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Epigenetic Modifications: Basic Mechanisms in Normal and Cancerous Cells

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Abstract

Epigenetics is one of the most rapidly expanding fields in biology that refers to the somatically heritable differences in gene expression that are not coded in the DNA sequence itself and work with genetic mechanisms to determine transcriptional activity. Aberrant epigenetic modifications including, DNA methylation, histone modifications, and small noncoding microRNAs (miRNA), probably occur at a very early stage in neoplastic development, and they are widely described as important players in cancer progression. However, the reversible nature of epigenetic alternations has encouraged the development of pharmacologic inhibitors as anti-cancer therapeutics. In this case, histone deacetylase inhibitors and DNA methylation inhibitors have been FDA-approved for several years and are clinically successful. In this article, we review the mechanisms of each epigenetic modification in both normal and tumor cells. Also, the potential of epigenetic alternations as a new emerging target in cancer therapy has been discussed.

Keywords: Epigenetics, Epigenetic modifications, Cancer, Epigenetic therapy

Introduction

The term ‘epigenetics’ defines all heritable changes in gene expression and chromatin organization that is not coded in the DNA sequence itself (Egger et al., 2004). Recent progresses have highlighted the key role of epigenetic mechanisms in ensuring the appropriate control of biological processes, such as imprinting, X chromosome inactivation, or the establishment and maintenance of cell identity (Altucci & Minucci, 2009). Epigenetic inheritance is an essential mechanism that allows the stable propagation of gene activity states from one generation of cells to the next (Herceg, 2007). Methylation of DNA, chemical modification of the histone proteins, and RNA-dependent regulation have been investigated as important mechanisms of epigenetic regulation.

Traditionally, cancer has been viewed as a genetic disease, and it is now becoming apparent that the onset of cancer is preceded by epigenetic abnormalities. All critical changes in every aspect of tumor biologies such as cell growth and differentiation, cell cycle control, DNA repair, angiogenesis, and migration, are caused not only by genetic but also by epigenetic mechanisms (Sharma et al., 2010). The genetic origin of cancer is widely accepted; however, recent studies suggest that epigenetic alterations may be the key initiating events in some forms of cancer. These findings have led to a global initiative to understand the role of epigenetics in the initiation and propagation of cancer.

In addition, epigenetic alternations, unlike genetic mutations, with changeable nature can be restored to their normal state (Jones & Martienssen, 2005; Yoo & Jones, 2006). They are reversible by pharmacological manipulation of the enzymes responsible for chromatin modification: indeed, epigenetic drugs (histone deacetylase inhibitors and DNA demethylating agents) are currently on the market, inducing proliferative arrest and death of tumor cells (Altucci & Minucci, 2009). In this review, we take a comprehensive look at the current epigenetic mechanisms in normal cells and their comparative aberrations that occur during carcinogenesis. We also discuss the great potential lies in the development of epigenetic therapies for some malignancies.

1- Epigenetic features

Chromatin is organized by repeating units of nucleosomes, which consist of 145_147 base pairs of DNA wrapped around an octamer of two copies of each histone protein (H3, H4, H2A, and H2B) (Luger et al., 1997). Despite the stability of the nucleosome and the high degree of compactness of the nucleus, chromatin is astonishingly dynamic. Epigenetic modifications include DNA methylation, histone modifications, and non-coding RNAs such as microRNAs (miRNAs) can be modified chromatin structure. The N-terminal tails of the histone proteins are protruding out from the nucleosomal core particles, and these tails serve as regulatory registers onto which epigenetic signals can be written. (Lund & van Lohuizen, 2004). Due to their impact on the genome, epigenetic modifications are involved in the regulation of many pathways including apoptosis, cell proliferation, and differentiation (Miceli et al., 2014; Sharma et al., 2010). Additionally, epigenetic aberrations, including global hypomethylation and miRNA deregulation, as well as promoter hypermethylation and deacetylation have been displayed in many human cancer types (Taby & Issa, 2010).

