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Distinct regulatory mechanisms of eukaryotic transcriptional activation by SAGA and TFIID

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Abstract

A growing number of human diseases are linked to abnormal gene expression which is largely controlled at the level of transcriptional initiation. The gene-specific activator promotes the initiation of transcription through its interaction with one or more components of the transcriptional initiation machinery, hence leading to stimulated transcriptional initiation or activation. However, all activator proteins do not target the same component(s) of the transcriptional initiation machinery. Rather, they can have different target specificities, and thus, can lead to distinct mechanisms of transcriptional activation. Two such distinct mechanisms of transcriptional activation in yeast are mediated by the SAGA (Spt-Ada-Gcn5-Acetyltransferase) and TFIID (Transcription factor IID) complexes, and are termed as “SAGA-dependent” and “TFIID-dependent” transcriptional activation, respectively. SAGA is the target of the activator in case of SAGA-dependent transcriptional activation, while the targeting of TFIID by the activator leads to TFIID-dependent transcriptional activation. Both the SAGA and TFIID complexes are highly conserved from yeast to human, and play crucial roles in gene activation among eukaryotes. The regulatory mechanisms of eukaryotic transcriptional activation by SAGA and TFIID are discussed here.

Keywords

Transcriptional activation; SAGA; TFIID; Activator; TBP; Proteasome; RNA polymerase II

1. Introduction

An altered pattern of gene expression is directly correlated with various types of human diseases. In eukaryotes, gene expression is largely controlled at the level of transcription that is mechanistically composed of different steps such as initiation, elongation, and termination. During transcriptional initiation, several general transcription factors (GTFs) such as TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH, as well as RNA polymerase II (RNAPII) holoenzyme are assembled at the promoter, thus resulting in the formation of preinitiation complex (PIC) to start transcription. Subsequently, transcriptional elongation follows, and finally termination occurs [1–4]. Among these, transcriptional initiation is an important step which is stimulated by gene-specific activator proteins (activators). A typical

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activator contains a promoter-targeting region, and a distinct activation domain that interacts with transcription factor(s) to promote transcription. Activation domains are generally acidic in nature (e.g., Gal4, Gcn4, VP16 and p53). However, several other activation domains of different types such as glutamine-rich (e.g., SP1), proline-rich (e.g., CTF/NF1), and zinc finger-containing (e.g., AdE1a) activation domains also exist in eukaryotes. An activator can stimulate multiple genes in the genome, thus generating a highly co-ordinated regulation of gene expression. However, a gene can also be controlled by the action of multiple activators, thereby leading to a combinatorial regulation.

A variety of studies indicate that activators work by increasing the PIC formation [3,5–7]. Such stimulation of the PIC formation is mediated by the interaction of activator with one or more components of the transcription machinery, termed as “target” (Figure 1A). A number of transcription factors have been identified as the direct targets of activators based upon *in vitro* protein-protein interaction experiments [8–24]. For example, at least ten different proteins interact with the yeast activator, Gcn4, *in vitro* [13,15–21,23]. Similarly, another well-characterized yeast activator, Gal4, has been shown to have a large number of targets based on *in vitro* studies [8,10,11,13,14,22]. However, whether any of these are *bona fide* targets *in vivo* was not known. Using the chromatin immunoprecipitation (ChIP) assay, we [25] and others [26] have identified SAGA (Spt-Ada-Gcn5-Acetyltransferase; a multi-subunit protein complex as described below) as an essential *in vivo* target of the yeast activator, Gal4. Further, our FRET (Fluorescence resonance energy transfer) studies have revealed that the Tra1 subunit of SAGA interacts directly with Gal4 *in vivo* [27]. Consistent with these results, Workman and colleagues [17] have also demonstrated that Tra1 interacts with Gal4, Gcn4, and several other yeast activators *in vitro*. Intriguingly, unlike Gal4, the activator Rap1 does not target the SAGA complex during transcriptional activation in yeast [25,28–34]. Rather, it targets TFIID (Transcription factor IID; a multi-subunit protein complex as described below) to stimulate transcription of the ribosomal protein genes [28,31,33–35]. And, these genes do not require the SAGA complex for their transcriptional activation [25,36–39]. Thus, there appears to be two distinct mechanisms of transcriptional activation, which are dictated by the target specificities of the activators. Consistently, the genome-wide DNA microarray analysis revealed the differential requirement of SAGA as well as TFIID in the regulation of transcription in yeast [36–38]. These results were further corroborated by the ChIP analysis which revealed the recruitment of the TFIID components to the core promoters of the TFIID-dependent, but not SAGA-dependent genes [25,28,35]. On the other hand, the SAGA components are recruited to the promoters of the SAGA-dependent genes [25,26,40]. Together, these studies have revealed two distinct mechanisms of transcriptional activation mediated by SAGA and TFIID. Intriguingly, the GTFs such as Mediator and TFIIB are dispensable for the recruitment of TBP/TFIID at the TFIID-dependent genes [28]. However, they are required for transcriptional initiation of the TFIID-dependent genes [28,41–44]. In contrast, these GTFs are essential for the recruitment of TBP at the SAGA-dependent promoters [27,28]. Thus, the transcriptional initiation complexes are differentially formed at the promoters of the TFIID and SAGA-dependent genes, hence leading to the complex regulation of gene activation. These two distinct mechanisms of eukaryotic transcriptional activation are discussed below.

2. Mechanisms of transcriptional activation by SAGA

SAGA was first identified as a histone acetyltransferase (HAT) for histone H3 [45]. It is a large multi-subunit protein complex, and is highly conserved among eukaryotes through evolution [46]. In yeast, SAGA has fifteen non-essential and six essential components [46–48]. The non-essential components include Ada1, Ada2, Ada3, Gcn5, Ada5, Spt3, Spt7, Spt8, Spt20, Sgf11, Sgf29, Sgf73, Ubp8, Sus1 and Chd1, while the essential components are ATM/PI-3-kinase-related protein Tra1 as well as a subset of TAFs (TBP associated factors)

