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Histone Modifications: The Double Edged Sword in Gynaecological Cancers

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ABSTRACT

Gynaecological cancers are one among the fatal cancers that affects women worldwide. It includes endometrial, ovarian, cervical, vaginal and vulvar cancers. Epigenetic aberrations play a crucial role in the development and progression of such cancers, which includes global genomic hypomethylation, Cytosine-Guanine (CpG) island promoter hypermethylation, changes in histone modifications and changes in chromatin-modifying enzymes. This review aims at elaborating the significance of epigenetic changes specifically the histone modifications, at H3K9, H3K27, H3K4 and others involved in gynaecological tumourigenesis. They can independently or synergistically act along with DNA methylation for repression of the tumour suppressor genes and possibly for the activation of various oncogenes like CLDN3, CLDN4, GATA4, etc. in gynaecological cancers. These modifications may pave the way in the future for the identification of biomarkers in early diagnosis and prognosis with an opportunity for targeted drug delivery. A systematic review was done using Internet based scientific databases. Relevant clues about the role of Histone modifications like acetylation, deacetylation, mono/di/trimethylation, demethylation of the histone tails (H3/H4) involved in tumour development and progression were reviewed.

Key words:
Gynaecological Cancer, Histone modification, Acetylation, Deacetylation, Methylation, Demethylation.

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INTRODUCTION

Gynaecological cancers are a bunch of malignancies that primarily initiate in the female reproductive parts and affects the entire women population. They are classified based on the regions they develop and grow, like the ovaries, endometrium, cervix, vagina and vulva. The most prevalent ones are the ovarian, endometrial and cervical cancers. The less common ones include vaginal and vulvar cancers, gestational trophoblastic tumours and fallopian tube cancer[1]. Approximately 94,000 females were diagnosed with a variety of gynaecological malignancies, each year between 2012 and 2016. The most commonly detected was uterine cancer (26.82 cases per 100,000) and the least was vaginal cancer (0.66 per 100,000) [2]. Almost 30,000 women in the United States are estimated to have died due to gynaecological cancers in 2014[3].

Many treatment options have been considered to overcome these malignancies. The common approaches include surgical resection, radiation therapy, chemotherapy, hormone therapy, targeted therapy and immunotherapy. The selection of the type of treatment given depends upon the type of cancer and the stage at the time of diagnosis. Apart from the aforementioned health status, comorbidities and personal factors like age and weight can play a pivotal role in selecting the suitable treatment plan[4]. Redirecting the treatments for gynaecological cancers to the epigenetic level specifically its regulation during tumorigenesis will provide a new insight into the field of gynaecological cancer.

Epigenetics, originally put forward by C.H.Waddington as 'the causal interactions between genes and their products, which bring the phenotype into being', points out the significance of chromatin structure and its effects on gene function[5]. The concept of epigenetics has advanced over the years and is now defined as 'the study of heritable changes in gene expression that occur independently of changes in the primary DNA sequence'[6]. The heritable changes are passed on during cell division and these changes are brought about by CpG island methylation, post-translational histone modifications and changes in the chromatin-modifying enzymes. Incorrect regulation of these epigenetic changes might result in the progression of tumorigenesis. The epigenome dictates the part of the gene to be expressed in its desired form. The genetic story of cancer has been widely heard of, but recent studies have given a new insight into the epigenetic alterations that can be a platform for different cancer events[7]. The various steps in epigenetics have been discussed here specifically the histone modifications in the light of gynaecological cancer development and treatment.