1.1. DNA methylation

DNA methylation was the first epigenetic modification found in humans in the early 1980s (Cooper, 1983). DNA methylation, the covalent addition of a methyl group to the cytosine base in DNA, has been recognized as a critical regulatory mechanism during development, cellular differentiation, and tissue homeostasis. It has been connected to different physiological and pathological processes, including genomic imprinting, X chromosome inactivation in females, tissue-specific gene expression, chromosome stability, and a number of abnormalities, including cancer (Bernstein et al., 2007; Hathaway et al., 2012; Kanwal & Gupta, 2010). In humans, DNA methylation occurs in the C^5 position of cytosines that precede guanines (CpGs) which are catalyzed by DNA methyltransferases (DNMTs) using S-adenyl methionine (SAM) as the methyl donor (Herman & Baylin, 2003; Ohm et al., 2007). Three enzymes are involved in the generation and maintenance of DNA methylation patterns. DNMT1 has a strong preference for hemimethylated CpG dinucleotides, thus can methylate CpG in a newly synthesized DNA strand based on the presence of methylation in the complementary template (Roberti et al., 2019) and Dnmt3a and Dnmt3b, defined as a de novo methyltransferase, show no preference for hemimethylated target sites and are present mainly in the early development stages and germ cells, whereas they are largely suppressed in the differentiated somatic cells (Wang & Shen, 2004) The majority of CpG dinucleotide are concentrated within CpG-rich DNA regions known as "CpG islands" that have been evolutionarily conserved to promote gene expression by regulating the chromatin structure and transcription factor binding (Bennett & Licht, 2018; Ramirez-Carrozzi et al., 2009). The methylation of CpG islands results in stable silencing of gene expression. During gametogenesis and early embryonic development, CpG islands undergo differential methylation and regulate gene expression during development and differentiation. As CpG islands are associated with the control of gene expression, it would be expected that CpG islands might display tissue-specific patterns of DNA methylation (Meissner et al., 2008; Moore et al., 2013). Fully methylated CpG islands in the silenced allele for specific imprinted autosomal genes and multiple silenced genes on the female inactivated X chromosome and deacetylation of histone proteins is the first step in the recruitment of methyltransferase to the CpG islands, resulting in hypermethylation of the promoter, which are two critical roles of DNA methylation that have been reported (Verma & Srivastava, 2002).

A vast amount of knowledge has been gained in the last few years about altered methylation patterns, both hyper- and hypo-methylation, in many different types of cancers including prostate, breast, gastric, liver, lung, glioblastoma, and leukemia (Park & Han, 2019). There are two types of general changes in DNA methylation that occur in tumor cells in comparison to normal cells of the same tissue type:

demethylation within many regions of the genome in coordination with de novo methylation of select CpG islands. Much of the hypomethylation is concentrated within broad late-replicating Lamin-associated domains that make up about 40% of the genome and contain many repetitive sequences. More striking is hypermethylation of a wide range of CpG islands that are usually unmethylated in every tissue that this occurs widely at promoters of tumor suppressor genes that cause uncontrolled growth cancerous cells (Klutstein et al., 2016; Siegfried et al., 1999). Tumor-specific methylation changes in different genes have been identified and documented. Despite no evidence of clearly identified actors in DNA demethylation, alteration of global DNA methylation patterns in cancer is often associated with an over-expression of DNMTs as described in various tumors (Akhavan-Niaki & Samadani, 2013). The exact degree of overexpression of DNMTs in tumors remains unclear but a low-level over-expression seems to be common (Delpu et al., 2013). Current studies have shown that the duplication of the DNMT3b gene in different cancer cell lines where copy number correlates to increased mRNA and protein levels, also, DNMT3b over-expression occurs through the stabilization of its mRNA in human colorectal carcinoma (López de Silanes et al., 2009; Simó-Riudalbas et al., 2011)

1.2. Histon Modifications

Histones are highly conserved small basic proteins that are found exclusively in eukaryotic cells, predominantly in the nucleus. Histones –and especially their N-terminal "tails" are recognized as being dynamic regulators of gene activity that undergo many post-translational chemical modifications, including acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation. Histone modifications have been linked to a number of chromatin-dependent processes, including X chromosome inactivation, genome stability, and meiotic chromosome dynamics (Esteller, 2007; Goll & Bestor, 2002; Xhemalce et al., 2006). Given the number of sites and the variety of possible modifications, the combinatorial possibilities are extremely large and it is tempting to believe that histone modification has a regulatory role (Lagger et al., 2002). It has been found that individual modifications can be associated with transcriptional activation or repression. Acetylation and phosphorylation generally accompany transcription, methylation, and ubiquitination are implicated in both activation and repression of transcription (Karlić et al., 2010).

1.2.1. Histon acetylation

Among all histone modifications, the status of acetylation and methylation of specific lysine residues have a crucial role in regulating chromatin structure and gene

expression (Esteller, 2007). Histone acetylation is catalyzed by a number of enzymes that act on the four core histones and transfer the acetyl moiety from Acetyl-CoA to the ε-amino group of lysine residues (HATs). Histone acetylation is generally associated with transcription activation due to destabilizing nucleosomes and promoting both nucleosomal rearrangements of chromatin remodeling complexes and binding of a diverse set of DNA-binding factors involved in transcription, DNA repair, and other processes (Fuchs et al., 2009). On the other hand, histone deacetylase enzymes (HDACs) are associated with nucleosome stabilization and repression of remodeling activities so, are generally thought to act in a repressive manner (Kurdistani & Grunstein, 2003).