such as TAF5, TAF6, TAF9, TAF10 and TAF12. The integrity of the SAGA complex is maintained by Ada1, Spt7 and Spt20 [49–51]. The Gcn5 and Ubp8 components possess HAT and histone deubiquitylase activities, respectively [47]. Both components are shown to regulate gene expression through modulation of the chromatin structure [47]. The other non-essential components play important roles in SAGA function and gene expression [47,48]. The essential component, Tra1, has been implicated as the target of several activators [17,24,27]. TAFs have been shown to play important roles for SAGA function and hence transcription activation [16,52]. Many conserved homologues of yeast SAGA components are found in human SAGA complex [46]. However, the human homologues of yeast Spt8 and Chd1 are not yet identified in human SAGA [46]. The human homologue of yeast Tra1 is TRRAP (transformation/transcription domain-associated protein). Like yeast Tra1, human TRRAP has been proposed to be the target of several activators, such as c-Myc and E2F [53] which regulate cell proliferation and apoptosis. Thus, Tra1/TRRAP functions as a direct target of many transcriptional activators such as Gal4, Gcn4, VP16, E1A, E2F, c-Myc, p53 and nuclear receptors in yeast and human [17,24,27,53–63]. The ATM/PI-3-kinase-like domain near the C terminus of Tra1/TRRAP is important for interaction with activators [17,63], and thus, plays a crucial role in targeting the HAT activity to the promoters. Like in yeast and human, the SAGA complex has also been identified and characterized in *Drosophila* [46]. The *Drosophila* SAGA shows remarkable similarity with yeast SAGA complex. However, several homologues of yeast SAGA components such as Spt8, Spt20, TAF6, Sgf73 and Chd1 are not yet identified in *Drosophila* [46]. Like yeast SAGA, the *Drosophila* SAGA complex also interacts with acidic activator VP16 and *Drosophila* p53 [64]. Thus, the targeting of the SAGA complex to the active genes appears to be evolutionary conserved.

Besides the roles of activators in targeting SAGA, histone covalent modifications also play important roles in stabilizing the interaction of SAGA with the promoters. Several studies have indicated that SAGA interacts with acetylated-histone H3 through the bromodomain of its Gcn5 subunit [47,65–72]. Thus, SAGA appears to write the acetylation mark on histone H3, and subsequently, reads it during the establishment of a transcriptionally competent chromatin structure. Further, the chromodomain of the Chd1 subunit of yeast SAGA has been shown to interact with di- and trimethylated-K4 (lysine 4) of histone H3 [73–75]. Such interaction of SAGA with methylated-K4 of histone H3 may play important role in recruitment and/or stabilization of SAGA onto chromatin. This interaction may also play a direct role to regulate the Gcn5's HAT activity, thus contributing to the establishment or maintenance of active chromatin. Intriguingly, several studies have also implicated that Gcn5 preferentially acetylate histone H3 that is phosphorylated at S10 [76–81], suggesting the role of histone H3 phosphorylation on SAGA's HAT activity. Together, these studies demonstrate that the interaction of SAGA with activator drives its recruitment, and subsequently, histone covalent modification leads to its stabilization onto the promoter.

How does activator-SAGA interaction stimulate PIC formation, and hence transcription? Genetic studies have implicated direct interaction between the Spt3 component of SAGA and TBP [26,82,83]. Further, biochemical experiments have demonstrated that the Spt8 component of SAGA interacts directly with TBP [49]. Consistent with the genetic and biochemical interactions, the ChIP experiments have revealed that Spt3 and Spt8 are required for recruitment of TBP at the promoters of several SAGA-dependent genes such as *ADH1*, *PHO84* and *VTC3* [51]. However, these components are not essential for global structural integrity of SAGA [25,49]. Together, these observations support that SAGA stimulates recruitment of TBP (and hence PIC formation) via its Spt3 and Spt8 components. Intriguingly, the Spt3 and Spt8 components of SAGA have also been shown to inhibit TBP recruitment at *HIS3*, *TRP3* and *HO* [84,85]. Thus, these two components of SAGA perform differential functions in recruiting TBP at the two different sets of promoters. Additional

factors such as Swi/Snf and FACT may play a role in such differential regulation of TBP recruitment. However, the factors associated with positive vs. negative regulation of TBP recruitment by Spt3 and Spt8 are not yet known. In addition to its role in recruiting TBP, SAGA also regulates transcriptional activation through its HAT activity [47,51,86–91]. When present within the SAGA complex, Gcn5 acetylates nucleosomal histone H3 at K9, K14, K18, and K23 [92–93]. The Gcn5-HAT activity is provided by other SAGA subunits [93,94]. It has been demonstrated that Gcn5 with Ada2 and Ada3 forms a catalytic core which is minimally capable of nucleosomal acetylation [51,95]. Ada2 has been implicated to potentiate the HAT activity of Gcn5, while Ada3 promotes acetylation and lysine specificity [95]. Although Gcn5, Ada2 and Ada3 form the core catalytic domain within SAGA, other SAGA subunits have also been implicated to regulate the HAT activity of Gcn5. For example, temperature-sensitive (ts) inactivation of TAF12 significantly impairs the SAGA's ability to acetylate nucleosomes, and subsequently, reduces transcriptional activation *in vitro* [52]. However, the molecular basis for such regulation of the Gcn5's HAT activity remains unclear. Nonetheless, SAGA-mediated acetylation of histone H3 is required to stimulate transcription [86–88]. Further, Yu et al [85] have demonstrated that such acetylation promotes the formation of the TFIIA-TBP-DNA complex. Consistently, the ChIP studies have demonstrated the requirement of Gcn5 for histone H3 acetylation as well as TBP recruitment (and hence transcriptional activation) at the SAGA-regulated promoters [90,91]. Intriguingly, the HAT activity of SAGA has also been implicated in transcriptional repression at a subset of genes [96]. For example, Gcn5-mediated acetylation reduces the binding of TBP with the *ARG1* promoter, and impairs significantly the expression of *ARG1* in the rich medium. Thus, Gcn5 plays a differential role in the regulation of transcriptional activation, hence further increasing the complexity of gene activation. However, SAGA can also regulate transcription independently of its HAT activity. For example, SAGA acts as a “physical adaptor” at several genes to stimulate the recruitment of TBP (and hence formation of the PIC) via its Spt3 and Spt8 components, but not Gcn5 [25,26,51,91]. Consistently, the DNA microarray analysis has demonstrated that a set of SAGA-dependent genes does not require Gcn5 for their expression [38]. Intriguingly, Qiu et al [97] have further demonstrated that SAGA can also exert its function by recruiting RNAPII independently of its stimulatory role for TBP recruitment. Together, these studies reveal that SAGA differentially controls transcriptional activation of a subset of RNAPII genes, thus leading to the complex regulation of gene activation.

