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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 histones 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 complexity 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.

Keywords

Chromatin, Histones, Post translational modification, Lysine acetylation, Lysine acetyltransferase, Epigenetic therapeutics

Abbreviations and Acronyms

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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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, aid 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, 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 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 **(Figure 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, onto the DNA template (Capell and Berger, 2013; Unnikrishnan et al., 2010; Vo and 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 which will be discussed in details 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 of KDAC 1,2,3 and 8), Class II (homologs of yeast Hda1, which comprises of 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 and 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 the 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 of 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 histones and non-histone proteins serve 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 malignancies. Details of KDAC and BrD inhibitors are beyond the scope of this review; they have been extensively reviewed in excellent articles previously (Falkenberg and Johnstone, 2014; Filippakopoulos and Knapp, 2014; Ropero and Esteller, 2007; You et al., 2012).

In this review, we will attempt to summarize the function of acetylation in the manifestation of malignancies, emphasizing on their role in inflammation and the maintenance of cancer stem-like cells. Here, we will also highlight the physiological functions of KATs, while giving an insight about their roles in the progression of cancer. Finally, we will discuss the achievements and drawbacks of epigenetic therapeutics targeting the lysine acetylation modification and the contribution of these small molecules to the field of anti-neoplastic drug development.

2. Lysine Acetylation in Cancer

2.1. The Role of Aberrant Histone Acetylation in Cancer Manifestation

Histone acetylation is well characterized in the context of gene regulation and global levels of many distinct histone marks have been mapped in cell lines, human and mouse tissues, allowing for the correlation of their presence or absence to gene expression or repression. Many studies have also correlated alterations in histone acetylation as potential diagnostic or prognostic biomarkers in human diseases such as cancer (Struhl, 1998).

H4K16ac is an important histone acetylation mark which regulates chromatin higher order structures. In mouse ESCs, acetylation on H4K16 marks active enhancers and is involved in transcription regulation (Taylor et al., 2013). H4K16ac, along with H4K20me3, is often lost in cancers and is considered a universal hallmark for malignant transformation (Fraga et al., 2005). Alteration of histone acetylation patterns is also predictive of prognosis and recurrence, as in the case of prostate cancer, where hypoacetylation of histone H3 at K9, K18 and H4K16 strongly correlates with cancer recurrence (Seligson et al., 2005). While elevated global histone hyperacetylation correlates with oral cancer manifestation (Arif et al., 2010). Loss of H4K16ac in breast cancer may serve as an early sign of cancer, and low levels of H3K9ac, H3K14ac and H4K12ac are prognostic of poor outcomes (Elsheikh et al., 2009). In non-small cell lung carcinoma (NSCLC), the reduction in H3K9ac is predictive of better survival while contrastingly, hypoacetylation at H2AK5 is correlated with poor prognosis (Barlesi et al., 2007). In another study, hyperacetylation of H4K5, H4K8 and hypoacetylation of H4K12, H4K16 correlated with the progression of NSCLC (Van Den Broeck et

al., 2008). Loss of H3K9 and K18 acetylation is predictive of better prognosis in glioma (Liu et al., 2010). The low levels of H3K18ac correlates with better survival in esophageal squamous cell carcinoma and poor survival in pancreatic adenocarcinoma patients (Manuyakorn et al., 2010; Tzao et al., 2009). The globular histone acetylation mark, H3K56ac, is often upregulated in cancers and undifferentiated cells (Das et al., 2009).

The alteration in the epigenetic landscape is an important hallmark in cancer progression and the dysregulation of histone acetylation patterns is a critical prognostic marker of the disease outcome. Thus, the gross deregulation of the epigenetic machinery justifies the necessity of epigenetic-based therapeutics. **Table 1** summarizes the alteration of global histone acetylation marks in cancer.

2.2. The Role of Non-Histone Protein Acetylation

Lysine acetylation is a reversible, dynamic modification, providing functional diversity to proteins. The acetyltransferases that acetylate histones are also capable of acetylating non-histone proteins, hence termed lysine acetyltransferases (KATs). Lysine acetylation of target proteins can have varied consequences to the function of the modified protein. Mechanistically, addition of an acetyl group neutralizes the positive charge, changing the electrostatic property and size of the residue, leading to different and often opposing functions in proteins.

Acetylation can lead to increase in DNA binding affinity of transcription factors such as p53, STAT3, E2F1 (Gu and Roeder, 1997; Martinez-Balbas et al., 2000; Marzio et al., 2000; Yuan et al., 2005), this in turn could lead to increase in transactivation and gene expression by these proteins. Alternatively, acetylation could also decrease the DNA binding ability of certain proteins such as YY1, RelA, HMG proteins (Kiernan et al., 2003a; Lührs et al., 2002; Munshi et al., 1998; Yao et al., 2001). Acetylation can increase the transactivation potential of proteins such as AR, GATA proteins, MyoD (Boyes et al., 1998; Fu et al., 2000; Gaughan et al., 2002; Hayakawa et al., 2004; Polesskaya et al., 2000; Sartorelli et al., 1999; Yamagata et al., 2000), but acetylation can also decrease transactivation potential of other proteins such as ERα, and HIF1α (Jeong et al., 2002; Wang et al., 2001). Protein stability can be increased on acetylation, by blocking ubiquitination of the same lysine residues, which will target the protein for proteosomal degradation, this has been observed in p53, c-Myc, Smad7 (Grönroos et al., 2002; Ito et al., 2002; Patel et al., 2004), contrastingly, acetylation of some proteins can decrease their stability, like acetylated DNMT1 has reduced stability and gets proteosomally degraded (Du et al., 2010). Protein acetylation can create new surfaces for interaction with other proteins, for example, acetylation of Importin-α at a single residue can promote its interaction with Importin-β enhancing nuclear import of HuR (Bannister et al., 2000; Wang et al., 2004). Conversely, acetylation can disrupt protein-protein interactions, as seen in the case of proteins such as Ku70, Hsp90 (Cohen et al., 2004; Kovacs et al., 2005). Another interesting regulatory

phenomenon mediated by acetylation is the sub-cellular localization of proteins. SRY protein gets localized to the nucleus upon acetylation and consequently interacts with Importin-β (Thevenet et al., 2004), c-Abl acetylation leads to its nuclear to cytoplasmic delocalization (di Bari et al., 2006). Acetylation of the histone chaperone NPM1 leads to change in its localization from the nucleolus to the nucleoplasm leading to RNA Polymerase II-mediated transcription co-activation (Shandilya et al., 2009). Recently, β-catenin acetylation has been implicated in its increased membrane localization (Iaconelli et al., 2015). Acetylation of certain enzymes can alter their enzymatic activity; p300 autoacetylation enhances its acetyltransferase activity (Thompson et al., 2004), acetylation of ATM kinase by Tip60 increases its kinase activity (Sun et al., 2005) on the other hand, KDAC1 acetylation can lead to dampening of its deacetylase activity (Qiu et al., 2006), similarly, acetylation of PTEN reduces its phosphatase activity (Okumura et al., 2006).

In summary, through these abundant mechanisms, acetylation of non-histone proteins has been implicated in varied processes such as transcription, signaling, DNA repair, DNA replication, cell cycle regulation, viral pathogenesis, metabolism, differentiation and development, cytoskeletal dynamics, mRNA stability, autophagy, apoptosis and many more (Glozak et al., 2005; Singh et al., 2010; Spange et al., 2009). Deregulation of these cellular processes upset the homeostatic balance of the cell, which is a hallmark of diseases such as cancer. Thus, numerous reports exist in current literature, correlating the acetylation of non-histone proteins to cancer. **Table 2** summarizes a few non-histone protein acetylations implicated in cancer manifestation.

2.3. Lysine Acetylation, Inflammation and Cancer

Inflammation refers to the set of symptoms including redness, swelling, heat and pain (cardinal signs) that is observed after innate immune response to infection, injury or irritation. The link between inflammation and cancer is now well established. Inflammation alone however does not lead to cancer, many factors including genetic and epigenetic factors, suppressed immunity and environmental agents are players in the genesis of inflammatory cancers (Schottenfeld and Beebe-Dimmer, 2006). Chronic inflammation occurs when immune cells get activated to produce excessive pro-inflammatory molecules, leading to prolonged inflammation. This creates severe and progressive tissue injury and fibrosis, creating a microenvironment conducive to the development of malignancies (Aggarwal et al., 2006).

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is an important and ubiquitous, pro-inflammatory transcriptional regulator and can be constitutively activated in the absence of external factors. In addition, NF-κB has emerged as a key transcription factor in chronic inflammation-driven initiation and progression of cancer (DiDonato et al., 2012; Hoffmann et al.,

2006; Karin, 1999; Sethi et al., 2008; Sethi and Tergaonkar, 2009; Shanmugam and Sethi, 2013). The NF-κB family of proteins is actually a group of structurally similar proteins. In mammals, these are; NF-κB1/p50, NF-κB2/p52, RelA/p65, RelB, and c-Rel. NF-κB exists as a heterodimer and is present in the cytoplasm in association with IκBα. Numerous physiological, environmental and stress factors have been shown to activate NF-κB in the cells (Sethi et al., 2008). Upon stimulation, IκBα and NF-κB are predominantly phosphorylated by their upstream kinase IKKα/β, this subsequently leads to rapid polyubiquitination and degradation of IκBα. The free phosphorylated NF-κB subsequently translocates to the nucleus and initiates transcription of genes that encode cytokines, chemokines, angiogenic factors which play roles in continuous tumor cell proliferation, survival, invasion and metastasis (Sethi et al., 2012; Sethi and Tergaonkar, 2009).

Just like the histone code, there seems to be an 'NF-κB signaling code' where many components of the NF-κB pathway and associated molecules are regulated by post translational modification in a stimulus responsive manner (Calao et al., 2008).

Chromatin-associated mechanisms such as chromatin remodeling, co-activator recruitment or deposition of positive histone marks (histone acetylation) and removal of co-repressors or negative histone marks play important roles in NF-κB mediated inflammatory gene expression (Reviewed in (Bhatt and Ghosh, 2014)). NF-κB associates with co-activators through the transactivation domain. The most well studied association is that of the RelA subunit. In non stimulated conditions, RelA interacts with KDAC complexes to keep the inflammatory genes repressed, but upon inflammatory signals, RelA is phosphorylated at Ser276 by many kinases. This event promotes the interaction of RelA with KAT3 and causes transactivation of the NF-κB responsive genes through histone acetylation (Chen et al., 2005; Dong et al., 2008; Gerlo et al., 2011; Mukherjee et al., 2013; Nihira et al., 2010; Vermeulen et al., 2003; Zhong et al., 2002; Zhong et al., 1998). Moreover, acetylation of RelA itself at Lysine 310 by KAT3, directs its interaction towards Tip60, Brd4, P-TEFb implicating this modification in transactivation. Brd4 can also recruit PTEF-B, which phosphorylates the CTD of Pol II , leading to successful transcription elongation (Barboric et al., 2001; Brasier et al., 2011; Hargreaves et al., 2009; Huang et al., 2009; Kim et al., 2012; Luecke and Yamamoto, 2005; Sharma et al., 2007). Conversely, SIRT1 deacetylates RelA at Lysine 310 and decreases its transactivation potential (Yeung et al., 2004).

Importantly, constitutive activation of NF-κB is often observed in chronic inflammation-driven cancers. The importance of the acetylation of RelA for constitutive activation of NF-κB can be inferred from a study in leukemia cells, where KDACi treatment led to the accumulation of acetylated RelA in the nucleus and constitutive NF-kappaB activation (Dai et al., 2005).

