Epigenetic Mechanisms: A Promising Frontier in Cancer Treatment

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Abstract

Epigenetics is the study of heritable chemical modifications that regulate gene expression and DNA transcription without directly modifying the DNA sequence. Two key epigenetic mechanisms are histone modifications and DNA methylation. Epigenetic changes influence many biological processes and diseases, including cancer. Cancer arises when genetic mutations in the DNA cause a cell to multiply rapidly. Malignant tumors can spread to other tissues, allowing cancer to affect many areas in the body. Cancer cells can have epigenetic alterations that allow them to evade current treatments. This review provides an overview of epigenetic mechanisms and discusses how targeting these mechanisms can lead to additional cancer therapies. Specifically, we explore the potential of epigenetic drugs to target the small percentage of cancer cells that resist conventional treatments due to their epigenetic states. By understanding how epigenetics contributes to cancer development and treatment resistance, researchers can develop more effective and targeted therapies.

Introduction

DNA Replication and Regulation

DNA, or deoxyribonucleic acid, is the genetic material that encodes for all life processes. The genetic blueprint of DNA exists in almost every cell of the body. It consists of a sequence of nucleotide bases—adenine, thymine, guanine, and cytosine—held together by hydrogen bonds to form a double-stranded helix. Different parts of the DNA nucleotide sequence encode different genes in the body. In order to contain all this genetic information, cells package double-stranded DNA as chromatin in the cell nucleus. Chromatin is further condensed into chromosomes, which are complex structures located inside the nucleus. Through a tightly-regulated mechanism, chromosomal DNA is wrapped around histone-containing proteins known as nucleosomes (Alberts et al.).

When a cell is ready to divide, the DNA must first be copied to ensure that genetic information is passed on to the newly divided cell. This process, known as DNA replication, is essential for cellular growth, development, and the replacement of damaged cells. As such, it is tightly regulated to maintain the integrity of the genetic code. When a cell is ready to replicate and divide, tightly packaged chromosomal DNA is “unwound” and its double-helix is separated to allow for DNA replication and transcription (T.M.).

Initially, the DNA unwinds so that the double stranded helix can be split into two separate strands by an enzyme called helicase. Then a short piece of RNA primer is attached to each one of the strands. DNA polymerase then matches each of the DNA nucleotide bases on the strand with a complementary base in the 5’ to 3’ direction on one strand, while the other strand is done in short segments called Okazaki fragments (Shen). Once both DNA strands go through this process, the primers are replaced with DNA nucleotide bases and the DNA ligase enzyme joins the Okazaki fragments together. This process results in two identical DNA molecules with one copy of the original strand and one copy of the new strand in each (Kornberg).

Overview of cell cycle/replication

DNA replication is especially important in the context of cell replication. There are two

primary types of cell division: mitosis and meiosis. While mitosis is how most cells in the body divide and replicate, meiosis occurs in germ cells such as sperm and egg cells (Potapova). Mitosis is the cell division process most implicated in cancer. In the cell division process, there are 3 main stages called the growth (interphase) stage, the mitosis stage, and the cytokinesis stage. The interphase stage is broken up into 3 parts called G1, S, and G2 phases. In the G1 phase, normal cell functions and cell growth occur. In the S phase, the DNA is replicated and produces two copies of each chromosome. During the G2 phase, the cell continues to grow and prepare for the next phase. The next phase is mitosis which includes prophase, metaphase, anaphase, and telophase where chromosomes condense, the microtubules are attached to each sister chromatid, the chromosomes move away from each other, and finally new nuclear envelopes are formed around the separated chromosomes. The last phase, called cytokinesis, is the division of the cell which forms two identical daughter cells (Cooper).

Epigenetics Role in Regulating DNA Transcription

While DNA provides the blueprint for many cell functions, epigenetics can affect how and when genes are expressed without affecting the DNA sequence. Specifically, epigenetic modifications are chemical changes to DNA or associated proteins that do not alter the underlying DNA sequence, but can influence gene activity (CDC). These modifications act as switches, turning genes on or off in response to various factors, including environmental cues and developmental signals. For example, in one study in preclinical rodent models, scientists were able to detect how maternal care affected gene expression and stress response through epigenetic changes (O'Donnell and Meaney).

