Role of Epigenetics in Neural Differentiation: Implications for Health and Disease

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Chapter 2
Role of Epigenetics in Neural Differentiation: Implications for Health and Disease

Estela G. Toraño, Agustin F. Fernandez, Rocio G. Urdinguio, and Mario F. Fraga

Abstract Neural differentiation is a complex process that requires highly accurate spatial and temporal regulation by extracellular and intracellular programs. Epigenetic mechanisms, such as DNA methylation, covalent histone posttranscriptional modifications, chromatin organization, and noncoding regulatory RNA, are key regulators of pluripotency maintenance and differentiation. The misregulation of these mechanisms could lead to neurological diseases and cancer.

Keywords DNA methylation • Histone modifications • Epigenetics • Neural differentiation • Neural diseases

2.1 Introduction

The development of the central nervous system (CNS) arises from the external layer of the embryo, the ectoderm (Bohacek et al. 2013). This is a complex and tightly regulated phenomenon which, briefly, consists in the initial formation of the

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neural tube which then develops to become the brain and spinal cord (Olynik and Rastegar 2012). The CNS is composed by many cell types, including neurons, astrocytes, oligodendrocytes, all of which are formed from the same multipotent precursor cells—neural stem cells (NSCs)—(Dietrich et al. 2006) which have the capacity to self-renew and differentiate in multiple lineages. NSCs are capable of generating specific neurons, of a particular length and at exactly the correct place and time for the requirements of each stage of development; neurons appearing first, and then astrocytes and oligodendrocytes (Olynik and Rastegar 2012). During development, NSCs firstly divide symmetrically to expand, and then start to divide asymmetrically, resulting in a new NSC and a neuron. In later stages of development, NSCs are able to become, in addition to neurons, to astrocytes, and/or to oligodendrocytes while at the same time maintaining their capacity for self-renewal. This differentiation has to be strictly regulated during development, both spatially and temporally, by extracellular cues such as the NOTCH signaling family, TGF-β, FGF, EGF, and FGF2 growth factors, neuregulins (NRG), and by intracellular programs including the expression of homeobox (HB) genes and epigenetic modifications (Mizutani et al. 2007; Namihira et al. 2008). Knowledge of exactly how the molecular determination of NSC differentiation takes place could have major implications for the study of many diseases such as cancer and neurodevelopmental disorders.

The term epigenetics was first introduced by Conrad Waddington in 1942 to explain the variations between genes and their products. However, the word has evolved to incorporate the study of mitotically and/or meiotically stable and heritable changes in gene expression which are not accompanied by changes in the DNA sequence. Epigenetic modifications are crucial for gene expression regulation during the cell cycle, development, differentiation, and in response to environmental or biological variations (Brooks et al. 2010). Epigenetic regulation comprises DNA methylation, covalent histone posttranscriptional modifications (such as methylation, acetylation, ubiquitination, and phosphorylation), chromatin organization, and noncoding regulatory RNA (Bernstein et al. 2007). Epigenetic mechanisms are key regulators of pluripotency maintenance and also of cell fate specification. During their differentiation from embryonic stem cells (ESCs) to NSCs, cells have already acquired epigenetic marks (Meissner et al. 2008). NSC maintenance requires epigenetic mechanisms that allow the inhibition of neuronal and glial cells, whereas differentiation of NSCs requires the elimination of the epigenetic suppression of neural and glial specification genes (Hsieh and Eisch 2010). During the differentiation process, neural genes can become activated due to the increased accessibility of their promoters, whereas pluripotency neural genes are silenced (Hirabayashi and Gotoh 2010) (Fig. 2.1).

In this chapter, we will discuss and summarize the epigenetic changes that occur during differentiation from ESCs to NSCs and then to mature neural and glial cells, and their relation with many neurological disorders.

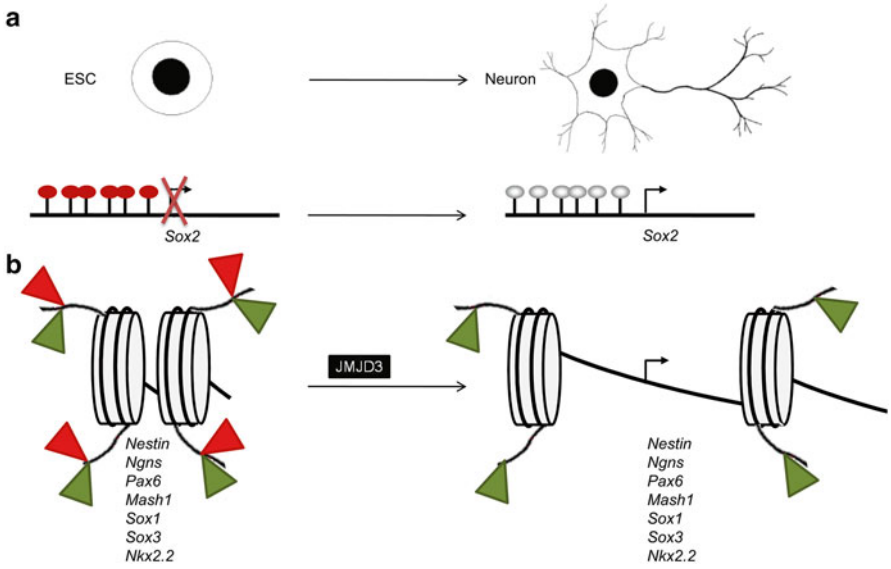

Fig. 2.1 Epigenetic changes during the differentiation process in neural genes. (**a**) During ESC differentiation, neuronal genes such as Sox2 are activated via decreased DNA methylation. (**b**) In ESCs, neural genes carry both the H3K27me3-repressed mark (*red triangle*) and the H3k4me3-activated mark (*green triangle*). During differentiation, JMJD3 acts to remove H3k27me3 on the promoter of many neural genes (*Nestin, Pax6, Ngns, Mash1, Sox1, Sox3, Nkx2.2*), which become expressed

2.2 Epigenetic Mechanisms and Neural Differentiation

2.2.1 DNA Methylation

One of the most extensively studied epigenetic modifications in mammals is DNA methylation, which plays an important role in many biological processes, such as genomic imprinting, X-chromosome inactivation (XCI) during development, regulation of gene expression, and maintenance of epigenetic memory, among others. DNA methylation consists of the covalent addition of a methyl (CH_3) group, from the methyl donor S-adenosylmethionine (SAM) to the 5′ carbon of the pyrimidine ring of the citosine base that precedes guanine (CpG) (Herman and Baylin 2003; Weber et al. 2007). CpGs are mainly associated in clusters called CpG islands and are located at the promoter region of more than 50 % of genes (Bird 1986). In healthy cells, most CpG islands are unmethylated when located at a transcription start site (TSS), and when methylated they are usually associated with silent genes. Indeed, hypermethylation of CpG islands in promoter regions is related to the

silencing of many tumor suppressor genes (TSG) in cancer. Conversely, CpG sites located in repetitive and transposon elements, intergenic regions, and gene bodies are usually heavily methylated (Ellis et al. 2009; Kanai 2008). During ESC differentiation, there is an increase in DNA promoter methylation regions (Delcuve et al. 2009) and many pluripotency genes are silenced by DNA methylation (Mohn et al. 2008), while neuronal genes such as *Sox2* are activated via decreased DNA methylation (Sikorska et al. 2008) (Fig. 2.1a).

