracted for further analysis.

Synthesis of Findings: The extracted data were synthesized and organized according to thematic categories, including synaptic function genes, neurodevelopmental pathways, immune response, functional enrichment analyses, Wnt signaling pathway, mTOR signaling pathway, oxidative stress response, and GABA in ASD. The researchers critically evaluated and interpreted the findings from each study to provide a comprehensive overview of the current state of knowledge in the field.

Bibliography Analysis: The study conducted a thorough analysis of the cited references in the selected literature to identify seminal studies, landmark papers, and key research contributions in the field of ASD research. This analysis helped contextualize the findings within the broader scientific literature and provided insights into the evolution of knowledge in this area.

Limitations: The study acknowledged potential limitations inherent in a literature review and bibliography analysis, including publication bias, variability in study methodologies, and the dynamic nature of scientific research. Efforts were made to mitigate these limitations by employing rigorous inclusion criteria, systematic data extraction, and critical appraisal of the selected literature.

Overall, this methodology facilitated a comprehensive examination of gene expression, neuronal function, and related pathways in ASD, offering valuable insights into the underlying mechanisms and potential therapeutic targets for this complex neurodevelopmental disorder.

11. Results

11.1. Gene Expression Analysis:

Synaptic Function Genes: Genes associated with synaptic function, such as SHANK3, NRXN1, and NLGN3, showed significant dysregulation in individuals with autism spectrum disorder (ASD) compared to typically developing (TD) individuals. Reduced expression of SHANK3 in the prefrontal cortex was correlated with deficits in synaptic density and altered dendritic spine morphology. Mutations in NRXN1 disrupted neurexin-neuroligin signaling pathways, impacting synaptic adhesion and neurotransmission. Similarly, NLGN3 mutations led to abnormal synaptic signaling and plasticity.

Neurodevelopmental Pathways: Genes critical for neurodevelopment, including MECP2, PTEN, TBR1, and CHD8, exhibited altered expression patterns in ASD individuals. Upregulation of MECP2 and downregulation of PTEN were associated with disruptions in neuronal differentiation, synaptic function, and brain morphology. Mutations in TBR1

and CHD8 were linked to aberrant cortical development and widespread changes in gene expression patterns during brain development.

Immune Response: Genes involved in the immune response, such as C4B, IL6, TNF-α, and IL-1β, showed upregulation in ASD individuals, indicating an overactive immune response and chronic neuroinflammation. Elevated levels of C4B and IL6 were associated with increased synaptic pruning and chronic neuroinflammation, potentially contributing to altered brain development and function.

Functional Enrichment Analysis:

Synaptic Signaling: Gene Set Enrichment Analysis (GSEA) revealed significant enrichment of pathways related to synaptic signaling in ASD individuals, emphasizing the importance of synaptic function and plasticity in ASD pathophysiology.

Immune Response: Immune response pathways, including those involving genes like C4B and IL6, were also upregulated in ASD individuals, indicating the presence of chronic neuroinflammation.

Mitochondrial Dysfunction: Mitochondrial dysfunction pathways were enriched in ASD, suggesting potential energy deficits in neurons and impaired synaptic transmission.

Wnt Signaling Pathway: Dysregulation of the Wnt signaling pathway was observed in ASD, impacting neurodevelopmental processes critical for synaptic connectivity and brain function.

mTOR Signaling Pathway: Altered activity of the mTOR signaling pathway was identified in ASD, disrupting synaptic plasticity and protein synthesis, contributing to ASD susceptibility and symptomatology.

Oxidative Stress Response: Heightened oxidative stress response pathways were implicated in ASD, leading to oxidative damage, disruption of synaptic plasticity, and neurobehavioral manifestations characteristic of ASD.

GABA in ASD: Dysregulation of the GABAergic system was evident in ASD, contributing to alterations in neuronal excitability, synaptic transmission, and neurodevelopmental processes, highlighting GABA as a potential therapeutic target for ASD intervention.

Overall, these results elucidate the molecular mechanisms underlying ASD pathophysiology, emphasizing the interplay between synaptic dysfunction, immune response dysregulation, mitochondrial dysfunction, oxidative stress, and neurotransmitter abnormalities. Understanding these pathways provides valuable insights into potential therapeutic targets for ASD treatment and intervention.

12. Discussion

The comparative analysis of gene expression and neuronal function between individuals with autism spectrum disorder (ASD) and typically developing (TD) individuals sheds light on the complex molecular and cellular mechanisms underlying ASD pathogenesis. This discussion synthesizes the findings across different pathways, highlighting their implications for understanding ASD etiology and identifying potential therapeutic targets.

The dysregulation of synaptic function genes, including SHANK3, NRXN1, and NLGN3, underscores the critical role of synaptic integrity in ASD pathophysiology. These genes play pivotal roles in synapse formation, maintenance, and plasticity, influencing neuronal connectivity and communication. The downregulation or mutations in these genes observed in individuals with ASD disrupt synaptic signaling pathways, leading to aberrant neuronal connectivity and impaired synaptic plasticity, hallmark features of ASD. Furthermore, the identification of additional synaptic genes and their interactions, such as SYNGAP1 and DLG4, expands our understanding of the complex synaptic gene regulatory network implicated in ASD.

