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Epigenetic Mistakes in Neurodevelopmental Disorders

Giuseppina Mastrototaro[1] · **Mattia Zaghi**[1] · **Alessandro Sessa**[1]

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Abstract Epigenetics is the array of the chromatin modifications that customize in cell-, stage-, or condition-specific manner the information encloses in plain DNA molecules. Increasing evidences suggest the importance of epigenetic mechanisms for development and maintenance of central nervous system. In fact, a large number of newly discovered genetic causes of neurodevelopmental disorders such as intellectual disability, autism spectrum disorders, and many other syndromes are mutations within genes encoding for chromatin remodeling enzymes. Here, we review recent findings on the epigenetic origin of human diseases, with emphasis on disorders that affect development of the nervous system, and discuss novel therapeutic avenues that target epigenetic mechanisms.

Keywords Epigenetics · Neurodevelopmental disorders · Intellectual disability

Introduction

Neurodevelopmental disorders (NDDs) represent a wide and variegated spectrum of diseases occurring in the childhood characterized by altered brain functionality leading to mild to severe psychiatric impairment. NDDs are relatively common mental illnesses including but not limited to intellectual disability (ID), autism spectrum disorders (ASD), and schizophrenia. These disorders occur often as syndromes with complex clinical manifestations that show a high grade of symptomatic overlap: cognitive deficits, poor learning, limitations in adaptive behavior, and seizures often found in affected children (Geschwind 2009; Maski et al. 2011).

Unfortunately, such a broad spectrum of phenotypic manifestations mirrors the extreme heterogeneity in the etiopathology of the disorders posing many limitations to both diagnosis and treatment. In fact, environmental factors, malnutrition, alcohol abuse, and prenatal disease of the mother are proven causes or cofactors of NDD together with a high genetic component. The introduction and widespread application of high-throughput sequencing platforms has marked a "new era" in understanding the genetics of NDD, with the addition of a number of new rare alterations, either heritable or de novo (e.g., microscopic duplication/deletions, copy number variations, single nucleotide mutations), to the list of the historically known chromosomal aberrations or gene mutations (e.g., trisomy 21 and expansion of CGG repeat in *FMR1* gene for Down syndrome and fragile X syndrome, respectively, two common causes of ID) (Lejeune et al. 1959; Vissers et al. 2015). Altogether, these novel datasets are proving extremely useful to infer the biological processes and the molecular mechanisms at the basis of the altered brain functions and thus new potential target for therapies. An unexpected result of these genome sequencing efforts is the increasing evidence that a large array of new, rare NDD-linked mutations are found in chromatin remodeling factors, thus pointing to epigenetics as a converging pathogenetic mechanism (Pinto et al. 2014; De Rubeis et al. 2014; Iossifov et al. 2014). In 1942, Conrad Waddington was the first to use the term epigenetics to describe environmental factors able to induce differences in equal cells; today, it is employed to group many and different phenomena that, acting on chromatin, can induce changes in gene expression, often in heritable way, without any modifications in underlying DNA sequence (Goldberg et al. 2007; Pujadas and Feinberg 2012).

✉ Alessandro Sessa
sessa.alessandro@hsr.it

[1] Division of Neuroscience, San Raffaele Hospital, Via Olgettina 58, 20132 Milan, Italy

Examples of these mechanisms are DNA methylation, covalent modification of histone proteins, modifications in nucleosome number/composition, and the action of noncoding RNAs that are responsible to make the chromatin, and thus the genes, more or less tightly packed, influencing the accessibility of the transcriptional machinery, as well as regulators of DNA replication, recombination, and repair. The importance of epigenetic control is further witnessed by the fact that it is established throughout the entire life of an organism—and beyond, since the transgenerational inheritance of epigenetic traits has been recently demonstrated (Siklenka et al. 2015). Thus, it is not a surprise that mutations in genes that encode for enzymes involved in the imposition, removal, or recognition of epigenetic marks often result in pathological conditions.

Herein we summarize some classical and recent findings on the epigenetic origin of NDDs (Table 1), their implication in the molecular mechanisms at the basis of the defective neurological functions, and useful experimental models to mimic and study the pathological conditions.

DNA Methylation

Mutations in Methylation-Associated Machinery

DNA methylation on cytosine (5-methylcytosine—5mC) residues in CpG sequences is a stable covalent modification that persist in post-mitotic cells throughout their lifetime. This modification is one of the most well-known example of epigenetic regulation that generally correlates with close chromatin conformation and thus transcriptional silencing. The general content of DNA methylation in the central nervous system (CNS) increases in adulthood and its role is of cardinal importance (Chen et al. 2013; Lister et al. 2013). De novo DNA methyltransferases (DNMTs) of DNMT3 family catalyze the chemical transformation that is preserved by DNMT1 (Kinney and Pradhan 2011). Genetic engineering in mouse has informed that *Dnmt1* and *3b* are essential for embryonic development, while *Dnmt3a* KO mice survive for few weeks after birth (Li et al. 1992; Okano et al. 1999). Strikingly, defects in the regulation or detection of 5mC cause severe disorders in humans (Klein et al. 2011; Xu et al. 1999; Jin et al. 2008).