DNA methylation is carried out by DNA methyltransferases—DNMT1, DNMT3A, and DNMT3B—the first being responsible for the maintenance of the DNA-methylated status following DNA replication and the two latter being de novo methyltransferases (Robertson 2001). High levels of DNMT1 have been found to maintain DNA methylation in NSCs in the embryonic nervous system. In the case of de novo methyltransferases, *DNMT3B* is expressed in embryonic NSCs, whereas DNMT3A is expressed at late developmental stages (Feng et al. 2007). *DNMT3A*-deficient ESCs have increased cell proliferation and premature glial differentiation (Wu et al. 2012). A decrease in DNMT3B causes the failure of neuronal differentiation in vitro, maybe due to the principal expression of this methyltransferase in early embryonic cells and neural progenitors (Bai et al. 2005; Feng et al. 2005; Watanabe et al. 2006).

The association between DNA methylation and gene repression can be mediated by methyl-CpG-binding proteins (MBPs) which recognize methylated DNA, bind to it, and recruit different chromatin remodeling complexes (Defossez and Stancheva 2011). In the brain, MBD1 and MeCP2, two MBPs that contain a methyl-CpG-binding domain (MBD), are strongly expressed and participate in neurodevelopment and plasticity through the regulation of other epigenetic factors (Fan and Hutnick 2005; Jobe et al. 2012).

2.2.2 Histone Tail Posttranslational Modifications

The basic unit of chromatin is the nucleosome. It consists of 147 bp of DNA wrapped twice around two copies of each of the histones H2A, H2B, H3, and H4. The N-terminus histone tails are susceptible to posttranslational modification (PTM) by acetylation, methylation, ubiquitination, phosphorylation, and other processes. PTMs need to be strictly regulated, both spatially and temporally, during development. Depending on the amino acid residues that the histone PTM is attached to, these covalent modifications have profound effects on chromatin organization and, as a consequence, on gene activation and inactivation depending whether transcriptional machinery has greater or lesser accessibility (Delcuve et al. 2009). Together, the different PTMs and the effects they exert are referred to as the "histone code" (Bernstein et al. 2007). Addition of acetyl groups to lysines correspond with the open chromatin state, which is very important in nucleosome formation and chromatin folding. In the case of histone methylation, it can occur at the lysine and arginine residues of histones, and depending on the amino acid residue, the effect

can be different. For example, H3K4me3 is associated with gene activation, whereas H3k27me3 and H3k9me3 are inhibitory epigenetic marks. In ESCs, chromatin structure is very open and active and during development, acetylation marks are substantially reduced and there is an overall increase in repressive marks which results in differentiated tissues having a more condensed chromatin structure (Meshorer et al. 2006).

Histone Acetyl Transferases and Histone Deacetylases

Histone acetyl transferases (HATs) are the enzymes responsible for catalyzing the acetylation of lysine residues of histone, and its reversion is carried out by histone deacetylases (HDACs) and both are implicated as regulators of neural-specific gene-expression patterns in the brain (Abel and Zukin 2008). Acetylation is the most widely studied histone modification and plays an important role in gene regulation (MacDonald and Howe 2009) and its regulatory role is evolutionarily conserved: in *Drosophila*, neural differentiation is connected with high acetylation levels whereas low levels are related to glial differentiation (Flici et al. 2011).

HATs comprise three major families: general control non-derepressible 5 (Gcn5)-related *N*-acetyltransferases (GNATs), and p300/CBP and MYST proteins (Lee and Workman 2007). It has been shown that knockdown of these HATs leads to aberrant ESC differentiation although HATs have not been extensively studied in a developmental context, neither in vivo nor in cellular systems. More studies in NSCs and of brain development are necessary to understand the role of histone acetylation in embryonic development (Lilja et al. 2013).

Histone deacetylation is catalyzed by the HDAC enzymes which are critical players in many biological processes, including differentiation (Haberland et al. 2009b). They can regulate stem cell self-renewal and differentiation through the control of a variety of target genes, and also regulate (NSC) differentiation. Also, HDACs can target nonhistone protein targets, such as transcription factors, transcription regulators, signal transduction mediators, DNA repair enzymes, and even each other (Xu et al. 2007). In mammals, there are 18 HDACs, which are classified into four classes depending on sequence identity and domain organization (Dokmanovic et al. 2007). Class I HDACs (1, 2, 3, and 8) are located in the nucleus and are known to have critical functions during early development (Yang and Seto 2008). HDAC1 and HDAC2 act together to maintain neuronal specification. Deletion of either one of these HDACs leads to severe brain abnormalities and postnatal lethality (Montgomery et al. 2009). HDAC1 is enhanced in glial cells in the adult brain, whereas HDAC2 is upregulated in the differentiation of NSCs to different neural lineages (MacDonald and Roskams 2008). Overexpression of *HDAC2* in neurons decreases synaptic plasticity and memory formation (Guan et al. 2009). HDAC1, 2, and 3 inhibit oligodentrocytic differentiation and HDAC2, in addition, inhibits astrocytic differentiation (Montgomery et al. 2009). In *HDAC8* global deletion mice, their development of scull morphogenesis points to it having a unique role in cranial differentiation (Haberland et al. 2009a).