More recently, an increasing number of disease processes have been observed to involve abnormalities of acetylating and deacetylating cellular events. Recent studies have been illustrated that a decrease in the amount of functionally available HDACs or an increase of functionally active HAT enzymatic activities affects the conformation and activity of associated transcription factors. As a consequence, genes that were previously silenced may now be activated or even overexpressed, whereas other genes, which were previously expressed, may now secondarily be repressed (Mahlknecht & Hoelzer, 2000)

1.2.2. Histone Methylation

Histone methylation, perhaps more than any other form of modification, has demonstrated an essential role in diverse biological processes ranging from transcriptional regulation to heterochromatin formation (Bannister & Kouzarides, 2005). Histones may be methylated on lysine (K), arginine (R), and/or histidine (H) residues using S-adenosylmethionine (SAM or AdoMet) as a methyl group donor. At present, there are 24 known sites of methylation on histones which 17 are lysine residues and 7 are arginine residues (Kim et al., 2014; Margueron et al., 2005). While the methylation of histidine is one of the rare histone modifications and has not been well characterized (Greer & Shi, 2012), Lysine methylation of histones is a remarkable and complex epigenetic mark that makes up both transcriptionally silenced and active chromatin domains, depending on which lysine residues are methylated and the degree of methylation (Greer & Shi, 2012). Lysine methylation has three methyl additions including mono-(H3K9me1), di-(H3K9me2), and tri-(H3K9me3) that each level of methylation produces different outcomes (Martin & Zhang, 2005). Among different types of lysin methylation including histone H3 lysine 4 (H3K4), H3K9, H3K27, H3K36, H3K79, and H4K20, histone H3K9 and H3K27 methylation is associated with silenced regions, whereas H3K4 and H3K36 methylation is correlated well with active genes (Berger, 2007; Tan et al., 2011). Arginine is another residue that can be mono(me1) symmetrically dimethylated

(me2s), or asymmetrically dimethylated(me2a) on their guanidinyl group (Greer & Shi, 2012).

The steady-state level of a covalent histone modification is controlled by a balance between enzymes that catalyze the addition and removal of a given modification. Although this notion is generally true for many histone modifications, an enzyme capable of removing methyl groups from a methyl-lysine residue has remained elusive, until recently (Tsukada et al., 2006). Histone demethylases, first described by Shi et al, have the opposite effect on transcription. The histone demethylase LSD1 is responsible for H3K4 demethylation, which leads to transcriptional inactivation. However, when LSD1 forms a complex with androgen receptors, it demethylates H3K9 and activates transcription. Other histone demethylases, such as JHDM1, can convert active chromatin marks H3K36me2 to an unmodified state (Bártová et al., 2008).

Aberrant histone modifications are known to play a key role in the pathogenesis of several human diseases such as cancer (Shanmugam et al., 2018). Promoters carry on important regulatory sequences for transcription control of their genes. Generally, the vast majority of deregulation of histone modifications at an individual promoter is intimately linked to misexpression of the downstream gene, which may have critical consequences for the cancer phenotype (Kurdistani, 2011). In this case, loss of trimethylation of H4K20 was identified as one of the common hallmarks of human cancers (Huang et al., 2017). Also, high levels of H3K27me2/3, and H3K79me3, as well as modest levels of H3K9me2/ 3 are linked to gene repression or silencing (Kanwal & Gupta, 2010). In addition, altered global levels of histone acetylation, particularly acetylation of H4K16, have been linked to a cancer phenotype in a variety of cancers. While gene expression especially in proto-oncogene can be activated by hyperacetylation, hypoacetylation of tumor suppressors often localizes to promoters, co-occurring with DNA methylation, causing the genes to be silenced (Audia & Campbell, 2016).

1.3. MicroRNAs

MicroRNAs (miRNA) comprise a class of short non-coding RNAs with 18–25 nucleotides in length that can have a profound effect in controlling gene expression post-transcriptionally (Chuang and Jones, 2007). miRNAs are involved in RNA interference (RNAi) machinery and they contribute to diverse physiological and pathophysiological functions, including the regulation of developmental timing and pattern formation, restriction of differentiation potential, cell signaling, and carcinogenesis (Sato et al., 2011). The transcription of most miRNA genes is mediated by RNA polymerase II (Pol II) and the primary transcripts (pri-miRNAs)

