Vidhyayana - ISSN 2454-8596
An International Multidisciplinary Peer-Reviewed E-Journal
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151

Post-Translational Modifications in Progression of Ovarian and Prostate Cancer

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ABSTRACT:

While the main primary structure of a protein is regulated by genetic codes whereas its functionality is mostly controlled by a dynamic transaction in which the functioning of multiple enzymes which are involved in post-translational modifications (PTM). These PTMs acts as crucial mechanism for regulating proteins providing a diversity of cellular activities. Proteins present in proteome could be modified after it has been translated or while it is being translated. The cells usually employ diverse repertory to co-ordinate their responses to regulate transcription and protein localization after external stimuli and to also maintain proteo-stasis. This article comprehends on a salient topic of post-translational changes that have been shown to induce prostate and ovarian cancer. A complete list of single and proteome-wide protein PTMs and their activity in cancer progression is detailed here. The evidence for tumor occurrence is being identifiable by proteome-wide (PTM) analysis is reviewed in this work. Proteome investigations in ovarian and prostate cancer reveals alterations in glycosylation, phosphorylation, ubiquitination, acetylation, SUMOylation and lipidation as well as the enzymes involved are termed as 'crucial modifiers' that controls the activation, deactivation,

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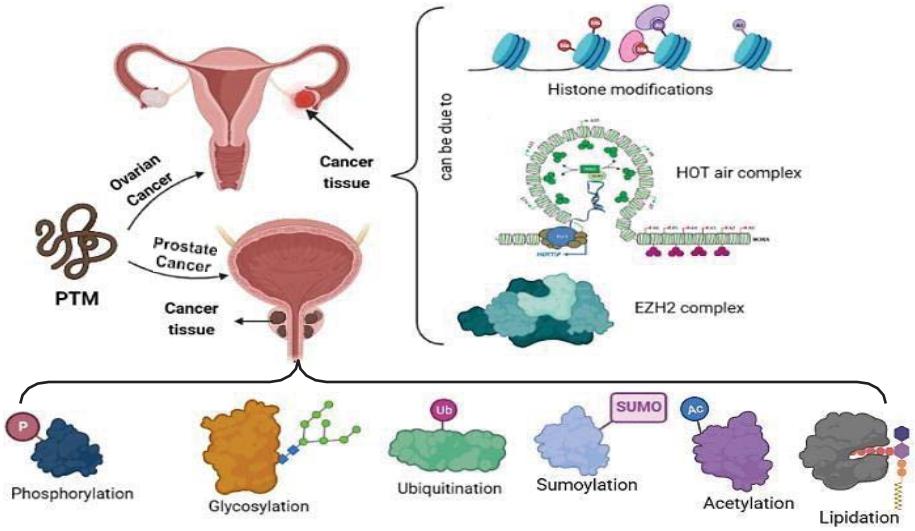
or subcellular localization of signaling proteins, allowing signaling to be initiated, amplified, and transduced more efficiently. Alterations usually result in wide involvement in DNA damage response causing carcinogenesis, proliferation, metastasis and apoptosis of cancer cells. Due to their driving roles in ovarian as well as prostate cancers, PTMs are intensively researched to enhance the treatments of cancer.

KEYWORDS: Post translational modifications, Ovarian Cancer, Prostate Cancer, Histones, Phosphorylation,SUMOylation, Acetylation, Glycosylation, Methylation, Ubiquitination.

GRAPHICAL ABSTRACT:



1. INTRODUCTION:

Scientists have revealed that in recent decades the human proteome is considered most complicated than the human genome. Human proteome contains around one million proteins whilehuman genome is considered to have only 1-2 percent of coding region. These statistics report that a numerous number of proteins can be coded from a single gene. Various mechanisms produce mRNA transcripts from the same gene, including recombination, initiation of transcription process, transcription termination, and transcript alternative splicing. Development of complexity from genome to proteome is supported by PTMs **(Figure 1).** PTMsare molecular alterations that control intracellular molecular interactions with co -

factors, enzymes, lipids, and nucleic acids as well as their activity, localization, and association. Since they control activity, location, and association with other cell components such as other cell components such peptides, biomolecules, lipid, and co - factors, they are essential to functioning systems [1].

Furthermore, because the human proteome is dynamic and changes in response to a variety of stimuli, post-translational modifications are frequently used to modulate cellular function [2] [3]. PTMs are interfered with by enzymes that execute more than 200 kinds of post-translational modifications are predicted to make about 5% of the proteome [4]. Functional groups, proteins,lipids, or sugars are altered by Kinases, phosphatases, transferases, and ligases from amino acid side chains, while proteases break down the peptide bonds to remove nucleotides of a particular sequence or some regulatory components. Many proteins, such as Auto-kinase and Auto- proteolytic domains, may change themselves via autocatalytic domain [5]. Aside from single modification, proteins are frequently changed through a step-wise procedure of protein maturation or activation that involves a combination of post-translational cleavage and the addition of functional groups [6]. Depending on the nature of the alteration, protein PTMs can potentially be reversible [7]. This review discusses the post translational modifications that can lead to various types of cancer like Ovarian and Prostate Cancer [8] [9].

2. POST TRANSLATIONAL MODIFICATIONS (PTMS):

As stated above, possible protein changes are conceivable due to modifications in PTMs. As a result, this review covers few of the most frequent forms of PTMs explored in Ovarian and Prostate cancer. Furthermore, PTMs caused because of phosphorylation, glycosylation, and ubiquitination will be discussed in details. Phosphorylation, acetylation, ubiquitination, and SUMOylation are some of the examples of post-translational changes that can affect target protein function, intracellular distribution, protein interactions, and protein lifespan [10] [11]. Phosphorylation is one of the most prevalent and well-studied protein modifications, with more than 500 distinct kinases catalyzing the process in mammals [12]. Serine, threonine, and tyrosine residues of target substrate proteins are the most often phosphorylated. Protein

stability, protein interactions, protein cellular localization, and enzyme activity are all influenced by the varied substrates and phosphorylation sites [13].

Ubiquitination a post-translational protein modification technique that governs a variety of biological processes, including immunological responses, apoptosis and cancer. The ubiquitin activating enzyme E1, the ubiquitin conjugating enzyme E2, and the ubiquitin ligase E3 are the primary enzymes involved, with the E3 ligase determining the substrate specificity [14]. As a commonly utilized post-translational protein modification, SUMOylation has gotten a lot of interest. This route is found in virtually all eukaryotes and is required for genomic integrity, transcriptional control, gene expression, and intracellular signal transduction regulation [15]. Mitochondrial division, ion channels, and biological rhythms are all regulated by small ubiquitin-like modifier (SUMO). As a result, in complicated protein regulatory networks, many levels of regulation or SUMOylation may play a crucial role. SUMOylation dysfunction can lead to the development of illnesses and malignancies [16] [17].