In addition to its above roles in gene activation, SAGA also regulates transcription through histone H2B deubiquitylase activity of its Ubp8 subunit [40,98–102]. Monoubiquitylation of lysine on histone H2B occurs by ubiquitin-activating, conjugating and ligase enzymes [101–106]. It is a reversible process. Ubiquitin moiety can be enzymatically removed from the ubiquitylated-H2B by Ubp8 deubiquitylating enzyme. Ubp8 hydrolyzes isopeptide bond at glycine 76 of ubiquitin, leading to deubiquitylated-H2B. Thus, the enzymatic activity of Ubp8 appears to provide another level of regulation. Further, monoubiquitylation of histone H2B is essential for di- and trimethylation of K4 of histone H3 [106–107] which is associated with active transcription. Therefore, it is anticipated that the loss of Ubp8 would increase histone H2B ubiquitylation, and subsequently, would promote histone H3 K4 di- and trimethylation, leading to the additional level of transcriptional regulation. Indeed, it has been demonstrated that the SAGA-associated Ubp8 is required for deubiquitylation of ubiquitinated-K123 of histone H2B at several SAGA-dependent genes [40,99,100]. Such alteration in the level of histone H2B ubiquitylation is correlated with histone H3 K4 methylation at several genes [40,99,100]. Intriguingly, Shukla et al [40] have demonstrated that the histone H2B deubiquitylation activity of Ubp8 can also differentially regulate H3 K4 methylation at the SAGA-dependent promoters. However, the molecular basis for such differential regulation of histone H3 K4 methylation by Ubp8 remains unclear. Nonetheless, the modulations of covalent modifications of histones by Ubp8 have been shown to promote

the transcription of SAGA-dependent genes [99,100]. However, Ubp8 has also been shown to repress transcription [102]. Such transcriptional repression has been correlated with the level of histone H2B ubiquitylation [102]. Interestingly, Shukla et al [40] have further demonstrated the dispensability of Ubp8 in formation of the PIC (and hence transcription) at the promoters of several SAGA-dependent genes. Thus, Ubp8 differentially controls transcription of the SAGA-regulated genes, revealing a complexity of gene activation *in vivo*. However, the factors associated with such differential regulation of transcriptional activation are not currently understood.

Recently, Ubp8 has been shown to form a distinct structural module with Sgf11 and Sus1 within the SAGA complex [46,108], and this module is termed as “deubiquitylation module”. Each component of the deubiquitylation module plays important role in histone H2B-K123 deubiquitylation as well as histone H3 K4 methylation [109]. Interestingly, Sus1 has also been found to be an integral component of the TREX-2 complex that is attached with nuclear pore complex for nuclear export of mRNA [46,110]. Thus, the deubiquitylation module appears to link the SAGA-dependent transcription with nuclear export of mRNA. Indeed, the sites of active transcription of the SAGA-dependent genes are found at the nuclear pore complexes [110–113]. Such localization of the SAGA-dependent genes during active transcription is dependent on Sus1 [110]. Consistent with these observations, the live-cell imaging studies at *GAL* genes have also revealed the presence of SAGA component at the nuclear envelope during transcriptional activation [112]. Such translocation of the SAGA-dependent genes by Sus1 during active transcription might be leading to an efficient mRNA export. However, it remains to be further elucidated how universal this link is. Nonetheless, these results point to the fact that Sus1 links SAGA with mRNA export machinery [46,110]. Intriguingly, the recent studies have also implicated the role of another non-essential component of SAGA, Sgf73, in the regulation of mRNA export [108,114,115]. These studies have demonstrated that the loss of Sgf73 impairs partly the association between Sus1 and TREX-2 as well as partial mislocalization of Sus1 to cytoplasm [108,114]. However, how Sgf73 is linked to Sus1 and TREX-2 remains to be further investigated. In addition to its role in mRNA export, Sgf73 has also been implicated in maintaining SAGA integrity (and hence PIC formation) at the SAGA-dependent genes [91,116]. In human, it is involved in neurodegenerative diseases through modulation of chromatin structure and gene activation [117–120].

Homologues of yeast Ubp8, Sgf11 and Sus1 have been identified in higher eukaryotes. Nonstop and USP22 are the homologues of yeast Ubp8 in *Drosophila* and human, respectively. Nonstop associates with *Drosophila* SAGA, and participates in an accurate axon guidance in the optic lobe in neural development [121]. Further, Nonstop appears to function as an enhancer of position-effect variegation [122]. Like in *Drosophila*, USP22 associates with human SAGA, and is recruited to specific genes by activators such as the MYC oncoprotein for transcription [123]. The enhanced transcription of MYC target genes is critical for malignant transformation in mammals. Further, MYC is the most potent activator involved in cell cycle progression, and its role in cancer is based on its ability to drive cell proliferation. Thus, it is expected to observe proliferative defect upon depletion of USP22. Indeed, proliferative defect and the G1 cell cycle arrest were observed upon depletion of USP22. Thus, a specific requirement of USP22 in cell cycle progression is linked to the etiology of cancer, and hence, can be used as a predictor of tumor growth [123]. Sus1 homologues in *Drosophila* and human are e(y)2 and ENY2, respectively [122,124,125]. Both e(y)2 and ENY2 are part of the *Drosophila* and human SAGA complexes [122,125]. ENY2 has been shown to function as a cofactor for the full transcriptional activity of nuclear receptors, while e(y)2 is required for the barrier activity of Su(Hw)-dependent insulators [122,125]. Sgf11 and ATXN7L3 are yeast Sgf11 homologues in *Drosophila* and human, respectively, and are part of the SAGA complex [46,122].

Drosophila Sgf11 is proposed to function in position-effect variegation [122]. Together, these observations support that deubiquitylation module and its components are evolutionary conserved among eukaryotes. Indeed, like in yeast, the deubiquitylation module containing USP22, ENY2 and ATXN7L3 has been characterized in human SAGA [122].

In addition to its above roles in gene activation, SAGA also regulates transcriptional activation via the Mediator complex. The Mediator is an evolutionarily conserved-complex that contains at least 22 proteins [41]. However, its precise mechanism-of-action in transcriptional activation is not clearly understood. Our recent ChIP studies [27] have revealed that the Mediator complex is recruited to the *GAL1* promoter subsequently to SAGA to stimulate the PIC formation. Consistently, Roberts and Winston [126] have demonstrated the functional interaction between SAGA and Mediator. Further, systematic genetic analysis has revealed that $\Delta spt20$ and $\Delta spt7$ show lethality with the null mutations of the two components (*GAL11* and *SIN4*) of the Mediator complex [126]. In addition, the suppressor mutant of the *Srb9* component of the Mediator complex has been shown to rescue partially the transcription defect of *GAL1* in $\Delta spt20$ [127]. Thus, SAGA interacts functionally and genetically with Mediator, and acts as an “adaptor” that recruits the Mediator complex to the activation domain of Gal4 (Figure 1B). Intriguingly, Mediator and SAGA have also been shown to be independently recruited to the SAGA-dependent promoters by other activators such as Gcn4 and Met4 for the PIC formation (Figure 1C) [21,128,129]. These observations fit well with the model that have implicated Mediator as a target of several transcriptional activators in yeast and mammalian cells [41], and demonstrates how different activator–target interactions stimulates the PIC formation (and hence transcriptional activation). Despite these advances, our understanding of a complete picture of the protein–protein and protein–DNA interactions during transcription activation remains elusive *in vivo*. Thus, further investigation is essential to delineate the specific protein interaction network within eukaryotic transcriptional activation machinery *in vivo*.

