AIMS Genetics, 3(4): 292-299.
DOI: 10.3934/genet.2016.4.292
Received: 08 September 2016
Accepted: 28 November 2016
Published: 09 December 2016

http://www.aimspress.com/journal/Genetics

Review

Epigenetic regulation in Autism spectrum disorder

Sraboni Chaudhury*

Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI-48109, USA

*** Correspondence:** Email: sraboni@med.umich.edu; Tel: +1-734-615-2995.

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by an impaired social communication skill and often results in repetitive, stereotyped behavior which is observed in children during the first few years of life. Other characteristic of this disorder includes language disabilities, difficulties in sensory integration, lack of reciprocal interactions and in some cases, cognitive delays. One percentage of the general population is affected by ASD and is four times more common in boys than girls. There are hundreds of genes, which has been identified to be associated with ASD etiology. However it remains difficult to comprehend our understanding in defining the genetic architecture necessary for complete exposition of its pathophysiology. Seeing the complexity of the disease, it is important to adopt a multidisciplinary approach which should not only focus on the "genetics" of autism but also on epigenetics, transcriptomics, immune system disruption and environmental factors that could all impact the pathogenesis of the disease. As environmental factors also play a key role in regulating the trigger of ASD, the role of chromatin remodeling and DNA methylation has started to emerge. Such epigenetic modifications directly link molecular regulatory pathways and environmental factors, which might be able to explain some aspects of complex disorders like ASD. The present review will focus on the role of epigenetic regulation in defining the underlying cause for ASD.

Keywords: Autism; DNA methylation; histones; GABA; reelin

1. Introduction

Brain development is a complex plastic process which involves coordination of specific sets of gene expression in a temporal space. The autism spectrum disorders (ASD) are a heterogeneous group of neuro developmental disorders, which show impairment in several behavioral features such as in reciprocal social communication along with restricted and repetitive patterns of behaviors. In

addition, some specific sensory-motor behavioral phenotypes including indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive sensation when smelling or touching objects, and fascination with lights or spinning objects are often refer to as the possible qualifying behavioral symptoms for a diagnosis of ASD [1-3]. Patients diagnosed with ASD also exhibit difficulties in integration of sensory modalities and alteration in motor control (for example, poor manual dexterity and coordination) [4-6]. It has been hypothesized that these abnormalities in sensory-motor modalities, which specifically affect the auditory pathway, could result in communication impairments thereby leading to autism [7-14]. Genetic studies have demonstrated that hundreds of genes may be involved in the pathogenesis of ASD [15-17]. Different genetic variants such as copy number variations, single-nucleotide polymorphisms and de novo mutations have been attributed to the etiology of ASD [18,19]. Altered linguistic style has been observed in ASD and there are number of genes which have been associated with it [20,21]. There are reports, which suggest that immune system plays an important role in the pathophysiology of autism. The altered levels of inflammatory markers, cytokines, and immunoglobulins have been found in brain tissues, cerebral spinal fluid, and in the sera of autistic patients in the autopsy [22]. Despite all of the information regarding genetic components associated with ASD, it is suggested that environmental factors may play a major role in the development of ASD. Within monozygotic twin pairs, there are notable differences for diagnosis and symptom severity in ASD [23]. In separate studies, the correlation for heritability of ASD among twin and sibling has moderate genetic component and a significantly larger environmental component [24]. Environmental factors such as maternal hospitalization due to viral infections during the first trimester of pregnancy and prenatal exposure to sodium valproate could be correlated to ASD occurrence [25,26]. Additional factors, such as drugs, pollutants and several xenobiotics are strongly attributed to ASD pathophysiology [27]. Therefore, one can hypothesize that the molecular changes that are involved in the development of ASD are likely to be regulated by mechanisms which are, in part, modulated by environmental cues. In this context, epigenetic mechanism, such as DNA methylation and histone modifications might provide a linkage between the environmental stimuli and gene expression altered in ASD [28-30]. Epigenetic regulation including DNA methylation, histone protein modifications, and microRNAs function regulate the transcriptional potential of a cell without altering its DNA sequence. The alteration in epigenetic marks is crucial during neurodevelopment and any disruption could lead to significant impacts on neurodevelopment and cognitive function [31-34]. Further, studies have revealed chromatin remodeling and mRNA translation are important biological pathways associated with ASD [35]. Thus, it is crucial to understand the role of epigenetic regulation in the pathophysiology and etiology of ASD.

2. Effect of DNA Methylation in ASD

DNA methylation is one of the most widely studied epigenetic modifications in neurodevelopment disorder including ASD. DNA methylation involves the covalent attachment of a methyl (CH3) group to the cytosine of a CpG dinucleotide [36,37]. DNA methylation is known to be associated with transcriptional repression either via direct inhibition of transcription factor binding or the recruitment of methyl CpG binding domain (MBD) proteins, which interact with histone modifiers to converse a repressive chromatin state with the help of DNA methyltransferase (DNMT). DNMT1 functions mainly in maintenance of DNA methylation whereas DNMT3A and DNMT3B are predominantly in de novo DNA methylation [38]. However, the function of these enzymes are

