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Anti-Tumor Drug Resistance and Modern Oncologic Pharmaco-Therapy: RNA and DNA Methylation, Mechanisms and Histone Modification, Epigenetic Regulation and Targeting Epigenetic Modifiers in Contemporary Cancer Therapy

Ziyad S. Haidar

Abstract

Metastasis, the spread of cancer cells from the primary tumor to the surrounding tissues and to distant organs, is one (and perhaps the primary) of the major causes of cancer-related death (or cancer morbidity and mortality). Indeed, it is estimated that metastasis is responsible for about 90% of cancer deaths. The major factors contributing to the metastasis of cancer cells are epithelial-mesenchymal transition (EMT) and cancer stem cells (CSCs). Herein, the cancer cells must detach from the primary tumor, intravasate into the circulatory and lymphatic systems, evade immune attack, extravasate at distant capillary beds, and invade and proliferate in distant organs. Accruing evidence suggests that the malfunction of epigenetic regulation in the functioning of a gene is directly related to the generation of tumors and cancer. Henceforth, the potential and capacity to change or re-program the epigenetic landscape within the epigenome of cancer is possibly the most promising and pursued targeted therapy, nowadays. Such would lead to reversing drug resistance and so, new therapeutic modalities. Indeed, contemporary oncologic pharmaco-therapy for cancer has and continues to undergo remarkable changes; especially lately, in terms of the introduction of effective cancer-specific molecular-targeted therapeutic agents. This introductory chapter to the book titled: "DNA Replication – Mechanisms, Epigenetics, and Gene Therapy Applications" discusses DNA and RNA methylation, the mechanisms of histone modification, and presents a variety of epigenetic modifications which can lead to anti-tumor drug resistance. It also explores how targeting epigenetic modifiers can reverse drug resistance.

Keywords: DNA replication, epigenetics, gene therapy, RNA methylation, histone modification, drug resistance, oncology, therapy

1. Introduction

Clinically, selecting the ideal anti-cancer therapy might consider combining epigenetic-related drugs. Indeed, epigenetic regulation and epigenetic changes, during treatment have been reported as one of the correlating mechanisms for anti-tumor drug resistance. This is due to the fact that during treatment, the development of drug-resistant tumors continues to pose a critical challenge in oncology; severely increasing the mortality rate, worldwide. This resistance can be categorized as either *de novo* or acquired depending on whether the resistance is inherent or has been acquired due to continuous drug administration [1]. Mostly, the research on cancer drug resistance has focused on the genetic aspect of the disease but the importance of epigenetic regulation is coming to light. Epigenetics events have always been important in the progression of cancer. Two very important epigenetic events that affect the expression of genes are methylation and acetylation which activates the oncogenes and reduces the tumor suppressor genes which lead to cancer drug resistance. Herein, both, ovarian and breast cancers are tumors whose epigenetic basis has been studied in detail [2]. Tyrosine kinase inhibitors have an important role in the therapy of cancer. The effectiveness of (TKIs) is good for both solid and liquid cancer. This is used to reduce the oncogenic activity with the epidermal growth factor receptor (EGFR), as well as tyrosine kinase receptor has developed resistance against EGFR-TKIs [3]. The role of demethylases in resistance against TKIs upregulation of these demethylases leads to resistance against TKIs. The events of epigenetics are not limited to solid tumors, a common childhood malignancy (lymphoblastic leukemia) where the changes in genetics are not enough to prove the increased relapse and chemo-resistance [4]. The less studied portion of the cell is the *centrosome* (archaically cyto-center) in the context of epigenetic regulation of drug resistance. The centrosome organelle (microtubule organizing center) has a very important role during the division of the cell in which the centrosome distributes cellular components within daughter cells. Any abnormal function of the centrosome in epigenetic events can degrade the integrity of the cells, resulting in genetic instability [5]. Consequently, the main issue in anti-cancer therapeutics is the development of resistance which has become the biggest problem in cancer survival rates. Indeed, resistance to cancer therapy can develop in a multitude of ways which also includes alteration in epigenetics in cancer cells [6]. There are many ways by which cancer cells reconstruct their epigenomics landscape so that they can resist anti-cancer treatment. To tackle the effects of chemo-resistance, there are various modifiers that are used, including histone deacetylase inhibitors, DNA hypomethylating agents, and histone demethylase inhibitors. A modifier has an average success, whether when used alone or in combination, yet the best result, to date, was achieved when modifiers were used with some of the conventional or traditional anti-cancer therapeutics [7]. Herein, pharmaco-therapeutics that modify epigenomes succeed in weakening cancer cells via different processes, such as restoring cell cycle control, damaging pro-survival signaling, preventing DNA damage, reparation, and/or suppression of the immune system, to mention a few [8].