Besides its role in transcriptional activation, SAGA also participates in other transcriptional regulatory steps such as transcriptional repression at telomere, transcriptional elongation, mRNA export, active gene translocation, and genome repair [46–48,110,130–133]. Thus, SAGA appears to act as a master regulator of gene expression. In yeast, SAGA is required for normal transcription of approximately 10 percent of the genes [36,38]. These genes tend to be inducible with consensus TATA box [36]. Thus, SAGA appears to promote the transcription of genes that respond to environmental stress such as heat, DNA damage and metabolic starvation [36]. However, majority of genes are regulated by TFIID [36–38], and they appear to be house keeping genes without consensus TATA box [36]. The mechanisms of transcriptional activation by TFIID are discussed below.

3. Mechanisms of transcriptional activation by TFIID

TFIID is a multi-subunit protein complex, and was first characterized in *Drosophila* and mammals [134–136]. Subsequently, it was biochemically characterized in yeast *Saccharomyces cerevisiae* [137–139]. TFIID is composed of TBP and a set of TAFs. TAFs are highly conserved from yeast to human [140,141], and are ubiquitously distributed. However, some TAFs are expressed in a tissue-specific fashion in higher eukaryotes [140,142–145]. In yeast, there are 14 TAFs, namely TAF1, TAF2, TAF3, TAF4, TAF5, TAF6, TAF7, TAF8, TAF9, TAF10, TAF11, TAF12, TAF13 and TAF14 [140,141]. The orthologues of each of these TAFs except TAF14 have been identified as the components of the TFIID complex in *Drosophila* and mammals [140,141]. In addition to the above TAFs, *Drosophila* genome encodes five additional TAFs. These are nht (no hitter) (TAF4L), can (cannonball) (TAF5L), mia (meiosis I arrest) (TAF6L), sa (spermatocyte arrest) (TAF8L), and rye (ryan express) (TAF12L), and are paralogues of TAF4, TAF5, TAF6, TAF8 and

TAF12, respectively [146,147]. These TAFs are specifically expressed in a co-ordinated fashion in spermatocytes, and are required for normal transcription of genes required for spermatid differentiation [146,147]. Further, these testis-specific TAFs have histone fold domain, and are, therefore, likely to form stable TAF complex(es) to regulate the testis-specific gene expression in primary spermatocytes for terminal differentiation of male germ cells. However, unlike in *Drosophila*, the mouse genome encodes two TAF paralogues which are involved in spermatogenesis [148,149]. Thus, the roles of the testis-specific TAFs do not appear to be evolutionary conserved.

Despite its significant importance in transcriptional initiation, it is not clearly understood how the canonical TFIID complex is assembled by TAFs. The primary structure analysis has revealed that there is a striking similarity in the amino acid sequences of TAF6, TAF9 and TAF12 with the core histones H4, H3 and H2B, respectively [150]. Such similarity suggests the existence of a histone octamer-like structure within the TFIID complex [150]. Further, nine TAFs have the histone fold domains, thus indicating the presence of distinct heterodimers within TFIID [151,152]. Indeed, these heterodimers were found in native TFIID [151]. Thus, the histone fold domain appears to function as a building block of the TFIID complex. However, very little is known about the supramolecular assembly of the TFIID complex, even though structural information is available at the atomic level for few TAF subdomains or TAFs [153–155]. The electron microscopic analysis has provided an overall shape of the TFIID complex in yeast and human at low resolution [156–160]. The TFIID complexes in both yeast and human have three lobes which are linked by connecting regions to form a “horseshoe”-shaped molecular clamp [156–160]. Further, the electron microscopic analysis with immunolabelling of TFIID revealed the localization of individual TAFs within this horseshoe-shaped structure, thus defining the composition of the lobes as reviewed by Cler et al. [161]. However, these structural informations were obtained at a very low resolution. Future studies at high resolution will provide accurate structural information of the TFIID complex, and thus, will provide the molecular insight of its mode of action.

In yeast, TFIID has been shown to be involved in transcription of the majority of genes [36,38]. How is the TFIID complex targeted to the active genes? Early studies have revealed that TAFs are required for transcription in response to activators [140]. Consistently, these factors have been shown to interact directly with activators in yeast and higher eukaryotes [33,34,161–165]. Thus, TAFs appear to be required for the flow of genetic information from the activators to the core transcription machinery at the TFIID-dependent genes. However, whether activators work at the TFIID-dependent genes by recruiting TFIID *in vivo* was not clearly known. We [28] and others [35] have demonstrated that TAFs are co-recruited with TBP in a manner consistent with direct activator-TAF interactions. Consistently, we have demonstrated that TAFs are essential for recruitment of TBP at the TFIID-dependent genes, while TBP is dispensable for recruitment of TAFs [28,39]. In addition, we show that TAF11 and TAF13 appear to mediate the interaction between TBP and other TAFs within the TFIID complex *in vivo* [39]. In support of this model, our studies have revealed that TAF11 and TAF13 are essential for recruitment of TBP, but not other TAF subunits of the TFIID complex [39]. Further, the physical and genetic interactions between TAF11 and TAF13 have been observed [39,153,166]. Together, these results provide some information on the structural organization of the TFIID complex *in vivo*. Further, these studies demonstrate that TAFs play crucial role in relaying the information from activator to TBP (Figure 1D). However, unlike the SAGA-dependent genes, the Mediator complex is dispensable for TBP recruitment at the TFIID-dependent genes, but essential for transcriptional activation [28]. Thus, the Mediator complex appears to be recruited following TFIID to the TFIID-dependent genes for promoting transcription. Like the Mediator complex, another GTF, namely TFIIB, is also dispensable for the recruitment of TBP at the TFIID-dependent genes, while TFIIB is essential for recruitment of TBP at the SAGA-dependent genes

[25,27,28,51]. Therefore, the Mediator complex and TFIIB play differential roles in regulation of transcriptional activation of the SAGA and TFIID-dependent genes. However, the molecular basis for such differential roles of the Mediator complex and TFIIB during transcriptional activation of the SAGA and TFIID-dependent genes is not clearly understood.