Acetylation of RelA is also associated with IκBα assembly in the cytoplasm, its subcellular localization, and subsequently targets NF-κB translocation to the nucleus and regulates NF-κB DNA binding affinity (Chen and Greene, 2003). Also, acetylation of RelA by p300 and PCAF at K122 and K123 decreases its affinity towards NF-κB binding DNA elements. Deacetylation of RelA by KDAC3 leads to its IκBα mediated nuclear export and a replenished pool of NF-κB in the cytoplasm, ready for the next activation signal (Chen Lf et al., 2001; Kiernan et al., 2003b).

The p50 subunit also gets acetylated at K431, K440 and K441 by p300 which augments the NF-κB transcriptional activation (Deng and Wu, 2003; Deng et al., 2003; Furia et al., 2002).

Some of the IKK complex proteins which are cytoplasmic can shuttle to the nucleus and can recruit KATs and KDACs. The NF-κB pathway upstream kinase IKKα, upon TNFα induction, is recruited to NF-κB dependent promoters where it can associate with CBP. This leads to a concerted H3S10 phosphorylation and H3K9 and H3K14 acetylation and activation of pro-inflammatory genes. IKKα can also promote RelA phosphorylation and also its acetylation by CBP at certain promoters. Cigarette smoke is known to induce pro-inflammatory gene transcription, interestingly; IKKα has been shown to mediate this effect through the concerted phosphorylation and acetylation of H3 as well as RelA (Gloire et al., 2007; Hoberg et al., 2006; Lubin and Sweatt, 2007; Yamamoto et al., 2003; Yang et al., 2008). The regulatory subunit of the IKK complex, IKKγ/NEMO can interact with CBP in the nucleus, it competes with RelA and IKKα for this interaction and can thus repress CBP induced transcriptional activation through RelA or IKKα (Verma et al., 2004).

IκBα is generally known as the inhibitor of NF-κB in the cytoplasm, but this protein can also shuttle to the nucleus and can repress non classical NF-κB target genes, like *hes1* by recruiting KDACs to their promoters (Aguilera et al., 2004).

Another protein, Poly (ADP-ribose) polymerase-1 (PARP-1) associates with NF-κB in chronic inflammation-driven diseases and is a promoter specific co-activator of NF-κB *in vivo* (Aguilar-Quesada et al., 2007; Hassa et al., 2003). It has been also reported that p300 can acetylate PARP-1 at specific lysine residues in a variety of cell lines and can also directly interact with p50 and RelA leading to synergistic activation of NF-κB in these cell lines (Hassa et al., 2005).

STAT family of proteins is another important class of transcription factors which mediate inflammatory responses. STAT1, 2, 3, 5 and 6 have all been shown to be acetylated by KAT3 proteins (Krämer et al., 2006; Ma et al., 2010; McDonald and Reich, 1999; Ray et al., 2005; Tang et al., 2007; Wang et al., 2005; Yuan et al., 2005) STAT3 gets acetylated by KAT3 at K685, which enhances its protein-protein interaction, dimerization, DNA binding affinity and transcriptional activity. This phenomenon can be reversed by deacetylase KDAC3, leading to loss of STAT3-DNA binding and

suppression of transcription (Yuan et al., 2005) (reviewed extensively in (Icardi et al., 2012) and (Zhuang, 2013)). In hepatocellular carcinoma (HCC) Hep3B cells and in HEK293T cells, Ohbayashi *et al.* showed that IL-6 or leukemia inhibitory factor induced STAT3 acetylation at lysine K685. However, this was abolished by PI3K inhibitor, LY294002 (Ohbayashi et al., 2007). Numerous studies have shown that cytokines mediate acetylation of STAT3, while inhibitors of deacetylases have also been implicated in rapid acetylation of STAT3. In diffuse large B-cell lymphoma (DLBCL) KDAC inhibitor LBH589 hyperacetylates STAT3 and inhibits its transcriptional activity (Gupta et al., 2012). In another interesting study it was observed that persistently activated STAT3 positively regulated NF-κB acetylation by p300. The cross-talk between constitutively active STAT3 and NF-κB was essential for driving tumorigenesis (Lee et al., 2009). It was also found that acetylated STAT1 has a cross-talk with NF-κB (RelA) and negatively regulates NF-κB activation in various tumor cells (Krämer et al., 2006). Thus, acetylation and deacetylation reaction constitute a novel signaling mechanism that regulates IL-6/STAT pathway in cancer.

Furthermore, the innate immune response activated by toll like receptors (TLRs) in response to lipopolysaccharide (LPS) often leads to chronic inflammation. Stimulation of TLRs induce the expression of mitogen activated protein kinase (MAPK) phosphatase-1 (MKP1) which when acetylated at K57, dephosphorylates p38 MAPK and c-Jun N-terminal kinase (JNK) resulting in attenuated production of pro-inflammatory cytokines .

Thus, it is evident that reversible acetylation of NF-κB pathway members and histones plays an important role in regulating inflammation specific gene expression. The critical role of lysine acetylation in regulating inflammation-associated cancer signaling pathways is depicted in **Figure 2**.

2.4. Lysine Acetylation in Cancer Stem Cells Maintenance

Cancer progression from an initiating tumor to an aggressive metastasis requires the cancer cells to acquire various cellular properties; these properties can enable cancer cells to invade and metastasize to various tissues in the body. Moreover, the ability to self renew is also essential for cancer cells to colonize a distant site (Scheel and Weinberg, 2012). Indeed cells capable of generating new tumors with high efficiency in immune-compromised host mice in limiting dilutions have been described previously. They are termed as cancer-initiating cells or cancer stem cells (CSCs) (Alison et al., 2010). There is still discordance in the field about their relative population in the tumors and their origin; nonetheless, CSCs have been described in acute myeloid leukemia, breast cancer, brain tumors, colon cancer and pancreatic cancer (Al-Hajj et al., 2003; Hermann et al., 2007; Lapidot et al., 1994; O'Brien et al., 2007; Ricci-Vitiani et al., 2007; Singh et al., 2004). Cancer cells gain these properties through the activation of a well-defined program called the Epithelial to Mesenchimal

Transition (EMT). Activation of EMT has been linked to normal and cancerous cells acquiring stem cell-like properties (Mani et al., 2008; Morel et al., 2008). EMT is a cellular program that usually occurs during development, generating mesenchymal cell types from epithelial or endothelial cells. It is an important cellular program during morphogenesis, enabling cellular movements (Acloque et al., 2009; Singh and Settleman, 2010; Thiery et al., 2009). EMT is controlled by a set of transcription factors (EMT-TFs) which are responsive to signals from the cellular microenvironment and can in turn regulate many genes and pathways. Since epithelial cells are characterized by strong cell to cell adhesion, EMT-TFs act to downregulate factors associated with cell adhesion such as E-cadherin. Some of the well characterized EMT-TFs are Snail, Slug, Zeb1, Twist (Bolós et al., 2003; Cano et al., 2000; Eger et al., 2005; Yang et al., 2010).

Histone modifications have been implicated in EMT (Micalizzi et al., 2010). Generally, active or permissive chromatin is marked by histone acetylation whereas deacetylation indicates a repressed or closed chromatin. EMT requires the repression of epithelial genes, thus the EMT-TFs recruit repressor complexes that include histone deacetylases to the target promoter and repress transcription. EMT-TFs have been demonstrated to bind to E-cadherin promoter and recruit Class I KDACs (Sims and Wade, 2011; von Burstin et al., 2009; Ye et al., 2010). KDACi treatments have been shown to promote EMT, suggesting the role of acetylation in maintaining the epithelial phenotype (Giudice et al., 2013). Some proteins interact or recruit co-activators such as p300 or CBP to maintain epithelial phenotype as seen in the case of HNF-3 in breast cancer cells which interacts with p300 and AML1 and upregulates E-cadherin expression, reducing the metastatic potential (Liu et al., 2005). In lung cancer cells, upon ZEB1 induction, H3K27ac mark was reduced on the ZEB1 responsive elements, thus favoring EMT (Roche et al., 2013). miR200b and miR200c increase H3 acetylation at E-cadherin promoter through the disruption of ZEB1 and KDAC interaction (Tryndyak et al., 2010). The expression of the EMT-TFs are themselves tightly regulated, H3 acetylation on Snail, ZEB1, ZEB2 promoters was seen to be facilitated by the lysine methyltransferase, DOT1L (Disruptor Of Telomeric Silencing 1-Like) protein, by associating with the c-Myc/p300 complex, conferring CSC-like properties in breast cancer cells (Cho et al., 2015), conversely UTX (an H3K27 demethylase) negatively regulates EMT by facilitating the reduction of H3 acetylation on the Snail, ZEB1, ZEB2 promoters, repressing their expression, thus loss of UTX was seen to induce EMT and CSC-like properties in breast cancer cells (Choi et al., 2015). Metadherin (MTDH) is implicated in drug resistance and metastasis; in a recent study it was seen to expand CSCs in breast cancer. MTDH was seen to interact with CBP, stabilize it and recruit it to TWIST promoter, facilitating promoter proximal H3 acetylation, thus regulating TWIST expression and driving EMT (Liang et al., 2015).

Wnt signaling pathway has also been linked to EMT. The current understanding is that CBP promotes self-renewal of stem cells and p300 promotes differentiation, in a Wnt/β-catenin-dependent pathway **(Figure 3)** (Ma et al., 2005; Moheimani et al., 2015). Cancer stem cells have also been

known to be resistant to chemotherapeutic agents, implicating them in recurrence. Furthermore, it has come to light that cancer stem cells can either be a cause or a consequence of drug resistance. In a recent study, it was observed that cancer cells that are highly tumorigenic and drug-resistant develop cancer stem cell-like phenotype through the PI3K/Akt/β-catenin pathway. Interestingly, β-catenin interacts with CBP to modulate this conversion. It is likely that this is mediated through histone acetylation (He et al., 2014). TGF-β signaling has also been implicated in EMT, the induction of this signaling is through H3 hyperacetylation on TGF-β gene promoter (Yang et al., 2015). Interestingly it has also been observed that TGF-β induces EMT through induction of KAT3 activity, this is through the acetylation of the Smad2 and Smad3 proteins in lung cancer cells (Ko et al., 2013).Thus lysine acetylation modulates EMT to drive cancer progression through the generation of cancer stem cells.

3. Lysine Acetyltransferases and their Link to Tumorigenesis

Lysine acetyltransferases play important roles in the maintenance of cellular homeostasis. Deregulation of these enzymes lead to pathological conditions including cancer, inflammatory disorders and neurological disorders. Chromosomal instabilities during cancer progression may lead to deletions, mutations, fusions and duplications in many vital cellular genes including KAT genes. In malignancies, the levels and functions of KATs have been observed to be severely dysregulated. KATs have also been associated with multidrug-resistance to conventional cancer therapies. In this section, we will discuss in-depth the intimate association of KATs with cancerous transformations.

3.1. CBP/p300 (KAT3) family

The transcription co-activators, CBP (KAT3A) and its paralog p300 (KAT3B) are large adaptor proteins possessing intrinsic acetyltransferase activity, which bridge the basal transcription machinery to DNA sequence-specific transcription factors. (Bannister and Kouzarides, 1996; Chan and La Thangue, 2001; Ogryzko et al., 1996). They share an overall 63% amino acid sequence identity and around 86% sequence identity at the histone acetyltransferase (HAT) domain. These highly homologous proteins are involved in a variety of cellular functions. As described earlier, they are integrally involved in transcription by virtue of their acetyltransferase activity and interaction with transcription factors. They are required for faithful cell cycle progression and cell proliferation. Interruption of KAT3 activity either by microinjection of specific antibodies or by chemical inhibition leads to G1/S arrest (Ait-Si-Ali et al., 2000) and an increase in senescence (Yan et al., 2013). Moreover, fibroblasts isolated from p300 null embryos have severe cell proliferation defects (Yao et al., 1998).