DNA METHYLATION AND HISTONE MODIFICATIONS IN CANCER

DNA Methylation is one among the most universally studied epigenetic modification. It plays a key role in the maintenance of gene silencing. This is done by methylating the CpG dinucleotide regions in the gene by recruiting de novo DNA methylases DNMT3A, DNMT3B and the maintenance DNA methylases DNMT1. The CpG regions are mainly found near the 5' end of the gene which occupies 60% of the human gene promoters and silences them by the promoter methylation[8]. The CpG sites are located in short stretches of DNA known as the 'CpG islands' and in repetitive sequences that are scattered all over the DNA, most of these sites are methylated but during development, they remain unmethylated. The naturally occurring DNA methylation includes the X chromosome inactivation and the imprinted genes that are stably silenced during the development process[9]. Another mechanism includes recruiting the MBD proteins in cooperation with the HDACs, which in turn will mediate the repression of various regions of the DNA[10, 11]. Thus, the DNA incorporates various ways to

ensure gene silencing and maintenance of the noncoding genomic regions.(Figure I)

Covalent post-translational histone modifications are comparatively less explored field of epigenetic mechanisms. It is an exceptional result of the close communication between the histone proteins and the DNA strand. The nucleosome consists of the DNA double helix wound around the histone proteins (a pair of H2A, H2B, H3, H4) known as the histone octamer[12]. The histone proteins have two ends namely the C terminal and the N terminal, histone modifications are undergone by the latter which comprises of methylation, acetylation, ubiquitylation, sumoylation and phosphorylation on specific residues. The close vicinity of the histones and the DNA is responsible for the accessibility of the DNA strand by the various enzyme complexes. This ensures the collaboration of the histone modifications and DNA methylation in synchrony to bring about the epigenetic regulation. These modifications play an important role in DNA repair, replication and transcription[13].

Generally in cancers, global hypomethylation occurs on the oncogenes, resulting in its activation along with the hypermethylation of many tumour suppressor genes which results in its silencing[14]. One such example is, transcriptional activation by acetylation at the lysine residues[15], while lysine methylation brings about transcriptional activation or repression depending on which residue is methylated and the magnitude of methylation. For example, trimethylation of lysine 4 on histone H3 (H3K4me3) is more at transcriptionally active gene promoters, [16] whereas trimethylation of H3K9 (H3K9me3) and H3K27 (H3K27me3) is present at the transcriptionally repressed promoters. H3K9me3 and H3K27 comprise the two main mechanisms of gene silencing. Here H3K9me3 associates with DNA methylation whereas H3K27 works alone without the involvement of DNA methylation to bring about gene silencing. The Polycomb Protein Group (PcG) is a group of proteins that plays a role in determining the fate of the cell and inhibition of transcription. Polycomb proteins include PRC1 and PRC2, which has a coordinated activity and brings out the post-translational covalent histone modifications. EZH2 is an enzyme that belongs to the PRC2 group and has an H3K27 methylase activity [17]. An open chromatin structure is indicative of active gene with an unmethylated promoter region and absence of the nucleosome upstream of the transcription initiation site. The active histone marks are acetylation, H3K4 methylation and high levels of H2A.Z on nucleosomes around the transcription start site. The transcription is favoured due to the open chromatin structure, dramatically increasing the accessibility of the transcription factors and RNA polymerase II to the transcription start sites. Transcriptional repression can be employed by two main mechanisms- Firstly, by the action of PRC1 and PRC2 that mediate gene repression by H3K27 methylation along with deacetylation of histone proteins by HDACs, loss of methylation at active histone marks like H3K4, chromatin compaction, nucleosome occupancy in the nucleosome-free region and ubiquitylation of H2A.Z. Secondly by H3K9 methylation that takes place along with DNA methylation for long term silencing, which brings about chromatin compaction. This is employed by incorporating proteins in heterochromatin formation like HP1.

