Epigenetics

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Abstract Cancer is one the most dreadful diseases in the world and its genetic origin has been undoubtedly proved and studied worldwide. Although, in recent decades, epigenetics has managed to shed light on many unknown mechanisms of carcinogenesis, being irrepressible by genetic laws. Epigenetic alterations represent a totality of heritable changes in gene expression that do not affect DNA sequence. Four major epigenetic alterations: DNA epigenetic alterations, histone post-translational modifications, remodeling complexes and non-coding RNAs are described in more detail in this chapter. In cancer, epigenetic deregulations are preceded by genetic mutations in genes of epigenetic machinery, and cause in result modifications of chromatin state. In this case, upregulation of oncogenes or downregulation of tumor suppressor gene expression became the worst outcome. In comparison with genetic mutations, epigenetic ones can be reversible. Therefore, different therapeutic strategies are developing to restore normal epigenetic landscape in tumor cells, pharmaceutical agents being classified by their main epigenetic targets. Common epigenetic regulators, such as HDAC inhibitors, DOT1L inhibitors, LSD inhibitors, EZH2 inhibitors and others are also described below. Besides of natural or synthetic regulators, epigenetic modifications can also be triggered by predisposition to different health conditions, onset of other non-cancerous diseases, virosis, aging or stress. Another background by which epigenetic profile is affected, and therefore can be reversed, includes different lifestyle factors such as environmental circumstances, diet or practicing exercises. For these reasons, we hope that this chapter will highlight the importance of epigenetic deregulations in cancer, and will also encourage further investigations of epigenetic mechanisms, validation of novel epigenetic biomarkers as well as development of new suitable epigenetic drug regulators in order to improve cancer therapy.

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1 Carcinogenesis

Nowadays, cancer is one of the most frightening diseases, characterized by the uncontrolled growth of abnormal cells. Unfortunately, its power over human lives continues to lie in a variety of well-orchestrated and precise dysregulations of important intra- and intercellular pathways that control vital cellular processes such as nutrition, growth, proliferation, survival, and intercellular communication, and mortality. Once these dysregulations have been initiated, they are difficult to control because even the slightest trigger factor—roots its effects into a vast network of interconnected cascades [1, 2]. In defiance of the fact that clinicians are not yet able to completely eradicate them, cancer is becoming more and more vulnerable due to all the revealing information which we have continued to accumulate since the understandings of the first basic tumorigenesis mechanisms were outlined. In 2000, Hanahan and Weinberg defined these driving forces as hallmarks of cancer, where six essential mechanisms acquired by tumor cells were described: self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion, and metastasis, limitless replicative potential, sustained angiogenesis and evading apoptosis [1]. These hallmarks had been instantly acknowledged in cancer's existing status as a "genetic" disease and a plethora of studies have been accomplished to demonstrate and strengthen this concept. Numerous genetic mutations have been identified and associated with a malignant profile, being used therefore as biomarkers for distinguishing normal versus cancerous tissues [2, 3], as well as different tumor types and even different stages of disease within the same cancer type [4]. However, the general trait of any malignant cell has been established as genomic instability, prone to aberrant and abnormal survival. Therefore, such alterations as deletions, substitutions, or translocations always led, in one way or another, either to the activation or overexpression of oncogenes, such as *MYC, RAS, RAF, AKT, BCL-XL, BCL-2*, or to the inactivation or silencing of tumor suppressor genes such as *P53, pRB, BAX, BAK*. The first ones favored proliferation, invasion, metastasis, expression of growth factors, and angiogenic or antiapoptotic signals, conversely acting the last one's [2–4].

Even though cancer development may have a genetic origin has been undoubtedly approved, there were still some discrepancies in terms of attempts to associate genotype with phenotype profile. Consequently, the studies of cancer mechanisms have continued so that at present, the data in the literature already list 14 hallmarks of cancer. The last 4 hallmarks, described with examples by Hanahan in 2022, are very different from the original ones and open much more horizons for a better understanding of complex tumor mechanisms than the first six originally described. One of these, which raise particularly increased interest in bringing to light the concept

of the genetic-independent evolution of cancer, is termed "nonmutational epigenetic reprogramming" [3, 5].

2 Major Epigenetic Alterations in Cancer

Epigenetic alterations are in general related to normal biological processes such as aging or differentiation, being considered a reversible process. Alteration of epigenetic signatures by a wide range of factors (particularly environmental), along with genetic and transcriptomic alterations, are considered as driving events in several diseases including cancer [6]. Therefore, the identification of tumor-specific epigenetics and the factors that affect epigenetic patterns should be evaluated to unmask truly disease-specific alterations.

Epigenetics, which means "upon the genes", represents the study of heritable changes in gene expression, that do not involve alterations in the DNA sequence, consequently involving phenotype changes without the genotype ones even in the cells which share identical genome. The term "epigenetics" appeared for the first time in 1942 when Conrad Waddington coined it to describe phenomena that do not follow "normal genetic rules" [7].

Epigenetic changes play an essential role in a series of normal biological processes, such as embryonic development, viral protection, genetic imprinting, and X-chromosome inactivation [8]; disruption of these epigenetic processes has been considered key mechanisms in a variety of pathologies including Beckwith-Wiedemann (BWS), Silver-Russell, Prader-Willi and Angelman syndromes as well as autoimmune diseases—systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), Sjogren's syndrome (SS), autoimmune thyroid diseases (AITD) and different neurological diseases [9–11].

Although epigenetic reprogramming is officially assigned as the hallmark of cancer just recently, as mentioned above, having an important role in growth-related pathways gave the earliest clues about the connection of these two about 40 years ago. In 1983, Feinberg and Vogelstein enlightened the first epigenetic mechanism attributed to cancer cells. Already knowing that the methylation process is related to the silencing of certain genes in some pathologies, they used Southern blotting and methylation-sensitive enzymatic restriction to demonstrate that the genome of cancer cells is hypomethylated at CpG dinucleotides compared to normal cells, which have generally hypermethylated genome [12, 13]. Other milestones in the history of human cancer epigenetics can be found comprehensively described by Feinberg and Tycko in 2004 [14].

