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EPIGENETICS AND CANCER: THE INFLUENCE OF POST-TRANSLATIONAL HISTONE MODIFICATIONS IN CARCINOGENESIS

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ABSTRACT

Cancer is a global concern, with alarming statistics on incidence and mortality. Genetic and epigenetic alterations play fundamental roles in carcinogenesis, influencing gene expression and genome stability. This study aimed to elucidate the main epigenetic modifications of histones related to cancer and the epigenetic inhibitors used as therapeutic methods. Using a narrative review approach, articles published between 2014 and 2024 were selected to discuss the key aspects related to the topic. Post-translational modifications of histones, such as acetylation, methylation, phosphorylation, ubiquitination, and sumoylation, were examined concerning cancer development and progression. Mutations and dysregulation of acetylases and deacetylases have been observed in various cancers, highlighting their role in carcinogenesis and as potential therapeutic targets. Histone methylation, regulated by methyltransferases and demethylases, affects gene expression and, along with changes in DNA methylation levels, contributes to tumor progression. Additionally, phosphorylation, ubiquitination, and sumoylation of histones are dynamic processes that regulate chromatin structure and gene expression; dysregulation of these processes has been implicated in cancer development and progression, underscoring their importance in carcinogenesis. Since epigenetic alterations are reversible, different epigenetic drugs have been developed and applied in cancer treatment. Given that histone epigenetic modifications play a crucial role in oncogenesis, influencing gene expression and tumor progression, understanding these mechanisms is essential for developing more effective preventive and therapeutic strategies against cancer.

Keywords: Epigenetic inhibitors. Erasers. Histone acetylation. Histone methylation. Writers.

INTRODUCTION

Cancer is one of the leading causes of death worldwide and also one of the most studied diseases. Global statistics indicate that in 2022, there were 20 million new cases of cancer and 9.7 million deaths due to the disease.

Demographic-based projections estimate that by 2050, the annual number of new cancer cases will reach approximately 35 million (Bray et al., 2024).

Initially, cancer was thought to be caused by a gradual series of genetic alterations. Later, it was discovered that mutations in specific regions of the genome, including proto-oncogenes and tumor suppressor genes, play a fundamental role in the process of carcinogenesis (Neganova et al., 2022; Zhuang et al., 2020). Today we know that carcinogenesis involves not only mutations in the nucleotide sequences of DNA but also epigenetic alterations. In cancer epigenetics, the focus is on complex pathways responsible for regulating gene expression through histones, which can alter chromatin structure, as observed in processes such as acetylation, ubiquitination, sumoylation, phosphorylation, and methylation, among others (Zhang et al., 2021).

Understanding the underlying mechanisms of cancer development has evolved considerably over time; however, the complexity of the carcinogenesis process requires an ongoing search for new information. Histone modifications are crucial for chromatin packaging and gene expression regulation. Therefore, alterations in the patterns of these modifications can profoundly impact genome stability and cellular function, leading to the development of diseases such as cancer. In this context, the present review aims to clearly and concisely address some of the main epigenetic alterations related to oncogenesis and some of the epigenetic drugs used in cancer treatment. It does not intend to exhaust the subject but rather to shed light on the epigenetic mechanisms involved in cancer development and thus promote the importance of studies in this area, aiming at the identification of therapeutic targets and more effective prevention strategies.

METHODS

OThis work constitutes a narrative literature review. According to Vosgerau and Romanowsk (2014), qualitative studies of narrative reviews provide a comprehensive analysis of the literature, offering valuable insights on a specific topic. Additionally, narrative reviews play a fundamental role not only in acquiring knowledge about a particular theme but also in updating this information and discussing related methods and subtopics, as noted by Elias et al. (2012).

The methodology began with the definition of the guiding question that outlined the entire research: what is the role of histone modifications in epigenetic processes related to the development and progression of different types of cancers? This initial step was crucial for the development of the review, as it allowed for a clear and specific delimitation of the central theme with the aim of developing an objective study, culminating in easily understandable conclusions.