What determines whether a promoter would be TFIID-dependent or independent? Is TFIID-dependency specified by the core promoter elements or upstream activating sequences (UAS)? Several studies have attributed the core promoter elements for the TFIID-dependency [140]. For example, *Drosophila* and human TAFs have been shown to interact with initiator or downstream promoter element in a sequence-specific DNA binding manner [167]. Similarly, TFIID-dependency of some yeast genes has been mapped to the core promoter elements [168]. Besides core promoter elements, histone H3 K4 trimethylation has also been implicated to stimulate the binding of TFIID [169]. Such stimulation is mediated by the interaction between trimethylated-K4 of histone H3 and the plant homeodomain of TAF3 (absent in yeast TAF3, but present in higher eukaryotes) [169]. Further, acetylated-K9 and K14 of histone H3 interact with the bromodomains of TAF1 (absent in yeast TAF1, but present in higher eukaryotes) [161,170]. The combination of histone H3 K4 trimethylation with histone H3 K9/14 acetylation significantly enhances the interaction of TFIID with promoter. However, such interaction is reduced when histone H3 K4 methylation is coupled with histone H3 R2 (arginine 2) dimethylation that is associated with transcriptional repression [161]. Together, these studies indicate that the core promoter elements as well as histone covalent modifications play important roles to regulate the stabilization of the interaction of TFIID with promoter. Interestingly, our studies [28,29] have demonstrated that UAS is also responsible for recruitment of TFIID to the core promoter. When the UAS of the TFIID-dependent promoter is fused with the SAGA-dependent or TFIID-independent core promoter, TFIID is surprisingly recruited to the TFIID-independent or SAGA-dependent core promoters [29]. Conversely, TFIID is not recruited to the TFIID-dependent core promoter when it is fused with the UAS of the TFIID-independent or SAGA-dependent promoter [29]. These results clearly demonstrate that UAS drives the recruitment of the TFIID complex to the core promoter. Consistent with these results, Struhl and colleagues [31] have shown that the Rap1 activator which is associated with the UASs of the TFIID-dependent ribosomal protein genes is sufficient to recruit TAFs/TFIID to both TFIID-dependent and independent core promoters. Further, TAFs/TFIID are recruited to the core promoter in a Rap1-dependent manner, but independently of GTFs such as TBP, TFIIB and Mediator [28,31], indicating that TAFs are the direct targets of Rap1. Indeed, the recent studies from the Weil laboratory [33,34] have biochemically demonstrated the direct interaction between Rap1 and TAFs. Similarly, TAFs have been shown to be the direct targets of activators in mammalian cells [162–165]. The well-characterized examples are the interactions of the transcriptional activators SP1 and CREB (cyclic AMP response element binding) with TAF4. Together, these results demonstrate that TAF-dependency maps to both the UAS and core promoter. Thus, the functional interaction between the activator and core promoter is required for efficient recruitment of TAFs or TFIID at the TFIID-dependent promoters, and hence, TAFs can be direct targets of activators as well as core promoter recognition factors to activate transcription.

In higher eukaryotes, there are multiple variant TAFs and TBP-related factors (TRFs) [4,171,172]. These factors play important roles in tissue-specific gene expression [4]. For example, several muscle-specific genes are regulated by a complex containing TAF3 and TRF3, but not TFIID complex [173,174]. It has been demonstrated that a very low level of canonical TFIID is present in differentiated muscle cells [173,174]. In addition to its role in muscle-specific gene expression, TRF3 is also essential for development of the hematopoietic lineage in zebrafish through activation of the key differentiation genes [175].

Thus, it is likely to have different TFIIID variants in higher eukaryotes for differential gene expression in a tissue-specific fashion. Further, it would be interesting to determine how TFIIID variants are targeted to the specific genes. Does specific activators or specific DNA sequence in the promoter or histone covalent modifications drive the recruitment of the TFIIID variants to the tissues-specific genes? The answers to these questions will significantly advance our understanding of the tissue-specific regulation of gene activation.

In addition to the above two distinct regulatory mechanisms for stimulation of the PIC assembly, activators also work through interaction with other histone modification factors and ATP-dependent chromatin remodeling complexes [3,60,176–178]. These chromatin remodeling/modification factors promote transcription by modulating the chromatin structures. Thus, besides SAGA and TFIIID, the chromatin structures/chromatin remodeling factors also play crucial roles in the regulation of transcriptional activation. Intriguingly, several recent studies have also implicated a protein degradation machine, namely the 26S proteasome complex, in the regulation of eukaryotic transcriptional activation [179–182]. The proteasome regulates gene activation through diverse mechanisms as reviewed recently [182]. The proteasomal regulation of SAGA and TFIIID-dependent transcriptional activation is discussed below.

4. Regulation of the SAGA and TFIIID-dependent transcriptional activation by the proteasome complex

The 26S proteasome is a non-lysosomal proteolytic machinery in eukaryotes [183,184], which consists of two subcomplexes, namely a 20S core particle (CP) and a 19S regulatory particle (RP). The 20S CP is responsible for the proteolytic activities, whereas the 19S RP shows ATP-dependence and specificity for ubiquitin protein conjugates. The 26S proteasome degrades polyubiquitylated proteins in an ATP-dependent manner. However, the 20S CP can also degrade non-ubiquitylated proteins without ATP [185,186]. The 20S CP has a cylinder-like structure that is formed by two α rings and two β rings. Each ring consists of seven related proteins ($\alpha 1$ – $\alpha 7$, or $\beta 1$ – $\beta 7$), and are stacked in the order of $\alpha \beta \beta \alpha$. The cavity of the cylinder-like structure of the 20S CP has the protease activities [183,184]. The binding of the 19S RP with the 20S CP opens the gate of the 20S CP in an ATP-dependent manner, and then allows the entry of the substrate into the 20S CP for degradation [183,184,187–189]. The 26S proteasome has the 19S RP attached on either end or both ends of the 20S CP. The 19S RP contains at least 17 different proteins, including six ATPases (Rpt1–Rpt6) belonging to the AAA (ATPases associated with a variety of cellular activities) family, as well as the non-ATPase proteins (Rpn1–Rpn3, and Rpn5–Rpn12) [182–184,190]. The 19S RP is further divided into two subcomplexes, namely “base” and “lid” [182–184,190]. The base has six AAA-ATPase proteins (Rpt1–Rpt6) and three non-ATPase proteins (Rpn1, Rpn2 and Rpn10), while the lid consists of eight non-ATPase proteins (Rpn3, Rpn5–Rpn9, Rpn11 and Rpn12) [183,184]. The non-ATPase protein, Rpn10, exists at the interface between the base and the lid. The lid subcomplex associates with, and hydrolyzes polyubiquitin chains [183,184]. The ATPases present in the base are required for the assembly of the 26S proteasome. Further, the base unfolds the substrate protein in an ATP-dependent manner, and then translocates it into the central chamber of the 20S CP for proteolysis [183,184,187].

