Chapter 2
Role of Alteration/Deficiency in Activation (ADA) Complex in Cell Cycle, Genomic Instability and Cancer

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Abstract In eukaryotes, DNA wraps around histone proteins to form highly condensed chromatin structures that usually remain inert and inaccessible to proteins involved in DNA-related processes. Thus, multitudes of important DNA-related biological processes, including transcription, replication, DNA repair, apoptosis, chromosome condensation, and segregation, are dependent upon alteration of this chromatin structure so that proteins involved in these processes can access the DNA. This required change in chromatin structure is brought about by binding of various chromatin modifying proteins that loosen the chromatin by distinct mechanisms, one of which is covalent histone modification. Various histone post-translational modifications, specifically acetylation, play a major role in opening up of this highly condensed chromatin allowing access to proteins involved in the several important processes. Histone acetyl transferases (HATs) and histone deacetylases (HDACs) are important for maintaining a steady-state level of this particular post-translational modification in cells and are present in multi-subunit complexes. One such multi-subunit HAT complex is the alteration/deficiency in

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R. Kumar (ed.), *Nuclear Signaling Pathways and Targeting Transcription in Cancer*, Cancer Drug Discovery and Development, DOI 10.1007/978-1-4614-8039-6_2,

activation (ADA) complex, which was originally discovered in yeast and is now known to be also present in mammalian cells as part of much larger HAT complexes. In this chapter, we discuss various components of the ADA complex with a special focus on the adaptor proteins Ada3 and Ada2 (Ada2a and Ada2b) for their role in important physiological processes, such as the cell cycle, genomic integrity, DNA repair response, and in pathology such as cancer. Further, we discuss recent developments using various inhibitors to target the HAT enzymes and disrupt HAT complex function as an anti-cancer strategy.

Keywords Ada3 • Ada2 • HATs • Cell cycle • DNA repair • p53 • Nuclear receptors • Viral oncogenes • Cancer • HAT inhibitors

2.1 Introduction

Precisely regulated cell proliferation is essential for embryonic development as well as adult tissue homeostasis, and uncontrolled cell proliferation is a hallmark of cancer [1, 2]. Coordination of cell-cycle progression with chromosomal duplication maintains genomic stability, a critical cancer-associated trait [3]. Deregulated cell-cycle components have now also emerged as key biomarkers and therapeutic targets in cancer [4]. Thus, a better understanding of the cell-cycle machinery and its aberrations in cancer are of fundamental importance in cell and cancer biology. In eukaryotes, DNA is wrapped tightly around histone proteins to form chromatin that facilitates higher order folding of DNA [5]. This greatly limits the accessibility of DNA by various proteins involved in transcription, replication, cell division, and DNA repair [6, 7]. Post-translational modifications of histones play an important role in modifying the folding of chromatin and affect the functions involving chromatin [8]. Acetylation of histones is one of the most important and widely studied post translational modification and it has emerged as a conserved mechanism that is invariably altered in cancer [9, 10] as it plays key roles in chromatin assembly, accessibility to transcription and replication machineries, and genome stability (Fig. 2.1) [11]. Acetylation of histones loosens the chromatin structure allowing proteins involved in various processes to bind to DNA (Fig. 2.1) [8]. Steady-state levels of histone acetylation and its dynamic changes represent a balance between histone acetyl transferases (HATs) and histone deacetylases (HDACs) [12].

HATs usually function in multi-subunit complexes and are evolutionary conserved [13]. One such complex is the yeast alteration/deficiency in activation (ADA) complex that consists of the HAT general control non derepressible 5 (Gcn5, originally called Ada4), ADA HAT complex component 1 (Ahc1) and adaptor proteins Ada2 and Ada3 [14]. The ADA genes were initially discovered in yeast based on mutations in them conferring resistance to GAL4-VP16 toxicity [15–18]. These genes included *Ada1*/*Hfi1*, *Ada2*, *Ada3*, *Ada4* and *Ada5* (*Ada4* and *Ada5* are commonly referred to as *Gcn5* and *Spt20*, respectively). The ADA complex has been shown to act as a co-activator complex in yeast and is involved in transcription [19, 20].

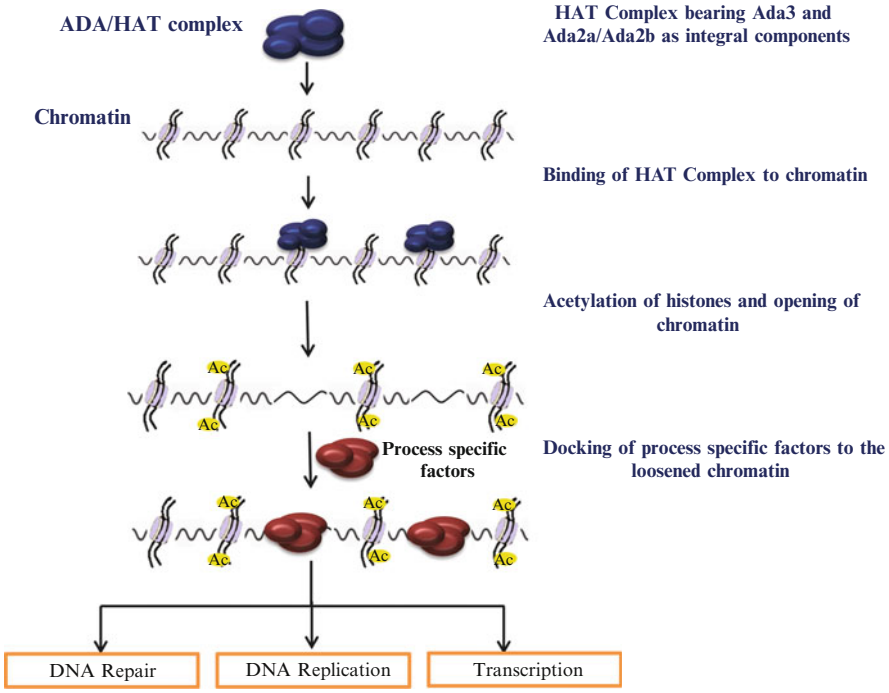

Fig. 2.1 A schematic model showing different cellular processes regulated by ADA complex or by HAT complexes, that contain Ada2a/Ada2b and Ada3 as core components, through histone acetylation and chromatin remodeling. ADA/HAT complex binds to chromatin at promoters/enhancers/DNA repair sites/origins of replication and aid in loosening up of chromatin by acetylating histones at the sites. This allows various factors involved in distinct processes such as transcription, DNA replication and DNA repair to have access to DNA and perform their functions

