REVIEW

Global histone post-translational modifications and cancer: Biomarkers for diagnosis, prognosis and treatment?

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Abstract

Global alterations in epigenetic landscape are now recognized as a hallmark of cancer. Epigenetic mechanisms such as DNA methylation, histone modifications, nucleosome positioning and non-coding RNAs are proven to have strong association with cancer. In particular, covalent post-translational modifications of histone proteins are known to play an important role in chromatin remodeling and thereby in regulation of gene expression. Further, histone modifications have also been associated with different aspects of carcinogenesis and have been studied for their role in the better management of cancer patients. In this review, we will explore and discuss how histone modifications are involved in cancer diagnosis, prognosis and treatment.

Key words: Epigenetics; Cancer; Diagnosis; Prognosis; Histone post-translational modifications; Treatment

Core tip: The purpose of the review is to describe the potential of histone post-translational modifications in the field of cancer.

INTRODUCTION

Cancer is a manifestation of both genetic and epigenetic alterations leading to the genomic instability and thus affecting several classes of genes, such as oncogenes, tumor suppressor genes, apoptotic genes and DNA repair genes. The field of cancer genetics which include the study of point mutation, deletion, insertion, gene amplification, chromosomal deletion/inversion/translocation, and allelic

loss/gain has got the attention of most cancer researchers in the last few decades. However, the appreciation of cancer epigenetics is more recent as several studies have now shown that in addition to numerous genetic alterations human cancers also harbor global epigenetic abnormalities[1,2].

Epigenetics, was initially defined by C. H. Waddington as "the causal interactions between genes and their products, which bring the phenotype into being"[3]. With time, the definition of epigenetics has evolved and is implicated in a wide variety of biological processes. The current definition is "the study of heritable changes in gene expression that occur independent of changes in the primary DNA sequence". Epigenetic mechanisms include DNA methylation[4], noncoding RNA[5,6], histone variants[7] and histone post translational modifications (PTMs). These mechanisms together alter the local structural dynamics of chromatin to regulate the functioning of the genome, mostly by regulating its accessibility and compactness. All together, these mechanisms govern the chromatin architecture and gene function in various cell types, developmental and disease states[2,8-12]. Disruption in the proper maintenance of these heritable epigenetic mechanisms can result in activation or inhibition of various critical cell signaling pathways thus leading to disease states such as cancer[1,13]. Epigenetic mechanisms also cooperate with genetic alteration and work together at all stages of cancer development from initiation to progression[14]. Unlike genetic alterations, epigenetic changes are reversible in nature and can be potentially restored back to their original state by epigenetic therapy. These findings have inspired many studies aimed to understand the role of epigenetics in tumorigenesis and further explore its utility in cancer diagnosis, prognosis and therapy[15]. In recent years, research focus has been shifted to understand various post translational modifications for gaining deeper insights in to the functioning of histone/chromatin associated proteins. Information about the PTMs and the related modifying enzymes is available in the database HIstome: The Histone Infobase (http://www.actrec.gov.in/histome/)[16]. This review will discuss the role of histone post-translational modifications and its utility in cancer diagnosis, prognosis and treatment.

HISTONE PTMS: A DYNAMIC PROCESS

Histones are highly conserved and basic proteins with a globular C-terminal domain and an unstructured N-terminal tail[17]. They are also the most important proteins for converting a linear naked genome in to physiologically sensible architecture, chromatin. Nucleosomes are fundamental units of chromatin, consisting an octamer of H2A, H2B, H3 and H4 (two each) around which 146 base pairs of DNA is wrapped-. There are sequence variants of these histones which are expressed and incorporated into chromatin in a context dependent manner in normal and disease related processes. In cancer, histone H2A variants, H2A.1, H2A.

Z and macroH2A have also been reported to express aberrantly[18-20]. Also, histones proteins can undergo a variety of PTMs some of which are methylation (me), acetylation (ac), ubiquitylation (ub), sumoylation (su) and phosphorylation (ph) on specific amino acid (Figure 1)[10]. Apart from these modifications, histones are also known to undergo homocysteinylation, crotonylation and glucosylation amongst others[21]. These histone modifications occur at several degrees, for example, methylation can be of monomethyl (me), dimethyl (me2) and trimethyl (me3).

Histone PTMs are added and removed from histones by enzymes called "writers" and "erasers" respectively. Histone acetyltransferases (HATs), histone methyltransferases (HMTs) and histone kinases are the examples of "writers" which add acetyl, methyl and phosphoryl groups, whereas histone deacetylases (HDACs), histone demethylases (HDMs) and histone phosphatases are examples of "erasers" which remove acetyl, methyl and phosphoryl groups, respectively (Figure 2)[22-24]. Histone-modifying enzymes are also known to interact with each other as well as other chromatin related proteins thus influencing key cellular processes such as transcription, replication and repair[10].