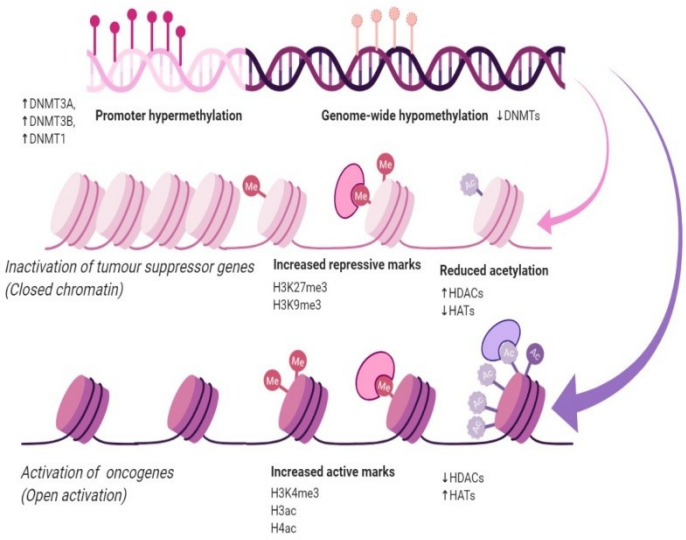

Fig I -Epigenetics in cancer

The two families of enzymes with opposite functions that regulate histone acetylation are - histone acetyltransferase (HAT) and histone deacetylase (HDAC).

Lysine residue on the histone tails has a positive charge which is neutralized by the addition of acetyl groups to it by HATs. As a result, the DNA is exposed from its highly condensed state to an open structure for the ease of active transcription. On the other hand, the HDACs remove the acetyl groups resulting in the reestablishment of the highly condensed and stable state conferring chromatin stability[19]. Hence histone modifications are carefully regulated by the various histone-modifying enzymes like Histone deacetylases(HDACs), Histone Acetyl Transferases (HATs), Histone methyl Transferases (HMTs) and Histone demethylases (HDMs) [18].

These above mentioned aberrant changes may provide a useful biomarker for the identification and diagnosis of various gynaecological cancers [19, 20].

OVARIAN CANCER

Ovarian cancer is the most lethal malignancy of the female reproductive tract, and its survival rate remains much worse than the 61.5% overall cancer survival rate for women.[21]Various cancer-associated genes have been reactivated and tumour suppressor genes repressed by histone modifications in different types of ovarian cancers. Few of them involved in ovarian tumorigenesis have been reviewed here.

CLDN3 and *CLDN4* genes are associated with are tight junction proteins Claudin 3 and Claudin 4 that maintain the cellular polarity and paracellular ion flux. In normal cells they are maintained in their stable state by the bivalent histone modifications, containing both the activating mark H3K4me3 and the repressive mark H3K27me3. Their overexpression in ovarian cancer enhances tumour cell motility, invasiveness and survival, possibly by enhancing proteolytic activation of basement membrane-degrading matrix metalloproteinases [22].They are upregulated and the underlying mechanisms are still unclear though recent studies have suggested an epigenetic mechanism that includes histone H3ac of the two genes [23, 24, 25]. Another possible underlying mechanism is the epigenetic derepression of *CLDN3* & *CLDN4* is by the loss of repressive histone marks. In the analysis of normal and malignant ovarian cell lines, it was found that H3K27me3 was lost in *CLDN3* expressing cells along with the other two

repressive marks, H4K20me3 and H3K9me3, independently of altered DNA methylation. Active chromatin marks such as H3K4me3 and H3ac were observed in the promoters of both the normal and ovarian cell lines irrespective of the *CLDN3* expression. *CLDN3* is also upregulated by the H3ac and H4ac regulation at the site of transcription. *CLDN4* expressing cells exhibited the loss of repressive histone marks H3K27me3 and H4K20me3 along with DNA methylation. It was also found that H4ac (5.1 fold) was more prominent than H3Ac(2.5 fold) in *CLDN4*. These evidences signify the role of histone modifications in the derepression of *CLDN3* and *CLDN4*. Hence these modifications can act as potential epigenetic targets for the treatment of ovarian cancer through their inactivation [26].