In addition to the ADA complex, Gcn5, Ada2 and Ada3 proteins are also a part of Spt-Ada-Gcn5 acetyltransferase (SAGA) and SAGA-like (SLIK) complexes in yeast [19–21]. These proteins and the ADA complex are highly conserved from yeast to mammals where they usually form a HAT module of large multi-functional complexes such as the Spt3/Taf9/Gcn5 acetyltransferase complex (STAGA) (human homolog of yeast SAGA complex), the Ada2a-containing complex (ATAC), and the TBP-free TAF complex (TFTC) [13, 22].

The mammalian cells are more complex and contain multiple HATs (e.g., p300, CREB-binding protein (CBP), p300/CBP-associated factor (PCAF), Tip60 and MOF) in addition to Gcn5. The mammals also contain adaptor proteins Ada3, and two different homolog proteins for yeast Ada2 – Ada2a and Ada2b – that, along with various HATs, form essential and functional module of several multi-subunit HAT complexes, as mentioned above [13, 23, 24]. Notably, *Ada2a* and *Ada2b* are two different homologs of the same yeast *Ada2* gene, and are present in separate complexes in higher eukaryotes; however, these two homologs are unable to complement each other functionally indicating that both have a distinct set of functions [25–27].

Although the main function of the ADA complex is in histone acetylation, the components of this complex have been shown to regulate functions of various non-histone proteins such as nuclear hormone receptors (e.g., estrogen receptor, retinoic acid receptor, retinoic X receptor, and androgen receptor), p53, c-myc, retinoblastoma protein (Rb), and various E2Fs [28–39]. As the role of various mammalian HAT proteins in various physiological and pathological processes is the focus of multiple reviews [11–13, 23], in this chapter we have kept our focus on Ada proteins, particularly focusing on Ada3 and Ada2 (Ada2a and Ada2b), as these adaptor proteins have been shown to be indispensible for the functions of various HATs. We will discuss their potential roles in cell cycle, genomic stability, and their disruption in pathology focusing on cancer. Given the current knowledge that adaptor proteins have no independent enzymatic function and only function as part of the HAT complex, we will also briefly discuss functions of various HATs as we go through reviewing functions of Ada2a, Ada2b, and Ada3. Lastly, as the therapeutic efficacy of relatively general HDAC inhibitors in cancers has recently gained importance [40], we will discuss current knowledge of various HAT inhibitors considering that it is likely that more-targeted agents to alter acetylation in cancer cells will provide improved anticancer strategies.

2.2 The ADA Complex, Histone Acetylation and Chromatin Remodeling

As mentioned earlier, histone acetylation plays a fundamental role in modeling of chromatin structures in order for proteins involved in important DNA-related processes to access the DNA. The primary function of the ADA complex has been shown to be transcriptional regulation of genes by modulating histone acetylation at gene promoters [19, 20]. Although yeast Gcn5 alone can acetylate free core histones in vitro, various studies in yeast have conclusively proven that Gcn5 requires both Ada2 and Ada3 for efficient acetylation of nucleosomes, both, in vitro and in vivo [19, 41, 42]. Thus, even though Ada2 and Ada3 do not possess intrinsic HAT activity, they are essential for acetylation of nucleosome histones by Gcn5. Accordingly, it has been shown that yeast Ada2, Ada3, and Gcn5 form a catalytic core of the ADA and SAGA HAT complexes, which is necessary and sufficient in vitro for nucleosomal HAT activity and lysine specificity of the intact HAT complexes [19, 42]. The yeast ADA complex has been shown to preferentially acetylate lysine residues 9, 14, and 18 (and to a lesser extent lysine 23) of histone H3; however, the yeast ADA complex is unable to acetylate histone H4 in vitro [42]. The authors further demonstrated that Ada2 enhances catalytic activity of Gcn5. Moreover, they demonstrated that Ada3 is necessary for Gcn5-dependent nucleosomal HAT activity in yeast extracts and is important for expanding the lysine specificity of the ADA complex [42]. Similar to yeast, studies with mammalian Gcn5, Ada2b (present in STAGA complex), and Ada3 proteins have shown that these proteins can form a heterotrimer in vitro and can efficiently acetylate nucleosomal

arrays [43]. Unlike yeast proteins, neither Ada2b nor Ada3 was demonstrated to enhance the acetylation of free-core histones by mammalian Gcn5 in vitro. However; efficient acetylation of chromatin by Gcn5 was shown to require both Ada2b and Ada3 [43]. Interestingly, unlike Ada2b, the Ada2a homolog of the yeast Ada2 was unable to facilitate acetylation of nucleosomal histone H3 in HAT assays in vitro, even though it could form a complex with Gcn5 and Ada3 both in vitro and in vivo [43]. Similar to earlier reports in *Drosophila*, the authors convincingly demonstrated that Ada2a and Ada2b have non-redundant functional roles in mammalian cells. Contrary to this report, which indicated that the mammalian Ada3 protein is unable to enhance HAT activity of Gcn5 on free core histones in vitro, a recent report from our laboratory demonstrated that mammalian Ada3 is able to enhance HAT activity of p300 even on free core histones [44].

