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Epigenetic Approaches in Neuroblastoma Disease Pathogenesis

Francesca Felicia Caputi, Sanzio Candeletti and Patrizia Romualdi

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Abstract

Neuroblastoma is an embryonal extracranial solid tumor originating from undifferentiated neural crest cell and it is the most common among children. Neuroblastoma is highly heterogeneous, and on these bases different outcomes are observed across the subtypes. Its clinical impact (~13% of all pediatric cancer mortality) has made this aggressive malignancy the focus of a considerable translational research effort. New insights into tumor biology are leading to the development of novel therapeutic approaches, which include small-molecule inhibitors as well as epigenetic approaches, noncoding-RNA, and cell-based immunologic therapies. Recently, chromatin immunoprecipitation with high-throughput sequencing and RNA-sequencing studies have demonstrated that epigenetic changes contribute to the aggressive pathophysiology of pediatric neuroblastoma disease. Epigenetic abnormalities are feature of human cancer cells and the epigenetic alterations may be the key toward tumorigenesis. In particular, the increase of deacetylation has been involved in epigenetically mediated tumor-suppressor gene silencing. In addition, several studies evaluated the 5-methylcytosine (5 mC) distribution patterns, which distinguish cancer cells from normal cells, and how CpG methylation contributes to the oncogenic phenotype.

In particular, histone changes and DNA methylation are fundamental biological processes representing versatile candidates for pharmacological manipulation with important therapeutic advantages.

Keywords: neuroblastoma, epigenetics, histone marks, DNA methylation, proteasome inhibitors

1. Introduction

Neuroblastoma is an embryonal extracranial solid tumor originating from undifferentiated neural crest cell and it is the most common among children. Neuroblastomas are highly...
heterogeneous, and on these bases different outcomes are observed across the subtypes from the spontaneous regression, asymptomatic tumors, as well as metastasized tumors to rapid progression and resistance to therapy. Its clinical impact (~13% of all pediatric cancer mortality) has made this aggressive malignancy the focus of a considerable translational research effort. Recent literature suggests that alterations in gene transcription programs drive disease-specific gene expression, thus highlighting the significance of transcription as a major mechanism for driving tumor growth and neoplastic transformation. In this chapter, the sophisticated language of the epigenetic code emerges as promising target for cancer therapy. It is generally accepted that epigenetic abnormalities are feature of human cancer cells and that epigenetic alterations may be the key toward tumorigenesis. Briefly, in eukaryotic nuclei, DNA is wrapped around an octameric histone (H) unit, which is composed of H2A, H2B, H3, and H4. This basic structure known as a nucleosome is repeated along the double-stranded DNA, with a fifth type of histone (the linker histone H1) bridging together consecutive nucleosomes (Figure 1). Based on the level of compaction, we can distinguish two main forms of chromatin: the euchromatin is the transcriptionally active form characterized by permissive marks such as the acetylation of different lysine residues; the heterochromatin is the transcriptionally silent configuration and contains repressive epigenetic marks [1]. These forms differ biochemically with respect to the presence of specific markers at the histone tails (see Figure 2) and to the binding of structural proteins.

Gene transcription in eukaryotic utilizes multiple mechanisms and it is mainly regulated by four families of the ATP-dependent chromatin-remodeling complexes (switching defective/sucrose non-fermenting = SWI/SNF; imitation-switch = ISWI; Mi-2/nucleosome remodeling and histone deacetylation = Mi-2/NuRD; inositol 80 = INO80), named “remodelers” [3–6]. A growing body

Figure 1. Schematic representation of the nucleosome. The nucleosome core is composed of a histone octamer [(H2A-H2B)x2, (H3-H4)x2]. The DNA double helix is wrapped around (~1.7 times) the histone octamer. With nuclease digestion, 146 bps of DNA are tightly associated with the nucleosome but ~200 bps of DNA in total are associated with the nucleosome [2].
of evidence suggests that the dysregulation of chromatin remodelers such as activating mutation, homozygous deletion, epigenetic silencing, and overexpression has a crucial role in cancer development and in its progression [7–10]. Advances in genomic technologies have allowed a better understanding of genomic signatures underlying human cancer.