An example of the importance of these regulatory mechanisms is provided by Rett syndrome, a devastating NDD characterized by reduced brain growth, gait abnormalities, distinctive hand movements, seizures, and ID. Rett syndrome affects predominantly girls in their early childhood (usually after 6 months of age), primarily due to mutations within X chromosome gene *MECP2* that codify for a reader of methyl-CpG in the DNA (Amir et al. 1999). Occasionally boys are affected, very often in a more severe way (most of them die prenatally or in early infancy), rarely in less aggressive form. More than 20 years of research have revealed multiple functionality in MECP2 spanning between negative regulator of transcription, silencer of repetitive elements and retrotransposons, transcriptional activator through the recruitment of CREB1, and other cell type-specific cofactors (Lyst et al. 2013; Muotri et al. 2010; Chahrour et al. 2008; Guy et al. 2011; Lyst and Bird 2015). The importance of its ability to bind CpG islands is underlined by the fact that most the missense mutations causing Rett syndrome are located within the methyl-CpG-binding domain (MBD) (Ballestar et al. 2000). Importantly, it has been demonstrated that re-expression of *Mecp2* can reverse neurological defects in mouse model indicating that the altered brain functions are not due to irreversible developmental malformations opening new expectations for novel therapies (Guy et al. 2007).

It has been recently reported that heterozygous mutations in *DNMT3A* cause a rare overgrowth condition called Tatton-Brown-Rahman syndrome (tall stature, large head, distinctive facial appearance, mild to moderate ID) (Tatton-Brown et al. 2014). Several de novo mutations (ten nonsynonymous, two small frameshift insertions, and one in-frame deletion) are found within the three functional domains of the protein: a proline–tryptophan–tryptophan–proline (PWWP) domain (three mutations), an ATRX-DNMT3A-DNMT3L-type zinc finger domain (three), and DNA methyltransferase (MTase) domain (seven) suggesting a pathological mechanism due to protein with an aberrant function rather than simple haploinsufficiency (Tatton-Brown et al. 2014). In addition, Xin et al. have recently reported six cases of inherited Tatton-Brown–Rahman overgrowth syndrome (TBRS) due to novel *DNMT3A* germline mutations in C-terminal DNA MTase domain (Xin et al. 2016). Studies in mouse models have evidenced defects in memory formation due to altered synaptic functions (Feng et al. 2010; Swiech et al. 2015). Regarding the overgrowth mechanisms, it has been reported that somatic mutations in *DNMT3A* are recognized causes of hematological malignancies and thus linked with uncontrolled cell proliferation (Hou et al. 2012; Scourzic et al. 2016). Moreover, a recent study has indicated DNA methylation, mediated by elevated expression of DNMT3A, as the main player in the silencing of CDK inhibitor $p18^{INK4C}$ that induces overproliferation in gastric carcinogenesis (Cui et al. 2015). This cancer-NDD comparison would suggest the presence of dominant negative alleles leading to a gain of DNMT3A function of the pathological variants causing overgrowth phenotype both in tumors and in Tatton-Brown-Rahman syndrome. However, this fascinating hypothesis is challenged by a recently reported new TBRS patient with 2p23 microdeletion including *DNMT3A*, which would support the idea of *DNMT3A* haploinsufficiency as cause of the overgrowth syndrome (Okamoto et al. 2016).

Immunodeficiency, centromere instability, and facial anomalies syndrome 1 (ICF1) (ID, facial dysmorphism, recurrent and prolonged infections) is largely due to homozygous or compound heterozygous mutations in *DNMT3B* (Hansen et al. 1999; Jin et al. 2008). These aberrations result in

Table 1 An overview of the discussed NDDs with the associated gene alteration(s)

