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Review

Epigenetics: The neglected key to minimize learning and memory deficits in Down syndrome

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ABSTRACT

Down syndrome (DS) is the most common genetic intellectual disability, caused by the triplication of the human chromosome 21 (HSA21). Although this would theoretically lead to a 1.5 fold increase in gene transcription, transcript levels of many genes significantly deviate. Surprisingly, the underlying cause of this gene expression variation has been largely neglected so far. Epigenetic mechanisms, including DNA methylation and post-translational histone modifications, regulate gene expression and as such might play a crucial role in the development of the cognitive deficits in DS. Various overexpressed HSA21 proteins affect epigenetic mechanisms and DS individuals are thus likely to present epigenetic aberrations. Importantly, epigenetic marks are reversible, offering a huge therapeutic potential to alleviate or cure certain genetic deficits. Current epigenetic therapies are already used for cancer and epilepsy, and might provide novel possibilities for cognition-enhancing treatment in DS as well. To that end, this review discusses the still limited knowledge on epigenetics in DS and describes the potential of epigenetic therapies to reverse dysregulated gene expression.

Contents

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1. Introduction: epigenetics underlying the cognitive deficits in DS?

With an incidence of approximately 1 in 650–1000 live births, Down syndrome (DS) is the most common genetic intellectual disability in humans (Bittles et al., 2007). In his 'Classification of Idiots' (1866), the British physician J.L.H. Down described various recurrent symptoms of the 'Mongolian type of idiocy' that he observed among more than 10% of the children that he treated for cognitive impairment (Down, 1995). Down stated that "it is difficult to realize [that the Mongolian type] is the child of Europeans". Without knowledge about genetics and neurobiology, he was ahead of his time by postulating "that there can be no doubt that these ethnic features are the result of degeneration."

It took almost a century to discover the cause of DS. Lejeune et al. (1959) demonstrated in 1959 that DS was due to a triplication of chromosome 21 (HSA21). In the majority of the cases (over 95%) this is a whole-chromosome trisomy due to meiotic non-disjunction, i.e. a failed separation of one of the paired chromosomes (Antonarakis et al., 2004; Lubec and Engidawork, 2002). Apart from the characteristic facial appearance, this triplication causes various neurological complications of which mental retardation (lower IQ) is the most well-known. DS is characterized by impaired linguistic skills and diminished learning and memory capacities, specifically impairment of the verbal short-term memory and explicit long-term memory (Lott and Dierssen, 2010). In addition to the congenital cognitive deficits, people with DS face accelerated ageing, including early-onset dementia due to Alzheimer's disease (AD) in 50–70% of the DS population (Zigman and Lott, 2007).

This strongly increased risk for AD in DS compared to non-DS individuals has been predominantly attributed to the triplication of the amyloid precursor protein (APP) gene on HSA21, yielding higher levels of amyloid-β (Aβ), the main constituent of the characteristic plaques in AD (Ness et al., 2012). Despite the fact that 95% of the DS cases is due to a whole-chromosome trisomy, the DS population is characterized by an enormous variability in the type and the severity of clinical features (Roper and Reeves, 2006). This phenotypical variability is strikingly illustrated by the observation that the onset of clinical dementia symptoms in DS differs tremendously. Remarkably, 30–50% of the DS individuals do not develop dementia, despite their full-blown AD-like neuropathology, including Aβ plaques, around midlife (Lott and Dierssen, 2010; Ness et al., 2012; Wilcock, 2012; Zigman and Lott, 2007).

As part of the Human Genome Project the complete DNA sequence of HSA21 was elucidated in 2000 (Hattori et al., 2000). Since, many researchers have investigated the overexpressed protein-encoding genes and their effects on learning and memory. Despite increased understanding of the possible underlying genetic mechanisms, it remains very difficult to explain the aforementioned variability among the DS population (Jiang et al., 2013; Prandini et al., 2007). The triplication of HSA21 would theoretically lead to a 1.5 fold increase in gene transcription. However, gene expression studies showed differently. For instance, analysis of HSA21 gene expression in DS lymphoblastoid cells showed that only 22% of the analysed genes had expression levels closely matching this 1.5 fold (class I), compared to control individuals. In particular, 7% had an amplified expression (significantly >1.5; class II), 56% had an expression level that was significantly lower than 1.5 (class III) and 15% of the genes had highly variable expression profiles between subjects (class IV) (Ait Yahya-Graison et al., 2007).