Initially, three main types of epigenetic mechanisms were distinguished: DNA methylation, loss of imprinting (LOI), and histone modifications [14]. Although they had already encompassed a significant amount of information regarding the most important epigenetic elements, nowadays four categories of epigenetic mechanisms have been established with more well-clarified mechanisms within one category. These epigenetic modifications include:

(1) DNA epigenetic alterations,
(2) histone post-translational modifications (PTMs),
(3) remodeling chromatin complexes, and
(4) noncoding RNAs regulation [10, 14–17], schematic representation presented in Fig. 1.

All four epigenetic mechanisms determine either gene expression or silencing by controlling the chromatin state (condensed or decondensed). This is achieved through differential expression of enzymes that have abilities to change the accessibility of chromatin for binding of DNA transcription factors. A common way to identify and distinguish these enzymes is to assign them one of the statuses "writer", "reader" or

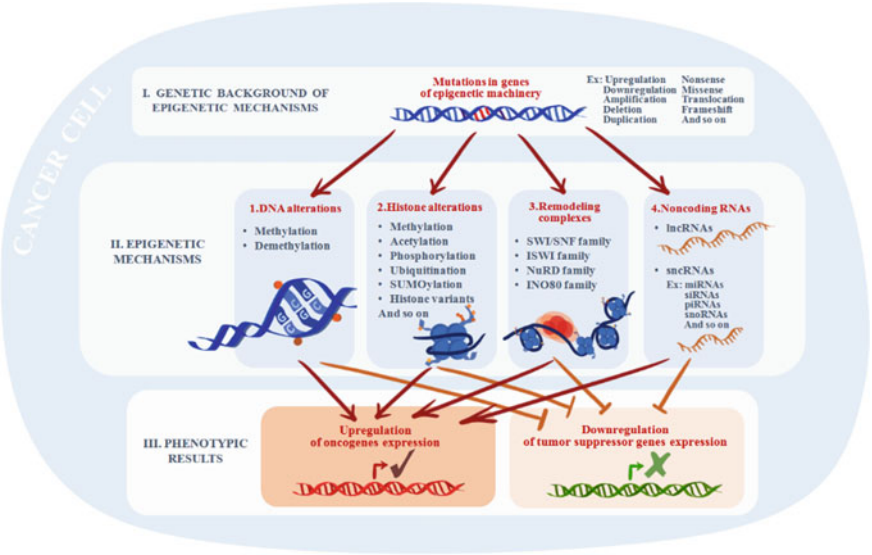

Fig. 1 Schematic representation of three main key steps of epigenetic regulation in cancer cells. **I. Genetic background of epigenetic mechanisms**. Initially, genetic mutations of certain genes that are involved in the functioning of the epigenetic machinery occur. **II. Epigenetic mechanisms**. Endpoint products of these altered genes, being either enzymes, protein complexes, or RNAs, become under- or overexpressed and lead to epigenetic changes which include DNA (1) and histone (2) alterations, aberrant functioning of remodeling complexes (3), and noncoding RNAs (4). **III. Phenotypic results.** Acting separately or in combination with each other, epigenetic changes specifically modulate the accessibility of promoters for binding with transcription factors thus regulating the expression of oncogenes or tumor suppressor genes. Aberrant expression of these target genes induces dysregulations in pathways of growth, proliferation, survival, invasion, apoptosis, and senescence, which play a crucial role in tumorigenesis and cancer development. *Abbreviations* SUMO—Small Ubiquitin-like Modifier; SWI/SNF—switching defective/sucrose non-fermenting; ISWI—imitation-switch; NuRD—nucleosome remodeling and histone deacetylase; INO80—inositol 80; lncRNAs—long noncoding RNAs; sncRNAs—small noncoding RNAs; miRNAs—microRNAs; siRNAs—small small interfering RNAs; piRNAs—PIWI-interacting RNAs; snoRNAs—small nucleolar RNAs

"eraser". The enzymes which deposit such modifications by adding different chemical groups are called "writers". They predominantly fall into the first two categories, contributing to DNA or histone modifications. The molecular marks which recruit chromatin remodelers and noncoding RNAs to mediate downstream effects, their interaction is controlled by proteins called 'readers'. Additionally, chemical modifications can be removed by 'erasers', a fact that can label epigenetic alterations as reversible ones [18]. Currently, all four categories of epigenetic mechanisms may be involved, separately or in combination with each other, in the development of cancer. Further, the main mechanisms from each category are briefly discussed. Some representative examples are presented in Table 1.

2.1 DNA Epigenetic Alterations

DNA epigenetic alterations include methylation, demethylation, hydroxymethylation, and its oxidation derivatives. The concurrence of DNA methylation and demethylation is in general related to transcription regulation. For DNA methylation an important role is attributed to DNA methyltransferases (DNMT) and for demethylation to the ten-eleven translocation (TET) [19].

