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How do alterations in epigenetic mechanisms cause intellectual disability?

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Abstract
Intellectual disability is associated with many syndromes, its main symptom includes low IQ. There are a variety of genetic and non-genetic causes of ID including environmental factors, chromosomal aberrations and single gene mutations. One example of ID that have been explored have to do with the enzyme ATRX which enhances transcription and remodels chromatin. Due to its involvement in chromatin remodeling ATRX can affect the expression of genes, through turning genes on. ATRX assists learning and memory hence leading to ID when organisms are ATRX-null. Chromatin remodeling enzymes can also cause ID by affecting neural progenitor generation, neural circuits and neural migration. These syndromes assist in comprehending the logistics in the KAT5 syndrome. The KAT5 syndrome comprises variants in the KAT5 enzyme and causes detrimental effects on neurodevelopment, leading to ID. TIP60-CB and acetyl-coA binding domains are 2 key domains in the lysine acetyltransferase enzyme (KAT5), mutations in these domains have been studied and have proven to cause ID. This data suggests that reduced acetyl of chromatin in neural cells, may lead to an impairment in cognition and memory (ID).
Keywords: Intellectual disability, neurodevelopment, chromosome, DNA, ATRX, Epigenetic, Chromatin remodeling, KAT5, histone, TIP60-CB, Acetyl-coA and DNA acetylation.
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1. Intellectual disability syndrome.

Intellectual disability (ID) is a symptom of many clinical syndromes characterized by impaired intellectual functioning and cognitive abilities[1]. Intellectual disability is usually defined as an IQ below 70[2]. Two of the most common causes of ID syndrome are Fragile X syndrome and Down syndrome[3]. Fragile x syndrome includes learning disabilities and other cognitive impairments while Down syndrome is recognized by delayed development and physical signs. Research has shown that some ID syndromes can be linked back to epigenetic regulators and chromatin modifying enzymes. Epigenetic regulators are proteins or enzymes that directly affect the chromatin.

2. Causes of ID

The causes of ID syndromes are heterogeneous and include environmental factors, chromosomal aberrations, and single gene mutations [4].

2. 1 Environmental factors

A study by Reichenburg et al[4] explores the plethora of environmental factors that could possibly lead to ID, specifically studying twins. Reichenburg reveals that in cases of mild ID the twin of the proband is likely to have low IQ as well, thus indicating that IQ distribution is normal in twins even with mild intellectual disability involved. However in cases of severe ID the twin of the proband is found to have an average IQ. Concluding that being twins plays a role in causing ID and is counted as an environmental factor. Furthermore Modabbernia has documented that hypoxia, excess supply of oxygen in tissues and organs, near birth can lead to severe ID[5]. Rantakallio[6] and McDermott[7] through their investigations exhibit the damage that toxins and infections in the prenatal stage have on the childs' neurodevelopment, explicitly how it can be the source of ID. It is evident that there are crucial stages of development throughout the pregnancy of the childs' brain, Roth Christine et al[8] observed that maternal nutrition at the early stages of pregnancy could have effects on the language development of a child. To summarize environmental factors such as the prenatal stage and IQ distribution in twins are potential causes of ID.

2.2 Chromosomal aberrations

Chromosomal aberrations are abnormalities in the structure or the number of chromosomes in a cell of an organism[9].

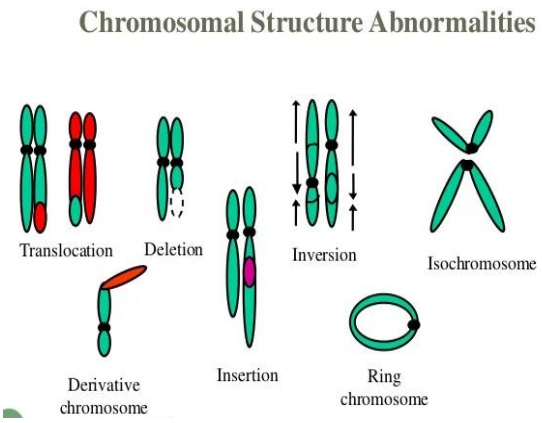

Figure 2[28]: These are the different types of chromosomal aberrations. Translocation refers to when a piece of one chromosome breaks off and attaches to a different chromosome. Deletion is self explanatory, when a piece of chromosome is deleted. Insertion is when a piece of chromosome is added from another chromosome. Inversion is when one chromosome is flipped. Isochromosome is a mirror image, it is when a copy of the long or short arm of a chromosome is made. Derivative chromosome is when the structure of a chromosome is rearranged. Finally the ring chromosome is when the ends of a chromosome have been fused together to create a ring.