Class II HDACs (4, 5, 6, 7, 9, and 10) have cell type-specific expression and may serve as key regulators of neural development, but their roles are not well defined. For instance, HDAC4, 5, 7, and 9 are upregulated in differentiated NSCs (Ajamian et al. 2003); HDAC5 regulates neuronal differentiation (Schneider et al. 2008) and, along with HDAC4, are involved in neuronal maturation (Majdzadeh et al. 2008). HDAC3 and 5 also participate in NSCs proliferation (Sun et al. 2007). The third class of HDACs, called sirtuins, requires nicotinamide adenine dinucleotide (NAD^+) for their activity, linking them with cell metabolism and redox state (Calvanese and Fraga 2011). Seven sirtuin members, SIRT1-7, have been identified in mammals, with different subcellular locations; SIRT1, 6, and 7 are located in the nucleus, SIRT2 is cytosolic, and SIRT3, 4, and 5 are found in the mitochondria (Verdin et al. 2010). SIRT1 has a role in ESC maintenance, through the epigenetic repression of many developmental genes (Calvanese et al. 2010). It has also been implicated in neuronal differentiation, but its role is not very clear as it has been associated with both activation and inhibition of neural differentiation (Lilja et al. 2013). HDAC11 alone forms HDAC class IV.

HDAC inhibitors (HDACis) are molecules that inhibit HDAC activities, which allow efficient control of gene expression (Kretsovali et al. 2012). They are classified into four different families: the short-chain fatty acids (sodium butyrate, phenylbutyrate, and valproic acid (VPA)), the hyroxamic acids (trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA)), the epoxyketones (trapoxin), and the benzamides (Abel and Zukin 2008). Their effects cause transcription alterations which result in no net gain in the number of induced or repressed genes. Sirtuins are not inhibited by compounds such as vorinostat or TSA in contrast to class I and II HDACs (Xu et al. 2007). The administration of HDACis such as VPA can induce differentiation into neural lineage and glial suppression due to the induction of a neurogenic bHLH transcription factor, *NeuroD* (Hsieh et al. 2004). HDACis have potent anticancer activities such as arresting tumor growth, induction of differentiation, and apoptosis (Minucci and Pelicci 2006). For these reasons, they represent a good therapeutic approach for tackling many neurological diseases.

Histone Methyltransferases

Histone methyltransferases (HMTs) catalyze histone methylation of lysine or arginine residues of PTMs. Histone methylation can be associated with either gene silencing or gene activation, depending on the number of methyl groups (1, 2, or 3) and the location of the residue. Examples of repressive marks are H3K9me2, H3K9me3, H3k27me3, and H4K20me3 while H3K4me3 and H3K36me3 are examples of active marks (Mosammaparast and Shi 2010).

Two members of the chromatin remodeling system, Polycomb-group (PcG) and Thithorax-group (TrxG) proteins, are evolutionarily conserved from *Drosophila* to humans and are responsible for the correct expression and regulation of the majority of key developmental genes in ESCs. PcG and TrxG protein complexes have antagonistic functions in that PcG proteins promote

heterochromatin formation via H3k27me3 inhibitory epigenetic mark, whereas TrxG proteins have the reverse effect due to the promotion of H3k4me3 associated with gene activation (Bernstein et al. 2006; Ng and Gurdon 2008; Ringrose and Paro 2007; Schuettengruber et al. 2007). PcG proteins play a key role in silencing developmental genes and, as a consequence, in pluripotency maintenance and inhibition of differentiation. They form two polycomb-repressive complexes, PRC1 and -2, of which each contains a different set of core proteins. Both silence an extensive range of key developmental genes in ESCs due to trimethylation at histone 3 lysine 27. In addition, most PcG target genes also carry H3k4me3. This histone signature (H3k27me3 and H3k4me3 together) occurs in regions referred to as bivalent domains, and collectively, means the gene is maintained poised for activation and prepares ESCs for differentiation.

During differentiation, active genes are enriched in H3k4me3 due to TrxG protein complex action, while the demethylase JMJD3 is recruited, which removes the H3K27me3 mark. In contrast, genes that remain silenced retain H3k27me3 and lose H3k4me3 through Rbp2 demethylase, which is recruited by PRC2 complex (Cloos et al. 2008; Pasini et al. 2008; Soshnikova and Duboule 2008). This "bivalent" state is resolved during the differentiation process when genes becomes univalent as a result of neural differentiation, leaving them in an "on" or "off" state of transcription. Among the genes carrying the "bivalent" mark are *Hox* genes (Barber and Rastegar 2010), the master regulators of embryonic development. The genome is composed of 39 *Hox* genes organized in four clusters, *Hoxa, Hoxb, Howc*, and *Hoxd*. They control the exact purpose of each developing tissue in the body and, during neurogenesis, they are responsible for dictating and leading somatogenesis, cellular migration, and axonal direction, and their misregulation leads to disease and cancer (Barber and Rastegar 2010; Oury and Rijli 2007).

In neural differentiation, JMJD3 acts to remove H3k27me3 on the *Nestin* promoter, a neurofilament gene whose activation is a step in the transition from ESC to NSC (Burgold et al. 2008). More examples of neural genes that lose repressive marks during differentiation into neural lineage are paired box gene 6 (*Pax6*), neurogenins (Ngns), *Mash1* (achaete–scute complex homolog 1, or *Ascl1*), SRY-Box 1 (*Sox1*), *Sox3*, and NK2 transcription factor-related locus 2 (*Nkx2.2*) (Hirabayashi and Gotoh 2010; Mikkelsen et al. 2007) (Fig. 2.1b). In addition, during transition from ESC to NSC, a new "bivalent" state is established in functioning genes in terminally differentiated neurons. These neuron-specific genes become poised for expression and lose the H3k27me3 mark in the final differentiation before becoming expressed.

2.2.3 Noncoding RNA

Noncoding RNA (ncRNA) refers to the part of the RNA that is not translated into protein and includes microRNAs (miRNAs), small interfering RNAs (siRNAs), small nucleolar RNAs, and PIWI-interacting RNAs (piRNAs) (Li and Zhao 2008).

They regulate gene expression through the control of chromatin structures, RNA modifications, DNA transcription, and mRNA translation and splicing (Mohamed Ariff et al. 2012). ncRNAs are important executers in epigenetic regulation and, in particular, miRNAs play a role in stem cells maintenance and differentiation through degradation of their target mRNAs (Guo et al. 2010). miRNA activities act in coordination with DNA marks and histone modifications to ensure the correct differentiation of all the cell types in the CNS (Olynik and Rastegar 2012). The most abundant miRNA in both the embryonic and adult CNS is miR-124, whose levels are increased during neuronal differentiation (Makeyev et al. 2007). miR-124 is critical in neurogenesis due to its targeting of *Sox9*, which is essential for multipotent NSC formation and maintenance (Cheng et al. 2009; Scott et al. 2010). Other examples of miRNAs involved in neural differentiation are *miR-9*, which is expressed in neurogenic areas of the brain and controls NSC proliferation and differentiation, and Let-79, which reduces proliferation and induces neural differentiation (Zhao et al. 2009, 2010). The misregulation of these miRNAs is related with cancer and many neurological diseases, such as Alzheimer's and Parkinson's (Junn and Mouradian 2012).