The bibliographic research was conducted using the tracking and indexing platform "Google Scholar." The publication date and language were used as inclusion criteria. Thus, articles published between 2014 and 2024 written in English were selected. For the indexing of the search, the boolean operator "AND" and the descriptors: "histone-modification" AND "cancer" AND "epigenetic" were applied. After screening the retrieved works through reading and analyzing the abstracts, articles that were not available for free in full text were excluded. Consequently, 13 relevant articles addressing the topic were selected. These articles specifically dealt with the role of histone modifications in epigenetic processes related to the development and progression of different types of cancer.

RESULTS AND DISCUSSION

The 13 articles selected for this study specifically address the role of histone modifications in epigenetic processes related to the development and progression of different types of cancer. A summary of the main aspects related to the works can be found in Table 1.

Table 1. Data from the articles retrieved from the search and indexing platform "Google Scholar" and used in the present study.

Author/year	Article title	Overview of the Study
Dancy et al., 2015	Protein lysine acetylation by p300/CBP	Highlights the importance of lysine acetylation mediated by p300/CBP for cellular health, emphasizing that the acetylation and protein binding functions of p300/CBP are intrinsically interconnected.
Zheng et al., 2015	SUMO-1 promotes Ishikawa cell proliferation and apoptosis in endometrial cancer by increasing SUMOylation of histone H4	Investigates the role of SUMO-1 (small ubiquitin-like modifier 1) in the processes of cell proliferation and apoptosis in endometrial cancer cells.
Audia; Campbell, 2016	Histone Modifications and Cancer	Shows the covalent modifications of histones that are altered in cancer, particularly acetylation and methylation. It also addresses anti-cancer epigenetic drugs.
Cutter; Hayes, 2016	A brief review of nucleosome structure	Presents the basic elements of nucleosome structure and stability, as well as the association of binding histones.
Biswas; Rao, 2018	Epigenetic tools (The Writers, The Readers and The Erasers) and their implications in cancer therapy	Highlights the different types of epigenetic enzymes and their role in the tumorigenesis process. It also discusses anti-cancer inhibitor epigenetic drugs.
Shanmugam et al., 2018	Role of novel histone modifications in cancer	Highlights the epigenetic alterations in tumorigenesis, emphasizing the role of histone modifications in tumor suppressor genes and oncogenes.
Liu et al., 2019	The function of histone acetylation in cervical cancer development	Discusses the role of histone acetylation in the development of cervical cancer related to HPV.
Zhuang et al., 2020	Perspectives on the role of histone modification in breast cancer progression and the advanced technological tools to study epigenetic determinants of metastasis.	Highlights the epigenetic factors driving breast cancer metastasis, focusing on histone modifications and the role of key enzymes such as HATs, HDACs, and DNMTs.
Zhang et al., 2021	Overview of histone modification	Explores the importance of epigenetics in cancer, highlighting epigenetic mutations as drivers of tumorigenesis.
Kong et al., 2022	Nucleosome-Omics: A Perspective on the Epigenetic Code and 3D Genome Landscape	Examines the discovery and research of nucleosomes, highlighting their importance and genomic techniques for studying epigenetic phenomena, including 3D genomics.
Neganova et al., 2022	Histone modifications in epigenetic regulation of cancer: Perspectives and achieved progress	Analyzes the role of histone epigenetic modifications and enzymes from the HAT/HDAC and HMT/HDMT families in cancer development, as well as the development of epigenetic inhibitors.

Yang et al., 2022	Interaction of ncRNA and epigenetic modifications in gastric cancer: focus on histone modification	Describes the molecular interactions between histone modifications and ncRNAs in epigenetics, focusing on their relationship with tumorigenesis and gastric cancer progression.
Janakova et al., 2022	Catechol-O-methyl transferase suppresses cell invasion and interplays with MET signaling in estrogen dependent breast cancer	Investigates the role of the enzyme Catechol-O-methyltransferase in estrogen-dependent breast cancer metastasis.