The first one is best-studied and refers to the addition of a methyl group (–CH3) at the fifth position on the pyrimidine ring of cytosine (5mC) within CpG dinucleotides. These are clustered together into "CpG islands" and are found in about 40–60% of human gene promoters and repetitive regions of the DNA [20]. Two aberrant forms of DNA methylation can be distinguished during tumor development and progression: global DNA hypomethylation and local hypermethylation. The first one implies an overall loss of 5-methyl-cytosine. The last one makes promoters inaccessible for binding with transcription factors (TFs) and therefore it is a significant mark of gene silencing associated with gene inactivation. In cancer, particularly tumor suppressor genes and certain regulatory antioncogenes have a hypermethylated promoter, that leads to important alterations responsible for the tumorigenesis [21]. The process of methylation is catalyzed by DNA methyltransferases (DNMTs) which transfer a methyl group from donor S-adenosyl-L-methionine (SAM) to the cytosine residue. There are three main types of DNMTs known in mammals: DNMT1, DNMT3a, and DNMT3b, each having a specific mechanism of action. DNMT1 maintains the existing methylation pattern following DNA replication, while DNMT3a and DNMT3b catalyze *din novo* unmethylated CpGs, especially at new-formed strands of DNA after replication. Another family member, DNMT-3L lacks intrinsic methyltransferase activity, instead, it interacts with DNMT3a and DNMT3b to facilitate the methylation of retrotransposons [22]. In addition to direct inhibition of gene expression, methylated sites can also recruit specific proteins from the methyl-binding domain (MBD) family, such as MBD1, MBD2, MBD3, and MBD4, which in their turn recruit histone-modifying enzymes and chromatin-remodeling complexes [23, 24]. This MBD1 inhibition in pancreatic cancer affected the antioxidant response element target genes through epigenetic regulation of KEAP1 [25]. MBD1 plays a

Table 1 Cancer mutations and expression levels affecting epigenetic mechanisms

Category of epigenetic mechanism (most representative)	Altered genes and type of mutation (most representative)	Gene function/role	Cancer type	References
DNA modifications				
DNA methylation	DNMT1↑	Maintenance of methylation, gene silencing	Colorectal cancer, ovarian cancer, hepatocellular carcinomas, prostate cancer	[69–72]
	DNMT3a↑, mutant	De novo methylation	Acute myeloid leukemia, myelodysplastic syndrome, prostate cancer	[72–74]
	DNMT3b↑	De novo methylation	Ovarian cancer, colorectal cancer, prostate cancer	[70–72]
	DNMT3L↑	Methylation through interaction with DNMT3a and DNMT3b	Prostate cancer, cervical cancer	[72, 75]
DNA demethylation/hydroxymethylation	TET1↑	Dioxygenase, convert 5mc into 5hmc, oncogenic role	Lung cancer	[76]
	TET1↓	Dioxygenase, convert 5mc into 5hmc, tumor suppressor role	Colon cancer, breast cancer, gastric cancer	[29, 77–79]
	TET2↓, mutant	Dioxygenase, convert 5mc into 5hmc, tumor suppressor gene	Non-Hodgkin lymphoma, myelodysplastic syndrome, chronic myelomonocytic leukemia, acute myeloid leukemia	[80, 81]
	TET3↑	Dioxygenase, convert 5mc into 5hmc, oncogenic role	Ovarian cancer	[82]

(continued)

Table 1 (continued)

Category of epigenetic mechanism (most representative)	Altered genes and type of mutation (most representative)	Gene function/role	Cancer type	References
Metyl-CpG-binding proteins	MBD1↑	Transcription repression, epigenetic regulation of KEAP gene	Pancreatic cancer	[25]
	MBD1↓	Transcription repression	Colorectal cancer	[83]
	Kaiso↑	Transcriptional regulator with bimodal DNA-binding specificity; signal transduction and cell adhesion molecule	Lung cancer	[27, 84]
Histone post-translational modifications				
Histone methylation	MLL1↑ (KMT2A)	Transmethylation	Breast cancer	[85]
	MLL2↑ (KMT2D)	Lysine N-Methyltransferase	Colon cancer, breast cancer	[85]
	MLL3, mutant (KMT2C)	Lysine methyltransferase, affect transcriptomic pattern	Colorectal cancer, prostate cancer	[86–88]
	EZH2↑	Lysine N-Methyltransferase, PCR2 subunit	Prostate cancer, lung cancer	[89, 90]
Histone demethylation	JHDM1A↑ (KDM2A)	Lysine demethylase	Osteosarcoma, ovarian cancer, breast cancer, lung cancer	[91–93]
	LSD1↑	Lysine-specific demethylase; promote carcinogenesis	Cervical cancer, prostate cancer, lung cancer, colorectal cancer, acute myeloid leukemia, bladder carcinomas	[94–96]

(continued)

Table 1 (continued)

Category of epigenetic mechanism (most representative)	Altered genes and type of mutation (most representative)	Gene function/role	Cancer type	References
Histone acetylation	HAT1↑	Histone acetyltransferase 1	Esophageal carcinoma, Pancreatic cancer	[97, 98]
	HAT1↓	Histone Acetyltransferase 1, promote apoptosis	Lung cancer, osteosarcoma	[99]
	p300↓	Transcription regulation via chromatin remodeling; increase protein instability	Colorectal cancer, multiple cancers	[100, 101]
	p300↑	Acetyltransferase, transcriptional co-activator protein; drug resistance	Pancreatic cancer, squamous cell carcinoma, colorectal cancer, hepatocellular carcinomas, lung cancer	[102–106]
	GCN5↑	Lysine acetyltransferase, oncogenic role; drug resistance	Breast cancer, lung cancer, colon cancer	[107–109]
Histone deacetylation	HDAC1↑	Histone deacetylation, gene repression	Ovarian cancer, lung cancer, gastric cancer, breast cancer	[70, 110–112]
	HDAC2 ↑	Histone deacetylation gene repression	Ovarian cancer, lung cancer	[70, 110]
	HDAC3↑	Histone deacetylation Gene regulation	Acute myeloid leukemia, lung cancer	[110, 113]
Histone variants	mH2A2↓	Core histone protein, tumor suppressor role	Malignant melanoma	[41]
	H2A.Z.2↑	Histone protein, oncogenic role	Malignant melanoma	[42]

(continued)

Table 1 (continued)