CBP and p300 also play an important role in DNA damage response and apoptosis, especially through the modulation of the p53 pathway. Surprisingly, in spite of the close homology between

CBP and p300, the roles of these proteins *in vivo* are relatively distinct, which is evident due to the haplo-insufficiency observed in germline mutations in CBP or p300, which lead to the genetic disorder known as Rubinstein-Tyabi syndrome. This disorder is marked by cranio-facial defects, mental retardation and a predisposition to cancer (Miller and Rubinstein, 1995; Rubinstein and Taybi, 1963). Hematological malignancies are frequent in mice heterozygous for CBP (Kung et al., 2000). Moreover, chimeric mice have tumors arising from the CBP-/- and p300-/- null cells (Rebel et al., 2002). Moreover, CBP or p300 knock-out and double heterozygosity for CBP and p300 result in embryonic lethality in mice (Yao et al., 1998).

Given the importance of these enzymes in the maintenance of cell homeostasis, perturbation in their functions can lead to severe pathological conditions. In cancers, KAT3 proteins can function both as tumor suppressors or oncogenes depending on several parameters which govern their cellular functions.

Somatic mutations of both p300 and CBP have been observed in many malignancies. In cell lines and primary tumors, the loss of heterozygosity (LOH) at the p300 or CBP loci due to chromosomal loss or inactivating mutations such as missense mutations, frameshift or truncations, have indicated a probable tumor suppressive role of these proteins. LOH at the p300 locus (22q13) has been observed in numerous cancers including hepatocellular, colorectal, oral, breast, ovarian, gastric carcinomas and glioblastomas (Iyer et al., 2004). The biallelic loss and inactivating mutations are rarer at the CBP locus (16p13). CBP gene mutations have been observed in lung, colon, breast and ovarian cancers (Kishimoto et al., 2005; Ozdağ et al., 2002; Tillinghast et al., 2003). Although the frequency of mutations at the p300 and CBP gene locus is significantly low in cancers, these proteins may still function as putative tumor suppressors.

In hematological malignancies such as acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL), chromosomal instability at the CBP or p300 loci occurs at a low frequency, but these mutations are often associated with poor prognosis of the disease (Diab et al., 2013). Chromosomal translocations resulting in chimeric proteins retain the KAT catalytic activity and BrDs of KAT3 proteins. In-frame translocation confer oncogenic potential to these fused proteins, like in the case of mixed lineage leukemia (MLL)-CBP t(11;16) (q23;p13) or in MLL-p300 t(11;22)(q23;q13) fusions (Krivtsov and Armstrong, 2007). These fusions are frequently encountered in patients who have been treated with topoisomerase II inhibitors for the treatment of other cancers, predisposing them to a secondary therapy-related leukemia (Rozman et al., 2004). Other oncogenic fusions such as AML1-ETO t(8;21)(q22;q22), require p300 for the induction of carcinogenic transformations (Wang et al., 2011).

CBP and p300 have multiple domains through which they interact with a large repertoire of proteins. Through this vast interactome, p300 and CBP can modulate cellular events in normal and

pathological conditions. KAT3 proteins can promote tumorigenesis by interacting with oncoproteins such as c-Myc, c-Myb, c-Fos, c-Jun, HIF1α, β-catenin and androgen receptor (AR) which are associated with malignant transformations (Bannister and Kouzarides, 1995; Bannister et al., 1995; Dai et al., 1996; Fu et al., 2000; Hecht et al., 2000; Vervoorts et al., 2003). Interestingly, disruption of the interactions between p300 and these oncoproteins has opened novel avenues in epigenetic drug development which will be discussed in the following section.

Taking into account the role of CBP and p300 in oncogenesis, it is expected that the expression levels of these proteins will be dysregulated with tumor progression. In HCC, the overexpression of p300 strongly correlates with the aggressiveness of the disease. Moreover, high expression levels of p300 are predictive of poor prognosis in patients with HCC (Li et al., 2011; Yokomizo et al., 2011). p300 levels correlate with the grade and tumor size in prostate cancer, where higher grades have higher expression of p300 and it is also observed that higher p300 expression increases the risk of recurrence among patients (Debes et al., 2003; Isharwal et al., 2008). p300 expression is also associated with the aggressiveness of cutaneous squamous cell carcinoma (CSCC) and nasopharyngeal carcinoma (Chen et al., 2015; Liao et al., 2012). In colorectal adenocarcinomas, higher expression of p300 predicted poor prognosis while higher CBP expression correlated with longer survival in patients (Ishihama et al., 2007). Higher p300 expression has also been linked to recurrence and poor prognosis in breast cancer and non-small cell lung carcinoma and may confer doxorubicin-resistance to bladder cancer cells (Hou et al., 2012; Takeuchi et al., 2012; Xiao et al., 2011).

PTMs also play an important role in the modulation of KAT3 function. Cyclin-dependent kinase 1 (CDK1) and ERK1/2-mediated phosphorylation of p300 on S1038 and S2039 leads to its degradation which promotes the progression of lung cancer (Wang et al., 2014). CBP and p300 can autoacetylate an unstructured activation loop at the active site leading to their hyperactivation (Thompson et al., 2004). Certain factors can regulate the autoacetylation of p300 under different cellular scenarios. It has been reported that the histone chaperone nucleophosmin (NPM1) is capable of enhancing p300 autoacetylation, leading to hyperactivation of the enzyme. This hyperactive p300-mediated aberrant histone acetylation and gene expression may play an important role in the manifestation of oral cancer (Arif et al., 2010).

3.2. GNAT family

PCAF (p300/CBP Associated Factor; KAT2B) and GCN5 (General Control Non-derepressible5; KAT2A) are the members of the GNAT family of the lysine acetyltransferases. These homologous proteins function as transcriptional co-activators in the large multisubunit 2MDa complexes such as human STAGA (SPT3-TAF9-GCN5 acetyltransferase), TFTC (TATA binding

protein (TBP)–free–TAF complex), PCAF complexes and in the 700-800 kDa ATAC (ADA two a containing) complex (Nagy and Tora, 2007). These multiprotein complexes regulate the substrate specificity of these enzymes in the cellular context, adding complexity to the functioning of these enzymes. They function as chromatin modifying enzymes and are closely linked to DNA repair machinery, especially the UV-damage mediated DNA damage response (Brand et al., 2001). PCAF mediated acetylation of p53 at K320 is important for p53 mediated cell cycle arrest in response to UV-induced DNA damage (Sakaguchi et al., 1998). Under stress conditions, the role of PCAF is critical as a co-activator for p53 mediated p21 expression and cell cycle arrest (Love et al., 2012). Moreover, PCAF has also been shown to be a p53 target gene (Watts et al., 2004). Interestingly, PCAF can also negatively regulate p53 through its ubiquitin E3 ligase activity, thus regulating the levels of p53 following DNA damage response (Linares et al., 2007). Since GCN5 and PCAF have an integral role in the maintenance of genome integrity, the perturbation in their activity may result in cancer. PCAF maps to the short arm of chromosome 3 (3p24) which is frequently lost in solid tumors such as renal cell carcinoma, lung cancer and esophageal squamous cell carcinoma (ESCC) (Kok et al., 1997; Qin et al., 2008; Yamakawa et al., 1991). PCAF locus was identified as a commonly deleted region in ESCC which correlated with advanced tumor stage and metastasis. The expression of PCAF was also found to be downregulated in primary ESCC tumors and cell lines and this downregulation was associated with DNA hypermethylation at the PCAF promoter. Furthermore, PCAF can suppress ESCC tumor growth *in vitro* and *in vivo* (Zhu et al., 2009). PCAF expression has also been reported to be downregulated in HCC, intestinal type gastric cancer (ITGC) and ovarian cancer (Sunde et al., 2006; Ying et al., 2010; Zheng et al., 2013).

Conversely, since PCAF is closely associated with DNA damage repair, it is often associated with endowing drug resistance to tumor cells in many advanced cancers. In cisplatin and doxorubicin-resistant cancer cells, the levels of PCAF have been observed to be elevated. Studies have shown that PCAF-mediated drug resistance in cancer cells may be through the enhanced expression of E2F1 or in a Twist1/Y box binding protein 1 (Yb1)-dependent manner (Hirano et al., 2010; Shiota et al., 2010b). Furthermore, elevated levels of KAT2-mediated H3K9 acetylation was observed at the Multidrug Resistance protein-1 (MDR1) promoter, while the knockdown of GCN5 and PCAF levels by RNAi led to the reduction in MDR1 expression and sensitized cancer cells to drugs (Toth et al., 2012). PCAF is also associated with Hedgehog (Hh)-Gli signaling pathway and is required for H3K9 acetylation at the Hh target genes. Thus, depletion of PCAF in medulloblastoma and glioblastoma cells leads to a decrease in Hh target genes which results in retarded cell proliferation and enhanced apoptosis (Malatesta et al., 2013). As stated earlier, PCAF and GCN5 exist in multiprotein complexes which are important chromatin modifiers and transcription co-activators. It has been reported that the oncoprotein c-Myc recruits PCAF/GCN5 complexes to its target gene promoters. Intriguingly, the N-terminal truncated form of c-Myc protein losses its ability to interact with the STAGA complex and hence possess reduced malignant transformation potential (Liu et al., 2003). GCN5 is found to be

overexpressed in NSCLC and its levels correlate with tumor size. GCN5 enhances cell proliferation and G1/S transition by regulating the expression of cell cycle proteins like cyclin D1, E1 and E2F1 (Chen et al., 2013).

KAT1, a cytoplasmic member of the GNAT family was the first KAT to be cloned and biochemically characterized (Kleff et al., 1995). It is known to acetylate free, nascent histones which are not assembled into chromatin (Parthun et al., 1996). KAT1 has also been linked to cancers and it has been observed that its expression is elevated in primary and metastatic colon cancer (Parthun, 2007; Seiden-Long et al., 2006). In an RNAi screen, KAT1 had been identified as a potential drug target in ESCC and it has been shown to be essential for the proliferation of cancer cells (Xue et al., 2014).

