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KATapulting toward pluripotency and cancer

Calley L. Hirsch[1,5], **Jeffrey L. Wrana**[1,2], and **Sharon Y.R. Dent**[3,4,5]

[1]Center for Systems Biology, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto M5G 1X5, Canada

[2]Department of Molecular Genetics, University of Toronto, Toronto M5S 1A8, Canada

[3]Center for Cancer Epigenetics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA

[4]Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Science Park, Smithville, Texas 78957, USA

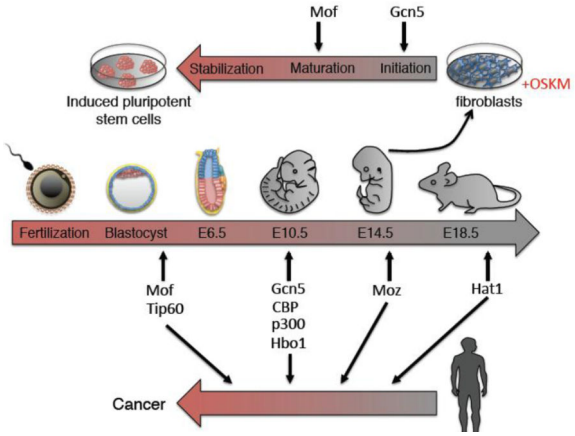
Abstract

Development is generally regarded as a unidirectional process that results in the acquisition of specialized cell fates. During this process, cellular identity is precisely defined by signaling cues that tailor the chromatin landscape for cell-specific gene expression programs. Once established, these pathways and cell states are typically resistant to disruption. However, loss of cell identity occurs during tumor initiation and upon injury response. Moreover, terminally differentiated cells can be experimentally provoked to become pluripotent. Chromatin reorganization is key to the establishment of new gene expression signatures and thus new cell identity. Here we explore an emerging concept that lysine acetyltransferase enzymes drive cellular plasticity in the context of somatic cell reprogramming and tumorigenesis.

Graphical Abstract

The role of KAT enzymes in embryonic development, pluripotency induction and tumorigenesis is depicted.

[5]Address for correspondence: sroth@mdanderson.org; hirsch@lunenfeld.ca.



Keywords

acetylation; histone; embryonic stem cells; reprogramming; plasticity

Introduction

Cell fate is established by signaling pathways that drive requisite gene expression programs. Central to modulation of these pathways are reversible protein post-translational modifications (PTMs) that permit dynamic cellular regulation and flexibility in response to signaling cues and stimuli. To date, over two hundred different PTMs have been identified that influence countless aspects of signaling regulation[1]. Importantly, PTMs also play a prominent role in altering chromatin structure and function.

Chromatin is composed of repeating nucleosome units of approximately 146bp of DNA wrapped around a histone core octamer, containing two copies of each histone protein H2A, H2B, H3 and H4[2]. Numerous PTMs occur on histones, including acetylation, phosphorylation, methylation, ubiquitylation, sumoylation, glycosylation, citrullination, ADP-ribosylation, and other types of acylations[3; 4; 5; 6; 7]. Collectively, these modifications translate cellular signals within the nucleus, functioning to negotiate chromatin accessibility as well as recruitment of additional proteins and enzymatic complexes for different biological processes[8]. Hence, histone modifications greatly impact folding of the 3D genome and play fundamental roles in establishing appropriate gene expression networks that dictate cell fate throughout development.

Lysine acetylation was first detected on histones over fifty years ago and has long been associated with gene activation[9; 10]. Reversible acetylation is balanced by the activities of lysine acetyltransferases (KATs), which are writer enzymes that catalyze acetyl group transfer from acetyl coenzyme A (acetyl-CoA) to the epsilon amino side chain of lysine resides, and histone deacetylases (HDACs), which are eraser enzymes that remove these marks. In this manner, specific lysines are acetylated within the globular domains of histones H3 and H4, as well as within the unstructured amino-terminal tails of H2A, H2B, H3 and H4[11; 12] (Figure 1). Acetylation of histones neutralizes the positive charge on lysine residues and relieves inter- and intra-nucleosomal interactions to create a less compact chromatin

environment that promotes transcriptional activation[13; 14; 15; 16; 17], as well as DNA repair, replication, and native centromere assembly[18; 19; 20]. Furthermore, acetylated residues cooperate with other PTMs to boost these pathways and block other lysine modifications, including methylation and ubiquitylation, which can elicit opposite regulatory outcomes[21]. Accordingly, depletion of individual KATs also vastly alters the pattern of other local histone modifications[22].

Beyond physically altering chromatin structure, deposition of acetyl-moieties on histones additionally creates docking sites for bromodomain[23], YEATS (named from the family members Yaf9, ENL, AF9, Taf14 and Sas5) domain[24], and select PHD (Plant homeodomain) finger containing reader proteins[25; 26; 27]. These domains are present within many transcription-related proteins and chromatin modifying enzymes, including KATs[28], and they act as adapter motifs that link acetylated histones to other regulatory factors and complexes. Therefore, histone acetylation is fundamental to promoting chromatin accessibility for the transcriptional machinery.

Reversible lysine acetylation also occurs on non-histone proteins, outside of chromatin. In mammals, over 8000 acetyl-lysine sites are present on proteins that reside primarily in nuclear, cytoplasmic and mitochondrial subcellular compartments[29; 30; 31; 32], and many of these modification sites are conserved across different species, implying their significance[33; 34]. Protein acetylation imparts a variety of functional outcomes, ranging from altering enzymatic activity and protein-protein interactions to influencing nucleic acid binding, protein stability and subcellular localization[35]. This includes auto-acetylation of a number of KATs, which promotes catalytic activity and/or substrate binding[36; 37; 38; 39; 40]. Acetylated sites also crosstalk with other PTMs in non-histone proteins. For example, acetylation blocks lysine ubiquitylation and ensuing degradation of proteins such as the p53 transcription factor[41] and the Smad7 negative regulator from the transforming growth factor beta (TGFβ) pathway[42]. Furthermore, many key mitochondrial proteins are subject to acetylation, including enzymes involved in glycolysis, gluconeogenesis, the tricarboxylic acid (TCA) cycle, the urea cycle, fatty acid metabolism and glycogen metabolism[43]. Although the contribution of KATs to mitochondrial protein acetylation remains unclear, as high acetyl-CoA levels within this organelle may drive non-enzymatic acetylation for the bulk of acetylation events, acetyl lysine deposition is tightly linked to cellular metabolism on multiple levels. For instance, acetyl-CoA supply across the cell is restricted by acetylation-mediated inactivation of both cytosolic Acetyl-CoA synthetase 1 (AceCS1) and mitochondrial Acetyl-CoA synthetase 2 (AceCS2) enzymes[44; 45]. Interconnection of acetylation states and carbon source utilization are particularly important in stem cells, as the glycolytic state of embryonic stem cells (ESCs) supports acetyl-CoA production to promote histone acetylation and maintain stemness[46]. In contrast, differentiating ESCs experience a rapid drop in glycolysis that leads to a reduction in both acetyl-CoA and histone acetylation.

Clearly lysine acetylation events on both histone and non-histone proteins control numerous biological processes. Thus, it is not surprising that multiple KATs and HDACs are required for embryonic viability and are de-regulated in cancer. These enzymes play important roles in delineating cell-specific gene expression pathways and therefore function as key

determinants of cell fate. Recent work indicates that specific KATs also promote cellular plasticity by creating a more open chromatin configuration amenable to activation of new gene expression networks and act as powerful drivers of chromatin reorganization during nuclear reprogramming processes, such as somatic cell reprogramming, trans-differentiation and oncogenesis. Here, we focus specifically on the multi-faceted ability of KATs to direct embryonic development, confer cellular plasticity, and contribute to nuclear reprogramming.