Category of epigenetic mechanism (most representative)	Altered genes and type of mutation (most representative)	Gene function/role	Cancer type	References
	mH2A1.1↓	Core histone protein, tumor suppressor role	Colorectal cancer	[43]
	mH2A1.2↑	Core histone protein, oncogenic role	Colorectal cancer	[43]
Chromatin remodeling complexes				
SWI/SNF complexes	BRG1↓ (SMARCA4)	Catalytic atpase and helicase subunit	Lung cancer	[47, 114]
	BRG1↑ (SMARCA4)	Catalytic atpase and helicase subunit, regulated transcription of cell proliferation and cell cycle related genes	Colorectal cancer, breast cancer	[48–50]
INO80 complexes	ARID1A↓, mutation	Variant subunit, BAF complex only; mediate endocrine resistance to therapy or metastasis	Breast cancer, gastric cancer, colorectal cancer	[115–117]
	SMARCA2↓	Catalytic atpase subunit	Lung cancer	[118]

Abbreviation ↓ downregulation ↑ upregulation

role in tumorigenesis by repressing tumor suppressor genes like *CDH1, RASSF1A, TIMP3, P14ARF*, and *Rb* [26].

Somatic mutations in DNMTs and MBD proteins have been associated with deregulated pathways in different cancers, having oncogenic or tumor suppressor roles [27]. As effect of MBD epigenetic gene silencing mechanisms a wide range of transcriptional factors are released (Table 1).

In contrast to DNMTs, the ten-eleven translocation (TET 1–3) family of proteins catalyzes the oxidation of 5mC into 5-hydroxymethylcytosine (5hmC) and further products which modulate the DNA methylation landscape. TETs proteins have two cofactors, Fe(II) and 2-oxoglutarate (2OG), which are indispensable for successively 5mC oxidation. TETs loss-of-function is commonly observed in various cancers [28]. DNA hydroxymethylation facilitated by TET1 controlling the WNT signaling is a key factor in the tumor growth [29]. TETs' role in cancer is considered as context-dependent tumor-suppressor genes and/or oncogenes in solid tumors [30]. The anti- or oncogenic roles are directly related to the combination of different signaling pathways in different tumors [31].

2.2 Histone Post-translational Modification

Another type of epigenetic alteration occurs at the chromatin level. Here, nucleosome forms the basic structural unit of chromatin. It consists of DNA wrapped around an octamer of histone proteins which are represented by two copies of proteins H2A, H2B, H3, and H4. Histone modifications can contribute to chromatin compaction, nucleosome dynamics, and transcription alteration regulated by a fine-tuning mechanism regulated by chromatin modifiers and histone modifications [6, 32].

Histones are characterized by N-terminal tails rich in positively charged lysine (K) which in combination with a negatively charged DNA backbone confer a tightly packed state of chromatin [33]. Epigenetic changes occur when histones undergo post-translational modifications (PTMs) which primarily involve the addition or removal of certain chemical groups by specific enzymes at their N-terminal tails. These modifications trigger conformational changes in the chromatin structure, conferring either condensed (heterochromatin) or relaxed (euchromatin) state. Tight nucleosomes can become loose when the positive lysine residues are neutralized, therefore the access of the transcriptional machinery to the adjacent promoter of the gene will be enabled and the gene will be expressed. Conversely, the addition of more positive residues or groups to the surface of histones can enforce a chromatin tightened state and increase gene repression, without involving any DNA alterations in both cases. Consequently, more types of PTMs can be distinguished depending on which chemical group was added. The most well-known modifications are methylation, acetylation, and phosphorylation. These modifications are also established as epigenetic histone marks.

2.3 Histone Methylation

Histone methylation is catalyzed by writer-enzymes, histone methyltransferases (HMTs). It typically includes the addition of methyl groups (–CH3) to lysine (K) and/or arginine (R) residues. Finale regulation (activation or repression of the gene) results not only from the process of methylation per se but also from the position of methylated amino acid and the number of methyl groups added. For example, one of the most recognizable histone marks is the addition of three methyl groups by lysine methyltransferases (KMTs) at lysine 9 of histone H3 (H3K9me3) which results in gene silencing. Meanwhile, mono- and dimethylation of the same residue (H3K9me and H3K9me2) has the opposite effect. Other activating and repressive marks are H3K4me3 and H3K27me3, respectively [34]. One specific methyltransferase is enhancer of zeste homolog 2 (EZH2), which is a catalytic component of the polycomb repressive complex 2 (PRC2) and plays the primary role in the trimethylation of H3K27. Therefore, it is one of the important epigenetic elements which is responsible for gene silencing, being usually overexpressed in cancers [35]. Removal of the methyl group is performed by histone demethylases (HDMs). The expression level of both HMTs and HDMs can be altered in different tumor types, more information is provided in Table 1.

2.4 Histone Acetylation

Histone acetylation is catalyzed by histone acetyltransferases (HATs) which add acetyl group (–CH3CO) and neutralize the positively charged histone thus leading to conformational changing in chromatin structure and activation of gene transcription. H3K27ac and H2BK5ac are some examples of histone marks that correspond with actively transcribed genes. Histone deacetylases (HDACs) act conversely, thus inducing a back shift to the repression state of the gene. HDACs bind to and deacetylate a diversity of protein targets including transcription factors, involved in the control of cell growth, differentiation, and apoptosis [36]. A particular type of HDACs is a highly conserved family of NAD(+)-dependent HDACs called sirtuins (SIRTs). Seven mammalian sirtuins (SIRT1–7) are known to be implicated in many cellular processes, especially in epithelial-mesenchymal transition (EMT), invasion, and metastases [37].