3.3. MYST family

MYST family acetyltransferases are an evolutionarily conserved group of enzymes. These proteins share the conserved MYST domain which comprises of a zinc finger domain and an acetyl-CoA binding domain. These enzymes are present in different protein complexes where they are involved in several important cellular responses like gene regulation, DNA damage repair, and replication (Avvakumov and Côté, 2007). In patho-physiological conditions like cancer, the levels of MYST family acetyltransferases are often seen to be altered. TIP60 (HIV1 TAT interacting 60 kDa protein; KAT5) a well studied member of the MYST family is intimately involved in the DNA damage response pathways. Tip60 acetylates and thereby activates the ATM kinase, an important effector in the double strand break (DSB) repair pathway. Tip60 also acetylates p53 at K120, a crucial modification for p53-mediated apoptosis, during prolonged genotoxic stress (Sun et al., 2005; Sykes et al., 2006). Tip60 expression is often downregulated in cancers including colorectal, gastric, cervical cancer and melanoma, which may suggest a putative tumor suppressive role (Chen et al., 2012; Sakuraba et al., 2009; Sakuraba et al., 2011; Subbaiah et al., 2015). Tip60 downregulation in colorectal and gastric cancer correlates with tumor size, invasiveness and malignancy (Sakuraba et al., 2009; Sakuraba et al., 2011). Tip60 levels are significantly reduced in melanomas, while the loss of Tip60 expression is correlated with poor disease specific survival (DSS) in primary and metastatic melanoma patients. Furthermore, overexpression of Tip60 in melanoma cells caused a remarkable reduction in invasiveness and increased chemosensitivity (Chen et al., 2012). Tip60 protein is destabilized in the presence of human papilloma virus (HPV) oncogenic E6 protein through the E3 ligase EDD1, this aids in the HPV-mediated cervical tumor formation (Subbaiah et al., 2015). In contrast, Tip60 can also act as a potential oncoprotein, depending on the cellular context and its interacting proteins. Tip60 is a transcriptional co-activator for androgen receptor (AR) and is involved in prostate cancer progression (Halkidou et al., 2003). Tip60 has also been implicated in the development of androgen-independent prostate cancer, by promoting the nuclear localization of AR in

advanced stages of prostate cancer. Tip60 knockdown reduced the growth of castration-resistant prostate cancer cells (Shiota et al., 2010a). Tip60 is a co-activator for the oncoprotein, c-Myc. c-Myc levels are stabilized by Tip60 and GCN5-mediated acetylation (Patel et al., 2004) Tip60/c-Myc complex is important for c-Myc-dependent cell transformation in adult T-cell leukemogenesis (Awasthi et al., 2005). Since Tip60 is involved in DNA damage response and the expression of DNA damage-related proteins, it is not surprising that Tip60 may also play an important role in conferring drug resistance to cancer cells. Tip60 is overexpressed in cisplatin-resistant cells, while Tip60 knockdown leads to cisplatin-sensitivity in lung cancer cell lines (Miyamoto et al., 2008; Van Den Broeck et al., 2012).

hMOF (human Males absent On First; KAT8), a MYST family acetyltransferase, is responsible for the larger part of H4K16 acetylation in human cells and the loss of hMOF leads to a dramatic reduction in H4K16 acetylation levels (Taipale et al., 2005). hMOF loss in cancers is a common phenomenon. In cancers such as colorectal, gastric, renal cell, ovarian, breast, hepatocellar carcinoma and medulloblastoma, loss of hMOF levels may serve as a prognostic marker in these cancers (Cao et al., 2014; Liu et al., 2013; Pfister et al., 2008; Wang et al., 2013; Zhang et al., 2014). Contrastingly, hMOF has also been observed to be upregulated in a few cancers as well. In oral tongue squamous cell carcinoma (OTSCC), upregulated hMOF correlates with poor overall and disease-free survival in patients (Li et al., 2015b). Moreover, hMOF stimulates the functions of AR and NF-κB leading to prostate cancer progression (Jaganathan et al., 2014). hMOF also confers drug-resistance in NSCLC in a Nrf2-dependent manner. Thus, the overexpression of hMOF in NSCLC predicts poor prognosis of the disease (Chen et al., 2014).

HBO1 (HAT bound to ORC1; KAT7) acetyltransferase is closely involved with replication and assists in pre-initiation complex formation and replication initiation (Iizuka et al., 2006). It is negatively regulated by p53 to stall replication during cellular stress (Iizuka et al., 2008). HBO1 has been reported to be upregulated in many primary tumors such as bladder, breast, esophagus, testis and stomach, in comparison to the normal tissue counterparts. HBO1 is also abundant in cell lines such as Saos-2 and MCF7 (Iizuka et al., 2009). HBO1 has been implicated in drug resistance and tumor progression. Polo-like kinase 1 (Plk-1)-mediated phosphorylation of HBO1 leads to the upregulation in c-Fos expression, which then in turn elevates the expression of MDR1, which is a c-Fos target gene. In the presence of high MDR1 levels, pancreatic cancer cells gain drug resistance (Song et al., 2013). HBO1 is also phosphorylated by Cyclin E/Cdk2 at Y88. The phosphorylated form of HBO1 plays an important role in enriching cancer stem-like cells in breast cancer (Duong et al., 2013).

MOZ (Monocytic Leukemia Zinc Finger Protein; KAT6A) was first reported as a chimeric protein fused with CBP in leukemia. The GOF fusion protein t(8;16)(p11;p13) formed due to in-frame translocation, leads to aberrant acetylation-mediated leukemogenesis (Borrow et al., 1996). The MOZ

gene locus is a site for recurrent translocations and MOZ also forms fusion proteins with CBP homolog, p300 t(8;22)(p11;q13), and transcription intermediary factor 2 (TIF2) inv(8)(p11q13) (Carapeti et al., 1998; Chaffanet et al., 2000; Kitabayashi et al., 2001). These fusion proteins are predictive of poor prognosis and resistance to chemo-therapy in AML patients (Borrow et al., 1996). The MOZ-TIF2 fusion protein recruits CBP or p300 through its CBP/p300 interacting domain (CID). This hyperactivation of the fusion protein leads to mistargeted acetylation. Moreover, the depletion of CBP/p300 from PML bodies prevents the activation of p53 signaling cascade. The CID domain has been shown to be essential for the MOZ-TIF2 mediated transformation in leukemia. Similarly, the highly homologous MORF (MOZ-related Factor; KAT6B) acetyltransferase has also been reported to be fused with CBP t(11;16)(q23;p13) in AML, leading to deregulated acetylation and gene expression programs (Champagne et al., 1999; Deguchi et al., 2003; Panagopoulos et al., 2001).

In a recent report, mutant p53 has been shown to upregulate MLL and MOZ expression leading to alteration in global chromatin modification. This may contribute to the GOF of mutant p53. This study also reveals the importance of epigenetic-based therapeutics in combating cancers (Zhu et al., 2015).

4. Lysine acetyltransferase: A potential target for therapeutics

Cancer, being a multifactorial disease, is caused by the interplay of genetic abnormalities and epigenetic aberrations. Since the reversal of epigenetic aberration is a comparatively feasible option, the development of epigenetic drugs has witnessed immense interest and research in recent years. Drugs targeting chromatin modifying enzymes and modifications have brought about the advent of 'Epigenetic therapeutics'. Since acetylation is involved in vital cellular functions and is dysregulated in diseases, the need for specific small modulators targeting KATs is mounting. In this section, we will attempt to highlight the promises, achievements and failures of the small molecule modulators targeting KATs **(Figure 4, Table 3)**.

4.1. Lysine acetyltransferase inhibitors (KATi)

4.1.1. Bisubstrate Inhibitors

KAT inhibitors (KATi), in comparison to KDAC inhibitors, have been relatively less explored. Most known KATis are designed against the major KAT families, p300/CBP, PCAF/GCN5 or MYST/Tip60. It was demonstrated as early as 1980 by Cullis *et al* that a multisubstrate analog (N-2-spermidine amide) formed by an acetic acid linkage between acetyl CoA and spermidine, had the potential to inhibit acetylases isolated from calf thymus (Cullis et al., 1982). But it was only in 2000 that the first selective KATis were reported; Lys-CoA a specific inhibitor for p300 and H3-CoA-20

for PCAF (Lau et al., 2000). These potent (IC_{50} ≅ 0.5 μM) and highly selective inhibitors are synthetic bisubstrate molecules. The rationale behind the peptide acetyl-CoA conjugates is that they can effectively mimic the ternary complex formed at the enzyme active site hence exhibiting high potency and specificity. Employing similar underlying principle, the bisubstrate inhibitor H4K16CoA was synthesized specific for Tip60 and Esa1 (Wu et al., 2009). The major drawback of these compounds is that they are cell impermeable, thus greatly restricting their utility. To overcome this hurdle, a cell permeabilizing 'tat' peptide was linked to Lys-CoA and H3-CoA-20 to make them cell permeable (Zheng et al., 2005). Utilizing the approach described by Cullis *et al*, spermidine was linked, via a thioglycolic acid bond, to the S-terminus of Co-enzymeA forming Spd-CoA, which proved to be a non-toxic, histone acetylation inhibitor. Spd-CoA blocked DNA damage repair pathways and thereby sensitized cells to chemotherapeutic drugs and UV-radiation (Bandyopadhyay et al., 2009).

4.1.2. Natural inhibitors and derivatives

The first naturally occurring KATi, anacardic acid (6-pentadecylsalicylic acid, AA), was isolated from *Anacardium occidentale* (cashewnut) shell liquid (Balasubramanyam et al., 2003). Although it could non-specifically inhibit p300, PCAF as well as Tip60, it proved to be a novel scaffold for the synthesis of series of potent KATis. AA has been shown to inhibit the NF-κB pathway by inhibiting the acetylation and nuclear localization of the RelA subunit of the NF-κB complex, hence acting as an anti-inflammatory agent. Consequently, AA was observed to induce apoptosis which correlated with the downregulation of proliferation, pro-survival and angiogenic factors (Hemshekhar et al., 2011). AA can also inhibit Tip60-mediated DNA damage response to cytotoxic agents and radiation, thus it can sensitize tumors to radiation therapy (Sun et al., 2006).

Utilizing molecular modeling to optimize the binding of AA to PCAF active site, a series of PCAF-specific KATis were derivatized by replacing the 6-alkyl chain of anacardic acid with different moieties. The salicylate derivative 6d exhibited histone acetylation inhibition in HepG2 cells (Ghizzoni et al., 2010). A benzamide derivative, related to AA, 4-cyano-3-trifluoromethylphenylbenzamides, has shown KAT3 inhibition similar to that of AA (Souto et al., 2008).

The specific p300/CBP KATi, curcumin, was isolated from the dietary spice, *Curcuma longa* (turmeric) rhizome (Balasubramanyam et al., 2004b). This polyphenol has been observed to be minimally toxic and a strong anti-inflammatory, anti-proliferative and anti-cancer agent (Palve and Nayak, 2012). The major limitation that prevents the application of curcumin is its poor bioavailability. It is sparsely soluble and is physio-chemically unstable. Derivatization of curcumin has led to the synthesis of hydrazinobenzoyl curcumin (HBC). HBC, a p300/PCAF inhibitor, is a

potent inhibitor of androgen receptor and can effectively reduce the growth of castration-resistant prostate cancer xenografts in nude mice (Wu et al., 2015). Moreover, the water-soluble salt of HBC, CTK7A has also been shown to prevent the growth of xenografted oral tumors in immuno-compromised mice (Arif et al., 2010). This potent activity in xenograft models is attributed to the ability of CTK7A to inhibit p300 activity in oral cancer cells.

Epigallocatechin-3-gallate (EGCG), present in green tea, is yet another naturally occurring polyphenol belonging to the domain of KATis. It is non-specific and can act as an anti-inflammatory agent by preventing p300-mediated RelA acetylation (Choi et al., 2009a).

Another phytochemical, garcinol, isolated from *Garcinia indica* or kokam fruit, is a potent non-specific KATi ($IC_{50}\cong$ 5 µM for p300 and 7 µm for PCAF) (Balasubramanyam et al., 2004a). Treatment of MCF-7 cells (breast cancer) with garcinol revealed that the chemo-preventive characteristic of garcinol depends on its modulation of p53 pathway and the expression of chromatin modifying enzymes (Collins et al., 2013). Garcinol has shown promising results in HCC cells and HCC xenograft models as an anti-proliferative, pro-apoptotic agent. At the molecular level, it has been observed that garcinol can prevent the activation, dimerization and acetylation of STAT3, which is essential for its oncogenic signaling cascades (Sethi et al., 2014). The anti-tumor effect of garcinol through the suppression of pro-inflammatory pathways has also been studied extensively in HNSCC cells and xenograft mice models (Li et al., 2013). To further improve the pharmacokinetic properties of garcinol, derivatization on the garcinol parent scaffold has led to many compound series with less toxicity, better potency and specificity. Intramolecular cyclization of garcinol resulted in isogarcinol (IG), the starting molecule for a structure-function-based design of novel specific KATis. Mono-substitution at the 14^{th} position of IG yielded 14-isopropoxy IG (LTK-13) and 14-methoxy IG (LTK-14), while di-substitution at the 13^{th} and 14^{th} position yielded 13, 14 disulfoxy IG (LTK-19). These derivatives are selective p300 inhibitors with no activity against PCAF (Mantelingu et al., 2007b). Molecular pruning and optimization of garcinol have led to another series of garcinol analogs, of which EML425 is characterized to be a cell permeable, reversible, potent p300-specific KATi *in vitro* as well as in cells (Milite et al., 2015).