Lysine acetyltransferase (KAT) families in development

KAT enzymes are functionally diverse and commonly exist within large multi-subunit complexes that collectively facilitate specific acetylation events. The human genome encodes 17 KATs[47], that are traditionally divided into two classes depending on their subcellular localization. A-type KATs reside in the nuclear compartment and accordingly facilitate changes in chromatin compaction and transcription, while B-type KATs are present in cytosol and acetylate newly synthesized histone H3 and H4 subunits prior to de novo nucleosome assembly[48; 49]. However, this classification is likely far too simplistic, as additional KATs have recently been uncovered in mitochondria[50; 51], golgi apparatus[52] and endoplasmic reticulum[53]. Based on sequence and structural similarities in the catalytic domain, KATs are more appropriately grouped into five major families: GNAT (Gcn5-related N-acetyltransferase), CBP/p300 (CREB-binding protein / E1A-associated protein of 300 kDa), MYST (Moz, Ybf2/Sas3, Sas2, Tip60), nuclear receptor co-activators, and basal transcription factors[11]. Many KATs play fundamental roles throughout development and more specifically within ESCs, which have the unique ability to both self-renew and differentiate into all cell types of the three primary germ layers. Comparatively, ESCs generally display higher histone acetylation levels, enhanced chromatin accessibility and transcriptional hyperactivity than their differentiated counterparts[54], implying that histone acetylation is an important driver of cellular plasticity. In the following section, the different KAT families and representative members that coordinate protein acetylation in the context of embryonic development are discussed (Table 1) (Figure 2).

GNAT Superfamily

The GNAT superfamily is evolutionarily conserved from bacteria to mammals. This family is composed of A-type (Kat2a/Gcn5, Kat2b/Pcaf, Kat9/Elp3) and B-type KATs (Kat1/Hat1), as well as KATs that reside in other subcellular compartments (Gcn5l1, Atat1, Hat4, Nat8 and Nat8b). Altogether, these KATs control a variety of cellular process, such as transcriptional activation[55; 56], transcript elongation[57], histone deposition[48], DNA repair[52; 58; 59] and microtubule stability[60]. GNAT family members characteristically contain three to four common motifs in the catalytic core[61], including a highly conserved Arg/Gln-X-X-Gly-X-Gly/Ala sequence that recognizes and binds acetyl-CoA[62]. Moreover, Kat2a/Gcn5 and Kat2b/Pcaf contain a carboxy-terminal bromodomain that associates with acetylated lysine residues[23].

Gcn5 and Pcaf

Kat2a, hereafter referred to as Gcn5 (general control non-repressible 5), was the first transcription-related KAT identified in eukaryotes and is arguably the best-studied member

of the GNAT family. Originally discovered in yeast as a transcriptional co-activator[63], the Gcn5 ortholog in *Tetrahymena thermophila* (p55) was later discovered to have acetyltransferease activity[17; 55]. Together, these observations established a molecular link between histone acetylation and the regulation of gene expression, and also provided a foundation for the discovery of additional KATs, including the closely related family member Kat2b, which will henceforth be discussed by its initial name Pcaf (p300/CBP-associated factor)[64].

Recombinant Gcn5 and Pcaf preferentially acetylate specific sites in free histones (e.g. lysine 14 in histone H3 (H3K14) for Gcn5), but fail to effectively acetylate nucleosomes in vitro, indicating that neither KAT is independently sufficient to modify chromatin[64; 65; 66]. In vivo, Gcn5 or Pcaf reside within two major native multi-subunit complexes, SAGA (Spt-Ada-Gcn5 acetyltransferase)[66; 67] and ATAC (ADA Two-A containing)[68; 69]. Incorporation into these complexes enhances KAT activity and has long been suggested to expand lysine target specificity[70] as well as the functionality of Gcn5 and Pcaf. However, recent work indicates that while the SAGA and ATAC increase catalytic efficiency of human Gcn5, by approximately 10- and 6-fold respectively, the specificity of Gcn5-mediated acetylation on histone octamers does not change when Gcn5 is alone or integrated into these complexes[71]. H3K14 still remains the primary acetylation site in vitro, while H3K9, H3K23, H3K27, H3K36, H4K5 and H4K8 residues are acetylated to a lesser extent by Gcn5[71]. Beyond promoting catalytic activity, the SAGA and ATAC complexes regulate different functions due to their structural modularity. The SAGA complex contains four functional units that elegantly control transcriptional activation, telomere maintenance[72], mRNA export[73] and DNA repair[74]. One module consists of the acetyltransferase unit (Gcn5, Ada2b, Ada3, Sgf29) that harbors KAT activity and facilitates SAGA recruitment to H3K4me2/3 sites via the tandem Tudor domains of Sgf29[75; 76] and/or to acetyl lysine residues through the bromodomain of Gcn5[77]. A second enzymatic module, called the deubiquitination (DUB) module (Usp22, Atxn7, Atxn7L3 and Eny2) promotes H2BK120 deubiquitination during transcription[78]. The Spt module (Trrap, Spt3, Spt20, Staf42, Staf65γ) mediates interactions with TBP (TATA-binding protein)[79] and various transcription factors, including Myc and E2f1[80; 81]. The Taf (TBP-associated factor) module (Taf5l, Taf6l, Taf9, Taf10, Taf12) further connects SAGA to the general transcription machinery[82].

In comparison to the SAGA complex, ATAC similarly contains a slightly modified KAT module (Gcn5, Ada2a, Ada3, Sgf29), but lacks many of the general transcription factors present in SAGA. Furthermore, ATAC houses a second KAT activity, which is mediated by Atac2, and contains Yeats2, which is a reader of both acetyl-lysine and crotonyl-lysine modifications [83; 84]. The different subunit compositions of SAGA and ATAC reflect their disparate functions, as SAGA primarily associates with gene promoters, while ATAC is found at both promoters and tissue-specific enhancers[85]. The SAGA and ATAC complexes also respond to different stimuli and activate distinct subsets of inducible genes[86; 87]. Additionally, SAGA has been described as a general transcriptional co-activator complex[88], although it is clearly recruited to specific gene promoters in ESCs[89]. SAGA and ATAC as well control distinct biological processes via non-histone acetylation, such as ATAC-specific acetylation of Cyclin A, which promotes mitotic progression[90].

In agreement with the wide functionality of both the SAGA and ATAC complexes, Gcn5 is required for normal embryonic development in mice[91; 92]. *Gcn5* null (*Gcn5*$^{-/-}$) mice fail to progress beyond 10.5 days of embryonic development (E10.5), largely due to increased apoptosis in mesoderm lineages[91]. Furthermore, *Gcn5*$^{hat/hat}$ mice lacking catalytically active Gcn5 die by E16.5 and display both cranial neural tube closure defects and exencephaly[93]. The delay in lethality of these mice compared to *Gcn5* null counterparts indicates that Gcn5 regulates embryogenesis through KAT-dependent as well as KAT-independent mechanisms. Gcn5 also mediates later stages of development, including neural stem cell (NSC) proliferation[94] and normal skeletal patterning[95], but is not required to maintain self-renewal or pluripotency of mouse embryonic stem cells (mESCs)[89; 96]. Gcn5 specifically co-activates Myc and E2f1 gene expression networks in mESCs, although loss of Gcn5 does not affect self-renewal or pluripotency, possibly due to redundancy with Pcaf or other KATs[89]. Contrary to Gcn5, Pcaf null mice develop normally[91; 92]. However, homozygous double null (*Gcn5*$^{-/-}$;*Pcaf*$^{-/-}$) embryos are severely developmentally delayed and die by E7.5[91], implying that Pcaf and Gcn5 share redundant functions during early embryogenesis. Compatible with this hypothesis, Gcn5 expression is increased in certain *Pcaf*$^{-/-}$ tissues that normally express *Pcaf*, such as liver and lung[92], partially explaining why *Pcaf* null mice develop normally. Additionally, Pcaf and Gcn5 act redundantly to regulate H3K9 acetylation (H3K9ac) in mouse embryonic fibroblasts (MEFs)[97] and control mouse adipocyte differentiation[98]. Nevertheless, Gcn5 does not universally compensate for Pcaf, as loss of *Pcaf* alone also produces notable phenotypes, including defective neurite outgrowth following spinal cord injury[99]. Interestingly, components of the SAGA and ATAC complex have also been linked to development. Trrap, the accessory subunit within SAGA and also the TIP60 complex that facilitates transcription factor interactions, is essential for early embryonic development and ESC self-renewal[100; 101; 102], while Atac2 is required for embryo viability[103].