Similar to important roles of these proteins in vitro for histone acetylation, several studies have shown that these proteins are important for histone acetylation in vivo. In yeast, it has been shown that depletion of Ada3 or Ada2 drastically affects the histone acetylation in vivo in cells and this has been linked to defects in replication and DNA damage repair in yeast cells (see later sections). Furthermore, *Drosophila* null for *Ada2b*, had reduced H3K9 and H3K14 acetylation during development; however, *Ada2a* deletion did not have any effect on acetylation of these residues [27]. Although, deletion of either *Ada2a* or *Ada2b* was lethal for *Drosophila* development, both proteins were shown to have non-redundant functions in *Drosophila*. Similarly, a later study demonstrated requirement of Ada3 for viability of *Drosophila* embryos [45]. These *dAda3* mutants were shown to be defective in histone acetylation at H3 K9, H3 K14, and H4 K12, whereas there were no defects observed in acetylation of H3 K18 or H4 K5, K8, or K16. These defects in histone acetylation were shown to affect the position effect variegation at certain loci and in the transcription of specific genes. Additionally, we recently demonstrated that depletion of Ada3 from mammalian cells results in drastic down-regulation of histone acetylation at various lysine residues such as H2A K5, H2B K5, H3 K9, H3 K56, and H4 K8 [44]. This dramatic down-regulation in various histone acetylations underscores the important role of the ADA complex in histone acetylation.

In order for appropriate proteins to bind DNA and carry out their function, the process of histone acetylation routinely needs to be coupled with chromatin remodeling, which occurs by nucleosome sliding leading to removal of nucleosomes at promoter regions or at DNA damage sites [46, 47]. The chromatin remodeling complex SWItch/Sucrose Non Fermentable (SWI/SNF) is an important complex that has been shown to be involved in nucleosome sliding [46, 47]. Interestingly, this complex has been shown to work in concert with HAT complexes at promoters of various genes and has been shown to be involved in gene activation [48]. More importantly, the recruitment of SWI/SNF complex onto various promoters is believed to be dependent on acetylation of nucleosomal histones by the SAGA complex [49]. Acetylated histones form a prerequisite for the recruitment of SWI/SNF complex through bromo domains present in Swi2/Snf2 [50]. Consistent with this observation, it has been shown that the SWI/SNF complex is capable of efficiently displacing

nucleosomes from chromatin that are specifically acetylated by SAGA complex compared to nucleosomes that are not acetylated [51]. Additionally, it has been shown that yeast Gcn5 directly regulates the binding of SWI/SNF complex to chromatin, through acetylation of Snf2 component of SWI/SNF complex [52]. Snf2 acetylation by Gcn5 results in the dissociation of SWI/SNF complex from acetylated histones, thus inhibiting SWI/SNF complex function [52]. Furthermore, the ATAC HAT complex in *Drosophila* has been shown to stimulate nucleosome sliding by stimulating the ISWI, SWI/SNF, and RSC chromatin remodeling complexes [53]. These findings highlight a fundamental and functional link between histone acetylating complexes and complexes involved in chromatin remodeling and also underline the importance of HAT complexes in chromatin remodeling as histone acetylation acts as a pre-requisite for chromatin modeling through nucleosome sliding.

2.3 The ADA Complex Functions as a Co-activator for Nuclear Hormone Receptor-Mediated Transcription

The ability of nuclear hormone receptors (NR) to up-regulate or down-regulate the target gene expression is determined by their association with cofactors that may fall under the category of co-activator or co-repressor [54]. When bound to a co-activator, nuclear receptors up-regulate the gene expression whereas binding of a co-repressor leads to the down-regulation of target gene expression. Over the past two decades a number of co-activators have been studied extensively by different laboratories and an important class of co-activators was identified as steroid receptor co-activators (SRC-1, -2 and -3) by Bert O'Malley's group [55]. X-ray crystallography studies have demonstrated that a typical co-activator contains α helical LXXLL binding motif (where L is leucine and X is any amino acid) referred to as NR box through which it binds to a groove on the surface of ligand binding domain of nuclear receptor [56, 57]. In addition to SRCs, several novel nuclear receptor co-regulators, such as BCAS3, PELP1, and DLC1, have also been identified and characterized [58].

In regard to the role of the ADA complex in NR activation, initial observations that the ADA complex plays a role in NR-mediated transcription came from yeast Ada3 (yAda3) [59]. Though yeasts do not have NRs, the yAda3 protein was found to be associated with exogenously expressed NRs. In this context, it was shown that the ADA complex is required for the transactivation function of the glucocorticoid receptor (GR) [59]. The investigators further demonstrated that deletion of any of the components of the ADA complex reduces the activity of the GR responsive-lacZ reporter compared to the wild type. Notably, deletion of *Ada3* was found to cause a greater reduction in this activity than deletion of either *Ada2* or *Gcn5* alone [59]. Furthermore, Ada2 was shown to enhance the activity of the GR responsive reporter in mammalian cells [59].

The yAda3 also interacts with other NRs such as ERα, RXRα, and TRα, but not with RARα [60]. Reporter assays in yeast have demonstrated that yAda3 potentiates

the AF-2 activity of ERα and RXRα when overexpressed in yeast and mammalian cells [60]. The authors further showed that, other subunits of the ADA complex, Ada2 and Gcn5, are also required for ERα- and RXRα-mediated transactivation [60]. Subsequently, our laboratory demonstrated that mammalian Ada3 interacts with ERα and RXRα and augments their transactivation and increases the levels of target gene expression [29–31]. More importantly, shRNA-mediated knockdown of *Ada3* significantly down-regulated estrogen-responsive genes and as a result suppressed ER-mediated cell proliferation, thus supporting an important role of co-activators in the NR-mediated functions [29, 30]. Subsequently, other investigators performed mutational analyses of Ada3, and observed that similar to classical NR co-activator, Ada3 binds to RAR through its LXXLL motifs [32]. In summary, these studies provide significant evidence that Ada3 functions as a co-activator in NR signaling.