Through proteolysis, the 26S proteasome complex is involved in regulating the functions and fates of many transcription factors in a coordinated manner to control important cellular events [182,191,192]. In yeast (*S. cerevisiae*), mutation of either the 19S RP or 20S CP alters the levels of ~70% of the genomic transcript at least by 2-fold [193]. The inactivation of the Rpt6 component of the 19S RP leads to the up-regulation of 1389 of 6400 yeast genes that encode proteasome subunits, ubiquitin-conjugating enzyme (Ubc5), and diverse proteins

involved in mitochondrial function under stress conditions [193]. The ts inactivation of the Pre1 ($\beta 4$) component of the 20S CP upregulates the expression of 1600 of 6400 yeast genes which encode proteins including protein folding factors, proteasomal subunits, mitochondrial proteins, stress sensors, and DNA repair factors (e.g., Rad7, Rad26, Rad59, and Hsh6). 60% of these genes were commonly up-regulated in both the ts mutants at the non-permissive temperature. However, 26% of genes were uniquely up-regulated in the ts mutant of Rpt6, while another 14% were up-regulated only in the *pre1*-ts mutant. Further, a large fraction of genes (2751 genes) were down-regulated in these two ts mutants at the non-permissive temperature [193]. 63% of genes were commonly down-regulated in both mutants. However, 16% of genes were uniquely down-regulated in the ts mutant of Rpt6, while the expression of 21% of genes was decreased only in ts mutant of Pre1. Thus, a large number of genes in yeast are differentially regulated by the 26S proteasome in a 20S CP dependent and independent manner. Therefore, like in yeast, a large number of human genes might be dependent on the proteasome for their expression. Indeed, inhibition of the proteolytic function of the proteasome by Bortezomib (also known as Velcade) in retinoblastoma cell lines alters the expression of genes encoding stress-response proteins, heat shock proteins, pro-apoptotic proteins, cell-cycle regulators, cytokines, anti-apoptotic proteins, adhesion molecules, and a set of transcription factors [194]. Similarly, Bortezomib-treated pancreatic adenocarcinoma, classical Hodgkin lymphoma, multiple myeloma, and primary neuronal cells revealed altered-expression patterns of a variety of genes including those involved in cell cycle and apoptosis [195–198]. Thus, the proteasome appears to play crucial roles in human gene expression, and hence, has become an attractive target for treating human diseases including cancer. Indeed, Bortezomib is currently being used in the clinics to treat multiple myeloma and mantle cell lymphoma [199]. Further, several other proteasome inhibitors are in clinical trials [199–203].

The genome-wide DNA microarray analysis revealed that the expressions of both stress-response genes as well as housekeeping genes are regulated by the proteasome [182]. As previous studies [36,38] have implicated SAGA and TFIID in the expression of stress-response and housekeeping genes, respectively, the proteasome thus appears to regulate the transcription of both SAGA and TFIID-dependent genes. However, whether the whole 26S proteasome or its subunits participate in the regulation of TFIID and SAGA-dependent transcriptional activation is not clear. Intriguingly, the genome-wide location analysis demonstrated that several hundred genes in yeast are associated with either the 19S RP or 20S CP [193,204]. In support of this observation, Sulahian et al. [181] have shown that the transcription of several stress-responsive genes is regulated by the 19S RP independently of the proteolytic function of the 20S CP. These stress-responsive genes are dependent on SAGA for their transcriptional activation. On the other hand, the 20S CP or the proteolytic function of the proteasome regulates the transcription of the ribosomal protein genes [193,205,206]. As mentioned above, the ribosomal protein genes are dependent on the TFIID complex for their transcriptional activation. Thus, the 26S proteasome seems to have distinct functions in stimulation of transcription of SAGA and TFIID-dependent genes in the proteolysis-independent as well as -dependent manners, respectively.

How does the proteasome regulate transcriptional activation of the SAGA-dependent genes in a proteolysis-independent manner? Recently, Lee et al [207] have demonstrated that the 19S RP of the proteasome promotes the targeting of SAGA to the Gal4-driven promoter independently of the 20S CP. They show that the 19S RP uses the energy of ATP hydrolysis to stabilize the interaction between Gal4 and SAGA. In support of this observation, they demonstrate that the 19S RP interacts physically and genetically with SAGA, and enhances the HAT activity as well as DNA binding activity of SAGA. Further, they demonstrate that it is the base, but not the lid, of the 19S RP which stimulates SAGA targeting to the promoter. Thus, their data have provided a nice biochemical model as to why the 19S RP is

required for *GAL* gene activation. However, the functional role of each 19S ATPase component in stabilization of the Gal4-SAGA interaction is not yet known. Further, it remains unclear whether the 19S RP regulates the transcriptional activation of other SAGA-dependent genes in a manner similar to the *GAL* genes. Moreover, it is yet to be elucidated whether the 19S RP functions similarly in the regulation of transcriptional activation of the SAGA-dependent genes in mammals. The answers to these questions will provide more functional insight on the 19S proteasomal regulation of the SAGA-dependent transcriptional activation.

In addition to its role in stimulation of activator-SAGA interaction, the 19S RP also plays a crucial role to regulate transcription by destabilizing the activator-promoter complex involved in the SAGA-dependent transcriptional activation [208]. For example, stability of the Gal4-promoter complex is regulated by the 19S RP [208]. Such regulation requires the ATPase activity of the 19S RP, but occurs independently of the proteolytic function of the 20S CP [208]. The monoubiquitylation of activator enhances the stability of the activator-promoter complex, while the 19S RP destabilizes activator-promoter interaction in the absence of monoubiquitylation [208]. Thus, the 19S RP and activator monoubiquitylation appear to function antagonistically in the regulation of activator-promoter interaction. In support of this model, Ferdous et. al. [208] have also demonstrated that the interaction of Gap71 (a Gal4 derivative that has a DNA binding domain, but is not monoubiquitylated) with promoter does not occur in the presence of the 19S RP. However, Gal4 forms a stable complex with promoter [208,209]. Such stabilization of Gal4-promoter interaction is mediated by the monoubiquitylation of Gal4 [208,209]. However, how activator is monoubiquitylated remains to be elucidated.