are usually several kilobases long and contain local stem-loop structures and are then processed in the nucleus by the RNase III Drosha and DGCR8 into the precursor miRNAs (pre-miRNAs) (Chuang and Jones, 2007, Kim et al., 2009). Pre-miRNAs are then processed by the RNAse III Dicer to generate a double-stranded (ds)RNA approximately 22 nucleotides long. After generation of the miRNA duplex, one strand (the miRNA-guide strand) is loaded onto the RNA-induced silencing complex (RISC) that is able to modulate the expression of target protein-coding mRNAs by base-pairing to partially complementary regions frequently located at the 3'-untranslated regions (3'-UTR) of the target transcript (Malumbres, 2013; Romero-Cordoba et al., 2014). It has been investigated that an individual miRNA can dramatically control the expression of more than one target mRNAs and that each mRNA may be regulated by multiple miRNAs (Cai et al., 2009). Several studies have reported links between aberrant miRNA expression and several aspects of cellular function from proliferation and differentiation to apoptosis (Ha, 2011).

In 2002, the role of miRNAs in cancer was suggested by Croce and colleagues with the discovery that regions of miR-15 and miR-16 frequently deleted in chronic lymphocytic
leukemia (CLL). Recently, deregulation of miRNAs has been definitively linked to the initiation and progression of tumorigenesis and the role-play of miRNAs have been investigated in many types of human cancer, including breast, colon, gastric, lung, prostate, and thyroid (Ha, 2011; Hatziapostolou & Iliopoulos, 2011; Reddy, 2015). Recent researches have been illustrated that in different types of cancers, particular miRNAs may show oncogenic or tumor-suppressive function. For instance, miR-29 was reported as an oncogene in breast cancer while acting as a tumor-suppressor gene in lung tumors. Additionally, loss of miRNA-23b caused migration and invasion in bladder cancer cells while decreasing the expression of miRNA-23b induced apoptosis and reduced invasive capabilities in renal cell carcinoma cell lines (Campos-Viguri et al., 2015; Reddy, 2015; Zaman et al., 2012).

In addition, miRNAs can both regulate and be regulated by other epigenetic mechanisms. In this case, dysregulation of miR-101 leads to reduced H3K27me3 and inhibits cancer cell proliferation. Expression of miR-143 in colorectal cancer cells and the miR-29 family in lung cancer cells reduces DNMT3A and DNMT3B levels, respectively, and consequently, cell growth and colony formation were decreased (Fabbri et al., 2007; Kelly et al., 2010; Ng et al., 2009).

Recently, miRNAs have been recommended as epigenetic biomarkers in the diagnosis of cancer. For example, miR-199a, miR-200a, miR-146, miR-214, miR-221, and miR-222 have been investigated to be overexpressed, whereas miR-100 is down-regulated in human cancers. Furthermore, 27 miRNAs are noticeably related

to chemotherapy response and consider as possible prognostic and diagnostic biomarkers (Kanwal & Gupta, 2012; Paranjape et al., 2009; Peter, 2009).

1.4. Epigenetic Therapy

Unlike stable genetic mutations, epigenetic modifications like DNA methylation and histone modifications have reversible nature (Ali et al., 2015). This fundamental difference between genetic and epigenetic alterations makes the epigenome much more amenable to the development of therapeutic strategies (Altucci & Minucci, 2009). The so-called epi-drugs are an elevating exciting field in anticancer research and therapy (Miceli et al., 2014). Epigenetic modifier drugs capable of reversing aberrant DNA methylation and histone acetylation patterns by inhibiting DNMTs and HDACs have been extensively discovered (Kristensen et al., 2009). The first successful drugs developed as epigenetic agents were DNA methyltransferase inhibitors; these were followed by histone deacetylase inhibitors (HDIs) (Yanis Boumber & Issa, 2011). DNA demethylating drugs, 5-azacytidine (Vidaza), and 5-aza-2′- deoxycytidine (decitabine) have been approved in 2004 and 2006 for myelodysplastic syndrome and leukemia (Yang et al., 2006). These small molecules are analogues of cytidine and they inhibit DNA methylation by the irreversible inhibition of DNMTs, causing hypomethylation of DNA, and reactivation of silenced genes (Platzbecker et al., 2012). DNMT inhibitors can be subdivided into three groups, nucleoside analogue, non-nucleoside analogue, and antisense oligonucleotides, based on their structures and functions (Peedicayil, 2006). While the first group of DNMT inhibitors is, S-phase specific drugs, phosphorylated to the deoxynucleotide triphosphate and then incorporated instead of cytosine into replicating DNA and inhibit DNMTs (Egger et al., 2004), the non-nucleoside analogue like RG108 is DNMT inhibitor that designed to target human DNMT1 at its active site without high levels of cytotoxicity and affecting the methylation status of centromeric repeats (Graça et al., 2014). Antisense oligonucleotides as a third group of DNMT inhibitors can block translation by inactivation of mRNA through complementary hybridization (Yan et al., 2003).