2.3 Epigenetics in Neural Diseases

As a whole, epigenetic mechanisms are thought to be involved in a number of neurological disorders. The inadequate control of proliferation, "poised" state, or the imbalance between HATs and HDACs and the promotion or inhibition of neural differentiation has been associated with many neurological disorders and tumorigenesis of the nervous system. Any malfunction of the epigenetic machinery during neural development could lead to neural diseases and knowledge of how aberrant epigenetic mechanisms take place in such development would provide good opportunities for therapeutic intervention (Fig. 2.2).

2.3.1 Rett Syndrome

Rett syndrome (RTT) is an X-linked dominant neurological disorder that predominantly affects females, with an incidence of 1 in 10,000–15,000 female births. It is characterized by normal development during the first 6–18 months after birth, followed by the appearance of severe problems, including autistic features, epileptic seizures, and poor motor and language skills (Rett 1986). This disorder is principally caused both by mutations and duplications in the *MECP2* gene (Bird 2008; Urdinguio et al. 2009; Van Esch et al. 2005). Although this gene disruption affects all tissues, its deregulation seems to be particularly damaging to brain function (Chen et al. 2001; Guy et al. 2001; Neul et al. 2008). Additionally, XCI is thought to cause a mosaicism of MeCP2 protein expression and differences in penetrance of the

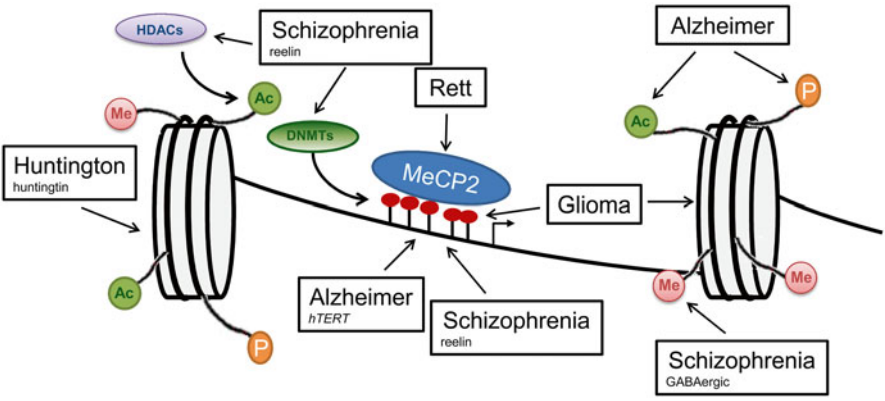

Fig. 2.2 Some epigenetic mechanisms implicated in neural diseases. Rett syndrome is principally caused by a mutation in MeCP2. It has been shown that the DNA methylation of telomerase inverse transcriptase (hTERT) promoter is increased in patients with Alzheimer's disease and an aberrant gene expression related to histone acetylation and phosphorylation has been found. In Huntington disease, huntingtin protein has been found to be modified by many PTMs. In schizophrenia patients, the extracellular matrix protein reelin is reduced; a decrease, which may be regulated by DNA methylation and HDACs, and its expression are increased by DNA methyltransferase. Also, an increase in GABAergic mRNA has been demonstrated and shown to be associated with a rise in H3k4me3. Gliomas present specific epigenetic patterns such as aberrant DNA methylation and changes in histone PTMs and their regulatory genes

symptoms, although a recent study showed that XCI patterns in various peripheral tissues did not differ between RTT discordant monozygotic twins (Miyake et al. 2013).

Currently, many works are focusing on understanding the different facets of MeCP2 function. One of the targets of MeCP2 is the brain-derived neurotrophic factor (*BNDF*) gene, whose protein is synthesized in response to neuronal activity and is essential for appropriate brain function. A recent work using ESCs has studied the maturation process of neurons and found that MeCP2 regulates not only BDNF levels but also the nuclear size and RNA synthesis during the process (Yazdani et al. 2012). Furthermore, RTT mutations in *MECP2* have recently been described which abolish the interaction of MeCP2 with the NCoR/SMRT corepressor, a finding in line with the hypothesis that brain dysfunction in RTT is caused by a loss of the MeCP2 connection between the NCoR/SMRT corepressors and chromatin (Lyst et al. 2013).

Microarray expression analyses have suggested that MeCP2 is able to regulate a wide range of genes in different regions of the brain (Jordan et al. 2007; Tudor et al. 2002; Urdinguio et al. 2009). Although MeCP2 was firstly described as interacting with repressor complexes and inhibiting gene expression, compelling evidence is pointing to MeCP2 being involved in the regulatory action of both activator and repressor functions (Ben-Shachar et al. 2009; Chahrour et al. 2008; Samaco and Neul 2011; Zachariah and Rastegar 2012). This indicates that adequate regulation

exerted by MeCP2 is essential for correct brain function. It has been reported that RTT symptoms are, fortunately, reversed by MeCP2 restoration in mouse models of RTT (Bird 2008; Guy et al. 2007), which brings hope for the treatment of this complex disease.

2.3.2 Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease associated with dementia and shows progressive memory loss and cognitive decline. It is associated with plaques containing amyloid-ß, and neurofibrillary tangles in the brain (Ittner and Gotz 2011). Many genetic risk factors for AD have been identified, although only a few cases of AD can be explained by specific gene mutations. Besides that, the phenotypic discordance between monozygotic twins where one has Alzheimer's might be explained by the existence of epigenetic mechanisms that contribute to the development of this illness (Poulsen et al. 2007). In addition, the fact that reduced neurogenesis is a common feature in AD could be due to failures in the differentiation process, including epigenetic failures. There are some studies that relate epigenetic mechanisms directly with AD: It has been shown that the DNA methylation of telomerase inverse transcriptase (*hTERT*) promoter is increased in patients with AD (Silva et al. 2008) and an aberrant gene expression related to histone acetylation and phosphorylation has also been found (Kilgore et al. 2010).

2.3.3 Huntington's and Parkinson's Diseases

Huntington's disease (HD) and Parkinson's disease are neurodegenerative diseases. Despite the fact that the molecular mechanisms implicated in their development appear to be very different, both are late-onset and have been associated with the accumulation of intracellular toxic proteins (Rubinsztein 2006).