The post-translational modifications of histone proteins include epigenetic changes involved not only in dynamic cellular processes such as transcription and DNA repair but also in the stable maintenance of repressive chromatin (Audia; Campbell, 2016). These proteins are important because they form the nucleosome, which is the fundamental unit of chromatin. The nucleosome is composed of two tetramers of histones (H2A, H2B, H3, and H4) that are rich in positively charged amino acids (arginine and lysine), to which 147 base pairs of DNA are bound and stabilized by a linker histone (H1/H5) (Cutter; Hayes, 2016; Neganova et al., 2022). The N-terminal tails of histone proteins extend out from the nucleosome, allowing for various epigenetic modifications to occur.

Nucleosomes perform a wide range of functions, ranging from the process of chromatin compaction to the control of transcription, replication, and DNA repair mechanisms, as well as the protection of the genome against harmful agents, functioning as a repository where a variety of epigenetic signals are deposited (Cutter; Hayes, 2016). Considering that the histones that make up the nucleosomes play a central role in the epigenetic code (Kong et al., 2022), changes in their post-translational modification patterns (such as acetylation, methylation, phosphorylation, ubiquitination, and sumoylation) can lead to cancer initiation and progression, either by activating oncogenes or inactivating tumor suppressor genes (Audia; Campbell, 2016; Neganova et al., 2022). Thus, although epigenetic modifications are temporary and do not change the DNA sequence, they contribute to cancer development and progression (Shanmugam et al., 2018). Within this process, there are three categories of epigenetic players: the writers: enzymes that introduce various chemical modifications to DNA and histones; the readers: proteins containing specialized domains that identify and interpret these modifications; and the erasers: a dedicated group of enzymes proficient in removing these chemical marks (Biswas; Rao, 2018).

Histone acetyltransferases (HATs) comprise a family of enzymes that catalyze the acetylation of lysine, neutralizing its positive charge, which disrupts the electrostatic interaction between histones and DNA (Zhang et al., 2021), affecting chromatin assembly and altering the process of gene transcription. In this way, acetylation is associated with the open and active conformation of chromatin. (Neganova et al., 2022; Yang et al., 2022). In contrast, in deacetylation, catalyzed by histone deacetylase enzymes (HDACs), histone proteins come closer together, forming a compact structure that prevents the activation of gene transcription. (Yang et al., 2022). Since both acetylation and deacetylation play a crucial role in regulating transcription, altered levels of histone acetylation are associated with many tumor phenotypes. (Neganova et al., 2022). Generally, hyperacetylation leads to an increase in gene expression, especially when proto-oncogenes are involved. (Yang et al., 2022). In cases of breast cancer, deacetylated chromatin inhibits the expression of tumor suppressor genes. (Zhuang et al., 2020).

Genetic alterations and functional dysregulation in various members of HATs and HDACs

are closely linked to the onset and progression of malignant neoplasms, as well as their spread to other target organs (Neganova et al., 2022). Two members of the HAT I family, CBP (CREB-binding protein) and p300 (transcriptional coactivator), form the CBP/p300 complex (Dancy et al., 2015; Zhang et al., 2021), which, when mutated, is implicated in several types of cancer, including acute myeloid leukemia, where it facilitates chromosomal translocation (Zhang et al., 2021; Zhuang et al., 2020). Additionally, these proteins are associated with the development of various forms of leukemia and B-cell non-Hodgkin lymphoma, as well as solid tumors (Dancy et al., 2015). Members of family II, such as GNAT (GCN5-related N-acetyltransferase), which acetylates both histone and non-histone proteins, are activated in human glioma, colorectal cancer, breast cancer, and lung carcinoma, among other cancers (Dancy et al., 2015). Beyond their carcinogenic effects, evidence suggests that HATs can significantly enhance the expression of the gene Catechol-O-Methyltransferase (COMT), which may act as a tumor suppressor in estrogen-dependent breast cancer (Janakova et al., 2023).

It is well known that HDACs can alter the expression of many cell cycle regulators, and elevated levels of these enzymes are associated with advanced disease and poor prognosis. For example, in prostate, gastric, and breast cancers, the overexpression of HDAC1 has been observed. The increased expression of HDAC1/2/3/4/5 and a member of the sirtuin family (SIRT1) has been found in colon tumors. Studies have shown that the increased activity of HDAC1 and HDAC2 correlates with an increase in mitotic failures and neoplastic transformation, while the inhibition of HDAC1/2 leads to a loss of cell viability (Liu et al., 2019).