2.5 Histone Phosphorylation

Histone phosphorylation, performed by kinases, occurs mainly at serine (S), threonine (T), and tyrosine (Y) residues and is associated with accessible chromatin conformation. Many histone marks have been found mutually working together,

for example, histone H3 phosphorylation at tyrosine41 (H3Y41) is enriched at active promoters close to transcription start-sites (TSS) together with the H3K4me3 mark [38], loss of the trimethylation of H4K20 (H4K20me3) and acetylation of H4K16 (H4K16Ac), along with DNA hypomethylation is labeled as the common hallmark of primary tumors [39] as well as reduced levels of lysine acetylation (H3K9ac, H3K18ac, H4K12ac) and methylation (H3K4me2, H4K20me3) and arginine methylation (H4R3me2) [39]. Other PTMs include ubiquitination, SUMO (small ubiquitin-like modifiers)-ylation, neddylation citrullination, deamination, formylation, biotinylation, O-GlcNAcylation, propionylation, butyrylation, crotonylation, proline isomerization, ADP-ribosylation and lactylation [32, 34].

Besides covalent histone modifications which affect directly the state of chromatin, some alterations involve the exchange of canonical histones in the nucleosome with histone variants. Histone variants arise from mutations in genes that encode histone proteins. They became considered potential drivers of cancer initiations, being either up or downregulated in different cancer types [40]. For instance, macroH2A (mH2A) is one of the most distinguishable known histone variants, due to its special *macro* domain with the 25-kDa-sized globular module. In malignant melanoma, mH2A2 turned out to be the downregulated [41]. In contrast with mH2A, overexpression of variant histone H2A.Z.2 isoform presented an oncogenic role and provided a proliferative effect in the same malignance [42]. Other studies showed that even different splice isoforms can discriminate between different stages of tumor development and show differential expression levels, such as maH2A1.1 which is downregulated in primary colorectal cancer samples compared to normal colon tissue, while mH2A1.2 is upregulated [43].

2.6 Remodeling Complexes

While PTMs of histone represent intrinsic epigenetic changes at the chromatin level, there is also an extrinsic way to manipulate the chromatin state which is performed by remodeling complexes. Chromatin remodeling is considered an important gateway to regulating gene transcription. Therefore, this mechanism has important implications for targeted cancer therapeutic strategies, considering that cancer can select a multi-subunit remodeler proteome for oncogenic advantage [44]. Based on the different structures and enzymatic activity of these complexes, they are categorized into four major families: the switching defective/sucrose non-fermenting (SWI/SNF) family, the imitation-switch (ISWI) family, the nucleosome remodeling and histone deacetylase complex (NuRD), and the inositol 80 (INO80) families. Remodeling occurs when the interaction between DNA and histone proteins is reconfigured by specific ATP-dependent enzymes which make up the subunits of remodelers [45]. As result, remodelers can manipulate nucleosome sliding along DNA, create access to transcription factors to gene promoters, and eject or replace certain histone variants [46]. Families also have different domain structures, such as SANT domains, bromodomains, PHD domains, DNA-binding domains, and chromo-domains that

assign them certain specificity. Having a pivotal role in transcriptional profile regulation, mutations in these remodeling complexes were immediately associated with cancer malignancies. The most studied is SWI/SNF complex. It activates predominantly in two forms, based on its constituent core subunits: BRG1-associated factors (BAF) and polybromo-associated BAF (PBAF). The first one, as results from the name, contains subunits as BRG1 or BRM, and ARID1A/ARID1B, while the last one contains BRG1 only, and ARID2 and BRD7. SWI/SNF complexes have been found to function close to promoter or enhancer regions and interact with transcription to modulate gene expression and contribute to lineage specification, differentiation, and development. Consequently, it has been recognized as tumor suppressor complexes [47], although recent data accumulate controversial evidence [48–50], most of the studies being related to the regulation of mitotic cell divisions and DNA repair mechanisms [49–51]. BRG1 is considered not only a prognostic marker but also a therapeutic target [50, 52]. Generally, genes that encode component subunits of BAF or PBAF are found to be mutated, especially downregulated or inactivated in a variety of cancers [47, 52]. In contrast with SWI/SNF complexes, elements of other complexes, such as INO80, have been elevated in some cancer types mediating oncogenic signaling and promoting tumor growth [52–55].

2.7 Noncoding RNAs

Noncoding RNAs took a step forward in the overall regulation of gene expression, interfering before transcription and translation levels as well. Varieties of noncoding RNAs are categorized into two major types, according to their length: small noncoding RNAs (sncRNAs, under 200 nucleotides) and long noncoding RNAs (lncRNAs, more than 200 nucleotides) [56–58]. The sncRNAs include small nucleolar RNAs (snoRNAs), PIWI-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), and microRNAs (miRNAs), the last ones being the most studied and strongly correlated with cancer development. These non-coding RNA transcripts regulate gene expression via complementarily binding to the 3′ UTR of the target mRNA [16]. Several studies revealed important aspects of epigenetics directly connected to this noncoding RNA transcript, particularly small RNAs that can direct the cytosine methylation and histone modifications that are involved in gene expression regulation [59].

The length of miRNAs represents approximately 22 nucleotides. Their role lies in complementary binding to a specific sequence of target mRNA and thus inducing mRNA-silencing. Therefore, many miRNAs have been found overexpressed in different tumor types, primarily downregulating the expression of tumor suppressor genes [23, 58, 60]. Nevertheless, some studies correlate the function of specific miRNAs with tumor suppressor activity [57, 58]. Differential expression of miRNAs is strongly correlated with the epigenetic process of DNA methylation due to the specific location of miRNA-encoding genes associated with CpG islands in their promoter regions. Additionally, miRNA genes might be located in

specific chromatin structures that predispose them even more to DNA methylation [61, 62]. For example, miR-200, which targets zinc finger transcription factor ZEB1 together with zinc finger homeobox protein ZEB2 and provides an inhibitory effect on the epithelial-mesenchymal transition (EMT) process, is subject to methylation and also trimethylation of H3K27 to favor EMT and promote cancer development [63] (Fig. 2a).