Hat1

Kat1, more commonly referred to as Hat1, is a cytoplasmic KAT enzyme that acetylates newly synthesized free histones during chromatin assembly[48]. Together, Hat1 and histone binding protein RbAp46 form the HAT-B complex[104]. Following new histone synthesis, HAT-B associates with sNasp (somatic Nuclear autoantigenic sperm protein)-bound H3-H4 dimers to acetylate H4K5 and H4K12[105]. These modified histones are then transported to the nucleus for de novo chromatin assembly and subsequently deacetylated during chromatin maturation[106]. In addition to functioning within the cytosol, Hat1 is also present in the nuclear compartment[107]. While the nuclear function of Hat1 is still poorly understood, studies performed in yeast suggest that Hat1 functions as part of the NuB4 (Nuclear type B HAT specific for H4) complex, containing Hat1, RbAp46, sNasp and H3-H4, dimers to control histone deposition and/or DNA repair-based chromatin reassembly[108]. Interestingly, the Hat4 GNAT family member also regulates many of these processes, but instead acetylates free histone H4 on K20, K79 and K91 residues[52].

Hat1 plays an essential role during embryonic development, as *Hat1*$^{-/-}$ mice die at birth or shortly after birth from lung maturation defects resulting from cellular hyperproliferation[109]. These mice are smaller in size than their wild-type counterparts and display craniofacial

abnormalities, likely due to enhanced bone growth and reduced cartilage production[109]. In addition, *Hat1*$^{-/-}$ mouse embryonic fibroblasts are strikingly sensitive to DNA damaging agents, and exhibit high genome instability[109].

CBP/p300 Family

The CBP/p300 family is composed of these two homologous enzymes[110], also known as Kat3a and Kat3b, respectively[47]. Both contain a well-conserved acetyltransferase domain[111], and a number of protein interaction domains that facilitate binding with over 400 proteins and promote many non-histone acetylation events[112]. Given their high sequence and structural similarity, CBP and p300 generally function in an analogous manner, yet still modulate distinct processes. Both proteins act as transcriptional co-activators, incapable of directly binding DNA and are hence recruited via interactions with sequence-specific transcription factors[113; 114; 115]. In vitro, recombinant CBP and p300 readily acetylate each of the four core histones in nucleosomes without the assistance of accessory factors[110; 116], and they appear to preferentially acetylate H3K18 and H3K27 residues in vivo[97]. CBP and p300 also contribute to H3K56ac, a modification that is elevated in both embryonic stem cells and multiple forms of cancer[117; 118]. Furthermore, CBP and p300 dually function as crotonyltransferase enzymes that deposit crotonyl moieties on histones to activate transcription[119]. At the genomic level, CBP and p300 binding is enriched at both promoters and enhancers[120; 121]. However, CBP/p300 and H3K27ac most notably mark active enhancers during early development that drive transcription programs associated with cell and tissue specification[122; 123; 124]. Similarly, p300 has also been linked to super-enhancers in mESCs[125], defined as enlarged enhancer regions densely co-bound by the Mediator transcriptional co-activator complex and pluripotency regulators Oct4, Sox2 and Nanog[126].

CBP and p300 are largely co-expressed during mouse embryogenesis and therefore share certain developmental functions. Both are required for normal embryonic development[127; 128; 129]. Knockout of *p300* (*p300*$^{-/-}$) in mice leads to embryonic lethality between E9 and E11.5, and is accompanied by defects in cell proliferation, heart development and neural tube closure[127]. Similarly, *CBP*$^{-/-}$ mice die between E9.5 and E10.5 of embryonic development with severe neurulation defects, and display abnormalities in hematopoietic differentiation. Interestingly, a subset of *p300* heterozygous (*p300*$^{+/-}$) mice are also embryonic lethal and compound heterozygote (*CBP*$^{+/-}$;*p300*$^{+/-}$) mice die in utero with open neural tubes, suggesting the combined level of *CBP* and *p300* expression is important for normal development[127]. Beyond this, *CBP* heterozygous mice exhibit skeletal defects, consistent with *CBP* mutations observed in patients with the haploinsufficiency disorder, Rubinstein-Taybi syndrome[130]. In mESCs, loss of *p300* leads to premature differentiation[131], while combined knockdown of *CBP* and *p300* further enhance this differentiation defect and abrogate normal self-renewal capacity[132]. In line with these observations, binding of CBP and p300 in mESCs overlaps with the pluripotency master regulators Oct4, Sox2 and particularly Nanog[132; 133]. Moreover, direct binding of CBP/p300 to Nanog establishes long-range chromatin interactions necessary for mESC maintenance.

Interestingly, both Gcn5 and Pcaf interact with p300 and CBP. These two KAT families share both distinct and overlapping functions during development, as illustrated by the

finding that about 25% of embryos that carry one null allele of both *Gcn5* and *p300* die, even though embryos that are heterozygous for either null allele alone are viable[134].

MYST Family

The MYST family has five mammalian members: Tip60 (Kat5/Htatip), Mof (Kat8/Myst1), Moz (Kat6a/Myst3), Morf (Kat6b/Myst4), and Hbo1 (Kat7/Myst2). Each member contains a well-conserved MYST domain that includes a C_2HC zinc finger as well as an acetyl-CoA binding motif homologous to that found in GNAT family members[135]. Furthermore, individual members harbor specialized domains that bind modified histones, including PHD and chromodomains[136]. Similar to the GNAT family, the MYST KATs also function in macro- molecular complexes and regulate a wide variety of biological and developmental processes.

Tip60

In mammals, the transcriptional co-regulator Tip60 (HIV Tat-interacting protein of 60 kDa) assembles into the multi-subunit TIP60 complex. This complex contains at least 16 proteins and has two enzymatic platforms, including Tip60 acetyltransferase activity that drives H2A and H4 acetylation, and p400 ATP-dependent chromatin remodeling activity that deposits the H2A.Z histone variant into chromatin[137]. Functionally, the TIP60 complex primarily associates with active promoters, via binding to proximal promoter R-loops and various transcription factors, including Myc, E2f1, and β-catenin[102; 138; 139; 140; 141; 142]. As well, TIP60 acetyltransferse activity functions in homologous recombination (HR)-based repair of DNA double strand breaks (DSB)[137; 143]. In agreement with these observations, multiple members of the TIP60 complex are vital regulators of normal embryogenesis and/or ESC regulation in mice. In developing mice, inactivation of either the TIP60 complex genes, *Tip60* (*Tip60*$^{-/-}$), *Trrap* (*Trrap*$^{-/-}$) or *Dmap1* (*Dmap1*$^{-/-}$) leads to early peri-implantation lethality[101; 144; 145]. The severe phenotype of the *Trrap*$^{-/-}$ embryos likely reflects disruption of TIP60 and SAGA complexes. Individual knockdown in the expression levels of seven TIP60 members (*Tip60*, *Trrap*, *p400*, *Dmap1*, *Ruvbl1*, *Ruvbl2* and *Yeats4*) also abrogates normal mESC identity[102]. Furthermore, the TIP60 complex regulates the Myc mESC network[142; 146] and maintains the primed state of developmental genes in mESCs[102].