The mechanism behind the regulation of key cellular processes by histone post-translational modifications is not fully understood; however, it can be generalized into two categories. First, the addition of any PTM on histone protein affects inter/intra-nucleosomal interactions and their binding to DNA by steric hindrance or charge interactions. Second, addition of these PTMs to histone proteins inhibits or facilitates the binding of various proteins to chromatin[10]. These mechanisms allow a vast range of flexibility in regulating chromatin dynamics and signaling transmission and thereby regulating the gene expression. As an example of first mechanism, histone acetylation is proposed to be associated with chromatin relaxation and transcription activation, H4K16ac inhibits the formation of compact 30 nm fibers and higher order chromatin structures[25,26]. As an example of second mechanism, evolutionarily conserved specialized proteins, termed "histone readers," possess the ability to specifically bind certain histone modifications and affects a defined nuclear process such as transcription, DNA repair and replication, *etc.* (Figure 2). For example, through its evolutionary conserved chromodomain heterochromatin protein 1 recognize and gets recruited to H3K9me3 and leads to the formation of compact chromatin which in turn inhibits the access of the transcriptional machinery[27,28]. Moreover, the fact that there are different variants of each histone protein differing from few to many amino acids adds another level of complexity in functional aspects of histone PTMs. Such complicated and multilayered regulatory mechanisms of cellular processes through histone modifications have led to the hypothesis of "histone code" where a set of histone variants and modifications together perform a specific function[29]. However, due to its complexity histone code is still not fully understood[30]. Further, the status of one histone modification also regulates that of another by
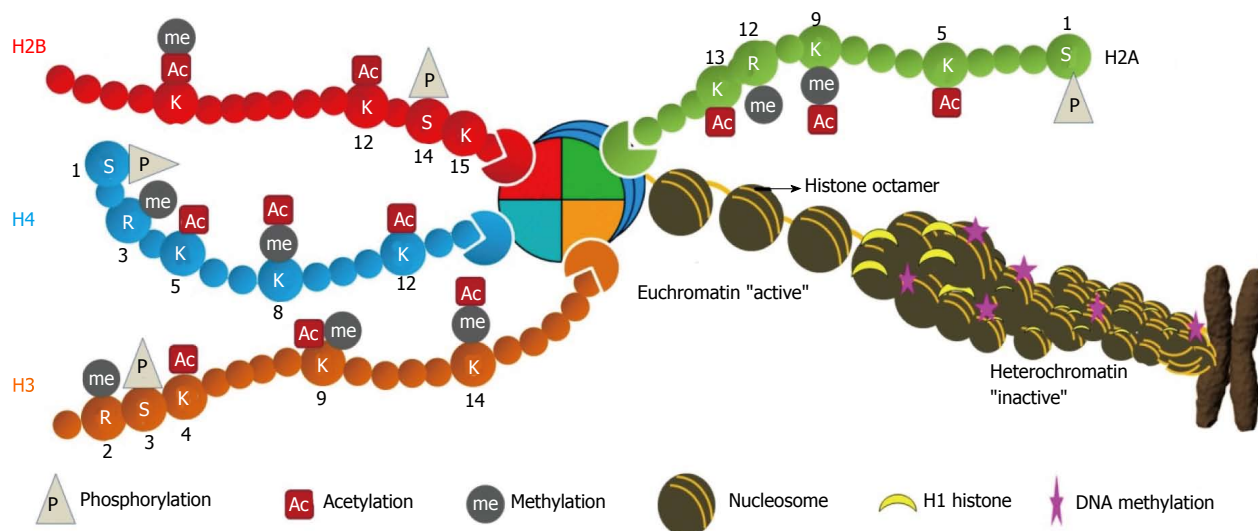
Figure 1 Chromatin architecture. The DNA is wrapped in two turns around histone octamers (nucleosomes) at intervals of about 200 bp along the DNA. Histones within the nucleosome (two each of H2A, H2B, H3 and H4) undergo numerous post-translational modifications at their N-terminal tail which protrudes from the nucleosome. Further folding of nucleosome with linker histone H1 creates a spiral structure, the heterochromatin leading to metaphase chromosome. These modifications directly regulate the chromatin structure and thus DNA-mediated cellular processes. The diagram indicates some modifications at specific residues: M: Methylation; A: Acetylation; P: Phosphorylation.
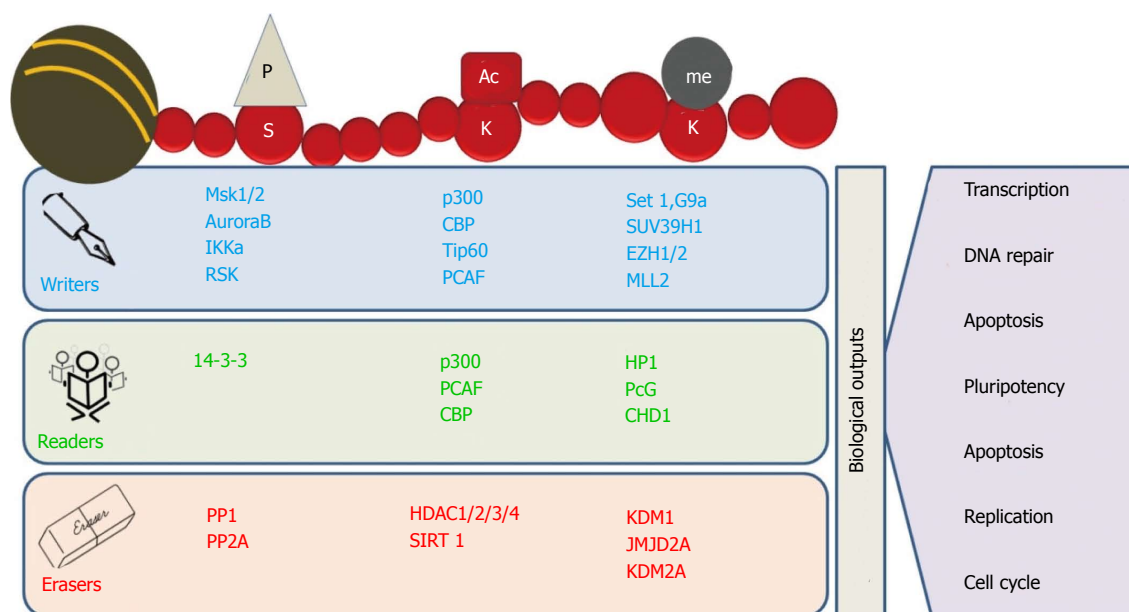