On the side of sncRNAs, lncRNAs encompass even more regulatory functions. They have been associated with modulation of mRNA processing, control of transcription in *cis* or *trans*, as well as of post-transcriptional process and protein activity, organization of nuclear domains, and interfering with chromatin remodeling complexes [58, 64]. Likewise, they have been positively correlated with both tumor suppression and tumorigenesis, being, therefore, up- and downregulated in a variety of cancers [58]. As aforementioned, lncRNAs can modulate epigenetic processes in multiple interconnected ways. For example, in prostate cancer—prostate cancer

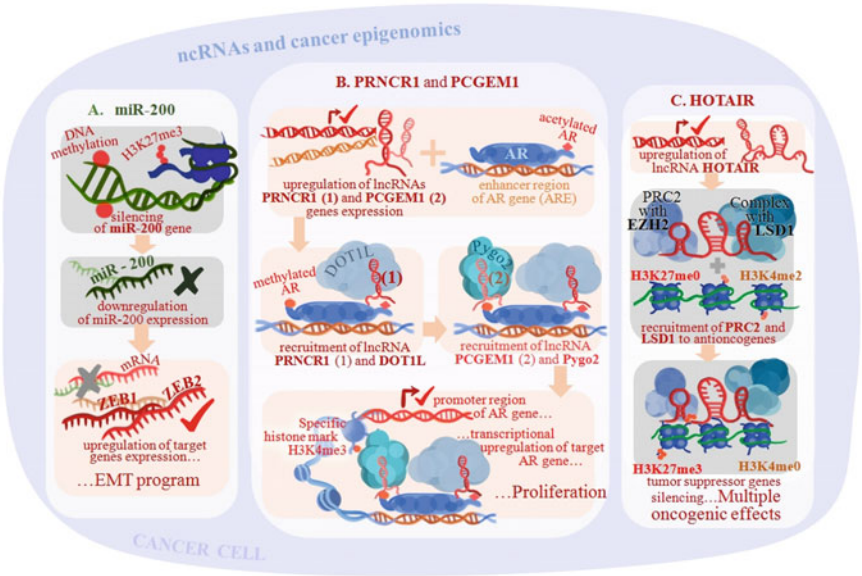

Fig. 2 Representative examples of ncRNAs that are involved in gene expression modulation through interaction with cancer epigenomics. **a** miR-200; **b** lncRNAs PRNCR1 and PCGEM1; **c** lncRNA HOTAIR. *Abbreviations* mRNA—messenger RNA; ZEB1—zinc finger transcription factor; ZEB2—zinc finger homeobox protein; EMT—epithelial-mesenchymal transition; PRNCR1—prostate cancer noncoding RNA1; PCGEM1—prostate cancer gene expression marker 1; AR—androgen receptor; ARE—AR response element; DOT1L—disruptor of telomeric silencing 1-like; Pygo2—Pygopus2; HOTAIR—HOX Transcript Antisense Intergenic RNA; PRC2—polycomb repressive complex 2; EZH2—enhancer of zeste homolog 2; LSD1—lysine-specific demethylase 1; H3K27me3—trimethylated lysine 27 of histone 3; H3K27me0—unmethylated lysine 27 of histone 3; H3K4me2—dimethylated lysine 4 of histone 3; H3K4me0—unmethylated lysine 4 of histone 3

noncoding RNA1 (PRNCR1) binds to the acetylated enhancer of androgen receptor and recruits histone H3K79 methyltransferase—disruptor of telomeric silencing 1-like (DOT1L). Consequently, methylation of androgen receptor facilitates the recruitment of another lncRNA, prostate cancer gene expression marker 1 (PCGEM1), to its N-terminal region. PCGEM1-recruited Pygopus2 (Pygo2) recognizes histone mark H3K4me3 and provide selective looping of enhancer with promoter, thus modulating gene expression of target gene androgen receptor (AR). AR enhance G1–S progression of cell cycle and therefore cell proliferation [65, 66] (Fig. 2b). In breast cancer, as well as in a variety of other cancers, well-known and overexpressed lncRNA HOX Transcript Antisense Intergenic RNA (HOTAIR) interacts with polycomb repressive complex (PRC2) and lysine-specific demethylase 1 (LSD1) thus recruiting them to the target gene and inducing gene silencing via H3K27-methylation and H3K4-demethylation [67] (Fig. 2c).

Different noncoding RNAs can also synergistically or antagonistically interact one with another to modulate gene expression. lncRNAs and circRNAs might act as miRNAs sponges by directly binding to them and abolishing their function. A study on breast cancer identified the lncRNA FAM83H-AS1 secludes miR-136-5p and therefore encourages metadherin-induced proliferation, migration, and invasion [68].

3 Epigenetics Drugs for Cancer Therapy

Considering the important function of the epigenetic dysregulation towards the origin and progression of cancer is considered an important cancer hallmark, an important number of preclinical and clinical studies are involved in testing and validation as a therapeutic strategy to restore the reversible normal epigenetic landscape in cancer cells by inhibiting enzymes of the epigenetic machinery in a wide range of cancer types [17, 119]. Until present, a wide range of natural or synthetic chemical agents as epigenetic regulators are tested and classified based on the main epigenetic target, the common DNMT inhibitors, HDAC inhibitors, DOT1L inhibitors, LSD inhibitors [120], EZH2 inhibitors, BET inhibitors [17]. Some of these inhibitors have been approved by the US FDA for the treatment of diverse malignancies and an important number of these compounds are undergoing clinical trials.

Inhibitors of *DNMT* and *histone acetyltransferases/deacetylases* have been revealed to inhibit tumor growth by reactivating epigenetically silenced tumor suppressor genes and silencing oncogenes [121].

DNMTs inhibitors can reverse the DNA hypermethylation status of tumor suppressor genes, they have been divided into two classes cytosine analog inhibitors and non-nucleotide analog inhibitors [16]. The most common demethylating are 5-azacytidine and 5-aza-2′-deoxycytidine, already approved for cancer therapy and hematologic pathologies. The main issue related to this type of agent is related to the unspecific reactivation of methylated sequences of tumor suppressor genes

CpG islands. In parallel, also a global genomic demethylation process that causes chromosomal instability was observed [24].