Plumabagin, a hydroxynaphthoquinone, another natural p300-specific KATi is isolated from the roots of *Plumbago rosea*, a medicinal herb (Ravindra et al., 2009). Though it too possesses anti-cancer properties, it is highly toxic, which limits its use as a therapeutic agent. To overcome this drawback, PTK1 was synthesized, a 1,4-naphthoquinone derivative, which harbors a methyl substitution on the 3^{rd} position of plumbagin. Remarkably, this monosubstituted derivative still retained its inhibitory characteristic whilst being near non-toxic to cells (Vasudevarao et al., 2014).

The DNA intercalator sanguinarine, isolated from the root of *Sanguinaria canadensis* and *Argemone mexicana* is a known anti-tumor and anti-inflammatory agent (Slaninová et al., 2013). Interestingly, it can also inhibit epigenetic enzymes including KAT3, G9a and CARM1, thus modulating the global epigenetic landscape and the underlying gene expression networks, in treated cells (Selvi B et al., 2009).

Delphinidin, isolated from pomegranate (*Punica granatum*), has been shown to be a p300-specific antagonist, without affecting the activity of other epigenetic enzymes such as KDACs and methyltransferases. At the molecular level, delphinidin leads to the hypoacetylation of RelA (NF-κB) resulting the cytoplasmic accumulation of NF-κB and the suppression of inflammatory signals (Seong et al., 2011). Gallic acid, a chemical identified in *Rosa rugosa*, a p300-specific KATi, also employs a similar mechanism to inhibit p300-dependent NF-κB signaling (Choi et al., 2009b).

Another phytochemical, procyanidin B3, is a p300-specific KATi. It is also effective in the inhibition of p300-mediated AR gene expression and hence resulting in reduction in cell proliferation and increase cell death in prostate cancer cells (Choi et al., 2011).

Embelin (hydroxybenzoquinone) is a cell permeable, anti-inflammatory, pro-apoptotic, XIAP and PCAF inhibitor, which has been shown to down regulate genes involved in proliferation and metastasis (Huang et al., 2014; Modak et al., 2013; Poojari, 2014). Recently, PCAF-regulated molecular pathways were deciphered using embelin, which specifically inhibits PCAF-mediated acetylation of H3K9 and MyoD during muscle differentiation (Modak et al., 2013).

4.1.3.Synthetic inhibitors

Even though natural compounds hold great value as KATis, their utilization is restricted due to their pleiotropic effects (a few listed in **Table 3**), limited cell permeability and poor bioavailability. In recent years, efforts are on to optimize these molecules, with the renewed understanding of enzyme-inhibitor binding and structure-function relationship. Nevertheless, the search for potent and novel scaffolds is still a necessity to identify molecules which can effectively overcome the drawbacks of the current line of naturally occurring KATis.

Beil *et al*, were the first group to report the synthesis of a cell permeable, small molecule inhibitor of the KAT GCN5. Based on structure-activity relationship they derivatized γ-butyrolactone to indentify MB-3 (α-methylene- γ-butyrolactone) as a GCN5-selective KATi (Biel et al., 2004).

High throughput screening through chemical libraries has led to the discovery of many potential KATis. C646, a potent p300 inhibitor with an IC_{50} value in the nanomolar range was identified by *in silico* docking of commercial small molecule library to the crystal structure of p300 HAT domain (Bowers et al., 2010). This potent molecule has been effective against p300 *in vitro* and

in vivo. C646 treatment can lead to cell cycle arrest and early induction of senescence. C646 can sensitize NSCLC cells to radiotherapy (Oike et al., 2014) and can promote chemo-responsiveness in melanoma cells (Yan et al., 2013).

L002, a p300 specific KATi, with an IC_{50} value of 1.98 μmol/L *in vitro*, was identified by high throughput screening of a 622,079-compound chemical library (Yang et al., 2013). Toxicity assays, biochemical assays and docking studies were done to validate the screened compounds. Utilizing high throughput compound library screening, isothiazolone-based KAT inhibitors, CCT077791 and CCT077792, were identified as antagonist of both p300 and PCAF (Stimson et al., 2005). Among isothiozolone-based inhibitors, 5-chloroisothiazolone was identified as a PCAF-specific KATi (Ghizzoni et al., 2009). The thiazole-based synthetic compound, BF1 (1-(4-(4-chlorophenyl) thiazol-2-yl)-2-(propan-2-ylidene) hydrazine) can inhibit p300 and GCN5 *in vitro*. Neuroblastoma and glioblastoma cell lines show a reduction in histone acetylation levels, when treated with BF1 (Secci et al., 2014). In another high throughput screen, 100,000 compounds were screened for activity against p300, of which 4-acetyl-2-methyl-N-morpholino-3,4-dihydro-2H-benzo(b)(1,4)thiazine-7-sulfonamide was observed to possess p300 inhibitory activity in the micromolar range (Zeng et al., 2013). PU139, a pan-inhibitor of p300, CBP, PCAF and GCN5, and PU141, a KAT3 selective KATi, were observed to be effective in retarding the growth of xenograpfted neuroblastoma tumors in mice. Moreover PU139 synergistically enhanced doxorubicin activity *in vivo* (Gajer et al., 2015).

Virtual ligand screening of a chemical library, for inhibition potential against Tip60 was done utilizing the knowledge of the crystal structure of Esa1 (the yeast homolog of Tip60). Novel candidate molecules were discovered possessing inhibitory activity in the micromolar level (Wu et al., 2011). A similar high throughput screen has led to the identification of a Tip60-selective isothiazole-based KATi, NU9056, which is effective against prostate cancer cells (Coffey et al., 2012). Utilizing computational tools to design drugs based on the binding pocket of Tip60, has led to the identification of TH1834, which can inhibit Tip60 *in vitro* and can sensitize breast cancer cells to ionizing radiation (Gao et al., 2014).

Though there are many KATis known, few have shown effective results in clinical trials. Recent efforts of identifying KATis through high throughput screening of chemical libraries by *in silico* and biochemical approaches hold promise of newer inhibitors, with improved efficacy and better toxicity profiles.

4.2. Lysine acetyltransferase activators (KATa)

Activation of lysine acetyltransferases is a new frontier for epigenetic therapeutics which is relatively unexplored in the context of anti-cancer therapy. N-(4-chloro-3-trifluoromethyl-phenyl)-2-

ethoxy-6-pentadecyl-benzamide (CTPB), an anacardic acid derivative, is the first KAT activator (KATa) which specifically activates KAT3 proteins (Balasubramanyam et al., 2003). Since this molecule is cell impermeable, a carbon nanoshere (CSP) was used as a carrier. Analysis have shown that CTPB is also capable of inducing KAT3 autoacetylation and thereby its activity (Selvi et al., 2008). Further derivatization of CTPB, has led to the synthesis of TTK21 (N-(4-chloro-3-trifluoromethyl-phenyl)-2-N-propoxy-benzamide), a potent KAT3 activator in vitro and *in vivo*. TTK21, when conjugated to CSP, could effectively extend memory duration in adult mice (Chatterjee et al., 2013). Another derivative, CTB, which lacks the pentadecyl hydrocarbon chain of CTPB could also activate p300 *in vitro* (Mantelingu et al., 2007a). To confer selectivity to the CTB, Han *et al* conjugated it to a synthetic DNA binding pyrrole–imidazole polyamides (CTB-I). As expected CTB-I could enhance the expression of a substantial number of genes, through the activation of KAT3 acetyltransferase activity. As the hyperacetylation could also be achieved by treating the cells with the KDACi, SAHA, it was observed that the SAHA conjugated artificial DNA binding domain (DBD) could also enhance the expression of a similar set of genes (Han et al., 2015). Results of these studies implicate that the proper targeting of KATa by using artificial DBD could also be exploited for therapeutic purposes instead of KDACi. The Another p300 activator, nemorosone, a polycyclic polyisoprenylated benzophenone, is cell permeable and can modulate histone acetylation (Dal Piaz et al., 2010). Interestingly, nemorosone has been shown to possess anti-cancer activities, but it is not clear whether these effects are mediated through its ability to activate p300 (Wolf et al., 2013).

Pentadecylidenemalonate 1b or SPV106 is another anacardic acid derivative that can activate PCAF acetyltransferase activity. Interestingly, this molecule is the first reported mixed-modulator of KAT activity; it can activate PCAF function and inhibit p300 activity (Sbardella et al., 2008). Moreover, this molecule can activate PCAF in mice leading to enhanced fear extinction (Wei et al., 2012). SPV106 can also reverse the cell proliferation defects observed in cardiac-mesenchymal cells of type II diabetic patients, where GCN5 and PCAF are downregulated (Vecellio et al., 2014).

Although, the efficacy of KATa have not been tested as an anti-neoplastic therapeutic, they may hold potential in development of a new line of epigenetic therapeutics to combat cancers in which KAT proteins are downregulated, deactivated or in cases where KDACs are overexpressed. But while using this approach, it should be kept in mind that the fine balance of acetylation is not perturbed.

4.3. Disrupting the Interaction between KATs and oncoproteins

Disruption of the interaction between KATs and oncogenic effector proteins has served as a novel and effective strategy in developing anti-cancer therapeutics. Since KATs play an extensive role

in cancer signaling pathways, targeting a specific module in this system can inhibit tumor progression without grossly affecting other pathways in cells.

Survival through hypoxia is a hallmark of cancerous cells in solid tumors. This adaptation is mediated through HIF1α, which accumulates under hypoxic conditions, culminating in altered metabolism, increased angiogenesis and enhanced tumor growth. p300 is a co-activator for HIF1α-target genes and the interaction between HIF1α-p300 could serve as a potential target for therapeutics. The interaction is through the C-terminal activation domain (CTAD) of HIF1α and the cysteine-histidine rich (CH1) domain of KAT3 proteins. The aminocoumarin antibiotic, novobiocin, can directly block the interaction between HIF1α and p300, thereby inhibiting proliferation and colony formation in MCF7 cells (Wu et al., 2013). A natural compound-based screen revealed indandione and benzoquinone as potent inhibitors of HIF1α/p300 interaction (Jayatunga et al., 2015). A marine alkaloid, eudistidine A, can inhibit CH1/CTAD binding of p300/HIF1α with an IC50 of 75 μM (Chan et al., 2015). Natural compounds belonging to the epidithiodiketopiperazine (ETP) family such as gliotoxin, chaetocin, and chetomin, have been shown to disrupt the HIF1α/p300 complex (Reece et al., 2014). Chetomin can synergistically enhance the inhibitory effect of enzalutamide (AR antagonist) on metastatic castrate-resistant prostate cancer (Fernandez et al., 2015). ETP treatment in cells have resulted in a downregulation of HIF1α-target genes such as VEGF, ENO1 and LDHA, leading to subsequent reduction in angiogenesis and tumor growth in prostate tumor xenografts (Reece et al., 2014). A synthetic ETP derivative, dimeric epidithiodiketopiperazine (ETP2) selectively blocks HIF1α-p300 interaction and treatment with ETP2 in a breast cancer model results in the regression of tumor growth (Dubey et al., 2013).