2.4 Interaction of the ADA Complex with Non-Nuclear Hormone Receptor Proteins

The p53 protein is a tumor suppressor protein that transactivates stress responsive genes and regulates the cell cycle in response to DNA damage [61]. The activation domain of p53 possesses notable similarity with the activation domain of other transcriptional activators such as the activator of herpes simplex virus, VP16 [61]. Like other transcription factors, VP16 also requires co-activators for its activity, and, in yeast, the requirement of the ADA complex was first shown for VP16 transactivation [15, 16, 62]. The similarity of the p53 activation domain sequence with the activation domain of VP16 and the requirement of the ADA complex for its activator function generated the rationale to study the interaction of ADA components with p53 [63]. Investigators identified two activation subdomains (ASD-1, -2) in the p53 amino-terminus that require yeast adaptor complex Ada2/Ada3/Gcn5 for transcriptional activation [63]. ASD-1 was less dependent on the ADA complex than ASD2, and Ada3 was the most critical component in the complex for the function of p53 [63]. Subsequently, work from our laboratory, and that of other laboratories, demonstrated a direct interaction of Ada3 with p53 and its function as a co-activator for p53-mediated transactivation [34, 35, 64].

Full transcriptional activation of p53 requires its C-terminal acetylation by p300/CBP and PCAF [65, 66], and we subsequently demonstrated that Ada3 recruits p300 to acetylate p53 and regulates its transcriptional activity [35]. In this context, shRNA-mediated knockdown of Ada3 dramatically down-regulated p53 target genes. Most importantly, loss of Ada3 led to inhibition of DNA damage-induced p53 acetylation and cell-cycle arrest [35]. Subsequently, another group delineated the role of Ada2 in the function of p53 [67]. Using chromatin immunoprecipitation assay, the authors demonstrated that Ada2b, but not Ada2a, gets recruited to the p53 response element on promoters of target genes [67]. Indeed, the study revealed that Ada2a and Ada2b function in a non-redundant manner and only Ada2b is found to be the component of STAGA complex in humans [67].

In addition to NRs and p53, Ada3 also interacts with IL-1α and β-catenin [36, 68]. Typically IL-1α mediates its action in a secreted form. However, a proteolytic maturation product of IL-1α, known as IL-1α N-terminal peptide (IL-1NTP) found in the nucleus, acts as a transcription factor and is involved in variety of cellular processes such as control of cell proliferation and apoptosis [69]. A study performed in yeast and mammalian systems delineated the interaction of IL-1NTP with p300, PCAF, Gcn5, and Ada3 [68]. In yeast, the fusion protein Gal4BD/IL-1NTP was found to have a growth inhibitory effect that requires an intact SAGA complex [68]. More importantly, deletion of any of the components of SAGA complex was found to completely attenuate the suppressive effect, confirming the necessity of an intact SAGA complex for the action of IL-1NTP [68]. In the mammalian system, IL-1NTP was found to interact with p300, PCAF, Gcn5, and Ada3, and eventually integrate into the p300-PCAF complex, thus enhancing the transcriptional activation of this complex [68].

The role of the ADA complex in the activation of β-catenin, which is involved in developmental processes through the Wnt pathway, has also been demonstrated [36]. The Wnt pathway is crucial for development and proliferation, and abrogation of this pathway is linked to cancer development. Both Ada2a and Ada3 have been shown to interact directly with β-catenin and mediate its acetylation [36]. As a consequence, Ada2a and Ada3 regulate the target gene expression of β-catenin. Also, reduced levels of these proteins lead to repression in β-catenin-dependent cell proliferation [36]. Further studies in this context are warranted to conclusively address the role of the ADA complex in the Wnt-β-catenin pathway.

2.5 The ADA Complex and Cell Cycle

The eukaryotic cell cycle consists of the following four phases: G1, S, G2, and M [70]. During the G1 phase, cells accumulate nutrients, grow, and duplicate various cell organelles, except chromosomes, which occurs later [70]. Before entering the S phase, cells examine their size, determine the availability of appropriate nutrients and growth factors, and ensure that there is no DNA damage [70]. The process of DNA replication occurs during the S phase, and it provides a means for duplication of genetic material that can then be equally segregated into daughter cells during the process of mitosis [70]. The eukaryotic cell-cycle progression thus depends on proper coordination of DNA replication and segregation of duplicated chromosomes to daughter cells, a process precisely regulated by modification of chromatin that allows accessibility to factors involved in these processes. Thus, the HAT complexes involved in modulating the structure of chromatin, as mentioned earlier, play an important role in the cell-cycle progression. Consistent with this, various ADA complex components have been shown to play indispensible roles in various phases of cell cycle.

Recently, our laboratory demonstrated an important role of Ada3 in the G1-S phase transition as well as in mitotic progression of cell cycle [44]. To elucidate the physiological function of Ada3, we generated a conditional knockout mouse for the *Ada3* gene. We observed homozygous $Ada3^{FL/FL}$ mice were viable, fertile, and

exhibited no gross abnormalities compared to *Ada3*$^{FL/+}$ or *Ada3*$^{+/+}$ controls, whereas Ada3$^{-/-}$ mice were lethal at E3.5 stage [44]. The failure of *Ada3*$^{-/-}$ embryos to remain viable beyond E3.5 suggested a potential role of Ada3 in cell proliferation because extensive cellular proliferation occurs during this early stage of embryogenesis.