HD is a heritable disease characterized by abnormal involuntary movements, cognitive dysfunction, and psychiatric symptoms (Walker 2007). It is caused by an autosomal-dominant mutation in the huntingtin gene (*HTT*), which produces an expansion of a poly-glutamine repeat within the amino terminus of the protein huntingtin (HTT). The mutant form of this protein has been found to interact with HATs, which suggests that epigenetics play a role in HD. Also, this protein associates with HDAC corepressors to repress transcription (Gray 2010, 2011; Steffan et al. 2000). These interactions between HTT protein and the regulation of the histone code can lead to aberrations of gene expression. Accordingly, genome-wide expression profiling patterns in HD patients have shown alterations in mRNA expression (Borovecki et al. 2005). Recently, a study has shown that treatment with HDACis in a mouse model of HD resulted in improved motor function, extended survival, and reduced brain atrophy (Chopra et al. 2012).

Parkinson's disease (PD) is a degenerative disorder of the CNS that affects 1–2 % of the population over the age of 65. The most common symptoms are resting tremor, rigidity, bradykinesia, and postural instability, which result from the loss of neuromelanin containing dopaminergic neurons (Thomas and Beal 2011). Many studies have related PD with specific/particular genetic mutations (Hardy 2010; Nuytemans et al. 2010; Ramirez et al. 2006), but in the last few years there is growing evidence pointing to epigenetic mechanisms contributing to PD development (Coppede 2012). For instance, the expression of the gene frequently altered in PD, alpha-synuclein (*SNCA*), can be regulated by DNA methylation (Matsumoto et al. 2010). Also, treatments with TSA performed in a rat model of PD have shown a neuroprotective action of this epigenetic drug (Monti et al. 2010), and levels of many miRNAs have also been shown to be altered (Gillardon et al. 2008). These studies evidence the relationship between epigenetic mechanism and PD, and more investigations in this area could help to make progress in discovering new targets and designing appropriate therapies.

2.3.4 Schizophrenia

Schizophrenia is a mental disease characterized by a serious disorder of cognition. Common symptoms include delusions, hallucinations, paranoid, bizarre thoughts, social dysfunction, poor motivation, and apathy, among others. Diagnosis is usually in adolescence or later, suggesting that it may will be a neurodevelopmental disorder (Sawa and Snyder 2002). To date, DNA methylation has been examined for only a small number of candidate genes (Roth et al. 2009). For instance, the levels of the extracellular matrix protein reelin are reduced in postmortem brains from patients diagnosed with schizophrenia or bipolar illness with psychosis. This downregulation is thought to be mediated by epigenetic mechanisms given that *Reelin* promoter contains several sites for DNA methylation and HDAC and DNMT inhibitors increase its expression. Furthermore, another gene influencing the GABAergic system, the glutamic acid decarboxylase 1 (GAD1) showed changes in schizophrenia patients related to chromatin remodeling modifications (Abel and Zukin 2008).

2.3.5 Glioma

Glioma is the most common primary brain tumor and causes more than 40 % of all CNS neoplasms. It is well known that aberrant epigenetic mechanisms lead to cancer and glioma progression (Nagarajan and Costello 2009). Gliomas are classified by their state of differentiation and present distinct epigenetic patterns such as aberrant DNA methylation (Martinez et al. 2009), changes in histone PTMs and their regulatory genes (Kreth et al. 2012), and also downregulation and upregulation of miRNAs (Croce 2009).

2.3.6 Therapeutic Applications

Targeting histone acetylation could provide benefits for the treatment of many neurological diseases. For example, HDACis might interfere in neurological diseases to provide a protective effect (Chuang et al. 2009). As mentioned earlier, VPA promotes neural differentiation and could have important clinical applications in the treatment of neurological diseases such as epilepsy, bipolar disorders, and serious depression (Blaheta and Cinatl 2002).

2.4 Conclusions

It is true to say that current knowledge of the epigenetic changes that take place during neural development, neural disorders, and cancer development and their clinical potential is quite wide. However, many aspects remain unknown and other aspects need to be fully explored for a truly complete understanding of the development of neural disease and cancer. The use of new technical tools such as high-throughput approaches, and the development of stem cell-based therapies should lead to the identification of new therapeutic targets and result in improvements in quality of life for patients.

References

Abel T, Zukin RS (2008) Epigenetic targets of HDAC inhibition in neurodegenerative and psychiatric disorders. Curr Opin Pharmacol 8:57–64

Ajamian F, Suuronen T, Salminen A, Reeben M (2003) Upregulation of class II histone deacetylases mRNA during neural differentiation of cultured rat hippocampal progenitor cells. Neurosci Lett 346:57–60

Bai S, Ghoshal K, Datta J, Majumder S, Yoon SO, Jacob ST (2005) DNA methyltransferase 3b regulates nerve growth factor-induced differentiation of PC12 cells by recruiting histone deacetylase 2. Mol Cell Biol 25:751–766

Barber BA, Rastegar M (2010) Epigenetic control of Hox genes during neurogenesis, development, and disease. Ann Anat 192:261–274

Ben-Shachar S, Chahrour M, Thaller C, Shaw CA, Zoghbi HY (2009) Mouse models of MeCP2 disorders share gene expression changes in the cerebellum and hypothalamus. Hum Mol Genet 18:2431–2442

Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, Cuff J, Fry B, Meissner A, Wernig M, Plath K, Jaenisch R, Wagschal A, Feil R, Schreiber SL, Lander ES (2006) A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell 125:315–326

Bernstein BE, Meissner A, Lander ES (2007) The mammalian epigenome. Cell 128:669–681

Bird AP (1986) CpG-rich islands and the function of DNA methylation. Nature 321:209–213

Bird A (2008) The methyl-CpG-binding protein MeCP2 and neurological disease. Biochem Soc Trans 36:575–583

Blaheta RA, Cinatl J Jr (2002) Anti-tumor mechanisms of valproate: a novel role for an old drug. Med Res Rev 22:492–511

Bohacek J, Gapp K, Saab BJ, Mansuy IM (2013) Transgenerational epigenetic effects on brain functions. Biol Psychiatry 73:313–320

Borovecki F, Lovrecic L, Zhou J, Jeong H, Then F, Rosas HD, Hersch SM, Hogarth P, Bouzou B, Jensen RV, Krainc D (2005) Genome-wide expression profiling of human blood reveals biomarkers for Huntington's disease. Proc Natl Acad Sci U S A 102:11023–11028

