



The involvement of epigenetic defects in mental retardation

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ABSTRACT

Mental retardation is a group of cognitive disorders with a significant worldwide prevalence rate. This high rate, together with the considerable familial and societal burden resulting from these disorders, makes it an important focus for prevention and intervention. While the diseases associated with mental retardation are diverse, a significant number are linked with disruptions in epigenetic mechanisms, mainly due to loss-of-function mutations in genes that are key components of the epigenetic machinery. Additionally, several disorders classed as imprinting syndromes are associated with mental retardation. This review will discuss the epigenetic abnormalities associated with mental retardation, and will highlight their importance for diagnosis, treatment, and prevention of these disorders.

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1. Introduction

The occurrence rate of many diseases with a suspected genetic basis often does not match predictions from traditional genetics. One of the most striking examples of such discordance is the disease risk of monozygotic twins who, despite having an identical genetic make-up, have notably different susceptibility to diseases (Haque, Gottesman, & Wong, 2009). Although still not well understood or explained, it is now largely recognized that further to the genome, the epigenome is of crucial importance for such differences, and influences an individual's disease risk. The epigenome is different in each individual, and significantly fluctuates across life. It is strongly influenced by the environment, and varies between each individual, including between monozygotic twins, depending on such factors as lifestyle, diet, living conditions, and age (Fraga et al., 2005). The epigenome therefore plays an extremely important role in many diseases ranging from cancer to neurodevelopmental and neurodegenerative disorders. Here we review the current evidence that anomalies in epigenetic marks, and in the components of the epigenetic machinery that recognize and respond to these marks, are strongly associated with neurodevelopmental disorders leading to mental retardation.

Mental retardation is characterized by an impairment of intellectual abilities, and by severe deficits in the capacity to adapt to the environment and the social milieu (American Psychiatric Association, 1994). The high prevalence of mental retardation

worldwide (2.3%), and its strong familial and societal impact, make it of extreme importance to investigate its mechanisms and find new avenues towards its potential prevention and treatment. Mental retardation is a feature expressed in several neurodevelopmental disorders including Rett syndrome, Fragile X, and Down syndrome. Although its causes have not been clearly identified, its potential underlying mechanisms have been linked to epigenetic alterations. These alterations of the epigenome may be due to duplications or loss-of-function mutations in key components of the epigenetic machinery, particularly those involved in reading and interpreting the epigenetic code, or to anomalies of the epigenetic marks themselves. These two mechanisms are not mutually exclusive, since impaired functions of core genes that regulate the epigenome can have a dramatic effect on the epigenetic profile. Interestingly, severe mental retardation is one of the major characteristics of imprinting disorders, that result from aberrant chromosomal marks in genes normally expressed monoallelically from either the maternal or paternal copy depending on its epigenetic state. These disorders are thought to result from errors in the erasure, the establishment, or the maintenance of imprints leading to aberrant expression of imprinted genes. Many of the genes involved in mental retardation are located on the X-chromosome (Jensen et al., 2011),

2. Misinterpretation of epigenetic marks

The posttranslational modification (PTM) of histone proteins in the chromatin is an important mechanism for the epigenetic marking of the genome. Histone PTMs are varied and co-occur in complex combinations on individual histones and in different nucleosomes. Because their combinations are not random but

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appear to follow specific rules, it was proposed that they form a “histone code” (Strahl & Allis, 2000). According to this concept, histone PTMs are established in a specific manner through complex cross-talk that form a particular code in individual genes, and determine whether chromatin is in an “on” or “off” state, and whether genes are activated or silenced (Baker, Allis, & Wang, 2008). This code is controlled by a complex machinery of histone-modifying enzymes. In most tissues, including the brain, multiple histone-modifying enzymes have been identified that can add or remove PTMs on specific sites or residues (known as “writers” or “erasers”, respectively) (Musselman & Kutateladze, 2009). Factors or complexes known as “readers” interpret the histone code by recognizing different histone PTMs. But through their own intrinsic activity or by recruiting cognate factors, many of these “readers” can also be “writers” or “erasers” and modify PTMs to alter chromatin structure. This combination of “read-write” or “read-erase” mechanisms may favor the spread or the erasure of epigenetic marks over particular stretches of DNA, and participate in the complex mechanisms of transcriptional control.

2.1. PHD domains

The plant homeodomain (PHD) finger is a motif that can recognize unmodified or methylated lysine residues in histone tails. When present in a protein, it confers the ability to act as “reader”, and recognize the methylation state of histone lysine residues (Baker et al., 2008). Two unique subclasses of PHD fingers that can recognize either trimethylated H3K4, a PTM commonly associated with actively transcribed genes (Berger, 2007), or unmethylated H3K4 have emerged. PHD domains in BPTF (bromodomain and PHD finger transcription factor) and ING2 (inhibitor of growth 2), preferentially recognize trimethylated H3K4 over mono- and unmodified H3K4, while PHD fingers in DNMT3L and BHC80 recognize unmethylated H3K4 (Lan et al., 2007; Ooi et al., 2007; Shi et al., 2006; Wysocka et al., 2006). Several other PHD fingers are also thought to associate with different methylated or acetylated lysine marks (Baker et al., 2008; Cosgrove, 2006; Musselman & Kutateladze, 2009). Recently, PHD fingers in two other proteins, SMCX and ICBP90, were demonstrated to recognize trimethylated H3K9, a mark associated with transcriptionally inactive genes (Berger, 2007), and tandem PHD fingers in DPP3 were shown to preferentially bind all acetylated lysine residues of H3 or H4 (Iwase et al., 2007; Karagianni, Amazit, Qin, & Wong, 2008). Many more PHD fingers are likely to act as “readers” of the histone code but more research is needed to identify them.