Subsequently, by using *Ada3* deletion in *Ada3*$^{FL/FL}$ mouse embryonic fibroblasts (MEFs) we showed that Ada3 is required for efficient cell-cycle progression through the G1 to S phase transition as well as for proper mitosis [44]. Detailed analyses in this system revealed that an Ada3-c-myc-Skp2-p27 axis controls the progression of the G1 phase to the S phase and partly contributes to cell-cycle delay upon deletion of *Ada3* [44]. Microarray analysis showed that loss of *Ada3* resulted in several changes in gene expression that were involved in mitosis [44]. Consistent with this, *Ada3* deletion led to severe mitotic defects and formation of multi-nucleated cells. Also, the transition from the G2/M phase to the G1 phase was delayed upon deletion of *Ada3* [44]. Thus, Ada3, a core component of the ADA complex, is important in G1 phase as well as in mitosis during the cell-cycle progression.

Another group also showed a role of the ATAC complex in mitosis [71], where knockdown of ATAC complex components, such as *Ada2a* and *Ada3*, led to severe mitotic defects. These defects included centrosome multiplication, defective spindle and midbody formation, generation of binucleated cells, and a slow transition from G2/M to G1 phase [71]. The mitotic defects were attributed to the inefficient acetylation of the Cyclin A/Cdk2 complex by Gcn5 due to knockdown of *Ada3* or *Ada2a* [71]. Similar to mammalian *Ada3*, deletion of *Ada3* as well as *Gcn5* in flies leads to defective H3S10 phosphorylation, an event that marks the initiation of mitosis. This suggests a role of the ADA complex in the process of mitosis in flies as well as mammals [45].

Several reports have shown the role of the ADA complex component Gcn5 in replication, which is consistent with the important role of histone acetylation in DNA replication. In yeast, it was shown that Gcn5 is required for replication-coupled nucleosome assembly [72]. *Gcn5* deletion mutants in yeast showed a reduced level of H3K56 acetylation, a mark linked to replication-coupled nucleosome assembly in yeast [72]. Similar to Gcn5, deletion mutants of *Ada3* and *Ada2* showed defects in replication suggesting an important role of these components in the replication process [72]. In mammals, Gcn5 has also been shown to play an important role in the process of replication by controlling the acetylation of Cdc6, an important replication licensing factor [73]. Although, the role of other ADA complex components in replication needs to be explored extensively, these initial reports show promising results for a role of the ADA complex in replication. Taken together, these studies unequivocally support a critical role of the ADA complex in cell-cycle progression.

2.6 Role of the ADA Complex in DNA Damage Response

In addition to metabolic and transcriptional processes, the chromatin structure plays an important role in the DNA damage response (DDR) process. The DDR is manifested by assembly of DNA damage repair proteins at the site of damage [74].

Histone modifying enzymes such as HATs along with ATP-dependent chromatin remodeling complexes allow these DNA damage proteins to access DNA at the damage sites [74]. In the context of DDR, the role of Gcn5 and Ada2 has been elucidated [75]. This study focused the role of Gcn5 and Ada2 in nucleotide excision repair of yeast *MET16*, a gene regulated by these two components of the SAGA/ADA complex [75]. The role of Gcn5 and Ada2 in nucleotide excision repair was revealed by the finding that deletion of either *Ada2* or *Gcn5* delays the cyclobutane pyrimidine dimer removal on the *MET16* locus [75]. In another study, investigators showed that the STAGA complex interacts with UV-damaged-DNA binding factors DDB1 and DDB2 and this interaction facilitates the recruitment of nucleotide excision repair machinery through HAT activity of Gcn5 [76]. Furthermore, another role of STAGA complex in p53-dependent gene activation through Gcn5 and its recruitment on *p21* and *GADD45* promoters upon UV damage was shown [67]. Besides STAGA, the TFTC HAT complex is also reported to have an important role in DDR [77]. Researchers identified SPT130 as an integral subunit of the TFTC complex. Interestingly, SPT130 possesses homology with the UV-damaged DNA binding factor [77]. Given the presence of SPT130 in TFTC, the investigators found that TFTC is recruited on UV-damaged DNA and brings about the acetylation of histone H3 on the UV-damaged site, clearly suggesting a role of TFTC in DDR [77]. The role of p300 in DDR is also documented where it has been shown to stabilize and transactivate p53 in response to DNA damage [78]. Other HATs, such as MOF, acetylate H4 K16 and mediate the recruitment of repair proteins, such as Mdc1, 53BP1, and Brca1, upon ionizing radiation-induced DNA damage [79]. Similarly, Tip60 also acetylates core histones, and inactive Tip60 has been found to be associated with late double strand breaks [80–82].

Although a fairly good number of studies have delineated the role of various HATs in DDR, the role of the ADA complex per se had not been studied until recently. We demonstrated that loss of *Ada3* leads to dramatic genomic instability as seen by various chromosomal aberrations, which were further enhanced upon DNA damage [83]. Loss of *Ada3* led to an increase in the levels of DDR proteins, such as pATM, p53BP1, pRAD51, and γH2AX [83]. Significantly, *Ada3*-null cells exhibited a delay in the disappearance of the DNA damage foci for γH2AX, 53BP1, and CtIP after ionizing radiation, suggesting the important role of Ada3 in DDR [83]. Together these findings reveal a new role of Ada3 in the DNA repair process and maintenance of genomic stability and warrant further research to determine if other components of the ADA complex also regulate genomic stability and repair foci disappearance.

2.7 The ADA Complex and Cancer

As described above, components of the ADA complex are fundamental in the cell-cycle progression, regulation of various transcriptional factors, and in maintaining genomic stability. Not surprisingly, several of the components of the ADA complex are hijacked by viruses and are known to interact with viral onco-proteins, such as

human papilloma virus 16 (HPV16) E6, simian virus 40 (SV40) large T, or adenoviral protein E1A, thus linking the ADA complex to oncogenesis [64, 84–91].