Mof

Mof (males absent on the first) was originally identified in Drosophlia as a regulator of dosage compensation, leading to H4K16ac and hyperactivation of the single male X chromosome[147]. However, it is still unclear whether Mof manages similar dosage compensation effects in mammals. In humans, Mof assembles into two primary KAT complexes: the highly conserved MSL (male-specific lethal) multi-protein complex that specifically acetylates H4K16[148], and the nine subunit NSL (non-specific lethal) complex that targets H4K5, K8 and K16 acetylation[149]. In vivo, *Mof* is required for mouse embryonic development beyond the blastocyst stage[150]. *Mof*$^{-/-}$ mice die at E4.5, display increased chromatin compaction and a striking loss of H4K16ac preceding apoptosis[150]. Accordingly, *Mof* is also needed to maintain pluripotency and self-renewal of mESCs[151]. Loss of *Mof* drives massive transcriptional changes, including down-regulation of the pluripotency genes

encoding Oct4, Sox2 and Nanog and up-regulation of lineage specific genes[151]. The MSL complex is largely responsible for maintaining H4K16ac levels in mESCs and primarily localizes within gene bodies of ESC-specific targets, whereas NSL associates with promoter regions of housekeeping genes[152]. However, Mof occupancy has also been linked to active enhancers[153; 154]. Moreover, the MSL complex protects mESC identity, as it directly enhances *Tsix* transcription to ensure X chromosome activation[154].

Moz, Morf and Hbo1

The MYST acetyltransferases, Moz (monocytic leukemia zinc-finger protein) and Morf (MOZ-related factor) have similar structural organization and independently form MOZ/MORF tetrameric complexes, containing Ing5 (inhibitor of growth 5), Eaf6 (homolog yeast of Esa1-associated factor 6), and either Brpf1/2/or 3 (bromodomain-and PHD finger-containing protein) paralogs[155]. Likewise, the HBO1 complex includes the Hbo1 acetyltransferase, Ing4/5, Eaf6 and either Brpf1/2/3 or Jade1/2/3 (gene for apoptosis and differentiation in epithelia)[155; 156]. Both MOZ and MORF complexes primarily acetylate H3K14 and function as co-activators for Runx and p53 transcription factors[155], while the Brpf-containing HBO1 complex targets H3K14/ K23 acetylation, and the Jade-containing HBO1 complex mediates H4K5/K8/K12 acetylation[157].

Although, each of these KATs participates within similar multi-subunit complexes, they exhibit very different developmental roles as reflected by different phenotypes of the null mice. Mice lacking *Moz* (*Moz*$^{-/-}$) die around E15 due to defective hematopoietic stem cell (HSC) development and maintenance[158; 159]. This fate is partially dependent on Moz KAT activity, as mice expressing catalytically inactive *Moz* (*Kat*$^{-/-}$ *Moz*) survive until birth, yet die sooner than their wild-type counterparts and generally display reduced body weight as well as decreased spleen and thymus size, corresponding to impaired HSC proliferation[160]. In comparison, a 90% reduction in *Morf* expression, within *Morf* gene trap mice (*Morf*$^{gt/gt}$), results in low birth weight, craniofacial abnormalities, and defective brain development[161], as well as reduced adult neural stem cell production[162]. *Hbo1* null mice die at E10.5, due to increased apoptosis in mesenchymal tissues and display near complete loss in H3K14ac[163].

Nuclear Reprogramming

Throughout development, pluripotent cells differentiate in a spatial and temporal manner to adopt stable somatic cell identities. Once established, specified cells are typically resistant to changes in cell fate. However, in rare contexts, such as during tumor initiation, gene networks are rewired resulting in cell identity changes[164]. Furthermore, cell specification is readily reversed and/or altered using experimental techniques, such as transcription factor directed somatic cell reprogramming[165] and transdifferentiation[166]. Simply put, the switch in cell fate that occurs when a committed cell is triggered to dedifferentiate or to adopt a new cell identity, based on transcriptional changes, is referred to as nuclear reprogramming[167; 168; 169; 170]. Predictably, massive reorganization and resetting of the original chromatin landscape is key to nuclear reprogramming, and both histone acetylation changes and KATs have been implicated as potential drivers of these processes. Next, we specifically discuss the ability of histone acetylation and KATs to modulate chromatin

plasticity in different nuclear reprogramming contexts including somatic cell reprogramming and tumor initiation.

Somatic cell reprogramming

In 2006, Takahashi and Yamanaka reported that ectopic expression of the stem cell-related transcription factors Oct4, Sox2 Klf4 and Myc (OSKM) was capable of reversing mature somatic cells back to a pluripotent state[165]. This process, known as somatic cell reprogramming, results in the generation of induced pluripotent stem cells (iPSCs), that closely resemble ESCs [171; 172; 173]. Reprogramming thus offers unparalleled potential to create undifferentiated patient-specific cells for regenerative medicine applications, disease modeling and drug discovery.

Mechanistically, somatic cells undergo reprogramming through three phases termed initiation, maturation and stabilization[174; 175] (Figure 3). The initiation phase is triggered by the induction of OSKM and is characterized by increased cellular proliferation and a requisite mesenchymal-to-epithelial transition (MET) driven by bone morphogenetic protein (BMP) signaling, which results in loss of the somatic cell profile (*Snai1/2*, *Zeb1/2*) and gain of epithelial-associated expression (*Cdh1*, *Epcam*, *Ocln*)[174; 176; 177]. Furthermore, additional transcriptional changes affect cytoskeletal organization, RNA processing and metabolism[178]. In comparison, the maturation phase is linked to activation of the first set of pluripotent genes (endogenous *Oct4*, *Nanog*, *Esrrb*), whereas the stabilization phase coincides with acquisition of a self-sustaining pluripotency network that is independent of ectopic OSKM transgene expression, marked by the full complement of pluripotent genes (endogenous *Sox2*, *Dppa4*, *Pecam*) and reactivation of the somatically silenced X chromosome[174; 179; 180; 181]. Wnt signaling is also necessary for late reprogramming events[182]. Moreover, changes in cellular metabolism are tightly linked to reprogramming, as dedifferentiating somatic cells suppress oxidative phosphorylation and acquire enhanced glycolytic potential to ramp up acetate supply, as seen in mESCs[183].

Throughout the reprogramming process, alterations in gene expression are coupled to reorganization of the chromatin landscape and DNA methylation patterns[184]. During the initiation phase, chromatin compaction is reduced due to a loss of repressive H3K27me3 and deposition of active H3K4me2 and H3K4me3 marks[178; 185; 186; 187]. Bivalent domains harboring both H3K27me3 and H3K4me3 are gradually established to poise developmental genes[178]. Furthermore, suppressive H3K9me3 modifications are erased and DNA demethylation occurs at pluripotency genes, such as *Nanog*[178; 188]. Beyond these differences, acetylation of nearly all H3 and H4 lysine residues are elevated in iPS cells compared to MEFs[188; 189]. Furthermore, high H3K9ac levels augment reprogramming[190] and the expression levels of distinct KATs increase as somatic cells dedifferentiate[89; 189], implying that histone acetylation is important for attaining pluripotency. Indeed, HDAC inhibitors enhance reprogramming efficiency[191; 192; 193], however, the mechanistic details of this enhancement remain unclear, as valproic acid promotes reprogramming in the absence of Myc[193], while butyrate drives initiation events in a Myc-dependent manner in mice[192], and only partially compensates for Myc loss during human reprogramming[191]. Nonetheless, these observations are particularly intriguing given that Myc facilitates recruitment of KAT

co-activator complexes (SAGA and TIP60)[80; 81; 138], and that Myc is required to maintain histone acetylation and gene activation in neural progenitor cells[194].

