

Histone Acetyltransferase GCN5

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Transcription of protein-encoding genes starts with forming a pre-initiation complex comprised of RNA polymerase II and several general transcription factors. To activate gene expression, transcription factors must overcome the repressive chromatin structure, which is accomplished with multiprotein complexes. Histone Acetyl Transferases (HAT) catalyze acetylation of specific lysine residues in histone N-tails, which are involved in transcriptional regulation and other nuclear processes. HATs are parts of large multiprotein complexes, like the SAGA complex, where their activity is enhanced, and their substrate specificity is altered. The whole complex is recruited to target sequences on the genome with other components involved in protein-protein interactions. A prototypical HAT which acts as a transcriptional adaptor is known as General Control Nonrepressed protein 5 (GCN5), first identified in *Saccharomyces cerevisiae*. GCN5 was defined biochemically as the first transcription-linked HAT with specificity for histone H3 lysine 14 (H3K14). However, GCN5 could also acetylate additional histone lysine residues, such as H3K9, H3K18, H3K23, H3K27, H3K36, other histones such as H4 and H2B and non-histone nuclear proteins. In *Arabidopsis*, GCN5 is required for many developmental processes such as leaf development, apical dominance, root meristem activity, inflorescence, floral meristem function and flower fertility.

Arabidopsis thaliana

Viridiplantae

GCN5

ADA2b

SGF29

ADA3

plant development

plant stress responses

SAGA

histone acetylation

1. The Discovery of Histone Acetyltransferase GCN5 and the Associated SAGA Complex

Transcription of protein-encoding genes starts with forming a pre-initiation complex comprised of RNA polymerase II and several general transcription factors ^[1]. To activate gene expression, transcription factors must overcome the repressive chromatin structure, which is accomplished with multiprotein complexes ^[2]. Chromatin-modifying coactivators dynamically deposit or remove post-translational modifications (PTMs) on histones, creating or erasing docking surfaces for specific regulatory factors ^[2]. One class involves complexes that modify the nucleosomal histones through acetylation, phosphorylation, methylation and other modifications ^[3]. Histone acetyltransferases (HATs) catalyze acetylation of specific lysine residues in histone N-tails, which are involved in transcriptional regulation and other nuclear processes. HATs are parts of large multiprotein complexes, like the SAGA complex, where their activity is enhanced and their substrate specificity is altered. The whole complex is recruited to target sequences on the genome with other components involved in protein-protein interactions ^[4]. HATs and histone deacetylases (HDACs) can target promoters for either the activation or suppression of gene expression ^[2]. A prototypical HAT which acts as a transcriptional adaptor is known as GENERAL CONTROL NON-REPRESSED

PROTEIN 5 (GCN5), first identified in *Saccharomyces cerevisiae* [5][6]. GCN5 was defined biochemically as the first transcription-linked HAT [7] with specificity for histone H3 lysine 14 (H3K14) [8]. However, GCN5 could also acetylate additional histone lysine residues, such as H3K9, H3K18, H3K23, H3K27, H3K36, and other histones such as H4 and H2B [9][10]. Furthermore, GCN5 was the HAT component of two distinct transcriptional adaptor complexes, SAGA (Spt-Ada-Gcn5-acetyltransferase) and ADA, capable of acetylating histones in nucleosomes [9]. These complexes are conserved in many eukaryotes [11] and have multiple distinct functions which lead to transcriptional activation. In yeast, SAGA is a large multi-subunit protein complex composed of at least 19 proteins [11][12]. These proteins are separated into four distinct modules, with two specific enzymatic activities: the HAT module that acetylates histones and contains GCN5, ADA2, ADA3, and SGF29; the deubiquitylase (DUB) module that triggers deubiquitination of histone H2B and includes UBP8, SGF11, SGF73, and SUS1; the suppressor of Ty (SPT) module that contains TRA1, ADA1, SPT3, SPT7, SPT8, and SPT20 (ADA5), and the TATA-binding protein (TBP)-associated factor (TAF) module that includes TAF5, TAF6, TAF9, TAF10, and TAF12 [4][12]. Recently, new structural studies showed that most of the proteins of SPT and TAF modules form a core module (COREm) [13][14]. The core module binds to TBP and consists of subunit TAF5, SPT20, and a histone octamer-like fold. The histone octamer-like fold comprises the heterodimers TAF6-TAF9, TAF10-SPT7, TAF12-ADA1, and two histone-fold domains in SPT3 [13][14]. SGF73 subunit is in association with DUBm and COREm. When a nucleosome binds to a SAGA complex, the HAT and the DUB modules are displaced from the COREm [14]. Several proteins in the SAGA complex have distinct protein-binding domains, writers, or readers domains (HAT, tudor, bromodomains etc.) that enable SAGA to associate with chromatin or other proteins through PTMs. Furthermore, SAGA proteins are also part of other complexes [11]. For instance, GCN5 is also part of the human ATAC complex [15]. TRA1 is also a component of the NuA4 acetyltransferase complex [16]. The proteins of the TAF module are also components of the TFIID complex [17].