Histone deacetylase (HDAC) inhibitors belong to a group of small-molecule drugs that induce a broad range of effects on cancer cells, including cell cycle arrest, apoptosis, cell differentiation, autophagy, and anti-angiogenic effects (Khan & La Thangue, 2012). Targeting HDACs is more complex than targeting DNA methyltransferases because this group of proteins has multiple subclasses with mechanisms of action still under contention (Azad et al., 2013). However, the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) was approved in 2006 for the treatment of persistent or cutaneous T cell lymphoma (Moufarrij et al., 2019).

Recently, regarding the parallel function of DNA methylation and histone modifications, is now being paid to testing combinations of drugs, which may increase the efficacy of each of the single agents. For example, the combination of HDACi and DNMTi can elevate the expression levels of tumor suppressor genes (Jones et al., 2019). Furthermore, combining conventional cancer therapies including chemotherapy and radiotherapy with the use of epigenetic therapy, reversing the changes of DNA methylation and histone acetylation patterns, holds a huge potential for successful treatment of hematological malignancies as well as solid tumors that may allow for lower dosing which can minimize side effects of treatment improving quality of life and treatment compliance (Kelly et al., 2010; Kristensen et al., 2009).

However, deeper understandings of the global patterns of these epigenetic modifications and their corresponding changes in cancer have enabled the design of better treatment strategies.

Conclusion

The recognition of epigenetics as a significant contributor to normal development and disease has opened new avenues for drug discovery and therapeutics. In this paper, we have summarized the complex epigenetic regulatory pathways in normal cells. Also, the key role of DNA methylation, histone modification, and miRNAs as epigenetic modifications in cancer progression and therapeutics were reviewed. Based on the above, epigenetic alterations in comparison with genetic changes are reversible and are typically acquired in a gradual manner. Given that the epigenetic changes induced by DNMTs and HDACi are transient and reversible, a number of studies are ongoing to help define the optimal doses and treatment schedules for these agents. Besides their methylation and acetylation, histones can be phosphorylated, ubiquitylated, and sumoylated. These modifications, which have been less well studied in the context of disease, may expand current possibilities for therapeutic intervention. So, the integration of the latest advances in epigenomic approaches like whole-genome microarray expression profiling and chromatin immunoprecipitation-based sequencing (ChIP-seq) methods will be allow mapping of all types of histones and DNA modification's state and miRNA levels in the genome with high accuracy, which will be helpful in the identification of biomarkers and the development of epigenetic drugs with greater specificity.

References

Akhavan-Niaki, H. & Samadani, A. A. (2013). DNA methylation and cancer development: molecular mechanism. Cell biochemistry and biophysics, 67, 501-513.

Ali, M., Hanif, M. & Farooqi, A. A. (2015). Epigenetic therapy for cancer. Pak. J. Pharm. Sci, 28**,** 1023-1032.

Altucci, L. & Minucci, S. (2009). Epigenetic therapies in haematological malignancies: searching for true targets. European Journal of Cancer, 45, 1137-1145.

Audia, J. E. & Campbell, R. M. (2016). Histone modifications and cancer. Cold Spring Harbor perspectives in biology, 8, a019521.

Azad, N., Zahnow, C. A., Rudin, C. M. & Baylin, S. B. (2013). The future of epigenetic therapy in solid tumours—lessons from the past. Nature reviews Clinical oncology, 10**,** 256-266.

Bannister, A. J. & Kouzarides, T. (2005). Reversing histone methylation. Nature, 436, 1103-1106.

Bártová, E., Krejčí, J., Harničarová, A., Galiová, G. & Kozubek, S. (2008). Histone modifications and nuclear architecture: a review. Journal of Histochemistry & Cytochemistry, 56, 711-721.

Bennett, R. L. & Licht, J. D. (2018). Targeting epigenetics in cancer. Annual review of pharmacology and toxicology, 58, 187-207.

Berger, S. L. (2007). The complex language of chromatin regulation during transcription. Nature, 447, 407-412.

Bernstein, B. E., Meissner, A. & Lander, E. S. (2007). The mammalian epigenome. Cell, 128**,** 669-681.

Cai, Y., Yu, X., Hu, S. & Yu, J. (2009). A brief review on the mechanisms of miRNA regulation. Genomics, proteomics & bioinformatics*,* 7, 147-154.

Campos-Viguri, G. E., Jiménez-Wences, H., Peralta-Zaragoza, O., Torres-Altamirano, G., Soto-Flores, D. G., Hernández-Sotelo, D., Alarcón-Romero, L. D. C., Jiménez-López, M. A., Illades-Aguiar, B. & Fernández-Tilapa, G. (2015). miR-23b as a potential tumor suppressor and its regulation by DNA methylation in cervical cancer. Infectious agents and cancer, 10, 1-10.