2.1. Overview of Ovarian Cancer:

Epithelial ovarian cancer (EOC) has the highest malignancy and mortality rate in United States. 75 percent of women are diagnosed with stage III-IV cancer, which has widely spread metastases at the time of diagnosis results in 25% of survival rate. Women identified before to metastatic dispersion, on the other hand, had a 95 percent chance of surviving. These figures underline the critical need of developing early detection tools and a complete understanding of molecular, cellular, and biological mechanisms that drive metastasis [18].

Direct extension of original ovarian or fallopian tube tumors, as well as exfoliation of single cells and multicellular aggregates (MCAs, or spheroids) into the peritoneal cavity, where spread is aided by the buildup of ascites fluid, causes EOC metastases. Ascites has a high prevalence of metastatic MCAs, which vary in size, quantity, and integrity. In vitro, patient-derived ascites MCAs have been shown to attach to live human mesothelial cell monolayers and sub-mesothelial extracellular matrix (ECM). In vivo, free floating cells and MCAs adheres to the peritoneal membrane of mesothelial cells that surrounds organs in abdomen region, causing them to retract and anchor with the collagen-rich sub-mesothelial extracellular matrix

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and proliferate to produce extensively spread secondary lesions. A novel hematogenous pathway for EOC metastases to the ovary and peritoneal cavity, accompanied by the formation of ascites, has recently been discovered. The mechanisms that control broad intraperitoneal metastasis, on the other hand, are yet unknown [19] [20]. **Figure 2** depicts the overall 4 stages of Ovarian cancer.

2.1.1. PTMs in progression of Ovarian Cancer:

The most frequent subtype of epithelial ovarian cancer (SEOC) is high grade serous epithelial ovarian cancer (HGSEOC), which has the greatest death rate of all gynecological malignancies. Surgical debulking is the gold standard, followed by platin-based medication combinations like carboplatin and paclitaxel. There have been reports of interactions between histone modifications and DNA methylation that regulate gene expression [21] [22].

i. Post-Translational Modifications in Histones:

Histones are basically small proteins with a high fraction of positively charged amino acids, weighing roughly around 14 kDa [23], the most prevalent proteins which are attached to the DNA and they primarily govern gene expression and DNA packing around nucleosomes, which are chromatin's functional units. A histone octamer comprises each of two copies of the key histone proteins i.e. H2A, H2B, H3, and H4 cloaked around the DNA of 147bp to frame a nucleosomes. H3:H4 is a tetramer in this structure, and there are two H2A:H2B dimers [24]. H1 is a histone linker that links nucleosomes together, resulting in chromatin compaction at a higher level [25]. NH2- terminal histone tails extend from the core octamer structure, with residues in these tailssensitive to a wide range of dynamic and reversible PTMs such as methylation,acetylation, phosphorylation, ubiquitination, and SUMOylation, to name a few [26]. This field has lately adopted new language to describe chromatin "writers" who recordsthe histone alterations, chromatin "erasers" which eliminate them, and chromatin "readers" who analyze signals and might influence subsequent variations. "Open" chromatin and effective transcription have also been associated with H3K4me2, H3K4me3, H3K79me, H3K36me, H2Bub1. Various other chromatin changes, including H3K9me, H3K27me, etc. are linked to transcriptional repression and "closed" chromatin. Due to a more relaxed and

open chromatin structure, suppressing H3K27me3 in cell lines overexpressing the dominant negative mutant H3-K27Rresulted in re-expression of the RASSF1 tumor suppressor and re-sensitization of ovarian cancer cells to cisplatin [27] [28].

Histone acetylation is controlled by HATs and HDACs in a dynamic way, which usually promotes transcription. Acetylation works by neutralizing the positive charge of lysine residues on histone tails, causing nucleosome structure to be disrupted and local DNA to be unfolded, making it more accessible to transcription machinery [29]. Enzymes known as HDACs are associated with gene regulation because they eliminateacetyl residues from DNA. In numerous cancers, including ovarian cancer, dysfunctional HDAC mechanisms are considered to promote cancer metastasis and tumor growth. Histone tail residues, like as lysine 120 of histone H2B, which may be acetylated in addition to being monoubiquitinated, can serve as platforms for various enzyme writers (H2BK120ac) [30].

According to **Figure 3**, Histone acetyl transferases (HATs) operate as a predecessor forH2B on the exact residue of amino acids when histone H2B's Lysine 120 is acetylatedin cases of ovarian cancer. (B) Histone H2B's lysine 120 is deacetylated by histone deacetylases (HDACs), which enables the RNF20/RN40 E3 ubiquitin ligase complex to work also with PAF1 transcriptional regulatory complex (PAFC) to render lysine 120 monoubiquitinated (H2Bub1). (C) SET1 is attracted to the H2Bub1 site, where it engages in an interaction involving COMPASS (complex of proteins associated with Set1) to promote the functional mark of methylation histone 3 at lysine 4. (H3K4me). (D) The activated chromatin marker of the H3, methylated at lysine 79 is created by DOT1L methyltransferase, which may be recruited and activated by H2Bub1 (H3K79me). H2BK120ac is likely to come before H2Bub1 in this scenario, implying that it might be an early marker of poised or active chromatin that acts as a dual switchfor keeping nucleosomes "hot" during cycles of induction and transcriptional elongation [31] [32].

Sirtuins, a family of seven histone de-acetyltransferases that are abnormally produced in cancer, are one type of histone de-acetyltransferase. They are human homologs of Sir2, which may operate as deacetylases for non-histone proteins like p53 in addition to acting as

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HDACs. Nicotinamide adenine dinucleotide (NAD+) is required for the lysine deacetylase SIRT1. SIRT1 expression was shown to be greater in malignant EOCthan benign EOC, and it was detected more frequently in SEOC than mucinous tumors[33].

The evidence supporting the idea that subpopulations of cells in SEOC that are like stem cells, exhibit chemotherapy resistance, and chemoresistance development in ovarian cancer patients. A recent research discovered that the bivalent chromatin mark H3K27me3/H3K4me3, which is expressed in embryonic stem cells and needed for the silencing of developmental genes, is also detectable in SEOC near the transcription startsites of repressed genes. In SEOC and cancer-associated stromal cells, EZH2 is overexpressed. In ovarian cancer, H3K27me has also been linked to chemoresistance. Histone PTMs are important for maintaining the undifferentiated stem cell phenotype [34] [35]. Histone PTMs in primary tumors have been demonstrated to correlate with tumor stage and prognosis, confirming findings in cancer cell line models with complexhistone modifications. The loss of global H3K27me3 has been linked to reduced overall survival in ovarian, breast, and pancreatic malignancies. In advanced breast tumors, as well as colon, lung, parathyroid, and ovarian malignancies, loss in H2Bub1 levels has been noted [36].

ii. Splicing of Histones in Differential Modes:

Although evidence shows that histone splice variants have a role in tumor growth, andslight structural alterations to the core histone octamer caused by the inclusion of differently spliced histones can influence the overall shape of the nucleosome, affectinghow DNA wraps around it and nucleosome dynamics [37]. These non-canonical variations can affect the function of chromatin domains and cause nucleosome stability differences, resulting in abnormal transcription and DNA repair [38]. In ovarian cancer, histone splicing has just recently been discovered to play a role. Proliferation has been linked to alternative histone splicing of a collection of H2A-type histone variants known as macroH2As (macroH2A1.1, macroH2A1.2, and macroH2A2) in a variety of malignancies, including ovarian cancer. MacroH2A1 alternative pre-mRNA splicing is regulated by the RNA binding protein QKI (Quaking). Surprisingly, macroH2A1.1- mediated proliferation inhibition involves a drop in

PARP1 protein levels, at least in part. Given the growing interest in PARP1 inhibition as a treatment option, further research is needed [39]. Histone variation H2A.Z, which was shown to be down- regulated in ovarian cancer and whose loss led in tumor development, was also discovered as being down-regulated [40]. H2A.Z was found to be missing from urokinase receptor (u-PAR) regulatory areas in the ovarian cancer cell lines A2780 and OVCAR3, resulting in u-PAR activation and proposing a mechanism for u-PARoverexpression reported in a variety of malignancies. Furthermore, expression of linkerhistone H1 splice variants has been demonstrated to distinguish ovarian adenocarcinomas from adenomas, indicating that they might be useful as ovarian cancerepigenetic biomarkers [41].

2.2. Overview of Prostate Cancer:

Prostate cancer (**Figure 4**) is the considered fifth most common cause of death and second most prevalent cancer in males. Because androgens and its receptors (AR) are considered as regulators of prostate cancer and the downregulation of AR signaling, which may be done by a variety of techniques, is one of the therapeutical approaches for treating prostate cancer. Although this strategy produces positive outcomes in the early stages of treatment, a significant portion of individuals acquire resistance to medication and develop castration-resistant prostate cancer (CRPC). Prostate cancer has a lower frequency of mutations and other genetic alterations than other cancer types [42]. The genetic changes in prostate cancer are due to formation of a TMPRSS2/ERG fusion protein, AR amplifications, PTEN deletions, and p53 mutations. Mutations in the E3 ubiquitin ligase adaptor SPOP, which is discovered early during prostate cancer development, are also common genetic abnormalities in a subgroup of prostate cancer patients [43].

2.1.2. PTMs in progression of Prostate Cancer:

Biological systems are known for their tremendous complexity, which is maintained through the coordinated activities of a large number of participants. Proteins are one of the most important macromolecules, performing a wide range of tasks including as signaling, transport, metabolic processes, and structural support. Majority of proteins undergo a variety of post-translational modifications (PTMs), which are chemical changes that have a significant impact

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on their activity and functional capacities. Phosphorylation, glycosylation, ubiquitination, SUMOylation, acetylation, and lipidation are the most prevalent PTMs [44]. A growing number of proteome-wide PTM investigations are revealing global alterations in PTMs in various experimental contexts. There are around 300 distinct forms of protein PTMs, however only a tiny percentage of them have been studied at the proteome level. PTMs increase the size of the proteome from dozens to millions of potential protein types, demonstrating the difficulty of assessing PTMs worldwide [45]. When protein expression and mutations do not alter across circumstances but changes the function or activity of proteins by PTM levels, the proteome-wide approach to studying PTMs is extremely helpful and reliable. Proteome investigations in prostate cancer reveal alterations in phosphorylation, glycosylation, ubiquitination, SUMOylation, and palmitoylation in various experimental situations [46].

iii. Phosphorylation:

Phosphorylation is one of the most common studies for PTMs. Around 60% of proteins are thought to be phosphorylated for a short period of time. This PTM governspractically every aspect of cellular activities, from growth, differentiation, and death tocell signaling, by acting as a molecular switch for protein function. Many malignancies,including prostate cancer, are caused by protein phosphorylation (kinases and phosphatases). AR and PTEN/PI3K/AKT/mTOR axis are controlled by phosphorylation guiding activities they take. Many distinct enzymes phosphorylate AR at 18 different locations, affecting its stability, nuclear localization, and transcriptional activity, which determines the prostate cancer cell destiny [47].

At every stage of the metastatic process, EphA2, steroid receptor coactivator (SRC) family tyrosine kinases, TGF, FAK, PKM2, TNF, and chemokine signaling, among other proteins, promote prostate cancer metastasis development. In prostate cancer bonemetastases (the major location of prostate cancer spread), the CXCL12/CXCR4 signaling axis is involved in the creation of the niche, and inhibiting this axis impairs the early establishment of tumors in the bone microenvironment. On the other hand, only members of the growth factor receptor inhibition family are vulnerable to increasing bone cancers [48]. Many kinases phosphorylate

and activate cytoplasmic adaptor proteins, which serve as a connection between kinases and other events in signaling cascades. Prostate cancer biology has been found to be influenced by a number of adaptor proteins. FRS2 (FGF receptor substrate 2), for example, is a FGF receptor-associated protein that has been demonstrated to control prostate growth, regeneration, tumorigenesis, and tumor angiogenesis. GRB10 (growth factor receptor-bound protein 10) has recently been found to have a pro-proliferative effect in prostatecancer and to maintain AR activity via interacting with PP2A [49]. As a result, phosphor-proteome research can provide light on their deregulations. Drake's lab discovered that the kinases MERTK and NTRK2 are involved in prostate cancer bone and visceral metastasis. Another mouse research found increased kinase signaling in prostate cancers, including EGFR, EPHA2, JAK2, ABL1, and SRC tyrosine kinase activation. Investigations on the activities of particular proteins, as well as phosphor- proteome studies, when combined, provide a comprehensive picture of phosphorylationdysregulation in prostate cancer and its driving role in prostate cancer biology [50].

iv. Glycosylation:

The carbohydrate (glycan) getting attached to functional groups of amino acids is known as glycosylation. N-glycosylation occurs when glycans are attached to the amide group of an asparagine (Asn) residue in the endoplasmic reticulum, whereas O- glycosylation occurs when glycans are added to the hydroxyl oxygen of serine/threonine residues (Ser/Thr) in the Golgi apparatus [51]. Glycosylation involves hundreds of enzymes, and attached glycans, unlike other PTMs, are exceedingly varied,adding greatly to the complexity of the final protein structure [52]. Glycosylation is the most prevalent PTM in cells, and it plays a role in cell adhesion and metastasis, as well as signal transmission across the plasma membrane and immunological regulation.