Figure 2 Readers, writers and erasers of chromatin marks. Histone modifications are highly dynamic in nature. The "writers" like histone acetyltransferases (HATs), histone methyltransferases (HMTs) and kinases add specific marks on specific amino acid residues on histone tails. These marks are identified by various proteins containing specific domains such as bromodomains, chromodomains and Tudor domain containing proteins called "readers". The written marks are removed by "erasers" like histone deacetylases (HDACs), lysine demethylases (KDMs) and phosphatases. In addition, removal and identification of these post-translational modifications on histone tails regulate various biological processes, including transcription, DNA replication and DNA repair.

cross-talk and affects chromatin remodeling and gene expression. Cross-talk between H3S10ph and H3K14ac, H2Bub and H3K4me and H3K4ac and H3K4me3 and H3K14ac are few prominent examples regulating gene expression[31]. For example, acetylation of H3K18 and H3K23 by CBP (CREB binding protein) can promote the methylation of H3R17 by Coactivator-Associated Arginine Methyltransferase 1 (CARM1), resulting in activation of estrogene-responsive genes[32].

HISTONE PTMS IN CANCER

In cancer, several histone PTMs have been reported to be misregulated; however, their involvement in cancer pathophysiological characteristics like cellular transformation, angiogenesis and metastasis *etc.*, is not well understood. Moreover, there are very few studies commenting on the cancer specific regulatory mechanism behind the alteration of histone PTMs. It has been a

decade when global loss of H4K16ac and H4K20me3 was reported for their association with cancer and considered as a common hallmark of tumor cells[33]. However, still there are no reports of their direct involvement in cellular transformation or any other cancer characteristics. Despite of the awareness of hMOF (human Male absent Of First) and HDAC4 as writer and eraser of H4K16ac, it is a recent development that low expression of hMOF has been implicated for its loss in gastric cancer[34]. Moving on to histone methylation, Lin *et al*[35] showed histone lysine demethylase KDM1A mediated loss of H3K4me2 is associated with epithelial to mesenchymal transition (EMT) in human breast cancer cells. Loss of H3ac, H3K9me3 and H3S10ph is observed at the promoters of Sfrp2, Sfrp5 and Wnt5a during genistein induced development of colon cancer in the rat model system[36]. Alterations in methylation patterns of H3K9 and H3K27 are related to aberrant gene silencing in many cancers[37,38]. Tissue microarrays done to compare the levels of H2B ub1 levels in normal mammary epithelial tissue as well as benign, malignant, and metastatic breast cancer samples have clearly shown a sequential decrease in H2B monoubiquitination with breast cancer progression and metastasis in comparision with normal epithelia[39]. A very important discovery has been made in term of phosphorylation of H3S10 as the only histone marks directly associated with cellular transformation. The knockdown and mutant (S10A) of histone H3 suppressed LMP1-induced proliferation of nasopharyngeal carcinoma cell line CNE1[40]. H3S10P has been reported to increase and has been established as indispensable for cellular transformation[41,42]. Cellular transformation by v-src constitutively activated phosphorylation of histone H3 at Ser10 in a transformation-specific manner; while, non-transforming mutant of v-src did not activate H3 phosphorylation[43]. Further, Mitogen- and stress-activated kinase 1 (MSK1) has been shown to phosphorylate H3S10 in TPA and EGF mediated cellular transformation[44]. Unpublished data from our lab has also shown increase in H3S10ph in gastric cancer, which is regulated by p38-MAPK/MSK1 pathway.

