Role of DNMTs in the Brain

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Abstract

DNA methyltransferases (DNMTs) are widely expressed in the brain, dictating the transcriptional activity of genes through various epigenetic mechanisms. Functional irregularities, alterations in the activity, and aberrant expression levels of DNMTs have been linked to various neurodevelopmental abnormalities, neuropsychiatric disorders, neurodegenerative diseases, and brain cancer. A continuously increasing number of studies address the roles DNMTs have in the brain, to reach a better understanding of their involvement in disease-related pathophysiologies, which in turn is required to dissect their applicability as potential therapeutic targets. This chapter provides an overview of DNMT function in the developing and the adult brain, putting a spotlight on their role in orchestrating diverse aspects of brain development, memory, and aging, followed by a discussion of associated neurodevelopmental and neurodegenerative disorders, and the implications in brain cancer.

Keywords

DNA methylation · Brain development · Synapse · Memory · Cell-intrinsic engram mechanisms · Aging · Neurodegeneration · Glioma · Cancer · lncRNAs

List of Abbreviations

5-AZA	5-azacytidine
5-hmC	5-hydroxymethylcytosine
5-mC	5-methylcystosinee
Aβ	Amyloid-beta protein
AD	Alzheimer's disease
aIPC	Apical intermediate progenitor cells
APP	Amyloid precursor protein
ARC	Activity regulated cytoskeletal-associated protein
BAX	Bcl-2-associated X protein
BCL2	B-cell lymphoma 2
BCL2L2	Bcl-2-like protein 2
BDNF	Brain-derived neurotrophic factor
bIPC	Basal intermediate progenitor cells
BIRC5	Baculoviral inhibitor of apoptosis repeat-containing 5; Survivin
bRGC	Basal radial glial cells
cAMP	Cyclic adenosine monophosphate
CASP8	Caspase-8
CDK5	Cyclin-dependent kinase 5
CDKN2A	Cyclin-dependent kinase inhibitor 2A

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CGE	Caudal ganglionic eminence
CNS	Central nervous system
CpG	Cytosine-phosphate-guanine
CREB	cAMP response element-binding protein
CRISPR	Clustered regularly interspaced short palindromic repeats
CTCF	CCCTC-binding factor
CTIP2	B-cell lymphoma/leukemia 11B
dCGE	Dorsal caudal ganglionic eminence
DNA	Deoxyribonucleic acid
DNMT	DNA methyltransferase
E-LTP	Early long-term potentiation
EZH2	Enhancer of zeste homolog 2
GABA	Gamma aminobutyric acid
GBM	Glioblastoma
GFAP	Glial fibrillary acidic protein
GluN2A	*N*-methyl D-aspartate receptor subtype 2A
GSK3B	Glycogen synthase kinase 3 beta
H3K27me3	Trimethylation of lysine 27 on histone H3
H3K4me3	Trimethylation of lysine 4 on histone H3
H3K9me3	Trimethylation of lysine 9 on histone H3
HD	Huntington's disease
HIC1	Hypermethylated in cancer 1 protein
HTT	Huntingtin protein
ICF	Immunodeficiency, centromere region instability, facial anomalies syndrome
IDH	Isocitrate dehydrogenase
IPC	Intermediate progenitor cells
iPSC	Induced pluripotent stem cell
iSVZ	Inner subventricular zone
JAK	Janus kinase
L-LTP	Late long-term potentiation
lncRNA	Long non-coding RNA
LTD	Long-term depression
LTP	Long-term potentiation
MAPT	Microtubule-associated protein TAU
MBD	Methyl-binding domain
MeCP2	Methyl-CpG binding protein 2
MGE	Medial ganglionic eminence
MGMT	O^6-alkylguanine DNA alkyltransferase
mHTT	Mutant Huntingtin protein
miRNA	Micro RNA
mRNA	Messenger RNA
MZ	Marginal zone
NDD	Neurodegenerative diseases
NF2	Neurofibromin 2; Merlin
NFIA	Nuclear factor 1 A-type
NMDA	*N*-methyl-D-aspartic acid
NMDAR	*N*-methyl-D-aspartic acid receptor
NPY	Neuropeptide Y
oSVZ	Outer subventricular zone
p21	Cyclin-dependent kinase inhibitor 1
PAK6	p21 activated kinase 6
PDGFRA	Platelet-derived growth factor receptor A
PET	Positron emission tomography
piRNA	Piwi-interacting RNA
POa	Pre-optic area
PR C2	Polycomb repressive complex 2
PSEN	Presenilin
PTCH1	Protein patched homolog 1
PV	Parvalbumin
REST	RE1-silencing transcription factor
RG108	*N*-Phthalyl-L-tryptophan
RGC	Radial glial cell
RNA	Ribonucleic acid
SCZ	Schizophrenia
SFRP	Secreted frizzled-related protein
SHH	Sonic-Hedgehog
sncRNA	Small non-coding RNA
SST	Somatostatin
STAT	Signal transducer and activator of transcription
SVZ	Sub-ventricular zone
TBRS	Tatton-Brown-Rahman syndrome
TET	Ten-eleven translocation enzyme
TF	Transcription factor
TMS1	PYD and CARD domain containing, transcript variant 1
TMZ	Temozolomide
VIP	Vasointestinal peptide
VZ	Ventricular zone
Wnt	Wingless and Int-1
ZIF268	Zinc finger protein 268; Early growth response protein 1

15.1 Introduction

DNMTs are widely expressed in the developing, adult, and aged brain, suggesting implications in neuronal differentiation, maturation, and function (Guo et al. 2011; Simmons et al. 2013; Fasolino et al. 2017). Moreover, DNMT functionality and expression are altered in neurons of the aged brain, and in the context of neuropsychiatric and neurodegenerative diseases (Linde and Zimmer-Bensch 2020; Zimmer-Bensch 2020; Zimmer-Bensch and Zempel 2021), for which they are proposed as putative therapeutic targets. In addition to their canonical function of catalyzing DNA methylation, DNMTs can act on gene expression through crosstalk with histone modifications (Du et al. 2015; Symmank et al. 2018, 2020), hence displaying a diverse mechanistic spectrum. Moreover, the different DNMTs exhibit a brain region and cell-type-specific expression and seem to fulfill partly redundant (Feng et al. 2010) but also distinct functions in the brain (Morris and Monteggia 2014; Morris et al. 2016). While DNMT3A seems crucial for learning (Morris and Monteggia 2014), DNMT1 appears to be involved in anxiety (Morris et al. 2016), where the subcellular mechanisms remain unknown. Similar to the particular implications of the different DNMTs in orchestrating brain development and function (Zimmer-Bensch 2019b; Reichard and Zimmer-Bensch 2021), DNMTs contribute to certain diseases (Klein et al. 2011; Ding et al. 2018) and are themselves distinctively affected in brain cancer such as glioma (Rajendran et al. 2011). To exploit DNMTs therapeutically, we need to dissect their precise functional implications in the developing, aging, and diseased brain, which is discussed in this chapter with the focus on mammals.

15.2 The Mammalian Brain

The human brain is extraordinary in many regards, being recognized as the crown of evolution (Pascual-Leone et al. 2005; Hofman 2014). Still, we are far away from understanding in detail how this fascinating organ evolved, how the human brain works, and is established during ontogenesis. Despite the extraordinary features that account for the elaborated cognitive ability of the human brain, there are essential common principles in the architecture, the development and the function of the mammalian brain. For this, rodent and primate models are frequently used in neuroscientific research to extend our understanding of human brain evolution, function, development, and related diseases.

The mammalian brain is anatomically divided into three major parts: the hindbrain (including the cerebellum and the brain stem), the midbrain, and the forebrain (including the diencephalon and the cerebrum) (Fig. 15.1a). The brain stem, incorporating the pons and the medulla (Fig. 15.1b), is processing involuntary activities such as vomiting and breathing, while the cerebellum coordinates muscular movements and, in concert with the midbrain, it monitors posture.

The thalamus and the hypothalamus are major parts of the diencephalon (Fig. 15.1b). While the thalamus is a relay station for incoming sensory information routing these to the appropriate higher centers, the hypothalamus regulates heartbeat, body temperature, and fluid balance, in addition to appetite and body weight control (Sherman and Guillery 2006; Saper and Lowell 2014).

By far the largest region of the mammalian brain is the telencephalon (cerebrum) (Fig. 15.1a, b), composed of the superficial gray matter (cerebral cortex) and the white matter (axonal tracts). The telencephalon is distinguished vertically into left and right hemispheres. The two hemispheres communicate with each other through a large axonal tract, the corpus callosum. The cerebral cortex, the most evolved structure of the human brain holding its higher cognitive function, is strongly folded in gyri and sulci in humans and other primates (Hilgetag and Barbas 2005). In the cortex sensory data are processed, and motor impulses are generated that initiate, reinforce, or inhibit the entire spectrum of muscle and gland activity. The cerebral cortex is further involved in learning and memory and the control of affection (Thompson 1986; Jin

