Published in final edited form as:
Trends Biochem Sci. 2017 November ; 42(11): 850–861. doi:10.1016/j.tibs.2017.09.001.

Sharing the SAGA

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Abstract

Transcription initiation is a major regulatory step in eukaryotic gene expression. Co-activators establish transcriptionally competent promoter architectures and chromatin signatures to allow the formation of the preinitiation complex, comprising RNA polymerase II and general transcription factors (GTFs). Many GTFs and co-activators are multi-subunit complexes, in which individual components are organized into functional modules carrying specific activities. Recent advances in affinity purification and mass spectrometry analyses have revealed that these complexes often share functional modules, rather than containing unique components. This observation appears remarkably prevalent for chromatin modifying and remodeling complexes. Here, we use the modular organization of the evolutionary conserved SAGA complex as a paradigm to illustrate how co-activators share and combine a relatively limited set of functional tools.

Keywords

Transcription; chromatin; multi-subunit complex; functional module; assembly; protein-protein interaction

Modular organization of transcription co-activator complexes

Formation of the transcription preinitiation complex (PIC), containing RNA polymerase II (Pol II) and general transcription factors (GTFs), is a major regulatory step in eukaryotic gene expression. PIC formation and accessibility of template DNA to the transcription machinery is controlled by the degree of chromatin compaction. Co-activator complexes have critical roles in this process, by regulating PIC formation through direct interactions with basal transcription factors, by ATP-dependent nucleosome remodeling, and by covalent modification of histones. Chromatin modifying co-activators dynamically deposit or remove post-translational modifications (PTMs) on histones, creating or erasing docking surfaces for specific regulatory factors ([1, 2] and refs therein).

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Numerous biochemical and genetic evidence indicate that each co-activator complex harbors several different activities that are coordinately regulated [3–9]. Typically, each activity is carried out by one specific module, which is composed of several subunits containing defined protein domains. Thus, co-activator complexes are built from the physical association of a defined set of functional tools, which, in combination, have specific regulatory roles. Until recently, these complexes were thought to be formed by unique components. Strikingly, however, it is becoming apparent that they share many subunits. Interestingly, the identification and characterization of transcription complexes and their components have established unexpected links between complexes with seemingly separate functions. Biochemical purifications of these complexes show that they form very stable assemblies that are resistant to high salt concentrations during purification (0.5-1M) [10–14]. Therefore, the evolutionary conserved modules discussed within this review cannot be considered as transient interacting modules that form and disassemble continuously.

Several, non-mutually exclusive possibilities may account for this phenomenon. First, shared components may be important to coordinate the activities of distinct complexes. For example, controlling the activity of a histone-modifying module in response to signaling cues may co-regulate all complexes containing it. Similarly, sharing a histone mark reader will allow the coordinated recruitment of distinct complexes to specific loci. Second, shared components may represent a common tool, which is used by different complexes to perform similar functions. However, in this scenario, it is equally possible that the specific subunit composition of each complex will modulate the activities, localization, or substrate specificity of the shared module. Third, this phenomenon may also reflect evolution from a common ancestor complex, particularly for complexes that carry related activities. Supporting this hypothesis, many different paralogous subunits can be found within co-activator complexes. As shown by others, interactions between paralogous proteins are highly versatile and appear systematically selected for during evolution [15].

The SAGA complex (Spt-Ada-Gcn5 acetyltransferase) is an evolutionary conserved, multifunctional co-activator composed of about 18-20 subunits [16]. Numerous genetic, biochemical and structural evidence indicate that SAGA subunits are organized into separate modules with distinct activities: a structural core, a histone acetyltransferase (HAT), a histone deubiquitinase (DUB), and an activator binding module (Table 1) [17, 18]. In metazoans, SAGA also contains a splicing module (Table 1). Early genetic studies, predominantly performed in yeast, first revealed the modular organization of SAGA. For example, genes encoding components of the HAT module, but not genes encoding the DUB module, were isolated as suppressors of VP16 toxicity in yeast [19]. Similarly, Spt3 was isolated as an allele-specific suppressor of a TATA binding protein (TBP) mutant and specific alleles of *SPT3* suppress an *SPT8* deletion mutation [20, 21]. Together with the biochemical characterization of SAGA, electron microscopy and cross-linking mass spectrometry studies then unequivocally demonstrated the modular nature of SAGA architecture [22–25]. In this review, we use the SAGA co-activator complex as a paradigm to illustrate the recently observed tool sharing phenomenon between complexes and discuss how and why functional modules of multi-subunit transcription regulators are shared with other complexes.