2.3 Single gene mutations

Single gene mutations involve an alteration in the DNA nucleotide[29]. Alterations could include: substitution, deletion and insertion of bases.

3. Epigenetic alterations and ID syndromes.

In the following section, I will be discussing mutations in the ATRX enzyme and chromatin remodelers and how that advances to ID. This overview will give a deeper understanding of

epigenetic mechanisms and how they alter chromatin structure giving rise to impairments in neurodevelopment.

3. 1 ATRX and ID

ATRX is a chromatin remodeling enzyme, the remodeling of the architecture of chromatin which enables condensed genetic data to access regulatory transcription machinery proteins, it uses ATP hydrolysis to move nucleosomes on the DNA template or promote nucleosome exchange[10]. It codes for a protein that plays an essential role in the developmental stage of a child. The ATRX protein controls the expression of two genes, HBA1 and HBA2, which are responsible for the production of hemoglobin[12]. ATRX syndrome patients present the following symptoms: ID, skeletal defects, microcephaly, autistic-like behavior, seizures, microcephaly, α-thalassemia, dysmorphic faces, dysmyelination, short stature, and urogenital abnormalities[10]. Furthermore this syndrome is limited to males as it is x-linked. Females with the mutant allele show x chromosome inactivation and are phenotypically normal[10]. The enzyme has recently surfaced as a fundamental factor in heterochromatin formation[13]. ATRX is also shown to encourage transcription. Experiments on mice have shown that the deletion of ATRX in the brain can lead to neuronal apoptosis, microcephaly and reduced survival after birth. Due to the enzyme playing a key role in transcription ATRX-null mice were documented to have DNA replication stress and therefore increased DNA damage[14]. Casanova [15] mated ATRX floxed mice with mice expressing CRE recombinase in postmitotic forebrain pyramidal neurons, in order to study the effects of ATRX on learning and memory. The tested mice presented no signs of microcephaly and high survival rates. However, they appeared to have deficits in hippocampal-dependent spatial learning and memory. This would suggest that ATRX is required in differentiated neurons for memory and spatial learning[1].

3. 2 Chromatin remodeling in neurodevelopmental disorders

Neurodevelopmental disorders (NDD's) are a group of disorders distinguished by impairments in cognition, memory, learning, communication, behavior and motor skills. Some commonly identifiable disorders that are categorized as NDD's are intellectual disability (ID), autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), schizophrenia (SCZ) and mood disorders (bipolar disorder (BD), major depressive disorder (MDD)[16]. NDD's can be caused by both genetic and non-genetic factors, one of the most common non-genetic factors being fetal alcohol syndrome[17]. The complex heterogeneity in NDD's is the major challenge in the diagnosis and early treatment of it. Nevertheless, advanced tools are being used to research the number of gene variants linked to the etiology of the disease[18]. By doing so, chromatin remodeling genes have been identified as highly concentrated in the majority of NDD patients, thus disclosing epigenetics as a potential cause. By modifying the state of genes and histones, chromatin remodelers play an intrinsic part in translating external signals into instructions for changes in gene expression. In addition, chromatin remodelers are versatile proteins that can serve functions across the developmental continuum including neural progenitor generation and specification, cell-type differentiation and expansion, migration and circuit integration[19]. Neural progenitors are cells that have the ability to differentiate into a restricted repertoire of neuronal cell types[20]. Neural migration is the movement of cells from

where they are produced to areas where they will settle into their neural circuits, which are a group of neurons connected by synapses adapted to carry out a specific function. Consequently it can be expected that NDD's caused by chromatin remodeling failure will ultimately result in circuit dysfunction[21]. On that account it can be concluded that mutations in the chromatin remodeling proteins induces mutations in the neurodevelopment of organisms due to the lack of supervision of neural circuits, migration, and progenitor generation.

4. KAT5 syndrome

A study on de novo KAT5 variants revealed ties to intellectual disability. This contemporary syndrome has been titled the KAT5 syndrome[22]. Subjects part of this inspection conferred mutations in the acetyl-coA binding and chromo barrel domain of the KAT5 enzyme. These mutations were associated with intellectual disability recognized by IQ levels below 70. Hence, confirming that these domains have involvement in neurodevelopment and cognition. The subsequent analysis probes on the details of how these specific domains could cause ID.

4. 1 KAT5 function

KAT5 or as some may refer to, Tip60: is an enzyme that adds acetyl groups to histone proteins. Specifically, KAT5 acetylates the amino groups of lysine residues on histones H2A and H4. Histone acetylation plays a critical role in the opening and closing of the chromatin structure which regulates the expression of the gene itself. Heterochromatin refers to a closed chromatin structure, while euchromatin refers to an open chromatin structure.