1.1. Histone modifications

Histone tails are subject to different post-translational modifications (PTMs), including acetylation, methylation, and phosphorylation. The best characterized chromatin PTM is the histone acetylation, which results from a dynamic balance of the activity of two enzymatic families: histone acetyl-transferases (HATs) and histone deacetylases (HDACs) [11, 12]. Alterations in the balance of these enzyme activities lead to a disruption of cellular integrity and are frequently observed in different tumors. In particular, the increase of deacetylation has been involved in epigenetically mediated tumor-suppressor gene silencing; thus, HDACs represent a promising class of anticancer drug targets [13] (Figure 2).

Methylation of histone proteins is generally found on arginine and lysine residues. Three different forms of methylation have been observed on the lysine residues (mono-, di-, and tri-methylation), whereas arginine can be mono-methylated and symmetrically or asymmetrically di-methylated; these modifications play different functions in gene transcription [14] (Figure 2).

In fact, methylation of histones can either increase or decrease gene transcription, depending on which amino acids on the histones are methylated, and how many methyl groups are attached.

For example, trimethylation of lysine 4 on histone H3 (H3K4me3) is abundant at active gene promoter, whereas trimethylation of lysine 9 on histone H3 (H3K9me3) is associated with transcriptionally repressed gene promoters [15]. Histone methylation process is catalyzed by three distinct families of methyltransferase enzymes namely the SET-domain containing protein.

Figure 2. All histones are subject to post-transcriptional modifications (PTMs) which mainly occur on the histone tails. The main PTMs are depicted in this figure: acetylation (○), methylation (●), phosphorylation (□) and ubiquitination (Ub). The number under each amino acid [K = lysine (Lys), R = arginine (Arg) and S = serine (Ser)] represents its position in the sequence (Adapted from Zhang and Reinberg, 2001) [16]. In addition, the position K4, K9, K27, K36 and K79 can be mono-/di-/ or trimethylated.
family, the non-SET domain protein family, and the protein arginine methyltransferase family 1 (PRMT1) [17]. Changes in histone methylation status take part in various physiological and pathological processes, including cancer.

1.2. DNA methylation

The understanding of DNA methylation contribution to cancer-specific alterations and the exact consequences of these mutations, in the key steps of tumorigenesis, will represent a useful tool in epigenetics therapy. In mammals, DNA methylation occurs predominantly at cytosine in CpG islands, and their methylation acts as a relatively stable gene-silencing mechanism. Over the last 40 years, several studies evaluated the 5-methylcytosine (5 mC) distribution patterns, which distinguish cancer cells from normal cells, and how CpG methylation contributes to the oncogenic phenotype.

DNA methylation is regulated by a family of DNA methyltransferases (DNMTs) which catalyze the transfer of methyl groups from S-adenosyl-L-methionine to the 5′ position of cytosine bases in the CpG dinucleotide. DNMT3A and DNMT3B establish new DNA methylation patterns early in development [19].

During replication, the original DNA methylation pattern is mainly maintained by DNMT1 activity, which prefers hemi-methylated DNA over non-methylated DNA as a substrate [20] and it is therefore responsible for the maintenance of methylation patterns during cell division, with some participation by DNMT3A and DNMT3B [21]. DNMT1, DNMT3A, and DNMT3B are often overexpressed in various cancers and they may contribute to the abnormal hypermethylation [18, 22].

In this view, it is interesting to note that the global DNA hypomethylation [18–20], the abnormal hypermethylation in promoter CpG islands [23–25] and the exact mutagenesis of sequences containing 5 mC [26, 27] may occur simultaneously suggesting that altered homeostasis of epigenetic mechanisms is central to the evolution of human cancer and plays an active role in increasing chromosomal fragility.