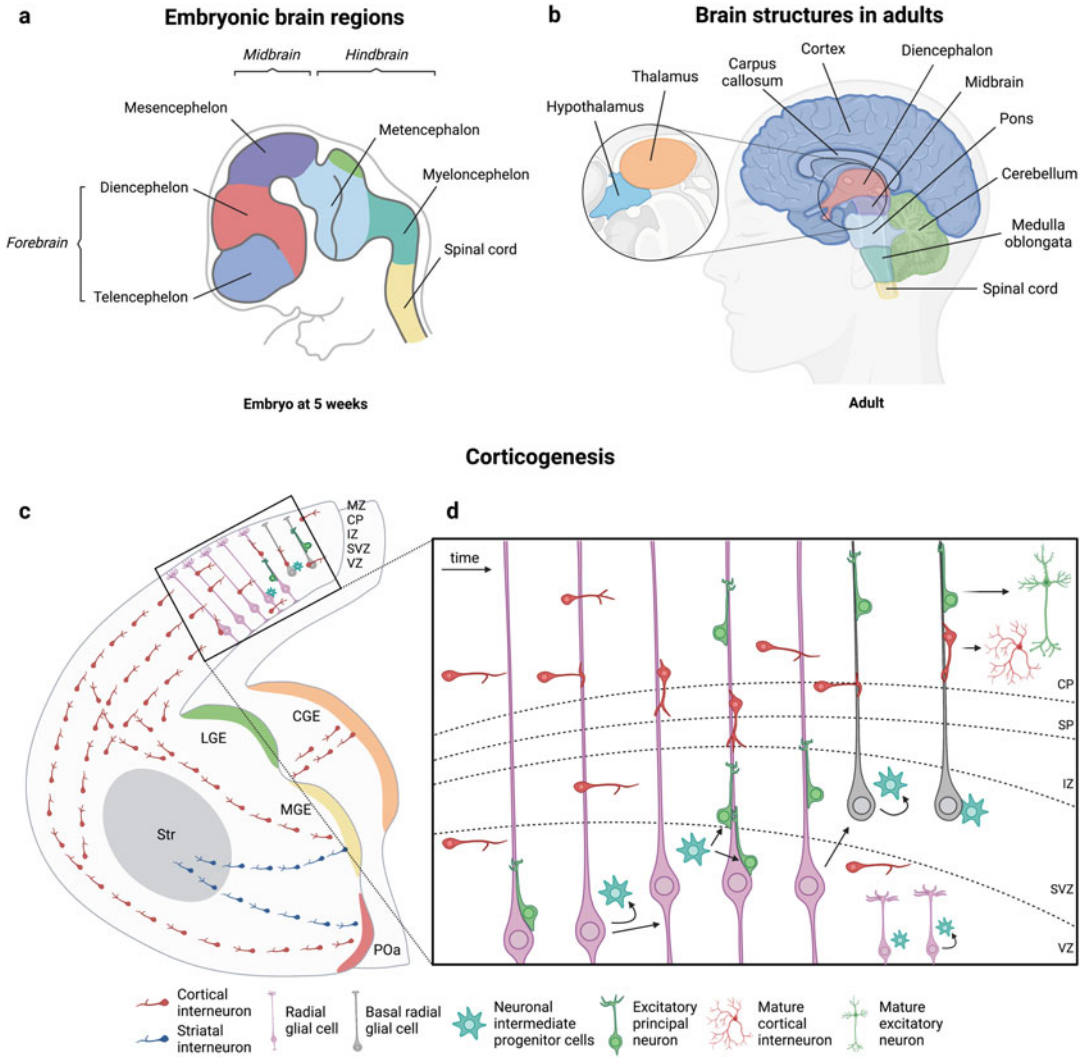

Fig. 15.1 Human brain anatomy and developmental principles of the mammalian brain. (**a**) Anatomical regions of the developing human brain. (**b**) Anatomy of the adult human brain. (**c**) Graphic depiction of a coronally sectioned hemisphere illustrating the sites of origin and the migratory streams of cortical inhibitory interneurons in the basal telencephalon (POA, MGE, and CGE), as well as of excitatory neurons in the dorsal telencephalon. (**d**) Schematic illustration of proliferation, differentiation, and migration of cortical precursor cells. Radial glial cells (RCGs) increase in number by symmetric division, and asymmetrically divide into basal radial glial cells (bRGCs) or neuronal intermediate progenitor cells (nIPCs). The latter further divide symmetrically to give rise to young excitatory principal neurons, which migrate into the cortical plate (CP). Inhibitory interneurons invade the developing neocortex along two migratory streams, the marginal zone (MZ), and the subplate (SP)/subventricular zone (SVZ), before they switch to radial migration to enter the cortical plate. *CGE* caudal ganglionic eminence, *CP* cortical plate, *IZ* intermediate zone, *LGE* lateral ganglionic eminence, *MGE* medial ganglionic eminence, *MZ* marginal zone, *POa* pre-optic area, *SP* subplate, *Str* striatum, *SVZ* subventricular zone, *VZ* ventricular zone

and Maren 2015). The cortex is composed of the six-layered neocortex, and the way smaller, three- or four layered allocortex. The allocortex consists of the paleocortex, the archicortex, and the periallocortex. The hippocampus and dentate gyrus are the main parts of the archicortex,

being functionally relevant for learning and memory.

Excitatory glutamatergic neurons and inhibitory local GABAergic interneurons represent the major neuronal subtypes of the cerebral cortex. While most glutamatergic cortical neurons display a long axon projecting either sub-cortically to other cortical areas or contralaterally to the other hemisphere, spiny stellate cells of layer IV are local excitatory interneurons receiving input from the thalamus (Shepherd 2004; Costa and Müller 2015). The glutamatergic neurons of the different cortical layers differ in their morphology, molecular features, and connectivity, establishing the neuronal circuits as basic modules of cortical information processing (Bayer and Altman 1991; Lodato et al. 2011; Greig et al. 2013). These circuits are shaped by the inhibitory action of the GABAergic cortical interneurons, which represent a highly diverse group of neurons differing in their electrophysiological features, morphology, targeting, and molecular properties (Nery et al. 2002; Fishell 2008; Gelman et al. 2009; Miyoshi et al. 2015; Wamsley and Fishell 2017; Lim et al. 2018; Zimmer-Bensch 2018) .

15.2.1 Developmental Principles of the Cerebral Cortex as the Seat of Higher Cognitive Functions

Prerequisite for correct cortical functionality is the proper establishment of the mammalian neocortex during embryonic and postnatal development. Processes such as progenitor proliferation and differentiation, cellular migration, morphological maturation, and the establishment of synaptic contacts, as well as programmed cell death, have to be highly controlled to form the circuits of billions of morphologically and functionally distinct neurons (Jones 2009; Huang and Paul 2018; Sultan and Shi 2018; Subramanian et al. 2020). Disturbances of these developmental processes cause a variety of neurodevelopmental disorders (Reichard and Zimmer-Bensch 2021).

The proportionally larger population of excitatory principal neurons (70–85% of the neuronal cells in the cortex) originates from progenitors of the dorsal telencephalon located in the zone delineating the lateral ventricles (ventricular zone; VZ) called radial glia cells (RGCs) (Fig. 15.1c) (Kriegstein and Alvarez-Buylla 2009; Sun and Hevner 2014). In addition to symmetric proliferative division to increase the pool of progenitors, RGCs' asymmetric division leads to the generation of neurons ("direct neurogenesis") (Kriegstein and Alvarez-Buylla 2009; Sun and Hevner 2014). Moreover, asymmetric division can result in the formation of intermediate progenitors, which translocate to the SVZ, where they generate neurons by symmetric divisions ("indirect neurogenesis") (Kriegstein and Alvarez-Buylla 2009; Agirman et al. 2017; Borrell 2019) (Fig. 15.1c). In humans, the developing cortex contains an inner (iSVZ) and an outer SVZ (oSVZ), hosting basal intermediate progenitor cells (bIPCs) and basal RGCs (bRGCs) (Sun and Hevner 2014). In contrast to humans and mammals with a high rate of gyrification such as ferrets, bRGCs are less prominent in lissencephalic species such as the mouse (Penisson et al. 2019; Subramanian et al. 2020). For this, bRGCs have been linked to cerebral gyrification. IPCs are also present in the VZ in humans and mice, being named apical IPCs (aIPCs) (García-Moreno et al. 2012; Sun and Hevner 2014).

Upon becoming post-mitotic, excitatory neurons migrate along the scaffold of radial glial cell processes spanning the whole cortical wall, into the cortical plate and settle in their target layer, establishing apical dendrites and axons (Zimmer-Bensch 2019a) (Fig. 15.1c). The inhibitory GABA-expressing interneurons originate in particular domains of the basal telencephalon (Lim et al. 2018; Mukhtar and Taylor 2018; Subramanian et al. 2020). The medial ganglionic eminence (MGE) generates parvalbumin (PV)-positive basket and chandelier cells, and somatostatin (SST)-expressing Martinotti and multipolar interneurons. The pre-optic area (POa) gives rise to neuropeptide Y (NPY)-, reelin-, SST-, and

CTIP2-expressing interneurons. Further reelin-expressing interneurons emerge in the caudal ganglionic eminence (CGE) alongside vasointestinal-peptide- (VIP)/calretinin-positive bipolar cells and VIP-/cholecystokinin-expressing basket cells (Gelman et al. 2011; Zimmer-Bensch 2019b). Thereby, the majority of interneurons is born in the MGE and the dorsal part of the CGE (dCGE) (Gelman et al. 2009; Marín et al. 2010; Faux et al. 2012; Lim et al. 2018; Sultan and Shi 2018; Zimmer-Bensch 2018). In humans and monkeys, some GABAergic interneurons appear to be generated in parts of the dorsal telencephalon at developmental later stages, proposing an evolutionary strategy of primate corticogenesis (Petanjek et al. 2009; Krienen et al. 2020).

Cortical inhibitory interneurons perform glial cell-independent long-range migration through the basal telencephalon toward the cortex, following defined routes depending on their site of origin, being guided by diverse sets of spatially and temporally expressed chemoattractive and repellent signaling molecules (Marín et al. 2003; Zimmer et al. 2007, 2010, 2011; Petanjek et al. 2009; Marín et al. 2010; Rudolph et al. 2010; Friocourt and Parnavelas 2011; Faux et al. 2012; Guo and Anton 2014; Symmank et al. 2019). Upon reaching the cortex, interneurons spread tangentially over the cortical areas along the SVZ/intermediate zone and the marginal zone (MZ) (Fig. 15.1c, d) (Tanaka and Nakajima 2012; Guo and Anton 2014), before they switch to radial migration invading the cortical layers that begin to be formed by the excitatory neurons at this embryonic stage (López-Bendito et al. 2004; Hatanaka et al. 2016).

Not all neurons being born successfully integrate into cortical circuits. It seems an evolutionarily conserved strategy to overproduce cortical neurons that are then being fine-tuned in their numbers by controlled cell death (Wong and Marín 2019). In matters of GABAergic interneurons about half of their embryonic population is reduced within there early postnatal period in mice (Yamaguchi and Miura 2015). At the same stage, improperly or disconnected pyramidal cells are also eliminated (Raff 1992). Apart from post-migratory regulation of the neuronal survival, regulatory mechanisms for survival regulation during neuronal migration have been described (Symmank et al. 2018).