2. The Plant SAGA Complex

Using the genome of *Arabidopsis thaliana* as a reference for plants, the SAGA complex is comprised of approximately 24 proteins (Figure 1). Using the current structure of the yeast SAGA complex [13][14] the HAT module (HATm) in *Arabidopsis* consists of the same proteins, GCN5, ADA2, ADA3, and SGF29. However, the *Arabidopsis* HATm contains two subunits of ADA2, ADA3, and SGF29 (designated as ADA2a, ADA2b, ADA3a, ADA3b, SGF29a, and SGF29b, respectively). Based on this structure, the *Arabidopsis* COREm consists of similar TAF proteins (TAF5, TAF6, TAF9, TAF10, and TAF12), and the adaptor proteins ADA1 and SPT20. The yeast SPT module consists of another three subunits SPT3, SPT7, and SPT8, distinct from the plant homologues. For instance, in *Arabidopsis* genome, SPT8 is not encoded; however, the presence of multiple WD40 domains in yeast Spt8 makes the evolutionary information challenging [15]. Furthermore, *Arabidopsis* SPT3 homologue is like TAF13, whereas SPT7 homologues appear to have a conserved bromodomain found in AtHAF1 (TAF1) subunit. Interestingly, several subunits from the COREm are duplicated in *Arabidopsis* including ADA1, TAF6, and TAF12. The COREm occupies a central position in the complex and is connected to the TRA1 module through TAF12-SPT20 interaction [13][14]. In *Arabidopsis*, TRA1 has two homologues (TRA1a and TRA1b). In yeast, Tra1 recruits SAGA to promoters through the interaction with transcription factors [16]. In *Arabidopsis*, TRA1a and TRA1b

promote H2A.Z deposition at the whole-genome level as part of the activity of SWR1 complex [18]. Finally, the DUB module (DUBm) is partially present in *Arabidopsis* genome, consisting of the UBP22 protein that deubiquitinates histone H2B, a second enzymatic activity of the complex, and the associated proteins SGF11 and ENY2. The fourth subunit of yeast DUBm, SGF73, is absent in *Arabidopsis*, suggesting that DUBm may function as H2Bub1 deubiquitinase independent from SAGA complex [19][20].

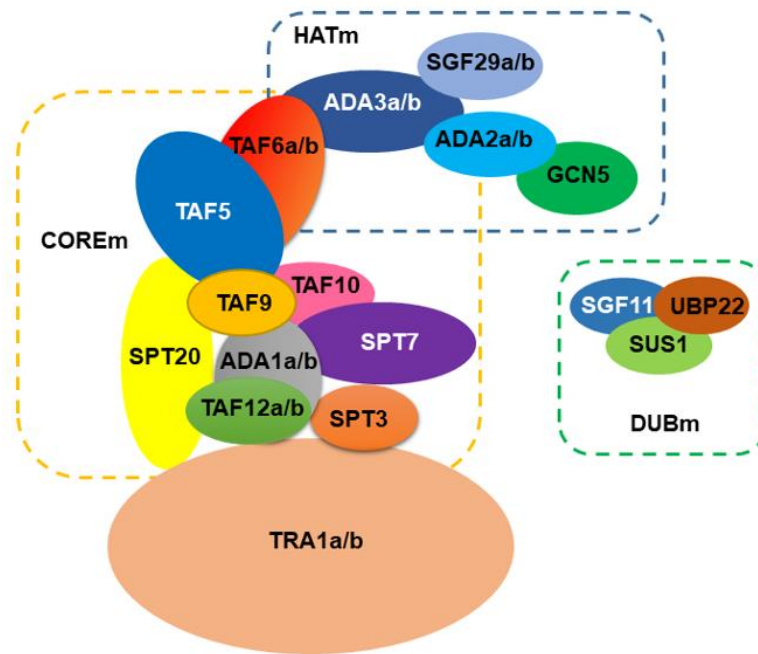


Figure 1. A model for the organization of SAGA complex in *Arabidopsis*.