2. Cancer epigenetics: epigenetic mechanisms, regulation, and modification

As aforementioned, abnormal epigenetic modifications in specific oncogenes and tumor suppressors genes can result in un-controlled cell growth and division. Indeed, alterations in epigenetic modifications in cancer regulate various cellular responses, including cell proliferation, apoptosis, invasion, and senescence. Through DNA methylation, histone modification, chromatin remodeling, and noncoding RNA regulation, epigenetics play an important role in tumorigenesis. Nevertheless, it is worth-mentioning that abnormal epigenetic modifications in regions of DNA outside of genes, alongside other environmental factors, can also lead to or result in cancer. Numerous studies in the literature studied and continue to investigate the different landscapes of the genome from oncogene-driven signaling to all the mutation spectrum in all types of cancer sub-types [9]. It can be stated that the epigenetic modification can be categorized into three sub-types (carcinogenic mechanisms): DNA methylation, RNA methylation, and modification of histones and non-coding RNAs [10]. Those will be discussed in the next pages.

2.1 DNA methylation

Briefly, alterations in DNA methylation are common in development as well as in a variety of tumors. For example, if a gene necessary for DNA repair is hyper-methylated, this would result in deficient DNA repair and lead to an accumulation of DNA damage. An Increase in DNA damage will then cause increased errors during DNA synthesis, therefore, leading to mutations that can or tend to give rise to cancer. Hence, the methylation of DNA is one of the most studied mechanisms in epigenetics which usually occurs in CpG islands which is located at 5´ promoter region studies in more than 50% of human genes, this usually displays function in diseases and development which also include embryonic development, X chromosome inactivation, epigenetics reprogramming, genomic imprinting, and the establishment of cell identity [11]. Generally, it shows gene silencing with the addition of the groups of methyl from S-adenosylmethionine also known as (SAM) to five positions (cytosine pyrimidine ring) [12]. Now, this 5-methylcytosine structure can either restrict access of many transcriptional factors to the sites of binding in DNA, or it can take methyl binding domain proteins with histone modification to re-configure the chromatins, thus they can show expression of genes [13]. Generally, there are three DNA methyltransferases, and are known as DNMT1, DNMT3b, DNMT3a; which help in catalyzing the methylation of the DNA (**Figure 1**) [10].

2.1.1 DNA methylation processes: de novo-, hyper-methylation, and demethylation

DNA methylation regulates gene expression via recruiting proteins involved in gene repression or by inhibiting the binding of transcription factor(s) to the DNA. During development, the pattern of DNA methylation in the genome changes as a result of a dynamic process involving both *de novo* DNA methylation and de-methylation. If hyper-methylation occurs in DNA, the methyl group will attach to the cytosine at Carbon 5 and is catalyzed by the DNA methyl transferase, also known as (DNMTs), which also includes DNMT1, DNMT3b, DNMT3a. This methylation step of cytosine occurs at the CpG dinucleotides, and DNMT1 is highly responsible for maintaining the methylation by sending the methyl group to DNA strands which

Nucleoside Analogue	Non-Nucleoside Analogue		Anti-Sense	Ref
Zebularine	RG 108 Procaine		MG98	(14)
5-Aza-2'-deoxycytidibe (Decitabine/ Dacogen)	RG 108			
5'-Azacytidine (Vidaza)	Procainamide			

Figure 1.
DNA methylation and regulators thereof. DNA methylation is a chemical modification process that involves the addition of a methyl group to the cytosine base of DNA molecules. It is an essential epigenetic mechanism that regulates gene expression and plays a crucial role in various biological processes. The process of DNA methylation is carried out by a group of enzymes called DNA methyltransferases (DNMTs), which are themselves regulated by various factors such as histone modifications, transcription factors, and non-coding RNAs. Regulators of DNA methylation are factors that control the activity and expression of DNMTs and thus modulate the level of DNA methylation. These regulators can be classified into two main categories: (1) positive regulators, which enhance the activity of DNMTs and increase DNA methylation levels, and (2) negative regulators, which inhibit the activity of DNMTs and decrease DNA methylation levels. Examples of positive regulators of DNA methylation include histone methyltransferases, which modify histone proteins and create a favorable chromatin environment for DNMTs to function, and certain transcription factors that recruit DNMTs to specific genomic regions. Negative regulators include DNA demethylases, which actively remove methyl groups from DNA, and some non-coding RNAs that can inhibit DNMT expression or activity. Overall, these regulators play a critical role in maintaining the appropriate DNA methylation patterns in cells and ensuring proper gene expression and cellular function. For example, RG108 and MG98 are both small molecules that have been developed as inhibitors of DNMTs. However, there are some differences between these two compounds. RG108 is a non-nucleoside inhibitor of DNMTs that works by binding to the catalytic site of the enzyme and blocking its activity. It has been shown to be effective in reducing DNA methylation levels in various cell types and has been used in several studies to investigate the role of DNA methylation in gene expression and other cellular processes. RG108 has also been evaluated for its potential therapeutic applications, including as a treatment for cancer and other diseases that are associated with abnormal DNA methylation patterns. On the other hand, MG98 is a nucleoside-based inhibitor of DNMTs that acts by incorporating into DNA during replication and inhibiting the activity of DNMTs. It has been shown to be effective in reducing DNA methylation levels in cancer cells and has been evaluated in several clinical trials as a potential treatment for various types of cancer, including non-small cell lung cancer and pancreatic cancer. Both RG108 and MG98, are promising compounds for the development of DNMT inhibitors, yet have different mechanisms of action and hence may be more suitable for different applications or disease indications.