It has now been clear that acetylation, methylation and phosphorylation of histones are the most studied histone marks. In cancer, most of the studies have been done for these modifications with respect to the identification of their enzymes, regulation, effect on cellular physiology and as well as molecular biological markers for the disease management. The National Institute of Health defines a biological marker (biomarker) as a biological molecule found in blood, other body fluids, or tissues that are an objective indicator of normal or abnormal process, or of a condition or disease[45]. From the next part of the review we will see how histone acetylation, methylation and phosphorylation can be exploited as biomarkers for cancer diagnosis, prognosis and treatment.

HISTONE PTMS IN CANCER DIAGNOSIS

Diagnosis of a disease majorly depends on the analysis of physical symptoms, body fluids and fecal samples. A sensitive and specific diagnostic marker is not only useful in early diagnosis, but also helps in assessing the risk of developing the disease. Advances in the technology have enabled investigators to isolate metabolites, proteins and DNA from body fluids and fecal material and correlate them with pathophysiological symptoms of diseases including cancer.

Decades of research have discovered a battery of markers for cancer diagnosis; however, only few could reach to clinics because of issues of sensitivity and specificity. Therefore, at one side there is a need to improve techniques and on the other hand discovery of new markers is of immense importance. The discovery of the presence of DNA in fecal and urine samples[46] and circulating nucleosomes in serum[47,48] has led to the foundation of identifying epigenetic markers such as DNA methylation and histone posttranslational modification for cancer diagnosis. Ahlquist *et al*[49] demonstrated the recovery of DNA from frozen fecal samples of colorectal cancer patients which was followed by other investigators showing matching DNA methylation patterns between DNA from tissue and fecal samples of gastric and colorectal cancer patients[50-52]. Methylation pattern of DNA isolated from urine samples was also used to diagnose bladder and prostate cancer[53-57]. All these methylation studies have successfully detected global hypomethylation and gene specific hypermethylation of DNA, as established from tissue based studies.

Presence of histone proteins is not known in fecal and urine samples; therefore, histone posttranslational modifications have been utilized as cancer diagnostic markers using circulating nucleosomes (cNUCs) in serum samples. Two histone methylation marks, H3K9me3 and H4K20me3, the hallmarks of pericentric heterochromatin[58], were investigated in circulating nucleosomes by subsequent studies. Gezer *et al*[59] investigated the correlation between the H3K9me3 and H4K20me3 of cNUCs in healthy subjects and patients with colorectal cancer (CRC) and multiple myeloma and found low levels of these PTMs in cancer. Sera of patients with malignant tumors including colorectal, lung, breast, ovarian, renal, prostate cancer, and lymphoma showed high level of nucleosome concentration compared with those of healthy persons and patients with benign diseases[60]. Further, the same group showed high level ALU115 DNA sequence associated H3K9Me in multiple myeloma patients compared to healthy individuals[61]. ChIP based analysis of circulating nucleosomes in serum samples by Gloria *et al* reported a low level of H3K9me3 and H4K20me3 in patients with colorectal, pancreatic, breast and lung cancer compared to healthy control[62,63]. Moreover, H3K9me3 and H4K20me3 have been found to be lower at the pericentromeric satellite Ⅱ repeat in patients with CRC when compared with healthy controls or patients with multiple myeloma. In summary, identification of histone PTMs from serum isolated circulating nucleosomes have open the doors of immense possibility that blood samples collected by

