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Advances and Implications of Histone Modifications in Prostate Cancer: A Brief Review

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Abstract. Prostate cancer, a leading cause of cancer-related mortality among men, is increasingly linked to epigenetic changes, particularly histone modifications that affect gene expression and tumor behavior. This review explores recent advances in understanding how aberrant histone acetylation, methylation, and other modifications contribute to prostate cancer progression, metastasis, and therapeutic resistance. By analyzing these modifications' roles in regulating critical pathways, this paper aims to elucidate their diagnostic and therapeutic potential, suggesting that targeted epigenetic therapies may offer new avenues for treatment.

Keywords: Prostate Cancer, Aberrant Histone Acetylation, Methylation, Histone Modifications.

1. Introduction

Prostate cancer is one of the most prevalent malignancies in men, accounting for approximately 29% of all male cancers, and the incidence rate increased by 3% annually from 2014 to 2019, with nearly half of these cases diagnosed at advanced stages [1]. Prostate cancer remains a leading cause of cancer-related mortality among men, ranking second in death rates from male malignancies [1]. This highlights the critical need for continued research into its underlying mechanisms and potential treatment avenues.

One area of growing importance in prostate cancer research is epigenetics, which significantly contributes to the cancer's development, progression, metastasis, and drug resistance [2-4]. As technologies in molecular biology continue to evolve, epigenetic studies have become more comprehensive, with histone modifications emerging as a crucial aspect of epigenetic regulation. These modifications play a pivotal role in controlling gene expression, chromatin dynamics, and cellular processes in prostate cancer [5].

In this review, we explore the latest advances in histone modification research in prostate cancer, discussing their biological significance and potential implications for diagnosis and therapeutic strategies. By consolidating current knowledge, this paper aims to offer new insights into the epigenetic regulation of prostate cancer and guide future clinical applications.

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2. Histone Modifications in Prostate Cancer

2.1. Aberrant histone acetylation patterns

Aberrant histone acetylation patterns are a hallmark of various cancers, including prostate cancer. In prostate cancer, dysregulated histone acetylation can result from either increased acetylation or the inhibition of histone deacetylases (HDACs), leading to changes in gene expression that drive tumorigenesis. One of the key mechanisms by which histone acetylation exerts its effects is through the modification of histone tails, which in turn affects chromatin structure and gene accessibility.

Damodaran et al. discovered a significant relationship between the downregulation of Sirtuin 2 (SIRT2), a member of the sirtuin family of NAD-dependent deacetylases, and the acetylation of histone H3K18 in prostate cancer [6]. Specifically, SIRT2 downregulation was associated with an increase in H3K18 acetylation, a modification known to promote a more open chromatin configuration, facilitating the transcription of oncogenes. These findings suggest that the loss of SIRT2 function may contribute to hyperacetylation states in a subset of prostate cancer patients, leading to tumor progression. Therefore, the combined analysis of SIRT2 levels and acetylated H3K18 through genomic or proteomic testing could serve as a potential biomarker for identifying patients who may benefit from therapeutic strategies targeting histone acetylation, particularly those involving histone acetyltransferase (HAT) inhibitors.

Similarly, research by Jang et al. highlighted the therapeutic potential of gallic acid, a natural polyphenol compound, in modulating histone acetylation in prostate cancer [7]. Their study demonstrated that gallic acid inhibits the expression of HDAC1 and HDAC2, two enzymes responsible for removing acetyl groups from histone proteins. By inhibiting these HDACs, gallic acid promotes histone acetylation, leading to increased expression of tumor suppressor genes and a reduction in prostate cancer cell proliferation. These findings underscore the potential of HDAC inhibitors, either from natural sources like gallic acid or synthetically designed compounds, as therapeutic agents in treating prostate cancer by restoring normal histone acetylation levels.

Beyond individual cases, aberrant histone acetylation patterns are part of a broader epigenetic landscape in cancer, where dysregulated acetylation and deacetylation processes can disrupt normal gene expression patterns. Investigating the role of histone acetylation in prostate cancer provides a window into the potential for targeted epigenetic therapies, aiming to reverse these aberrations and restore normal cellular functions.

2.2. Altered histone methylation

Altered histone methylation is a double-edged sword in prostate cancer, as it can both promote and inhibit tumor growth and progression. These modifications occur at specific residues on histone proteins, influencing gene expression patterns that regulate cancer cell proliferation, survival, and therapeutic resistance.

Metzger et al. demonstrated that the histone methyltransferase KMT9 plays a pivotal role in prostate cancer by methylating histone H4 at lysine 12 (H4K12me). This methylation event controls the proliferation of prostate cancer cells and positions KMT9 as a potential target for therapeutic intervention, especially in castration-resistant prostate cancer (CRPC), which no longer responds to androgen deprivation therapy (ADT). The study suggests that KMT9 inhibitors could become first-class treatments for CRPC by halting the tumor-promoting effects of H4K12me [8].