Wnt/β-catenin pathway regulates signaling cascades which decides cell fate either towards maintenance of pluripotency or towards differentiation. In cancers the Wnt/β-catenin pathway is often deregulated which leads to tumor progression. Since CBP is involved in the maintenance of an undifferentiated state, disrupting the Wnt/β-catenin/CBP axis may prove to be an invaluable resource to counter tumorigenic transformations. The small-molecule antagonist, ICG-001, specifically inhibits the CBP/ β-catenin interaction without affecting the p300/β-catenin interaction and it was observed that it could induce apoptosis in colon carcinoma cells while not affecting normal colon cells (**Figure 3**)(Emami et al., 2004). It is also reported that CBP/β-catenin interaction is important for the expression of MDR1, thereby conferring drug-resistance to cancer cells (Xia et al., 2015). Thus, inhibition of this interaction can also sensitize cancer cells to chemo-therapeutics. ICG-001 has also been reported to suppress pancreatic ductal adenocarcinoma (PDAC) and prevent EMT in HCC (Arensman et al., 2014; Kuang et al., 2015). ICG-001 has also been reported to reverse drug-resistance in ovarian carcinoma and leukemia cells (Gang et al., 2014; Nagaraj et al., 2015).

c-Myb, is a key transcription factor in hematopoiesis and an important regulator of self-renewal in hematopoietic stem cells. The deregulation of c-Myb leads to leukemia and certain solid tumors (Ramsay and Gonda, 2008). The interaction of c-Myb and p300 is essential for the maintenance of hematopoietic stem cells and also the induction of c-Myb-mediated leukemia (Pattabiraman et al., 2014; Sandberg et al., 2005). Naphthol AS-E phosphate, is a small molecule inhibitor of interaction between c-Myb and the KIX domain of p300. This antagonist inhibits c-Myb mediated gene expression and induces myeloid differentiation (Uttarkar et al., 2015).

Among the protein-protein interaction inhibitors known, inhibitors targeting BrDs in KATs have proved to be potent, highly selective, druggable options over the difficult to drug acetyltransferase activity (Vidler et al., 2012). Ischemin was discovered as a CBP BrD-specific inhibitor which could inhibit apoptosis in cardiomyocytes. But this is a rather weak inhibitor with a dissociation constant K_D =21 µM (Borah et al., 2011). Recently, more KAT3-specific BrDis have been discovered with affinities in the nanomolar range. CBP30 is a potent BrDi exhibiting selectivity towards CBP (K_D =26 nM) and p300 (K_D =32 nM) over BRD4 (K_D =885 nM). CBP30 has been shown to inhibit KAT3-driven pathways such as human Th17 responses (Hammitzsch et al., 2015; Hay et al., 2014). Another KAT3 BrDi, I-CBP112 (K_D = 151 ± 6 nmol/L for CBP and K_D = 167 ± 8 nmol/L for p300) reduced the self-renewal property of leukemic cells and could synergistically inhibit leukemia-initiating cells along with doxorubicin, providing opportunities for the development of combinatorial therapeutics (Picaud et al., 2015).

5. Conclusion and Perspectives

The reversible lysine acetylation has undoubtedly emerged as a key modification that maintains cellular equilibrium. The dysregulation of KATs, KDACs or readers that integrate the 'acetylation-centric' cellular programs, can often lead to major abnormalities, often culminating in cancer. The involvement of lysine acetylation in disease progression has led to the generation of therapeutics targeting this modification. KDACis have shown efficacy in cancer treatment. Vorinostat (suberanilohydroxamic acid or SAHA), romidepsin, belinostat, and panobinostat are FDA approved drugs in use against hematological malignancies. Vorinostat, romidepsin, panobinostat, valproic acid and other KDACis are also being extensively studied in clinical trials for treatments of different solid cancers such as breast cancer, pancreatic cancer and NSCLC (Falkenberg and Johnstone, 2014). Several pan-BrD inhibitors (BrDis) and subtype specific inhibitors have also shown promising results against cancers in preclinical studies, few of which have proceeded to clinical trials against hematological malignancies. Triazolobenzodiazepine I-BET762, an acetyl-lysine mimic inhibitor of BET BrDs has entered clinical trials against NUT Midline carcinoma (NMC). Clinical studies against hematological malignancies have been initiated using the

triozolothienodiazepine OTX015 and CPI-0610 (Filippakopoulos and Knapp, 2014). Unfortunately, not many KATis have reached clinical trials. The non-specificity, pleiotropic effects, toxicity profiles and IC_{50} values in the micromolar range have been major road blocks in the field of KAT inhibitor advancement. Curcumin is the only KAT inhibitor to be tested in clinical trials against cancer. There are currently numerous studies involving curcumin alone or with conventional drugs being tested in breast, prostate, colorectal and other solid cancers.

In the recent past the druggablity of KATi molecules have shown little promise but KATi-scaffolds have the potential to be further tweaked to yield more specific inhibitors, with fewer pleiotropic effects and greater efficacy. Current KATis are being designed through rational and systematic approaches, thus we can project that better KATis will be available for clinical use. Moreover, modulating KAT function has emerged as a promising option over inhibiting KAT activity. Several small molecules targeting other conversed domains like BrD and KIX domains have immense therapeutic potential. PRI-724 (ICG-001 derivative), a small molecule antagonist of CBP/β-catenin interaction is currently in Phase I/Phase II of clinical trials for the treatment of advanced cancers including myeloid malignancies (NCT01606579), metastatic colorectal cancer (NCT02413853) and pancreatic adenocarcinomas (NCT01764477) (https://clinicaltrials.gov/).

Several pre-clinical studies have highlighted the synergistic effects of epigenetic therapies with other conventional anti-cancer therapeutics. The state of the epigenetic landscape has direct consequences on functional outcomes in diseases such as cancer. There are many studies directly implicating dysregulation of epigenetic machinery and drug-resistance in cancers. Drug-resistance has been a major impediment in the field of chemo-therapeutics, thus it is of growing importance to understand the causal molecular events and to utilize this knowledge in the administration of combinatorial therapy to eliminate drug-resistance. Currently, pre-clinical and clinical studies have shown that the administration of DNA methyltransferase inhibitors (DNMTis) could sensitize advanced tumors to cisplatin and doxorubicin (Ahuja et al., 2014; Clozel et al., 2013; Fu et al., 2011). Moreover, the use of KDACis along-side DNMTis have increase the effectiveness of the treatment and has greatly reduced the drug-dose, thus preventing cytotoxicity and off-target effects (Cameron et al., 1999). It has also been shown that the combination of KDACis with imanitib has better efficacy towards targeting quiescent CML stem cells over imanitib alone (Zhang et al., 2010). Pre-clinical studies have also demonstrated that the inhibition of KATs can also potentiate the effect of conventional drugs. Garcinol has been shown to enhance the effect of anti-cancer agents like doxorubicin and paclitaxel (mitotic inhibitor) in an HCC xenograft model (Sethi et al., 2014). Garcinol has also been shown to sensitize HNSCC xenograft tumors to cisplatin (Li et al., 2015a). The potent p300-specific KATi, C646, has shown promising effects in sensitizing resistant tumor cells to radiotherapy and cisplatin in pre-clinical studies (Oike et al., 2014; Yan et al., 2013). The disruption of CBP/β-catenin interaction by ICG-001 has been shown to reverse drug-resistance to cisplatin

(Nagaraj et al., 2015). The current interest in the field of anti-cancer therapeutics is the effective targeting of tumor-initiating cells. KATs have been implicated in the maintenance of CSCs. Moreover, RNAi screens have exhibited the importance of KAT genes in conferring pro-survival properties to cancer cells. hMOF has been shown to be important for the survival of lung cancer cells (Zhang et al., 2013) and KAT1 was identified as a target for ESCC (Xue et al., 2014). Other epigenetic proteins are also being investigated as targets for potential anti-cancer therapy. Notably, several inhibitors targeting the protein methylation have entered clinical trials such as DOT1L inhibitor EPZ-5676 (NCT01684150 and NCT02141828 at https://clinicaltrials.gov/), Enhancer of Zeste Homolog 2 (EZH2) inhibitors (NCT01897571 (Drug: EPZ-6438), NCT02082977 (Drug: GSK2816126) and NCT02395601 (Drug: CPI-1205) at https://clinicaltrials.gov/), Lysine-specific demethylase 1 (LSD1) inhibitors (NCT02177812 (Drug: GSK2879552) and NCT02261779 (Drug: Tranylcypromine) at https://clinicaltrials.gov/) (reviewed in (Cai et al., 2015)). KDACi in combination with lysine methylation inhibitors have shown promise in targeting AML. Therefore, it is fairly apparent that modulating epigenetic language is essential for anti-neoplastic therapeutics along with the existing chemo- and radio- therapies. In this direction, the regulation of lysine acetylation either by KDACi, KATi, BrDi or KATa, in conjunction with other therapeutics, has opened opportunities in the development of anti-cancer therapeutics.

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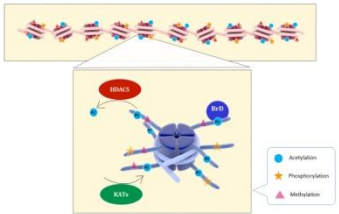