Brooks WH, Le Dantec C, Pers JO, Youinou P, Renaudineau Y (2010) Epigenetics and autoimmunity. J Autoimmun 34:J207–J219

Burgold T, Spreafico F, De Santa F, Totaro MG, Prosperini E, Natoli G, Testa G (2008) The histone H3 lysine 27-specific demethylase Jmjd3 is required for neural commitment. PLoS One 3:e3034

Calvanese V, Fraga MF (2011) SirT1 brings stemness closer to cancer and aging. Aging (Albany NY) 3:162–167

Calvanese V, Lara E, Suarez-Alvarez B, Abu Dawud R, Vazquez-Chantada M, Martinez-Chantar ML, Embade N, Lopez-Nieva P, Horrillo A, Hmadcha A, Soria B, Piazzolla D, Herranz D, Serrano M, Mato JM, Andrews PW, Lopez-Larrea C, Esteller M, Fraga MF (2010) Sirtuin 1 regulation of developmental genes during differentiation of stem cells. Proc Natl Acad Sci U S A 107:13736–13741

Chahrour M, Jung SY, Shaw C, Zhou X, Wong ST, Qin J, Zoghbi HY (2008) MeCP2, a key contributor to neurological disease, activates and represses transcription. Science 320:1224–1229

Chen RZ, Akbarian S, Tudor M, Jaenisch R (2001) Deficiency of methyl-CpG binding protein-2 in CNS neurons results in a Rett-like phenotype in mice. Nat Genet 27:327–331

Cheng LC, Pastrana E, Tavazoie M, Doetsch F (2009) miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. Nat Neurosci 12:399–408

Chopra V, Quinti L, Kim J, Vollor L, Narayanan KL, Edgerly C, Cipicchio PM, Lauver MA, Choi SH, Silverman RB, Ferrante RJ, Hersch S, Kazantsev AG (2012) The sirtuin 2 inhibitor AK-7 is neuroprotective in Huntington's disease mouse models. Cell Rep 2:1492–1497

Chuang DM, Leng Y, Marinova Z, Kim HJ, Chiu CT (2009) Multiple roles of HDAC inhibition in neurodegenerative conditions. Trends Neurosci 32:591–601

Cloos PA, Christensen J, Agger K, Helin K (2008) Erasing the methyl mark: histone demethylases at the center of cellular differentiation and disease. Genes Dev 22:1115–1140

Coppede F (2012) Genetics and epigenetics of Parkinson's disease. ScientificWorldJournal 2012:489830

Croce CM (2009) Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet 10:704–714

Defossez PA, Stancheva I (2011) Biological functions of methyl-CpG-binding proteins. Prog Mol Biol Transl Sci 101:377–398

Delcuve GP, Rastegar M, Davie JR (2009) Epigenetic control. J Cell Physiol 219:243–250

Dietrich J, Han R, Yang Y, Mayer-Proschel M, Noble M (2006) CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. J Biol 5:22

Dokmanovic M, Clarke C, Marks PA (2007) Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res 5:981–989

Ellis L, Atadja PW, Johnstone RW (2009) Epigenetics in cancer: targeting chromatin modifications. Mol Cancer Ther 8:1409–1420

Fan G, Hutnick L (2005) Methyl-CpG binding proteins in the nervous system. Cell Res 15: 255–261

Feng J, Chang H, Li E, Fan G (2005) Dynamic expression of de novo DNA methyltransferases Dnmt3a and Dnmt3b in the central nervous system. J Neurosci Res 79:734–746

Feng J, Fouse S, Fan G (2007) Epigenetic regulation of neural gene expression and neuronal function. Pediatr Res 61:58R–63R

Flici H, Erkosar B, Komonyi O, Karatas OF, Laneve P, Giangrande A (2011) Gcm/Glide-dependent conversion into glia depends on neural stem cell age, but not on division, triggering a chromatin signature that is conserved in vertebrate glia. Development 138:4167–4178

Gillardon F, Mack M, Rist W, Schnack C, Lenter M, Hildebrandt T, Hengerer B (2008) MicroRNA and proteome expression profiling in early-symptomatic alpha-synuclein(A30P)-transgenic mice. Proteomics Clin Appl 2:697–705

Gray SG (2010) Targeting histone deacetylases for the treatment of Huntington's disease. CNS Neurosci Ther 16:348–361

Gray SG (2011) Targeting Huntington's disease through histone deacetylases. Clin Epigenetics 2:257–277

Guan JS, Haggarty SJ, Giacometti E, Dannenberg JH, Joseph N, Gao J, Nieland TJ, Zhou Y, Wang X, Mazitschek R, Bradner JE, Depinho RA, Jaenisch R, Tsai LH (2009) HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 459:55–60

Guo H, Ingolia NT, Weissman JS, Bartel DP (2010) Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature 466:835–840

Guy J, Hendrich B, Holmes M, Martin JE, Bird A (2001) A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome. Nat Genet 27:322–326

Guy J, Gan J, Selfridge J, Cobb S, Bird A (2007) Reversal of neurological defects in a mouse model of Rett syndrome. Science 315:1143–1147

Haberland M, Mokalled MH, Montgomery RL, Olson EN (2009a) Epigenetic control of skull morphogenesis by histone deacetylase 8. Genes Dev 23:1625–1630

Haberland M, Montgomery RL, Olson EN (2009b) The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat Rev Genet 10:32–42

Hardy J (2010) Genetic analysis of pathways to Parkinson disease. Neuron 68:201–206

Herman JG, Baylin SB (2003) Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 349:2042–2054

Hirabayashi Y, Gotoh Y (2010) Epigenetic control of neural precursor cell fate during development. Nat Rev Neurosci 11:377–388

Hsieh J, Eisch AJ (2010) Epigenetics, hippocampal neurogenesis, and neuropsychiatric disorders: unraveling the genome to understand the mind. Neurobiol Dis 39:73–84

Hsieh J, Nakashima K, Kuwabara T, Mejia E, Gage FH (2004) Histone deacetylase inhibition-mediated neuronal differentiation of multipotent adult neural progenitor cells. Proc Natl Acad Sci U S A 101:16659–16664

Ittner LM, Gotz J (2011) Amyloid-beta and tau–a toxic pas de deux in Alzheimer's disease. Nat Rev Neurosci 12:65–72

Jobe EM, Mcquate AL, Zhao X (2012) Crosstalk among epigenetic pathways regulates neurogenesis. Front Neurosci 6:59