2. Epigenetics landscape in mammalian development

Notwithstanding the neuroblastoma, tumorigenesis arise from the disrupted development of neural crest precursors, no single genetic or epigenetic mutation has been found after the DNA and RNA sequencing of over 1000 cases [28]. Recently, chromatin immunoprecipitation with high-throughput-sequencing and RNA-sequencing studies have demonstrated specific epigenetic patterns which distinguish neuroectoderm, neural crest, and more mature neural states, since a cardinal property of neural stem cells (NSCs) is their ability to adopt multiple fates upon differentiation [29]. Fascinating studies focused their attention on the epigenome as indicator of cell fate, and numerous observations highlight significant alterations within chromatin structure during mammalian development [30, 31]. In this frame, the developmental epigenetic regulation is the most deeply documented in the embryonic stem cell (ESC) research. Even though many promoters of developmental genes in ESCs contain permissive as well as repressive
epigenetic marks, they are transcriptionally silent and maintained in a transcriptionally silent state until differentiation [32]. Analogously, the NSCs differentiation is a unidirectional process tightly regulated to ensure the acquisition of specific neuronal phenotypes [33]. A novel chromatin modification pattern known as “bivalent domains” may explain these processes. Mainly, genes that are active in cells throughout development originally have active promoters which are characterized by the presence of the bivalent histone modification pattern consisting of H3K4me3 (permissive mark), trimethylation of lysine (K) 27 on histone H3 (H3K27me3, repressive mark), and a lack of DNA methylation. Genes enriched for K27me3 in ESC include those involved in early embryonic development, organogenesis, and cell fate decisions. In fact, genes that become transcriptionally active lose much of their polycomb-mediated repressive H3K27 methylation, conversely those that become silenced lose their H3K4 methylation or increases the polycomb-mediated repressive chromatin mark [32, 34]. However, recent works suggest that the loss of H3K27me3 is not sufficient to lead the increased transcription of all genes.

In the same direction, it has been shown that during the differentiation of ESC-derived NSCs, to immature GABAergic interneurons, all non-GABAergic promoters maintain the H3K27me3 repressive monovalency mark, whereas GABAergic promoters maintain the H3K4me3 mark (permissive monovalency) [29].

However, little is still known about the overall genomic distribution of K4 rather than K27 methylation in ESCs; the hypothesis is that bivalent domains consist of large regions of K27 methylation which hid smaller regions of K4 methylation. This bivalence condition is usually lost during ESC differentiation and in the differentiated cells [32].

Besides histone modification, the DNA methylation is equally essential for mammalian development and it is also linked to tumorigenesis [35, 36]. Unlike bivalent domains, cytosine methylation provides a methylated genome which can self-protect from environment changes due to the ability to repress specific promoters [37]. Among the three active DNA cytosine methyltransferases, identified in human and mouse [38, 39], the DNMT1 is responsible for copying the parental-strand methylation pattern onto the daughter strand after each round of DNA replication; DNMT3A and DNMT3B are strongly expressed in ESCs where they are essential for the de novo methylation and in maintaining methylation patterns [36, 40]. In 2003, it has been reported that the inactivation of both DNMT3A and DNMT3B results in progressive loss of methylation in various repeats and single-copy genes in ESCs. Moreover, the introduction of DNMT isoforms into highly demethylated mutant ESCs showed that the DNMT3A, DNMT3A2, and DNMT3B1 restore genomic methylation patterns, whereas DNMT1 and DNMT3B3 failed to restore DNA methylation patterns due to their inability to catalyze de novo methylation in vivo [41].