GATA transcription factor gene plays a significant role in ovarian cancer. Loss of *GATA4*, *GATA5, GATA6* have been implicated in ovarian tumorigenesis,[27] Epigenetic modifications at the GATA gene promoters should be considered to explain the transcriptional silencing of these genes in the absence of genetic alterations. Additionally *DAB2*, a candidate tumour suppressor gene, also the target for *GATA6* was found to be downregulated which can lead to neoplastic growth [28]. Hypoacetylation of histone H3 and H4 and the associated reduction in di- and trimethylation of histone H3K4 were found at the promoters of *GATA4* and *GATA6*. On the treatment of ovarian cancer cell lines, with an HDAC inhibitor, Trichostatin A, it exhibited reexpression of *GATA4, GATA6* and *DAB2* gene. This points out the role of histone deacetylation alone for gene repression in this case. Therefore, altered histone modification of the promoter loci is one mechanism responsible for the silencing of *GATA* transcription factors and the subsequent loss of a target gene, the tumour suppressor Disabled-2, in ovarian carcinogenesis [29].

A tumour suppressor gene, *p16*, a mismatch repair gene, human mutL homolog 1 *hMLH1*, and a DNA repair gene, O6-alkylguanine-DNA alkyltransferase *MGMT* were studied to find their role in ovarian carcinogenesis. It was found that the loss of expression of the *p16, hMLH1* and *MGMT* genes was due to the epigenetic regulation of both DNA methylation and histone acetylation. H3K9ac played a significant role in determining the transcriptional activation of these genes. The greater the H3K9ac the larger is the ability of the gene to undergo transcriptional activation. Furthermore, histone H3K9ac in different regions of the promoters correlated well with the DNA methylation status of each gene. When the CpG island was hypermethylated, the lowest levels of histone H3K9ac were detected. When the CpG island was hypomethylated, the highest levels of acetylation were detected.[30] The results strengthen the idea that there is some interdependence between reversal of histone acetylation and reactivation of a gene silenced by aberrant DNA hypermethylation. Hence, suggesting the role of histone deacetylation along with the existing DNA methylation for gene silencing.

SMYD2, another HMT, is a member of the *SMYD* family which functions as an oncogene. It is a SET and MYND domain-containing histone (lysine) methyltransferase that methylates histone proteins H3K4 and H3K36 associated with active transcription[31]. *SMYD2* was significantly overexpressed in high grade serous ovarian carcinoma(HGSOC) specimens than the normal ovarian cancer [32]. It methylates several non-histone proteins, such as *PTEN*, a tumour suppressor gene and which can induce apoptosis [33]. A decrease in this apoptotic activity may result in the progression of tumour progression. These data suggest that the knockdown of *SMYD2* induces apoptosis. Therefore targeted therapy with a selective *SMYD2* inhibitor, such as LLY-507, or combination molecular targeted therapy might be a promising strategy to effectively treat high-risk HGSOC patients.

ENDOMETRIAL CANCER

Endometrial carcinoma is the most prevailing neoplasm of the female reproductive system. They can be categorized into two different types namely, Type I and Type II. Endometrioid carcinoma, type I, is recognised with elevated serum estrogen and expresses ERs and PRs. In contrast, the typical type II carcinoma, serous carcinoma, is not estrogen-related as it generally occurs in a small uterus with atrophic endometrium [34]. In 2017, ~61000 new uterine cancer diagnoses were estimated and nearly 11,000 women were estimated to die from the disease, commonly affecting postmenopausal women with a mean age of 62 years [35].

Histone lysine methylation has a significant role in endometrial cancer. H3K4me2 expression levels increased with the malignant status of the epithelial endometrial tissues, indicating that H3K4me2 was responsible in the oncogenesis of endometrial cancer. Hence, highly invasive endometrial cancer had high expression levels of H3K4me2; however, the specific underlying mechanism remains to be further explored. The factor p53 has a high level of association with tumours in humans[36]. The overexpression of p53 is often observed in malignant tumours and can be a reliable marker for enhanced proliferation [37]. In the given study, a low expression level of H3K4me3 in the stroma was associated with p53-negativity, which predicts a benign prognosis in humans with endometrial cancer. Another marker is the expression level of H3K27me3, a repressive histone mark in the endometrial stroma, which was lower in Type 1 endometrial cancer compared within the normal endometrium and precancerous lesions. A low expression level of H3K27me3 may predict a more aggressive biological behaviour in endometrial carcinoma.