15.3 DNMT Expression in the Brain

DNA methylation is catalyzed by the DNA methyltransferases DNMT1, DNMT3A, and DNMT3B in the mammalian brain. In line with the well-known function of DNMT1 in maintaining DNA methylation in dividing neural progenitor cells, and its reported functions in post-mitotic and mature neurons (Pensold et al. 2017, 2020), DNMT1 expression is remarkably high in the embryonic as well as adult nervous system (Goto et al. 1994; Inano et al. 2000; Fan et al. 2001; Kadriu et al. 2012). In the developing brain, DNMT1 is expressed in neuronal progenitors (Feng et al. 2007; Noguchi et al. 2015) and oligodendrocyte progenitor cells (OPCs) (Moyon et al. 2016), as well as in newly generated post-mitotic neurons. DNMT1 expression is maintained until adulthood, with prominent expression in GABAergic interneurons of the cerebral cortex (Kadriu et al. 2012; Pensold et al. 2020), as well as in excitatory cortical neurons (Hutnick et al. 2009; Feng et al. 2010), hippocampal neurons (Noguchi et al. 2015), and cerebellar neurons (Fan et al. 2001). Similar to DNMT1, DNMT3A can be detected in the developing, postnatal, and adult central nervous system (CNS) (Watanabe et al. 2002; Feng et al. 2005). DNMT3A was detected in progenitors of the cerebral cortex, in post-mitotic and adult cortical neurons, as well as in post-mitotic cerebellar cells. Similar findings were reported for the olfactory epithelia, which revealed expression of DNMT3A in maturing olfactory receptor neurons (MacDonald et al. 2005). In contrast to its neuronal expression, GFAP-positive astrocytes seem to only have a weak or no expression of DNMT3A. However, strong expression of DNMT3A was detected in postnatal cerebellar oligodendrocytes (Feng et al. 2005). Different from DNMT3A, DNMT3B expression is mainly restricted to neuronal precursor during early neurogenesis (Feng

et al. 2005). These stage- and cell-type-specific patterns of DNMT expression are suggestive of important roles in brain development, adult functionality, and associated diseases.

15.4 DNMT Function in the Developing Brain: Neurogenesis

Neuronal circuit formation depends on the correct generation of its neuronal constituents. Neurons derive from neuronal stem cells, which become progressively restricted to give first rise to the different neuronal subtypes (neurogenesis) and afterwards to glia cells (gliogenesis). Moreover, the sequential generation of the excitatory neurons destined for the distinct layers of the cerebral cortex, with deep layer neurons being born prior to the upper layer neurons, relies on progressive fate restriction (Martynoga et al. 2012). Apart from such temporal confinement, a spatial determination becomes evident early in embryonic development (Kiecker and Lumsden 2005). A prominent example is the distinct site of origin of inhibitory and excitatory neurons of the cerebral cortex in the ventral and dorsal telencephalon, respectively (Martynoga et al. 2012; Hu et al. 2017). Further, discrete spatial domains in the ventral telencephalon are suggested to give rise to different cortical interneuron subtypes (Hu et al. 2017).

Subtype-specific transcriptional programs orchestrate cell fate determination of both excitatory principal cortical neurons and inhibitory interneurons, directing subsequent developmental steps such as migration and morphological differentiation (Franco and Müller 2013; Hu et al. 2017). Thereby, a close connection between the stage- and subtype-specific transcriptional programs and the epigenetic machinery including DNMTs is proposed by an ever-increasing body of evidence. Indeed, as mentioned above, DNMTs are found widely expressed in neuronal precursors of the CNS (Feng et al. 2005). DNMT1 is suggested to be implicated in driving the differentiation into neurons by inhibiting the astroglial cell fate through DNA methylation of astroglia-associated genes during the neurogenic period. *Dnmt1* deficiency in progenitor cells of the spinal cord was reported to trigger precocious astroglial differentiation and hypomethylation of genes related to the gliogenic JAK/STAT pathway (Fan et al. 2005). Similarly, in the dentate gyrus, *Dnmt1* deficiency drives the differentiation of neuronal stem cells into astrocytes (Murao et al. 2016). The role of DNA methylation as an intrinsic driver of astrocyte differentiation in the embryonic brain has already been shown by Takizawa et al. (2001). The promoter sites of *Gfap* (glial fibrillary acidic protein) and *s100β* become demethylated at later stages of corticogenesis, promoting the generation of astrocytes from cortical progenitors. Demethylation of *Gfap* has been found to depend on the binding of NFIA (Nuclear Factor I/A), which is activated downstream of Notch and JAK/STAT signaling, leading to the dissociation of DNMT1 (Namihira et al. 2009), which then results in reduced methylation levels.

DNA demethylation further involves the oxidation of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) and subsequent oxidized forms by ten-eleven translocation (TET) methylcytosine dioxygenases, enabling cells to edit methylation patterns and thus maintain epigenomic flexibility during embryogenesis (Kohli and Zhang 2013). In line with this, TET1 function was reported to mediate the onset of neurogenesis by favoring the expression of neuronal genes (Kim et al. 2016).

In support of the functional implications of DNMTs and TETs in neurogenesis, dynamic temporal alterations of DNA methylation signatures have been detected during the sequential generation of neuronal subtypes (Lister et al. 2013; Lister and Mukamel 2015; Mo et al. 2015; Sharma et al. 2016). The use of epigenome editing approaches has already provided support for an instructive role of DNA methylation in neuronal differentiation driving subtype-specific developmental programs (Baumann et al. 2019).

15.5 DNMT Function in the Developing Brain: Post-mitotic Neuronal Maturation

Newly generated post-mitotic neurons usually migrate out of their proliferative zones to respective target regions, finally adopting subtype-specific morphological features mediated by axonal and dendritic growth as well as the formation of synapses, which underlie their specific connectivity and firing patterns. Intrinsically programmed cell death represents another crucial aspect of post-mitotic neuronal maturation, removing unconnected neurons and ultimately determining the final neuron numbers (Southwell et al. 2012). Subtype-specific establishment of DNA methylation signatures during neuronal and glial maturation has been reported by numerous studies (Lister et al. 2013; Lister and Mukamel 2015; Mo et al. 2015; Sharma et al. 2016), implying an important function of DNMTs in setting up the maturation-related DNA methylation patterns.

It was already shown that *Dnmt1* deletion in nestin expressing progenitor cells of the CNS is associated with increased rates of cell death in postnatal animals (Fan et al. 2001). In addition to this, morphological maturation was found to be impaired upon *Dnmt1* deletion in excitatory forebrain neurons (Hutnick et al. 2009), and after deletion of both *Dnmt1* and *Dnmt3A* (Feng et al. 2010). Together, these findings indicate that DNMTs regulate important aspects of postnatal neuronal development such as cell survival and morphological maturation.

Similar to morphological maturation, e.g., dendritic/axonal elaboration, neuronal migration critically relies on cytoskeleton remodeling. In addition to morphological refinement of the excitatory neurons of the cerebral cortex (Hutnick et al. 2009; Feng et al. 2010), DNMT1 function was found to regulate the migration of cortical inhibitory interneurons generated in the pre-optic area (POa) by acting on cytoskeletal organization, thereby promoting their polarized migratory morphology. Moreover, *Dnmt1* deficient interneurons showed increased rates of cell death. One of the involved target genes repressed by DNMT1 is *Pak6* (Pensold et al. 2017). PAK6 belongs to the p21-activated kinases known to drive neurite complexity in excitatory cortical neurons (Civiero et al. 2015) and is implicated in cell survival regulation (Kumar et al. 2017). Hence, the increased *Pak6* expression detected in *Dnmt1*-deficient POA-derived interneurons seems to account for their abnormal multipolar morphology and their impaired survival (Pensold et al. 2017). Another cell survival-associated gene, repressed by DNMT1 in migrating cortical interneurons, is *Lhx1* (Symmank et al. 2020). This homeobox transcription factor drives cell the expression of death associated genes and its downregulation promotes neuronal survival (Symmank et al. 2019; Symmank et al. 2020).

Of note, despite increased expression levels, DNA methylation signatures of the *Pak6* and the *Lhx1* gene locus were not changed in *Dnmt1*-deficient embryonic interneurons (Pensold et al. 2017; Symmank et al. 2018, 2020), implying DNMT1 to have activities beyond locus-specific DNA methylation, which may account for the transcriptional regulation of *Pak6* and *Lhx1*. Indeed, DNMT1 is known to affect histone modifications in neuronal and non-neuronal cells by transcriptional regulation of associated genes as well as through interactions with key enzymes at protein level (Du et al. 2015) (Fig. 15.2). Interactions between DNMTs and histone modifying enzymes have been reported to influence the catalytic activity of their binding partners and the recruitment to protein complexes (Viré et al. 2006; Smallwood et al. 2007; Clements et al. 2012). DNMT1 has been described to interact with EZH2 in non-neuronal cells (Viré et al. 2006; Ning et al. 2015; Purkait et al. 2016). EZH2 represents the core enzyme of the polycomb repressor complex 2 (PRC2) catalyzing repressive trimethylations on lysine 27 at the N-terminal amino acid tail of histone 3 (H3K27me3) (Margueron and Reinberg 2011). In addition to such putatively non-canonical functions via interactions with histone modifying proteins, DNMT1 has been reported to affect