Glycogene expression is mostly controlled by gene polymorphisms or stable epigenetic regulation, which is frequently disrupted in cancer [53]. Glycosylation and the enzymes involved in it are important in the development of prostate cancer. In prostate cancer, glycogens involved in the synthesis of both O- and N-linked glycans are dysregulated,

affecting a wide range of cellular processes such as cell proliferation, migration, apoptosis, and viability, as well as tumor development and metastasis formation in vivo.In malignancies, sialic acid residues or sialylation is disrupted. The cancer-associated sialyl-Tn glycan (sTn), which enhances prostate cancer cell adherence and whose expression is demonstrated to be controlled by AR, as well as the sialylated blood group antigen Sialyl Lewis X (SLeX) regulates prostate cancer development through several ways. The addition of a fucose to a glycan, either as a terminal glycan or to the core structure, is known as fucosylation [54] [55]. Proteins that are heavily glycosylated are known as proteoglycans. Versican, decorin, biglycan, lumican, and syndecan-1 are among the proteins that have been demonstrated to impact prostate cancer cell survivaland metastasis [56]. Galectins are glycan-binding proteins that have been investigated extensively in the field of prostate cancer research, with galectin-3 being one of them. Galectin-3 has been connected to tumor growth as well as bone remodeling in the bonemetastases niche. In addition to playing key roles in prostate cancer, glycosylation hasthe potential to act as a source of biomarkers for disease development and severity, which is a valuable contribution to the area of prostate cancer research [57] [58].

v. Ubiquitination:

Given the importance of ubiquitination in so many biological processes, it's no surprisethat its lack of precise regulation contributes to a variety of diseases, including prostate cancer. Speckle-type poxvirus and zinc finger (POZ) protein (SPOP) has been reported to be the most prominent enzyme in ubiquitination in prostate cancer [59]. The number of instances with genetic mutations in prostate cancer ranges from 4.4 percent to 28.6 percent, while the number of cases with downregulation varies from 25.2 to 93.5 percent. SPOP mutations are frequently found in the domain of substrate binding, indicating that it has a biological function [60]. While the function of SPOP protein varies by tumor type, it appears to operate as a tumor suppressor in prostate cancer, and its targets include AR, ERG, BRD4, MYC, TRIM24 and steroid receptor coactivator 3 (SRC3, among others for degredation. SPOP's critical function in prostate carcinogenesis has been demonstrated in a variety of mice models, in which mutations in SPOP activate the PI3K/mTOR pathway and cause prostate cancer [61].

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vi. SUMOylation:

Small Ubiquitin-related MOdifier (SUMO) proteins are covalently added to proteins through an iso-peptide bond forming between the SUMO protein's C terminal and the lysine in the amino group of the substrate protein. There are four different types of SUMO proteins (SUMO-1, SUMO-2, SUMO-3, and SUMO-4). Ubiquitin and SUMO-1 are somewhat similar at the structural levels, and hence the mechanisms of ubiquitination and SUMOylation are also similar, despite their amino acid sequence differences. The SUMOylation process also involves three enzymatic steps: SUMO activation by enzyme E1 (such as the SUMO-activating enzyme SAE1/2); SUMO conjugation by enzyme E2 (UBC9—the only SUMO E2 conjugating enzyme discovered to date and the best-characterized E2 enzyme); and SUMO ligation by enzyme E3 (such as PIAS/RANBP2/hPC2) [62].

Wen *et al*. identified SUMOylated proteins in SUMO stably transfected PC-3 cells using quantitative proteomics. He discovered over 900 possible SUMO target proteins. They also discovered that mutating USP39's recently discovered SUMO modification sites enhances USP39's proliferation-enhancing impact on prostate cancer cells. SUMO-1 modification of PTEN controls carcinogenesis via modulating its interaction with the plasma membrane, which impacts the PI3K/AKT pathway, among other proteins important in prostate cancer. Furthermore, testosterone promotes treatment- resistant prostate cancer via inducing SUMO-mediated p53 nuclear export. SUMOylation regulates the pro-invasive features of prostate cancer cells; it was shown that SUMOylation regulates SNAIL1 in response to TGF stimulation, and that p14ARF stabilizes SLUG by increasing SUMOylation at lysine residue 192 The Palvimolaboratory discovered that PIAS1 is a chromatin-bound AR coregulator that regulates prostate cancer cell proliferation by targeting certain genes [63]. SENP1 is a cleaving enzyme for SUMO-1 and also promotes prostate cancer cell EMT by modulating SMAD4 de-SUMOylation and PTEN stability, all of which contribute to prostate cancer progression. SPOP induces cellular senescence by degrading SENP7, which hasbeen linked to the ubiquitination pathway in prostate cancer. Taken together, these findings suggest that the SENPs studied in prostate cancer cause cancer development and a malignant phenotype, whereas the studies on SUMOylation demonstrated that prostate cancer driving proteins are

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often modified [64].

vii. Acetylation:

Protein acetylation is highly specialized post translational modification method in which proteins accept from acetyl donors such as acetyl CoA via acetyltransferase catalysis and is one of the most important regulators of gene transcription. Acetylation was initially recognized as a mechanism affecting histones, and when lysine is acetylated, histones become less positively charged, allowing DNA to attach more easily to the histone, facilitating gene transcription [65]. In prostate cancer, acetylation of H2A.Z is linked to oncogenes and neo-enhancers activation. Because the number ofcellular proteins undergoing acetylation in androgen-dependent prostate cancer was higher than in androgen-independent prostate cancer, it was suggested that the transition from androgen-dependent to androgen-independent prostate cancer waslinked to changes in protein lysine acetylation [66]. Studies showing that resveratrol increases p53 acetylation and apoptosis in prostate cancer via blocking the MTA1/NuRD complex have provided mechanistic insights into p53 acetylation [67]. Prostate cancer development is aided by the transcription factors Krüppel-like factor 5 and 6 (KLF5 and KLF6). KLF5 acetylation is implicated in TGF-induced docetaxel resistance and governs luminal differentiation of basal progenitors in prostate growth and regeneration. It's also been proposed that acetylation regulates KLF6's function.

Finally, abnormal acetylation of several proteins, as well as single proteins, isimplicated in many facets of prostate cancer development [68].

3. RESULTS AND DISCUSSION:

Numerous anatomical variants and intricate gene expression profiles of Ovarian Cancer (OC) all contribute to its stealthy beginning. Prior studies is constrained by the limited documented study data sets, the paucity of a causative link between the connection of miRNA with illness incidence and the absence of particular OC diagnostics which may guide overall assessment of miRNA. Moreover, it is challenging to evaluate research findings owing to the absence of defined techniques for acquisition of samples as well as RNA isolation, in addition to just under

perfect screening of specific clinical variances. LncRNAs have a role in the progression, incursion, and spread of OC.