Fig. 1

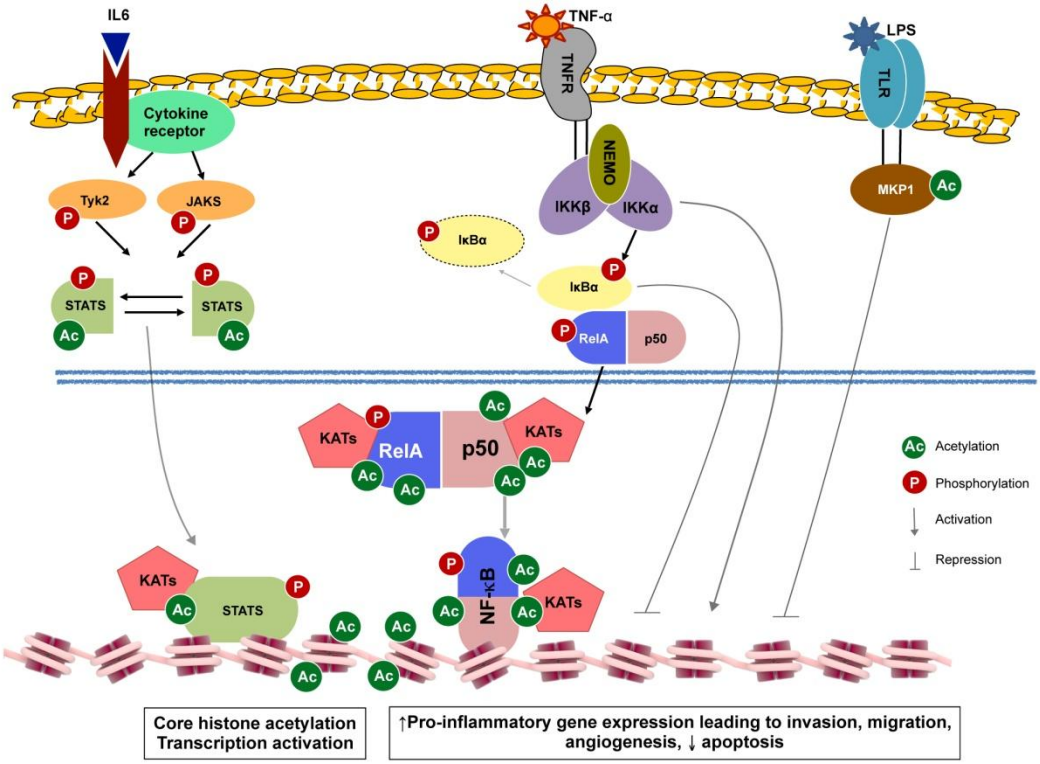

Fig. 2

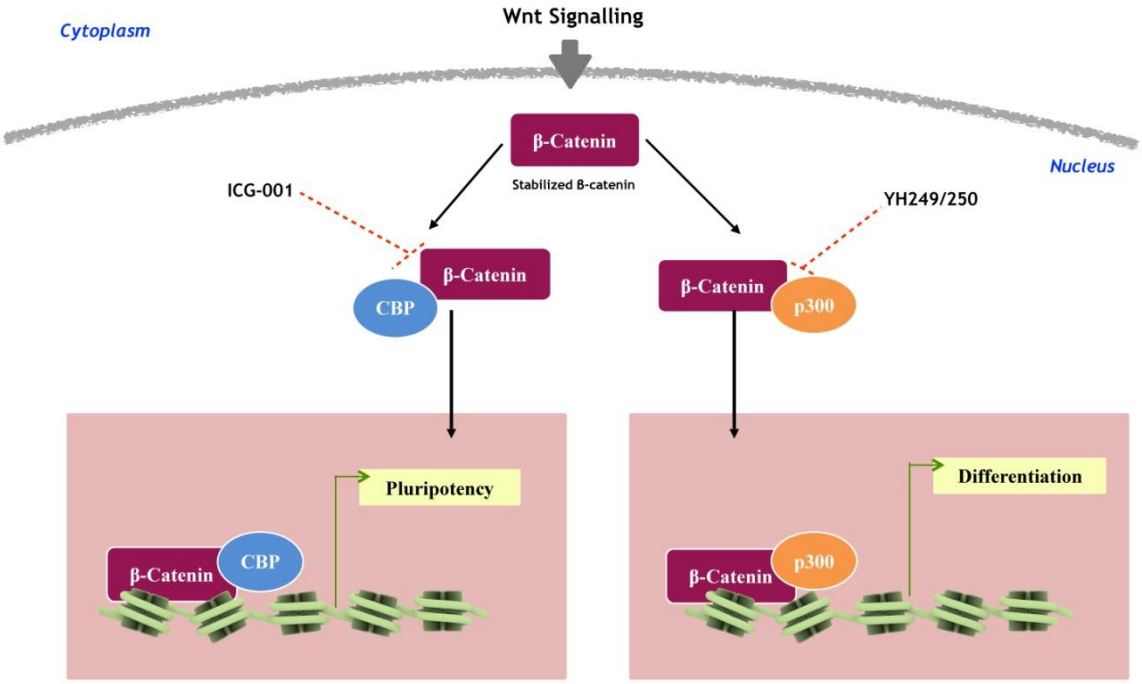

Fig. 3

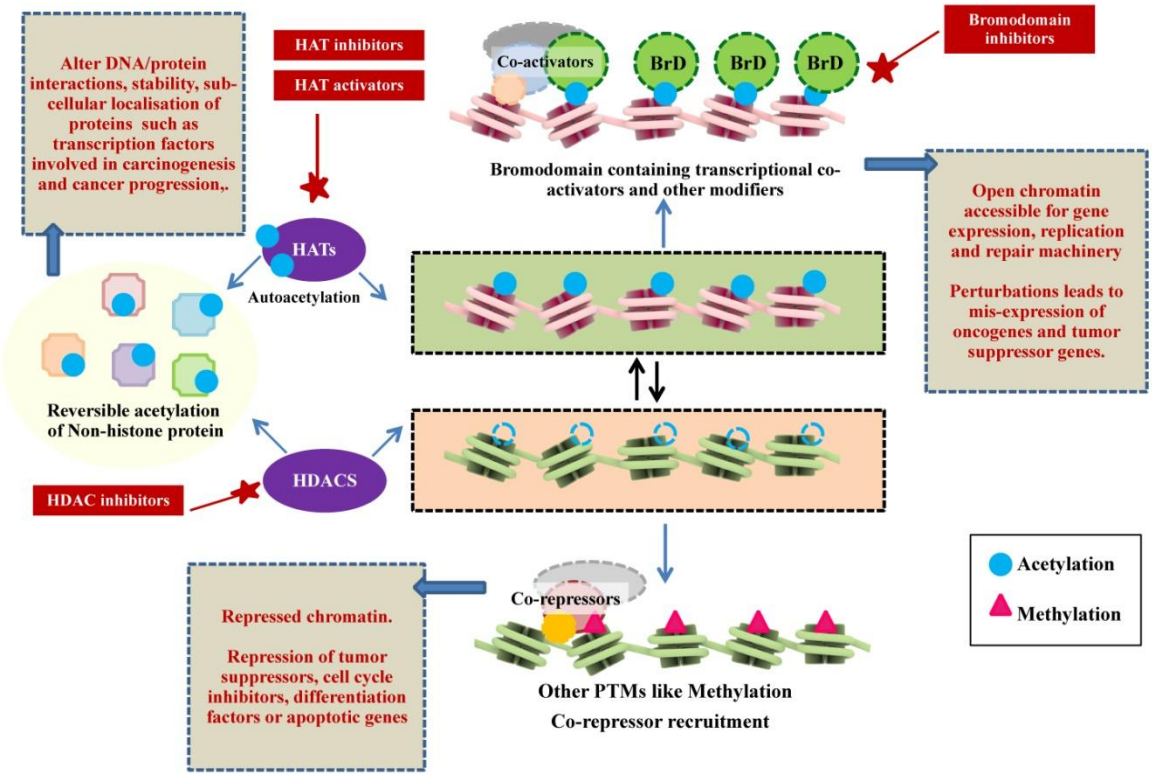

Fig. 4

Figure 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 (HDACs removing acetylation marks) and readers (Bromodomain (BrD)) containing proteins are depicted.

Figure 2: The role of acetylation in inflammation and cancer: Upon inflammatory signals, IκB kinase (IKKα, IKKβ, regulated by IKKγ/NEMO) gets activated, this phosphorylates the IκBα protein leading to its proteosomal degradation rendering NF-κB active. RelA phosphorylation by kinases leads to its acetylation by KAT3, increasing its DNA binding and recruitment of co-activators. p50 acetylation by KAT3 also enhances transcriptional activation of pro-inflammatory genes. IKKα can translocate to the nucleus and activate pro-inflammatory genes. Similarly, upon stimulation through upstream signaling, STAT3 gets modified. STAT3 acetylation increases DNA binding and transcriptional activation. NEMO and IκBα can also translocate to the nucleus, but act to repress pro-

inflammatory genes. Stimulation of TLRs induces the expression of MKP1 which when acetylated, dephosphorylates p38MAPK and c-Jun N-terminal kinase (JNK) resulting in attenuated production of pro-inflammatory cytokines.

Figure 3: The distinct roles of CBP and p300 in the Wnt/β-catenin pathway; Therapeutic interventions leading to differential cellular responses.

Upon stabilization of β-catenin, through the upstream Wnt-signaling cascade, β-catenin interacts with co-activators and gets recruited to Wnt-responsive genes. Upon interaction with CBP, β-catenin induces the expression of pluripotency-related genes, whereas if it interacts with p300, it activates differentiation-related gene expression. Since these pathways are important in cancer, small molecule inhibitors will be useful as therapeutics. ICG-001(Emami et al., 2004) specifically inhibits interaction with CBP, whereas YH249/250 (Higuchi et al., 2015) are antagonists of p300-β-catenin interaction, allowing for specific modulation of this pathways.

Figure 4: Therapeutic intervention to target lysine acetylation in cancer: *1,* the link between histone acetylation and cancer. Histone acetylation is a reversible process, regulated by KATs and HDACs. The acetylation mark is read by proteins containing recognition motifs such as bromodomain-containing proteins (BrD), which relay downstream effects by recruiting other co-activators. *2,* the link between histone deacetylation and cancer; deacetylation of histones is a signal for recruitment of co-repressor complexes. *3,* the link between non-histone protein acetylation/deacetylation and cancer. KATs and HDACs also mediate acetylation dynamics of non-histone proteins, which are important in various processes in the cell. In such an acetylation mediated network, many steps can be targeted for therapeutic intervention; these are represented as red boxes with wands pointing at their respective site of modulation.

Table 1: Histone acetylation Dynamics in Cancers

	Altered Histone Acetylation Marks	Enzymes	Cancer Type	References
Upregulated	**H2AK5**	CBP/p300	Oral cancer	(Arif et al., 2010)

	H3K9	Gcn5/PCAF, MOZ, SRC1	Oral cancer, NSCLC, Glioma, HCC	(Arif et al., 2010; Barlési et al., 2007; Fullgrabe et al., 2011; Zhu et al., 2015)
	H3K14	Gcn5/PCAF, CBP/p300	Oral cancer	(Arif et al., 2010)
	H3K18	CBP/p300	Glioma, esophageal carcinoma	(Liu et al., 2010; Tzao et al., 2009)
	H3K56	CBP/p300, Gcn5	Oral, breast, lung, thyroid, skin cancer	(Arif et al., 2010; Das et al., 2009)
Downregulated	**H2AK5**	CBP/p300	NSCLC	(Barlesi et al., 2007)
	H3K9	Gcn5/PCAF, MOZ, SRC1	Prostate, ovarian cancer	(Fullgrabe et al., 2011; Seligson et al., 2005)
	H3K18	CBP/p300	Prostate, pancreatic, breast, lung, kidney cancer	(Fullgrabe et al., 2011; Seligson et al., 2005)
	H4K12	Tip60, CBP/p300	Prostate cancer, NSCLC	(Barlesi et al., 2007; Seligson et al., 2005)
	H4K16	MOF	Breast, gastric and lung carcinoma, medulloblastoma, renal, ovarian cancer	(Cao et al., 2014; Chen et al., 2014; Fraga et al., 2005; Liu et al., 2013; Pfister et al., 2008; Seligson et al., 2005; Wang et al., 2013)

Table 2: Non-histone acetylation and its consequence in cancer

Protein	**Lysine Residues acetylated**	**Enzymes Involved**	**Consequence/ Function**	**References**
Regulation of DNA binding and transcription				

RelA	K218, K221, K310	p300/CBP, SIRT1	Increased DNA binding and recruitment of co-activators.	(Chen et al., 2002; Huang et al., 2009)
	K122, K123	p300/CBP	Decreased DNA binding, Increased IκB binding	(Kiernan et al., 2003)
p50	K431, K440, K441	p300/CBP	Enhanced transcriptional activation.	(Deng and Wu, 2003)
STAT3	K685	p300/CBP	Increased DNA binding, transcriptional activation.	(Wang et al., 2005; Yuan et al., 2005; Zhuang, 2013)
WNT/β-catenin	K354	p300, SirT1	Transcriptional activation of WNT target genes.	(García-Jiménez et al., 2014; Levy et al., 2004)
c-MYC	K143, K157, K275, K317, K323, and K371	p300	Reduced Transcriptional activity; Negative regulation of MYC induced transformation in cancer.	(Wasylishen et al., 2014; Zhang et al., 2005)
p53	K120	Tip60 and hMOF	Mediates expression of genes involved in DNA damage induced apoptosis.	(Sykes et al., 2006; Tang et al., 2006)
	K320	PCAF	Increases p53's ability to bind to its cognate DNA site.	(Liu et al., 1999)
	C-Terminal	p300	Increased DNA binding and transcription	(Gu and Roeder, 1997)
	K117, K161, K162	p300	Essential for p53 to mediate cell cycle arrest, apoptosis and senescence.	(Li et al., 2012)
ERα	K229, K299, K302 and K303	p300	Induces aberrant expression and proliferation of breast cancer cells.	(Wang et al., 2001)
AR	K630, K632, K633	p300, PCAF	Enhanced transcriptional activation, promotes cancer cell growth	(Fu et al., 2003; Fu et al., 2000)
RFPL3	-	CBP	Upregulates hTERT activity and promotes cancer growth	(Qin et al., 2015)
Ku80	-	CBP	Promotes COX-2 expression and tumor growth.	(Xiao et al., 2015)
PTEN	K125, K128	PCAF, SIRT1	Control of growth factor signaling and gene expression.	(Okumura et al., 2006)
Notch-1	K2019,2039,2044, 2068	Tip60	Suppression of Notch-1 signaling.	(Kim et al., 2007)
Smad2	K19, K20, K39	p300/CBP	Modulates TGF-β and Activin responses.	(Tu and Luo, 2007)