Table 1 Global post-translational modifications of histones in cancer

Histone PTM	Writer	Eraser	Function	Cancer Diagnosis/ Prognosis/ Treatment
H3K9ac	GCN-5	SIRT-1; SIRT-6	Transcription initiation	Diagnosis: ? Prognosis: Lung, breast, ovarian Treatment: ?
H3K18ac	CBP/p300	?	Transcription initiation and repression	Diagnosis: ? Prognosis: Lung, prostate, breast, esophagus Treatment: ?
H4K5ac	CBP/P300; HAT1; TIP60; HB01	?	Transcription activation	Diagnosis: ? Prognosis: Lung Treatment: ?
H4K8ac	TIP60; HB01	?	Transcription activation	Diagnosis: ? Prognosis: Lung, Treatment: ?
H4K16ac	TIP60; hMOF	SIRT-1; SIRT-2	Transcription activation	Diagnosis: Colorectal Prognosis: Lung, breast Treatment: ?
H3K4me	SETD1A; SETD1B; ASH1L; MLL; MLL2; MLL3: MLL4; SETD7	KDM1A; KDM1B; KDM5B; NO66	Transcription activation	Diagnosis: ? Prognosis: Prostate, kidney Treatment: ?
H3K4me2	SETD1A; SETD1B; MLL; MLL2; MLL3; MLL4; SMYD3	KDM1A; KDM1B; KDM5A; KDM5B; KDM5C; KDM5D; NO66	Transcription activation	Diagnosis: ? Prognosis: Prostate, lung, kidney, breast, pancreatic, liver, Treatment: ?
H3K4me3	SETD1A; SETD1B; ASH1L; MLL; MLL2; MLL3; MLL4; SMYD3; PRMD9	KDM2B; KDM5A; KDM5B; KDM5C; KDM5D; NO66	Transcription elongation	Diagnosis: ? Prognosis: Kidney, liver, prostate Treatment: ?
H3K9me	SETDB1; G9a; EHMT1; PRDM2	KDM3A; KDM3B§; PHF8; JHDM1D	Transcription initiation	Diagnosis: Myeloma Prognosis: Kidney, pancreas, prostate Treatment: ?
H3K9me2	SUV39H1; SUV39H2; SETDB1; G9a; EHMT1; PRDM2	KDM3A; KDM3B§; KDM4A; KDM4B; KDM4C; KDM4D; PHF8; KDM1A; JHDM1D	Transcription initiation and repression	Diagnosis: ? Prognosis: Prostate, pancreas Treatment: ?
H3K9me3	SUV39H1; SUV39H2; SETDB1; PRDM2	KDM3B§; KDM4A; KDM4B; KDM4C; KDM4D	Transcription initiation and repression	Diagnosis: Colorectal, myeloma, prostate, breast and lung Prognosis: Lung, prostate, breast, leukemia, stomach Treatment: ?
H3K27me	EZH2; EZH1	JHDM1D	Transcription activation	Diagnosis: ? Prognosis: Kidney Treatment: ?
H3K27me3	EZH2; EZH1	KDM6A; KDM6B;	Transcription repression	Diagnosis: ? Prognosis: Breast, pancreatic, ovarian, prostate, stomach, Esophagus, Liver Treatment: ?
H4K20me3	SUV420H1; SUV420H2	?	Transcription repression	Diagnosis: Colorectal, myeloma, prostate, breast and lung Prognosis: Breast, lymphoma, colon, ovarian Treatment: ?

PTM: Post translational modification.

cancer patients can also be used for histone PTM based cancer diagnosis.

HISTONE PTMS IN CANCER PROGNOSIS

In cancer, to date, histones PTMs have been mostly studied for their potential as prognostic marker (Table 1). The first report in this area strongly suggested the utility of histone PTMs in cancer diagnosis and showed loss of H4K16ac and H4K20me3 in several cancers and establish these two marks as a hallmark of tumor and establishes the correlation of H4K16ac with tumor progression[33]. Further, loss of H4K20me3 is as also detected in various cancer animal models[64,65]. A study on prostate cancer showed a positive correlation of H3K18ac, H4K12ac and H4R3me2 with increasing tumor grade[66]. Another

study on prostate cancer showed independently of other clinical and pathologic parameters, high rate of tumor recurrence in low-grade prostate carcinoma patients with low level of H3K4me2[66]. Loss of H3K4me2/me3 is reported in various neoplastic tissues such as non-small cell lung cancer, breast cancer, renal cell carcinoma and pancreatic adenocarcinoma serving as a predictor of clinical outcomes[67-72].