Our laboratory identified human Ada3 as a HPV16-E6-binding protein [64]; importantly, HPV16 is the most common HPV associated with human cancers. Significantly, Ada3 bound to immortalization-competent E6 mutants, and also to mutants that were incapable of binding to p53 [64]. We further demonstrated that E6 targets Ada3 for degradation, thus abrogating the function of p53 through an alternate pathway [64]. Subsequently, other investigators showed that degradation of Ada3 by E6 abrogated p14ARF-p53-mediated senescence pathway and led to E6-induced immortalization [92]. Further, p300/CBP have been shown to be associated with HPV16 E6/E7, adenoviral E1A, as well as SV40 large T antigen [84–88]. Also, the yeast SAGA complex has been shown to be important in adenoviral E1A induced growth inhibition [89, 90]. Recently, the HAT Gcn5 was shown to functionally interact with the adenoviral E1A protein [91]. Together, these studies underscore the important role of the ADA complex in viral oncogenesis.

Moreover, functions of several important cellular oncogenes (e.g., c-myc, E2Fs) and/or tumor suppressors (e.g., p53 [see above], Rb, BRCA1) have been shown to be regulated by various HATs and HAT complexes [37–39, 93–98]. c-myc oncogene was shown to be associated with TRRAP, a subunit of the Ada2b and Ada3 containing mammalian STAGA complex [93]. Upon mitogenic stimulation, c-myc, a sequence specific transcription factor, was shown to induce histone acetylation at its target gene promoters through recruitment of TRRAP [93]. More importantly, the C-terminal ATM-related domain of TRRAP has been shown to be required for c-myc driven transformation [94]. Furthermore, another study demonstrated that c-myc recruits TRRAP as well as Gcn5, by interacting with the STAGA HAT complex [95]. Both TRRAP and Gcn5 were shown to enhance the transcriptional activation of c-myc through its N-terminal activation/transformation domain [95]. Accordingly, an N-terminal deletion mutant of c-myc was unable to bind to STAGA complex and showed reduced transcription activation potential [95]. Interestingly, a similar naturally occurring truncated form of c-myc has been shown to be deficient in transforming primary cells [96]. These studies reveal an essential role of the STAGA HAT complex in c-myc induced oncogenic transformation.

E2F family of transcription factors regulate several cell cycle associated genes and have been shown to be regulated by various HATs [38, 39]. Two independent studies demonstrated that PCAF, p300 and CBP HATs bind to and acetylate E2F-1, -2 and -3 [38, 39]. This reversible acetylation of E2Fs by various HATs was shown to enhance their stability and increase their DNA binding ability as well as transactivation potential [38, 39]. Furthermore, transactivation domains of E2F1 and E2F4 were shown to directly bind and recruit Gcn5 and TRRAP, most likely as subunits of HAT complexes [97]. This study suggests that E2F transcription factors stimulate their transcriptional activation by recruiting the HAT complex components TRRAP and Gcn5, thus providing a mechanism to relieve the transcriptional repression at E2F target gene promoters [97]. Similar to E2Fs, p300 and PCAF have been shown to acetylate and regulate the function of the important cell-cycle regulator and tumor suppressor retinoblastoma (Rb) protein [37, 98]. This acetylation event has also

been shown to be essential in nuclear localization of Rb and plays an important role in cellular differentiation. Thus, de-regulation of these HATs could potentially disrupt the function of Rb and contribute to oncogenesis. Additionally, the tumor suppressor BRCA1 has been shown to bind Gcn5 and TRRAP-containing HAT complexes [99]. This interaction has been shown to be indispensible for BRCA-1 mediated transcriptional regulation as well DNA repair. These studies emphasize an essential role of HAT complexes in regulating various functions of important cellular oncogenes as well as tumor suppressors.

p300 and CBP HATs have also been shown to be involved in leukemogenesis [100]. Somatic mutations of p300 and CBP have been reported in hematological malignancies [100]. These mutations include translocations of p300 and CBP genes that result in their fusion with the monocytic leukemia zinc finger (MOZ) gene or with the mixed lineage leukemia (MLL) gene [100]. These translocations lead to the formation of MOZ-p300/CBP or MLL-p300/CBP fusion proteins that can have aberrant loss-of-function or gain-of-function properties and can play an important role in cellular transformation [100]. Also, germline mutation of CBP causes Rubinstein-Taybi syndrome, a condition that predisposes its patients to cancer [101, 102]. Interestingly, recent reports from two different laboratories show that high expression of p300 in hepatocellular carcinoma correlates with poor survival and aggressive features in HCC, such as epithelial to mesenchymal transitions [103, 104]. Although further investigation is required in this area of research, the above observations highlight the importance of HAT complex components in the regulation of oncogenesis.

Our previous findings demonstrated Ada3 is a critical component of HAT complexes that regulate ER function [30]. These findings and the observations that overexpression of other ER co-activators, such as SRC-3 predicts clinical outcomes in breast cancer patients [105, 106], prompted us to examine potential significance of Ada3 expression/localization in human breast cancer patients [107]. Using immunohistochemical analysis of Ada3 expression in breast cancer tissue specimens from a large cohort of patients with known clinico pathological parameters and survival data, we reported that predominant nuclear Ada3 expression correlated with ER expression and predicted a favorable clinical outcome while predominant Ada3 expression in the cytoplasm correlated with ErbB2/EGFR expression and poor patient survival. These studies suggest an important role of Ada3 in breast cancer progression. Further studies are needed to examine the molecular mechanism of differential localization of Ada3 (and other components of the ADA complex) in the promotion of breast oncogenesis.