In this process, there are two main mechanisms: histone modification and DNA methylation. In histone modification, acetyl and methyl groups are added onto the histone tails directly, acting as chemical tags. DNA methylation is a process by which a methyl group is added onto the cytosine-guanine residues on strands of DNA.

Mechanisms Contributing to Cancer

Cancer is caused by certain mutations that can lead to abnormal cell growth. These mutations can occur due to environmental factors like tobacco smoke, alcohol, obesity, pollution, certain infections, and sun exposure (Trichopoulos et al.). The mutations can also occur spontaneously due to random errors that happen during the DNA replication process.

Although there are DNA repair mechanisms, at times such mechanisms fail, causing cells to continue through the cell cycle unchecked, ultimately leading to more cell division. For example, a gene called the p53 tumor suppressor gene plays a crucial role at the G1 checkpoint. Its function is to sense DNA damage. When it does, p53 halts the cell cycle allowing time for DNA repair to happen. However, when there is a certain mutation in the p53 tumor suppressor gene, it can cause the cell cycle to proceed through the G1 checkpoint without fixing the DNA damage, leading to the replication of the mutation (Torii et al.). Usually, the cell division process is well regulated and prevents cell division from occurring uncontrollably. However, cancer cells are able to extensively replicate and divide to an extent that is hard to be controlled (Williams and Stoeber).

Cancer hallmarks and their importance

There are six key hallmarks of cancer. These include: sustained proliferative signaling, evasion of growth suppressors, activation of invasion and metastasis, replicative immortality,

angiogenesis, and resistance to cell fatality. These hallmarks are a set of characteristics that scientists use to define cancer cells to distinguish them from normal cells (Lazebnik). By identifying which characteristics a cell or tumor has relevant to these hallmarks, scientists can develop diagnostic tools and therapeutics that are more targeted to the condition. Also, having knowledge of the hallmarks can help scientists predict how the cancer might develop and progress, leading to better treatment (Lazebnik).

Cancer Diagnosis and Existing Treatments

The clinical course and underlying mechanisms of cancer can vary extensively from patient to patient, making it difficult to treat. The risk of cancer occurring can also increase with age due to changes in metabolic profile, weakening of the immune systems, compounding genetic mutations, and chronic inflammation (Pesheva and University). It is crucial to diagnose cancer at an early stage as once it undergoes metastasis, it makes it far more challenging to treat. Metastasis can occur microscopically and silently across various locations, leading to multiple treatment targets, the development of drug resistance, and evasion of the immune system (Gerstberger et al.). Some examples of methods used to diagnose cancer include biopsy, laboratory tests, imaging tests, and physical exams (Hamilton).

Many different types of treatment options for cancer also exist, including surgery, chemotherapy, radiotherapy, immunotherapy, hormone therapy, and gene therapy (Miller et al.). A key goal of cancer treatment is to remove the cancerous tumors while minimizing the effect of the treatment on healthy cells. However, targeting the cancer cells specifically while leaving the healthy cells unaffected is very challenging. For example, chemotherapy's goal is to target rapidly dividing cells. Although this does kill cancer cells, it also kills other healthy cells that rapidly divide such as the cells in the hair, bone marrow, and digestive tract (Nygren). The effect of cancer treatments on healthy cells can lead to many side effects. Some examples of side effects patients may experience from chemotherapy can include fatigue, mouth sores, skin irritation, hair loss, digestive issues, and nausea (Silveira et al.).

Literature Review

Tumor Suppressor and Proto-Oncogene Mutations in Cancer

Despite cells having identical DNA, cells can vary vastly based on how genes are expressed. When a cell gains certain mutations that lead to inappropriate over- or under-expression of key genes involved in regulating cell cycle, this can lead to the development of cancer. This could happen in a variety of ways such as through mutations in tumor suppressor genes or oncogenes (Figure 1).

