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Growth Factors, Cell Receptors, Intracellular Kinases, and Transcription Factors Associated with Autism

Russo AJ[1,2]*, Albert Mensah[2] and Judith Bowman[2]

[1]*Visiting Professor, Hartwick College, Oneonta, New York, USA.*

[2]*Mensah Research Institute, Warrenville, USA.*

***Correspondence:**
Russo A J, Visiting Professor, Hartwick College, Oneonta, New York, USA, Tel: 240-394-0351.

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ABSTRACT

Autism is a spectrum of complex neurodevelopmental disorders characterized by a wide range of symptoms affecting social interaction, communication, and behavior. Research has shown that cellular growth factors, receptors, intracellular kinases, and transcription factors may be involved in the etiology of the spectrum of these disorders. This paper is a review of some of the associated research.

Keywords

Autism, Growth Factors, Cell Receptors, Intracellular Kinases.

Growth Factors Associated with Autism

Autism is a complex neurodevelopmental disorder characterized by a wide range of symptoms affecting social interaction, communication, and behavior. Research has shown that cellular growth factors play a significant role in the pathogenesis of autism. Several studies have highlighted the involvement of various growth factors in the development and progression of autism. One of the key growth factors associated with autism is the Met signaling pathway. The Met gene has been implicated in regulating cerebellar development and facial motor neuron migration, processes crucial for proper brain development [1].

Additionally, studies have shown that the Met/HGF signaling pathway is essential for cerebellar morphogenesis, emphasizing the importance of this pathway in hindbrain cell migration [2]. Brain overgrowth, a well-established biological feature of autism, has been linked to abnormal cellular growth factors. Accelerated brain growth during early childhood followed by premature arrest of growth has been observed in individuals with autism [3]. This abnormal brain growth has been associated with cellular abnormalities and processes that affect brain structures, including the cerebellum [4].

Furthermore, various growth factors such as Fibroblast Growth Factor (FGF) and Brain-Derived Growth Factor (BDNF) have been implicated in the pathogenesis of autism due to their roles in embryonic growth and differentiation [5]. Studies have also reported elevated levels of growth-related hormones like IGF-1, IGF-2, and IGFBP-3 in children with autism, indicating dysregulation of growth factor signaling in individuals with autism spectrum disorder [6]. Moreover, neurotrophic factors like nerve growth factor (NGF) have been found to differ in individuals with autism, suggesting a potential role in the neurobiological mechanisms underlying the disorder [7]. Additionally, abnormalities in growth factors such as Epidermal Growth Factor (EGF) have been associated with autism, with studies reporting decreased EGF levels in young autistic children [8].

In conclusion, cellular growth factors play a crucial role in the pathogenesis of autism. Dysregulation of growth factor signaling pathways, abnormal brain growth patterns, and altered levels of growth-related hormones have been identified in individuals with autism. Understanding the intricate interplay of these cellular growth factors is essential for unraveling the underlying mechanisms of autism and developing targeted interventions for affected individuals.

Cell Receptors Associated with Autism

Research has identified several cell receptors associated with autism, shedding light on the underlying neurobiological mechanisms. One of the key findings is the involvement of the

γ-aminobutyric acid (GABA) system in autism. Studies have shown that GABA receptor genes are linked to autism through linkage and copy number variation studies, with fewer GABA receptor subunits observed in post-mortem tissue of autistic individuals [9,10]. Additionally, disruptions in GABAergic signaling have been noted in various mouse models of autism [9].

Furthermore, the endocannabinoid system has been implicated in autism spectrum disorders. Dysregulation of endocannabinoid signaling, particularly through the upregulation of CB2 receptors, has been associated with autism-related neuro-immune alterations [11]. Moreover, the oxytocin receptor (OXTR) gene has been identified as a candidate gene for susceptibility to ASD, with studies showing an association between OXTR gene polymorphisms and autism spectrum disorder [12,13].

In addition to GABA and endocannabinoid systems, other receptors such as glutamate receptors and adrenergic receptors have also been linked to autism. For instance, the glutamate receptor 6 gene (GRIK2) has been suggested as a candidate gene for autism, due to its localization in an autism-specific region and its role in cognitive functions [14]. Moreover, the activation of β2-adrenergic receptors and genetic polymorphisms in these receptors have been associated with an increased risk for autism, particularly when overstimulated during prenatal development [15,16].