Chuang, J. C. & Jones, P. A. (2007). Epigenetics and microRNAs. Pediatric research, 61**,** 24-29.

Cooper, D. N. (1983). Eukaryotic DNA methylation. Human genetics, 64, 315-333.

Delpu, Y., Cordelier, P., Cho, W. C. & Torrisani, J. (2013). DNA methylation and cancer diagnosis. International journal of molecular sciences, 14, 15029-15058.

Egger, G., Liang, G., Aparicio, A. & Jones, P. A. (2004). Epigenetics in human disease and prospects for epigenetic therapy. Nature, 429, 457-463.

Esteller, M. (2007). Cancer epigenomics: DNA methylomes and histone-modification maps. *Nature reviews genetics,* 8, 286-298.

Fabbri, M., Garzon, R., Cimmino, A., Liu, Z., Zanesi, N., Callegari, E., Liu, S., Alder, H., Costinean, S. & Fernandez-Cymering, C. (2007). MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. Proceedings of the National Academy of Sciences, 104, 15805-15810.

Fuchs, S. M., Laribee, R. N. & Strahl, B. D. (2009). Protein modifications in transcription elongation. Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms, 1789, 26-36.

Goll, M. G. & Bestor, T. H. (2002). Histone modification and replacement in chromatin activation. Genes & development, 16, 1739-1742.

Graça, I., J Sousa, E., Baptista, T., Almeida, M., Ramalho-Carvalho, J., Palmeira, C., Henrique, R. & Jerónimo, C. (2014). Anti-tumoral effect of the non-nucleoside DNMT inhibitor RG108 in human prostate cancer cells. Current pharmaceutical design, 20, 1803-1811.

Greer, E. L. & Shi, Y. (2012). Histone methylation: a dynamic mark in health, disease and inheritance. Nature Reviews Genetics, 13, 343-357.

Ha, T.-Y. (2011). MicroRNAs in human diseases: from cancer to cardiovascular disease. Immune network, 11, 135-154.

Hathaway, N. A., Bell, O., Hodges, C., Miller, E. L., Neel, D. S. & Crabtree, G. R. (2012). Dynamics and memory of heterochromatin in living cells. Cell, 149, 1447-1460.

Hatziapostolou, M. & Iliopoulos, D. (2011). Epigenetic aberrations during oncogenesis. Cellular and Molecular Life Sciences, 68, 1681-1702.

Herceg, Z. (2007). Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. Mutagenesis, 22, 91-103.

Herman, J. G. & Baylin, S. B. (2003). Gene silencing in cancer in association with promoter hypermethylation. New England Journal of Medicine, 349, 2042-2054.

Huang, T., Lin, C., Zhong, L. L., Zhao, L., Zhang, G., Lu, A., Wu, J. & Bian, Z. (2017). Targeting histone methylation for colorectal cancer. Therapeutic advances in gastroenterology, 10, 114-131.

Jones, P. A. & Martienssen, R. (2005). A blueprint for a human epigenome project: the AACR human epigenome workshop. Cancer research, 65, 11241-11246.

Jones, P. A., Ohtani, H., Chakravarthy, A. & De Carvalho, D. D. (2019). Epigenetic therapy in immune-oncology. Nature Reviews Cancer, 19, 151-161.

Kanwal, R. & Gupta, S. (2010). Epigenetics and cancer. Journal of applied physiology, 109, 598-605.

Kanwal, R. & Gupta, S. (2012). Epigenetic modifications in cancer. Clinical genetics, 81, 303-311.

Karlić, R., Chung, H.-R., Lasserre, J., Vlahoviček, K. & Vingron, M. (2010). Histone modification levels are predictive for gene expression. Proceedings of the National Academy of Sciences, 107, 2926-2931.

Kelly, T. K., De Carvalho, D. D. & Jones, P. A. (2010). Epigenetic modifications as therapeutic targets. Nature biotechnology, 28, 1069-1078.

Khan, O. & La Thangue, N. B. (2012). HDAC inhibitors in cancer biology: emerging mechanisms and clinical applications. Immunology and cell biology, 90, 85-94.

Kim, V. N., Han, J. & Siomi, M. C. (2009). Biogenesis of small RNAs in animals. Nature reviews Molecular cell biology, 10, 126-139.

Kim, W., Choi, M. & Kim, J.-E. (2014). The histone methyltransferase Dot1/DOT1L as a critical regulator of the cell cycle. Cell Cycle, 13, 726-738.