Tumor suppressor genes function as the "brakes" of the cell cycle, ensuring that cells only divide when necessary. The proteins encoded by these genes act as checkpoints, halting the cell cycle to prevent abnormal cell division and promoting apoptosis in cells that do not meet specific criteria. Overall, tumor suppressor genes are involved in inhibiting cell growth and repairing damaged DNA, while making the cell undergo apoptosis if the damage is not repairable (Williams and Stoeber). However, with DNA methylation and histone modifications, these tumor suppressor genes can be silenced, causing the cell to evade growth control mechanisms. Therefore, the cell is able to go through the cell cycle process unchecked when there are inactivating mutations in tumor suppressors, potentially leading to the formation of a

tumor.

Similarly, there are proto-oncogenes. Proto-oncogenes are genes that promote cell growth and division. When these genes are overexpressed, they can become oncogenic, meaning they can cause uncontrolled cell growth leading to cancer development. While the two main mechanisms of epigenetics most commonly affect tumor suppressor genes, they can also affect proto-oncogenes. Ultimately, the interplay between epigenetic mechanisms, tumor suppressors, and proto-oncogenes can disrupt cell division and growth, opening the way for cancer (Lee and Muller).

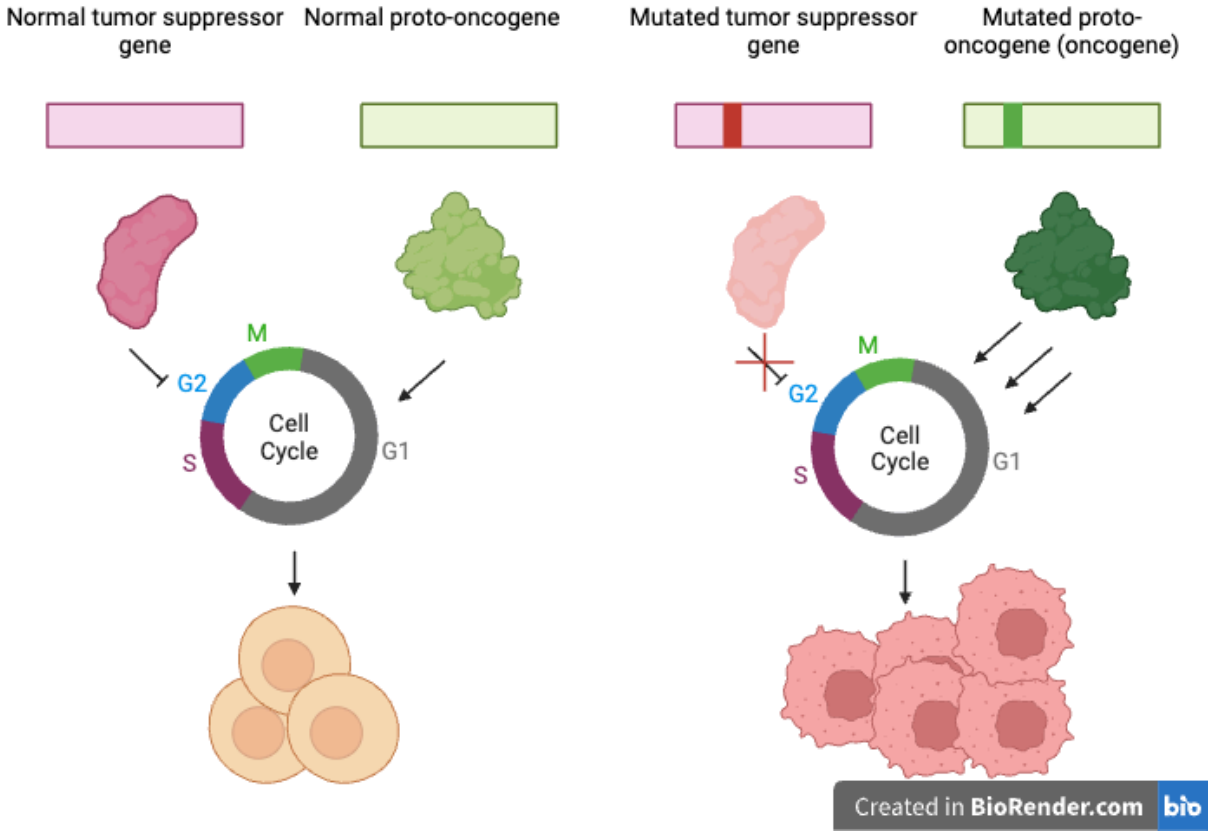

Figure 1. This figure is a diagram representing the difference in the function of a normal tumor suppressor gene and proto-oncogene compared to mutated versions of these genes. The mutated tumor suppressor gene as represented, stops the inhibiting mechanism of the cell cycle while the oncogene (mutated proto-oncogene) is overexpressed causing the cell cycle to continue.

Histone Modifications

Histones are the proteins that DNA is wrapped around in the chromatin structure. Histone modifications, as the name suggests, are the modifications that alter the structure of histones, which can affect DNA transcription and gene expression. Tiny chemical tags are added to or removed from the histone protein in this process. There are 4 main mechanisms of histone modification: acetylation, deacetylation, methylation, and demethylation. These mechanisms

can affect gene expression based on how tightly the DNA is wrapped (Cheriyedath).