The methylation of histones occurs mainly on the side chains of lysine and arginine and is regulated by the activity of two functionally antagonistic groups of enzymes, histone methyltransferases (writers) and histone demethylases (erasers) (Biswas; Rao, 2018). These enzymes cause changes in the structure and conformation of chromatin, in the stability of DNA, and the way DNA interacts with proteins, thus controlling gene expression (Zhuang et al., 2020).

It is widely understood that anomalies in the methylation of lysine residues by histone-lysine methyltransferases (HMTs) might alter gene expression in specific types of cancer cells (Negonova et al., 2022; Zhang et al., 2021). Deregulated activity of histone-lysine methyltransferases has been discovered in cells with high plasticity and resistance to apoptosis throughout tumor processes, indicating that these enzymes have carcinogenic features (Shanmugam et al. 2018).

Almost all cancers exhibit abnormal levels of DNA methylation in their cells. Breast cancer cells, for example, exhibit global hypomethylation and focal hypermethylation (gene-specific) that is similar to other cancers (Zhuang et al., 2020). In fact, changes in the methylation and demethylation profiles of histones are associated with a large number of distinct cancers, such as lymphoma, myeloma, gastric, colorectal, prostate, and lung cancer (Neganova et al., 2022).

Histone phosphorylation occurs at the serine, tyrosine, and threonine residues of the protein tails. It is regulated by various kinases and phosphatases and plays a role in several cellular processes, such as DNA damage repair, chromatin remodeling, transcriptional activation, apoptosis, and asymmetric cell division (Zhang et al., 2021; Yang et al., 2022). During mitosis, histone phosphorylation disrupts the balance of interactions between these proteins and DNA, resulting in chromatin instability. Notably, histone phosphorylation particularly mediates the transcription of genes that regulate the cell cycle and, therefore, cell proliferation (Neganova et al., 2022). For example, the threonine 45 residue of histone H3 (H3T45) is

phosphorylated by protein kinase C1, which promotes acetylation of the H3K56 residue, regulating apoptosis and DNA replication. Additionally, phosphorylation of the H3S10 residue mediates the transcriptional activation of proto-oncogenes such as c-myc and c-fos. Increased levels of H3S10 phosphorylation have been implicated in the proliferation of gastric cancer cells and may be considered a prognostic marker for this type of neoplasia (Yang et al., 2022).

Protein ubiquitination is a cascade reaction that relies on adenosine triphosphate (ATP) to attach ubiquitin to a substrate protein, a common process in cells (Yang et al., 2022). Ubiquitination occurs at lysine residues of histones and represents one of the key early modifications that activate the DNA repair pathway (Audia; Campbell, 2016). The addition of ubiquitin groups to histones is crucial for various cellular functions, including DNA damage repair, gene transcription regulation, and maintenance of genomic stability. Furthermore, the monoubiquitination of H2A at Lys119 is involved in transcriptional repression through Polycomb Repressive Complex (PRC) proteins, which are responsible for gene silencing (Audia; Campbell, 2016). Additionally, deubiquitinating enzymes (DUBs) are responsible for removing ubiquitin from proteins, ensuring a dynamic balance between ubiquitination and deubiquitination, which is essential for proper cellular function. Thus, alterations in the expression of these enzymes are associated with the development and progression of certain types of cancer (Yang et al., 2022).

Sumoylation, a mechanism similar to ubiquitination, allows the attachment of small modifiers known as SUMO to lysine residues. Sumoylation regulates the activity of enzymes that modify histones, indicating a close relationship with epigenetic regulation. Studies have shown that SUMO-1 plays a key role in regulating the proliferation and programmed cell death of endometrial cancer cells by increasing the sumoylation levels of histone H4. Additionally, the sumoylation of the transcription factor ETV1 promotes prostate cancer growth, highlighting the importance of this mechanism in tumor formation and progression (Zheng et al., 2015).