Conversely, Baratchian et al. revealed that histone H3K9 trimethylation (H3K9me3) plays an important role in promoting resistance to AR antagonist therapies. H3K9me3 is an epigenetic mark associated with transcriptional repression, and its accumulation in prostate cancer cells represents an adaptive response to androgen resistance. By silencing AR-target genes, H3K9me3 allows prostate cancer cells to evade the effects of androgen receptor blockade, thereby contributing to the progression of the disease despite ongoing treatment [9]. This trimethylation event is particularly critical in promoting resistance to ADT, which is a major challenge in the management of advanced prostate cancer.

These examples highlight the complexity of altered histone methylation in prostate cancer. While certain methylation marks like H4K12me drive tumor growth and may be therapeutically targeted,

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others like H3K9me3 foster resistance to treatment. This underscores the importance of understanding the specific histone modifications involved in the disease to develop more effective therapeutic strategies. Future research into the context-dependent roles of histone methylation could unveil new ways to combat both the growth and resistance mechanisms in prostate cancer. Moreover, combination therapies that target multiple epigenetic regulators might offer a more comprehensive and effective approach to managing the disease, particularly in advanced or treatment-resistant stages.

2.3. Other related modifications

Phosphorylation, ubiquitination and sumoylation also play a role in the occurrence and development of prostate cancer. Gao et al. showed that CDK1 and CDK9 act as kinases to phosphorylate the androgen receptor at Ser81, thereby activating the transcriptional pathway of the androgen receptor [10]. Androgen receptor plays an important driving role in castration-resistant prostate cancer, and c-Myc is also an oncogene in prostate cancer. Pornour et al. confirmed that the deubiquitinase USP11 upregulates androgen receptor and c-Myc levels through two mechanisms: deubiquitinating androgen receptor and c-Myc proteins to increase their stability, and deubiquitinating the inhibitory histone mark H2A-K119Ub on the promoters of androgen receptor and c-Myc genes to increase their transcription [11]. Therefore, USP11 may be a potential target for combating prostate cancer. Fan et al. demonstrated that ablation of non-canonical ubiquitination of the histone demethylase JMJD1A reduced DNA damage repair gene expression, impaired DNA double-strand break repair, and enhanced the response of prostate cells to radiation, topoisomerase inhibitors, or PARP inhibitors [12]. Therefore, drugs targeting non-canonical ubiquitination of JMJD1A may enhance the response to genotoxic therapy and enhance the response of prostate cancer to radiotherapy. Wang et al. found that in metastatic prostate cancer, upregulated E2 conjugating enzyme UBC9 SUMOylates Flotillin-1 (Flot-1, a lipid raft protein) through small ubiquitin-like modifier (SUMO)-2/3 modification, thereby inhibiting Snail degradation, identifying a SUMOylation signaling axis in the epithelial-mesenchymal transition of metastatic prostate cancer [13]. Xun et al. showed that human hexokinase 2 can be SUMOylated, and SUMO-deficient hexokinase 2 preferentially binds to mitochondria, resulting in increased glucose consumption and lactate production and decreased mitochondrial respiration [14]. This process can lead to prostate cancer cell proliferation and protect cells from chemotherapy-induced apoptosis.

3. Implications for Prostate Cancer Biology

3.1. Impact on gene expression, cell proliferation and survival

Histone modifications play a pivotal role in regulating gene expression, influencing cell proliferation and survival in prostate cancer through various pathways. One key area under investigation is the regulatory mechanism of sex-determining region Y-box 2 (SOX2) in prostate cancer. SOX2 is a transcription factor involved in maintaining stem cell pluripotency, and its dysregulation has been linked to cancer development. Kar et al. demonstrated that histone modifications contribute to the overexpression of SOX2, which, in turn, plays a critical role in the tumorigenesis and progression of prostate cancer [15]. Aberrant SOX2 expression driven by altered histone marks may help sustain the self-renewal and undifferentiated states of cancer stem-like cells, fostering tumor growth and resistance to therapies.

In addition, histone modifications can regulate critical oncogenes like c-Myc, a well-known driver of cancer cell proliferation. Fan et al. showed that histone demethylase JMJD1A plays a crucial role in this regulation by modulating the stability and transcriptional activity of c-Myc in prostate cancer cells. JMJD1A reduces the degradation of c-Myc by inhibiting the activity of HUWE1, an E3 ubiquitin ligase responsible for tagging c-Myc for proteasomal degradation. Furthermore, JMJD1A enhances c-Myc transcription via androgen receptor (AR)-dependent transcriptional activation. The combined effect of stabilizing c-Myc protein and increasing its transcription leads to the proliferation and survival of prostate cancer cells, reinforcing the importance of histone modifications in maintaining oncogene activity in prostate cancer progression [16].