is hemi-methylated following the replication of the DNA [14, 15]. There are several methylating agents capable of methylating cytosine residues such as DNMT3A and DNMT3B, also known as *de novo* methylation [16]. Dinucleotide CpG is separated all over the human genome and are compiled up in regions rich in CpG in some regions with big repetitive sequences [17]. There are many processes of hyper-methylation that induce suppression of transcriptional factor; the first step is the CpG island which is methylated and absorbs proteins which have inhibitory factors proteins that stop the interaction with the transcription factor and with the sequences of DNA. There is also another mechanism the CpG-methyl protein that basically can recognize the methylated CpG and could suppress the activity of the methylated DNA. Over the years, many scientists have actually exposed the fact that the proliferation of tumors and initiation of human cancer is indeed caused by the silencing of various tumor suppression genes which once methylated, will lead to changing the pathways and then will eventually result in carcinogenesis [18].

2.2 RNA methylation

Even in cells with the correct DNA sequencing, the RNA may go through changes that would alter which proteins are produced. Herein, clinically, such changes may

lower the protein levels that impact killing the cancer cells or even increase the protein levels that prompt a cancer cell to continue dividing.

The modified version of RNA N^6-methyladenosine can also be referred to the residues of adenosine at the position of the N-6. It was originally discovered in the 1970s taking epigenetics and cancer biology by storm [19]. Modifications of the m^{6}A usually start near the stop codon, 3 UTR, and also, within the long internal exons. Such usually affects all the processing of the RNA, including degradation, transcription, translation as well as splicing. Furthermore, there are studies that suggest that m^{6}A is dynamic and reversible [20]. Briefly, the formation of the m^{6}A requires multiple methyl-transferases. Examples include: METTL3, METTL16, and also METTL14 [21].

2.2.1 Is "m^{6}A" the most common RNA modification involved in various cancers?

The most common modification in RNA is m^{6}A, confirmed worldwide, in various yeasts, drosophila, mammals, viruses and are involved in various aspects of biology and medicine [22]. The modification of the RNA m^{6}A can lead to different consequences such as affecting mitosis, cell division, gametogenesis, immune homeostasis, and a different biological rhythm [23]. In recent studies, the modification of m^{6}A is investigated elaborately, primarily in mammals. The methylation of the m^{6}A RNA takes place within a sequence of purine [G>A] m^{6}AC [A/U/C], but m^{6}A is not situated at all methylated sites [24]. Further, the modification of m^{6}A takes part in different pathogenesis of several other human diseases; particularly in cancer. Indeed, the modification of m^{6}A RNA is so dynamic that it plays important role in cancer progression and carcinogenesis [25]. As a target, modification of m^{6}A is taken as a potential tumor marker for diagnosis. There are mainly three components for m^{6}A regulation: the m^{6}A methyltransferases ("writers"), m^{6}A demethylases ("erasers"), and the binding protein decoder called m^{6}A methylation ("readers"). Also, it is noteworthy that m^{6}A is present in different forms of RNA but not present in the small nuclear RNA, ribosome RNA, long non-coding RNA, and circular RNA [26]. There are several enzymes involved in m^{6}A modification: methyl transferase complex, which is a composition of several components including methyltransferase-like protein 14 (METTL14), methyltransferase-like protein 3 (METTL3), and Wilms' tumor 1–associated protein (WTAP) [27]. The earliest known of these three enzymes is the "m^{6}A-writers". Some of the newly discovered writer proteins are zinc finger CCCH domain-containing protein 13 (ZC3H13) [28], methyltransferase-like protein 16 (METTL16) [29], KIAA1429 (VIRMA) [30], CBLL1 (an E3 ubiquitin ligase) [31], and RNA-binding motif protein 15 (RBM15) [32]. These enzymes play role in different pathways [33] and in RNA modification. Different capabilities were revealed in a recent study where distinct genes were silenced (siRNA) like WTAP, METTL3, and METTL14, in cell lines such as HeLa and 293FT (**Figure 2**) [34].

2.3 Histone modifications and modifiers

Histones are a family of small, positively charged proteins that are responsible for packaging DNA into chromatin structures in eukaryotic cells. They play a crucial role in the organization and compaction of DNA, which is necessary to fit the long DNA molecules into the small nucleus of a cell. Histones are divided into five main classes: H1, H2A, H2B, H3, and H4, based on their sequence and structure. They contain a high proportion of positively charged amino acids, particularly lysine and arginine, which enable them to interact with the negatively charged DNA backbone

Nucleoside Analogue	Regulators	Ref
m⁶A	METTL3	(22)
	METTL14	
	METTL16	
	KIAA1429	
	RBM15	
m⁵C	NSun2	
	NSun1/3/7	
	NSun4	
	NSun5	
	NSun6	
m¹A	TRMT61B	
	TRM61	
	TRMT10C	
	TRMT6	
	ALKBH1/3	
	ALKBH3	
m³C	METTL6	
	METTL8	
m⁷G	METTL1-WDR4 complex	