Accordingly, multiple components of the SAGA complex act as essential regulators of reprogramming, including Gcn5, Trrap, Sgf29 and Taf12[89]. Early in reprogramming, Myc directly up-regulates both *Gcn5* and *Sgf29* expression to facilitate a positive feedforward mechanism, whereby Myc subsequently interacts with Gcn5 to co-activate gene expression[89]. During this time, Myc plays fundamental roles in accessing open chromatin within promoter regions to drive early gene activation, suppressing the fibroblast expression signature, and boosting OSK engagement at enhancers [186; 195]. Although, Myc has been proposed to work as a general amplifier of transcription, based on its role in cancer[196; 197], Gcn5 is not a universal Myc co-activator during early reprogramming. Instead, Gcn5 cooperates with Myc at specific target genes, including a subset of genes that encode RNA processing factors linked to alternative splicing.[89] Similar to transcription and epigenetic changes that occur as somatic cells become pluripotent, alternative splicing networks are also altered[198]. Interestingly, elevated expression of the RNA processing factors, mediated by Myc and Gcn5, corresponds with downstream changes in alternative splicing patterns linked to reprogramming and pluripotency[89; 198; 199]. Furthermore, these splicing events are compromised by depletion of Gcn5, Trrap, Sgf29 and Taf12 subunits of the SAGA complex[89]. Thus, Myc and the SAGA complex establish a key alternative splicing pathway by promoting expression of RNA processing factors within the initiation phase of reprogramming. Since this discovery, Myc-mediated alternative splicing has also been implicated in tumorigenesis, but the role of Gcn5 in this context remains unclear[200; 201].

The impact of KATs on the maturation and the stabilization phases of reprogramming has yet to be systematically investigated, but Mof appears to be important for progression through these phases. As mentioned above, *Mof* is needed to ensure proper chromatin organization and mESC-specific expression patterns through acetylation of H4K16[151]. Ectopic *Mof* expression also improves OSKM-mediated reprogramming of human fibroblasts, while knockdown of *Mof* abrogates the process[202]. Interestingly, both *Mof* mRNA and protein levels increase throughout reprogramming and peak in iPSCs, in a manner similar to the *Nanog* maturation marker[202]. Notably, this spike in *Mof* expression also correlates with global enhancement in H4K16ac, a modification linked to chromatin decompaction[203]. During the maturation phase, Mof directly binds both the *Oct4* and *Nanog* promoters to deposit H4K16ac and promote Wdr5-mediated H3K4me3[202]. Thus, Mof plays a fundamental role in establishing the pluripotency network of iPSCs. However, the role of Mof in reprogramming may extend beyond these observations. Given that the MSL complex controls X chromosome activation in mESCs[154], and the necessity for X chromosome reactivation during iPSC generation[181], it will be of interest to see if Mof also directs reactivation of the X chromosome during reprogramming.

It is also likely that additional KATs are necessary for iPSC generation. In particular, members of the CBP/p300 family may function late in reprogramming. Recently, Tex10 was identified as a Sox2-interacting protein that recruits p300 to deposit H3K27ac at super-enhancers in order to maintain self-renewal and pluripotency of mESCs[125]. During reprogramming, *Tex10* expression levels are elevated with similar kinetics to that of the late

reprogramming marker, endogenous *Sox2*. Also, Tex10 is required for both mouse and human reprogramming[125], suggesting that p300 also contributes to defining active super-enhancers within iPSCs. Based on their roles in mESCs, CBP and p300 may facilitate long-range chromatin interactions in iPSCs[132]. Moreover, CBP/p300 may either positively or negatively effect reprogramming based on selective interactions with distinct transcription factors. For instance, Wnt signaling drives late-stage iPSC formation[182], and CBP is a well-known transcriptional co-activator of β-catenin[182], implying that CBP modulates Wnt signaling in this context. In agreement, reprogramming performed in the presence of conditioned Wnt3a media enhances reprogramming efficiency, but is completely abrogated upon treatment with ICG-001, an inhibitor that specifically blocks CBP binding to β-catentin[204; 205]. Therefore, CBP and β-catenin appear to facilitate reprogramming, yet the underlying mechanism remains to be explored.

Tip60 may also be important for reprogramming, given that seven TIP60 complex components, including Tip60 itself, are required to maintain mESC identity[102] and Myc interacts with the TIP60 complex in mESCs[146]. However, it is currently unknown if TIP60 regulates conversion of somatic cells to iPSCs. Furthermore, the expression of other MYST family members, including Hat1, Morf and Hbo1, is elevated in iPSCs (unpublished observation)[189]. Of these, Morf has also been implicated in neural stem cell (NSC) maintenance[162; 206], while Hat1 is highly expressed in mESCs, NSCs, and hematopoietic stem cells (HSCs)[207; 208; 209], further suggesting a role for these enzymes in promoting cellular plasticity during reprogramming.

Tumor Initiation and progression

Pluripotent cells and tumor initiating cells share many common features, including acquired self-renewal capacity, restricted differentiation, enhanced proliferation and glycolytic energy preference[210]. Cancer cells also establish ESC-like gene expression patterns[211], and loss of tumor suppressor function promotes somatic cell reprogramming[212; 213; 214; 215; 216]. Furthermore, the OSKM reprogramming factors each play roles in tumorigenesis[217; 218; 219; 220; 221], suggesting that common epigenetic and transcription pathways drive pluripotent properties during reprogramming and tumor development. Accordingly, several KATs have been linked to tumorigenesis. Here we discuss the impact of select KATs on cancer development and progression (Figure 4).

Myc is a commonly amplified proto-oncogene that promotes cell growth in human cancers[221] and self-renewal in ESCs[211]. Thus, precise Myc regulation is crucial for normal cellular behavior. In cancer, Myc has been implicated as both a general amplifier of active genes, as well as a gene-specific transcriptional regulator[196; 197; 222]. As noted above, both TIP60 and Gcn5/SAGA act as co-activator complexes for Myc in mESCs. Tip60 interacts with Myc at approximately 50% of target genes[102; 142; 146], and Gcn5-bound loci strongly associate with sites bound by Myc, E2f1 and H3K9/14ac[89]. N-Myc and Gcn5 also regulate common transcription programs in NSCs[94]. Therefore, given these precedents, it seems likely that TIP60 and/or SAGA may similarly contribute to the activation of Myc transcriptional networks in cancer[146]. Gcn5, Pcaf, and Tip60 also directly acetylate Myc to increase protein stability [223], implying that these enzymes facilitate Myc-driven

tumorigenesis on multiple levels. Moreover, recent work indicates that Myc actively promotes these mechanisms, as Myc up-regulates Gcn5 expression in NSCs[194], reprogramming cells[89] and human colon cancer[224]. Beyond these observations, Gcn5 is overexpressed in a variety of carcinomas including advanced stage gastric cancer[225], colon cancer[224], and non-small cell lung cancer (NSCLC), where Gcn5 specifically promotes cell growth by functioning as an E2f1 co-activator at Cyclin D1, Cyclin E1 and E2f1 genes[226].

Like Gcn5, Pcaf functions as a co-activator in tumor maintenance. For example, in medulloblastoma and glioblastoma cells, Pcaf interacts with Gli1 to promote hyperactive Hedgehog-Gli1 signaling and high cellular proliferation[227]. Notably, Pcaf mediates many of its oncogenic functions via acetylation of non-histone targets including Ezh2[228], Akt1[229], Acly (ATP-citrate lyase)[230], and β-catenin[231]. Pcaf-mediated acetylation of Ezh2, Acly and β-catenin leads to improved protein stability and tumor-promoting characteristics in lung[228; 230] and colon cancer[224], respectively. Additionally, the GNAT family member, Hat1, has also been reported to promote cell growth in esophageal squamous cell carcinomas[228].