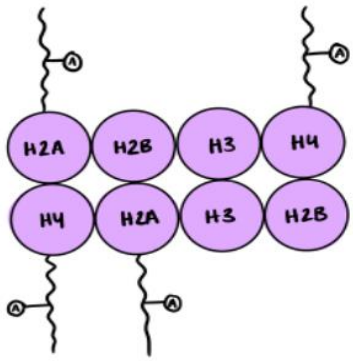

Figure 1: This shows the 8 histone proteins in the nucleosome and the tails of the H4 and H2A type. KAT5 adds acetyl groups to the tails of these proteins, as illustrated in the diagram.

KAT5 has also been involved in several cancer studies regarding the acetylation of the oncogene H2A.Z, which is a variant of the H2A protein. They found that the acetylation of this protein with KAT5 promoted the transcription of downstream genes, leading to the development of tumors. Downstream genes are regulated and affected later in the developmental process.

4. 2 Overview of the Acetyl-coA binding domain

Acetyl- coA is a intermediate involved in many biochemical reactions. Its main purpose is to transport an acetyl group to the citric cycle to be oxidized for energy production. The citric cycle is the prime source of energy for somatic cells and a supporting system for aerobic

respiration. It can be reasoned that this protein is necessary for the functioning of other mechanisms requiring acetylation and therefore essential for the activity of the KAT5 enzyme.

4. 3 Overview of the chromo barrel domain

KAT5 contains a N-terminal chromobarrel domain (TIP60-CB). TIP60-CB acetylates histone and non-histone proteins. Abnormal expression of TIP60 is associated with tumorigenesis of several carcinomas, such as lymphomas, head-and-neck, breast and prostate cancers[24]. TIP60-CB in somatic cells recognizes trimethylated lysine at site 9 of histone H3, this protein triggers TIP60 to acetylate and promotes DSB repair pathway. Therefore it can be assumed that they perform a similar function in neural cells. DSB is DNA -double strand breaks that can result in cell death or a wide variety of genetic alterations including large- or small-scale deletions, loss of heterozygosity, translocations, and chromosome loss[25]. Deducting that TIP60-CB plays an essential role in the KAT5 enzyme by exciting the acetylation of histone proteins, which is the main function of the KAT5 enzyme.

4. 4 DNA acetylation and gene expression

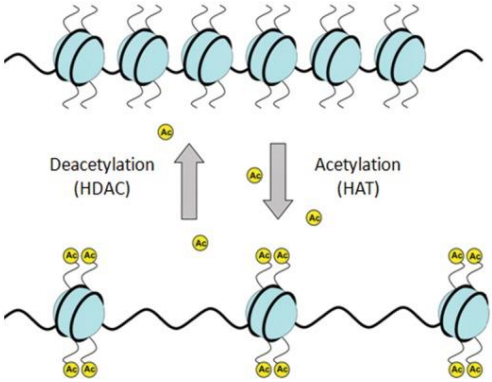

Figure 3: In this diagram histone acetylation is demonstrated to be a mechanism where DNA bonds are expanded and therefore the structure of the DNA is opened. This mechanism causes the DNA to become less compacted and transform into euchromatin. This is called chromatin remodeling which leads to the genes being more accessible and therefore “turned on”. In conclusion this mechanism results in the expression of the acetylated gene thus changing the phenotype of the organism.

4.5 Conclusion of the KAT5 syndrome

The two researched domains of the KAT5 enzyme are chromo barrel and acetyl-coa binding domains. The following domains are allocated key roles in the functioning of the KAT5 enzyme, transporting acetyl groups. Through Jonathan Humberts study it can be deduced that mutations in the two domains lead to low IQ and therefore ID. After studying the epigenetic mechanisms of the domains it can be concluded that KAT5 is necessary for opening up the chromatin structure, euchromatin, and therefore turning the genes on. This in turn changes the gene expression enabling cognition, without this enzyme low IQ and ID can be expected.

5. Future experimental suggestions

Returning to the ATRX study on mice, where mice had ATRX deleted from their neurons. The studies revealed the function of ATRX in neurons by displaying the symptoms of ATRX-null neurons. Through this it was deduced that ATRX was required for learning and memory. I propose a similar study that could be carried out instead for the KAT5 enzyme. Mice could be

tested for memory and learning impairments without the deletion of KAT5 enzyme and then again with the deletion of the enzyme. With this data the exact purpose of the KAT5 enzyme in the brain could be discovered. The mice could be studied using the novel object recognition test (ORT) [31]. This test is usually carried out over a matter of 3 days: habituation day, training day, and testing day.The ORT involved introducing a mouse to 2 objects on day 1 and then replacing one of the objects with a novel object. Since mice have an innate preference for unfamiliar objects, if the mouse recognizes the familiar object it will tend to stay around the new object.

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