2.8 New Emerging Functions of the ADA Complex

In the previous sections of the chapter, we discussed well documented functions of the ADA complex. However, several laboratories have recently demonstrated an important role of the ADA complex and its components in endoplasmic reticulum stress. Endoplasmic reticulum is a cellular organelle that is involved in proper

folding and post-translational modifications of secretory and transmembrane proteins and thus houses many chaperone proteins [108, 109]. Interestingly, endoplasmic reticulum has also been shown to act as a sensor of cellular stress [108]. Various forms of cellular stress cause an increase in the demand for protein folding, challenging the capacity of chaperones present in the endoplasmic reticulum [110–112]. This leads to accumulation of unfolded and misfolded proteins in the endoplasmic reticulum lumen that causes cells to initialize a cascade of signaling events which are collectively called the unfolded-protein response (UPR) [110–112]. Three distinct endoplasmic reticulum localized transmembrane protein sensors, inositol requiring 1α (IRE1 α), double-stranded RNA-dependent protein kinase (PKR)-like ER kinase (PERK) and activating transcription factor 6 (ATF6) initiate three different UPR signaling cascades in the cells [110–112]. The ADA complex and its components have been shown to be involved in at least two of the three UPR signaling cascades [113–117]. In this context, it was first shown in yeast that Gcn5 interacts with Ire1 protein kinase and that ADA complex is specifically required for UPR but not for heat shock protein response [113]. The authors proposed that Ire1 activation recruits the ADA complex specifically to the promoters of the genes involved in UPR [113]. In a follow-up study, the authors demonstrated that ADA complex components Gcn5, Ada2, Ada3 and Ada5 interact with Ire1 and HacI [114]. HacI is a transcription factor that is required for UPR and its translation is regulated by Ire1 [111]. HacI is constitutively expressed; however, its mRNA is not efficiently translated [111]. Activation of Ire1 leads to formation of a new processed form of HacI mRNA that gets efficiently translated and induces UPR [111]. The authors showed that the transcriptional activation of endoplasmic reticulum stress related genes was reduced upon deletion of *Gcn5*, *Ada2* or *Ada3*, whereas deletion of *Ada5* (Spt20) completely abrogated the transcriptional activation [114]. The same group further demonstrated that Ada5 is essential for Ire1 dependent processing of HacI mRNA in vivo, thus proving an important role of ADA complex components in the UPR in yeast [115]. Similar to yeast, it was shown that mammalian SAGA complex plays an important role in endoplasmic reticulum stress related genes [116]. The authors demonstrated that mammalian Spt20, like its yeast counterpart, was indeed a subunit of the SAGA complex [116]. By chromatin immunoprecipitation studies, the authors showed that Spt20 and other SAGA complex components are recruited onto the endoplasmic reticulum stress response genes and knockdown of Spt20 abrogates the endoplasmic reticulum stress response [116]. Again, similar to yeast, the recruitment of Spt20 was shown to be specific to endoplasmic reticulum response genes but not to other stresses [116]. Furthermore, in a recent study it was shown by multidimensional protein identification technology (MudPIT), that mammalian ATF6 transcription factor recruits the SAGA and ATAC complexes onto the endoplasmic reticulum stress response enhancer elements present on endoplasmic reticulum stress response genes and thus are involved in controlling the transcription of these genes [117]. Taken together, these studies point towards a potential role of the ADA complex and its components in UPR.

Further, the STAGA HAT complex has been shown to interact with spliceosome-associated protein 130 (SAP130), a component of the SF3b splicing factor [76].

SF3b gets recruited to pre-spliceosomal complexes in association with U2 snRNP. This points to an important role of STAGA complex in mRNA splicing [76]; however, further studies are required to provide more insights into this function. Another phenomenal study in yeast revealed the role of the SAGA complex and its components Ada2 and Sus1 in tethering of transcriptionally active genes to the nuclear envelope [118]. It has been known that certain genes come closer to the nuclear periphery upon their transcriptional activation. In this study, the authors demonstrated that yeast SAGA complex components Ada2 and Sus1 are involved in confinement of active *GAL* reporter genes to the nuclear periphery [118]. Ada2 and Sus1 achieve this by physically linking the active *GAL* genes to the nuclear pore complex component, Nup1 [118]. Accordingly, deletion of *Ada2* or *Nup1* was shown to abrogate this confinement of *GAL* genes to nuclear periphery [118] suggesting an important role of the SAGA complex in regulating transcription of genes by a novel mechanism of nuclear periphery tethering.

Recent evidence demonstrates mammalian Gcn5 and SAGA complex to be involved in telomere maintenance by controlling the ubiquitination of a component of the shelterin protein complex [119]. Shelterin is a multi-subunit protein complex involved in structural maintenance of telomeres [120]. The authors show that *Gcn5* deletion leads to telomere dysfunction in mammalian cells [119]. This phenomenon was shown to be dependent upon the deubiquitination module of the SAGA complex [119]. The authors demonstrated that the SAGA complex component, ubiquitin-specific protease 22 (Usp22), is involved in deubiquitinating TRF1 (a shelterin complex component) and thus plays an important role in controlling the stability of TRF1 [119]. Interestingly, Gcn5 was shown to be required for association of the Usp22 deubiquitinating module to the SAGA complex and is thus, involved in the maintenance of proper telomere structure through TRF1 [119]. These studies demonstrate the role of the ADA complex components in various important cellular processes and suggest further studies must be carried out to gain more insights into role of the ADA complex components in maintaining genomic integrity.