Sharing the core structural module between SAGA and TFIID

SAGA and the Pol II GTF, TFIID, share a subset of TBP associated factors (TAFs) that are important for the function of both complexes. Interestingly, nine TAFs of TFIID and seven subunits of SAGA contain histone fold domains [26, 27] (Table 1). Five subunits are shared between SAGA and TFIID in *Saccharomyces cerevisiae* (sc). These are Taf5, 6, 9, 10, and 12 (Figure 1). In metazoans, gene duplication has led to the appearance of genes that encode for proteins that are similar to TAF5 and TAF6, called TAF5L and TAF6L, which became SAGA specific subunits (Table 1). In contrast, TAF9, TAF10 and TAF12 are shared between SAGA and TFIID in most species, although there are notable exceptions to this rule. A recent study has identified two paralogs of Taf12 in the human pathogenic yeast *Candida albicans*, each encoding a distinct protein, Taf12 and Taf12l, which specifically associates with TFIID or SAGA, respectively [28]. Furthermore, *Schizosaccharomyces pombe* (sp) has two paralogous Taf5 proteins, Taf5, which is found in both SAGA and TFIID, and Taf5l, which is only found in TFIID [29]. It is therefore conceivable that *S. pombe* Taf5 represents an intermediate of Taf5 specialization between SAGA and TFIID. Similarly, *Drosophila melanogaster* (dm) has two paralogous Taf10 proteins, one specific to TFIID (dmTAF10) and one shared between TFIID and SAGA (dmTAF10b) [30, 31].

We have recently reported the cryo-electron microscopy structure of a human TFIID core subcomplex, which is comprised of two copies of the histone fold containing proteins TAF4-12, TAF6-9, and the WD-40-containing protein TAF5. Incorporation of the histone fold containing TAF8-TAF10 heterodimer into this complex generates an asymmetric TFIID core complex. We have also suggested that this core subcomplex acts as a scaffold to assemble the remaining TFIID subunits [32]. All of the above-mentioned TAFs are also subunits of scSAGA, with the exceptions of TAF4 and TAF8, which are functionally replaced by Ada1 and Spt7, respectively. The SAGA subunit Ada1 has a histone fold domain homologous to that of TAF4 and forms a histone fold pair with TAF12 [33]. scSpt7/hSUPT7L has a histone fold domain homologous to TAF8 and pairs with TAF10 [34, 35]. Crosslinks between scTaf12 and scAda1, and between scTaf10 and scSpt7, have been observed next to the histone fold domains, suggesting that these proteins form heterodimers through histone fold pairing within the SAGA complex [24, 25]. Altogether, these observations suggest that SAGA contains a TFIID-like structural core [25, 32]. In good agreement, crosslinking experiments further suggest that the central TFIID-like core structure of SAGA is a scaffold for assembling all the other SAGA modules [24, 25] (Figure 1). It has been reported that in the human TFIID core, TAF4, 5, 6, 9, and 12 are present in two copies, however, whether this is the case for SAGA it is not yet entirely clear and needs further investigations. In SAGA, an additional protein, scSpt3/hSUPT3H, contains an intramolecular double histone fold domain (Table 1) resembling the TAF11/13 histone fold pair [36]. Therefore, it is possible that the incorporation of scSpt3/hSUPT3H into the TFIID-like core structure of SAGA further increases the resemblance between the TFIID and SAGA scaffolds. In conclusion, it seems that SAGA and TFIID evolved from a common ancestor transcription complex, with a shared structural scaffold composed of histone fold-containing proteins and a WD-40 repeat-containing subunit, which may be present at earlier evolutionary steps.

Sharing the histone acetyl transferase (HAT) module between SAGA, ADA and ATAC complexes

Histone acetylation on lysine residues activates gene expression by opening chromatin structure and by creating docking surfaces for other regulatory factors [37–40]. GCN5 (also called KAT2A) was the first histone acetyltransferase (HAT) enzyme identified with a role in transcription. It contains a bromodomain, which binds to acetylated lysine residues. Gcn5 forms an independent HAT module, together with Ada2, Ada3, and Sgf29 (Table 1), which is connected to the rest of SAGA by Ada2 [17]. In budding yeast, SAGA shares the HAT module with the scADA complex, which additionally contains two specific subunits, Ahc1 and Ahc2 (Figure 1) [17, 41]. The HAT module within the SAGA and ADA complexes acetylates histone H3, mainly on residues K9 and K14. The observation that the ADA complex does not contain Tra1 to target it to gene promoters through activators (see below) suggests that the ADA HAT complex may contribute to maintain overall H3 acetylation in the genome [17].