Figure 2.
RNA methylation regulators and N⁶-methyladenosine (m⁶A). RNA methylation, particularly N6-methyladenosine (m⁶A) modification, is an essential post-transcriptional regulatory mechanism that affects RNA stability, splicing, localization, and translation. Several regulators have been identified that control the activity and expression of the m⁶A writer and eraser complexes, as well as other factors that affect m6A modification. These regulators can be classified into three main categories: (1) writer complex regulators, (2) eraser complex regulators, and (3) reader protein regulators. The m⁶A modification is added to RNA molecules by a complex of proteins known as the m⁶A writer complex, which includes methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and Wilms tumor 1-associating protein (WTAP). The m⁶A modification is removed by a complex of proteins known as the m6A eraser complex, which includes fat mass and obesity-associated protein (FTO) and alpha-ketoglutarate-dependent dioxygenase homolog 5 (ALKBH5). Writer complex regulators include proteins such as RNA-binding motif protein 15/15B (RBM15/15B), which enhances the activity of the writer complex, and heterogeneous nuclear ribonucleoprotein C (HNRNPC), which competes with the writer complex for RNA binding sites and can inhibit m⁶A modification. Eraser complex regulators include proteins such as insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), which stabilizes m6A-modified RNA and can protect it from eraser complex-mediated demethylation. Reader protein regulators include proteins such as YTH domain-containing proteins (YTHDFs), which bind to m6A-modified RNA and affect RNA stability and translation. The regulation of RNA methylation is a complex process that involves multiple factors, and a better understanding of these regulators and their interactions is critical for elucidating the functional roles of RNA methylation in various biological processes and diseases. Indeed, recent studies have shown that dysregulation of m⁶A modification and its regulators can contribute to various diseases, including cancer, neurological disorders, and viral infections. Therefore, to re-emphasize, understanding the mechanisms of RNA methylation and its regulation by different factors is crucial for developing novel therapeutic approaches targeting this pathway.

and form tight complexes. Histones can be modified by various post-translational modifications, such as acetylation, methylation, phosphorylation, ubiquitination, and sumoylation, which can affect their structure, function, and interactions with other proteins and DNA. These modifications are critical for regulating gene expression, DNA replication, DNA repair, and other cellular processes. Histone modification is an important post-translational process that plays a key role in gene expression. The modifications impact this gene expression by changing the structure of chromatin or through the recruitment of histone modifiers. The modification of histones, proteins that bind to the DNA, has been documented to be involved in the pathogenesis of autoimmune diseases, including rheumatoid

arthritis, systemic lupus erythematosus, systemic sclerosis, primary biliary cirrhosis, and type 1 diabetes. Basically, histones are highly basic proteins abundant in the lysine and arginine residues that are found in the eukaryotic cell nuclei. Histones act as spools around which the DNA winds to create the structural units called nucleosomes, which in turn are wrapped into fibers (30 nm) that form the tightly-packed chromatin. The DNA in the chromatin which is packed in a highly compact structure, and which is wrapped with histones where it forms a nucleosome structure; is also referred to as "beads on a string". This also helps in controlling the ability to access the DNA sequence [35]. Briefly, all histone octamer consists of tetramer two copies of histones 2A and also two copies of histones 2B, bounded by histone 4 and histone 3. There are five types of histones namely H2A, H2B, H3, H4, and H1 linker histone. These proteins generally consist of a C-terminal domain and a tail of a terminal N that results in post-translational modification are acetylation, phosphorylation, methylation, SUMOylation, citrullination, and also biotinylation at some of the specific amino acid group [36]. Among the post-translational modification, acetylation and methylation are the most studied on the residues H3 and H4 [37]. Histone modifications impact gene expression either via changing the structure or regulating the physical properties of chromatin or through the recruitment of histone modifiers (**Figure 3**).

HYDROXAMATE	ALIPHATIC ACID	BENZAMIDE	CYCLIC TETRAPEPTIDE	Ref
SUBEROYLANILIDE HYDROXAMIC ACID (SAHA, VORINOSTAT)	Valproic acid (VPA)	MGCD0103	Depsipeptide (FK228)	(46)
TRICHOSTATIN A	Baceca	MGCD0103 MS-275 (SNDX-275)	CHAPs	(14)
LAQ824, LBH589	Savicol		Apicidin	(47)
PXD101	AN-9 (prodrug)		Trapoxin A	
OXAMFLATIN, SCRIPTAID, SBHA	Phenylbutyrate		---	
SK-7041, SK-7068	---		---	
PYROXAMIDE	---		---	
TUBACIN	---		---	