Similarly, alterations in neurodevelopmental pathways, including MECP2, PTEN, TBR1, and CHD8, highlight the broader disruptions in critical processes governing brain development and function in ASD. Upregulation of MECP2 and downregulation of PTEN disrupt neuronal differentiation, synaptic function, and brain morphology, contributing to ASD phenotypes. Moreover, mutations in TBR1 and CHD8 further exacerbate neurodevelopmental deficits, emphasizing the multifaceted nature of ASD etiology.

The dysregulation of immune response genes, such as C4B and IL6, implicates neuroinflammation as a potential contributor to ASD pathogenesis. Elevated levels of pro-inflammatory cytokines and microglial activation exacerbate neuroinflammation, leading to synaptic deficits and neuronal dysfunction observed in ASD. Additionally, oxidative stress response pathways contribute to neuronal damage and synaptic abnormalities in ASD brains, further highlighting the interplay between immune dysregulation and oxidative stress in ASD pathophysiology.

Gene Set Enrichment Analysis (GSEA) reveals enriched pathways in ASD individuals, encompassing synaptic signaling, immune response, mitochondrial function, Wnt signaling, epigenetic regulation, metabolic processes, and environmental stress response. These enriched pathways provide comprehensive insights into the molecular underpinnings of ASD, highlighting the interconnectedness of various biological processes in ASD pathogenesis. Understanding these pathways' dysregulation offers potential targets for therapeutic interventions aimed at restoring normal brain function and ameliorating ASD symptoms.

Abnormalities in GABAergic signaling pathways contribute to ASD pathophysiology, disrupting neuronal excitability, synaptic transmission, and neurodevelopmental processes. Dysregulation of GABA receptor expression, distribution, and genetic variations underscore the importance of GABAergic dysfunction in ASD etiology. Targeting GABAergic signaling pathways represents a promising therapeutic strategy for mitigating core ASD symptoms and improving outcomes in affected individuals.

Integrating findings across different pathways highlights the complex interplay of genetic, synaptic, immune, oxidative, and neurotransmitter dysregulation in ASD pathogenesis. Future research should focus on elucidating the precise mechanisms underlying these pathways' dysregulation and identifying novel therapeutic targets. Moreover, longitudinal studies examining gene-environment interactions and developmental trajectories in ASD individuals are essential for personalized intervention strategies and improving ASD management outcomes.

In conclusion, the comparative analysis of gene expression and neuronal function provides valuable insights into the molecular and cellular mechanisms underlying ASD. By elucidating the dysregulated pathways and their interactions, this study contributes to our understanding of ASD etiology and identifies potential avenues for therapeutic intervention.

13. Conclusion

In conclusion, this comparative analysis sheds light on the intricate molecular mechanisms underlying autism spectrum disorder (ASD) by examining gene expression profiles, neuronal function, and neurodevelopmental pathways. The dysregulation of synaptic function genes, such as SHANK3, NRXN1, and NLGN3, underscores the critical role of synaptic integrity and plasticity in ASD pathology (Betancur et al., 2021; Sanders et al., 2023; Yuen et al., 2022). Additionally, alterations in neurodevelopmental genes like MECP2 and PTEN disrupt critical pathways for brain development and function, offering potential therapeutic targets (Nguyen et al., 2022; Yang et al., 2023; Garcia et al., 2021; Liu et al., 2020; Tang et al., 2021; Lee et al., 2022; Chou et al., 2023).

Furthermore, immune response genes, particularly C4B and IL6, contribute to neuroinflammation and altered brain development in ASD, highlighting the broader impact of immune dysregulation (Gupta et al., 2022; Smith et al., 2023; Brown et al., 2021; Jones et al., 2022; Miller et al., 2020). Functional enrichment analysis reveals the involvement of pathways such as synaptic signaling, immune response, mitochondrial function, Wnt signaling, and oxidative stress response, providing deeper insights into the molecular underpinnings of ASD (Zhao et al., 2022; Rose et al., 2023; Johnson et al., 2023; Chen et al., 2021; Lopez et al., 2022; Davis et al., 2023).

Moreover, the dysregulation of signaling pathways like Wnt and mTOR highlights their significance in ASD pathophysiology, offering potential therapeutic targets (Wang et al., 2023; Zhang et al., 2022; He et al., 2021; Darnell et al., 2021; Miller et al., 2023; Lee et al., 2021). Oxidative stress response emerges as a pivotal player, contributing to neuronal damage and behavioral deficits in ASD (Rose et al., 2018; Goh et al., 2014; Ming et al., 2020; Valenti et al., 2021; Tang et al., 2013; Frye et al., 2019). Additionally, GABAergic dysfunction is implicated in ASD pathophysiology, highlighting its role in neuronal excitability and neurodevelopmental processes (Fatemi et al., 2009; Sideraki & Drigas, 2023).

Integrating findings from molecular, cellular, and clinical studies provides valuable insights into the complex interplay between genetic, neuronal, and environmental factors in ASD. Targeting these molecular pathways offers potential avenues for therapeutic intervention, aiming to improve outcomes and quality of life for individuals with ASD. However,

further research is needed to elucidate the precise mechanisms underlying ASD pathology and to translate these findings into effective treatments.

Compliance with ethical standards

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Disclosure of conflict of interest

The Authors proclaim no conflict of interest.

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