In multi-cellular eukaryotes, SAGA (or GCN5-containing) complexes appear to have an essential role in development [21]. Likewise, in *Arabidopsis*, *gcn5* mutants have pleiotropic effects on every development aspect (Table 1) [22][23]. Furthermore, mutations in another HATm subunit ADA2b, result in pleiotropic phenotypes on every part of the whole plant life cycle; however, some are different from *gcn5* mutants [22][24]. Moreover, both *gcn5* and *ada2b* mutants are implicated in plant responses to abiotic and biotic stress [22][25][26][27]. The other components of HATm in *Arabidopsis* do not affect plant development; however, the role of ADA2a on plant development is made redundant by the ADA2b function, since the *Arabidopsis* double mutant *ada2aada2b* phenocopies the *gcn5* mutation [28]. Mutation in *SGF29a* is implicated in salt stress responses by having an auxiliary role to ADA2b [29]. These genetic interactions, together with the biochemical data showing that GCN5 acts through ADA2b and ADA2a [30][31], suggest that different versions of GCN5-containing (SAGA) complexes may exist in plants.

Several subunits of the COREm, like TAF5 and TAF6a, are required for plant viability [32][33]. In addition, both TRA1 genes are also essential for plant life cycle [33]. These functions may not be specific to SAGA complex since TAF5 and TAF6 are also present in the TFIID complex, and TRA1 is also a component of the NuA4 histone acetyltransferase complex. The other members of COREm, like the SPT20 and TAF10, are implicated in environmental stresses [34][35]. TAF12b (also known as EER4 or CHK1) is involved in ethylene and cytokinin responses [36][37]. Finally, the DUBm components in *Arabidopsis* are not crucial for proper plant development [20][38].

Table 1. Comparison between *Arabidopsis* and known yeast SAGA subunits.

SAGA Modules	Yeast	<i>Arabidopsis thaliana</i>	<i>Arabidopsis</i> Mutant Phenotype
HATm	GCN5	GCN5 (AT3G54610, HAG1)	Pleiotropic effects on development and responses to stress [22] [23] [25] [26]
	ADA2	ADA2b (AT4G16420, PRZ1)	Pleiotropic effects on development and responses to stress [22] [24] [27]
		ADA2a (AT3G07740)	No developmental abnormalities [28]
	ADA3	ADA3a (AT2G19390)	Involved in flowering (Vlachonasios, under review)
		ADA3b (AT4G29790)	No developmental abnormalities [39]
	SGF29	SGF29a (AT3G27460)	No developmental abnormalities [29]
		SGF29b (AT5G40550)	No developmental abnormalities [29]
	ADA1	ADA1a (AT2G24530)	Not available
		ADA1b (AT4G31440)	Not available
	SPT3	TAF13 (AT1G026280)	Seed development [40]
COREm	SPT7	HAF1 (AT1G32750, HAC13, TAF1)	Light responses [41]
	SPT8	Not detected	

	SPT20	SPT20 (AT1G72390)	Late flowering [34]
	TAF5	TAF5 (AT5G25150)	Lethal [31]
	TAF6	TAF6a (AT1G04950)	Lethal [32]
		TAF6b (AT1G54360)	
	TAF9	TAF9 (AT1G54140)	Not available
	TAF10	TAF10 (AT4G31720)	Involved in osmotic stress [35]
	TAF12	TAF12a (AT3G10070)	
		TAF12b (AT1G17440, EER4, CKH1)	Involved in ethylene and cytokinin responses [36] [37]
TRA1m	TRA1	TRA1a (AT2G17930)	Early flowering [33]
		TRA1b (AT4G36080)	No developmental abnormalities [33]
	SGF73	Not detected	
DUBm	SGF11	SGF11 (AT5G58575)	No developmental abnormalities [38]
	UBP8	UBP22 (AT5G10790)	No developmental abnormalities [20]
	SUS1	SUS1 (AT3G27100, ENY2)	No developmental abnormalities [38]

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