The development of tumors as well as medication sensitivity are significantly affected by aberrant histone modification and DNA methylation. The methyl status of certain loci in healthy and OC tissues is frequently compared using DNA methylation. Nevertheless, because to the considerable variation in response rate, biological makeup, and processing method, study of the DNA methylation patterns is constrained. Scientific trials for antagonists are still being conducted, and research of histone-modified molecules is still in its early stages. In order to make informed treatment choices and identify novel chemotherapeutic drugs targets, it is essential to comprehend the biological processes driving chemotherapy sensitivity. The precision medicine of Ovarian Cancer with DNMT inhibitors and HDAC inhibitors, or possibly a blend of the two, demonstrated massive promise.

In order to incorporate the physiological functions as well as clinical manifestations of tumor characterization at the cellular scale into medical care, further research will be necessary with in foreseeable. Additionally, quasi methods are preferable to intrusive biopsies techniques, such as potential marker discovered in the plasma or urination. When employing epigenetic-based treatments, immune toxicities and other responses will be crucial factors to take into account. In this way, epigenetic research has indeed impacted our knowledge of OC, even if our rational design of how cellular processes work is still in its infancy. Main hurdles currently exist as a result of inadequate therapy objectives as diagnostic methods for OC. The rise of epigenetics offers created an unique window again for search for precise diagnostics but also treatments which may well one day revolutionize this field of OC diagnostic.

PTMs' crucial role in prostate cancer development has been demonstrated in methodology earlier. As a result, targeting PTMs provides a chance to disrupt critical processes in cancer biology because the enzyme known as kinase, are the driving proteins in cell proliferation andspread, multiple medicines using tyrosine kinase receptor as a target and been employed in neoplasia as the primary or secondary therapies in a variety of tumor types throughout the previous two decades. Despite promising exploratory results, targeting the PI3K-AKT-mTOR

system in prostatic malignancy is anticipated to really be challenging due to numerous regulatory and feedback control looping along with redundancy measures that restrict total route inhibition. As a result, researchers are looking at combining medicines.

Due to the reasons of drug tolerance, they are likely to differ greatly across individuals and tumors, phosphor-proteome investigations provide another avenue for prostate cancer management based on phosphorylation. Analyzing cancer patients' phosphor-proteomic patterns might help utilizing patient categorization and the information shall be employed in customized therapeutic environments. Tailored phosphor-proteomics, as well as investigation of regulatory pathways underlying distinct malignancies, aids customized treatment by identifying indicators of route movement and, as a result, identifying possible targets. As indicated in the introduction, CRPC affects a significant subgroup of patients, making treatment choices poorer. The invasive subset of prostatic malignancy termed as neuronal prostate cancer (NEPC) is a source of therapeutic response and carries a bad prognostic. It is most frequently observed in final phases of prostate tumors i.e. T3 or T4.

In the search for new anti-cancer medications, the method of targeting oncogenic proteins for degradation is frequently employed. PROTAC, short for proteolysis targeting chimaera, is a protein-binding enzyme that can interact with an ubiquitin ligase called E3 and the other that binds to a protein that is intended for disintegration. In this way, PROTAC can eliminate some unwanted proteins. In men with metastatic CRPC, AR PROTAC's initial trial findings, which were just released, demonstrated a modest efficacy and a good safety record. Additional PTMs may be prescribed to cure prostate cancer since they possess a significant impact on AR.

In vitro investigations have shown that SENP and the inhibitors of SUMO enzymes are effective in treatment of prostate cancer. While further research into this technique in prostate cancer is needed, (de-)acetylation inhibitors are currently being employed in clinical studies. Vorinostat, pracinostat, panobinostat, and romidepsin, HDAC inhibitors, were tested in phase II clinical trials for prostate cancer, however the findings were insufficient to propose phase III studies since the majority of patients had either toxicity or disease progression. The CBP/p300 bromodomain inhibitor CCS1477, which is presently the sole in the clinical trials, is being

studied for the treatment of prostate cancer. In an *in vivo* model, inhibiting SRC myristoylation results in the decrease of activity of kinase and slowed the progression of prostate tumor. Furthermore, "statins" also termed to be cholesterol synthesis inhibitors have been linked to prostate cancer prevention and positive clinical results. Despite their critical role in cancer progression, glycans continue to be ignored in drug development methods, owing to the intricacy of the glycosylation approaches and the technological limitations in investigating PTMs. Furthermore, other researchers believe that glycans when targeted might usher in a new age of cancer therapy, owing to the fact that glycans are implicated in carcinogenesis and are mandatory in the failure of current oncogenic treatments. The Glycosylation process is a globally known to be an androgen-governed process that is required for prostatic carcinoma cell survival, indicating that loss of certain glycosylation enzymes may contribute to malignancy regression after ADT. PTMs' key involvement in prostate cancer biology is generally acknowledged in attempts to discover novel medications to treat the illness, with several promising compounds making significant progress in (pre)clinical and epidemiological investigations of prostate cancer. PTMs have the potential to be biomarkers that may guide future research and therapeutic methods, in addition to being therapy targets.

4. CONCLUSION:

In the epigenome of ovarian carcinoma, targeting histone alterations and the enzymes that regulate them provides a largely untapped option. With more attention paid to this research, new medications targeting DUBs HTMases, and HDACs are likely to emerging as the next cancer therapies within the next decade. To guarantee that patients obtain the most benefit from these medicines, intricate signaling and dysregulation of histones must be researched. PTMs affect the activity, expression, stability, and location of the key drivers of prostate cancer development, such as AR, PTEN/PI3K/AKT/mTOR, STAT3, and NKX3.1. Furthermore, numerous PTM enzymes are unregulated in prostate cancer, which influences prostate cancer cell activity. PTMs have been extensively studied in attempts to enhance prostate cancer therapy due to their pivotal involvement in the disease. Although overexpression and/or mutational status of proteins do not change in neoplasia but somehow the proteins merely vary throughout the Posttranslational modifications. Furthermore, single protein PTM investigations

are used in conjunction with proteomics to provide a comprehensive list of PTMs in prostate cancer.

5. CONFLICT OF INTEREST:

Author declares no conflict of interest.

6. FUNDING:

The author declares that no funding was received for the present work.

7. ETHICAL APPROVAL:

This study does not involve experiments on animals or human subjects.

8. DATA AVAILABILITY:

This study paper contains all of the gathered and analyzed data.

REFERENCES:

[1] Khoury GA, Baliban RC, Floudas CA. Proteome-wide post-translational modification statistics: frequency analysis and curation of the swiss-prot database. Sci Rep. 2011; 1:90.

[2] Oo HZ, Seiler R, Black PC, *et al*. Post-translational modifications in bladder cancer: Expanding the tumor target repertoire. Urol Oncol Semin Orig Investig. 2020; 38:858–866.

[3] Chen L, Liu S, Tao Y. Regulating tumor suppressor genes: post-translational modifications. Signal Transduct Target Ther. 2020; 5:90.

[4] Qian M, Yan F, Yuan T, *et al*. Targeting post-translational modification of transcription factors as cancer therapy. Drug Discov Today. 2020; 25:1502–1512.