Similar results were obtained using the most widely used Ts65Dn mouse model of DS. Ts65Dn mice carry an additional chromosome, consisting of a duplicated part of the mouse chromosome 16 that is translocated to a small segment of the mouse chromosome 17 (Davisson et al., 1990). As a consequence, Ts65Dn mice are trisomic for about 50% of the genes on HSA21 (Reeves et al., 1995). However, it was demonstrated that many of these genes have transcript levels that significantly deviate from the theoretical 1.5 fold increase (Antonarakis et al., 2004; Kahlem et al., 2004; Lyle et al., 2004). For instance, Lyle et al. (2004) reported that not more than 37% of the genes in Ts65Dn matches the theoretical expression level of 1.5. Accordingly, certain genes are more dosage sensitive than others, thereby contributing in varying extents to the DS phenotypes (Antonarakis et al., 2004). Whereas various studies have tried to identify the crucial phenotype-determining genes, the underlying cause of the gene expression variation has been largely neglected.

Conceivably, epigenetic (epi = above (Greek)) mechanisms play a role in gene expression regulation and as such might play a crucial role in the development of the cognitive deficits in DS. An epigenetic trait is defined as "a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" (Berger et al., 2009). That is, epigenetic mechanisms regulate gene expression without affecting the DNA itself. Importantly, epigenetic marks, including DNA methylation and post-translational histone modifications, are reversible and thus offer a huge therapeutic potential to alleviate or cure certain genetic deficits.

Indeed, an increasing body of evidence illustrates the role of epigenetic mechanisms in synaptic plasticity and learning and memory. Memory formation, for example, relies on increased DNA methylation of memory suppressor genes and diminished DNA methylation of memory promoting genes (Day and Sweatt, 2010; Weng et al., 2013). Furthermore, histone acetylation has been shown to play a major role in promoting synaptic plasticity and memory formation and, in turn, inhibition of histone deacetylation has been shown to rescue memory deficits (Graff and Tsai, 2013).

Surprisingly, epigenetic mechanisms have been hardly investigated in DS. Most DS studies have focused on genomic aspects, neglecting the increasing body of evidence that demonstrates the contribution of epigenetics to impaired learning and memory. Therefore, this review aims to summarize and evaluate the limited knowledge on epigenetics in the neurobiology of DS, as well as provide additional arguments for its role in learning and memory that are distilled from epigenetic studies of other intellectual disabilities.

Importantly, current epigenetic therapies are already used for cancer and epilepsy, and might provide novel possibilities for cognition-enhancing treatment in DS as well. To our knowledge, no studies so far have investigated epigenetic therapy in (mouse models of) DS. However, it offers potentially important new avenues, as classical pharmacological treatment has not been successful yet in diminishing cognitive deficits in DS (Braudeau et al., 2011). To that end, the huge potential of epigenetic therapies (epidrugs and Epigenetic Editing) to reverse deregulated gene expression will be discussed.

2. Epigenetic mechanisms – an overview

To enable organized storage of all DNA in the nucleus, DNA in eukaryotic cells is packaged about 10,000 times into a more compact form: chromatin. The basic level of this chromatin is the nucleosome that consists of approximately 147 base pairs of DNA wrapped around a histone core in 1.7 turns. This core is an octamer, containing two copies of each histone type: histone 2A (H2A), H2B, H3 and H4 (Luger et al., 1997), as also shown in Fig. 1. Considering the higher level of compaction, this string of nucleosomes ('beads on a string') is folded into a fiber, which in turn, is folded into even more condensed structures (Felsenfeld and Groudine, 2003).

Epigenetic mechanisms affect the nucleosomal packaging and thereby alter the accessibility of the DNA for molecular interactions