MBDs are considered a valuable target for cancer inhibition, to avoid problems related to genomic instability, by inhibiting DNA methylation per se [24].

HDAC proteins are related to multiple oncogenic steps, HDAC inhibitors are involved in the prevention of tumor suppressor genes if recruited to promoters together with fusion oncogenes such as *PML-RAR*α. Another application of HDAC inhibitors is to prevent the expression of HDACs proteins, that are in general overexpressed in multiple solid tumors or hematological malignancies, with high expression levels being in general related to an unfavorable prognostic [122].

Several *HDACi* are already approved in the clinic (Vorinostat, romidepsin, panobinostat, and belinostat in hematological malignancies), meanwhile others are tested currently in phase I or II clinical trials including pracinostat, givinostat, resminostat, abexinostat, entinostat, quisinostat [16].

Vorinostat and romidepsin were the first drugs to be approved that influence epigenetic post-translational modification of histone proteins [123]. Suberoylanilide hydroxamic acid (SAHA; vorinostat) is a non-selective broad-spectrum HDACI that induces acetylation of histones, this was demonstrated to be relegated with the overexpression of p21 as the effect of activation of the acetylated histone H3 and H4 in bladder carcinoma and endometrial stromal sarcomas [16, 124]. MS-275 inhibits HDACs 1–3 and 9, generally, this inhibitor was tested in conjunction with other agents [125]. Generally, this class of compounds is used to impede oncogenesis by acting apoptosis and cell cycle arrest and affecting the DNA damage pathway [122].

Preclinical work with BET inhibitors was focused on the comprehension of the relationship of BET proteins in regulating the cell cycle [122]. BET inhibition is generally related to transcriptional repression and cell cycle arrest [122]. Transcription factors are implicated in a wide range of pathologies, in a large number of human diseases such as cancers [126]. Accumulating investigations reveal that repression of EZH2 by small molecular inhibitors or gene knockdown leads to a decreased cell proliferation and tumor formation capacity [127] (Table 2).

4 How Epigenetic Processes Can Be Manipulated for Cancer Patient Benefit

The epigenetic processes are composed of DNA methylation, chromatin remodeling, histone modification, and non-coding RNA regulation [148–150]. These processes have a significant role in genome function and are dynamic, which means that they can be modified during their whole life by different factors [151, 152]. Because epigenetic processes are reversible, different factors can be used for epigenetic manipulation that can be implemented in cancer research. Epigenetic changes take place during our whole life and some epigenetic changes can be transferred from generation to generation [153]. Another important fact is that environmental conditions affect the

Table 2 Relationship between drugs and epigenetic mechanisms

Epigenetic mechanism	Altered expression	DRUG	Disease	Observation	References
DNMT	DNMTs↓	5-Aza-2-deoxycytidine	Myelodysplastic syndrome	Reverse the DNA hypermethylation status of tumor suppressor genes	[16, 128]
	DNMT1↓	Zebularine	Bladder carcinoma	DNA demethylating agent reactivate an epigenetically silenced gene	[129]
	DNMT1↓	MG98a	Renal carcinoma	Methylate DNA, local chromatin condensation and consequent repression of gene expression; reducing tumor progression	[130, 131]
	DNMT1↓	RG108	Colon cancer	Demethylation and reactivation of tumor suppressor genes	[15]
	DNMT1↓	Decitabine	Acute myeloid leukemia; myelodysplastic syndrome	–	[128]
HDAC	HDAC2, HDAC3, HDAC7	SAHA	Bladder carcinoma and endometrial stromal sarcomas	Antitumoral effect via p21 regulation and	[16, 124]
	HDAC1 and HDAC3↓	Valproic and acid RGFP966	**Acute myeloid leukemia**	**Reversal of chemoresistance in via DNA damage response**	[113]

(continued)

Table 2 (continued)

Epigenetic mechanism	Altered expression	DRUG	Disease	Observation	References
	HDAC3 and HDAC4↓	Valproic acid	Myocardial infarctions	Stimulatory effect on vascular endothelial tissue-type plasminogen activator expression	[132]
	HDACI↓, MS275↓	Entinostat (MS-275)	Malignant ascites	Inhibit malignant ascites development and tumor growth	[133]
	HDACi↓	Panobinostat	Multiple myeloma, pancreatic cancer	Relapsed and refractory disease	[134, 135]
EZH2		Quinoline derivatives	Solid tumors	Inhibition of EZH2 by evaluation of the H3K27 methylation	[136]
		GNA022	Human head and neck and breast cancer cell lines	Specifically, and covalently binds to Cys668 within the EZH2-SET domain, enhancing EZH2 degradation and inhibiting tumor growth	[137]
		Astemizole	Diffuse large B-cell lymphoma cell lines	Disrupting the EZH2-EED interaction of polycomb repressive complex 2	[138]
DOT1L inhibitors		UNC0642 and EPZ-5676	Human U2OS Osteosarcoma, Human leukaemia cell lines MV4-11	Inhibits of H3R2me2a and H3K79me2, cooperation between DOT1L and CARM1, increase apoptosis and reduced cell proliferation	[139]

(continued)

Table 2 (continued)

Epigenetic mechanism	Altered expression	DRUG	Disease	Observation	References
		EPZ004777	Leukemia cells	Strong affinity for the SAM-binding pocket of the protein	[140]
		EPZ004777	Colorectal cell lines	Marked reduction of cell viability and tumorigenicity	[141]
		Pinometostat	MLL-fusion leukemia	Inhibited H3K79 methylation and MLL-fusion target gene expression	[142]
		EPZ5676	Gastric cancer	Regulating cyclins and H3K79 methylation	[143]
LSD inhibitors		Tranylcypromine derivatives	Acute myeloid leukemia cells	Myeloid differentiation and *Gfi1b* and *Irf8* upregulation	[144]
		Arborinine	Cervical cancer	Activated caspase-dependent apoptosis, suppressed cancer cell migration by downregulating expression of key regulators of epithelial-mesenchymal transition	[145]
		Higenamine	MLL-rearranged leukemia therapy	Increases expression of LSD1 substrates H3K4me1 and H3K4me2	[146]
		Kavalacotones	Prostate cancer	Inhibition of development and progression of tumor cells	[147]