very important as global deletion of mouse Dnmt1, Dnmt3b, or both Dnmt3a + Dnmt3b cause midgestation lethality (gestational day (GD) 9.5–11.5), while deletion of only Dnmt3a results in severe growth retardation and is lethal by 4 weeks of age [39-41]. It was found that in ASD, GAD1 (glutamate decarboxylase 1) expression is likely regulated by epigenetic mechanisms including DNMT-mediated DNA hypermethylation and DNA demethylation, which is associated with the initial hydroxylation of 5-mC to form 5-hmC by members of the TET protein family [42]. These studies suggest that alteration in the enzymes catalyzing DNA methylation is critical for normal neurodevelopmental processes. Genetic and environmental variation, and an interaction between the two, can influence epigenetic change. Like genome wide studies, epigenome-wide association studies (EWAS) have been done to understand the epigenetic state in ASD [43-49]. Studies have shown that in ASD hypo methylated genes are often overexpressed. Further there is an inverse correlation between gene expression (C1Q, C3, ITGB2 (C3R), TNF-α, IRF8 and SPI1) and DNA methylation within the ASD individuals. These genes are involved in synaptic pruning and microglial cell specification [46]. In the same article it was observed that HDAC4 was significantly overexpressed in autistic subjects and gene expression of HDAC4 has complex relation with DNA methylation in the autistic brain especially in the cortical regions. Studies have shown that oxidative DNA lesions and an altered pattern of DNA methylation are important molecular features of the autism cerebellar phenotype. It is also demonstrated that DNA isolated from the cerebellum of BTBR T+tf/J mice and post-mortem cerebellum of individuals with autism, is characterized by an increased levels of 8-oxodeoxyguanosine, 5-methylcytosine, and 5-hydroxymethylcytosine [50]. The development of ASD has been long associated with increased paternal age. DNA methylation is responsible for errors during spermatogenesis and could help is explaining a potential cause this phenomenon. DNA methylation in paternal sperm has been linked to an early risk for autism in children [51]. There are DNA-binding proteins with methyl-CpG binding domains (MBDs), known as the MBD protein family which are associated with DNA methylation. They act as transcriptional repressors by binding to 5mC and interact with many components. RTT (Rett Syndrome) is caused by mutation of methyl-CpG binding protein 2 (MeCP2) [52]. MeCP2 is a nuclear protein that attaches to methylated DNA and regulates gene expression by transcription repression. Loss or mutation of MeCP2 causes transcriptional deregulation and is characteristics of RTT. RTT subjects do have ASD like phenotypes. Also, patients with Fragile X syndrome have a characteristic physical appearance and impaired behavior with co-occurrence of ASD in 25% of male and 6% of female patients [53]. These studies suggest that DNA methylation plays an important role in the pathophysiology of ASD and related disorders.

3. Effect of chromatin remodeling in ASD

Chromatin remodeling is a dynamic process, which regulates the gene expression by altering condensed genomic DNA accessibility. Chromatin structure is influenced by posttranslational modifications on N-terminal tails of histone proteins. With the advancement in next-generation sequencing, the lists of histone modifiers that are mutated in human neurodevelopmental disorders have been identified in large number. In ASD large-scale exome sequencing, studies have highlighted the dysregulation of histone methylation to be one of the major factor [54,55]. Therefore, regulation of modified histone is very critical for the development and function of the central nervous system. Histone lysine methyltransferases which is the primary regulator of methylated H3K4 has been

shown to be mutated in ASD [56]. Studies have shown a reduction in the levels of H3K9me3 and increased acetylated H3K9 in the deficient MeCp2 mouse which is considered to be mouse model for Rett syndrome (that has ASD like phenotype) as well as in RTT patients [57]. Exposure to valproic acid (VPA) during pregnancy has been implicated in the etiology of children with ASD [58-61]. In rodents prenatal VPA exposure showed behavioral alterations similar to those observed in humans with autism [62,63]. Inhibiting HDACs is one of the likely mechanisms responsible for the VPA-induced ASD-like phenotype. The inhibition of histone deacetylation causes increased levels of acetylated histones along with changes in DNA methylation [64]. Both mechanisms act in a coordinated fashion to relax the chromatin states which finally results in promoting gene expression [65]. During embryonic brain development, VPA-mediated histone modifications which regulate genes associated with ASD are likely to be more vulnerable. On the other hand, postnatal exposure to VPA is shown to increase the expression of genes linked to the GABAergic phenotype in terminally differentiated neurons. It has been reported that in terminally differentiated neurons, VPA increases expression of GAD1 and REELIN [64,66], both of which have been implicated in the pathophysiology of ASD [67]. Studies have shown the implication of dysregulation of epigenetically modified genes including GABA receptor genes, and REELIN in ASD [68]. From all these studies it is clear that chromatin remodeling is an important feature that plays a differential role in various phase of brain development. Thus, understanding regulation of chromatin remodeling might be a crucial aspect in the etiology of ASD.

4. Conclusion

It has been observed that ASD is a complex syndrome with alteration in behavior as well as in structural and molecular changes in developing brain. It is evident that the alteration in various brain areas in ASD is due to ablation in various genes as well as several environmental factors. With the new insight of epigenetic regulation it is possible that alteration of genes might be induced by environmental factors via epigenetic modifications. There are several genes which are associated with ASD such as GAD67 (GAD1), Reelin, GABA β3, Oxytocin receptor (OXTR), Brain-derived neutrophic factor (BDNF), Ubiquitin–protein ligase E3A (UBE3A), Engrailed-2 (EN-2), SH3 and multiple ankyrin repeat domains (SHANK3). Additionally, it has also been shown that there is an abnormality in the methylated region of the UBE3A coding exons [69]. It was found that the action of these genes in ASD is mediated by either DNA methylation or chromatin remodeling. Therefore, more studies are required to understand the detail mechanism associated with different epigenetic regulation to identify more specific drug target for the complex disease like ASD.

Conflict of interest

The author declares no conflict of interest.

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