Disease	Epigenetic trait involved	Gene(s) associated	Gene function	Mutations
Rett syndrome	DNA methylation	*MECP2*	DNA methyl binding protein–multifunctional protein, chromatin remodeler	Deletions, insertions, nonsense, frameshift, missense; (X-linked)
Fragile X syndrome	DNA methylation	*FMRI*	mRNA-binding protein	Triplet (CGG) expansion; (X-linked)
Tatton-Brown-Rahman syndrome	DNA methylation	*DNMT3A*	De novo DNA methyltransferase	Mainly missense (het)
Instability-facial anomalies syndrome-1 (ICF1)	DNA methylation	*DNMT3B*	De novo DNA methyltransferase	Missense (bi-allelic)
Kabuki syndrome	Histone tail methylation	*KMT2D*	H3K4 methyltransferase	Nonsense, frameshift, missense; (het)
		KDM6A	H3K27 demethylase	Nonsense, frameshift, deletions, splice-site; (het)
Schizophrenia/ID	Histone tail methylation	*SETD1A*	H3K4 methyltransferase	Nonsense, frameshift, deletions, splice-site; (het)
Wiedemann-Steiner syndrome	Histone tail methylation	*KMT2A*	H3K4 methyltransferase	Nonsense, missense, frameshift; (het)
Kleefstra syndrome	Histone tail methylation	*EHMT1*	H3K9 methyltransferase	Deletions, frameshift; (het)
Weaver syndrome	Histone tail methylation	*EZH2*	H3K27 methyltransferase	Missense, deletions (3′ level); (het)
Sotos syndrome	Histone tail methylation	*NSD1*	H3K36 and H4K20 di-methyltransferase	Deletions, frameshift, missense; (het)
Wolf-Hirschhorn syndrome	Histone tail methylation	*NSD2*	H3K36 di-methyltransferase	Deletions; (het)
Sotos-like syndrome	Histone tail methylation	*SETD2*	H3K36 tri-methyltransferase	Frameshift, missense; (het)
Williams-Beuren syndrome	Histone tail methylation/acetylation	*GTF2I*[a]	Transcription factor	Deletions; (het)
Williams-Beuren region duplication syndrome	Histone tail methylation/acetylation	*GTF2I*[a]	Transcription factor	Duplications; (het)
Rubenstein-Taybi syndrome	Histone tail acetylation	*CREBBP*	Histone acetyltransferase	Deletions, duplications; (het)
Rubenstein-Taybi syndrome	Histone tail acetylation	*EP300*	Histone acetyltransferase	Deletions; (het)
Brachydactyly–mental retardation syndrome	Histone tail acetylation	*HDAC4*	Histone deacetylase	Deletions, frameshift; (het)
KGB syndrome	Histone tail acetylation	*ANKRD11*	Chromatin regulator	Deletions, nonsense, frameshift; (het)
Coffin-Siris syndrome	Nucleosome remodeling	*ARID1B*	DNA binding subunit of SWI/SNF (BAF) complex	Deletions, translocation, inactivating (?) point mutations; (het)
		ARID1A	DNA binding subunit of SWI/SNF (BAF) complex	Deletions, nonsense; het
		SMARCA4	ATP-dependent helicase, subunit of SWI/SNF (BAF) complex	Missense, in-frame deletions; (het)
		SMARCB1	Invariant subunit of SWI/SNF (BAF) complex	Missense, in-frame deletions; (het)
		SMARCE1	DNA binding subunit of SWI/SNF (BAF) complex	Missense; (het)
		SOX11	Transcription factor	Missense; (het)
Nicolaides-Baraitser syndrome	Nucleosome remodeling	*SMARCA2*	ATP-dependent helicase, subunit of SWI/SNF (BAF) complex	Missense, in-frame deletions; (het)
CHARGE syndrome	Nucleosome remodeling	*CHD7*	ATP-dependent helicase	Nonsense, frameshift, missense; (het)
Epileptic encephalopathy/ID/ASD	Nucleosome remodeling	*CHD2*	ATP-dependent helicase	Deletions, missense, nonsense, splice-site; (het)
ASD	Nucleosome remodeling	*CHD8*	ATP-dependent helicase	Nonsense, frameshift; (het)

[a] The genetic alteration associated is with 7q11.23 containing 26–28 genes, including *GTF2I*

hypomorphic proteins since the complete loss of the enzyme is probably lethal as demonstrated in mice (Okano et al. 1999). The reduced DNMT3B activity in patients and cell lines leads to significant changes in transcription in subset of genes important for immune functions, development, and neurogenesis which, at least in part, bear subtle but significant hypomethylation in their promoters associated with alteration in the histone modifications in the surrounded area (loss of H3K27me3, gain of H3K9ac, and K4me3) that together sustain genic upregulation (Jin et al. 2008).

Recent genome-wide studies of schizophrenic patients have revealed an enrichment in DNA methylation quantitative trait loci in regions associated with the disease (Jaffe et al. 2016; Hannon et al. 2016). Interestingly the majority of the methylation-sensitive sites associated with schizophrenia are implicated in the transition from fetal to neonatal life, strengthening the hypothesis that genetic or environmental factors acting at this critical developmental stage may influence susceptibility to schizophrenia through alteration in DNA methylation. This concept is supported by several reports of increase expression of *DNMT1* and *DNMT3A* in schizophrenia and bipolar patients that results in hypermethylation nearby the controlling regions of specific GABAergic genes (e.g., RLN and GAD67) causing their strong downregulation (for review Guidotti et al. 2011).