Since epigenetic alterations constitute a critical factor in the development and progression of tumorigenesis, and the modifications established by epigenetic enzymes are reversible, studies exploring epigenetic methods for treating cancer have been developed (Biswas; Rao, 2018; Yang et al., 2022). The current challenge is to develop new molecules that target multiple oncogenic pathways simultaneously. Multi-target drugs offer advantages over drug combinations, such as more predictable pharmacokinetics. Additionally, one component can enhance the bioavailability of the other, increasing efficacy, reducing toxicity, and ensuring simultaneous action on the affected cells (Neganova et al., 2022).

Several drugs targeting epigenetic pathways have shown clinical efficacy, including inhibitors of DNA methyltransferase 1 (DNMT) enzymes and histone deacetylases (Yang et al., 2022). DNA methylation changes, including global hypomethylation and hypermethylation in tumor suppressor gene promoter regions, are prevalent in cancer cells and regulated by DNMTs. These enzymes are now promising targets for drug development, including DNMT inhibitors (DNMTi). Notably, 5-azacytidine (Azacitidine) and 5-aza-2′-deoxycytidine (Decitabine) are commonly used to treat acute myeloid leukemia and myelodysplastic syndrome, respectively. The DNMTi SGI-110 (Guadecitabine) is under clinical development for advanced hepatocellular carcinoma. Additionally, 4′-Thio-2′-deoxycytidine is in clinical trials for advanced solid tumors, while RX-3117 is being developed clinically in combination with Nab-paclitaxel (Abraxane®) for metastatic pancreatic cancer (Biswas; Rao, 2018).

Histone lysine methyltransferase inhibitors like EPZ-5676 (pinometostat) and SYC-522 have been

developed to treat leukemia and mixed-linkage leukemia (MLL) by targeting the DOT1L methyltransferase enzyme, crucial for these cancers (Biswas; Rao, 2018; Neganova et al., 2022). A more refined compound, EPZ015938 (GSK3326595), which selectively targets PRMT5—an enzyme that methylates arginine residues on histones is currently in clinical trials for patients with solid tumors and non-Hodgkin lymphoma (Biswas; Rao, 2018).

Several studies indicate that histone deacetylase enzymes (HDACs) regulate the expression and function of various proteins involved in the process of tumorigenesis, and for this reason, drugs capable of inhibiting these enzymes have been studied. For example, Trichostatin A, a natural derivative of dienohydroxyamic acid obtained from the Streptomyces genus, is capable of inhibiting zinc-dependent HDACs. Vorinostat, a hydroxamic acid derivative, was the first broad-spectrum histone deacetylase inhibitor (pan-HDACi) approved by the US-FDA for the treatment of advanced primary cutaneous T-cell lymphoma (Audia; Campbell, 2016; Biswas; Rao, 2018). The pan-HDAC inhibitor Resminostat (4SC-201) has also been clinically evaluated for the treatment of Hodgkin's lymphoma and advanced colorectal carcinoma (Biswas; Rao, 2018). Most breast cancer drugs focus on altering histone modifications, especially those involving HDACs (Zhuang et al., 2020), with HDAC inhibitors being developed to promote cellular differentiation and/or apoptosis, leading to tumor growth inhibition (Zhang et al., 2021).

CONCLUSION

OGiven the complexity and impact of cancer as one of the leading causes of global mortality, understanding the underlying mechanisms of its development is essential. In this context, histone modifications emerge as crucial components in genetic regulation and genome stability, playing a central role in the oncogenesis process. Since epigenetic alterations play a fundamental role in tumorigenesis and cancer progression, epigenetic enzymes become promising targets for the development of new therapies. The search for drugs that act on multiple oncogenic targets simultaneously can increase efficacy and reduce treatment toxicity. DNMT and HDAC inhibitors have proven effective in various types of cancer, including hepatocellular carcinoma, leukemia, lymphoma, and breast and pancreatic cancers. Therefore, progress in epigenetic research opens new opportunities for cancer diagnosis and treatment, aiming for a more precise and personalized approach. It is crucial to investigate the contribution of epigenetics at every stage of cancer, from its onset to tumor spread.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any relationships that could be construed as a potential conflict of interest.

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