Jordan C, Li HH, Kwan HC, Francke U (2007) Cerebellar gene expression profiles of mouse models for Rett syndrome reveal novel MeCP2 targets. BMC Med Genet 8:36

Junn E, Mouradian MM (2012) MicroRNAs in neurodegenerative diseases and their therapeutic potential. Pharmacol Ther 133:142–150

Kanai Y (2008) Alterations of DNA methylation and clinicopathological diversity of human cancers. Pathol Int 58:544–558

Kilgore M, Miller CA, Fass DM, Hennig KM, Haggarty SJ, Sweatt JD, Rumbaugh G (2010) Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. Neuropsychopharmacology 35:870–880

Kreth FW, Thon N, Tonn JC (2012) Low-grade gliomas. J Neurosurg 116:468–70; author reply 469–70

Kretsovali A, Hadjimichael C, Charmpilas N (2012) Histone deacetylase inhibitors in cell pluripotency, differentiation, and reprogramming. Stem Cells Int 2012:184154

Lee KK, Workman JL (2007) Histone acetyltransferase complexes: one size doesn't fit all. Nat Rev Mol Cell Biol 8:284–295

Li X, Zhao X (2008) Epigenetic regulation of mammalian stem cells. Stem Cells Dev 17: 1043–1052

Lilja T, Heldring N, Hermanson O (2013) Like a rolling histone: epigenetic regulation of neural stem cells and brain development by factors controlling histone acetylation and methylation. Biochim Biophys Acta 1830:2354–2360

Lyst MJ, Ekiert R, Ebert DH, Merusi C, Nowak J, Selfridge J, Guy J, Kastan NR, Robinson ND, De Lima Alves F, Rappsilber J, Greenberg ME, Bird A (2013) Rett syndrome mutations abolish the interaction of MeCP2 with the NCoR/SMRT co-repressor. Nat Neurosci 16:898–902

Macdonald VE, Howe LJ (2009) Histone acetylation: where to go and how to get there. Epigenetics 4:139–143

Macdonald JL, Roskams AJ (2008) Histone deacetylases 1 and 2 are expressed at distinct stages of neuro-glial development. Dev Dyn 237:2256–2267

Majdzadeh N, Wang L, Morrison BE, Bassel-Duby R, Olson EN, D'Mello SR (2008) HDAC4 inhibits cell-cycle progression and protects neurons from cell death. Dev Neurobiol 68: 1076–1092

Makeyev EV, Zhang J, Carrasco MA, Maniatis T (2007) The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing. Mol Cell 27:435–448

Martinez R, Martin-Subero JI, Rohde V, Kirsch M, Alaminos M, Fernandez AF, Ropero S, Schackert G, Esteller M (2009) A microarray-based DNA methylation study of glioblastoma multiforme. Epigenetics 4:255–264

Matsumoto L, Takuma H, Tamaoka A, Kurisaki H, Date H, Tsuji S, Iwata A (2010) CpG demethylation enhances alpha-synuclein expression and affects the pathogenesis of Parkinson's disease. PLoS One 5:e15522

Meissner A, Mikkelsen TS, Gu H, Wernig M, Hanna J, Sivachenko A, Zhang X, Bernstein BE, Nusbaum C, Jaffe DB, Gnirke A, Jaenisch R, Lander ES (2008) Genome-scale DNA methylation maps of pluripotent and differentiated cells. Nature 454:766–770

Meshorer E, Yellajoshula D, George E, Scambler PJ, Brown DT, Misteli T (2006) Hyperdynamic plasticity of chromatin proteins in pluripotent embryonic stem cells. Dev Cell 10:105–116

Mikkelsen TS, Ku M, Jaffe DB, Issac B, Lieberman E, Giannoukos G, Alvarez P, Brockman W, Kim TK, Koche RP, Lee W, Mendenhall E, O'Donovan A, Presser A, Russ C, Xie X, Meissner A, Wernig M, Jaenisch R, Nusbaum C, Lander ES, Bernstein BE (2007) Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. Nature 448:553–560

Minucci S, Pelicci PG (2006) Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer 6:38–51

Miyake K, Yang C, Minakuchi Y, Ohori K, Soutome M, Hirasawa T, Kazuki Y, Adachi N, Suzuki S, Itoh M, Goto YI, Andoh T, Kurosawa H, Oshimura M, Sasaki M, Toyoda A, Kubota T (2013) Comparison of genomic and epigenomic expression in monozygotic twins discordant for Rett syndrome. PLoS One 8:e66729

Mizutani K, Yoon K, Dang L, Tokunaga A, Gaiano N (2007) Differential Notch signalling distinguishes neural stem cells from intermediate progenitors. Nature 449:351–355

Mohamed Ariff I, Mitra A, Basu A (2012) Epigenetic regulation of self-renewal and fate determination in neural stem cells. J Neurosci Res 90:529–539

Mohn F, Weber M, Rebhan M, Roloff TC, Richter J, Stadler MB, Bibel M, Schubeler D (2008) Lineage-specific polycomb targets and de novo DNA methylation define restriction and potential of neuronal progenitors. Mol Cell 30:755–766

Montgomery RL, Hsieh J, Barbosa AC, Richardson JA, Olson EN (2009) Histone deacetylases 1 and 2 control the progression of neural precursors to neurons during brain development. Proc Natl Acad Sci U S A 106:7876–7881

Monti B, Gatta V, Piretti F, Raffaelli SS, Virgili M, Contestabile A (2010) Valproic acid is neuroprotective in the rotenone rat model of Parkinson's disease: involvement of alpha-synuclein. Neurotox Res 17:130–141

Mosammaparast N, Shi Y (2010) Reversal of histone methylation: biochemical and molecular mechanisms of histone demethylases. Annu Rev Biochem 79:155–179

Nagarajan RP, Costello JF (2009) Epigenetic mechanisms in glioblastoma multiforme. Semin Cancer Biol 19:188–197

Namihira M, Kohyama J, Abematsu M, Nakashima K (2008) Epigenetic mechanisms regulating fate specification of neural stem cells. Philos Trans R Soc Lond B Biol Sci 363:2099–2109

Neul JL, Fang P, Barrish J, Lane J, Caeg EB, Smith EO, Zoghbi H, Percy A, Glaze DG (2008) Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurology 70:1313–1321

Ng RK, Gurdon JB (2008) Epigenetic inheritance of cell differentiation status. Cell Cycle 7:1173–1177

Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C (2010) Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. Hum Mutat 31:763–780