[5] Martín-Bernabé A, Balcells C, Tarragó-Celada J, *et al*. The importance of post-translational modifications in systems biology approaches to identify therapeutic targets in cancer metabolism. Curr Opin Syst Biol. 2017; 3:161–169.

[6] Zhao Y, Jensen ON. Modification-specific proteomics: Strategies for characterization of post-translational modifications using enrichment techniques. Proteomics. 2009; 9:4632–4641.

[7] Wang Y-C, Peterson SE, Loring JF. Protein post-translational modifications and regulation of pluripotency in human stem cells. Cell Res. 2014; 24:143–160.

[8] Spoel SH. Orchestrating the proteome with post-translational modifications. J Exp Bot. 2018; 69:4499–4503.

[9] GAO Y, HA Y-S, KWON TG, *et al*. Characterization of Kinase Expression Related to Increased Migration of PC-3M Cells Using Global Comparative Phosphoproteome Analysis. Cancer Genomics - Proteomics. 2020; 17:543–553.

[10] Xu Y, Chou K-C. Recent Progress in Predicting Posttranslational Modification Sites in Proteins. Curr Top Med Chem. 2015; 16:591–603.

[11] Ramazi S, Allahverdi A, Zahiri J. Evaluation of post-translational modifications in histone proteins: A review on histone modification defects in developmental and neurological disorders. J Biosci. 2020;45.

[12] Mann M, Jensen ON. Proteomic analysis of post-translational modifications. Nat Biotechnol. 2003; 21:255–261.

[13] Blom N, Sicheritz-Pontén T, Gupta R, *et al*. Prediction of post-translational glycosylation and phosphorylation of proteins from the amino acid sequence. Proteomics. 2004; 4:1633–1649.

[14] Huang K-Y, Lee T-Y, Kao H-J, *et al*. dbPTM in 2019: exploring disease association and cross-talk of post-translational modifications. Nucleic Acids Res. 2019;47: D298–D308.

[15] Ryšlavá H, Doubnerová V, Kavan D, *et al*. Effect of posttranslational modifications on enzyme function and assembly. J Proteomics. 2013; 92:80–109.

[16] Sedek M, Strous GJ. SUMOylation is a regulator of the translocation of Jak2 between nucleus and cytosol. Biochem J. 2013; 453:231–239.

[17] Mustfa SA, Singh M, Suhail A, *et al*. SUMOylation pathway alteration coupled with downregulation of SUMO E2 enzyme at mucosal epithelium modulates inflammation in inflammatory bowel disease. Open Biol. 2017;7.

[18] Krzystyniak J, Ceppi L, Dizon DS, *et al*. Epithelial ovarian cancer: the molecular genetics of epithelial ovarian cancer. Ann Oncol Off J Eur Soc Med Oncol. 2016;27 Suppl 1: i4–i10.

[19] Farley J, Fuchiuji S, Darcy KM, *et al*. Associations between ERBB2 amplification and progression-free survival and overall survival in advanced stage, suboptimally-resected epithelial ovarian cancers: a Gynecologic Oncology Group Study. Gynecol Oncol.

2009; 113:341–347.

[20] Spentzos D, Levine DA, Ramoni MF, *et al*. Gene expression signature with independent prognostic significance in epithelial ovarian cancer. J Clin Oncol. 2004; 22:4700–4710.

[21] Visintin I, Feng Z, Longton G, *et al*. Diagnostic Markers for Early Detection of Ovarian Cancer. Clin Cancer Res. 2008; 14:1065–1072.

[22] Lisio M-A, Fu L, Goyeneche A, *et al*. High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. Int J Mol Sci. 2019; 20:952.

[23] Luger K, Mäder AW, Richmond RK, *et al*. Crystal structure of the nucleosome core particle at 2.8 Å resolution. Nature. 1997; 389:251–260.

[24] Medrzycki M. Profiling of linker histone variants in ovarian cancer. Front Biosci. 2012; 17:396.

[25] Th'ng JPH, Sung R, Ye M, *et al*. H1 Family Histones in the Nucleus. J Biol Chem. 2005; 280:27809–27814.

[26] Barski A, Cuddapah S, Cui K, *et al*. High-Resolution Profiling of Histone Methylations in the Human Genome. Cell. 2007; 129:823–837.

[27] Hayashi A, Horiuchi A, Kikuchi N, *et al*. Type-specific roles of histone deacetylase (HDAC) overexpression in ovarian carcinoma: HDAC1 enhances cell proliferation and HDAC3 stimulates cell migration with downregulation of E-cadherin. Int J Cancer. 2010; 127:1332–1346.

[28] Zhang K, Dent SYR. Histone modifying enzymes and cancer: Going beyond histones. J Cell Biochem. 2005; 96:1137–1148.

[29] Gatta R, Dolfini D, Zambelli F, *et al*. An acetylation-monoubiquitination switch on Lysine 120 of H2B. Epigenetics. 2011; 6:630–637.

[30] Ropero S, Esteller M. The role of histone deacetylases (HDACs) in human cancer. Mol Oncol. 2007; 1:19–25.

[31] Roth SY, Denu JM, Allis CD. Histone acetyltransferases. Annu Rev Biochem. 2001; 70:81–120.

[32] Marmorstein R, Roth SY. Histone acetyltransferases: function, structure, and catalysis. Curr Opin Genet Dev. 2001; 11:155–161.

[33] Wen L, Chen Z, Zhang F, *et al*. Ca 2+ /calmodulin-dependent protein kinase kinase β phosphorylation of Sirtuin 1 in endothelium is atheroprotective. Proc Natl Acad Sci. 2013;110.

[34] Makris G-M, Manousopoulou G, Battista M-J, *et al*. Synchronous Endometrial and Ovarian Carcinoma: A Case Series. Case Rep Oncol. 2017; 10:732–736.

[35] Heitz F, Amant F, Fotopoulou C, *et al*. Synchronous ovarian and endometrial cancer--an international multicenter case-control study. Int J Gynecol Cancer. 2014; 24:54–60.

[36] Wei Y, Xia W, Zhang Z, *et al*. Loss of trimethylation at lysine 27 of histone H3 is a predictor of poor outcome in breast, ovarian, and pancreatic cancers. Mol Carcinog. 2008; 47:701–706.

[37] Zlatanova J, Bishop TC, Victor J-M, *et al*. The Nucleosome Family: Dynamic and Growing. Structure. 2009; 17:160–171.

[38] Vardabasso C, Hasson D, Ratnakumar K, *et al*. Histone variants: emerging players in cancer biology. Cell Mol Life Sci. 2014; 71:379–404.

[39] Novikov L, Park JW, Chen H, *et al*. QKI-Mediated Alternative Splicing of the Histone Variant MacroH2A1 Regulates Cancer Cell Proliferation. Mol Cell Biol. 2011; 31:4244–4255.