Aberrant Methylation Pattern

Another important role of DNA methylation is occurring in genomic imprinting; examples linked with NDDs are given by mutations within chromosomal region 15q11-13 leading to Angelman or Prader-Willi syndrome depending on which parental chromosome is affected (Knol et al. 1989; Buiting et al. 1995). In neurons, differently to other cell types, 15q11-13 region, that control the expression of the ubiquitin ligase E3A (UBE3A), is strongly imprinted. In particular, in the Prader-Willi/Angelman syndrome (PWS-AS) locus, the heavy DNA methylation in the PWS/AS imprinting centers found in the maternal chromosome suppresses the downstream genes that, on the contrary, in the paternal chromosome leads to the production of long non coding RNAs (lncRNAs) including the UBE3A-antisense transcript (ATS) to suppress *in cis* *UBE3A* gene expression (Nicholls and Knepper 2001). When the genetic defects (mutations or deletions) are carried by the maternal allele, they result in *UBE3A* KO in neuronal cells of patients with Angelman syndrome (ID, absent speech, ataxia, seizures, episodes of inappropriate happy demeanor). Conversely, when the paternal allele is affected, the loss of paternal-derived genes causes the Prader-Willi syndrome (hyperphagia, short stature, cognitive dysfunctions, hypotonia, behavioral problems) (Nicholls and Knepper 2001; Sell and Margolis 2015). This complex local regulation is maintained in human-induced pluripotent stem cells (hIPSC), deriving from AS and PWS patients, that retain the appropriate methylation imprinting in 15q11-13 following the reprogramming process resulting in a robust model to study these disorders (Chamberlain et al. 2010). Moreover, the neural differentiation of AS-hIPSC is effectual into generating mature neurons in which the paternal *UBE3A* is "correctly" repressed through the action of UBE3A-ATS (Chamberlain et al. 2010). The strong epigenetic architecture of the locus is a complication for our understanding of the diseases but offers interesting intervention options to try to de-repress imprinted alleles that remain intact in patients, to restore functional gene products. For instance, Philpot and co-workers have achieved the pharmacological reactivation of the paternal *Ube3a* in maternal *Ube3a* null neurons (Huang et al. 2011). Surprisingly, this was not due to drugs known to influence the epigenetic marks (e.g., DNA methyltransferase inhibitors or chromatin remodeling compounds) but thanks to topoisomerase inhibitors (e.g., the FDA-approved drug Topotecan) that silence Ube3a-ATS in epigenetic independent manner (Huang et al. 2011). Comparable results have been obtained by silencing Ube3a-ATS genetically or with antisense oligonucleotides that can ameliorate the cognitive deficits of AS mouse model (Meng et al. 2013, 2015).

In early 90s, it has been identified the abnormal expansion of CGG repeats in the 5′ UTR of the *FMRI* gene on the X chromosome as the molecular cause of the most common form of inherited mental retardation, the fragile X syndrome (FXS) (moderate to severe mental retardation, facial dysmorphisms) (Pieretti et al. 1991; Verkerk et al. 1991; Kremer et al. 1991). The CGG repeat region is located immediately downstream of a CpG island that become hypermethylated upon the strong methylation associated to the CGG repeats when their number exceeds 200; this entails histone modifications nearby (H3K9, K27, and H4K20 methylation and H3K4 demethylation, histone deacetylation) resulting in deficiency of the fragile X mental retardation protein (FMRP), a neuronal mRNA-binding protein encoded by *FMRI*. Treatment with a potent agent against DNA methylation (5′-azadeoxycytidine) leads to the re-expression of *FMRI* strongly indicating DNA methylation as the pioneering mechanism in the etiology of the pathology (Coffee et al. 1999). However, the findings of (i) cases of CGG expansion with unmethylated *FMRI* and (ii) the phenotype of pre-mutation carriers (55–200 repeats) than can display autistic traits or develop fragile X associated tremor/ataxia syndrome (FXTAS) suggest that alternative pathogenetic processes involving aberrant functions of RNA molecules might also be involved (Tassone et al. 2000; Greco et al. 2006; Hagerman et al. 2001).

Histone Tail Modifications

Histone proteins can be covalently modified on specific residues, especially in their N- or C- terminus, or tails, with functional consequences on chromatin biology and ultimately in gene expression (Strahl and Allis 2000). These modifications are an array of biochemical transformations of a great variety of amino acids in the histone tails including lysine acetylation and multiple methylation, arginine mono- and di-methylation, serine/threonine phosphorylation, and others that compose a proper histone code (Strahl and Allis 2000; Sweatt 2013). As for the DNA methylation, dedicated enzymes, working as writers, erasers, or readers, grant the dynamical regulation and interpretation of this code in cell- and stage-specific manner. Novel evidences started to strongly link this epigenetic level of regulation with CNS and its development. An example is given by the dynamic state of gene promoters during differentiation from stem cells to neural precursors and, finally, to differentiated neurons. Lineage-specific genes, that in stem/progenitor level are kept silenced but prompted to be activated in the following stages, present their promoters/regulative regions with both activating (e.g., H3K4me3, H3K9ac) and repressive marks (H3K27me3). During fate transitions, specific enzymes (e.g., KDM6B, an H3K27-specific demethylase) can resolve these "bivalent" or "poised" state removing the first or the latter, to keep the genes silenced (e.g., neuronal genes in astrocytes) or to switch on them (Mikkelsen et al. 2007; Mohn et al. 2008; Hirabayashi

and Gotoh 2010; Broccoli et al. 2015). Accordingly, to their importance in neural progenitors and post-mitotic neural cells, dysregulation in histone posttranslational modifications can result in major human NDDs. Moreover, recent large studies have identified new disease variants in confirmed or putative chromatin-modifying enzymes or epigenetic readers, such as KDM6B, KDM5B MLL5, PHF2, CHD2, CHD8, and SETD5, causing autistic phenotype and/or intellectual disabilities (Iossifov et al. 2012; Rauch et al. 2012; Neale et al. 2012; O'Roak et al. 2012; Gilissen et al. 2014; De Rubeis et al. 2014; Iossifov et al. 2014).