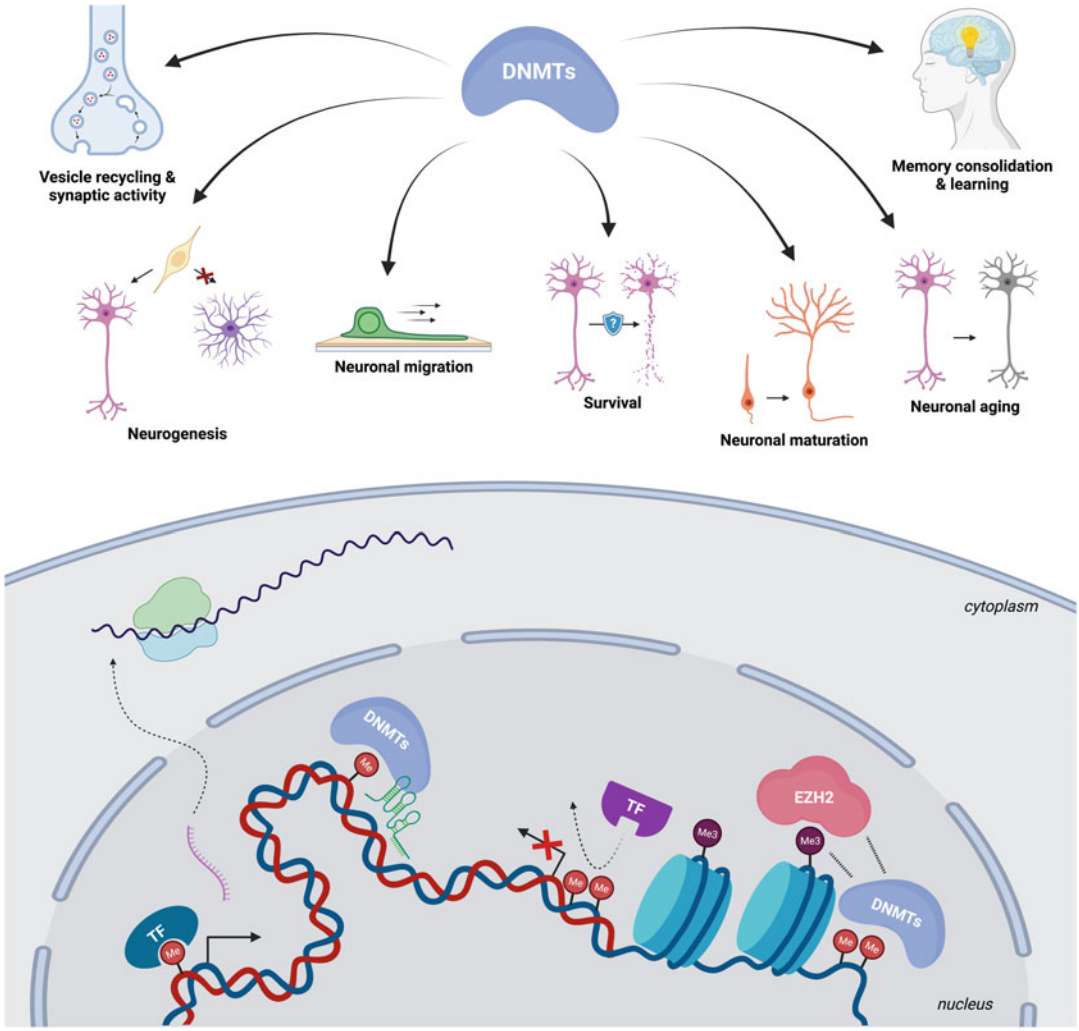

Fig. 15.2 The functional spectrum of DNMTs in the brain. Upper panel: DNMTs are involved in the regulation of neuronal development (neurogenesis, differentiation, neuronal migration, and maturation as well as survival), but also neuronal functionality by modulating synaptic function, learning and memory, in addition to neuronal aging. Lower panel: At molecular level, DNMTs act on gene expression through different mechanisms. The methylation of DNA segments via DNMTs can facilitate or hinder transcription factor (TF) binding and thereby modulate the expression of a gene. The recruitment of DNMTs may occur via long non-coding RNAs acting as adapters as well as through cross-talking with histone modifying complexes and histone marks. *DNMTs* DNA methyltransferases, *EZH2* enhancer of zeste homolog 2, *Me* methylation, *Me3* trimethylation, *TF* transcription factor

H3K27me3 levels by regulating the expression of *Ezh2* (So et al. 2011; Purkait et al. 2016).

In migrating cortical interneurons, the interaction of DNMT1 with EZH2 at protein level seems implicated in the establishment of H3K27me3 marks that represses the transcription of *Pak6* (Symmank et al. 2018), which is essentially involved in maintaining the migratory morphology and promoting the survival of migrating interneurons (Pensold et al. 2017). In support of this, inhibition of EZH2 causes similar defects in neuronal complexity as *Dnmt1* deletion, which

were rescued by *Pak6* depletion (Symmank et al. 2018). LHX1, another regulator of post-mitotic cortical interneuron development (Symmank et al. 2018), is likewise indirectly transcriptionally controlled by DNMT1 by interfering with histone acetylation and deacetylation through transcriptional control of genes coding for relevant enzymes (Symmank et al. 2020). Hence, DNMT1 regulates the migration and survival of post-mitotic cortical interneurons through distinct mechanisms (Fig. 15.2).

The post-mitotic development of other neuronal subtypes such as retinal ganglion cells, motor neurons, and dentate gyrus neurons has also been reported to involve DNMT1-mediated survival regulation (Chestnut et al. 2011; Rhee et al. 2012; Noguchi et al. 2016).

In sum, DNMTs regulate important aspects of post-mitotic neuronal development, such as migration, morphological maturation, neuronal survival, and cell death through canonical as well as non-canonical mechanisms (Fig. 15.2).

15.6 Role of DNMTs in Brain Function, Learning, and Memory

15.6.1 Functional Implications of DNMTs in Learning and Memory

Communication of nerve cells in neuronal circuits via their synaptic connections is considered the basis of brain functionality, learning, and memory. DNMTs and DNA methylation seem to be critically implicated in all these processes (Fig. 15.2). Downregulation of DNMT1 in excitatory neurons of the cerebral cortex differentiated from human induced pluripotent stem cells (iPSCs) reduced the proportion of active neurons as revealed by calcium imaging studies (Bachmann et al. 2021), indicating that DNMT1 function promotes neuronal activity of excitatory neurons. In contrast, in the inhibitory interneurons of the cerebral cortex, DNMT1-mediated DNA methylation was shown to reduce synaptic transmission by repressing endocytosis-related genes and endocytosis-dependent vesicle recycling (Pensold et al. 2020). Hence, by affecting the neuronal activity in excitatory versus inhibitory cortical neurons differently, DNMT1 could balance the net excitation of cortical networks. This process is critical for proper cortical functionality that is shown to be disturbed in diverse neurodevelopmental and neuropsychiatric diseases (Linde and Zimmer-Bensch 2020; Reichard and Zimmer-Bensch 2021).

It was already described that alterations in neuronal activity can induce global changes in the DNA methylation landscape (Guo et al. 2014). As DNA methylation modulates synapse- and plasticity-related gene expression that can mediate memory formation, DNMT function and DNA methylation could act on neuronal plasticity as well as metaplasticity, which is discussed in more detail below.

The concept of experience- and activity-dependent synaptic changes has long been accepted as the fundamental mechanism of learning and memory retention and is nowadays dubbed the synaptic plasticity and memory (SPM) hypothesis (Abraham et al. 2019). Several observations have made synaptic plasticity a leading candidate cellular mechanism for memory formation and storage. As numerous forms of learning have been shown to induce synaptic plasticity in learning-relevant brain regions, diverse forms of reversal learning were shown to trigger a reversal of synaptic plasticity, complementary to what has been induced by the initial learning paradigm (Abraham et al. 2019). The SPM hypothesis involves activity-dependent long-lasting changes in synaptic efficacy such as long-term potentiation (LTP) and long-term depression (LTD) (Bliss and Collingridge 1993; Roberts and Glanzman 2003). Recent studies with modern imaging methods capable of real-time monitoring of changes in synaptic spine morphology accompanied by well-established electrophysiological measures to detect functional synaptic changes have opened a new door for a better understanding of pre- and post-synaptic LTP and LTD (Abraham et al. 2019).

LTP is the most intensively investigated form of synaptic plasticity, captured by the Hebbian

phrase: "cells that fire together wire together" (Lowel and Singer 1992). It has been shown to depend on DNMTs and DNA methylation in addition to other chromatin modifications (Levenson et al. 2006; Miller and Sweatt 2007; Muñoz et al. 2016). Joint firing of the pre- and post-synaptic cell generates LTP, a strengthening of the synapses, while asynchronous firing generates the opposite, LTD. LTP and LTD are induced by different mechanisms, involving ionotropic and metabotropic receptor activation by neurotransmitters, such as the amino acid glutamate acting mainly as excitatory neurotransmitter in the mammalian nervous system. Hallmarks of LTP involve input specificity and associativity, which can be achieved by the activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor (Abraham et al. 2019). The NMDA receptor is an ion channel, which requires glutamate binding (specificity) and coincident depolarization achieved by multiple co-active synapses (association) for opening and channel unblocking, hence functioning as "coincidence detector" (Bliss and Collingridge 1993). These channels are also permeable for calcium ions, well-known second messenger and initiators of signaling cascades triggering LTP (Bear and Abraham 1996; Cummings et al. 1996).

LTP persistence is prerequisite for long-term memory. LTP can be categorized in early LTP (E-LTP) and late-LTP (L-LTP), or alternatively, in LTP1, LTP2, and LTP3 (Racine et al. 1983; Morrell 1991). While E-LTP or LTP1, which lasts only a few hours in maximum, occurs independently of de novo protein synthesis, L-LTP involves protein synthesis. L-LTP can be further subdivided into LTP that is transcription-independent (LTP2) or dependent (LTP3) (Racine et al. 1983). Transcription-independent (LTP2) can be achieved by the local protein translation machinery present in dendritic-synaptic compartments using existent local mRNA species. Transcriptional activation involved in LTP3 is mediated by transcription factors such as cAMP response element-binding protein (CREB), serum response factor, and nuclear factor kappa B, which in turn trigger the expression of downstream-induced transcription factors like ZIF268, c-FOS, JUNB. Manipulations of diverse epigenetic writers and erasers, including DNMTs and TET enzymes, have been shown to affect the different forms of LTP as well as the expression of key genes such as CREB (Kandel 2012; Rajasethupathy et al. 2012), and thus, memory formation.

Indeed, variable forms of learning and memory formation and/or consolidation involve DNMT function and DNA methylation (Day and Sweatt 2010). *Dnmt1* and *Dnmt3A* deletion in excitatory forebrain neurons has been shown to affect learning and memory in the hippocampus (Feng et al. 2010). Inhibition of DNA methyltransferases or genetic deletion of *Dnmt3A* potently hampers LTP (Levenson et al. 2006; Morris et al. 2014). *Dnmt3A* knockout mice display deficits in associative and episodic memory tasks and synaptic alterations, indicating that DNMT3A function in post-mitotic neurons is crucial for normal memory formation. Furthermore, associative learning tasks impact *Dnmt3A* expression, underlining the implication of DNMT3A in learning-related processes (Morris et al. 2014). Moreover, synaptic plasticity and fear memory consolidation in the lateral amygdala in addition to hippocampal structures seem to depend on DNA methylation and DNMT activity (Monsey et al. 2011). Of note, it was also found that E-LTP is dependent on DNA methylation, as the DNA methylation inhibitor 5-aza-2-deoxycytidine (5-AZA) impaired hippocampal long-term potentiation (LTP) induced by a twenty-minute theta burst stimulation. In contrast, 5-AZA treatment 2 hours after stimulation had no effect on transcription-dependent LTP in the applied experimental setup (Muñoz et al. 2016). This indicates that early alterations in DNA methylation are sufficient to impair LTP. The role of DNMTs in the induction of synaptic plasticity was already reported by Levenson et al. (2006). This study showed that inhibiting DNMT changed the DNA methylation signatures within promoters of *Reln* (reelin) and *Bdnf* (brain-derived neurotrophic factor), two factors essential for synaptic plasticity induction in the adult hippocampus (Levenson et al. 2006).