Figure 3.
Examples of histone deacetylase inhibitors. Histone deacetylase inhibitors (HDAC inhibitors) are a class of compounds that interfere with the activity of histone deacetylases, which are enzymes that remove acetyl groups from histone proteins. By inhibiting these enzymes, HDAC inhibitors increase the acetylation of histones and other proteins, leading to changes in chromatin structure and gene expression. HDAC inhibitors have been studied for their potential therapeutic applications in various diseases, including cancer, neurodegenerative disorders, and inflammatory diseases. Some examples of HDAC inhibitors include: (1) Vorinostat (also known as SAHA): This was the first HDAC inhibitor to be approved by the US FDA for the treatment of cutaneous T-cell lymphoma. It works by inhibiting class I and II HDACs. (2) Romidepsin: This is another HDAC inhibitor that is approved for the treatment of cutaneous T-cell lymphoma. It works by inhibiting class I HDACs. (3) Belinostat: This is an HDAC inhibitor that is approved for the treatment of peripheral T-cell lymphoma. It works by inhibiting class I, II, and IV HDACs. (4) Panobinostat: This is an HDAC inhibitor that is approved for the treatment of multiple myeloma. It works by inhibiting class I, II, and IV HDACs. (5) Entinostat: This is an HDAC inhibitor that is being investigated for its potential use in breast cancer, lung cancer, and other types of cancer. It works by inhibiting class I HDACs. (6) Trichostatin A: This is a natural product that was the first HDAC inhibitor to be discovered. It works by inhibiting class I and II HDACs. These are just a few examples of the many HDAC inhibitors that have been developed and studied over the years. Each inhibitor has its unique characteristics, including its peculiar mechanism of action, target specificity, and potential therapeutic applications.

3. Role of histone modification and associated inhibitors in tumorigenesis

Cancer is a complex disease, and the first human disease to be correlated with epigenetic alterations. As mentioned throughout this chapter, it is today clear that epigenetics plays a key role in tumorigenesis (tumor development and metastasis) via the regulation (and control) of gene expression. This is mainly through DNA methylation, histone modifications (established and removed by the modifier enzymes: *writers* and *erasers*, respectively), histone variant incorporation, chromatin remodeling, and non-coding RNAs. Briefly, mutations within the chromatin remodeling complexes or the histones affect the cell phenotype, thereby, leading to various human diseases, including cancer. Indeed, with the promoter-targeted histone modification, the studies have recently shown that the modification of histones at the cellular level is highly related to the prognosis of cancer. The initial interest evolved when there was a histone modification derived from yeast [38], and all the patterns of the histone modification at the promoter to the expression of the gene in the yeast suggested that the histone can keep multiple biological information in the pattern of modification [39]. Histone modification takes place throughout the genome, and any possible changes if occur in the specificity or activity of the enzymes (which helps in the modification of the histones) can result in changes. Those are detectable at many specific modifications of the histones and at the level of the individual nuclei, in the process of immunostaining [40].