In histone acetylation, an acetyl group is added onto the Lysine or Arginine residues on the histone tail. The process of forming acetyl-lysine and acetyl-arginine is done by an enzyme called HAT, which stands for histone acetyltransferase. Since it is an enzyme, its purpose is to catalyze the transfer of the acetyl group onto the Lysine or Arginine residues on the histone proteins. The acetylation process is associated with the euchromatin state, also known as the active chromatin state. Essentially, this means that the chromatin structure is loosely packed, making it accessible to RNA polymerase during transcription (Figure 2). The genes in this loosely packed structure are more accessible and have the potential to be transcribed and expressed (Liebner et al.).

The reverse reaction, which is deacetylation, is instead triggered by the HDAC enzyme, also known as histone deacetylase. Deacetylation is the removal of the acetyl group from the residues on the histone protein. Deacetylated histones are associated with the heterochromatin state, which is a tightly packed up state, limiting transcription in the unexposed areas. Since RNA polymerase cannot access the tightly wrapped up structure, it will not be transcribed (Barnes et al.).

Methylation and demethylation work in similar ways. While methylation is the addition of a methyl group onto the Lysine or Arginine residues, demethylation is the removal. However the heterochromatin state is associated with histone methylation where the HMT (histone methyltransferase) enzyme is responsible, while the euchromatin state is associated with demethylation where the LSD (lysine-specific demethylase) is responsible (Figure 2). Methylation can occur in several ways. It includes monomethylation, dimethylation, and trimethylation, which are names that indicate the amount of times the methyl group is engaged with the particular residue (Deng et al.).

Histone acetylation, deacetylation, methylation, and demethylation are all epigenetic mechanisms which can contribute to cancer development. When the structure is packed tightly, it can lead to the silencing of certain tumor suppressor genes. When the structure is loosened, it can cause oncogenes to activate. These mechanisms can both lead to genomic instability making them strongly linked to cancer.