Smad3	K378	p300/CBP	Positively regulates Smad3 mediated transcription.	(Inoue et al., 2007)
E2F1	K117,K120, K125	PCAF, HDAC1	Increased DNA-binding ability, activation potential and protein half-life. Leads to Increased cell proliferation.	(Martinez-Balbas et al., 2000) (Marzio et al., 2000)
p73a	K321,327,331	p300	Gets recruited to pro-apoptotic promoters and induces apoptosis.	(Costanzo et al., 2002)
FoxO1	K242,K245,K262	p300/CBP, PCAF, SIRT1	Diminishes DNA binding, reduces activity.	(Calnan and Brunet, 2008)
RUNX1	K24, K43	p300	Increases DNA binding ability.	(Wang et al., 2009)
NPM1	K212, K215,K229, K230, K257, K267 and K292	p300, SIRT1	Delocalizes to nucleoplasm, activates NPM1 mediated transcription.	(Shandilya et al., 2009)
HMGA1	K65, K71	CBP, PCAF	Modulates transcription of IFN-β upon viral infection.	(Munshi et al., 2001) (Munshi et al., 1998)
HMGB1	K2, K11,	CBP	Acetylated upon LPS activation in monocytes and macrophages, triggers inflammation.	(Pasheva et al., 2004) (Sterner et al., 1979)
YY1	K261-233	HDAC1	Suppresses DNA binding.	(Yao et al., 2001)
Regulation of Protein Stability				
c-MYC	K149,K323, K417	PCAF/GCN5, TIP60	Increased stability.	(Patel et al., 2004)
	C-terminal domain	CBP	Increased stability.	(Vervoorts et al., 2003)
MATIIα	K81	p300, HDAC3	Destabilizes protein, leads to repression of cell growth.	(Yang et al., 2015)
DNMT-1	-	Tip60, HDAC1	Destabilization of DNMT1.	(Du et al., 2010)
MPP-8	K439	PCAF, SIRT1	Destabilizes MPP-8, inhibits EMT.	(Sun et al., 2015a)

Smad7	K64, K70	p300	Increases protein stability.	(Grönroos et al., 2002) (Simonsson et al., 2005)
HIF-1α	K709	p300, HDAC1	Stabilizes protein, sensitizes cells to hypoxia-induced growth arrest.	(Geng et al., 2012)
E2F1	K117,K120, K125	PCAF, HDAC1	Increased DNA-binding ability, activation potential and protein half-life. Leads to Increased cell proliferation.	(Martinez-Balbas et al., 2000) (Marzio et al., 2000)
Influencing Protein-Protein Interactions				
RAS	K104	-	Negative regulation of RAS oncogenecity.(destabilization of the interactions with guanine nucleotide exchange factors)	(Yang et al., 2012)
p53	K382	CBP	Increases p53 affinity to CBP bromodomain and interaction with tandem bromodomains of TAF1.	(Li et al., 2007; Mujtaba et al., 2004)
PTEN	K402	CBP, SIRT1	Modulates PTEN interaction with PDZ domain-containing proteins.	(Ikenoue et al., 2008)
pRB	K873, K874	p300, PCAF	Increased affinity to MDM2 , hinders phosphorylation and cell cycle progression.	(Chan et al., 2001; Nguyen et al., 2004)
E2F1	K117,K120, K125	PCAF, HDAC1	Increased DNA-binding ability, activation potential and protein half-life. Leads to Increased cell proliferation.	(Martinez-Balbas et al., 2000) (Marzio et al., 2000)
Enzyme activity Modulation				
PTEN	K163	HDAC6	Activates protein and causes tumour inhibition.	(Meng et al., 2015)
HDAC1	K218, 220, 432, 438, 439, and 441	p300, SIRT1	Ac-HDAC1 shows reduced deacetylation function. Loses ability to deacetylate p53, stabilizing p53 during heat stress.	(Qiu et al., 2006; Yang et al., 2015)
Changing Sub cellular Localization				

NPM1	K212, K215,K229, K230, K257, K267	p300, SIRT1	Delocalizes to nucleoplasm, activates NPM1 mediated transcription.	(Shandilya et al., 2009)
Others				
Beclin-1	K430, K437	p300, SIRT1	Inhibits autophagosome maturation	(Sun et al., 2015b)
Snail	K146,K187	CBP	Switches Snail from being a repressor to an activator.	(Hsu et al., 2014)
Tubulin	K40	HDAC6, SIRT2	Modulates organization of microtubule network.	(Hubbert et al., 2002) (Matsuyama et al., 2002) (North et al., 2003)

Table 3

Types of KAT3 modulators	Compounds	Source/Parent Compound/ Scaffold	Consequences	Off-targets	Reference
KATi: Natural compounds	Anacardic acid	*Anacardium occidentale* (cashewnut) shell liquid	Anti-inflammatory, anti-angiogenic, sensitizes tumors to radiotherapy	PCAF, Tip60, Xanthine oxidase,tyrosinase, urease, LOX15 inhibition and Aurora kinase A activation	(Balasubramanyam et al., 2003; Hemshekhar et al., 2012)
	Curcumin	*Curcuma longa* (turmeric) rhizome	Anti-inflammatory, anti-proliferative	IκK, c-Jun N-terminal kinase, protein tyrosine kinases, serine/threonine kinases	(Balasubramanyam et al., 2004b; Yogesh Panditrao Palve and Nayak, 2012)
	Plumbagin	*Plumbago rosea*	proapoptotic, anti-angiogenic and anti-metastatic	topoisomerase-II inhibitor	(Ravindra et al., 2009)
	Garcinol	*Garcinia indica* (kokam fruit)	anti-oxidative, anti-inflammatory, anti-proliferative and anti-angiogenic	PCAF, NF-κB, STAT3	(Balasubramanyam et al., 2004a; Liu et al., 2015)
	Gallic acid	*Rosa rugosa*	Inhibits cancer growth, angiogenesis and metastasis	COX, ribonucleotide reductase, GSH, UDP-glucose	(Choi et al., 2009; Verma et al., 2013)

				dehydrogenase, NF-κB inhibition and ATM kinase activation	
	Sanguinarine	*Sanguinaria canadensis* and *Argemone mexicana*	anti-tumor and anti-inflammatory	DNA intercalator, AT1 receptor blockers,COX1/2, G9a, CARM1	(Mackraj et al., 2008; Selvi B et al., 2009)
	Delphinidin	*Punica granatum*	Anti-inflammatory and anti-oxidant	Activates superoxide dismutase, NAD(P)H- quinone oxidoreductase, glutathione S-transferases	(Dayoub et al., 2013; Seong et al., 2011)
	Procyanidin B3	Grape seeds	Inhibition of prostate cancer cell growth	-	(Choi et al., 2011)
KATi: Natural compound derivatives	4-cyano-3-trifluoromethylphenylbenzamides	Anacardic acid	Inhibits KAT3 activity	-	(Souto et al., 2008)
	hydrazinobenzoyl curcumin (HBC), CTK7A	Curcumin	Retards tumor growth in colorectal, prostate and oral cancer	Calmodulin	(Wu et al., 2015)
	LTK13, LTK14, LTK19	Garcinol (isogarcinol)	Inhibits global histone acetylation and HIV replication	-	(Mantelingu et al., 2007)
	PTK1	Plumbagin	Non-toxic histone acetylation inhibitor	-	(Vasudevarao et al., 2014)
	EML425	Garcinol	Inhibits histone acetylation, cell cycle arrest in G0/G1 phase	-	(Milite et al., 2015)
KATi: Synthetic compound	Lys-CoA	Bi-substrate analog	Specifically inhibits KAT3 activity *in vitro*	-	(Lau et al., 2000)
	C646	Pyrazolone-based	Cell cycle arrest, senescence, tumor cell migration	-	(Bowers et al., 2010)

	L002	Synthetic	Suppressed tumor growth in MDA-MB-468 xenografts	GCN5, PCAF, angiotensin II receptor-like1[1]	(Yang et al., 2013)
	CCT077791, CCT077792	Isothiazolone-based	Inhibition of KAT activity *in vitro*	PCAF	(Stimson et al., 2005)
	BF1	Thiazole-based	Reduction in histone acetylation in neuroblastoma and glioblastoma cell lines	GCN5	(Secci et al., 2014)
	PU139	pyridoisothiazolone	Inhibition of tumor growth, synergize doxorubicin effect	GCN5, PCAF	(Gajer et al., 2015)
	PU141	Pyridoisothiazolone	Inhibition of tumor growth in neuroblastoma xenografts	-	
KAT activators	CTPB, CTB	Anacardic acid	Histone acetylation, Long term memory formation	-	(Balasubramanyam et al., 2003)
	TTK21	Anacardic acid (CTPB)		-	(Chatterjee et al., 2012)
	Nemorosone	*Clusia rosea*	Reduced tumor growth	Estrogen Receptor, Mitotoxic	(Dal Piaz et al., 2010; Wolf et al., 2013)
Interaction inhibitors: Brd	Ischemin	diazobenzene analogs	Inhibition of apoptosis in cardiomyocytes	-	(Borah et al., 2011)
	CBP30	5-isoxazolyl-benzimidazoles	Inhibition of KAT3-dependent human Th17 responses	-	(Hammitzsch et al., 2015; Hay et al., 2014)
	I-CBP112	benzo-oxazepine core structure	Inhibition of leukemia-initiating cells	-	(Picaud et al., 2015)
Interaction inhibitors: CH1 domain	Novobiocin	Aminocoumarin	Inhibition of angiogenesis and tumor growth, radiosensitizes tumor cells	Anti-bacterial (bacterial DNA gyrase)	(Wu et al., 2013)
	Gliotoxin	Fungal toxin/ epipolythiodioxopiperazine (ETP)		farnesyl transferase, 20S proteasome	(Reece et al., 2014)

	Chaetocin	Fungal toxin/ETP		Lysine methyltransferases	
	Chetomin	*Chaetomium cochliodes*/ETP		-	
	ETP2	Synthetic dimeric ETP		-	(Dubey et al., 2013)
	Indandione and benzoquinone	quinone derivatives	induce Zn(II) ejection from enzyme active site	Lysine Demethylase-4A (KDM4A)	(Jayatunga et al., 2015)
Interaction inhibitors: KIX domain	Naphthol AS-E phosphate	Synthetic	Increased myeloid differentiation and apoptosis	-	(Uttarkar et al., 2015)
	ICG-001 (CBP-specific)	Synthetic	Inhibits EMT, reduces tumor growth, sensitizes drug-resistant cancer cells	-	(Emami et al., 2004)

[1] National Center for Biotechnology Information. PubChem BioAssay Database; AID=488811, https://pubchem.ncbi.nlm.nih.gov/bioassay/488811 (accessed Dec 22, 2015).