CBP/p300 and Moz/Morf KATs undergo recurrent chromosomal translocations in acute myeloid leukemia (AML), resulting in MOZ-CBP, MOZ-p300, and MORF-CBP fusion proteins[232]. These KATs also rearrange with other genes, such as MLL (mixed lineage leukemia) to generate MLL-CBP and MLL-p300 fusion proteins that retain the bromodomain and KAT domain. MLL-CBP models of therapy-related myeloproliferative disease in mice demonstrate that MLL-CBP not only promotes proliferation but also alters gene expression patterns[233]. Furthermore, MOZ fuses with the nuclear receptor co-activator, TIF2 (transcription intermediary factor 2), to drive the conversion of committed myeloid progenitors into self-renewing leukemic stem cells that promote AML in mice[234; 235]. Chromosomal translocations also occur between MOZ and LEUTX (leucine twenty homeobox) genes in therapy-related AML[236], and MORF fuses with KANSL1 in retroperitoneal leiomyoma[237]. While a detailed functional understanding of many of these fusion proteins is lacking, it is predicted that translocations involving KATs have multiple potential effects on tumor development, including altered co-factor recruitment and enzymatic activity, resulting in KAT mistargeting and changes in the acetylation landscape of histone and non-histone proteins. For example, the MOZ-TIF2 fusion protein contains both the MYST domain of MOZ and the CBP interaction domain (CID) of TIF2. However, the KAT domain of MOZ is not required, but rather the C_2HC nucleosome recognition domain of MOZ and the CID of TIF2 are essential for transformation, suggesting that CBP constitutively co-activates MOZ target genes[235].

Numerous reports indicate KATs also function in the progression of solid tumors. In particular, p300 overexpression correlates with poor patient prognosis in prostate cancer, hepatocellular carcinoma and nasopharyngeal carcinoma, while increased cytoplasmic CBP and p300 levels are linked to melanoma progression and tumor size[112]. Given that CBP and p300 interact with a multitude of proteins, it is predicted that overexpression of these KATs impacts their protein binding selectivity. Hence, oncogenes may exploit this phenomenon to reorganize chromatin, and direct tumorigenic pathways. Moz and Morf have also recently been found in a pan-cancer analysis as being recurrently amplified across 11 cancer types[221]. Furthermore, Moz is required to drive Eμ-Myc lymphoma in mice[238], implying its

involvement in tumor initiation. Hbo1 expression is elevated in testicular, ovarian, bladder, stomach / esophageal as well as breast carcinomas[239; 240], and Hbo1 expression often anti-correlates with ERα (estrogen receptor α) levels due to Hbo1 KAT-specific destabilization of ERα in human breast tumors[241]. Moreover, Mof is commonly overexpressed in NSCLC[242; 243], where Mof both acetylates Nrf2 (nuclear factor erythroid-2-related factor 2) to promote nuclear retention and downstream transcription of Nrf2 target genes[242], as well as drives S-phase progression by directly activating Skp2 (S-phase kinase-associated protein 2) transcription[243].

Conclusions

It is clear that KATs play a central role in ESC maintenance and development. Comparatively, these enzymes differ in substrate specificity and complex formation, and hence control a variety of biological processes. Interestingly, these enzymes are also important regulators of reversing the more rigid states of differentiated cells, during both somatic cell reprogramming and tumor development. Distinct KATs directly control the expression of ESC-specific genes, which are commonly elevated in cancer. They acetylate non-histone proteins to drive pluripotency and tumorigenesis. Furthermore, KATs act as co-activators for multiple transcription factors, such as Myc, to drive changes in chromatin organization and ultimately cell state. Understanding these mechanisms offers new potential for anti-neoplastic interventions. For instance, cancer cells often become addicted to high levels of Myc, implying they may also be addicted to KAT activity. Given that KAT complexes harbor druggable domains, such as the KAT domain and bromodomain, targeting these complexes presents a novel therapeutic approach.

Based on the fact that KATs effectively promote cell plasticity, it is also conceivable that these enzymes mediate directed transdifferentiaiton pathways. Furthermore, KATs, may act in normal tissue homeostasis and injury response networks, where dedifferentiation drives mammalian progenitor cell production within the intestine, skin, lung and nervous system[164]. In the future, it will be interesting to see if KATs function in these pathways, and whether distinct KATs can be exploited to improve cellular transdifferentiaiton and tissue regeneration.

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Research Highlights

1. KATs play major roles in ESC maintenance and normal embryonic development
2. KATs coordinate chromatin reorganization during reprogramming and tumor development
3. Gcn5 and Myc activate an alternative splicing network essential for reprogramming
4. Mof mediates activation of the first wave of pluripotency genes during reprogramming
5. Multiple KATs are misregulated in various forms of cancer

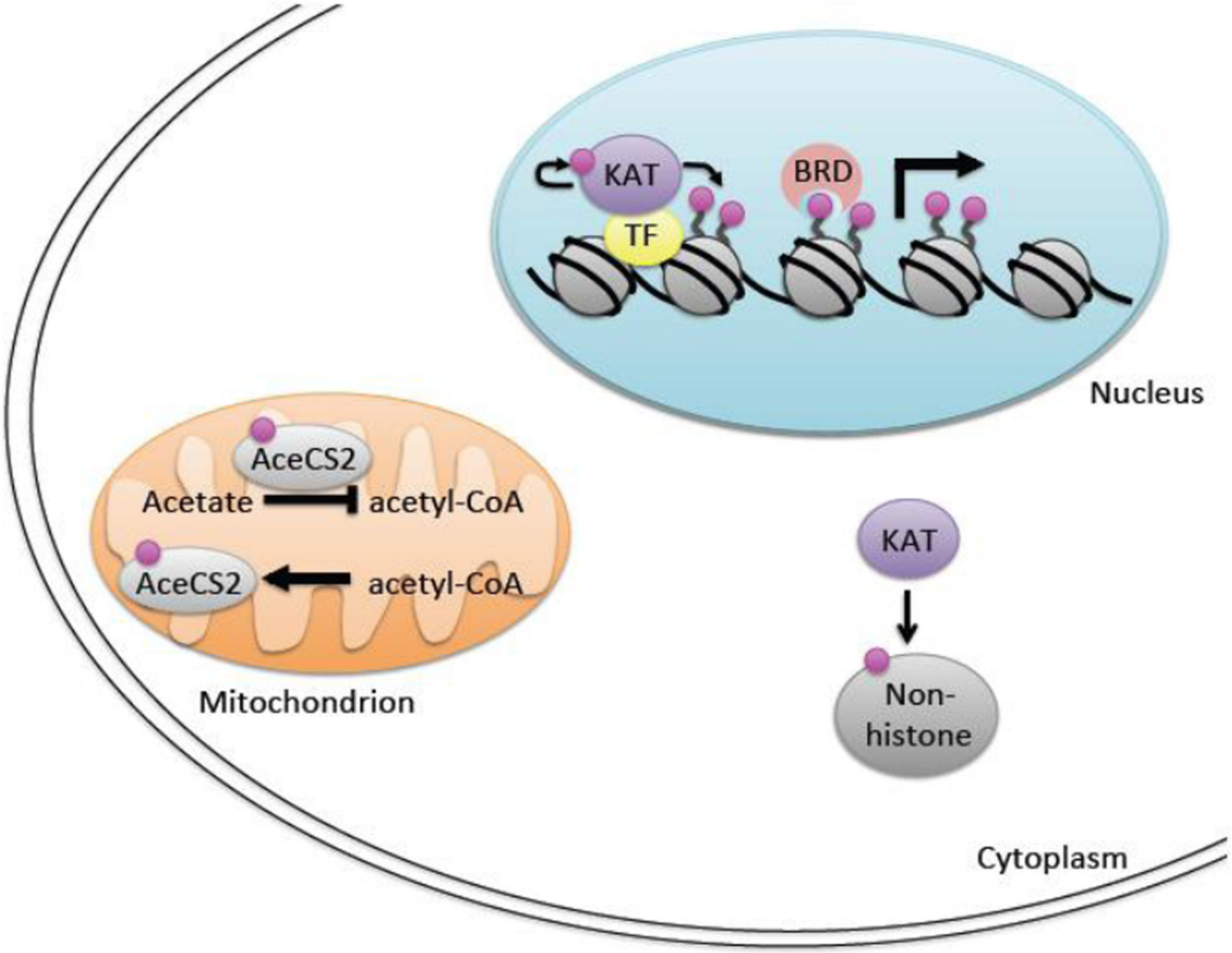

Figure 1.