Metazoan GCN5 was identified in SAGA, but also as a subunit of a second co-activator complex with HAT activity in *Drosophila* and mammals, named ATAC (Ada Two A Containing) [42, 43]. Remarkably, metazoans have two paralagous Ada2 proteins: ADA2a and ADA2b [44, 45]. Whereas ADA2b is specific to the HAT module of the SAGA complex, ADA2a is specific to the HAT module of the ATAC complex, together with GCN5, ADA3 and SGF29 [16, 44, 45] (Figure 1). All four subunits of the SAGA or ATAC HAT modules are needed for full and specific acetylation activity [46].

Whereas SAGA complexes preferentially acetylate histone H3K9 and H3K14 lysine residues *in vivo* [47–50], the substrate specificity of the metazoan ATAC complexes is less well understood [43, 51, 52]. Knock down of dmATAC subunits reduces acetylated H4K5, H4K12, and H4K16 levels [53–55]. In contrast, similar loss of function experiments in mammalian cells suggested that hATAC acetylates preferentially histone H3 rather than H4 [43, 51, 52]. A recent mass spectrometry-based strategy in *Drosophila* KC cells following RNAi ablation of GCN5 (present in dmATAC and dmSAGA), demonstrated a decrease in H3 acetylation marks, in the following order: H3K9+K14> H3K9 > H3K14 > H3K27 = H3K36 [50]. Note that in this study no changes in H4 acetylation were reported after GCN5 knockdown suggesting potentially redundant activity of other HATs on H4. Interestingly, this compensatory activity did not occur on H3 *in vivo*. Furthermore, knockout of yeast Gcn5, or knockdown of the ATAC and SAGA HAT module activity in mammalian cells significantly decreased H3K9ac levels at all active gene promoters [49]. Likewise, deletion of GCN5 and of its paralog PCAF (also called KAT2B) specifically and dramatically reduced acetylation of H3K9 in mammalian cells [56].

To conclude, the HAT module of SAGA is shared with two related HAT complexes. ADA likely acetylates similar histone H3 residues as SAGA, whereas it is possible that the HAT module of ATAC changes its substrate specificity to histone H4, at least in *Drosophila*. In agreement, it has been suggested that the C-terminal regions of dmADA2a and dmADA2b is crucial for their specific incorporation into either SAGA or ATAC, respectively, which in turn determines H3- or H4-specific histone targeting [57]. Moreover, the ATAC2 subunit of

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dmATAC carries a second HAT activity, different from GCN5, and histone H4K16 acetylation is reduced in Atac2 mutant embryos [55]. It is therefore tempting to speculate that SAGA, ADA, and ATAC acetylate histone H3, and possibly H4, at different genomic locations through distinct mechanisms of recruitment and/or because of the different overall subunit context of each complex.

Variants of the histone deubiquitination (DUB) module of SAGA

Mono-ubiquitinated histone H2B is deubiquitinated by the DUB module of SAGA [58–62]. The scSAGA DUB module contains the catalytic subunit Ubp8 as well as Sgf11, Sus1, and Sgf73 [63, 64]. The DUB module is an independently structured module, which is connected to the remainder of the SAGA complex by the C-terminal portion of Sgf73 [25, 65]. The subunit composition and organization of the DUB module are conserved in metazoans, in which it is composed of USP22, ATXN7L3, ATXN7 and ENY2 (Table 1) [31, 60, 62]. The structure of the scDUB module revealed a highly-intertwined arrangement for its four subunits, Ubp8, Sgf11, Sgf73, and Sus1 [64, 66]. Consistent with these results, DUB activity assays using both yeast and human DUB modules show that all four subunits are required to maintain the scUbp8/hUSP22 catalytic enzymes in an active conformation [62, 66]. Interestingly, one of the gene coding for a human SAGA DUB module subunit has undergone diversification through gene triplication, as mammalian genomes contain two other paralogs of the *ATXN7* (*SCA7*) gene, called *ATXN7L1* and *ATXN7L2*. Thus, mammalian cells express three proteins that belong to the ATXN7 family (ATXN7, ATXN7L1 and ATXN7L2). Mass spectrometric analyses of purified human or mouse SAGA complexes indicated that ATXN7, ATXN7L1 and ATXN7L2 can all incorporate in SAGA. Together with structural data, these observations suggest that the presence of ATXN7, ATXN7L1 and ATXN7L2 in the mammalian SAGA DUB module is mutually exclusive ([67], our unpublished data and Table 1). Thus, in mammalian cells, three distinct SAGA DUB modules may exist, but whether they have distinct functions it is not yet known.