### 3. Novel therapeutic approaches in neuroblastoma

#### 3.1. Epigenetic therapy

Since neuroblastoma is a complex disease, driven by multiple genetic and epigenetic alterations, it is subject of intensive ongoing genomic research. In particular, during tumor initiation and progression the epigenome goes through multiple alterations. Promoter hypermethylation...
of tumor-suppressor genes [42], together with promoter methylation of several DNA repair genes and histone modifications [43], is commonly observed in cancer cells. Neuroblastoma is frequently associated with numerous genetic alterations and in this regard it has been reported that the restored expression of the zinc-finger transcription factor castor (human castor gene: CASZ1) inhibits cell proliferation in vitro and decreases tumor growth in vivo [44]. In addition, the expression of CASZ1 appears significantly decreased in aggressive phenotype of patients with unfavorable prognoses [45], thus indicating CASZ1 as a tumor-suppressor gene in neuroblastoma tumor. However, the absence of consistent CpG methylation of CASZ1 in neuroblastoma excludes a gene-silencing mechanism due to DNA methylation [46]; on the contrary, it seems that trichostatin A, a histone deacetylase inhibitors, induces CASZ1 expression in neuroblastoma cells [46], suggesting an epigenetic mechanism mainly dependent on histone regulation. In addition, histone modifications may affect the recruitment of transcription factors and of other components of the transcription machinery, thereby contributing to aberrant gene expression [21]; notably, altered histone modifications have been found in neuroblastoma tumors and have been correlated to tumor aggressiveness [45, 47]. Despite this evidence, the epigenetic changes, which contribute to the aggressive pathophysiology of neuroblastoma, are still poorly known. In this frame, preclinical studies have demonstrated that the DNA methylation appears to play a role in angiogenesis inhibitor thrombospondin-1 (TSP-1) regulation [48]. Neuroblastoma growth might be closely related to angiogenesis, since the angiogenesis inhibitors downregulation has been observed in highly malignant neuroblastoma cells and the administration of antiangiogenesis agents successfully inhibits neuroblastoma growth in vivo [49, 50]. In this regard, Yang and colleagues tested the efficacy of 5-Aza-dC (a demethylating agent) to restore the TSP-1 transcription in the TSP-1-negative neuroblastoma cell lines confirming that the silencing of this gene was triggered by a methylation process (Figure 3) [48]. Therefore, demethylating agents may be effective candidates for neuroblastoma-affected children.

Because epigenetic changes caused by DNA methylation are critical for the initiation and for the cancer progression, it has been also demonstrated that aberrant splicing of DNMTs is frequently exhibited in cancer cells [22, 51]. Notably, it has been suggested that high levels of truncated DNMT3B7 isoform alter DNA methylation and might be related to embryonic development and a less aggressive clinical neuroblastoma phenotype [52]. To test this hypothesis, Ostler and colleagues forced the expression of DNMT3B7 isoform in neuroblastoma cells to evaluate its effects on DNA methylation, tumor growth, and angiogenesis. They observed an increase of global DNA methylation, the decrease of aggressive neuroblastoma growth, and the suppression of angiogenesis, respectively, consistent with a nonmalignant phenotype [52].

3.2. Combined therapy with proteasome inhibitor

The presence of cancer stem cell population in the neuroblastoma increases the migratory properties of cancer cells, and this is a major concern in cancer therapeutics since the relapse of tumor and resistance to therapy are due to the self-renewing cancer cells [53, 54]. Doxorubicin (Dox), a Food and Drug Administration (FDA)-approved chemotherapeutic agent widely used in numerous cancer type, would benefit neuroblastoma patients and lead to better outcomes [55].
However, Dox induces nuclear factor-κB (NF-κB) activation which is believed to contribute to the development of chemoresistance [56]; thus, a viable option in cancer therapy could be the inhibition of NF-κB activation to overcome the chemoresistance. Among various biological systems exploited to obtain therapeutic benefits, the ubiquitin-proteasome system has been associated with tumor cell survival [57]. Notably, pharmacological inhibition of proteasome activity by small-molecule inhibitors shows anti-tumor efficacy in various cancer types [57]; proteasome activity has been also reported to be involved in NF-κB activation by promoting the degradation of its inhibitor IκBα [58].