15.6.2 DNMTs as Potential Mediators of Cell-Intrinsic Mechanisms for Memory Consolidation and Maintenance

It is still under debate whether the stability of such synaptic changes is prerequisite for memory maintenance. Highly varying degrees of spine turnover were detected by high resolution imaging in the neocortex (Bhatt et al. 2009), while experimentally triggered LTP can be long-lasting (Abraham et al. 2002). Alternative views involve the idea that there may be multiple synaptic weight distributions being capable of properly coupling inputs with outputs. Learning new information would result in an update of synaptic weights to enable the incorporation of new information, while at the same time retaining the old ones. In artificial network models with highly coupled layers of cells, such changes of synaptic weights have been revealed to be necessary (Abraham and Robins 2005). Another model based on experimental data implies that learning establishes specific connectivity patterns between cells of a memory circuit, which is named engram. These new connections, rather than the potentiation of existing synapses, are suggested to support memory storage. According to this view, the LTP of existing synapses rather serves to recall the memory (Tonegawa et al. 2015). Still, both models somehow support the synaptic plasticity and memory hypothesis, with synapses representing critical units of memory storage. A strong argument being discussed against this general hypothesis is the observation that synaptic molecules in the adult brain are not stable with half-lives of only 2–5 days (Cohen et al. 2013), although it should be mentioned that individual molecules might not need to last for the duration of a memory (Lisman 1985). Moreover, the successful transfer of memory from a trained to an untrained animal via RNA injection tremendously challenged the synaptic plasticity hypothesis of memory storage (Bédécarrats et al. 2018). Of note, synaptic transmission is not the only way of communication between neurons. Non-synaptic flow of information between neuronal somata in the form of non-coding and protein coding RNA as well as proteins can be achieved through neuronal activity triggered release of miRNA-containing exosomes (Chivet et al. 2014; Goldie et al. 2014; Higa et al. 2014) or channeling nanotubes (Ariazi et al. 2017), and it has been described to mediate learning-related epigenetic alterations in neurons (Abraham et al. 2019). An important example is the activity regulated cytoskeletal-associated protein ARC, an immediate early gene product and a vital regulator of synaptic activity. Upon neural activity, ARC is released alongside *Arc* mRNA via exosomes that are taken up by neighboring neurons where the transferred mRNA is translated locally (Ashley et al. 2018; Pastuzyn et al. 2018).

An alternative model involves the cell-intrinsic storage of memory enabled by thermodynamically stable molecules, which is supported by numerous studies that are discussed elsewhere in more detail (Abraham et al. 2019). As firstly suggested by Holliday (1999), DNA methylation represents an attractive mechanism for cell-intrinsic engram storage, which brings DNMT function into play. Besides relative stability, DNA methylation comes with the advantages of compactness and energy efficiency. Apart from that, this epigenetic signature is capable of storing a vast amount of information, due to the extraordinary numbers of methylation sites in the whole genome (Holliday 1999). The finding of active DNA demethylation involving TET-mediated oxidation of 5-mC allows cytosines in neurons to function as on-off switches, hence providing principally a “binary code” (Abraham et al. 2019).

Since the hypothesis raised by Holliday in 1999, studies in mammals and invertebrates confirmed the functional implication of DNA methylation and DNMTs in diverse learning paradigms (Day and Sweatt 2010; Biergans et al. 2015; Pearce et al. 2017). It was shown that contextual fear conditioning triggers global genome-wide changes in DNA methylation seen after an hour persisting for at least 24 h (Mizuno et al. 2012), but not after 4 weeks (Halder et al.

2016). These changes in DNA methylation, mostly detected in neurons that correlated with the spatio-temporal location of memory, were specific for genes and *cis*-regulatory sites and were reported to be dynamic or stable (Halder et al. 2016; Duke et al. 2017). In line with these studies, inhibition of DNMTs has been shown to block remote memory in rats (Miller et al. 2010). Moreover, DNMT inhibition impairs memory formation and consolidation and even eliminates well-consolidated long-term memory in Aplysia (Pearce et al. 2017). DNMTs and DNA methylation further seem to be implicated in the RNA injection-mediated memory transfer described previously. Blocking DNMTs by RG108 immediately after RNA injection successfully impeded the behavioral enhancement and, hence, memory transfer (Bédécarrats et al. 2018). The learning-triggered changes in DNA methylation were reported to regulate the transcription or splicing of plasticity-, neuronal transmission- and function-related genes in different learning paradigms (Halder et al. 2016; Duke et al. 2017). Hence, DNMTs and DNA methylation might play a key role in long-term memory being stored either as RNA-induced epigenetic alterations and/or synaptic plasticity.

Both models, the synaptic plasticity and the cell-intrinsic model of memory formation, do not necessarily exclude each other and rather could be integrated, with epigenetic writers such as DNMTs as key mediators. A prerequisite for that would be a synapse-nucleus communication to provide an explanation for how nuclear changes can account for input (or synapse) specificity, shown to be evident in LTP, as well as other forms of learning-related long-term synaptic plasticity (Martin et al. 1997; Schuman 1997). Hence, a challenging question in this context is how the synaptic information is translated into discrete changes of DNA methylation and how the signaling mechanisms from the nucleus back to specific synapses occur?

A recent study showed that protein levels of DNMT3A1 are intimately linked to the activation of *N*-methyl-D-aspartate receptors (NMDAR) containing the GluN2A subunit. Synaptic NMDARs were found to promote the degradation of this DNMT in a neddylation-dependent process. Interference with neddylation leads to reduced degradation of DNMT3A1, which causes changes in promoter methylation of activity-driven genes and deficits in synaptic plasticity and memory formation. Hence, plasticity-relevant signals from GluN2A-containing NMDARs seem to orchestrate activity-dependent DNA methylation implication in memory formation (Bayraktar et al. 2020).

Moreover, non-coding RNAs provide possible alternative mechanisms to control DNA methylation. Similar to mRNAs, which undergo local translation at dendrites/synapses (Donnelly et al. 2010), also non-coding RNAs have been reported to shuttle from the neuron's nucleus to dendritic compartments (Qureshi and Mehler 2012). Shuttling back from the cytosol to the nucleus has already been shown for piRNAs, a class of small-non-coding RNAs, which in addition to cytosolic functions influence transcription in the nucleus, e.g., by recruiting DNMTs and through this targeting DNA methylation (Liu et al. 2019). Of note, piRNAs are known to be key for establishing stable long-term changes in neurons in memory persistence by mediating the methylation of a conserved CpG island in the *Creb2* promoter in a serotonin-dependent fashion (Rajasethupathy et al. 2012). CREB, a critical plasticity-related protein, acts as crucial inhibitory constraint of memory in Aplysia (Bartsch et al. 1995). Hence, cytosine methylation of the *Creb2* promoter triggered by the Piwi-piRNA complex containing a DNMT could provide a mechanistic link for how transient external stimuli culminate in long-lasting alterations in the expression of genes implicated in long-term memory storage in neurons.

DNMTs have been further reported to interact with long non-coding RNAs (lncRNAs), defined as non-coding transcripts longer than 200 nucleotides (Hung and Chang 2010), which were suggested to either recruit DNMTs to specific genomic loci or prevent their binding (Rinn and Chang 2012; Merry et al. 2015; Zhao et al. 2016; Somasundaram et al. 2018; Zimmer-Bensch 2019a), similar to piRNAs. The expression of lncRNAs has been described to be

modulated by altered neuronal activity (Barry et al. 2017), and they can be shuttled from the nucleus to the cytoplasm (Bridges et al. 2021). Thereby, their subcellular location determines their function (Carlevaro-Fita and Johnson 2019). LncRNAs can be precursors for miRNAs, representing a class of small non-coding RNAs which modulate translation in the cytoplasm (Leung 2015). Hence, lncRNAs could influence the translation of synapse-related gene expression, "transferring" information from the nucleus into the cytoplasm, and potentially in discrete microcompartments of a neuron "hitting" local translation. The ability of lncRNAs to localize to diverse yet specific subcellular locations has further been described (Bridges et al. 2021), where they regulate synapse stability (Wang et al. 2021), synaptic activity (Raveendra et al. 2018; Keihani et al. 2019), or structural plasticity of dendritic spines in an activity-dependent manner (Grinman et al. 2021). However, in contrast to piRNAs, whether and how shuttling of lncRNAs back from the cytoplasm to nucleus occurs, is still largely unknown.

15.7 DNMTs in Neurodevelopmental and Neuropsychiatric Diseases

After having discussed the crucial functions of DNMTs in neurodevelopment and brain function, it is not surprising that mutations or defective expression of DNMTs are implicated in a broad spectrum of neurodevelopmental and neuropsychiatric diseases, being the cause or mediator of the underlying pathophysiology. Biallelic missense mutations in *DNMT3B* are causative for the immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome, a rare autosomal recessive disorder presenting with cognitive and intellectual disability (Miniou et al. 1997; Kondo et al. 2000; Jin et al. 2008). *DNMT3B* mutations are associated with DNA hypomethylation of genes relevant for the immune system, but also for neurogenesis, neuronal differentiation, and migration in the affected patients (Jin et al. 2008). In line with this, another study found that conditional *Dnmt3B* deletion in the hippocampus impairs recognition memory and revealed differential expression of K+ channel subunits in mice (Kong et al. 2020). Mutations in *DNMT3A* that lead to different variants of this methyltransferase (Lane et al. 2020) were reported for the Tatton-Brown-Rahman syndrome (TBRS), a rare neurodevelopmental congenital anomaly syndrome characterized by macrocephaly and characteristic facial features (Yokoi et al. 2020).

Patients suffering from schizophrenia (SCZ) show a significant upregulation of *DNMT1* expression in *postmortem* GABAergic interneurons (Veldic et al. 2005), which is suggested to alter the expression of genes relevant for GABAergic transmission (Linde and Zimmer-Bensch 2020). These observations are in line with the finding of disturbed interneuron functionality as crucial hallmark of schizophrenia (Nakazawa et al. 2012), and DNMT1 was found to modulate GABAergic transmission of cortical interneurons by regulating endocytosis-dependent vesicle replenishment through DNA methylation-dependent transcriptional control of associated genes (Pensold et al. 2020). *DNMT1* overexpression in SCZ patient brains is proposed to cause hypermethylation of *RELN*, coding for Reelin that is a key player in cortical development (Kirkbride et al. 2012). In addition to abnormal functionality in mature neurons, defects during interneuron development are suggested to contribute to the manifestation of neuropsychiatric diseases such as schizophrenia (Linde and Zimmer-Bensch 2020). In agreement with this, altering the expression levels of *Dnmts* in embryonic cortical interneurons in mice elicited SZ-like phenotypes in offspring (Matrisciano et al. 2013). In line with the reported relevance of DNMT1 for interneuron migration (Pensold et al. 2017), dysregulated expression levels during development could contribute to the manifestation of SCZ. Furthermore, increased activity of DNMTs as well as DNA hypermethylation has been suggested to be implicated in the development of epilepsy in humans as well as in rodent models (Jesus-Ribeiro et al. 2021).