Recently, two previously uncharacterized DUB modules have been described [68]. Two human SAGA DUB subunits, ATXN7L3 and ENY2, interact with either of two different USP22-related deubiquitinating enzymes, USP27X or USP51. In agreement with the absence of interaction with the human ortholog of scSgf73, ATXN7, these variant DUB modules are indepdnent complexes and do not interact with SAGA [68] (Figure 1). This work suggested that the SAGA DUB and the two related DUB modules have redundant functions in H2Bub1 deubiquitination and compete for limiting amounts of cellular ATXN7L3 and ENY2. Imbalance in one USP may affect the activities of the other DUBs by modulating the availability of the ATXN7L3 and ENY2 adaptor proteins. Importantly, the exact substrate specificity of the SAGA DUBs containing ATXN7, ATXN7L1, or ATXN7L2 and of the two newly identified DUB variants is not well understood and needs further investigation.

ATXN7L3 also has a paralog in humans, called *ATXN7L3B*. ATXN7L3B and ATXN7L3 share 74% identity within their N-terminal ~60 amino acid residues, including a region that interacts with ENY2 and called the Sus1-binding region, after the yeast ENY2 homolog [69]. Despite their sequence similarity, ATXN7L3B predominantly localizes to the

cytoplasm, whereas ATXNL3 is nuclear, similar to SAGA [70]. Accordingly, ATXN7L3B interacts strongly with ENY2, but not with other SAGA components ([70] and our unpublished observations) (Figure 1). Thus, the ATXN7L3B-ENY2 interaction could limit SAGA DUB activity by sequestering ENY2 in the cytoplasm and competing with ATXN7L3 for the formation of active DUB modules [70].

To conclude, the existence of many related DUB modules suggest that an intricate and well-controlled mechanism allows cells to modulate DUB-containing complex composition and activity, for example in response to changing conditions. Competition between related DUB components may favor the assembly of one type of functional module over another one.

Sharing the DUB module component, Sus1/ENY2, with TREX-2

The DUB module subunit, scSus1/hENY2, is also a subunit of the nuclear pore associated transcription export complex 2 (TREX-2) [71, 72]. Within scTREX-2, Sus1 binds to the Sac3 scaffold to which Thp1, Sem1, and Cdc31 associate. In humans, the evolutionary conserved TREX-2 complex contains ENY2, which binds to the GANP scaffold together with PCID2, DSS1, CENT2 and CENT3. In both cases, it was suggested that two molecules of scSus1, or hENY2, wrap around the α-helical region of the carboxy-terminal domains of either scSac3, or hGANP proteins. These interactions seem to be crucial for the stabilization of the scaffolds and thus for the function of the corresponding TREX-2 complexes [73, 74]. Similarly, ENY2 has been also shown to stabilize ATXN7L3 in the above-described mammalian DUBs [74] (Figure 1). Structural analyses confirm that the architectural role of Sus1 is conserved between SAGA and TREX-2. Therefore, sharing scSus1/hENY2 between both complexes appear to result from the selection of a similar structural interface. In addition, the sharing of Sus1 between SAGA and TREX-2 may serve to couple transcription with mRNA export, although Sus1 interactions with either Sgf11 or Sac3 are mutually exclusive, leaving this question open.

Sharing the Tra1/TRRAP subunit between SAGA and NuA4/TIP60

The SAGA subunit scTra1/hTRRAP is the largest component of SAGA (~420 kDa) (Table 1). Yeast scTra1 and hTRRAP belong to the family of phosphoinositide 3 kinase-related kinases (PIKKs), with which it shares many structurally related protein-protein interaction domains [75]. However, scTra1/hTRRAP lack the catalytic residues required for kinase activity and is the only pseudo-kinase of the PIKK family. Most relevant to the sharing of SAGA components, scTra1/hTRRAP is also an integral component of the NuA4/Tip60 complex, which is another conserved transcriptional co-activator with HAT activity (Figure 1) [76]. However, in contrast to the SAGA HAT module, which preferentially acetylates histone H3, the NuA4/TIP60 subunit scEsa1/hTip60 acetylates histone H4, H2A, and H2A.Z [77–79]. Therefore, sharing Tra1/TRRAP between these two co-activator complexes appear as an example of sharing a similar structural platform for the recruitment of distinct HAT complexes to chromatin.