Therefore, in order to improve therapeutic outcomes, the ability of Ixazomib to suppress neuroblastoma cell proliferation and to induce cell apoptosis has been recently reported. Ixazomib is a selective second-generation proteasome inhibitor able to enhance the Dox cytotoxicity (Figure 4) and capable to inhibit Dox-induced NF-κB activation [59]. Li and colleagues demonstrated the anti-tumor efficacy of Ixazomib in combination with Dox corroborating the hypothesis that combination therapies of proteasome inhibitors and chemotherapeutic agents will achieve better outcomes in neuroblastoma therapy. Similar results were also obtained using another second-generation proteasome inhibitor, the Carfilzomib [60] indicating the relevance of proteasome machinery in the therapeutic strategy for treating neuroblastoma patients.
Clinical trials for neuroblastoma

Since epigenetic dysregulation is a fundamental process underlying the pathogenesis of pediatric brain tumors, the use of epigenetic modifiers is currently under evaluation in the early phase of clinical trials. Epigenetic modifiers FDA approved mainly comprise two classes of agents: HDACs inhibitors (Vorinostat, Romidepsin, and Valproic Acid) and DNA methylation inhibitors (5-azacytidine and Deoxyazacytidine (Decitabine)).

Figure 4. Cell viability results after Dox plus ixazomib (1 or 5 μM) for 48 h; data showed that Ixazomib enhances dox-induced cytotoxicity in different types of Neuroblastoma cell lines. (a–f) IMR-32 (a) NGP (b) NB-19 (c) SH-SY5Y (d) SK-N-AS (e) and LA-N-6 (f) cells were seeded in 96-well plates (Li et al., 2016) [59].

4. Clinical trials for neuroblastoma

Since epigenetic dysregulation is a fundamental process underlying the pathogenesis of pediatric brain tumors, the use of epigenetic modifiers is currently under evaluation in the early phase of clinical trials. Epigenetic modifiers FDA approved mainly comprise two classes of agents: HDACs inhibitors (Vorinostat, Romidepsin, and Valproic Acid) and DNA methylation inhibitors (5-azacytidine and Deoxyazacytidine (Decitabine)).
In November 2015, a phase I trial aiming to test the toxicity of Vorinostat in combination with Isotretinoin and to see how well they work in treating patients with high risk of refractory or recurrent neuroblastoma has been completed. Results showed that Vorinostat may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth; in addition, Isotretinoin may help Vorinostat to work better making tumor cells more sensitive to the drug. The deduction aroused from results has been that Vorinostat together with Isotretinoin may be an effective treatment for neuroblastoma [61]. Simultaneously, another study tested the efficacy of Vorinostat and Iobenguane I 131 (131-I MIBG) to treat patients with resistant or relapsed neuroblastoma. The results demonstrated that the association of Vorinostat together with 131-I MIBG kills more tumor cells, since 131-I MIBG is a radioactive drugs which carry radiation directly to the tumor cells [62, 63].

A phase I study on Decitabine with Doxorubicin in children with neuroblastoma, and other solid tumors, revealed dose-limiting hematologic toxicities which were experienced by children [64]. It is still controversial whether drug toxicity and response rates to HDAC and DNA methylation inhibitors are strictly determined by the somatic tumor genotype or whether heritable germline factors may also contribute to the final outcomes [65]. Thus, it will be crucial to establish the optimal dose and treatment schedule of available drugs, especially considering heavily pretreated patients. To this end, biomarkers of drug efficacy should be used to ascertain whether pharmacological agents, such as epigenetic modifiers, have the predicted biologic effect. Subsequently, tissue availability should be essential for pathologic assessment of the response whenever new epigenetically targeted agents are introduced into the clinical setting.