15.8 DNMTs in Neuronal Aging

Brain aging is a dynamic process characterized by structural, neurochemical, and physiological alterations that altogether cause memory decline, cognitive impairments, and behavioral changes (Rozycka and Liguz-Lecznar 2017; Zimmer-Bensch 2019b). Cognitive aging predominantly manifests itself as attention and memory deficits involving the function of the hippocampus and frontal brain areas, such as the prefrontal cortex, with the working memory function being affected the most in aged individuals (Nolde et al. 1998; Davidson and Glisky 2002; Glisky 2007). Neuronal circuits formed within the hippocampus and the synaptic connections with other brain regions are widely considered to constitute the basis for its function in learning and memory, indicating that age-associated perturbances in these regions increase susceptibility to learning deficits later in life (Eichenbaum et al. 1992; Glisky 2007). Thereby, healthy adult neurogenesis in the hippocampus is proposed to be essential for higher cognitive functions (Bekinschtein et al. 2010).

In the mature CNS, neuronal plasticity and long-term memory are modulated by DNA methylation through DNMT activity in the hippocampus (Levenson et al. 2006). The neuronal methylome changes dramatically upon neuronal activity, in association with synaptic plasticity genes gaining or losing DNA methylation (Guo et al. 2011). Additionally, adult neurogenesis is defined as a pivotal process in the generation of neurons in adulthood, thus directly affecting learning and memory functions (Ming and Song 2011). It has been shown that hypomethylation in the brain during aging is responsible for a decline in adult neurogenesis (Liu et al. 2009), which is in line with the reported decline in the expression of DNMTs in the brain upon aging (Oliveira et al. 2012).

The aging process hits different brain regions and neuronal cell types distinctively. In addition to reduced excitability and plasticity (Clark and Taylor 2011), an increased vulnerability of inhibitory interneurons and GABAergic synapses (Rozycka and Liguz-Lecznar 2017) has been reported for particular regions of aged brains (Shetty and Turner 1998; Stanley and Shetty 2004; Cheng and Lin 2013). Besides functional and structural changes of GABAergic synapses, several studies have reported reduced numbers of cortical interneuron subtypes across different species and brain regions upon aging (Zimmer-Bensch 2019b). Features of cortical inhibitory defects involve loss of synaptic contacts, decreased neurotransmitter release, and reduced post-synaptic responsiveness to neurotransmitters. Due to the critical function of GABAergic interneurons in cortical information processing, the age-related structural and functional defects are strongly suggested to be implicated in the age-associated cognitive decline (Rozycka and Liguz-Lecznar 2017).

DNMT1 has been described to be implicated in the age-associated loss of cortical interneurons (Hahn et al. 2020) (Fig. 15.2). Conditional deletion of *Dnmt1* in parvalbumin-expressing cortical interneurons ameliorates their age-related decline, which is accompanied by improved senso-motoric performances of aged mice (Hahn et al. 2020). However, DNMT1-dependent regulation of cell death- and survival-associated genes seems to play a rather subordinate role, whereas the DNMT1-dependent regulation of proteostasis-related gene expression might be important (Hahn et al. 2020).

15.9 DNMTs in Neurodegeneration

Neurodegenerative diseases (NDDs) encompass a wide variety of disorders characterized by functional perturbances in neurons accompanied by neuron loss and tissue degeneration in the peripheral or central nervous system (Vila and Przedborski 2003). Aspects of cellular homeostasis underlying NDDs range from dysfunctional mitochondria and compromised proteostasis to altered gene expression and abnormal transcriptional regulation, with epigenetics gaining significant attention over the years due to its involvement in these processes (Lovrečić et al. 2013). Furthermore, modern research has

frequently highlighted the role of epigenetics in brain development where dynamic epigenetic signatures, such as histone modifications and DNA methylation, drive and coordinate important processes such as neuronal differentiation and cell survival (Zimmer-Bensch, 2018). Interestingly, the dynamicity of epigenetic signatures was revealed to carry on into the adult brain with implications in memory acquisition and consolidation as well as age-related loss of neural cells (Sweatt 2016; Hahn et al. 2020). Unsurprisingly, these findings have propelled epigenetic mechanisms and dysregulations to the forefront in investigations of NDDs for better diagnostic agents and therapeutics.

15.9.1 Alzheimer's Disease and Tauopathies

The vast majority of NDD patients are affected by Alzheimer's disease (AD) (Selkoe and Lansbury Jr 1999; Zimmer-Bensch and Zempel 2021). Symptomatically, AD manifests itself initially as cognitive deficits, such as memory loss, confusion, and poor judgment, with a high risk of developing into a full-blown dementia where it accounts for 60–80% of all cases (Korolev et al. 2016; Fishman 2017). The patient demise mainly results from concomitant lack of adequate nutrition and severe loss of body weight, but also from typical diseases that affect bedridden patients, such as pneumonia (Korolev et al. 2016). The pathophysiology of AD is characterized by the extracellular accumulation of plaques made up of the Amyloid-beta (Aβ) protein, and the intracellular aggregation of the microtubule-associated protein TAU, encoded by the *MAPT* gene (Zimmer-Bensch and Zempel 2021).

Albeit heavily debated, several studies agree that abnormal levels of Aβ protein, cleaved out of the amyloid precursor protein (APP) primarily by the PSEN1/PSEN2 complex, as well as the extracellular deposition of Aβ are the main culprits behind the development and progression of AD (Selkoe and Hardy 2016; Gulisano et al. 2018). Indeed, mutations in the genes *APP*, *PSEN1*, and *PSEN2* were found to be causative for patients with autosomal dominant inheritable forms of early-onset AD (Zimmer-Bensch and Zempel 2021).

Interestingly, in the absence or suppression of TAU protein, mouse and cell culture models for AD failed to show a significant effect upon exposure to Aβ or its overproduction, hinting toward a possible role of the TAU protein as a mediator in neurodegeneration (Roberson et al. 2007; Zempel et al. 2013). Furthermore, the accumulation and aggregation of TAU protein was found to correlate better with the AD-associated loss of synapses and cognitive impairment, with PET-imaging technologies being able to predict structural brain deterioration in full-blown AD (La Joie et al. 2020; Biel et al. 2021).

As the importance of the TAU protein in neurodegeneration and neuronal dysfunction became more evident, many studies went beyond AD and started to investigate the heterogenous group of TAU protein-related NDDs called tauopathies that are characterized by the neural and/or glial deposition of TAU. Histopathological hallmarks of tauopathies include but are not limited to the hyperphosphorylation of the TAU protein and the formation of neurofibrillary tangles (Zimmer-Bensch and Zempel 2021). Tauopathies clinically manifest themselves as cognitive deficits, motor neuron disease, and movement disorders in diverse combinations or in an isolated manner (Murley et al. 2020) and can be classified into primary and secondary tauopathies depending on whether TAU is instrumental to the pathology or appears secondary alongside other cerebral pathologies (Zimmer-Bensch and Zempel 2021). Despite growing appeals, genetic and signaling-based aberrations, such as familial mutations in the *MAPT* gene, fail to illustrate a mechanistic basis for the emergence and progression of both sporadic and genetic forms of AD and tauopathies. Epigenetics may provide a further piece of the puzzle and contribute to a better understanding of environmental triggers that are involved in AD and tauopathies.

Abnormal gene expression, loss of chromatin structure, and genomic instability are considered to be hallmarks of both aging and complex diseases such as AD (López-otín et al. 2013;

Spiegel et al. 2014). These changes in cellular homeostasis are deeply associated with epigenetic mechanisms that can respond to environmental cues (Grant et al. 2002; Rowbotham et al. 2015), such as DNA methylation catalyzed by DNMTs (Greenberg 2020). Prior studies have pointed out that altered expression levels of DNMTs (Cui and Xu 2018) are associated with changes in synaptic plasticity, memory, and learning (Levenson et al. 2006; Morris and Monteggia 2014), further emphasizing the role of DNMTs in aging and AD-related symptoms. In particular, the aging-associated decrease in *Dnmt3A2* expression is implicated in cognitive impairment, as the symptoms were alleviated upon a rescue of the *Dnmt3A2* expression levels in mice (Oliveira et al. 2012).

As mentioned previously, the expression of *DNMT*s decreases upon aging, accompanied by a global hypomethylation and local hypermethylation in aging brains of various species (Johnson et al. 2012; Hahn et al. 2020). Such changes are presumed to contribute to transcriptional alterations seen in AD and tauopathies (McKinney et al. 2019; Salameh et al. 2020). Hence, DNA methylation could pose as a mechanism in the transcriptional regulation of AD-associated genes. Indeed, previous studies have revealed an age-related hypomethylation in the promoter region of *APP*, *PSEN1*, and *PSEN2* (Fig. 15.3), which were linked to the extracellular deposition of Aβ in the aged brain (Tohgi et al. 1999a, b).

Similarly, an age-related decrease in *MAPT* expression was evidenced alongside alterations in the methylation levels of its promoter region, emphasizing the role of DNA methylation in tauopathies (Tohgi et al. 1999b). Furthermore, aberrant methylation levels in the promoter regions of genes involved in TAU phosphorylation, such as *GSK3B* (Nicolia et al. 2017) and *Cdk5* (Li et al. 2015), as well as their increased expression, were shown to play a crucial role in tauopathies and AD (Yu et al. 2019). In addition to DNMTs, the hyperphosphorylation of TAU could be further influenced by TET-dependent, active DNA demethylation (Zimmer-Bensch and Zempel 2021). Indeed, this becomes evident for BDNF, a key player in synaptic plasticity and synaptogenesis in the hippocampus (Song et al. 2015). *BDNF*, whose transcriptional accessibility is regulated partly via TET1 (Ambigapathy et al. 2015), is implicated in TAU hyperphosphorylation (Tanila 2017), indicating that a TET-mediated demethylation of *BDNF* could influence the phosphorylation of the TAU protein.

Overall, these findings underline the role of DNMTs as well as TETs in AD and tauopathies (Fig. 15.3). Although a substantial number of the affected genes are proposed to be downstream effectors of Aβ pathology, the majority are suggested to be upstream of TAU pathology which seems to be the driving force behind the cognitive dysfunction seen in AD and tauopathy patients (Zimmer-Bensch and Zempel 2021). In the future, the modulation of DNMT activity to restore its healthy function or locus-specific gene editing methods to re-establish DNA methylation patterns could open new doors for targeted epigenetic therapies against AD and tauopathies.

15.9.2 Huntington's Disease

The interest in the role of epigenetics in neurodegenerative diseases was further fueled by recent developments in Huntington's disease (HD) research. HD is a neurodegenerative disease predominantly caused by an inherited expansion mutation in the Huntingtin protein (HTT), leading to N-terminal polyQ repeats and a subsequent misfolding of HTT (Zimmer-Bensch 2020). This mutant form of HTT (mHTT) is prone to aggregations and forms intracellular inclusion bodies, ultimately leading to severe atrophy in the dorsal striatum accompanied by an abnormal increase in astrocytes as well as a loss of striatal and cortical neurons (Hedreen et al. 1991; DiFiglia et al. 1997; Lee et al. 2013).