Repressive Histone Methylation Marks

Mutations in one allele of *EHMT1* gene decrease the level of functional euchromatic histone-lysine *N*-methyltransferase 1, an H3K9-specific methyltransferase, and are the genetic basis of Kleefstra syndrome (developmental delay, ID, limited or absent speech, and hypotonia) (Kleefstra et al. 2009). H3K9me3 is typically found in highly compacted heterochromatin or anyway silenced genomic regions. Mouse model that mimics the genetic alteration exhibits clinical manifestations of the disease. In particular, this deficiency causes learning and memory defects associated with significant reduction in dendritic arborization and in the number of functional spines (Balemans et al. 2013). The molecular mechanisms underlying these defects are poorly understood; however, it has been reported how EHMT1 and even its homologue EHMT2 interact with core members of polycomb repressive complex, namely enhancer of zeste homologue 2 (EZH2) that catalyzes the deposition of H3K27me3 negative mark (Mozzetta et al. 2014). Thus, an important functional relationship between H3K9me3 and K27me3 takes place at the promoter of neuronal genes, since EZH2 recruitment is dependent on the specific H3K9 methyltransferase activity, suggesting they both contribute to gene silencing (Mozzetta et al. 2014).

Mutations in *EZH2* lead to an overgrowth condition called Weaver syndrome (WVS) (skeletal abnormalities, macrocephaly, mild ID, poor coordination, and balance) (Tatton-Brown et al. 2011; Gibson et al. 2012; Seal et al. 2013). *EZH2* haploinsufficency is unlikely the sole cause since the vast majority of the mutations are missense and the few leading to premature STOP codons are located at the end of the gene and therefore maintain an intact SET domain (Tatton-Brown et al. 2013). Moreover, heterozygous and homozygous activating and inactivating mutations in EZH2 cause hematological cancers (Chase and Cross 2011). The molecular basis of the disorders seems linked to defects in the content of H3K27me3 due to the reduced function as HTM of WVS variants of EZH2 protein (Cohen et al. 2016), although other mechanisms, as the lacking of some important protein-protein interactions, cannot be excluded.

Activating Histone Methylation Marks

Kabuki syndrome (KS) (ID, microcephaly, postnatal dwarfism, long palpebral fissures) clearly illustrates the importance of histone tail modifications for human health (Kuroki et al. 1981; Niikawa et al. 1981; Bögershausen and Wollnik 2013). KS is an autosomal dominant disorder caused by the heterozygous loss-of-function mutations in either *KMT2D* or *KDM6A*. These codify for a lysine-specific methyltransferase (KMT2D) and a lysine-specific demethylase (KDM6A), which are involved in the apposition of H3K4me3 and the removal of H3K27me3, respectively. The two histone tail modifications generally have opposite effects: K4me3 marks open and permissive chromatin while H3K27me3 labels silenced inactive genes. Therefore, the two KS-linked genes promote chromatin laxity and gene expression (Ng et al. 2010; Hannibal et al. 2011; Kokitsu-Nakata et al. 2012; Lederer et al. 2012).

The majority of the mutations are loss of function, thus both in patients with mutation *KMT2D*, the more frequent genetic cause of KS, and in those with aberrant *KDM6A*, the final outcome is chromatin in closed conformation. A mouse model for KS, in which the part of the sequence of one *Kmt2d* allele codifying for the SET (Suvar, enhancer of zeste, Thritorax) domain, responsible for the enzymatic activity has been replaced by β-Geo cassette, showed a striking defect in hippocampal memory with a decrease in dentate gyrus volume and altered neurogenesis (Bjornsson et al. 2014). Interestingly, it has been demonstrated that usage of histone deacetylase (HDAC) inhibitor AR-42 is able to rescue the H3K4 hypomethylation and importantly the defects of the mouse model opening new possibilities for therapeutic intervention not only for KS but possibly for other disorders involving histone modifications (Bjornsson et al. 2014). In fact, the involvement of H3K4 methylation with NDD results deep and intricate since other enzymes, homologous of *Drosophila* Trithorax genes, are associated with congenital disorders of the developing CNS. Rare loss of function variants found in *SETD1A* codifying for an H3K4 HMT have been recently associated with schizophrenia and developmental disorders (Singh et al. 2016). Wiedemann-Steiner syndrome (WSS) (facial features, short stature, ID) is a rare genetic disease, initially known as atypical Kabuki syndrome, caused by the loss of one allele of *KMT2A* gene responsible to produce another HMT-specific for H3K4 residue (Jones et al. 2012; Miyake et al. 2016). Thus, understanding the role and the broad impact of K4 hypomethylation on gene enhancers and promoters in pathological contexts could help to better comprehend and possibly cure a high number of NDD.