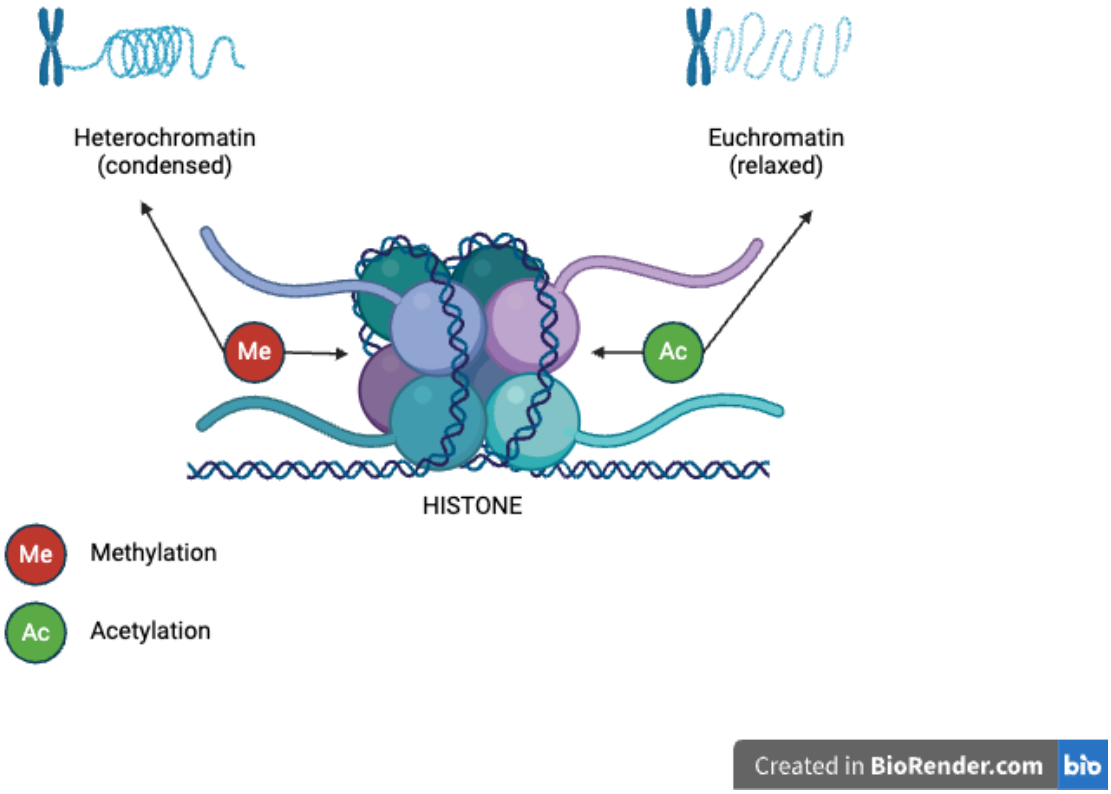

Figure 2. This is an image representing how methylation and acetylation work as chemical tags on the histone protein to either condense or relax the chromatin for transcription needs.

DNA Methylation

DNA methylation is another epigenetic process in which a methyl group is added to the DNA molecule by a group of enzymes called DNMTs (DNA methyltransferases). While this methyl group being added doesn't alter the DNA sequence itself, it can alter the activity of segments. There are two types of DNA methylation, *de novo* methylation and maintenance methylation, and there are 3 enzymes, called DNMT3A, DNMT3B, and DNMT1 (Feinberg and Vogelstein). *De novo* methylation involves adding methyl groups to unmethylated sequences. This is usually done by DNMT3A and DNMT3B enzymes in early embryonic cells. DNMT1 maintains DNA methylation in the maintenance methylation process. The methyl groups that are attached to the sequence are usually added at cytosine-guanine sites, also called CpG sites. The methylation occurring at these promoter CpG islands affects DNA transcription as the methylated CpG islands can prevent transcription regulators from binding to the gene, hindering transcription.

There are also TET enzymes that, instead of adding methyl groups, remove them from the DNA. They help restore the original state of the DNA, allowing for accurate gene expression by converting the 5-methylcytosine (methylated cytosine) to cytosine (Moore et al.). This process is essentially called DNA demethylation. After demethylation, transcription factors have the ability to bind to genes and the genes can be expressed.

In cancer however, DNA methylation patterns may be disrupted either causing hypermethylation or hypomethylation. Hypermethylation refers to excess methylation at CpG

sites which can cause gene silencing, and hypomethylation is decreased methylation at the CpG sites which can cause increased gene expression (Singal and Ginder) .While DNA methylation is crucial for normal gene regulation, its disruption in cancer can lead to uncontrolled cell growth by altering gene expression patterns.