Acetylation of histone H3K9 has shown ambiguous results with the increase in some and decrease in other cancers. Decrease of H3K9ac has been linked with tumor progression, histological grading and clinical stage in prostate and ovarian tumors, hence is coupled with a poor prognosis for these patients[66,73-75]. Patients with non-small cell lung adenocarcinoma exhibited better prognosis on the reduction of the H3K9ac expression

level[68,76]. In contrast, increase in H3K9ac levels was reported in liver cancer[73]. Methylation of the same residue K9 of histone H3 requires loss of H3K9ac and is also linked to number of cancers. An association with the increase in methylation of H3K9 and aberrant gene silencing, has been found in many cancers[37,77] and its high level is associated with poor prognosis in gastric adenocarcinoma patients[77]. However, in patients with acute myeloid leukemia decrease in H3K9me3 has been found to be associated with better prognosis[78]. Decrease in H3K18ac is correlated with poor prognosis in prostate, pancreatic, lung, breast and kidney cancers[66,69,71]. It has also shown a strong correlation with tumor grade, signifying its importance in tumor progression[69]. In this regard, Kurdistani laboratory has confirmed that oncogenic transformation by the adenovirus protein E1a is associated with drastic changes in the global H3K18 acetylation pattern[79,80]. In addition, H3K18 hypoacetylation has been associated with an high risk of tumor recurrence in low-grade prostate cancer patients[66]. However, in contrast to this, low expression of H3K18ac has been correlated with a better prognosis for esophageal squamous cell carcinoma and glioblastoma patients[76,81]. This suggests that a single histone modification could predict differential prognosis in different cancers depending on it tissue specificity.

Another histone mark, H3K27me3 has been evaluated as a prognostic factor in patients with prostate, breast, ovarian, pancreatic and esophageal cancer[81-84], however, some of the results are perplexing and need further investigation. High level of H3K27me3 correlates with poor prognosis in esophageal cancers[81,84]. On the other hand H3K27me3 showed a negative correlation with overall survival time in breast, prostate, ovarian and pancreatic cancer patients[83]. Zhang *et al*[85] have identified many genes like oncogenes, tumor suppressor genes, cell cycle regulators, and genes involved in cell adhesion with significant differences in H3K27me3 pattern in gastric cancer samples in comparison to adjacent non-neoplastic gastric tissues. Further they were able to correlate changes in H3K27me3 to gene expression pattern of MMP15, UNC5B, and SHH. In non-small cell lung cancer enhanced H3K27me3 was correlated with longer overall survival (OS) and better prognosis. Moreover, both univariate and multivariate analyses indicated that H3K27me3 level was a significant and independent predictor of better survival[86]. Recently, a study showed K27M mutations of histone H3.3 variants in 31% pediatric glioblastoma tumors suggesting another level of complexity in alteration of histone PTMs in cancer which is independent of histone modifying enzymes[87]. Mass spectrometry based analysis showed high level of H3K27ac in colorectal cancer than the corresponding normal mucosa[88]. Immunohistochemical analysis on metachronous liver metastasis of colorectal carcinomas by Tamagawa *et al*[89] has correlated H3K4me2 and H3K9ac with the tumor histological type. In addition, lower levels of H3K4me2 correlated with a poor survival rate and also found to be an independent prognostic factor.

Recently DNA damage mark γH2AX also have shown its prognostic value. In triple negative breast tumors, high level of γH2AX was associated poor overall survival[90] and which was further found to be associated with shorter telomere length[91]. In colorectal cancer a high γH2AX expression in CRC tissues was associated with tumor stage and perineurial invasion. Furthermore, a high γH2AX expression was associated with poor distant metastasis-free survival (DMFS) and OS. Cox regression analysis also revealed that γH2AX was an independent predictor of DMFS and OS. A high γH2AX expression in CRC tissues is associated with a more malignant cancer behavior, as well as poor patient survival[92]. ELISA based analysis in glioblastoma multiformes tumors showed the high level of H3T6ph,H3S10p and H3Y41ph as signatures associated with a poor overall survival[93]. Increase in H3S10ph has been associated with poor prognosis in several cancers including glioblastoma multiformes[93], cutaneous nodular melanoma[94], cutaneous melanoma[95], breast cancer[96,97], esophageal squamous cell carcinoma[98], gastric cancer[99,100], melanoma[101] and nasopharyngeal carcinoma[40].

HISTONE PTM'S IN CANCER TREATMENT

Reversible nature of epigenetic changes or mechanisms has drawn major attention of scientific community to study the molecular mechanism regulating the alteration in epigenetic marks, specifically the histone post-translational modifications. Such efforts have led to the discovery of several histone modifying enzymes[102] and their chemical inhibitors[103] which has emerged as an attractive strategy in cancer treatment. Targeting these enzymes can reactivate epigenetically silenced tumor-suppressor genes by modulating the levels of histone posttranslational modifications[104]. Further, these drugs have also given additional advantage in the area of combinatorial chemotherapy[105,106].