Cellular lysine acetylation. Representative lysine acetylation events are displayed in the nucleus, cytoplasm, and mitochondria. Within the nucleus, KATs are recruited by transcription factors (TFs) to chromatin, where they acetylate surrounding histones and function to reduce chromatin compaction. Following acetylation, bromodomain-containing proteins (BRD) may interact with acetylated histones to further promote gene activation. In the cytoplasm, it is shown that KATs acetylate non-histone proteins. KAT-mediated non-histone acetylation further occurs in the nucleus and mitochondria. As an example, lysine acetylation of the Acetyl-CoA synthetase 2 enzyme (AceCS2) blocks acetyl-CoA production in mitochondria. Pink circle: acetylation.

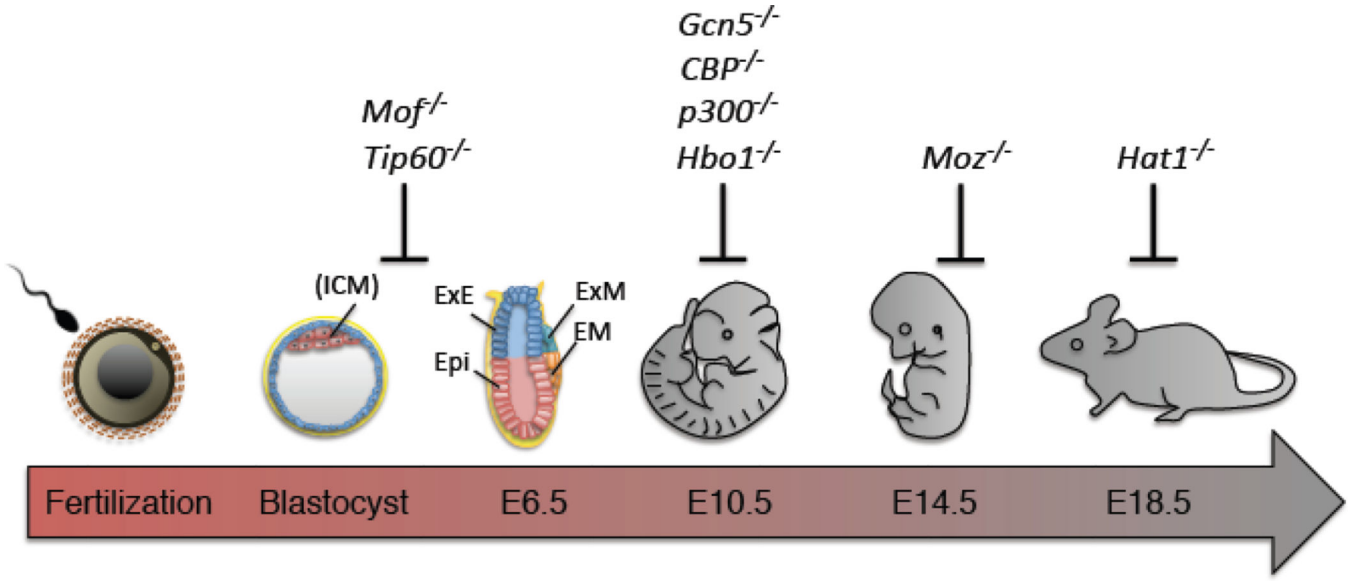

Figure 2.

The involvement of KATs in development. A timeline of mouse development is shown highlighting the points of embryonic lethality in different KAT null mouse lines. ICM: inner cell mass, Epi: Epiblast, ExE: extra-embryonic ectoderm, EM: embryonic mesoderm, ExM: extra-embryonic mesoderm.

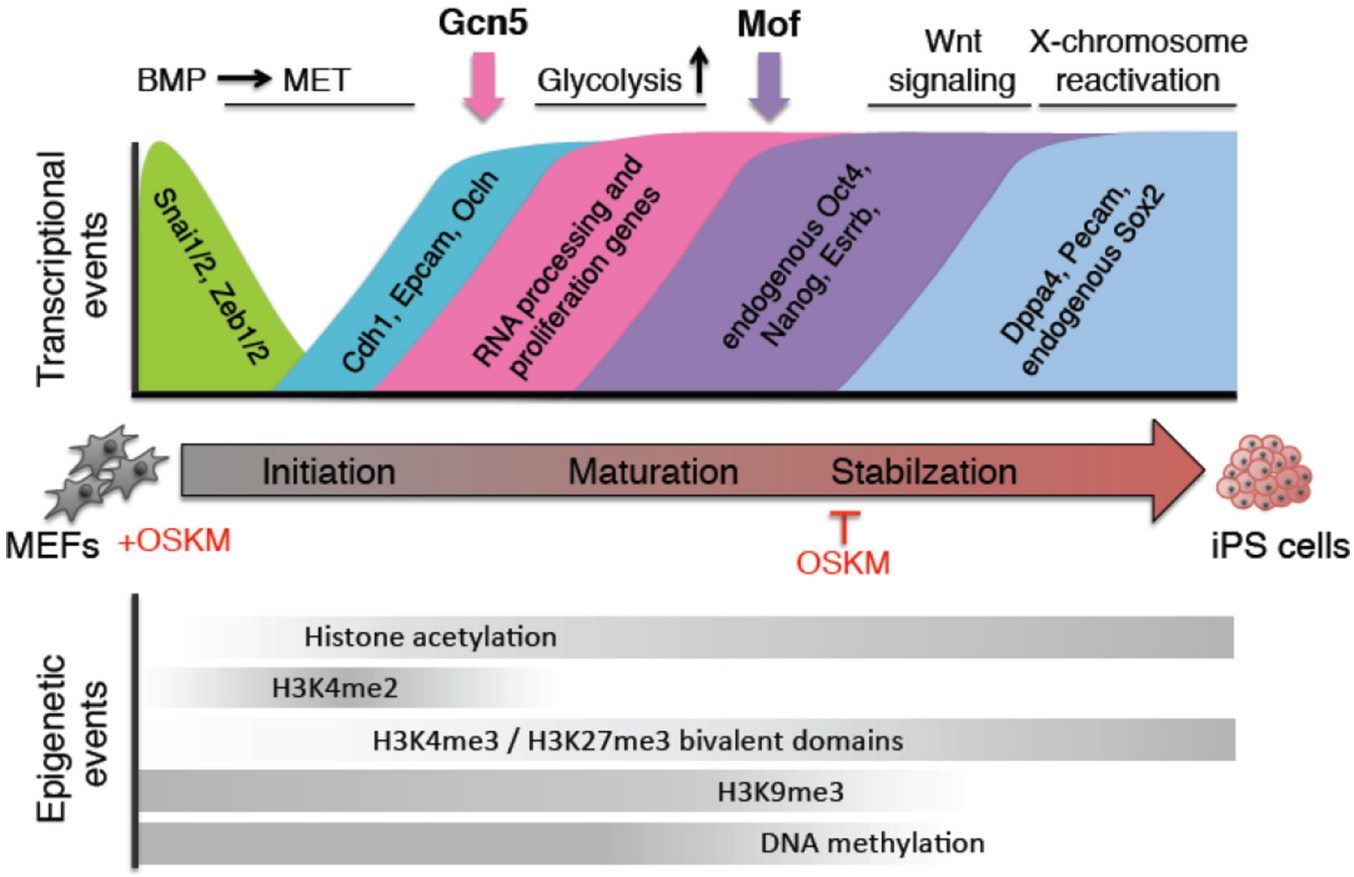

Figure 3.