Olynik BM, Rastegar M (2012) The genetic and epigenetic journey of embryonic stem cells into mature neural cells. Front Genet 3:81

Oury F, Rijli FM (2007) [Hoxa2: a key gene for the facial somatosensory map]. Med Sci (Paris) 23:247–9

Pasini D, Hansen KH, Christensen J, Agger K, Cloos PA, Helin K (2008) Coordinated regulation of transcriptional repression by the RBP2 H3K4 demethylase and Polycomb-Repressive Complex 2. Genes Dev 22:1345–1355

Poulsen P, Esteller M, Vaag A, Fraga MF (2007) The epigenetic basis of twin discordance in age-related diseases. Pediatr Res 61:38R–42R

Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J, Al-Din A, Hillmer AM, Karsak M, Liss B, Woods CG, Behrens MI, Kubisch C (2006) Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet 38:1184–1191

Rett A (1986) Rett syndrome. History and general overview. Am J Med Genet Suppl 1:21–25

Ringrose L, Paro R (2007) Polycomb/Trithorax response elements and epigenetic memory of cell identity. Development 134:223–232

Robertson KD (2001) DNA methylation, methyltransferases, and cancer. Oncogene 20: 3139–3155

Roth TL, Lubin FD, Sodhi M, Kleinman JE (2009) Epigenetic mechanisms in schizophrenia. Biochim Biophys Acta 1790:869–877

Rubinsztein DC (2006) The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 443:780–786

Samaco RC, Neul JL (2011) Complexities of Rett syndrome and MeCP2. J Neurosci 31: 7951–7959

Sawa A, Snyder SH (2002) Schizophrenia: diverse approaches to a complex disease. Science 296:692–695

Schneider JW, Gao Z, Li S, Farooqi M, Tang TS, Bezprozvanny I, Frantz DE, Hsieh J (2008) Small-molecule activation of neuronal cell fate. Nat Chem Biol 4:408–410

Schuettengruber B, Chourrout D, Vervoort M, Leblanc B, Cavalli G (2007) Genome regulation by polycomb and trithorax proteins. Cell 128:735–745

Scott CE, Wynn SL, Sesay A, Cruz C, Cheung M, Gomez Gaviro MV, Booth S, Gao B, Cheah KS, Lovell-Badge R, Briscoe J (2010) SOX9 induces and maintains neural stem cells. Nat Neurosci 13:1181–1189

Sikorska M, Sandhu JK, Deb-Rinker P, Jezierski A, Leblanc J, Charlebois C, Ribecco-Lutkiewicz M, Bani-Yaghoub M, Walker PR (2008) Epigenetic modifications of SOX2 enhancers, SRR1 and SRR2, correlate with in vitro neural differentiation. J Neurosci Res 86:1680–1693

Silva PN, Gigek CO, Leal MF, Bertolucci PH, de Labio RW, Payão SL, Smith Mde A (2008) Promoter methylation analysis of SIRT3, SMARCA5, HTERT and CDH1 genes in aging and Alzheimer's disease. J Alzheimers Dis 13:173–176

Soshnikova N, Duboule D (2008) Epigenetic regulation of Hox gene activation: the waltz of methyls. Bioessays 30:199–202

Steffan JS, Kazantsev A, Spasic-Boskovic O, Greenwald M, Zhu YZ, Gohler H, Wanker EE, Bates GP, Housman DE, Thompson LM (2000) The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proc Natl Acad Sci U S A 97: 6763–6768

Sun G, Yu RT, Evans RM, Shi Y (2007) Orphan nuclear receptor TLX recruits histone deacetylases to repress transcription and regulate neural stem cell proliferation. Proc Natl Acad Sci U S A 104:15282–15287

Thomas B, Beal MF (2011) Molecular insights into Parkinson's disease. F1000 Med Rep 3:7
Tudor M, Akbarian S, Chen RZ, Jaenisch R (2002) Transcriptional profiling of a mouse model for Rett syndrome reveals subtle transcriptional changes in the brain. Proc Natl Acad Sci U S A 99:15536–15541
Urdinguio RG, Sanchez-Mut JV, Esteller M (2009) Epigenetic mechanisms in neurological diseases: genes, syndromes, and therapies. Lancet Neurol 8:1056–1072
Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, Hollanders K, Lugtenberg D, Bienvenu T, Jensen LR, Gecz J, Moraine C, Marynen P, Fryns JP, Froyen G (2005) Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet 77:442–453
Verdin E, Hirschey MD, Finley LW, HAIGIS MC (2010) Sirtuin regulation of mitochondria: energy production, apoptosis, and signaling. Trends Biochem Sci 35:669–675
Walker FO (2007) Huntington's disease. Lancet 369:218–228
Watanabe D, Uchiyama K, Hanaoka K (2006) Transition of mouse de novo methyltransferases expression from Dnmt3b to Dnmt3a during neural progenitor cell development. Neuroscience 142:727–737
Weber M, Hellmann I, Stadler MB, Ramos L, Paabo S, Rebhan M, Schubeler D (2007) Distribution, silencing potential and evolutionary impact of promoter DNA methylation in the human genome. Nat Genet 39:457–466
Wu Z, Huang K, Yu J, Le T, Namihira M, Liu Y, Zhang J, Xue Z, Cheng L, Fan G (2012) Dnmt3a regulates both proliferation and differentiation of mouse neural stem cells. J Neurosci Res 90:1883–1891
Xu WS, Parmigiani RB, Marks PA (2007) Histone deacetylase inhibitors: molecular mechanisms of action. Oncogene 26:5541–5552
Yang XJ, Seto E (2008) The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. Nat Rev Mol Cell Biol 9:206–218
Yazdani M, Deogracias R, Guy J, Poot RA, Bird A, Barde YA (2012) Disease modeling using embryonic stem cells: MeCP2 regulates nuclear size and RNA synthesis in neurons. Stem Cells 30:2128–2139
Zachariah RM, Rastegar M (2012) Linking epigenetics to human disease and Rett syndrome: the emerging novel and challenging concepts in MeCP2 research. Neural Plast 2012:415825
Zhao C, Sun G, Li S, Shi Y (2009) A feedback regulatory loop involving microRNA-9 and nuclear receptor TLX in neural stem cell fate determination. Nat Struct Mol Biol 16:365–371
Zhao C, Sun G, Li S, Lang MF, Yang S, Li W, Shi Y (2010) MicroRNA let-7b regulates neural stem cell proliferation and differentiation by targeting nuclear receptor TLX signaling. Proc Natl Acad Sci U S A 107:1876–1881

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