Leveraging Epigenetic Drugs Against Cancer

Primary mechanisms of epigenetic cancer therapies include inhibiting the enzymes or mechanisms that add or remove chemical tags to stop the overexpression or silencing of certain genes. Some examples of epigenetic cancer therapies that already exist are HAT inhibitors, HDAC inhibitors, Histone methylation inhibitors, and DNA methylation inhibitors. For example, HAT inhibitors called Garcinol and Anacardic Acid downregulate global gene expression and induce apoptosis (Kopytko et al.). HDAC inhibitors such as Vorinostat (SAHA) induce hyperacetylation of histones and non-histone proteins, promoting apoptosis and sensitizing tumors to other treatments (Li and Seto). Histone methylation inhibitors like DZNep inhibit the trimethylation of certain histone residues, causing the reactivation of silenced genes (Miranda et al.). Finally, DNA methylation inhibitors such as 5-Azacytidine (Vidaza) can cause degradation of DNMT1 and result in reduced methylation (Palii et al.) (Table 1). By targeting these epigenetic mechanisms and enzymes, the drugs can restore normal gene expression and stop the growth of cancer cells.

There also exist several other epigenetic therapies, such as HAT inhibitors. Curcimin inhibits p300/CBP HAT activity, leading to cell cycle arrest and apoptosis (Marcu et al.). C646, a p300 inhibitor, replicates the proapoptotic effects of RNA-mediated p300 knockdown (van den Bosch et al.). Some HDAC inhibitors like Entinostat are used with other drugs for enhanced demethylation (Connolly et al.). ACY-1215 targets HDAC6, which has been shown to work in combination with other treatments for certain conditions (Wen et al.). Another example of a histone methylation inhibitor is Tazemetostat which targets the EZH2 enzyme, preventing histone protein methylation (Li and Seto). Finally, other examples of DNA methylation inhibitors include Zebularine which inhibits DNMT1, which have been shown to be effective in mouse models and can be taken orally (Yoo et al.). RG108 is a small molecule that inhibits the active site of DNMT1, reducing toxicity and demethylating certain genes (Zheng et al.). Overall, there exist many epigenetic drugs against cancer that target the mechanisms and enzymes responsible for promoting cancer.

Table 1. Overview of the epigenetic drugs for cancer based on mechanism

HAT inhibitors	**Garcinol + Anacardic Acid** → downregulate global gene expression and induce apoptosis **Curcimin** → inhibits p300/CBP HAT activity, leading to cell cycle arrest and apoptosis **C646** → a p300 inhibitor that replicates the proapoptotic effects of RNA-mediated p300 knockdown

HDAC Inhibitors	**Vorinostat (SAHA)** → induces hyperacetylation of histones and non-histone proteins, promoting apoptosis and sensitizing tumors to other treatments **ACY-1215** → targets HDAC6, and has been shown to work in combination with other treatments for certain conditions
Histone Methylation Inhibitors	**DZNep** → inhibits the trimethylation of certain histone residues, causing the reactivation of silenced genes **Tazemetostat** → targets the EZH2 enzyme, preventing histone protein methylation
DNA Methylation Inhibitors	**5-Azacytidine (Vidaza)** → causes degradation of DNMT1, resulting in reduced methylation **Zebularine** → inhibits DNMT1, showing efficacy in mouse models and can be taken orally **RG108** → a small molecule that inhibits the active site of DNMT1, reducing toxicity and demethylating certain genes

Conclusion

This review overviewed the role of epigenetic mechanisms in cancer and the potential gap in cancer treatment that can be addressed with epigenetic drugs. By targeting the small percentage of cancer cells that have epigenetic states allowing them to resist cancer therapeutics, we are one step closer to developing more effective cancer treatments for resistant tumors. While there already exist some epigenetic therapeutics for cancer, in the future, the development of additional drugs and combining these drugs with other treatments such as immunotherapy or chemotherapy may enhance how efficient they are. Therefore, a potential area for future research is to conduct clinical trials where epigenetic drugs are used with existing cancer treatments, to make them more targeted to cancer cells. Additionally, understanding the epigenome in each individual can help scientists build personalized medicine to expand the possibilities of treatment. Epigenetic drugs combined with existing cancer treatments, may improve the effectiveness of therapeutics in treatment-resistant tumors.

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