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Aberrant lysine acetylation in tumorigenesis: Implications in the development of therapeutics

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ABSTRACT

The 'language' of covalent histone modifications translates environmental and cellular cues into gene expression. This vast array of post-translational modifications on histones are more than just covalent moieties added onto a protein, as they also form a platform on which crucial cellular signals are relayed. The reversible lysine acetylation has emerged as an important post-translational modification of both histone and non-histone proteins, dictating numerous epigenetic programs within a cell. Thus, understanding the complex biology of lysine acetylation and its regulators is essential for the development of epigenetic therapeutics. In this review, we will attempt to address the complexities of lysine acetylation in the context of tumorigenesis, their role in cancer progression and emphasize on the modalities developed to target lysine acetyltransferases towards cancer treatment.

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1. Introduction

Internal and external environmental cues are translated into cellular responses via the modulation of differential gene expression. The extensive repertoire of post-translational modifications (PTMs) on histone as well as non-histone proteins, aids in the integration of these various stimuli leading to distinct gene expression profiles. These modifications often dictate important cellular events such as gene expression, replication, cell cycle, DNA damage response, cell signaling pathways and metabolism. PTMs such as phosphorylation, N-terminal acetylation,

Abbreviations: AA, Anacardic acid; AML, Acute myeloid leukemia; AML1-ETO, Acute Myeloid Leukemia1-Eleven Twenty One; AP-1, Activator Protein-1; AR, Androgen receptor; ATM, Ataxia Telangiectasia Mutated; CBP, CREB-binding protein; CTCL, Cutaneous T-cell lymphoma; DNA, Deoxyribonucleic acid; DNMT, DNA methyltransferase; ECM, Extracellular matrix; ERK1, Extracellular signal-regulated kinase; ESCC, Esophageal squamous cell carcinoma; GCN5, General Control Non-derepressible5; GNAT, GCN5-related N-acetylatransferase; GOF, Gain of Function; HAT, Histone acetyltransferase; HBO1, HAT bound to ORC1; HCC, Hepatocellular carcinoma; HIF1α, Hypoxia-inducible factor 1α; HMG, High Mobility Goup; HNSCC, Head and Neck Squamous Cell Carcinoma; HPV, Human papilloma virus; KAT, Lysine acetyltransferase; KDAC, Lysine deacetylase; LOH, Loss of heterozygosity; MDR1, Multi drug resistance; MLL, Mixed-lineage leukemia; MOF, Males absent On First; MORF, MOZ-related factor; MOZ, Monocytic leukemia zinc-finger protein; MYST, MOZ, Ybf2, Sas2, TIP60; NPM1, Nucleophosmin; NF-κB, Nuclear factor κB; NOS, Nitric oxide synthase; NSCLC, Non-small cell lung carcinoma; PCAF, p300/CBP-associated factor; PTM, Post-translational modification; SMAD, Sma and Mad (mothers against decapentaplegic); SIRT1, Sirtuin 1; STAGA, SPT3-TAF9-GCN5 acetyltransferase; STAT3, Signal Transducer and Activator of Transcription 3; TIF2, Transcription intermediary factor 2; Tip60, HIV1 Tat interacting protein.

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methylation, sumoylation, ubiquitination, propionylation, butyrylation, carbonylation, neddylation, proline isomerization and ADP ribosylation regulate the diverse protein functions (Kouzarides, 2007; Lee et al., 2010). In addition to these, N-ε-lysine acetylation has been identified to play a pivotal role in various cellular processes and is known to be a key modification involved in the manifestation of patho-physiological conditions such as tumorigenesis.

Lysine acetylation is the transfer of an acetyl group from Acetyl Coenzyme A (acetyl-CoA) to the ε-Nitrogen on the lysine residue. The dynamics of acetylation is regulated by lysine acetyltransferases (KATs) which are the 'writers' of this modification and lysine deacetylases (KDACs), the 'erasers' of acetylation (Fig. 1). Lysine acetylation of histones neutralize the positive charge on the lysine residue and loosens the chromatin, this in turn facilitates the access of protein machineries involved in replication, transcription or DNA repair, to the DNA template (Capell & Berger, 2013; Unnikrishnan et al., 2010; Vo & Goodman, 2001). Lysine acetylation has been associated with chromatin architecture (Shogren-Knaak et al., 2006), DNA repair (Chatterjee et al., 2012), protein stability and protein–protein interaction (Kouzarides, 2007), and has emerged as the ubiquitous post-translational modification that is found across the entire proteome (Choudhary et al., 2009; Zhao et al., 2010). The extensive presence of lysine acetylation on proteins involved in a range of cellular functions emphasizes the importance of the modification in the maintenance of cellular homeostasis. The first global acetylome analysis was accomplished by Choudhary et al., in which 3600 acetylation sites were identified on 1750 proteins, which were distributed across the different compartments of the cell and were not confined to the nucleus (Choudhary et al., 2009). Currently, public repositories such as phosphositeplus database show over 35,000 acetylation sites in human cells (Hornbeck et al., 2012).