Klutstein, M., Nejman, D., Greenfield, R. & Cedar, H. (2016). DNA methylation in cancer and aging. Cancer research, 76, 3446-3450.

Kristensen, L. S., Nielsen, H. M. & Hansen, L. L. (2009). Epigenetics and cancer treatment. European journal of pharmacology, 625, 131-142.

Kurdistani, S. K. (2011). Histone modifications in cancer biology and prognosis. Epigenetics and Disease, 91-106.

Kurdistani, S. K. & Grunstein, M. (2003). Histone acetylation and deacetylation in yeast. Nature reviews Molecular cell biology, 4, 276-284.

Lagger, G., O'carroll, D., Rembold, M., Khier, H., Tischler, J., Weitzer, G., Schuettengruber, B., Hauser, C., Brunmeir, R. & Jenuwein, T. (2002). Essential function of histone deacetylase 1 in proliferation control and CDK inhibitor repression. The EMBO journal, 21, 2672-2681.

López De Silanes, I., Gorospe, M., Taniguchi, H., Abdelmohsen, K., Srikantan, S., Alaminos, M., Berdasco, M., Urdinguio, R. G., Fraga, M. F. & Jacinto, F. V. (2009). The RNA-binding protein HuR regulates DNA methylation through stabilization of DNMT3b mRNA. Nucleic acids research, 37, 2658-2671.

Luger, K., Mäder, A. W., Richmond, R. K., Sargent, D. F. & Richmond, T. J. (1997). Crystal structure of the nucleosome core particle at 2.8 Å resolution. Nature, 389**,** 251-260.

Lund, A. H. & Van Lohuizen, M. (2004). Epigenetics and cancer. Genes & development, 18, 2315-2335.

Mahlknecht, U. & Hoelzer, D. (2000). Histone acetylation modifiers in the pathogenesis of malignant disease. Molecular Medicine, 6, 623-644.

Malumbres, M. (2013). miRNAs and cancer: an epigenetics view. Molecular aspects of medicine, 34, 863-874.

Margueron, R., Trojer, P. & Reinberg, D. (2005). The key to development: interpreting the histone code? Current opinion in genetics & development, 15**,** 163-176.

Martin, C. & Zhang, Y. (2005). The diverse functions of histone lysine methylation. Nature reviews Molecular cell biology, 6, 838-849.

Meissner, A., Mikkelsen, T. S., Gu, H., Wernig, M., Hanna, J., Sivachenko, A., Zhang, X., Bernstein, B. E., Nusbaum, C. & Jaffe, D. B. (2008). Genome-scale DNA methylation maps of pluripotent and differentiated cells. Nature, 454, 766-770.

Miceli, M., Bontempo, P., Nebbioso, A. & Altucci, L. (2014). Natural compounds in epigenetics: A current view. Food and chemical toxicology, 73, 71-83.

Moore, L. D., Le, T. & Fan, G. (2013). DNA methylation and its basic function. Neuropsychopharmacology, 38, 23-38.

Moufarrij, S., Dandapani, M., Arthofer, E., Gomez, S., Srivastava, A., Lopez-Acevedo, M., Villagra, A. & Chiappinelli, K. B. (2019). Epigenetic therapy for ovarian cancer: promise and progress. Clinical epigenetics, 11, 1-11.

Ng, E., Tsang, W., Ng, S., Jin, H., Yu, J., Li, J., Röcken, C., Ebert, M., Kwok, T. & Sung, J. (2009). MicroRNA-143 targets DNA methyltransferases 3A in colorectal cancer. British journal of cancer, 101, 699-706.

Ohm, J. E., Mcgarvey, K. M., Yu, X., Cheng, L., Schuebel, K. E., Cope, L., Mohammad, H. P., Chen, W., Daniel, V. C. & Yu, W. (2007). A stem cell–like chromatin pattern

may predispose tumor suppressor genes to DNA hypermethylation and heritable silencing. Nature genetics, 39, 237-242.

Paranjape, T., Slack, F. & Weidhaas, J. (2009). MicroRNAs: tools for cancer diagnostics. Gut, 58, 1546-1554.

Park, J. W. & Han, J.-W. (2019). Targeting epigenetics for cancer therapy. Archives of pharmacal research, 42, 159-170.

Peedicayil, J. (2006). Epigenetic therapy-a new development in pharmacology. Indian Journal of Medical Research, 123, 17.

Peter, M. E. (2009). Let-7 and miR-200 microRNAs: guardians against pluripotency and cancer progression. Cell cycle, 8, 843-852.