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3.2. Role in metastasis and tumor progression

Histone modifications also significantly impact metastasis and tumor progression in prostate cancer, often by modulating key signaling pathways and transcription factors. For instance, the *phosphatase and tensin homolog* (PTEN) is a critical tumor suppressor gene frequently lost in advanced prostate cancer. Li et al. discovered that the loss of PTEN enhances *AKT* signaling, a major pathway involved in cell survival and growth. Activated AKT phosphorylates the histone methyltransferase *WHSC1* (also known as NSD2), which prevents its degradation, leading to sustained AKT pathway activation. This feedback loop further promotes the aggressive, metastatic behavior of prostate cancer cells, illustrating how histone modifications can be interwoven with oncogenic signaling networks to drive metastasis [17].

Another histone-related mechanism affecting metastasis involves the demethylase JARID1D (also known as KDM5D or SMCY), which targets the trimethylation of histone H3 at lysine 4 (H3K4me3), a mark associated with active gene transcription. Li et al. demonstrated that the expression of JARID1D is significantly downregulated in metastatic prostate tumors. JARID1D normally represses invasion-related genes by removing the activating H3K4me3 mark from their promoters. However, when JARID1D is lost or its expression is reduced, this repression is lifted, allowing for the increased expression of genes that promote invasion and metastasis, leading to a more aggressive tumor phenotype [18].

Furthermore, mutations in histone-modifying enzymes such as *SETD2* have also been implicated in metastasis. Yuan et al. discovered that mutations in SETD2, a methyltransferase responsible for catalyzing H3K36 trimethylation (H3K36me3), can lead to dysregulated interactions with the histone methyltransferase EZH2. Specifically, the loss of SETD2 activity disrupts the methylation of EZH2 at lysine 735 (K735), which is normally required for its degradation. As a result, EZH2 stability is increased, allowing it to persist and promote the metastatic potential of prostate cancer cells through epigenetic silencing of tumor suppressor genes. The accumulation of these epigenetic changes fosters a metastatic phenotype, highlighting the interplay between different histone modifications in driving tumor progression [19].

4. Diagnostic and therapeutic potential

4.1. Histone modifications as biomarkers

Histone modifications have emerged as potential biomarkers for prostate cancer, offering insights into tumor behavior and prognosis. For instance, Nowak et al. found that the phosphorylation of histone H3 in prostate cancer correlates with the proliferation index, Ki-67 expression, and serum prostate-specific antigen (PSA) levels. Ki-67 is a widely used marker for cell proliferation, and the study suggests that histone H3 phosphorylation may serve as a marker for tumor aggressiveness, as its levels parallel those of Ki-67 and PSA, both of which are indicators of tumor progression in prostate cancer [20]. This finding highlights the potential of histone H3 phosphorylation as a prognostic marker for prostate cancer, offering a non-invasive measure of tumor growth and aggressiveness.

Additionally, histone demethylation enzymes like JARID1D (KDM5D) are being studied as potential biomarkers. Li et al. showed that JARID1D inhibits invasion-related genes by demethylating trimethylated histone H3 at lysine 4 (H3K4me3), a gene activation mark. The downregulation of JARID1D in advanced metastatic prostate cancer suggests its potential as a prognostic marker, where lower levels of JARID1D could be indicative of increased invasiveness and poor prognosis [18]. This research provides a theoretical basis for considering JARID1D as a biomarker in advanced prostate cancer, helping to identify patients at higher risk for metastasis.

4.2. Histone deacetylase (HDAC) inhibitors

Histone deacetylase (HDAC) inhibitors have gained attention as a new class of anticancer agents due to their ability to regulate gene expression by altering chromatin structure. HDAC inhibitors can inhibit cancer cell proliferation, induce apoptosis, and sensitize tumor cells to other therapies. Schade et al. found that combining EZH2 and HDAC inhibitors showed promising results in treating castration-

resistant prostate cancer (CRPC). EZH2, a histone methyltransferase, is often overexpressed in aggressive prostate cancers, and the combination of EZH2 and HDAC inhibitors was effective in killing CRPC cells. This combination therapy appears to alleviate the cellular stress response, which often contributes to treatment resistance, improving the therapeutic outcomes for CRPC patients [21].

Moreover, Corno et al. demonstrated that targeting histone deacetylase 6 (HDAC6) in combination with MEK inhibitors has synergistic effects in CRPC cells. The study suggests that this combination can be used to enhance the apoptotic response of prostate cancer cells, presenting a new avenue for targeted therapy. The use of HDAC6 inhibitors in conjunction with MEK inhibitors offers a promising strategy to overcome the treatment resistance seen in advanced prostate cancer, with potential applications in improving patient survival and response to treatment [22].

5. Conclusion

The insights gained from studying histone modifications underscore their critical role in the biology of prostate cancer, influencing gene expression, metastasis, and treatment response. These modifications not only provide valuable biomarkers for diagnosis and prognosis but also highlight potential therapeutic targets, such as histone deacetylase inhibitors. Continued research into these epigenetic mechanisms will be essential for developing more effective strategies to combat prostate cancer, ultimately enhancing patient outcomes.

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