Besides the regulation of activator-promoter/coactivator interaction, the 19S RP also promotes formation of the PIC at the SAGA-dependent genes, possibly through its molecular chaperonin activity. For example, using the ChIP assay in conjunction with mutational and transcriptional analyses, we [210] have recently demonstrated that the 19S proteasomal subcomplex establishes a specific protein interaction network of Gal4-SAGA-Mediator at the *GALI* UAS during transcriptional activation (Figure 2). Such an interaction network is essential for formation of the PIC at the core promoter to initiate transcription (Figure 2). Further, we [210] have demonstrated that formation of the transcriptional initiation complex at the *GALI* promoter is dependent on the 19S ATPase activity. Intriguingly, we [210] also find that the 19S ATPases function in a co-operative manner to facilitate the assembly of transcription factors at the *GALI* promoter. Thus, 19S RP is essential for formation of the PIC at the SAGA-dependent *GALI* promoter for transcriptional activation *in vivo* by establishing a specific protein interaction network at the UAS via its ATPase activity (Figure 2). However, it is not known whether the 19S RP directly participates in the PIC formation *in vivo*. Previous biochemical studies have implicated the interaction of the 19S RP with the components of the PIC assembly [211–213]. Thus, the 19S RP may directly regulate the PIC formation *in vivo*. Together, these studies have provided important insight on the regulatory mechanisms of transcriptional activation by the 19S RP. However, whether other SAGA-dependent genes in yeast are also regulated in a similar fashion by the 19S RP remains to be elucidated. Further, it will be interesting to verify whether 19S RP also regulates the PIC formation at the SAGA-regulated genes in mammals in a similar manner.

Although the non-proteolytic function of the proteasome has been implicated to regulate the transcriptional activation of the SAGA-dependent genes, the proteolytic function of the proteasome can also provide additional levels of regulation to the SAGA-dependent genes by controlling activator abundance, localization and destruction as reviewed recently [182]. Further, the destruction of the co-activator or co-repressor can also regulate transcriptional

activation [182]. In addition, the proteasome has been implicated to regulate transcription by disassembling the PIC formation and modulating chromatin structures [182]. Possibly through these mechanisms, the TFIID-dependent genes are also regulated. Although the detailed mechanisms-of-action of the proteasome in regulation of the TFIID-dependent transcriptional activation has not been explored, the DNA microarray analysis in yeast has revealed that the TFIID-dependent ribosomal protein genes are regulated by the proteolytic function of the proteasome [193,205,206]. Similarly, several TFIID-dependent genes such as hormone-regulated genes [161,214–220] in human are also controlled by the proteasome [182]. The activators or steroid receptors of hormone-regulated genes are polyubiquitylated, and then degraded by the 26S proteasome complex for tight regulation of gene activation [182]. The proteasome degrades estrogen receptor in response to estradiol during transcriptional activation, and subsequently, leads to the disassembly of the active transcriptional initiation complex from the promoter [182]. Such turnover of estrogen receptor in response to estradiol leads to periodic dissociation/association of estrogen receptor with the promoter for disassembly and reassembly of the active transcriptional initiation complex for gene activation as the inhibition of the proteolytic activity of the proteasome lowers transcription of the target genes of the estrogen receptor [182]. Similarly, several other steroid receptors of hormone-regulated genes are controlled by the proteasome [182]. The proteolytic turnover of steroid receptors is regulated by basal transcription factors. For example, the Cdk7 subunit of TFIIH phosphorylates estrogen receptor for recruitment of ubiquitin ligase and subsequent polyubiquitylation. Then polyubiquitylated estrogen receptor is degraded by the proteasome (Figure 3). Similarly, progesteron receptor and retinoic acid receptors are also phosphorylated prior to proteasomal degradation. Thus, basal transcription machinery plays an important role in activator turnover or disassembly of transcriptional initiation complex in a feedback manner (Figure 3). Likewise, certain activators in yeast undergo proteasomal degradation by basal transcription machinery [182]. Together, these studies shed some light on the proteasomal regulation of transcriptional activation of a selective set of TFIID-dependent genes. However, it is not yet known whether other TFIID-dependent genes are also similarly regulated by the proteasome. Further, the complete regulatory mechanisms of transcriptional activation of the TFIID-dependent genes by the proteasome are not clearly understood. Thus, future investigations are crucial to delineate as to how the proteasome regulates the transcriptional activation of the TFIID-dependent genes. Further, the global genome-wide studies will advance our understanding on the proteasomal regulation of the SAGA and TFIID-dependent transcriptional activation.

5. Concluding remarks

Here, I have discussed two distinct mechanisms of eukaryotic transcriptional activation by SAGA and TFIID. These distinct mechanisms of gene activation are dictated by the target specificity of the activator. In case of SAGA-dependent transcriptional activation, the activator targets SAGA which subsequently promotes the recruitment of TBP, and hence formation of the PIC to initiate transcription. On the other hand, TBP is recruited to the promoter of the TFIID-dependent gene via the interaction of activator with the TAF components of TFIID, subsequently promoting formation of the PIC. Intriguingly, the Mediator complex plays differential roles in these two distinct gene activation pathways. Mediator is essential for recruitment of TBP at the SAGA-dependent genes, but dispensable for TBP recruitment at the TFIID-dependent genes. Like the Mediator complex, another GTF, namely TFIIB, also differentially participates in the SAGA and TFIID-dependent transcriptional activation. TFIIB is essential for recruitment of TBP at the SAGA-dependent genes. However, the recruitment of TBP to the TFIID-dependent genes does not require TFIIB. Although both the Mediator complex and TFIIB are dispensable for recruitment of TBP at the TFIID-dependent genes, they are required for transcriptional initiation

subsequent to TBP recruitment at the TFIID-dependent genes. Thus, GTFs function at the different steps of the transcriptional activation pathways of the SAGA and TFIID-dependent genes, implying a complex regulation of gene activation. Such a complex regulation of gene activation is further complicated by the involvement of the proteasome complex as discussed above and in a recent review article [182]. Briefly, the proteasome complex regulates transcriptional activation in a proteolysis dependent as well as independent manner. The proteolytic function of the proteasome regulates gene activation by controlling the abundance, localization and destruction of activators, destruction of co-activator or co-repressor, and disassembling the PIC. The non-proteolytic function of the proteasome has been implicated to control the interaction of activator with co-activator or promoter, and modulate chromatin structure for regulation of gene activation.