For decades, researchers have been trying to decipher the exact functions of healthy and mutated HTT where prominent progress has been made on the epigenetics front. Multiple studies have suggested that HTT can interact with transcription factors and histone modifying

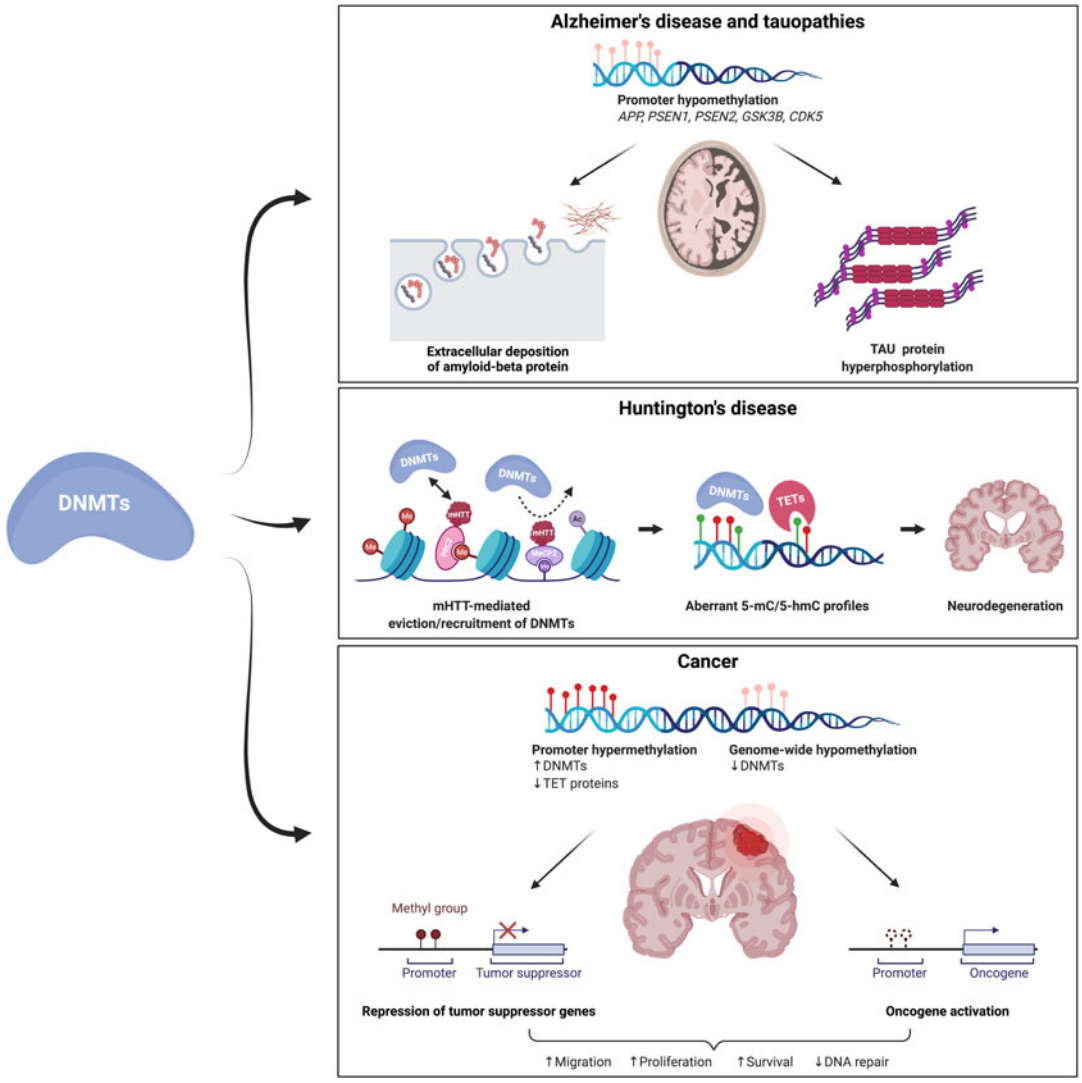

Fig. 15.3 The implications of DNMTs in neurodegenerative diseases and cancers of the brain. Upper panel: Altered methylation level in Alzheimer's disease and other tauopathies. Promoter hypomethylation of amyloid precursor protein gene (*APP*) and *PSEN1/2*, encoding for proteins involved in APP-cleavage, leads to increased extracellular deposition of amyloid-beta protein (Aβ), regarded as a hallmark for the development and progression of Alzheimer's disease (AD). Genes encoding for proteins involved in the hyperphosphorylation of TAU protein such as *GSK3B* and *CDK5* are similarly hypomethylated in their promoter regions in AD and related tauopathies. Middle panel: In Huntington's disease (HD), the recruitment or eviction of DNMTs mediated by the mutant Huntingtin protein (mHTT) and its interactions with epigenetic writers and readers, such as PRC2 and MeCP2, is proposed to lead to aberrant 5-mC/5-hmC profiles of genes involved in neuronal development, function, and survival, leading to significant cerebral atrophy. Lower panel: In the context of cancer, differential global activity of DNMTs, as well as reduced TET activity in promoter regions, results in promoter hypermethylation and genome-wide hypomethylation, leading to the repression of tumor suppressor genes and the activation of oncogenes. Resulting aberrant expression profiles facilitate tumorigenesis and metastasis by enhanced migration, invasion, proliferation, and survival while decreased DNA repair activity accelerates the mutation rate

enzymes, e.g., REST, PRC2, and MeCP2, thus highlighting HTTs ability to interact with key epigenetic players (Seong et al. 2009; Buckley et al. 2010). In the case of mHTT, disruptions of these interactions could potentially contribute to the abnormal transcriptional regulation which is a hallmark of HD.

In addition to HTT's interaction with histone modifying complexes and transcription factors, the academic community has extensively explored changes in DNA methylation levels and signatures, such as 5-mC and 5-hmC patterns, where aberrations were reported in HD patients and transgenic mice (Fig. 15.3) (Ng et al. 2013; Villar-Menéndez et al. 2013; Wood 2013). The oxidation of 5-mC to 5-hmC is a vital step in active DNA demethylation and crucial for the dynamic DNA methylation-dependent transcriptional regulation (Xu and Wong 2015). Abnormal 5-mC/5-hmC profiles were seen for genes implicated in neuronal development, function, and survival (Wang et al. 2013) and could thus be attributed to the decline in neuronal function and neuronal death present in HD. Yet, little research has been conducted to investigate the mechanistic behind such changes in DNA methylation patterns in full molecular detail, whether they are direct consequences due to the altered interactome of mHTT, or whether these occur indirectly, e.g., as adaptive response to impaired cellular physiology.

Beside the ability of HTT to directly interact with histone modifying enzymes, abnormal, mHTT-mediated deposition and/or removal of histone marks can lead to the eviction or recruitment of DNMTs (Zimmer-Bensch 2020) (Fig. 15.3). Prior studies suggest the enrichment of histone marks to correlate with DNA methylation, inversely or positively, depending on whether they are associated with the decondensed euchromatin or the tightly packed heterochromatin. The euchromatin-associated H3K4me3 has an inverse correlation with DNA methylation levels and was shown to preclude DNMT3-dependent DNA methylation (Rose and Klose 2014). In contrast, the heterochromatin-associated H3K9me3 and H3K27me3 were found to have a positive correlation with DNA methylation where both were shown to directly recruit DNMTs (Lehnertz et al. 2003; Viré et al. 2006; Hashimoto et al. 2009; Liu et al. 2018). Similarly, the binding of DNA demethylases such as TETs could be influenced, adding another layer to this mechanistic conundrum.

Based on observations made in prior studies, another scenario could be that altered expression of DNMTs leads to the abnormal DNA methylation signatures seen in HD (Thomas 2016). The expression of *Dnmt1* was found to be decreased in a HD cell model (Tobin and Signer 2000), and a reduced striatal and cortical *Dnmt1* expression was documented in transgenic HD mice. Despite the assumption that reduced *Dnmt1* expression correlates with lower levels of DNA methylation, mHTT-expressing neurons showed increased methylation levels in promoter regions of key HD-relevant genes such as *Bdnf* (Pan et al. 2016). These counter-intuitive findings were attributed to reduced expression levels of DNA demethylases leading to elevated methylation levels in HD patients and model systems (Thomas 2016). It was proposed that this increase in methylation levels could lead to a diminished expression of *Dnmt*s by means of a feedback-regulation. Indeed, the reduced expression of *Dnmt*s may be favorable in the context of HD, as both the inhibition of DNMTs and a knockdown of *Dnmt1* and *Dnmt3A* were shown to decrease mHTT-associated neurotoxicity in primary striatal and cortical neurons (Pan et al. 2016).

Altogether, these findings add another level of complexity to the pathophysiology of NDDs, while further emphasizing the hierarchical dilemma of epigenetics, i.e., the imperative distinction between the cause and the consequence of the observed changes in DNA methylation.

15.10 Role of DNMTs in Brain Cancer

Cancer is a group of diseases, arising from abnormal gene expression programs that shift the balance of oncogenic and tumor suppressive mechanisms. Making up 2% and 23% of all primary tumors in adults and children, respectively, brain cancer is one of the most malignant forms of cancer with more than a quarter of all pediatric cases resulting in the patient's demise (Marie and

Shinjo 2011). Gliomas are the most frequent and malignant type of brain tumor in adults, with glioblastoma (GBM) having a median overall survival of 14.6 months. In turn, medulloblastoma, which starts in the cerebellum, accounts for the most cases of malignant, pediatric brain tumors (Marie and Shinjo 2011; Bartlett et al. 2013). Prior studies on glioblastoma (Parsons et al. 2008) and medulloblastoma (Parsons et al. 2011) demonstrated the presence of mutations implicated in their initiation and development. Yet, in the case of medulloblastoma, the tumors tend to have a low mutational burden as pediatric patients are incapable of acquiring spontaneous mutations due to their young age (Blaeschke et al. 2019). Indeed, cumulative evidence points to the involvement of other mechanisms beside somatic mutations in the formation of brain tumors, such as structural and numerical aberrations in chromosomes (Larsen 2010) and epigenetic alterations (Sharma et al. 2010).