Platzbecker, U., Wermke, M., Radke, J., Oelschlaegel, U., Seltmann, F., Kiani, A., Klut, I., Knoth, H., Röllig, C. & Schetelig, J. (2012). Azacitidine for treatment of imminent relapse in MDS or AML patients after allogeneic HSCT: results of the RELAZA trial. Leukemia, 26, 381-389.

Ramirez-Carrozzi, V. R., Braas, D., Bhatt, D. M., Cheng, C. S., Hong, C., Doty, K. R., Black, J. C., Hoffmann, A., Carey, M. & Smale, S. T. (2009). A unifying model for the selective regulation of inducible transcription by CpG islands and nucleosome remodeling. Cell, 138, 114-128.

Reddy, K. B. (2015). MicroRNA (miRNA) in cancer. Cancer cell international, 15, 1-6.

Roberti, A., Valdes, A. F., Torrecillas, R., Fraga, M. F. & Fernandez, A. F. (2019). Epigenetics in cancer therapy and nanomedicine. Clinical epigenetics, 11, 1-18.

Romero-Cordoba, S. L., Salido-Guadarrama, I., Rodriguez-Dorantes, M. & Hidalgo-Miranda, A. (2014). miRNA biogenesis: biological impact in the development of cancer. Cancer biology & therapy, 15, 1444-1455.

Sato, F., Tsuchiya, S., Meltzer, S. J. & Shimizu, K. (2011). MicroRNAs and epigenetics. The FEBS journal, 278, 1598-1609.

Shanmugam, M. K., Arfuso, F., Arumugam, S., Chinnathambi, A., Jinsong, B., Warrier, S., Wang, L. Z., Kumar, A. P., Ahn, K. S. & Sethi, G. (2018). Role of novel histone modifications in cancer. Oncotarget, 9, 11414.

Sharma, S., Kelly, T. K. & Jones, P. A. (2010). Epigenetics in cancer. Carcinogenesis, 31, 27-36.

Siegfried, Z., Eden, S., Mendelsohn, M., Feng, X., Tsuberi, B.-Z. & Cedar, H. (1999). DNA methylation represses transcription in vivo. Nature genetics, 22, 203-206.

Simó-Riudalbas, L., Melo, S. A. & Esteller, M. (2011). DNMT3B gene amplification predicts resistance to DNA demethylating drugs. Genes, Chromosomes and Cancer, 50, 527-534.

Taby, R. & Issa, J. P. J. (2010). Cancer epigenetics. CA: a cancer journal for clinicians, 60, 376-392.

Tan, M., Luo, H., Lee, S., Jin, F., Yang, J. S., Montellier, E., Buchou, T., Cheng, Z., Rousseaux, S. & Rajagopal, N. (2011). Identification of 67 histone marks and histone lysine crotonylation as a new type of histone modification. Cell, 146, 1016-1028.

Tsukada, Y.-I., Fang, J., Erdjument-Bromage, H., Warren, M. E., Borchers, C. H., Tempst, P. & Zhang, Y. (2006). Histone demethylation by a family of JmjC domain-containing proteins. Nature, 439, 811-816.

Verma, M. & Srivastava, S. (2002). Epigenetics in cancer: implications for early detection and prevention. The lancet oncology, 3, 755-763.

Wang, K.-Y. & Shen, C. J. (2004). DNA methyltransferase Dnmt1 and mismatch repair. Oncogene, 23, 7898-7902.

Xhemalce, B., Dawson, M. A. & Bannister, A. J. (2006). Histone modifications. Reviews in Cell Biology and Molecular Medicine.

Yan, L., Nass, S. J., Smith, D., Nelson, W. G., Herman, J. G. & Davidson, N. E. (2003). Specific inhibition of DNMT1 by antisense oligonucleotides induces re-expression of estrogen receptor a (ER) in ER-negative human breast cancer cell lines. Cancer biology & therapy, 2, 552-556.

Yang, A. S., Doshi, K. D., Choi, S.-W., Mason, J. B., Mannari, R. K., Gharybian, V., Luna, R., Rashid, A., Shen, L. & Estecio, M. R. (2006). DNA methylation changes after 5-aza-2′-deoxycytidine therapy in patients with leukemia. Cancer research, 66, 5495-5503.

Yanis Boumber, M. & Issa, J.P. J. (2011). Epigenetics in cancer: what's the future? Oncology, 25, 220.

Yoo, C. B. & Jones, P. A. (2006). Epigenetic therapy of cancer: past, present and future. Nature reviews Drug discovery, 5, 37-50.

Zaman, M. S., Thamminana, S., Shahryari, V., Chiyomaru, T., Deng, G., Saini, S., Majid, S., Fukuhara, S., Chang, I. & Arora, S. (2012). Inhibition of PTEN gene expression by oncogenic miR-23b-3p in renal cancer. PloS one, 7, e50203.