Although a large number of studies have significantly enriched our knowledge on the regulatory mechanisms of gene activation by TFIID and SAGA, these two distinct mechanisms of transcriptional activation have been deciphered from the studies of a selective set of RNAPII genes. However, how general these two distinct mechanisms of transcriptional activation are not fully explored. In addition, there is a small subset of RNAPII genes whose transcription is dependent on both the TFIID and SAGA complexes [38]. However, the mechanisms of transcriptional activation of these genes remain unclear. Further, how these gene regulatory mechanisms are controlled by the proteasome in a proteolysis-dependent or independent manner is yet to be deciphered. It would also be interesting to determine in mammals how conserved these mechanisms are. Investigations of these important questions will shed much light on the complex regulatory mechanisms of gene activation, and thus, will certainly provide crucial information for designing the therapeutic agents to maintain normal cellular function, since a large number of human diseases are correlated with the altered patterns of gene expression.

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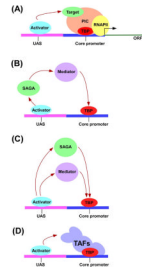


Figure 1.

Schematic representations of SAGA and TFIID-dependent transcriptional activation. **(A)** The transcriptional activator that binds to the UAS of the promoter stimulates the formation of the PIC assembly at the core promoter through interaction with one or more components of the transcriptional initiation machinery, termed as “target”. The schematic representation of how different activator–target interactions stimulate TBP recruitment at the **(B and C)** SAGA and **(D)** TFIID-dependent promoters. Subsequent to TBP recruitment, formation of the PIC continues to initiate transcription [1–4].

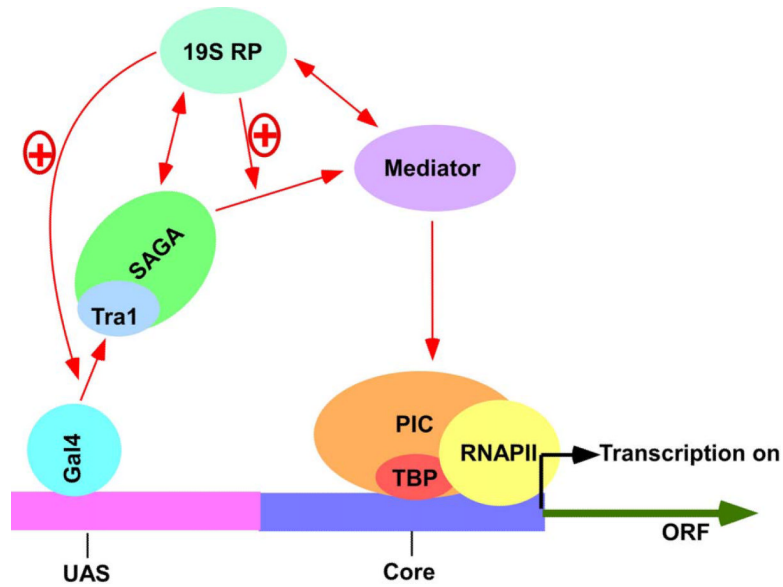


Figure 2.

A model showing the role of the 19S RP in regulation of transcriptional activation of the *GAL1* genes *in vivo*. The activator, Gal4p recruits SAGA to the *GAL1* UAS through its interaction with Tra1p [27]. However, the targeting of SAGA to the *GAL1* UAS is less efficient in the absence of the 19S RP [210]. The ATPase activity of the 19S RP enhances SAGA targeting to the *GAL1* UAS in a positive feedback manner [210]. Similar enhancement of SAGA targeting has also been demonstrated by biochemical studies [207]. The 19S ATPase activity is also essential for recruitment of the Mediator complex [210]. Mediator is required for formation of the PIC [27]. Further, in support of this model, several interactions have been demonstrated by biochemical and genetic studies [126,127,207,211–213,221]. For example, Lee et al. [207] have shown the physical and genetic interaction between SAGA and 19S RP. Sun et al. [221] have demonstrated the physical interaction between Mediator and the 19S RP. Functional and genetic interactions between SAGA and Mediator have also been reported [126,127]. Further, several biochemical studies have shown the physical interaction of the 19S RP with the components of the PIC [211–213]. However, whether these interactions occur directly *in vivo* remains to be investigated. “+” refers “stimulation”.

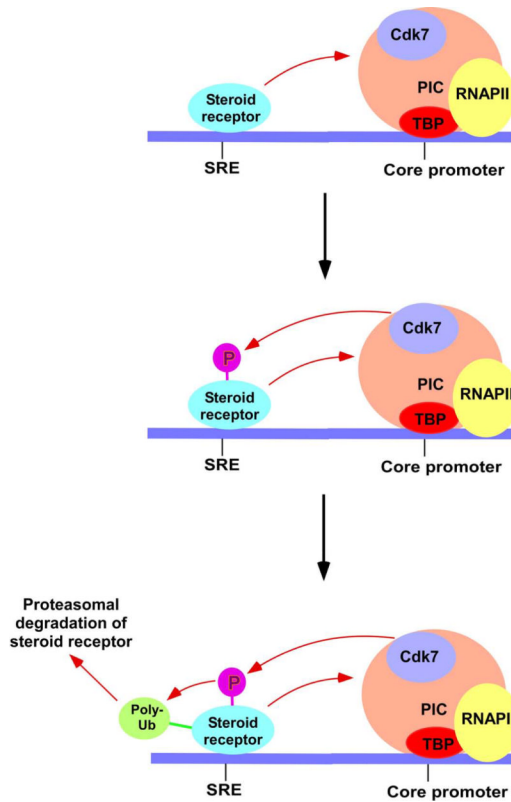


Figure 3.

Schematic representations showing the destruction of the steroid receptors in a transcription-dependent manner. In the first round of transcriptional activation, receptor stimulates the assembly of GTFs to form the PIC, and then the component of the basal transcription machinery (e.g. the Cdk7 component of TFIIF) facilitates phosphorylation of the steroid receptor. Such phosphorylation triggers polyubiquitination of steroid receptor which is subsequently recognized and degraded by the 26S proteasome. SRE, steroid response element; p, phosphorylation; and Ub, ubiquitylation.