[40] Gévry N, Hardy S, Jacques P-É, *et al*. Histone H2A.Z is essential for estrogen receptor signaling. Genes Dev. 2009; 23:1522–1533.

[41] Gévry N, Chan HM, Laflamme L, *et al*. p21 transcription is regulated by differential localization of histone H2A.Z. Genes Dev. 2007;21:1869–1881.

[42] Uo T, Sprenger CC, Plymate SR. Androgen Receptor Signaling and Metabolic and Cellular Plasticity During Progression to Castration Resistant Prostate Cancer. Front Oncol. 2020; 10:580617.

[43] Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019; 10:63–89.

[44] Khoury GA, Baliban RC, Floudas CA. Proteome-wide post-translational modification statistics: frequency analysis and curation of the swiss-prot database. Sci Rep. 2011;1.

[45] Shorning BY, Dass MS, Smalley MJ, *et al*. The PI3K-AKT-mTOR Pathway and Prostate Cancer: At the Crossroads of AR, MAPK, and WNT Signaling. Int J Mol Sci. 2020;21.

[46] Kaler J, Hussain A, Haque A, *et al*. A Comprehensive Review of Pharmaceutical and Surgical Interventions of Prostate Cancer. Cureus. 2020;12: e11617.

[47] Venkadakrishnan VB, Ben-Salem S, Heemers H V. AR-dependent phosphorylation and phospho-proteome targets in prostate cancer. Endocr Relat Cancer. 2020;27: R193–R210.

[48] Shah K, Bradbury NA. Kinase modulation of androgen receptor signaling implications for prostate cancer. Cancer cell Microenviron. 2015;2.

[49] Conley-LaComb MK, Semaan L, Singareddy R, *et al*. Pharmacological targeting of CXCL12/CXCR4 signaling in prostate cancer bone metastasis. Mol Cancer. 2016; 15:68.

[50] Shamaladevi N, Lyn DA, Escudero DO, *et al*. CXC receptor-1 silencing inhibits androgen-independent prostate cancer. Cancer Res. 2009; 69:8265–8274.

[51] Lauc G, Krištić J, Zoldoš V. Glycans - the third revolution in evolution. Front Genet. 2014; 5:145.

[52] Pinho SS, Reis CA. Glycosylation in cancer: mechanisms and clinical implications. Nat Rev Cancer. 2015; 15:540–555.

[53] Vojta A, Samaržija I, Bočkor L, *et al*. Glyco-genes change expression in cancer through aberrant methylation. Biochim Biophys Acta. 2016; 1860:1776–1785.

[54] Vajaria BN, Patel KR, Begum R, *et al*. Sialylation: an Avenue to Target Cancer Cells. Pathol Oncol Res. 2016; 22:443–447.

[55] Munkley J, Mills IG, Elliott DJ. The role of glycans in the development and progression of prostate cancer. Nat Rev Urol. 2016; 13:324–333.

[56] Munkley J, Vodak D, Livermore KE, *et al*. Glycosylation is an Androgen-Regulated Process Essential for Prostate Cancer Cell Viability. EBioMedicine. 2016; 8:103–116.

[57] Tzeng S-F, Tsai C-H, Chao T-K, *et al*. O-Glycosylation-mediated signaling circuit drives metastatic castration-resistant prostate cancer. FASEB J. 2018; fj201800687.

[58] Li J, Guillebon AD, Hsu J, *et al*. Human fucosyltransferase 6 enables prostate cancer metastasis to bone. Br J Cancer. 2013; 109:3014–3022.

[59] Chen F-Z, Zhao X-K. Ubiquitin-proteasome pathway and prostate cancer. Onkologie. 2013; 36:592–596.

[60] Vlachostergios PJ, Voutsadakis IA, Papandreou CN. The ubiquitin-proteasome system in glioma cell cycle control. Cell Div. 2012; 7:18.

[61] Wang Z, Song Y, Ye M, *et al*. The diverse roles of SPOP in prostate cancer and kidney cancer. Nat Rev Urol. 2020; 17:339–350.

[62] Vlachostergios PJ, Papandreou CN. The Role of the Small Ubiquitin-Related Modifier (SUMO) Pathway in Prostate Cancer. Biomolecules. 2012; 2:240–255.

[63] Sutinen P, Malinen M, Heikkinen S, *et al*. SUMOylation modulates the transcriptional activity of androgen receptor in a target gene and pathway selective manner. Nucleic

Acids Res. 2014; 42:8310–8319.

[64] Kaikkonen S, Jääskeläinen T, Karvonen U, *et al*. SUMO-specific protease 1 (SENP1) reverses the hormone-augmented SUMOylation of androgen receptor and modulates gene responses in prostate cancer cells. Mol Endocrinol. 2009; 23:292–307.

[65] Xia C, Tao Y, Li M, *et al*. Protein acetylation and deacetylation: An important regulatory modification in gene transcription (Review). Exp Ther Med. 2020; 20:2923–2940.

[66] Narita T, Weinert BT, Choudhary C. Functions and mechanisms of non-histone protein acetylation. Nat Rev Mol Cell Biol. 2019; 20:156–174.

[67] Cang S, Feng J, Konno S, *et al*. Deficient histone acetylation and excessive deacetylase activity as epigenomic marks of prostate cancer cells. Int J Oncol. 2009; 35:1417–1422.

[68] Zhang B, Ci X, Tao R, *et al*. Klf5 acetylation regulates luminal differentiation of basal progenitors in prostate development and regeneration. Nat Commun. 2020; 11:997.

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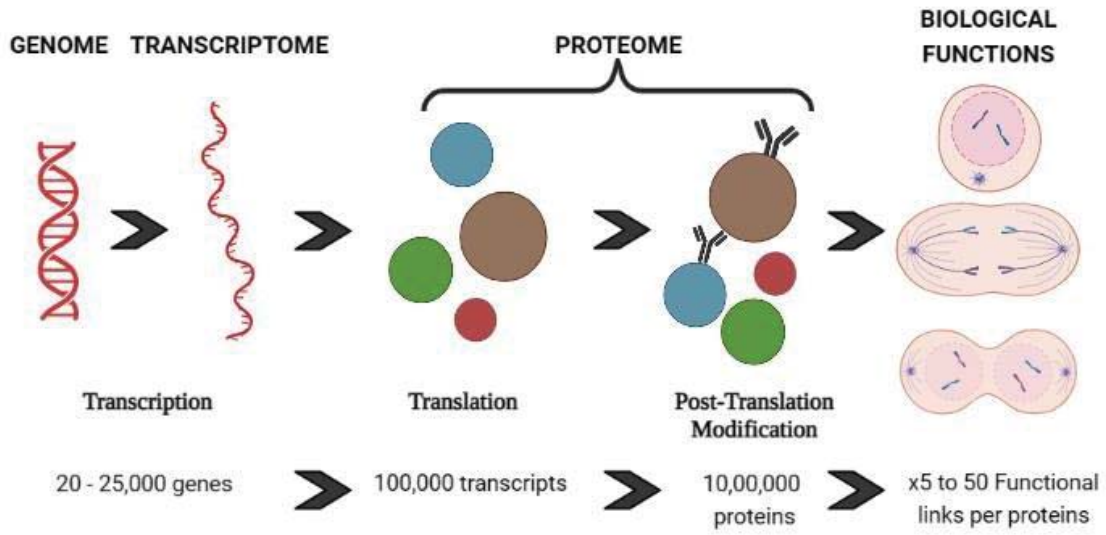