Human chromosome 7 open reading frame 24 *C7orf24*/c-glutamyl cyclotransferase is a novel malignant-associated de-repression gene which has been considered to be a potential diagnostic marker for endometrial epithelium cancers. Elevation of H3K4me3 and H3K9ac active histone marks in cancer cell lines were found at the transcription start site. The H3K4me3 modified histone mark is recognized by chromodomain helicase DNA binding protein-1. HATs are then recruited, which results in the promotion of histone H3K9Ac and further changes that lead to an active chromatin state [38]. Therefore, in human cancer cells, the *C7orf24* promoter region is opened for active gene transcription. Accumulation of euchromatin marks (i.e. H3K4me3 and H3K9ac) was found around the transcription start site of the *C7orf24* gene in *C7orf24*-expressing cancer cells [39]. Therefore, considering the aforementioned role of active marks, targeted suppression of these modifications can be a future prospect for the control of endometrial carcinogenesis.

Another important hormonal regulator in the development of endometrial cancer is ovarian progesterone. One well-documented action of it is in the human uterus, by protecting the endometrium against the hyperplastic and tumorigenic activities caused by excessive levels of estrogens [40, 41]. Endometrial glandular cells express two types of progesterone receptors, PR-A and PR-B. They are synthesized through with differing transcription start sites with alternative promoters. PR-B accounts for most of the inhibitory effects of progestins

on cancer cell growth [42]. A general association of higher levels of histone acetylation and H3K4me3, and lower levels of H3K9me3, with the transcriptional activation of the methylated and silenced *PR-B* gene was found [43]. These results suggest histone modifications as a mechanism for the activation of the *PR-B* gene and thereby in controlling the progesterone deficit endometrial cancer.

CERVICAL CANCER

Cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female cancers [44]. High-risk specific types of human papillomavirus (HPV) are also associated with cervical cancer progression in humans [45].

LMX1A is a LIM homeobox-containing genes and plays a significant role during development. More recently, *LMX1A* has been reported as a tumour suppressor gene. The specificity protein 1 (Sp1) protein expression pattern is similar to that of *LMX1A* in cervical cancer and several predicted Sp1 sites are located in the *LMX1A* promoter region [46]. Moreover, the EZH2 expression pattern is highly associated with tumour cell invasion in cervical cancer due to its repressive action. It was shown that overexpression of EZH2 could repress *LMX1A* expression in cancer cells. It was also demonstrated that Sp1 binds directly to the *LMX1A* promoter and activates *LMX1A* expression. Knockout of EZH2 can decrease H3K27me3 histone modification and may increase H3K14ac level in the *LMX1A* promoter and prevent *LMX1A* silencing [47]. This study points out the striking role of epigenetic aberration specifically histone modification in dictating cervical tumorigenesis.

CONCLUSION

From the above data, it can be inferred that histone modifications is the road less travelled for the treatment and diagnosis of gynaecological cancers. The active histone marks responsible for the activation of various oncogenes may act as potential targets that can be inhibited to prevent tumour growth and invasiveness. The reactivation of tumour suppressor genes is equally a powerful method to overcome the states of malignancy in gynaecological cancers. An already studied HDAC inhibitor belinostat was administered to platinum-resistant ovarian cancers but caused severe adverse events such as neutropenia, thrombocytopenia, and vomiting [48]. The aim of developing an epigenetic drug with lesser side effects can prove to be an answer to most of our questions and hence a strategic way to overcome oncogenesis. In the therapeutic field, epigenetic therapy is a very promising field treatment that is being extensively investigated. It is too early to judge its usefulness. However, it has now been demonstrated that inhibitors of DNA methylation and histone deacetylases in combination or alone can reactivate the expression of tumour suppressor genes and induce histone hyperacetylation in the tumours of patients with gynaecological cancers.

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