It is perhaps worth mentioning herein, that while there are several approved (by the US Food and Drug Administration or FDA) epigenetic-based drugs or *epi-drugs* to treat cancer with abnormal histone modifications, many are still in the pre- or clinical phase. Such indicates the need to better understand the regulatory pattern of epigenetics, especially histone modifications, in cancer. The modification of histones suggests replacing "histone code" to follow and maintain the interaction of histones with a protein associated with chromatin and allow all the downstream functions [41]. Consistently, the HATs enzymes which are known as the "writers" transfer the acetyl groups to some targeted lysine group and arginine group residues in the histone tails, which often results in the activation of the gene [42]. Also, the well-known "erasers" and the HDAC enzyme often delete the acetyl group from the histone tail and downregulate the targeted gene. The "writers" and "erasers" can modify the histones and control the silent and active state of chromatin and thus can transcriptionally control the transcription of all genetic information present in the DNA [43]. For treatment and clinical diagnosis, therapeutic targets are key [44]. Various modified drugs are useful to block cancer metastasis and the progression of the tumor via a major impact on the modification of histones, mainly via histone acetylation [45, 46]. Indeed, the dysregulation of histone modification enzymes plays an important role in tumorigenesis. Herein, miRNA acts directly on two pathways, the translational silencing mechanism, and the transcriptional silencing mechanism [47, 48]. In one of these cases, the miRNA ties up with the sequence, for example, mutation, and the regulation of the main gene gets out of control and can often result in chemo-resistance and tumorigenesis, subsequently [49]. For example, in ovarian cancer, the regulation of miRNA is downregulated and the let-7i resistance toward cisplatin is consequently increased with slower progression. The survival time for the patient decreases in the late stage of ovarian cancer [50] and the possible treatment for those patients is gene therapy; the only way to silence aberrant miRNA expression or restore the lost endogenous miRNA expression. Therefore, therapeutically, this can often be accompanied by an approved epi-drug [51]. Remember, both, acetylation or
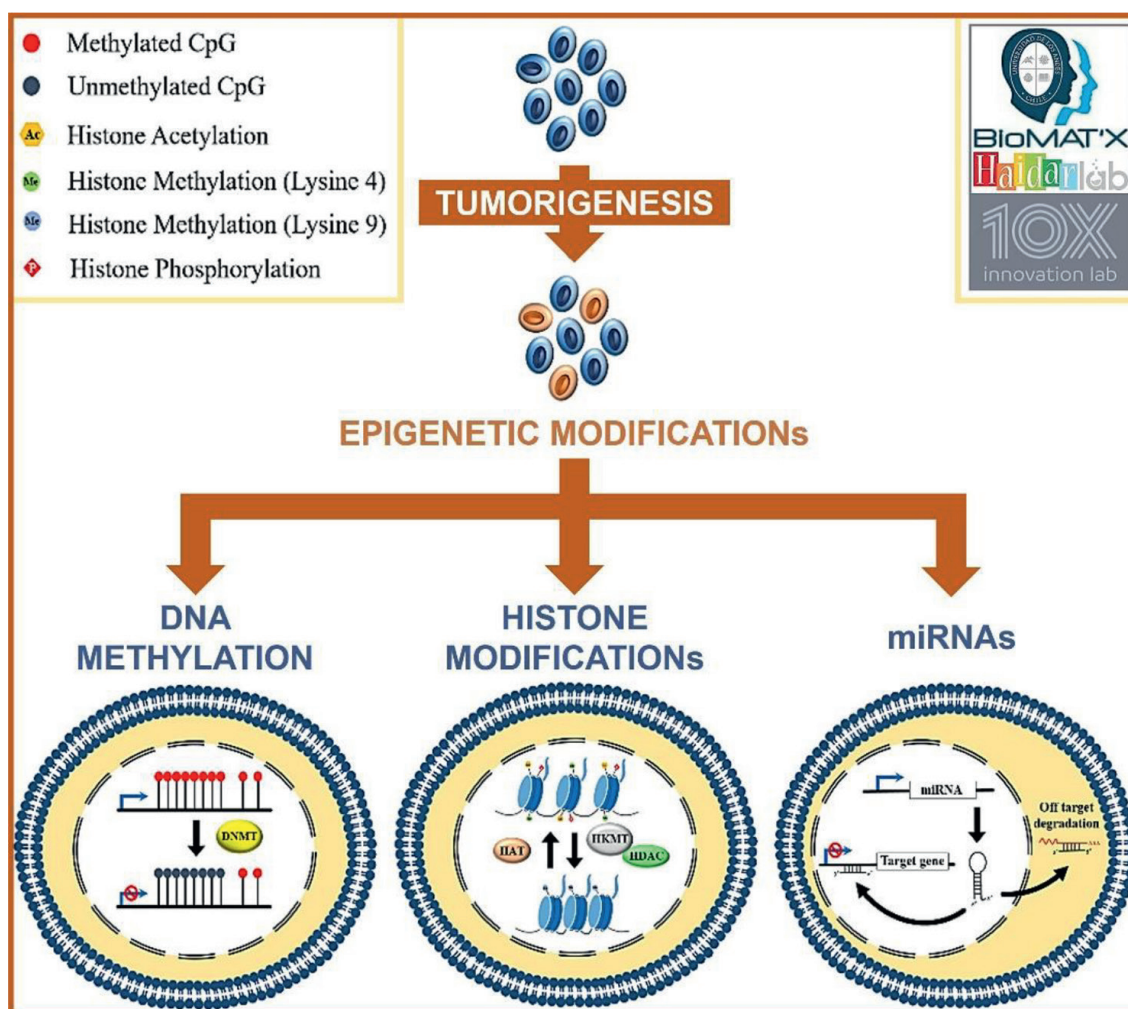
Figure 4.
Epigenetic regulation in tumorigenesis. Epigenetic regulation plays a critical role in tumorigenesis, which is the process of tumor formation. Alterations in DNA methylation, histone modifications, and non-coding RNA expression can lead to abnormal gene expression patterns that contribute to tumor development and progression. Epigenetic changes can affect various cellular processes, including cell proliferation, apoptosis, DNA repair, and immune response, among others. Additionally, epigenetic alterations are reversible, making them an attractive target for developing new cancer therapies. Hence, understanding the epigenetic changes associated with tumorigenesis is deemed crucial for identifying new targets for cancer treatment and developing personalized therapies based on the unique epigenetic profile of the patient.

deacetylation of histone proteins regulates gene expression, and the combination of epi-drugs together or with other inhibitors has displayed favorable clinical outcomes (**Figure 4**).

Histone modification is a key step in gene regulation that determines cell fate. For epigenetic therapy, the main target is chemo-resistant cells. DNA methylation that occurs at GHD CpG islands can often result in the inactivation of the transcriptional gene which is highly present in tumors. Inhibition of some enzymes such as DNMTs (which catalyze the methylation of the DNA), results in a decrease of the DNA methylating agent, and therefore re-activates the genes which are potentially anti-cancerous [52]. Modification of histones is un-altered via some special set of enzymes including the HDACs and HKMTs. Furthermore, targeting atypical hypo-acetylation through HDACi can result in and/or lead to the re-activation of the foregoing and transcriptionally inadequate chromatin [53]. Likewise, the suppression of the special atypical histone methyltransferases or HKMTs stops the methyl marks that may cause

gene repression; HP1 to H3K9me3, for example. Two vital processes of epigenetics are: histone modification and DNA methylation. Also, remember that atypical expression of miRNA (*21–23 nucleotides small and non-protein-coding RNAs*) has a direct connection with tumorigenesis [54]. Cancer is a complex and systemic disease instead of a single organ or tissue failure. Therefore, a single drug cannot solely treat or cure the tumor completely; often resulting in tumor recurrence or resistance. Precision oncology medicine is the hope.