Abbreviation ↓ downregulation; ↑ upregulation

epigenetic processes that occur during our life. Fraga et al. observed that monozygotic twins have similar DNA methylation and histone acetylation patterns; while older twins have significant differences in these epigenetic patterns meaning that the environmental conditions and diet influence their epigenetic profile [154]. Epigenetic changes have been linked also to exercise and Denham et al. described in their review how exercise can change the epigenetic profile of people and how it can prevent several diseases. They also showed that the epigenetic changes induced by exercise are reversible [155]. Diet is also a very important factor in diseases and it was demonstrated that poor nutrition in mothers during pregnancy can be linked to different diseases in humans and mice and most of the mechanisms involved are epigenetic [156–158]. Another epigenetic factor that has been shown to have an important role in the heritability of health and diseases is non-coding RNAs, where psychological stress and low protein diet affect the expression level of sperm non-coding RNAs, and these alterations are transmitted to offspring [159–162]. Studies showed that aging and obesity can also modify the sperm epigenome in humans [163, 164]. Alcohol is an important factor that can dysregulate epigenetic mechanisms by inhibiting the activity of methionin synthase (MTR), methionine adenosyl transferase (MAT) and DNA methyltransferases (DNMTs) [165]. Rossi et la observed that alcohol consumption is correlated to colorectal cancer development [166]. Heterocyclic amines are known for their genotoxic effect, but the mechanism through which they activate carcinogenesis still is not well understood. A study on rats observed that 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) tumors have a specific signature of dysregulated miRNAs including let-7 family, mir-21, mir-126, mir-29c, mir-145, and mir-215 [167]. Rodriguez-Miguel et al. observed that high corn-oil diet of rats can induce epigenetic changes that can be related to breast cancer progression [168].

Another important factor that can modulate epigenetic changes is chronic inflammation. One factor that can induce chronic inflammation is stress. It was observed that stress can induce chronic inflammation in patients with thyroid disease, and in some cases by epigenetic regulation can induce thyroid cancer [169]. He et al. observed that chronic inflammation of colon mucosa have different methylation patterns in genes involved in cancer development like PIK3CA, AKT, MAPK, Ras, Wnt or TGFb [170]. Chronic inflammation in cystic fibrosis or chronic obstructive pulmonary disease is related to epigenetic reprogramming of airways macrophages, which in turn favor tissue damaging and diseases progression [171]. Ahmad et al. observed that inflammation in COVID-19, lung cancer and other imflammatory lung diseases are regulated by different miRNAs and environmental induced inflammation is strictly regulated by epigenetic changes [172]. Also, oncogenic viruses have been shown to influence carcinogenesis through epigenetic modifications, including DNA methylation, chromatin remodeling histone modification, long noncoding RNA, microRNA, and circular RNA [173]. Rattan et al. discussed in their review the importance of gut microbiome and epigenetic changes in hepatocellular carcinoma [174].

5 Conclusions and Perspectives

Throughout an increasing amount of studies, epigenetics became a very intricate field in the overall understanding of cancer initiation and progress. The majority of epigenetic deregulations are the results of genetic mutations of certain genes that encode enzymes involved in the functioning of the epigenetic machinery. The final products of these mutations, being either solitarily enzymes, catalytic subunits from protein complexes, or noncoding RNAs, interconnections between them can regulate, through different specific mechanisms, the access of transcription factors to gene promoters, facilitating either expression or repression of particular target genes. On the other hand, this indirect regulation creates a "ladder of a multistep processes" and therefore gives the opportunity to additionally influence these "intermediate steps" before they reach the worse outcomes. Fortunately, in comparison with already established mutations that trigger altered functioning of genes that play roles in initiating events in the tumorigenesis cascade, epigenetic alterations can be reversible due to their increased plasticity and sensitivity to environmental factors.

Epigenetic changes, including DNA methylation, histone modification, and noncoding RNA expression, have also been reported in a wide range of solid tumors, emphasizing important alteration in cell proliferation, apoptosis, invasion, or metastasis. Epigenetics enables us to explore the potential mechanism underlying cancer phenotypes. Great effort has been devoted to understanding the role of these epigenetic alterations involved during development and cancer progression. Precise techniques should be developed and standardized for epigenetic evaluation in the genome or from a specific population of cells to hopefully a few or even a single cell.

An important role is related to the crosstalk between DNA methylation and histone modifications regulated by different nuclear factors. Pharmacological restoration of the epigenetic balance of gene expression is used in biomarker discovery and as a therapeutic target for human cancers.

Validation of novel epigenetics biomarkers will assist in diagnosis, prediction of drug response and eventually identifying the responsive patients. All in all, multidisciplinary field researchers need to work together to optimize the drug engineering process (novel compounds or drug derivatives from existing ones, in different combinations) to be tested in preclinical and clinical trials. The main aspiration is to translate epigenetic therapy into the clinic for the treatment of cancers and tailor effective strategies based on cancer types and epigenome-specific alterations. For this a better understanding of anticipatory processes in the living becomes a preliminary. We make reference here only to a suggestion originating from the biomolecular scientist Harry Rubin (communicated in Nadin, [175])—healthy cells keep cancer cells under control. Only when the anticipatory function is affected, does the cancerous cells get out of control. Louie [176] defined Nadin as the "anticipation guru"—enough for us to take his reference to cancer and anticipation at heart.

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