Currently, a cohort observational study is ongoing and still recruiting participants at the St. Jude Children’s Research Hospital of Memphis, Tennessee (US). The aim of the study is to characterize the molecular, cellular, and genetic properties of primary and metastatic neuroblastoma, osteosarcoma, and other solid tumors. The isolated cells will be used for gene expression analysis, genomic analysis by single nucleotide polymorphism (SNP), comparative genomic hybridization, and next-generation sequencing. Epigenetic studies will be also performed investigating at the methylation profile of these cells [66].

At present, there are approximately 500 ongoing clinical trials for neuroblastoma using different therapeutic strategies [67], and only two of these comprise an epigenetic approach [68]. By contrast, as regard the use of proteasome inhibitors there are approximately 80 and 130 ongoing clinical trials, respectively, on Ixazomib and Carfilzomib, to test the side effects and best dose in different cancer conditions [69], but none of these is exclusive for patients affected by neuroblastoma disease [70].

5. Taking advantage of neuroblastoma cells: versatile model for neurobiology studies

The ability to produce in vitro cultures of neuronal cells has been crucial for the understanding of central nervous system (CNS) function regulation. The neuronal cell ability to proliferate,
as well as to differentiate, makes them an excellent *in vitro* system for several studies. The secondary cell lines derived from neuronal tumors are usually immortalized; they have the advantage to grow easily, to give unlimited proliferation *in vitro*, and to minimize variability between cultures. Cell lines are often induced to display a more neuronal phenotype by manipulations of the culture conditions, for example, through the addition of specific differentiation factors such as retinoic acid.

Neuroblastoma SH-SY5Y cells retain the ability to differentiate into neuronal cell types by all-trans-retinoic acid treatment which causes substantial alterations in the abundance of distinct G protein subunits [71]. In this regard, they have been used to examine the relationships between proliferation, differentiation, and apoptosis and this feature has been useful for the development of therapeutic strategies.

Neuroblastoma cells are extensively used for testing neurotoxicity of putative drugs, and also for understanding neuroplasticity phenomena, such as those evoked by the exposure of drugs of abuse. In particular, studies conducted in human neuroblastoma SH-SY5Y cells demonstrated that ethanol exposure influences epigenetic regulation through histone acetylation, hence regulating DNA transcription at specific portions of the genome [72]. Drugs of abuse have also been associated with proteasome inhibition which seems to be a key player in epigenetic mechanisms underlying the accumulation of oxidatively damaged histones [73]. In this frame, recent finding showed that ethanol exposure reduced intracellular 20S proteasome chymotrypsin-like activity in SH-SY5Y cells [74], in agreement with findings obtained in liver and brain demonstrating that ethanol decreased proteasome activity by interfering with 20S-CP (core particle) and 19S-RP (regulatory particle) assembly [75, 76]. By contrast, cocaine has been reported to exert an opposite effect on the 20S proteasome, since the chymotrypsin-like activity [74] increases.

Although some studies failed to demonstrate the correlation between the increased risk of neuroblastoma in offspring and parental alcohol or tobacco use [77, 78], neuroblastoma cell cultures currently represent a useful tool for the study of neuroplasticity phenomena.

### 6. Highlights and conclusions

In the last decades, a great variety of novel therapeutic strategies have become available for cancer. These therapies are often very specific and effective only in subsets of cancer patients, thus increasing the needs for the clinician to choose specific therapeutic strategy. This situation exerts a notable impact on the methods in diagnostic tumor pathology, since it requires precise tumor characterization to support the clinical management of the individual case. In this frame, epigenetic changes are important for the initiation and progression of cancers, including neuroblastoma. New insights into tumor biology are driving the development of novel therapeutic approaches which include small-molecule inhibitors as well as epigenetic approaches. The reversible nature of epigenetic modifications, the better knowledge of mechanisms underlying these changes and the consequent alterations of regulatory networks, may provide an interesting opportunity for the development of clinically relevant therapeutics. In particular, histone changes and DNA methylation are fundamental biological processes and
they seem to be promising candidates for pharmacological manipulation with encouraging therapeutic advantages.

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Appendices

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histones (H)</td>
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<td>R</td>
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