Several proteins have been identified as lysine acetyltransferases. KATs are mainly classified into two groups depending on their cellular localization and the ability to acetylate chromatinized histones. Type-B KATs are predominantly located in the cytoplasm and acetylate histone H4 on lysine-5 (-K5) and lysine-12 (-K12) on nascent histones. Type-A KATs are nuclear KATs which can acetylate histones incorporated into chromatin. The major families of KATs are GNAT (GCN5-related N-acetylatransferase) family, p300/CBP (KAT3) family and MYST (MOZ, Ybf2, Sas2, and TIP60) family, these will be discussed in detail in Section 3. Apart from these, two other KAT families exist, which belong to transcription factor-related KATs and nuclear receptor family of KATs. The KDACs are broadly classified as the classical KDACs consisting of Class I (homologs of yeast Rpd3, which comprises KDAC 1,2,3 and 8), Class II (homologs of yeast Hda1, which comprises KDAC 4,5,6,7,9,10) and Class IV (KDAC 11) and NAD^+-dependent Class III KDACs or Sirtuins which resemble yeast Sir2. KDACs have been implicated in many diseases and they play an active role in the progression of cancer (Falkenberg & Johnstone, 2014).

Lysine acetylation is 'read' by specialized protein domains which can specifically bind to the acetylated lysine residue. These are bromodomains (BrD), tandem plant homeodomain (PHD) and the YEATS domain (Dhalluin et al., 1999; Li et al., 2014; Zeng et al., 2010). Bromodomains are protein domains that contain an evolutionally conserved structural fold, 'BrD fold', consisting of a left-handed four-helix bundle motif that specifically recognize ε-N-lysine acetylation modification of proteins (Dhalluin et al., 1999). The tandem PHD domain consists of two typical PHD fold, each fold comprises two-strand anti-parallel β-sheet and an α-helix stabilized by two zinc atoms, placed in tandem (Zeng et al., 2010). The YEATS domain of AF9 protein specifically recognizes H3K9 acetylation. The domain acquires an eight-strand immunoglobin fold and the acetyl-lysine is recognized by a serine-lined aromatic cage (Li et al., 2014). The acetyllysine moiety on histone and non-histone proteins serves as docking sites for effector-proteins possessing these 'reader' domains, which recognize specific acetylation patterns leading to the downstream readouts and resulting in various cellular signaling cascades. Thus, it is not unlikely to find that BrDs play a role in the perturbation of transcription programs in different

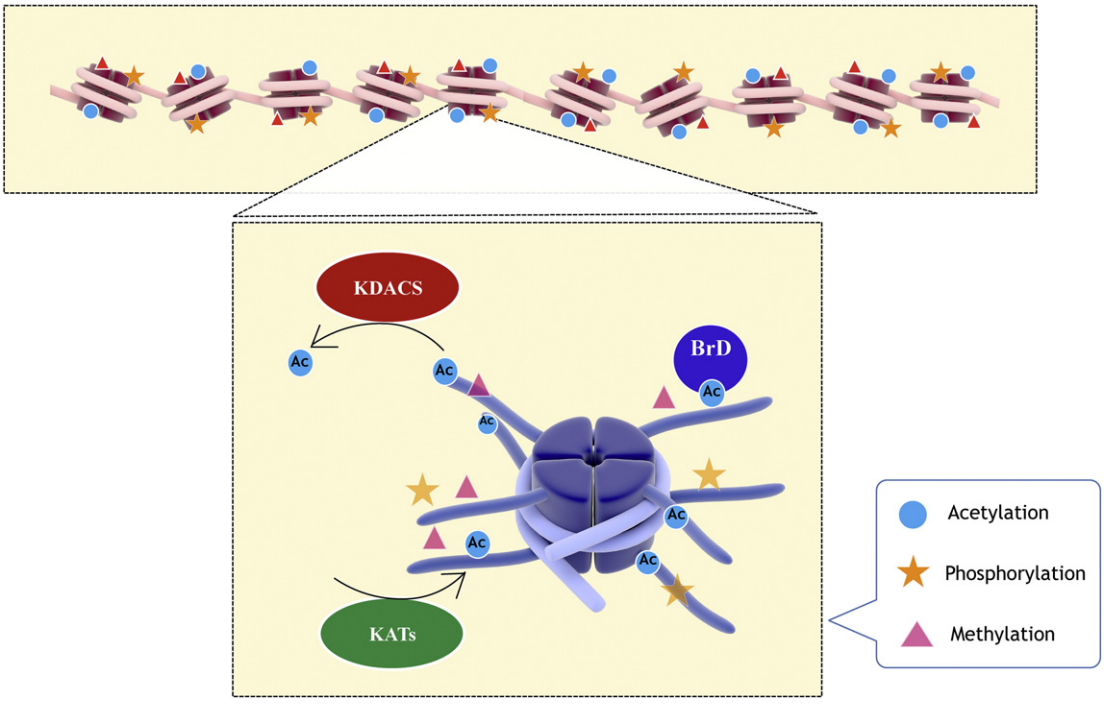

Fig. 1. Acetylation dynamics in chromatin: A brief overview of histone acetylation. The upper panel represents the multiple histone modifications that coexist in chromatin (represented here are acetylation, methylation and phosphorylation). The lower panel zooms-in on one nucleosome where writers (KATs adding acetylation marks), erasers (KDACs removing acetylation marks) and readers (Bromodomain (BrD)) containing proteins are depicted.