The killer-cell immunoglobulin-like receptors (KIR) and their cognate HLA ligands have also been implicated in autism, suggesting a role for immune system interactions in the development of the disorder [17]. Furthermore, alterations in GABA receptors, GABAB receptors, and oxytocin levels have been observed in individuals with autism, pointing towards disruptions in neurotransmission systems in the brain [18,19]. Overall, the research indicates a complex interplay of various cell receptors and neurotransmitter systems in the pathophysiology of autism spectrum disorder. Understanding these molecular mechanisms is crucial for developing targeted interventions and treatments for individuals with autism.

Intracellular Kinases Associated with Autism

Several intracellular kinases have been implicated in the pathogenesis of autism based on research findings. Among these kinases, protein kinase B (AKT) [20] and cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) have been identified as playing key roles in neuron membrane trafficking associated with autism [21].

Additionally, the ERK/MAPK pathway has been highlighted as commonly affected in autistic patients, suggesting a potential link to autism [22]. The ERKs, part of the ERK/MAPK pathway, have genetic links to autism spectrum disorders (ASDs) and other cognitive disorders [23]. Mutations in elements of the ERK/MAPK pathway can alter ERK activity, leading to a group of genetic disorders known as "RASopathies" [24]. Moreover, abnormalities in interactions of Rho GTPases with scaffolding proteins have been associated with neurodevelopmental disorders, including autism [25]. The Rho GTPases, along with SHANK proteins and associated signaling pathways, are believed to contribute to the development of autism symptoms in various conditions. Furthermore, defects in phosphoinositide metabolism have been observed in autism spectrum disorders, with mutations in PTEN and altered activity of phosphoinositide kinases and phosphatases implicated in certain forms of autism [26].

The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt/FASN and adenosine 5′-monophosphate-activated protein kinase (AMPK)/ACC pathways have also been suggested to be involved in the pathogenesis of autism [27].

Intracellular pathways associated with autism involve a complex interplay of various kinases and signaling molecules. The dysregulation of these pathways can lead to altered cellular signaling, affecting neuronal function, and contributing to the development of autism. The intricate network of intracellular kinases associated with autism underscores the importance of understanding the molecular mechanisms underlying this disorder for the development of targeted therapeutic interventions.

Transcription Factors Associated with Autism

Transcription factors play a crucial role in gene regulation and have been implicated in various neurodevelopmental disorders, including autism spectrum disorder (ASD). Several studies have highlighted the involvement of specific transcription factors in the pathogenesis of ASD. Mutations in chromatin regulators and transcription factors are among the most common genetic causes of neurodevelopmental disorders, with over 150 of them listed in the Simons Foundation Autism Risk Initiative database [28]. These findings underscore the importance of understanding the molecular pathways and circuits involved in ASD [29].

One such transcription factor is T-brain-1 (TBR1), which has been identified as a high-confidence risk gene for ASD [30]. TBR1 is a critical neuron-specific transcription factor for forebrain development and controls a transcriptional cascade relevant to autism pathogenesis by regulating genes like Auts2, Nfia, Nr4a2, and Sox5 [31]. Additionally, Forkhead box p1 (FOXP1), another transcription factor, has been associated with ASD, as heterozygous loss-of-function mutations in FOXP1 are strongly linked to autism [32]. Furthermore, transcription factors such as Transcription factor 4 (TCF4) have been identified as critical regulators of neurodevelopment and have been linked to the pathogenesis of ASD, intellectual disability, and schizophrenia [33].

The disruption of activity-regulated transcription may represent a common pathophysiological mechanism in genetically heterogeneous causes of autism [34]. Moreover, large-scale genetic studies have revealed that chromatin regulators mediating histone methylation/demethylation play a central role in ASD, suggesting the significance of epigenetic dysfunction in this disorder [35].

CREB (cAMP response element-binding protein) is a cellular transcription factor which plays a role in neuronal plasticity and

long-term memory formation in the brain. CREB levels were found to be significantly lower in individuals with autism [36]. Additionally, the nuclear respiratory factor-1 (NRF1) transcription factor has been shown to regulate several autism-related genes, including Cntnap2 and the fragile X-related 2 gene, highlighting its role in ASD pathophysiology [37].

In conclusion, transcription factors are key players in the complex molecular pathways underlying ASD. Understanding the roles of specific transcription factors such as TBR1, FOXP1, TCF4, and NRF1 can provide valuable insights into the pathogenesis of ASD and may offer potential targets for therapeutic interventions aimed at addressing the underlying molecular mechanisms of this neurodevelopmental disorder.

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