4. Mechanisms of acquired anti-tumor and -cancer drug resistance

Resistance to anti-cancer drugs can be acquired by several mechanisms within neoplastic cells. Some include the alteration of drug targets, expression of drug pumps, expression of de-toxification mechanisms, reduced susceptibility to apoptosis, and increased ability to repair DNA damage, among others. Similarly, anti-tumor drug resistance of cancer cells is chiefly acquired through one of the three mechanisms of (a) mutation in gene, (b) gene expression increase, and (c) decrease in gene expression [55]. An example of anti-tumor drugs is the PI (Protease Inhibitor)-based drugs which act by inhibiting important cell signaling pathways [56]. Mono-therapy with PI has failed miserably, nonetheless, in patients with multiple myeloma (MM), for instance, due to the development of slow drug tolerance. It is also a common observation that many ovarian cancer patients treated with only platinum-based drugs do change into refractory cancer from being advanced and recurrent [57]. It has also been reported that cisplatin resistance is associated with hypomethylation of CpG sites in the first intron of S100A4 [58]. Anti-tumor drug resistance is associated with down-regulation of tumor protein p53 (TP53) and interferon regulatory factor 1 (IRF1) and activation of HDAC [59]. Hence, to avoid the development of drug tolerance in MM patients combination therapy (HDAC inhibitors + PI-based therapy) has shown an overall good therapeutic effect and negated the drug tolerance pathways [60]. Remember that resistance can occur when even a small group of cancer cells within a tumor contain or undergo molecular changes rendering them insensitive to a or any specific drug before the oncology treatment even begins (**Figure 5**).

5. Targeting of epigenetic modifiers via acting against drug resistance

Today, despite the availability of several potential drugs targeting HDACs (histone deacetylases) and DNMT/HMT (DNA/histone methyltransferases) for treating a wide range and types of cancers; yet, are often limited in efficacy to function only at certain stages of the disease. Indeed, in some cases and even after the drug treatment, the reversible nature of methylation persists. Hence why, recent studies tend to increasingly emphasize the need to develop novel drugs capable of specifically targeting the HDACs and DNMT inhibitors as an emerging bio-effective anti-cancer strategy. On the other hand, there are several studies that have proved that mutation in a gene, and modification in the epigenetics do play a very vital role in chemo-resistance in the cells which are infested by cancer [61]. The alterations in the epigenetic are very much reversible and must be maintained by epigenetic modifiers rendering them a good target for therapeutic interference [62, 63]. The recent research and understanding of the CSC epigenome provide a new perception of anti-cancer therapy which is much targeted by many epigenetic drugs to overcome
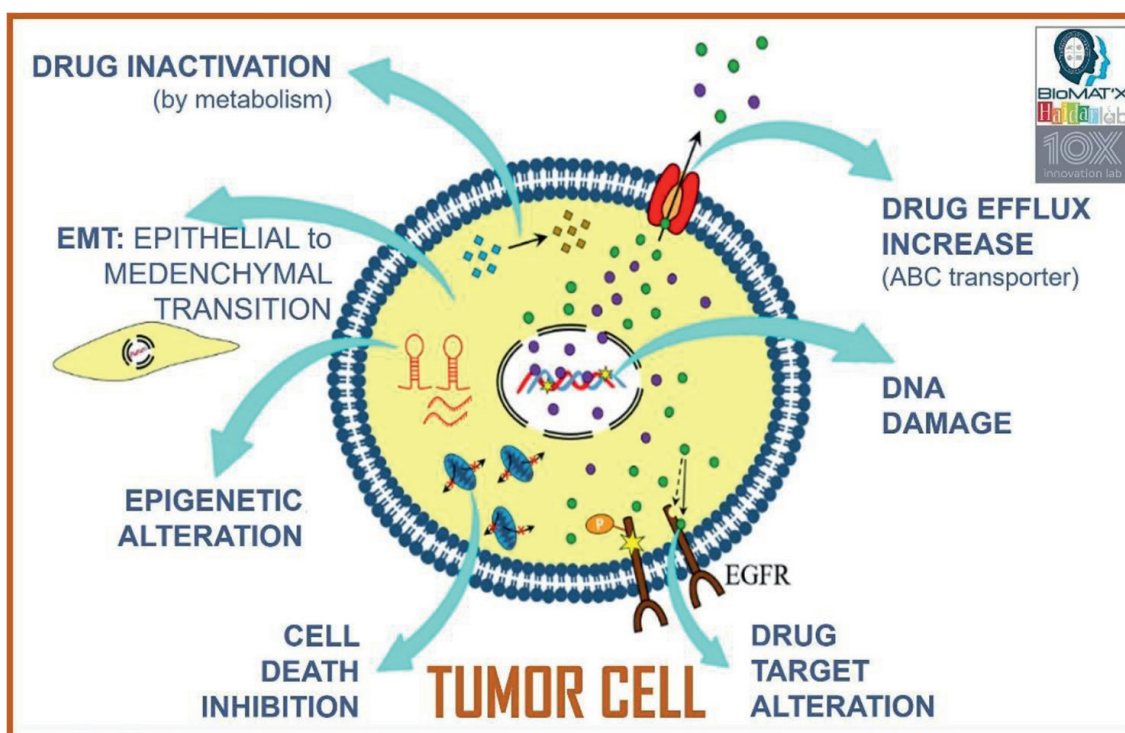
Figure 5.
Epigenetic modifications can be tumorigenic and contribute to the development and progression of cancer. The study of epigenetic modifications in cancer has revealed new insights into the molecular mechanisms of tumorigenesis, as well as potential biomarkers for cancer diagnosis, prognosis, and treatment. Epigenetic changes can affect key pathways involved in DNA damage response, cell cycle regulation, and immune surveillance, leading to genomic instability and immune evasion. Furthermore, epigenetic changes can drive cancer cell heterogeneity, making tumors more resistant to therapy. The reversibility of epigenetic changes makes them an attractive target for developing new and innovative translational cancer therapies. However, there are still significant challenges to developing effective epigenetic therapies, including identifying specific epigenetic targets and minimizing off-target effects. Understanding the complex interplay between epigenetic modifications and cancer is deemed crucial for developing new strategies to prevent, diagnose, and treat cancer. Indeed, it is worth noting that epigenetic modifications are not always tumorigenic and can play essential roles in normal cellular processes, including development and differentiation. Remember that epigenetic regulation is a complex and dynamic process that involves the interplay of various enzymes, chromatin-associated proteins, and non-coding RNAs. The dysregulation of these epigenetic regulators can lead to aberrant gene expression patterns that contribute to tumorigenesis. Therefore, identifying the specific epigenetic modifications that contribute to cancer development and progression is henceforth deemed critical for developing novel targeted therapies that can "selectively" reverse these changes and later, restore normal cellular function.