Histone acetyl-transferases and histone deacetylases as the targets

Loss of histone acetylation has a strong correlation with aberrant gene silencing in cancer. Treatment with HDAC inhibitors reactivate silenced tumor suppressor genes by increasing histone acetylation levels and act as anti-tumorigenic agent by promoting growth arrest, apoptosis and cell differentiation[107]. Additionally, HDACi have shown their potential in reversing chemoresistance and induce antiproliferative effects on a number of cancer cell lines[108-113]. However, the question still remains whether the promise shown in the above studies by HDAC inhibitors are mainly due to their potency to alter epigenetic mechanisms or mere its effect on key cellular growth regulatory pathways.

Initial results upon treatment with HDACi like valproic acid and phenylbutyrate, as a single agent against hematologic malignancies were not encouraging[81]. However, the field showed much promise with the development of more

potent HDACi such as the class-specific inhibitors (entinostat and romidepsin) and the pan HDAC inhibitors (vorinostat, belinostat and panobinostat). The field however gained boost when in a landmark Phase IIb multicenter trial, Yu et al[82] have shown vorinostat as effective treatment modality for refractory cutaneous T-cell lymphoma. Further, in Phase II multi-institutional trial, romidepsin has also been shown to have significant and durable efficacy against cutaneous T-cell lymphoma[83]. Due to their great successes in many studies, HDACi romidepsin and vorinostat have been approved by FDA as the treatment regime of cutaneous T-cell lymphoma, and romidepsin also for the treatment of relapsed peripheral T-cell lymphoma[84]. Since then many other HDACi have been under study of phase I and/or II trials as monotherapy, including belinostat, panobinostat, entinostat, chidamide, SB939 and LAQ824 in various cancers like ovarian, lung, soft tissue carcinoma, non-small-cell lung and breast[114-121]. However, unlike that of earlier success in treatment of lymphomas the majority of the results among solid tumor patients have been disappointing. In spite of achieving only intermittent anecdotal clinical responses, HDACi been related with severe toxicities.

Interactions between different epigenetic mechanisms have led to the foundation of research on combinatorial approach of cancer treatment using epigenetic drugs. Indeed, combinations of DNA methyltransferase and histone deacetylase inhibitors appear to synergize effectively in the reactivation of epigenetically silenced genes[107,122-124]. Such combinatorial approaches of cancer treatment have been found to be more effective than treatment with a single therapeutic agent. For example, treatment with 5-Aza-CdR and trichostatin-A in combination led to the derepression of certain putative tumor suppressor genes unlike individual treatments[107]. Pre-treatment of HDAC inhibitor SAHA relaxes the chromatin sensitizes cells to DNA damage induced by Topoisomerase II inhibitor[125]. Similarly pretreatment of valproic acid act in synergy with epirubicine and reduces the tumor volume in breast cancer mouse model[126].

Furthermore, synergistic activity of decitabine and HDACi sodium phenylbutyrate was shown to decrease the lung cancer formation by more than 50% in comparison with decitabine alone in a murine model based study by Belinsky et al[124]. The same group also reported that the combination of HDACi entinostat with the DNMTi azacitidine was able to decrease tumor size and reduce the growth of K-ras/p53 mutant lung adenocarcinomas orthotopic engrafted in immunocompromised nude rats[127]. In another case HDACi sodium butyrate reduces the cell proliferation of MCF-7 cell when combine with vitamin-A[128].

Histone methyl-transferases and histone demethylases as the targets
Studies on histone methylation and their modifiers have been slow. Only few histone methylases (HMT) and demethylases (HDM) and their inhibitors have been discovered. However, studies on histone methylation

could be more fruitful for their therapeutic potential because the less redundancy in HMTs and HDM compared to HATs and HDACs in targeting specific amino acid residue of histone[129]. This property of HMTs and HDMs provides exciting opportunities with more tailored treatment, while potentially minimizing side effects.

LSD1/KDM1 was among the first identified histone demethylases selectively targeting H3K4me1 and H3K4me2[130] and mediate gene repression. LSD1 has been reported to be overexpressed in many cancers like brain, breast, and prostate, thus thought to be a promising target for drug therapy[130-132]. Small molecules such as SL11144 and tranylcypromine have been developed to inhibit LSD1[133,134], Since then have shown to restore expression many silenced tumor suppressors like secreted frizzled-related protein and GATA transcription factors in many cancer cell lines. They have also been shown to possess antitumor activity in a study involving neuroblastoma xenografts model[132]. However, similar to HDACi, HDM and HMT inhibitors also have off-target effects on H3K9me2 and DNMT1 thus limiting their use[135] and further in-depth studies are required. EZH2 is another methyltransferase responsible for H3K27me3 leads to gene silencing by promoting DNA methylation[136]. EZH2 is overexpressed in head and neck, breast, and prostate cancers[137] and can be targeted by a hydrolase inhibitor called 3-deazaneplanocin A (DZNep). It induces differentiation as well as apoptosis in cancer cell lines and xenografts by countering EZH2 and inhibiting H3K27 trimethylation[138,139], while sparing normal cells.