2.9 The ADA Complex and HAT Inhibitors

As discussed above, acetylation of histones and other proteins plays an important role in a variety of physiological processes in cells, and deregulation of the proteins that regulate acetylation leads to oncogenesis. Consistent with this idea, various laboratories have focused on discovering new synthetic or natural drugs that inhibit enzymes such as HDACs and HATs, which are involved in maintaining homeostasis in acetylation. Inhibitors targeting HDACs have been studied extensively [40, 121, 122]. Many of those inhibitors have shown promising anti-cancer activities without affecting non-cancerous cells, and, accordingly, these inhibitors are currently involved in ongoing clinical trials [40, 121, 122]. Recently, two HDAC inhibitors (HDACi), Vorinostat and Depsipeptide, were approved by the FDA for use as

nti-cancer agents after their validation in cancer patients [122]. Vorinostat was the first HDAC inhibitor to be approved by FDA for the treatment of cutaneous T-cell lymphoma. Many other HDAC inhibitors are in clinical trials for use as anti-cancer drugs, either alone or in combination with other drugs [122]. On the other hand, inhibitors of HATs have seen a slow development, and only in recent years have considerable efforts been made to identify various HAT inhibitors (HATi). The HATi identified till now can be classified into the following three categories: (1) bi-substrate inhibitors, (2) small molecule synthetic inhibitors, and (3) natural compounds [123]. Bi-substrate-based inhibitors include the spermidinyl-CoA-based HAT inhibitors. These inhibitors induce a transient block in DNA replication and impair DNA repair in cancer cells but not in normal cells [124]. However, these compounds alone have been found to be incapable of affecting cancer cell proliferation [124]. Interestingly, these inhibitors were shown to provide cancer-specific chemo- and radio-sensitization due to their ability to affect the DNA repair process [124].

Various natural compounds have been shown to have HAT inhibitory properties. These include anacardic acid (potent inhibitor of p300 and PCAF HAT activity), garcinol (also inhibits HAT activity of both p300 and PCAF), Epigallo Cathenin (present in green tea) and curcumin (a specific inhibitor of p300/CBP HAT activity). Out of these inhibitors, curcumin has been extensively studied for its anti-cancer activities, and various clinical trials involving curcumin are in progress [123]. Furthermore, several small molecule synthetic inhibitors have been designed to inhibit HAT activity such as γ-butyrolactone MB-3 (a GCN5-specific inhibitor), isothiazolones (p300 and PCAF-specific inhibitor) as well as various quinoline derivatives.

Recently, an isothiazole inhibitor NU9056 (Tip60 inhibitor) was shown to have anti-cancer effects on prostate cancer cells [125]. Notably, several of these small molecule inhibitors were designed as analogs of naturally occurring HATi including anacardic acid and garcinol [123]. Although much progress has been made in discovering novel HATi, our knowledge of anti-cancer activities of HATi is limited in comparison with HDACi. This could be attributed to the fact that HATi are less efficient than HDACi, and also because the current HATi doses are not physiologically feasible. Clearly, other than curcumin, which is in clinical trials, HATi need to be improved, and further studies are required to accept these as anti-cancer agents.

2.10 Conclusions and Future Perspectives

Studies carried out at the end of the twentieth century and in the beginning of the twenty-first century have shown the importance of the ADA complex and its components in several important cellular processes in organisms ranging from yeast to humans (Fig. 2.2), thus indicating an indispensible role of these components during evolution. In this chapter we focused on the ADA complex and its components

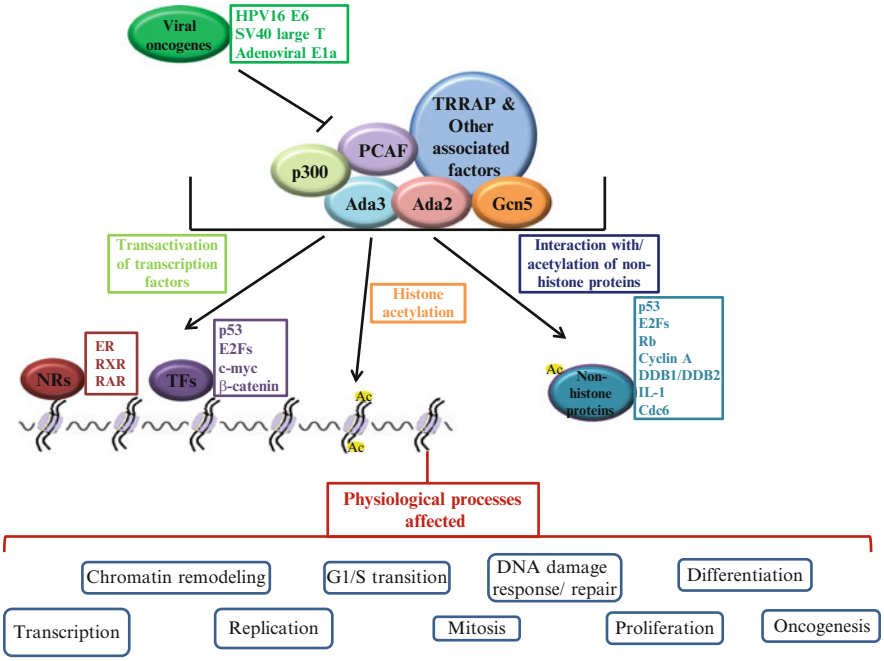

Fig. 2.2 The ADA complex and its components regulate several cellular processes by associating with and/or acetylating various transcription factors (*TFs*), nuclear receptors (*NRs*), histones and non-histone proteins. Viral oncogenes, by associating with different components of ADA complex, disrupt its function

Ada2 and Ada3, which do not seem to have intrinsic HAT activity. We also discussed various important HATs that are present in ADA complex. Although, a distinct functional ADA complex has been shown to be present in yeast, there is no in vivo evidence of such a complex in mammals, clearly indicating that more work is required in this context. Importantly, most known functions of the proteins Ada2 and Ada3 are dependent on their association with HATs. However, it remains possible that these proteins could have HAT-independent functions. Based on the role of these complex components in various important processes, including cancer, several laboratories are now focusing on making and testing new HAT inhibitors (HATi) that could prove useful in treating cancer as well as other diseases. However, novel HATi need to be designed to be specific, to have lower IC50, and to be potent against tumor cells sparing normal cells. Importantly, development of chemical inhibitors that can prevent protein-protein interaction of Ada proteins with HATs is expected to be an alternative strategy to treat cancer. Taken together, although we have made tremendous progress in understanding role of mammalian ADA complex in various physiological processes, more studies particularly in animal models need to be carried out to understand the role of each component in vivo.

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