resistance toward CSC drugs [64], as mentioned earlier. Accruing research tends to show that drugs with epigenome modifying capabilities or epi-drugs, alone or combined with other treatments may/can modify the epigenetic treatment and decrease the resistance toward the drug. Also, drugs which have the capability to alter the genome are "non-specific" in nature and can affect the expression of the global-gene, with increasing evidence in the literature that such drugs can make changes in gene expression depending on the chromatin environment [65]. Furthermore, other studies demonstrated that the sensitivity toward epigenetic alternators can be genomic loci specific depending upon the three-dimensional structure of the chromatin itself [66]. As noted earlier, there are various epigenetic modifiers which are mostly used in the present-time anti-cancer therapy clinical trials and research, i.e., HDACs, DNMTs, and HMTs [67]. Noteworthy that various inhibitors used for HDACs, DNMTs, histone demethylases (HDMs), HMTs and bromodomain proteins are generally, in clinical trial studies, used in combination with or without chemotherapy [68].

6. Conclusions

Cancer is a complex disease. For carcinogenesis and tumorigenesis, epigenetic changes are fundamental mechanisms and can serve as potential methods for early detection, treatment, and prognostic assessment for our oncology patients. Epigenetics was first introduced by Conrad Waddington in 1942 to define stable and heritable changes in the cell phenotype and gene expression without genetic alterations or DNA sequence. Today, epigenetic modifications and processes include DNA and RNA methylation, histone covalent modifications, chromatin remodeling, and the effect of non-coding RNAs and polycomb proteins in gene expression. Herein, and in the landscape of epigenetics, the methylation of DNA and RNA and modifications of histone in the cancerous cells may be responsible for drug resistance and the recurrence of cancer. While epigenetic changes may be used as tools to diagnose, treat, and provide prognostic information for our cancer patients, a better understanding of such mechanisms associated with epigenetic modifications; an ongoing investigation and research effort, will eventually not only result in the development of new epigenetic bio-markers capable of early detection of tumors and the maintenance of continuous surveillance but also in the identification of distinct epigenetic profiles that will corroborate to the identification of prognostic tools and a potential predictor of tumor response to therapy. Further, as we move toward personalized and precise medicine, it is important to remember that the genetic material is identical in every cell, while epigenetics is highly variable within different cells and tissues of an organism and is also affected by aging and environmental factors. Herein, identifying and validating such novel epigenetic modifications associated with cancer chemoresistance, in clinical studies, cannot be underestimated. Together, the discovery of new epigenetic biomarkers for individual cancer chemo-resistance can and will open the possibility for the development of novel epi-drugs, which can be used as an adjuvant therapy associated with conventional chemotherapeutic drugs, enhancing tumor sensitivity to traditional agents and ultimately increasing therapeutic efficacy. Regardless of the type or location of the cancer, epigenetic modifications induced by epi-drugs, aligned with the prospective identification of epigenetic biomarkers, are an exciting frontier in cancer biology, awaiting to be explored.

Conflict of interest

The author declares no conflict of interest.

Notes/thanks/other declarations

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Author details

Ziyad S. Haidar
BioMAT'X (HAiDAR R&D&I LAB) I+D+i Labratory, Biomedical Research
and Innovation Center/Centro de Investigación e Innovación Biomédica (CiiB),
Faculties of Medicine and Dentistry, Universidad de los Andes, Las Condes,
Santiago, Chile

*Address all correspondence to: zhaidar@uandes.cl; zhaidar78@gmail.com

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