Over the past decade, epigenetics has taken a center stage in cancer research due to its crucial role in the maintenance and regulation of gene expression programs. Many studies have shown how exposure to environmental agents, genetic alterations, or even aging can perturb the epigenetic machinery, creating a permissive environment for cancer to develop and progress (Easwaran and Baylin 2019). As one of the key epigenetic mechanisms, aberrant DNA methylation signatures were implicated in various types of cancer, with diverse gene-bodies, intergenic regions, and repetitive elements being hypomethylated (Ehrlich and Lacey 2013) (Fig. 15.3). The global hypomethylation seen in cancer has been implicated in the dysregulation of the genome, leading to genomic instability, oncogenic activation, loss of genomic imprinting, and the reactivation of transposable elements, ultimately resulting in increased mutational rates and tumorigenesis (Chen et al. 1998; Eden et al. 2003; Gaudet et al. 2003; Holm et al. 2005; Hur et al. 2014). Interestingly, a local hypermethylation accompanies this global hypomethylation, potentially indicating a differential activity of epigenetic modifiers, such as DNMTs, depending on the genomic region (Easwaran and Baylin 2019).

15.10.1 Promoter Methylation

One of the proposed mechanisms for the abnormal activation of oncogenes and the inactivation of tumor suppressor genes is the methylation of cytosines in promoter regions of genes, with the gain/presence of methylation being associated with gene silencing, and the loss/absence being associated with transcriptional activation (Ehrlich and Lacey 2013) (Fig. 15.3). DNA methylation in the promoter region prevents the binding of key transcription factors (TFs) and by this directly inhibits gene expression (Moore et al. 2013). Additionally, DNA methylation can also influence post-translational modifications of histones through methyl-binding proteins (MBD). MBDs act as adaptors for histone modifying enzymes that can change the chromatin state and regulate the accessibility of the methylated site (Ng et al. 2000). In addition, DNMTs themselves were found to crosstalk with histone modifying enzymes in a methylation-independent fashion (Symmank et al. 2018), further complexifying DNMT-mediated transcriptional regulation.

In the context of glioma, mutations in isocitrate dehydrogenase genes *IDH1* and *IDH2* lead to the production and accumulation of 2-hydroxyglutarate instead of α-ketoglutarate, the subsequent inhibition of α-ketoglutarate-dependent enzymes such as TET2, and ultimately to DNA hypermethylation (Dang et al. 2009; Figueroa et al. 2010; Scourzic et al. 2015). Furthermore, the epigenetic silencing of the DNA repair gene *MGMT* via promoter hypermethylation represents another prominent epigenetic alteration in glioma with the promoter methylation status of the *MGMT* gene becoming a predictive biomarker in neuro-oncology. The hypermethylation of the promoter, resulting in the absence of MGMT, was found to be beneficial in the treatment of glioma via temozolomide (TMZ), as active MGMT can repair O6-methylguanine, a toxic DNA lesion caused by TMZ, and diminish the effects of the treatment (Hegi et al. 2005).

In medulloblastoma, the promoters of tumor suppressor genes *CASP8*, *HIC1*, and *CDKN2A* (Lindsey et al. 2004; Sexton-Oates et al. 2015)

and the DNA repair gene *MGMT* (von Bueren et al. 2012) were found to be methylated. In line with the role of Sonic-Hedgehog (SHH) and Wnt signaling pathways in the activation of tumor formation in medulloblastoma (Cambruzzi 2018), *PTCH1* and the *SFRP* family of proteins that are involved in the negative regulation of SHH and Wnt signaling, respectively, were found to be silenced via promoter methylation (Pritchard and Olson 2008; Kongkham et al. 2010).

15.10.2 Methylation of Distal Regulatory Elements

Distal regulatory elements in the genome are able to modulate the transcription of distinct genes through structuring the chromatin organization. Due to their enrichment for TF binding sites, changes in methylation levels and/or patterns in enhancer regions might interfere with the binding of TFs (Easwaran and Baylin 2019), either by changes in methylation itself or by secondary changes in histone modifications that result in an altered chromatin structure. Indeed, this was shown to be the case in gliomas with mutated *IDH*, where the hypermethylation of the binding site for the transcriptional regulator CTCF leads to the eviction of the CTCF/cohesion complex, resulting in an interaction between the enhancer and the oncogene *PDGFRA*. Notably, this interaction was not found in healthy individuals or glioma cases without the IDH mutation (Flavahan et al. 2016).

15.10.3 Implications of Altered DNMT Expression and Targeting in Brain Cancer and Therapy Resistance

As DNMTs catalyze DNA methylation, alteration in their expression could mediate the aberrant methylation signatures in cancer. Indeed, significant overexpression of *DNMT1* and *DNMT3B* was shown in gliomas where the promoter regions of *DNMT1* and *DNMT3B* had a differential histone code with distinct marks for euchromatin, compared to normal tissue that are predominantly enriched with repressive histone marks (Rajendran et al. 2011) (Fig. 15.3). In human glioma biopsies, the expression levels of *DNMT1* and *DNMT3B* were shown to coregulate the methylation status of the apoptosis-related *BIRC5*, *TMS1,* and *CASP8*, but not of other apoptosis-related genes such as *BCL2*, *BCL2L2,* and *BAX*, indicating that DNMTs could orchestrate the emergence of the apoptosis evasion phenotype in glioma by mediating the regulation of distinct apoptosis-associated genes (Hervouet et al. 2010).

A similar overexpression of *DNMT*s was observed for medulloblastoma patients, with the overexpression of *DNMT3B* being the most common (Pócza et al. 2016). Yet, no correlation was found between the expression levels of *DNMT*s and the age of onset, histological subtype, or overall survival in medulloblastoma (Pócza et al. 2016).

Apart from transcriptional dysregulation of DNMTs, their targeting to specific genomic loci could cause the alterations in DNA methylation signatures seen in the different types of brain, mediating pathophysiological processes and/or therapy resistance. Emerging evidence proposes lncRNAs to orchestrate the recruitment of epigenetic writers such as DNMTs or histone modifying complexes to specific genomic sites (Wang et al. 2015; Jain et al. 2016; Xiong et al. 2018). Modern research has enabled genome-wide studies of tumor samples, which have identified a great number of lncRNAs implicated in various types of cancer (Bhan et al. 2017). Even though lncRNAs were shown to directly interact with DNMTs as well (Wang et al. 2015), relatively little is known about this interaction in the context of cancer. Recent studies have begun to slowly close the gap in literature, with the lncRNA–DNMT interactions having been demonstrated in renal, breast, and thyroid cancer (Wu et al. 2018; Song et al. 2019; Zhao and Hu 2019). In GBM, an overexpression of the lncRNA *HOTAIRM1* was found to promote

tumor growth and upregulate the expression of the oncogene *HOXA1* by evicting DNMTs, G9A, and EZH2, leading to the demethylation of H3K9 and H3K27 and a reduction in DNA methylation levels (Li et al. 2018). In TMZ-resistant glioma, the lncRNA *SNHG12* was shown to be upregulated due to a loss of DNA methylation in its promoter region, with clinical studies evidencing poor survival of GBM patients in presence of an *SNHG12* overexpression (Lu et al. 2020).

15.10.4 Crosstalk of DNMTs and miRNA-Mediated Translational Control

In addition to the transcriptional level within the nucleus, lncRNAs but also small non-coding RNAs (sncRNA) such as microRNAs (miRNAs) can modulate post-transcriptional events in the cytoplasm (Wei et al. 2017). miRNAs can regulate the expression of target genes on a post-transcriptional level by binding to complementary sequences in mRNA molecules and silencing them (Bartel 2009). The expression of many miRNAs is increased or decreased in brain cancer leading to dysregulations in cellular pathways involved in proliferation, apoptosis, cell survival, and metastasis (Li et al. 2013; Haltom et al. 2020). The expression of miRNAs can be modulated via DNMT-mediated DNA methylation, underlining the crosstalk between the two epigenetic regulatory mechanisms (Chuang and Jones 2007). Indeed, this was evidenced by Zhou et al. (2015), as *DNMT1* expression was shown to be downregulated in a TMZ-resistant GBM cell line compared to the control, leading to a hypomethylation of the miR-20a promoter and an increase in its expression. The overexpression of *DNMT1* was shown to suppress miR-20a expression and restore sensitivity to TMZ, highlighting the crucial role of DNMT1 in the development of chemoresistance in glioma. Conversely, miRNAs are able to influence the expression of *DNMT*s. In a previous study, miR-152-3p was shown to directly target *DNMT1* and lower its expression (Sun et al. 2017). Due to the downregulation of miR-152-3p in GBM tissue and glioma cells, the expression of *DNMT1* was found to be increased, leading to a hypermethylation of the tumor suppressor gene *NF2* and its subsequent downregulation. Both the overexpression of miR-152-3p and the knockdown of *DNMT1* were shown to result in a rescue of *NF2* expression, increased apoptosis, and reduced invasive activity (Sun et al. 2017).

In summary, abnormal DNA methylation signatures seen in brain cancer could be attributed to alterations in the recruitment and activity of DNMTs in distinct genomic regions, rather than a global loss or gain of their activity, as the global hypomethylation is accompanied by a concomitant hypermethylation of specific genomic loci. Indeed, preclinical studies, where DNMT activity was inhibited in in vivo and in vitro models of glioma, have shown efficacy (Rajendran et al. 2011), but have not been translated into successful therapies so far (Stewart et al. 2009). Beyond changes in the expression levels or activity of DNMTs, understanding how DNMTs target or avoid distinct loci in the genome, which results in the global hypomethylation and the local hypermethylation seen in cancer, remains the most challenging problem to this date, and solving it might be the key in discovering epigenetic biomarkers or therapies for cancer.

15.11 Conclusions

DNMTs are widely and distinctively expressed in different cell types of the brain, being implicated in orchestrating brain development, functionality, and age-related processes. Their dysregulated expression and function have been proposed to be implicated in a wide range of diseases, including neurodevelopmental and neuropsychiatric disorders, neurodegenerative diseases as well as brain cancer. However, to approach their full-blown potential as therapeutic targets, we need to dissect their interactome, mechanisms of transcriptional regulation, context-specific targeting to specific genomic sites, and regulation of their activity. DNMTs have been shown to crosstalk with histone modifying and miRNA-mediated

mechanisms, and to bind specific lncRNAs. How are these specific interactions and the recruitment to distinct genomic sites achieved? What role do post-translational modifications of the different DNMTs play in this diverse spectrum of interactions? These questions have to be addressed in cell-type specific contexts. The enormous progress that has been achieved in sequencing-based technologies, allowing single cell resolution even at multi-omics level, might provide an answer to these challenging questions in the near future. Furthermore, we need to combine multi-omics approaches with functional readouts, reaching a higher integrational level of analyses. CRISPR-Cas mediated epigenomic and genomic editing in combination with iPSC approaches might allow the development of targeted and personalized therapeutics, even for so-far incurable diseases of the brain.

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