Somatic cell reprogramming. The key transcriptional (top) and epigenetic events (bottom) are detailed across the initiation, maturation and stabilization phases of reprogramming. The involvement of Gcn5 and Mof is highlighted. MEF: mouse embryonic fibroblast, iPS: induced pluripotent stem cells, MET: mesenchymal-to-epithelial transition, OSKM: Oct4, Sox2, Klf4, Myc.

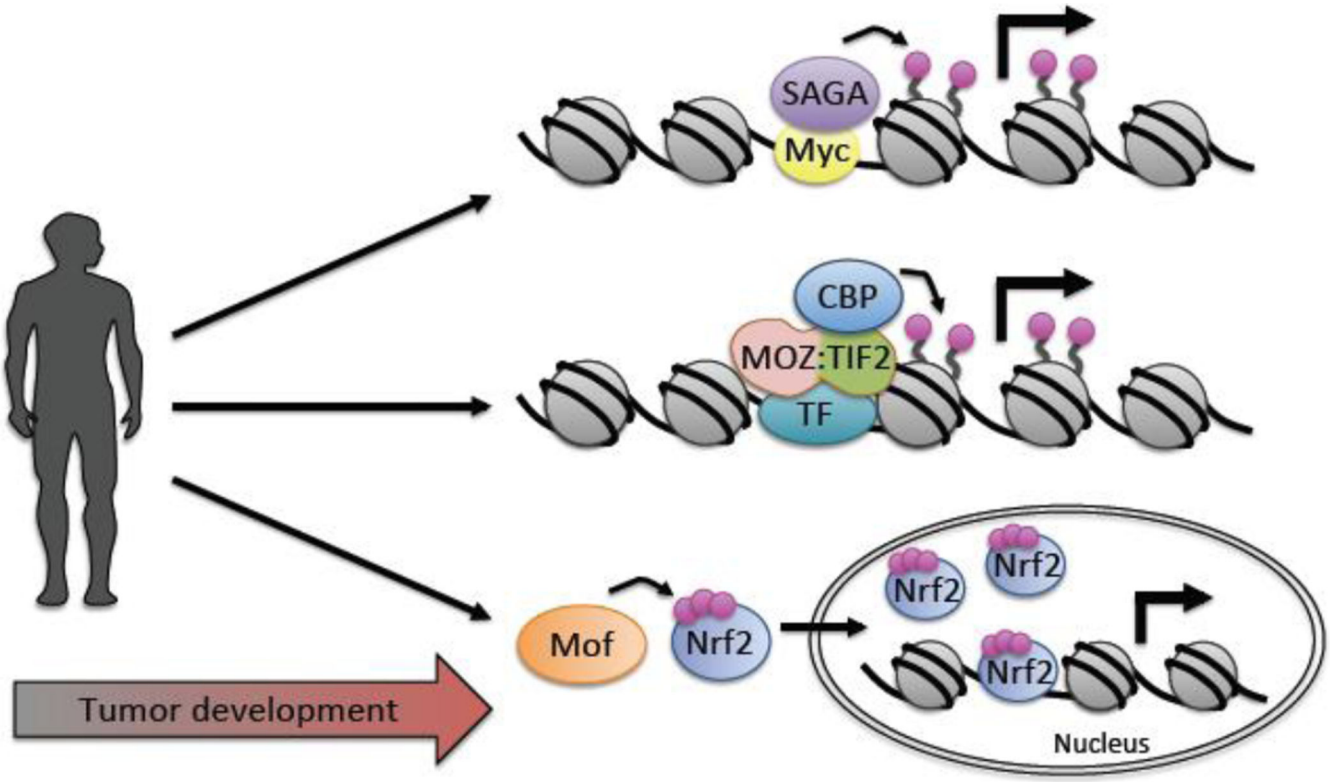

Figure 4.

The impact of KATs on tumorigenesis. Representative themes and examples of KAT involvement in tumor development are highlighted. Top. Functioning as co-activators, KATs promote transcriptional up-regulation of oncogene targets. Here, Myc recruits KAT co-activator complexes including SAGA (shown) and TIP60 (not shown) that drive histone acetylation and subsequent gene activation. Middle. KAT fusion proteins result in mistargeting of KAT activity. Here, the MOZ:TIF2 fusion protein triggers CBP recruitment and gene activation of Moz target genes. Bottom. KATs mediate non-histone acetylation. Here, Mof acetylates Nrf2 resulting in nuclear retention and activation of Nrf2 gene targets. Pink circle: acetylation.

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Table 1

Summary of KAT enzymes. The family, subcellular localization, multi-subunit complex name, substrates, and reported mouse phenotypes are listed for select lysine acetyltransferases.

Family	Name	Subcellular localization	Multi-subunit complex	Primary histone substrates and non-histone substrate examples	Mouse phenotypes	References
GNAT	Kat1 / Hat1	Nucleus / Cytoplasm	HAT-B / NuB4	free H4K5/K12	*Hat1*$^{-/-}$: die at birth	48, 104, 105, 108, 109
	Kat2a / Gcn5	Nucleus	SAGA / ATAC	H3K9/K14, Myc, C/EBPα	*Gcn5*$^{-/-}$: embryonic lethal (E8.5)	64–69, 71, 91, 92, 97
	Kat2b / Pcaf	Nucleus	SAGA / ATAC	H3K14, E2f1, Myc, Ezh2, Akt1, Acly, β-Catenin	*Pcaf*$^{-/-}$: viable with no reported embryonic phenotypes	64–69, 91, 92, 97
	Hat4 / Naa60	Golgi		free H4K20/K79/K91	Not determined	52
CBP/ p300	Kat3a / CBP	Nucleus / Cytoplasm		H3K18 / K27	*Cbp*$^{-/-}$: embryonic lethal E9.5-E10.5	97, 127, 128
	Kat3b / p300	Nucleus / Cytoplasm		H3K18 / K27	*p300*$^{-/-}$: embryonic lethal E9-E11.5	97, 127, 128
MYS T	Kat5 / Tip60	Nucleus / Cytoplasm	TIP60	H4K5/K8/K12, H2AK5, H2A.Z, H2A.X, p53, Atm	*Tip60*$^{-/-}$: embryonic lethal between E3.5-E7.5	135–137, 144
	Kat6a / Moz / Myst3	Nucleus	MOZ	H3K14, p53, Runx2	*Moz*$^{-/-}$: embryonic lethal around E15	155, 158, 159
	Kat6b / Morf / Myst4	Nucleus	MORF	H3K14, Runx2	*Morf*$^{gt/gt}$: viable / brain development defect	155, 161, 162
	Kat7 / Hbo1 / Myst2	Nucleus	HBO1	H3K14, H4K5/K8/K12	*Hbo1*$^{-/-}$: embryonic lethal E10.5	155–157, 163
	Kat8 / Mof / Myst1	Nucleus	NSL / MSL	H4K16, p53, Atm, Nrf2	*Mof*$^{-/-}$: embryonic lethal E4.5	148–150