In strong support of this interpretation, many biochemical studies have shown direct interaction between scTra1/hTRRAP and several different transcription factors, including

yeast Gal4 and Gcn4 or human c-MYC and E2F1 [80–85]. Additionally, a kinetic analysis of the recruitment of SAGA and TIP60 subunits upon transcription activation revealed that TRRAP is recruited before GCN5 or TIP60 [86]. Together with its large size and lack of kinase activity, this function of scTra1/hTRRAP suggests that it serves as a major target of promoter-bound activators, providing a flexible scaffold for the assembly and recruitment of co-activator complexes to target loci.

Genetic analyses using partial loss of function or conditional mutant alleles have implicated Tra1/TRRAP in a number of important processes, including cell proliferation and differentiation, but it has been difficult to determine whether these roles are mediated through SAGA or NuA4/Tip60 [80]. However, our work has shown that *S. pombe* provides a unique opportunity to address this issue. In marked contrast with *S. cerevisiae* and mice, spTra1 is not required for viability in *S. pombe* because its genome encodes two paralogous proteins, spTra1 and spTra2, which have non-redundant roles that are specific for SAGA or NuA4, respectively [18]. Indeed, a *tra2*Δ deletion mutant is inviable in *S. pombe* and biochemical analyses demonstrated that spTra1 specifically associates with SAGA, whereas spTra2 is only found in NuA4. These results suggest that, in *S. cerevisiae*, the single *TRA1* gene is essential for viability because of its role within the NuA4 complex [87]. *S. pombe* therefore allows to address the specific contribution of Tra1/TRRAP to SAGA or NuA4/TIP60 functions and to decipher whether Tra1/TRRAP assembles and functions similarly between both complexes.

Sharing splicing factors between SAGA and U2 snRNP

In 2001, we and others have described that hSAGA associates with spliceosome-associated protein 130 (SAP130, now called SF3B3) [88, 89]. SF3B3 is a component of the splicing factor SF3B that associates with U2 snRNP and is recruited as a first step to the pre-spliceosomal complexes. This finding was then confirmed by quantitative SILAC-based interaction proteomics and by Orbitrap-based mass spec identification of endogenous SAGA complex subunits [67] and our unpublished data). In addition, both studies also identified SF3B5, an SF3B3 interaction partner in the SF3B complex, as a *bona fide* SAGA subunit (Figure 1 and Table 1). Recently, in *D. melanogaster* the orthologous SF3B U2 snRNP complex subunits, SF3B3 and SF3B5, were also detected in dSAGA [90]. Thus, metazoan, but not yeast, SAGA complexes contain an additional module with two splicing factors, which we named the splicing module (Figure 1). However, the function of this module is not well understood. As SF3B3 shares homology with the large subunit of UV-damaged DNA-binding factor, DDB1 (p127), which is a UV-damaged-DNA-binding protein involved in nucleotide excision repair, early studies suggested that SF3B3 could play a role as a molecular link coupling SAGA-dependent chromatin modifications to DNA damage recognition [88, 89]. In contrast, recent work in *Drosophila* concluded that the SF3B3/SF3B5 module has independent roles when associated with the U2 snRNP spliceosome or SAGA [90]. However, an intriguing possibility remains that this module would mediate interactions between SAGA and the U2 snRNP, and thereby contribute to co-transcriptional splicing. Further studies will be necessary to define the role of these spliceosomal factors in metazoan SAGA.

Concluding remarks and future perspectives

Transcription and chromatin regulation have been studied extensively and involve many large, multi-functional complexes. For obvious technical reasons, these complexes have been traditionally studied and considered in isolation. Strikingly, however, these complexes often share subunits and functional modules. Here, we describe this phenomenon for the well conserved transcriptional co-activator SAGA, which shares all of its functional modules with at least one other regulatory complex (Figure 1). These related complexes are involved in transcription initiation, chromatin modification, mRNA export, and splicing.