Point mutations, deletions or chromosomal translocations in the PHD fingers of several proteins have been associated with mental retardation, cancer, and immunological diseases. In mental retardation, PHD fingers within proteins such as mental retardation syndrome X-linked (ATR-X), alpha thalassaemia, KDM5C, PHD finger protein 6 (PHF6), nuclear receptor-binding SET domain containing 1 (NSD1), and CREB binding protein (CBP) have been implicated. These mutations are thought to have a strong impact on the activity of the genes and alter their functions in the brain.

2.1.1. ATR-X

ATR-X is a protein coded by the X-linked gene *atrx*, whose mutations can result in ATR-X syndrome, a disorder characterized by severe mental retardation, microcephaly, seizures and delayed growth (Baker et al., 2008). In the mouse brain, ATR-X is necessary for neuronal survival during corticogenesis, and its alteration interferes with neurodevelopmental processes (Berube et al., 2005). Although the impact of *atrx* mutation on the syndrome is not well defined, it has been suggested to involve anomalies in chromatin structure and gene expression. This derives from the property of ATR-X to interact with several heterochromatin-associated

proteins such as heterochromatin protein alpha 1 (HP1alpha), histone lysine N-methyltransferase (EZH2), and methyl-CpG binding protein 2 (MeCP2) (Kramer & van Bokhoven, 2009). The N-terminus of *atrx* also contains an ATR-X-DNMT-DNMT3L (ADD) domain, named based on its sequence homology exclusively with members of the DNA methyltransferase family, and an atypical “PHD-like” domain, implying that ATRX most likely interacts directly or indirectly with DNA or chromatin (Kramer & van Bokhoven, 2009). While more than 40 disease-causing *atrx* mutations have been recognized, 26 are within the PHD finger, suggesting that this region plays a particularly important role in the pathogenesis of the disease (Argentaro et al., 2007).

2.1.2. KDM5C

Another X-linked protein associated with mental retardation is KDM5C. KDM5C contains a PHD that recognizes trimethylated H3K9, and a JmjC domain, which catalyzes demethylation of H3K4. Since trimethylation of H3K9 represses gene transcription while trimethylation of H3K4 activates it, the binding of KDM5C acts synergistically to repress gene transcription. In patients with X-linked mental retardation, a point mutation in the PHD finger of KDM5C (A388P) reduces the protein's binding to H3K9 and decreases demethylase activity (Iwase et al., 2007; Tzschach et al., 2006). Likewise, PHF6 is another protein that contains 2 PHD fingers, whose gene (also X-linked) is mutated in Borjeson-Forssman-Lehmann syndrome, a disorder characterized by mental retardation (Baker et al., 2008). Currently, it is thought that 23% of all Borjeson-Forssman-Lehmann syndrome mutations lie within the first PHD finger in *phf6*, suggesting that the potential role of PHF6 in chromatin remodeling is of key functional importance (Mangelsdorf, Chevrier, Mustonen, & Picketts, 2009).

2.1.3. NSD1

NSD1 is another protein involved in epigenetic regulation that acts as either a co-repressor or a co-activator. NSD1 contains a su(var)3–9, enhancer-of-zeste, trithorax (SET) domain with histone methyltransferase activity, and multiple PHD domains (Huang et al., 1998). Mutations in the PHD fingers are associated with two overgrowth syndromes, Sotos syndrome and more rarely, Weaver syndrome. These diseases are characterized by both, pre- and postnatal somatic overgrowth, craniofacial abnormalities, advanced bone age, and mild mental retardation. The fifth PHD finger in NSD1 is necessary for the recruitment of the protein to the promoter, however the sequence of this domain does not contain the known H3K4-engaging residues, suggesting that its interaction with chromatin may be via another yet unknown mechanism (Baker et al., 2008).

2.1.4. CBP

CBP is a transcriptional regulator linked to mental retardation in Rubenstein-Taybi syndrome. CBP has HAT activity and its haploinsufficiency alters brain functions. Such insufficiency has been modeled in mice, and was shown to have severe consequences on cognition. Thus, transgenic mice expressing an inducible form of CBP that lacks HAT activity have deficits in long-term spatial and recognition memory, suggesting that HAT activity of CBP is necessary for long-term memory formation (Korzus, Rosenfeld, & Mayford, 2004). Point mutations or internal deletions in the PHD located within the HAT domain have been implicated in this disorder, including one that alters a conserved PHD finger amino acid (E1278 K) and a second that deletes the exon encoding the central region of the PHD finger, exon 22 (Kalkhoven et al., 2003). Mutations in the PHD finger reduce endogenous CBP HAT activity, suggesting that this domain has functional importance for maintaining a normal epigenetic profile (Kalkhoven, Teunissen, Houweling, Verrijzer, & Zantema, 2002; Kalkhoven et al., 2003).

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