Figure 1: Overview of Post-Translational Modifications

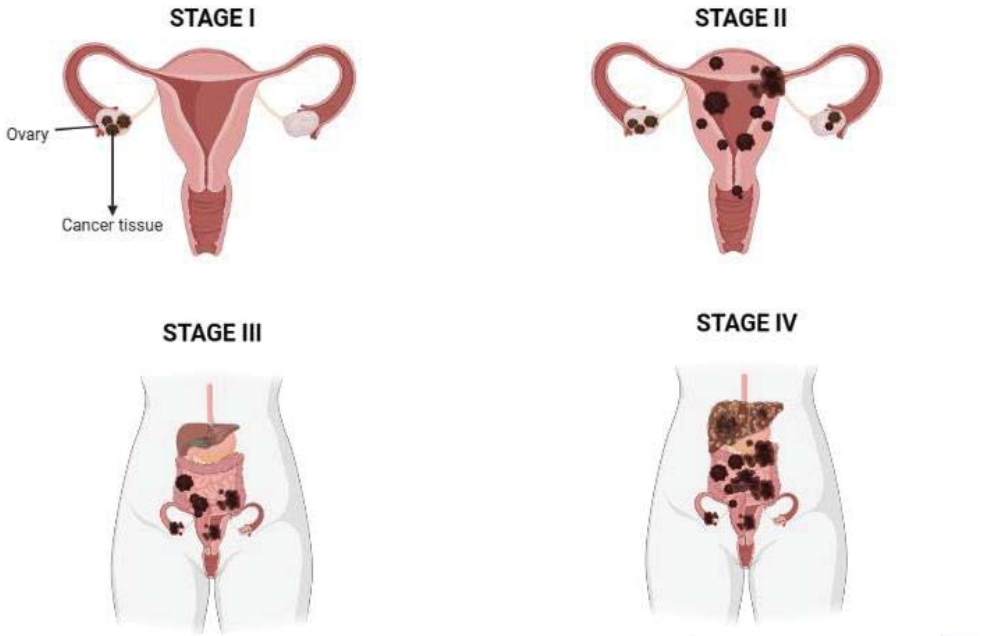

Figure 2: Stages of Ovarian Cancer

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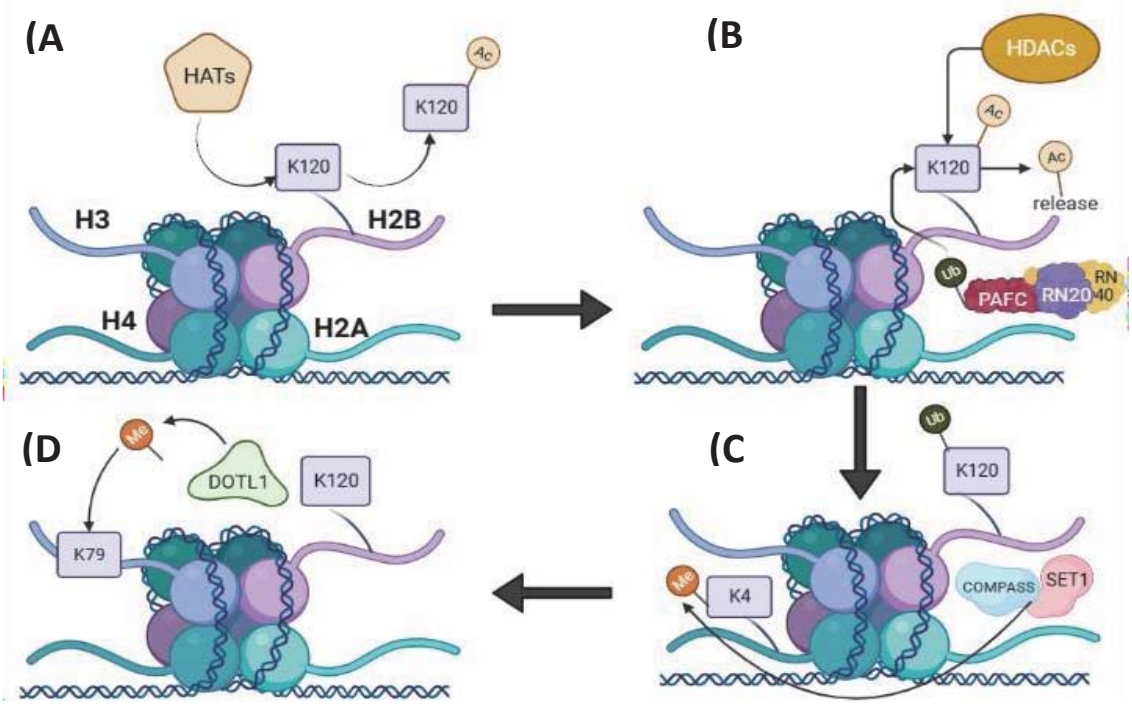

Figure 3: Post-translational modifications of core histone proteins regulate gene transcription, replication, andDNA repair processes by influencing chromatin configuration

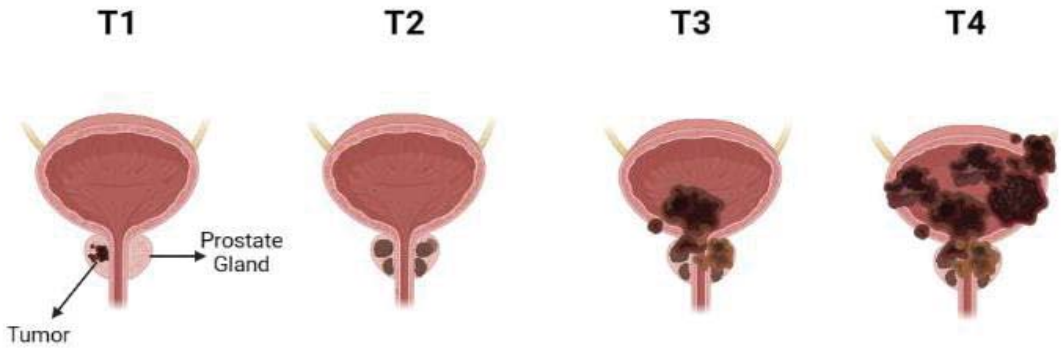

Figure 4: Stages of Prostate Cancer