Haploinsufficiency of another HMT, NSD1, leads to an overgrowth syndrome called Sotos syndrome (SS) (narrow face, high forehead, behavioral problems including attention deficit hyperactivity disorder (ADHD), ID) (Kurotaki et al. 2002). However, NSD1 specifically controls a different set

of epigenetic modifications, namely the methylation of H3K36 (up to the di-methyl form) and H4K20 (Kudithipudi et al. 2014). H3K36 methylation is commonly associated with active transcription (gene body) but even other processes including alternative splicing, dosage compensation, DNA repair, and recombination while H4K20 is usually linked to gene silencing, chromatin condensation, and S-phase progression (Wagner and Carpenter 2012). It has been demonstrated that loss of *NSD1* causes hypomethylation at these two marks. Interestingly, this is not only observed in Sotos patients but also in neuroblastomas and glioblastoma cell lines, where *NSD1* expression is inhibited by DNA hypermethylation (Berdasco et al. 2009), suggesting that NSD1 may function as a tumor suppressor-like gene, inhibiting key factors responsible for either overgrowth syndrome or tumorigenesis. The ability of NSD1 to bind H3K4me and K9me through its plant homeodomains (PHDs) might also play a role. In fact, when SS single point mutations hit these domains, they produce the same phenotype of the deletion of the entire gene or the SET domain (Cecconi et al. 2005; Pasillas et al. 2011).

Mutations in *NSD2*, a paralog of *NSD1*, cause Wolf-Hirschhorn syndrome (WHS) (delayed growth, heart defects, ID, seizures) (Nimura et al. 2009). As for NSD1, NSD2 deficiency causes defects in H3K36 methylation, although WHS is not an overgrowth syndrome and *Nsd2* knockout mice do not exhibit gigantism but rather smaller size (Nimura et al. 2009). Moreover, the translocation t(4;14), implicated in multiple myeloma, results in NSD2 overexpression causing changes in H3K36 and K27 methylation and alterations in EZH2 binding at genome-wide level (Kuo et al. 2011; Popovic et al. 2014). Thus, in this case, it appears that the increase rather than lowering of H3K36 methyltransferase activity results in cell cycle progression. Consistent with these observations, mutations in SETD2, the only known enzyme able to directly catalyze H3K36 tri-methylation, produce a variegated phenotype ranging from cancer (deletions/missense mutations) to Sotos-like syndrome and ASD (likely through its haploinsufficiency) (Wagner and Carpenter 2012; Luscan et al. 2014; O'Roak et al. 2012; Iossifov et al. 2014; Lumish et al. 2015). Therefore, the changes in the levels of the H3K36 epigenetic mark do not have a unique clinical manifestation but are instead influenced by other factors, such as the complex domain structure of the enzymes implicated in H3K36 regulation, association with other chromatin marks, cell type-specific requirements, etc. Further comparison of the mechanisms of action of the different H3K36 HMTs will clarify their role as promoter or suppressor of cell proliferation as well as of other pathological processes.

A striking example of the effects of either deficiency or overactivation of an epigenetic regulator is provided by two genetic syndromes due to copy number variation of 7q11.23 (26–28 genes) which exhibit both some similar and some symmetrical, opposite features (Merla et al. 2010). Both Williams-Beuren syndrome (WBS), due to the loss of the region in one allele, and Williams-Beuren region duplication syndrome (7dupASD), due to its heterozygous microduplication, are characterized by anxiety and ADHD; conversely, hypersociability, difficulties in visual tasks, cardiovascular symptoms, and facial dimorphisms are WBS-specific while speech impairment and autistic behavior were found only in 7dupASD. A recent study using human iPSCs derived from healthy donors, as well as WBS and 7dupASD patients, has helped to clarify the molecular mechanisms at the basis of the diseases. The gene *GTF2I* has been identified as particularly relevant for the establishment of the opposite phenotypes since its dosage is important for transcriptional dysregulation (Adamo et al. 2015). This seems due to the ability of the relative protein, a transcription factor also known as TFII-I, to form repressive complexes with two repressive chromatin modifiers, the H3K4- and K9-specific demethylase LSD1 and histone deacetylase HDAC2, that accordingly are hypo- or hyper-activated in WBS and 7dupASD, respectively (Adamo et al. 2015).

Histone Acetylation

The acetylation of residues in histone tails removes the positive charges thereby decreasing the interaction with the negatively charged DNA resulting in a more relaxed chromatin. The relative activities of histone acetyltransferases (HATs) and HDACs help to define the DNA regions competent for gene transcription, and their balance is required for the correct development and maintenance of the brain. Mutations in *CREBBP* and *EP300* genes codifying for CBP and P300, two known HATs, are responsible for Rubenstein-Taybi syndrome (RTS) (ID, short stature, broad thumbs and first toes) (Lopez-Atalaya et al. 2014). $Cbp^{+/-}$ mice display behavioral impairment and inhibition of neuronal and glial differentiation due to a decrease in histone acetylation of crucial lineage-specific genes (Wang et al. 2010). Most of RTS cases are due to emideletions that decrease protein levels; however, CBP overexpression due to duplications of the region 16p13.3 is also associated with the disease (Stef et al. 2007). Likewise, loss of function mutations in HDAC4 gene are responsible for the another mental retardation syndrome (brachydactyly–mental retardation syndrome) (Williams et al. 2010). Mutations or deletion of one allele of *ANKRD11* gene cause KGB syndrome (severe cognitive dysfunctions, hyperactivity, anxiety) (Lo-Castro et al. 2013). The related protein has been revealed as an important chromatin regulator through its binding to HDAC3 which is crucial for the deacetylase activity. In vivo and in vitro studies have revealed a general upregulation of gene expression upon loss of ANKRD11 function, which affects neural progenitor proliferation. Notably, forced expression of HDAC3 or HDAC inhibitors is, once again, able to rescue these defects (Gallagher et al. 2015).