Histone kinases and phosphatases as the targets
Compared to histone acetylation and methylation, the effort of regulating histone phosphorylation by targeting kinases and phosphatases for therapeutic uses is new. High level of several histone H3 phosphorylations such as H3S10ph, H3T6ph has been reported in a number of cancers. Unpublished data from our lab shows increase of H3S10ph in cisplatin resistance gastric cancer cell lines AGS and KATOIII. Our observation further supported the finding that p38 MAPK pathway mediated increase in H3S10ph in response to cisplatin treatment[140] in HeLa and MCF7 cells. Pacaud et al[93] recently reported that the kinase inhibitors like Enzastaurin (PKC-beta inhibitor), AZD1152 (Aurora-B inhibitor) and AZD1480 (Jak2 inhibitor) increases the cell death of TMZ-Irrad resistant GBM and decreases H3T3ph, H3S10ph and H3Y41ph respectively. Further, H89 (MSK1 inhibitor) treatment reduces the TPA and EGF mediated cellular transformation and by decreasing H3S10ph[44]. All these studies represent the potential of regulating histone phosphorylation for therapeutic use in cancer; however, these observations need to be further explored.

Despite of all this progress in the utilization of histone PTMs in chemotherapeutic interventions, a very little is known about their utility in monitoring the response to chemotherapy. For this purpose, levels of cNUCs and their modifications can be utilized. Because, circulating nucleosomes in serum are a result of apoptosis of

actively dividing cells; therefore, after chemotherapy/radiotherapy increase in the circulating nucleosomes correlates with progressive disease and decrease was associated with disease regression. Increase in the concentration of serum nucleosomes has been shown at 24-72 h after the first application of chemotherapy and 6-24 h after the start of radiotherapy[60]. Thus, the concentration of nucleosomes in serum might be a useful tool for monitoring the biochemical responses during antitumor therapy, particularly for the early estimation of therapeutic efficacy. Histone modifications such as H4K16ac for example, can be utilized in this regard as its loss has been reported in several cancers and also chemosensitize cancer cells[33,69,141]. Histone modifications like H3K27me3 have indeed showed perplexing results when analyzed with respect to various cancers. This can be attributed to tissue type, and indeed histone PTMs are known to be showing their abundance in a tissue specific manner[142]. This might be as because many writers and erasers utilize co-factors or substrates like acetyl CoA, SAM, NAD$^+$, FAD$^+$ or ATP which are crucial metabolites in core pathways of intermediary metabolism[143]. The cellular concentrations of these metabolites fluctuate with the metabolic status of the cells and thus, the activity of these enzymes gets affected thus the histone PTMs.

CONCLUSION AND FUTURE DIRECTIONS

The role of histone modifications in governing cellular functions has been not yet fully understood. However, with increased research over the past decade, all the organisms studied so far (from yeast to man) have bought to light the importance of chromatin environment especially histone PTMs in development and disease. These observations have revolutionized the field of epigenetics and have challenged the old hypothesis of the genetic code being the sole determinant of the pathophysiology of any disease. In cancer, especially this is further established with the discovery of small molecule inhibitors targeting histone modifying enzymes, which can restore the expression of various genes to normal and can induce apoptosis of transformed cells. The best studied examples of these drugs are HDACi, which have proven to be highly effective anticancer drugs, thus are in clinics. Although the exact nature of the mechanism by which these drugs act is not understood yet, still these drugs are faring better against cancer. Future studies need to be directed more towards understanding these mechanisms and increasing the potency of these drugs. Though many histone PTMs are known to change during cancer, less is understood regarding the significance and mechanistic details of the change observed. Much of the work done in this direction has been hindered due to technical limitations. However with the advent of new technologies, and also decrease in the cost of high throughput technologies like ChIP-seq and TMA amongst other global approaches, it is a matter of time we have more knowledge of these mechanisms. Also, new targets for development of more potent drugs need

to be explored by careful understanding of an already existing chromatin atlas of various cancer cell lines and tissues. Further work in the next decade may gain deeper understanding of the global patterns of histone posttranslational modifications and their corresponding changes which will hopefully reveal many molecular targets that can be employed as new weapons in long fought battle against cancer.

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