Although it is not classified as a NDD, Friedreich's ataxia (FRDA) provides an interesting example of a severe degenerative disorder in which GAA repeats within intron 1 of the *Frataxin* (*FXN*) gene cause heterochromatin-mediated gene silencing leading to decreased levels of the mitochondrial protein Frataxin (Campuzano et al. 1996) (Saveliev et al. 2003). Therefore, epigenetic-based therapies have been proposed to cure FRDA. An approach tested in clinical trial is based on the use of nicotinamide (vitamin B3), a histone deacetylase inhibitor (Libri et al. 2014). Patients treated daily with nicotinamide showed higher levels of frataxin concentration and reduced heterochromatin modification at the FXN locus, although there were no significant clinical improvements.

ATP-Dependent Chromatin Remodeling

In addition to the aforementioned covalent histone modifications, non-covalent energy-dependent chromatin modifications are important epigenetic mechanisms for nucleosome mobility and transcriptional control. In fact, chromatin or nucleosome remodeling complexes can drift, remove, or reshuffle nucleosome structure in an ATP-dependent fashion (López and Wood 2015). The enzymatic complexes that act as remodelers are subdivided in four groups: SWI/SNF, INO80/SWR1, ISWI, and CHD (Hargreaves and Crabtree 2011). Their remodeling activity, well known in other systems, is only moderately studied in neuronal cells. Nevertheless, a number of mutations in genes related to this process are found associated with NDDs, including ASD, ID, schizophrenia, and related syndromes (López and Wood 2015).

Vertebrate SWI/SNF (switching defective/sucrose nonfermentable), a.k.a. BAF (Brg1/Brm associated factor) complex, is formed by several subunits inclusive of core ATPases (Brg1 or Brm), invariant core subunits (SMARCB1/BAF47, SMARCC1/BAF155, SMARCC2/BAF170), and a number of cell-specific components (Narayanan and Tuoc 2014). In fact, BAF complex exists in different flavors even within neural cell types, e.g., in neural progenitors (npBAF), neurons (nBAF), oligodendrocytes (olBAF), etc. (Lessard et al. 2007). Several members of this complex are linked to Coffin-Siris syndrome (CSS) (mild to severe ID or delayed development of speech, hypoplasia of the tips of the fingers) (Tsurusaki et al. 2012; Kleefstra et al. 2014). The most common causes are mutations in *ARID1B* gene, while mutations in *ARID1A*, *SMARCA4*, *SMARCB1*, and *SMARCE1* are rare (Tsurusaki et al. 2012; Kosho et al. 2014). Mutations in another SWI/SNF component, namely *SMARCA2*, cause a very similar condition called Nicolaides-Baraitser syndrome, while alterations in the *ADNP* gene are responsible for ASD (Van Houdt et al. 2012). These genes encode for subunits of neural chromatin remodeling complexes and, although the mutational spectrum and genotype/phenotype correlation are not completely resolved, disease-linked mutations seem to lead to hypofunctional complexes. Mouse transgenic models have recently demonstrated the dramatic effect of BAF loss-of-function on brain development, inducing rearrangement of global chromatin modifications (H3K27me2/3) by abolishing the activity of the specific demethylases KDM6B/UTX on H3 histones (Tuoc et al. 2013; Narayanan et al. 2015). Interestingly, npBAF complex directly interacts with PAX6, a key transcription factor expressed in cortical progenitors and adult NSCs that collaborate with SOX11 to promote neurogenic programs (Ninkovic et al. 2013). Recently, heterozygous mutations in *SOX11* have been identified as additional causes of CSS (Tsurusaki et al. 2014).

Within the chromodomain helicase DNA binding (CHD) protein subfamily, three proteins have been found related to NDDs. Mutations in *CHD7* are the most common cause of coloboma, hearth anomaly, choanal atresia, retardation, and genital and ear anomalies (CHARGE) syndrome (Vissers et al. 2004). Pathogenic *CHD7* variants range from inactivating (nonsense and frameshift) to missense mutations with a broad spectrum of clinical manifestation; however, the major and common pathogenic mechanism seems to be related to a loss or decrease in CHD activity (Hale et al. 2016). Studies in mouse model of *CHD7* haploinsufficiency have showed severe malformation in the ear and reduced proliferation in neural stem cells, while in vitro approaches have underlined the role of CHD7 in binding H3K4me3-enriched chromatin to directly enhance gene transcription (Layman et al. 2009; Hurd et al. 2010; Schnetz et al. 2009). Proteomic and genomic approaches in NSCs have identified CHD7 as transcriptional cofactor of SOX2, an HMG-box transcription factor critical for neurogenesis (Engelen et al. 2011). The interaction between these two factors regulates Notch and Sonic Hedgehog pathways, which explains why CHARGE syndrome patients display penetrant alterations in semicircular canals of the inner ear and the accompanying vestibular defects. *CHD2* haploinsufficiency, either caused by deletion of the entire gene (Chénier et al. 2014) or by missense mutations (Hamdan et al. 2014), is associated to ID, epilepsy, and ASD. Moreover, studies have shown that de novo CHD2 mutations are correlated with epileptic encephalopathy (Carvill et al. 2013; Lund et al. 2014). The precise molecular mechanism is still unclear, although a mouse mutant for *Chd2* (gene trap) has revealed the tumor suppressor activity of CHD2 that can modulate DNA damage responses and in turn genome stability (Nagarajan et al. 2009). Finally, large studies on ASD cohorts have identified recurrent de novo inactivating mutations in CHD8 associated with ASD and macrocephaly (Neale et al. 2012; O'Roak et al. 2012; Iossifov et al. 2014, Wang et al. 2016). Inactivation of *cdh8* in zebrafish resembles the human phenotype including the increased head size (Bernier et al. 2014; Sugathan et al. 2014). In line with these findings, moderate gene expression changes and physical interaction with neuronal silencing factor REST cause macrocephaly in *Chd8* heterozygous mice (Katayama et al. 2016). Conversely, a developmental study in the mouse brain has illustrated the important role of

Chd8 in neural progenitor proliferation through WNT-dependent activation of cell cycle genes; moreover, the authors showed the repression of PRC2 complex genes (e.g., *Ezh2* and *Suz12*) causing reduced dendritic complexity and behavioral abnormalities in adult mice (Durak et al. 2016). Whether the contradiction on cell cycle dynamics maybe due to different experimental setup (chronic vs. acute downregulation of *Chd8*), this latter aspect could explain the autistic behavior in *Chd8* heterozygous mice and in patients. As reported in a recent study in human NSCs and fetal brain, CHD8 genomic targets include a number of ASD risk gens (e.g., *ARID1B*, *NCOR1*, *POGZ*, *PTEN*, *TBL1XR1*) that are dysregulated upon CHD8 knockdown (Cotney et al. 2015). CHD8 binding to promoter regions enriched in active marks H3K4me3 and K27ac is positively correlated with gene expression (Cotney et al. 2015). An interesting study mapped the genome-wide interactions with nucleosomes for a number of ATP-remodeling complexes including CHD2 and CHD8 in mouse ESCs revealing that they are able to bind one or both the nucleosomes surrounding the nucleosome free promoter regions (NFRs) (De Dieuleveult et al. 2016). From this work emerged that the remodelers function either in positive or negative manner altering nucleosome dynamics at active gene level or at bivalent promoters. Specifically, CHD2 has high correlation with H3K36me3 in active genes while CHD8, at least in mESCs, is mainly involved in transcriptional repression through association with H3K4me3 in active or bivalent promoters (De Dieuleveult et al. 2016). Expanding this analysis to other cell type/organism will help to unravel the role of these enzymatic complexes in the pathogenic processes of human disorders.

Conclusions

All the observations above indicate an intricate landscape in which the epigenetic modifications are involved, a wide array of consequences upon their defects, and the need of a strong crosstalk among the different modifications to ensure the biological processes. Questions as "is there a common theme underlying in neurodevelopmental disorders?" are difficult to answer for many reasons, starting from the fact that we are still far from a complete understanding of the pathological processes at the basis of the different "chromatinopathies." We could try to identify general rules from the phenotypes associated to certain epigenetic traits, but again the situation is nonlinear and complex; for example, a situation in which an increase of cell proliferation resulting in overgrowth phenotype could be due to a general relaxation of the chromatin as in polycomb defective Weaver syndrome or as in the cases of Sotos syndrome in which mutations in *NSD1* should cause less permissivity to gene transcription. Moreover, there are debated cases, as for the mutations in DNMT3A in which overproliferation could be due by either closed or opened conformation. Besides these considerations, another important aspect to consider is that chromatin enzyme can act also on non-chromatin targets, and therefore a disease could be the results of multifactorial events; an example is provided by SETD2, known as methyltransferase specific for H3K36me3 that has been recently described to be able to methylate also lysine 40 in alpha-tubulin, and thus controlling cytoskeleton dynamics (Park et al. 2016).

Very informative are those cases in which the very same disease is caused by different genetic factors, as in Kabuki syndrome or different kind of mutations on the same genetic traits are causative for different diseases, as for Williams-Beuren syndrome and 7dupASD. In the first example, we can easily relate a closed chromatinic landscape with developmental delay and microcephaly resulting in intellectual impairment. In the cases of deletion or duplication of *GTF2I*, a state in which the genes are prone to be activated is linked to hypersociability while chromatin marks leading to gene silencing are associated with an opposite, autistic behavior.

The challenge of the near future for physicians and researchers is to identify more of these dualisms. To do so, it is necessary to establish a strong correlation between mutational spectrum and clinical manifestations and consider the possibly divergent effects of either changes at the gene level (true loss-of-functions, duplications, etc.) or missense mutations. Whether the former are useful to gain information on the complete lack or the overrepresentation of the main enzymatic product, the latter represent extremely valuable tool to possibly comprehend the functions of different modules of the protein that can shed new light on their role and on the different symptoms, in the affected people. In this direction, the use of cellular (e.g., hIPSCs) and animal models coupled with new ways to generate site-specific editing (e.g., CRISPR/Cas9 system) will help addressing these unsolved questions in the near future.

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