Sharing functional tools between different regulatory factors is observed for many other chromatin modifying and remodelling complexes. For examples, the yNuA4/hTIP60 complex, which shares the activator binding subunit TRRAP with SAGA, itself shares a protein-protein interaction module with the SWR1-C complex, which itself shares components with the INO80 complex [91]. The SET1 and MLL complexes share a conserved core, important for enzymatic activity, but specific subunits direct each complex to distinct genomic locations to perform non-redundant functions [92, 93]. The RSC and SWI/SNF complexes also share several components, including actin-related proteins, which are crucial for the assembly and function of each complex [94, 95]. Finally, the polycomb repressive complex (PRC) 1 was originally described as a single complex in *Drosophila*. In contrast, mammals possess several paralogs for each *Drosophila* PRC1 subunit, building up at least 6 different, but related, PRC1 complexes (PRC1.1 to PRC1.6) [96]. Such diversification allows each PRC1 complex to carry different combinations of enzymatic activities, *i.e.* histone demethylation or deacetylation, and histone PTM reading properties [97].

As exemplified with SAGA, there are distinctive advantages for reusing and combining similar functional tools. These include the targeting of an enzymatic activity to specific genomic locations or the building of a complex on stable structural folds. However, sharing components between different complexes also pose specific challenges that open novel questions and raise exciting research avenues for the future. First, sharing implies that cells have dedicated mechanisms and chaperones to assemble a shared subunit, or a pre-assembled building block, into complexes with distinct subunit composition and structure. Identifying such chaperones and their mechanisms of action will be critical to understand how cells combine the correct set of tools into an active complex to regulate gene expression in response to signalling cues. Furthermore, it is conceivable that these mechanisms might be subject to regulation. For example, the decision to assemble one or another complex might be controlled by compartmentalization, either during co-translational assembly in the cytoplasm or soon after each building block has been imported into the nucleus. Finally, the expression and localization of shared building blocks may be regulated, depending on different cellular requirements.

Little is known about how cells coordinate the activities of different transcription and chromatin regulatory complexes in response to external cues, beyond their recruitment to chromatin. At present, several distinct signalling pathways involve SAGA and its related complexes, consistent with their prominent roles in the expression of stress-regulated genes.

Shared components are relevant targets for signalling kinases that would coordinate the activities of regulatory factors to establish a specific gene expression program. For example, SAGA and TIP60 function redundantly at some genes [98, 99] and it is tempting to speculate that targeting TRRAP would allow the concomitant recruitment of both co-activators. Alternatively, such kinases may induce rearrangements in the distribution of modules over distinct complexes, thereby promoting the activity and the recruitment of one complex at the expense of another. Biochemical characterization of SAGA complexes from various organisms or cell types suggest that their subunit composition is rather invariant. However, very few studies have yet performed such analyses from cells grown in stress conditions or in which signalling pathways are activated.

Finally, as described for the DUB and HAT modules, many co-activator subunits are encoded by distinct paralogous genes, particularly in metazoans, though not exclusively. The existence of paralogs that are mutually exclusive potentially expands the repertoire of existing SAGA-related complexes. For examples, whether SAGA contains GCN5 or PCAF, or whether it incorporates ATXN7, ATXN7L1, or ATXN7L2, may allow SAGA to diversify its activities and to control additional genes and processes. However, many paralogs have yet unknown functions and little is known about their tissue or cell-type specific expression. Much effort is needed to describe the functions of these paralogs and how they modulate the activity, localization, recruitment, or substrate specificity of each transcription or chromatin regulatory complex. These issues represent other exciting opportunities for future research.

Acknowledgments

This work was supported by the CNRS, INSERM, University of Strasbourg, and University of Montpellier. Work in D.H. laboratory is supported by funds from the CNRS (ATIP-Avenir), the FP7 Marie Curie Actions (FP7-PEOPLE-2012-CIG/COACTIVATOR), the Fondation ARC (PJA-20131200471), the Agence Nationale de la Recherche (ANR-15-CE12-0009-01) and the Labex EpiGenMed, an « Investissements d'avenir » program (ANR-10-LABX-12-01). Work in L.T. laboratory is funded by the European Research Council (ERC) Advanced grant (ERC-2013-340551, Birtoaction) and a grant ANR-10-LABX-0030-INRT, a French State fund managed by the Agence Nationale de la Recherche under the frame program Investissements d'Avenir ANR-10-IDEX-0002-02.

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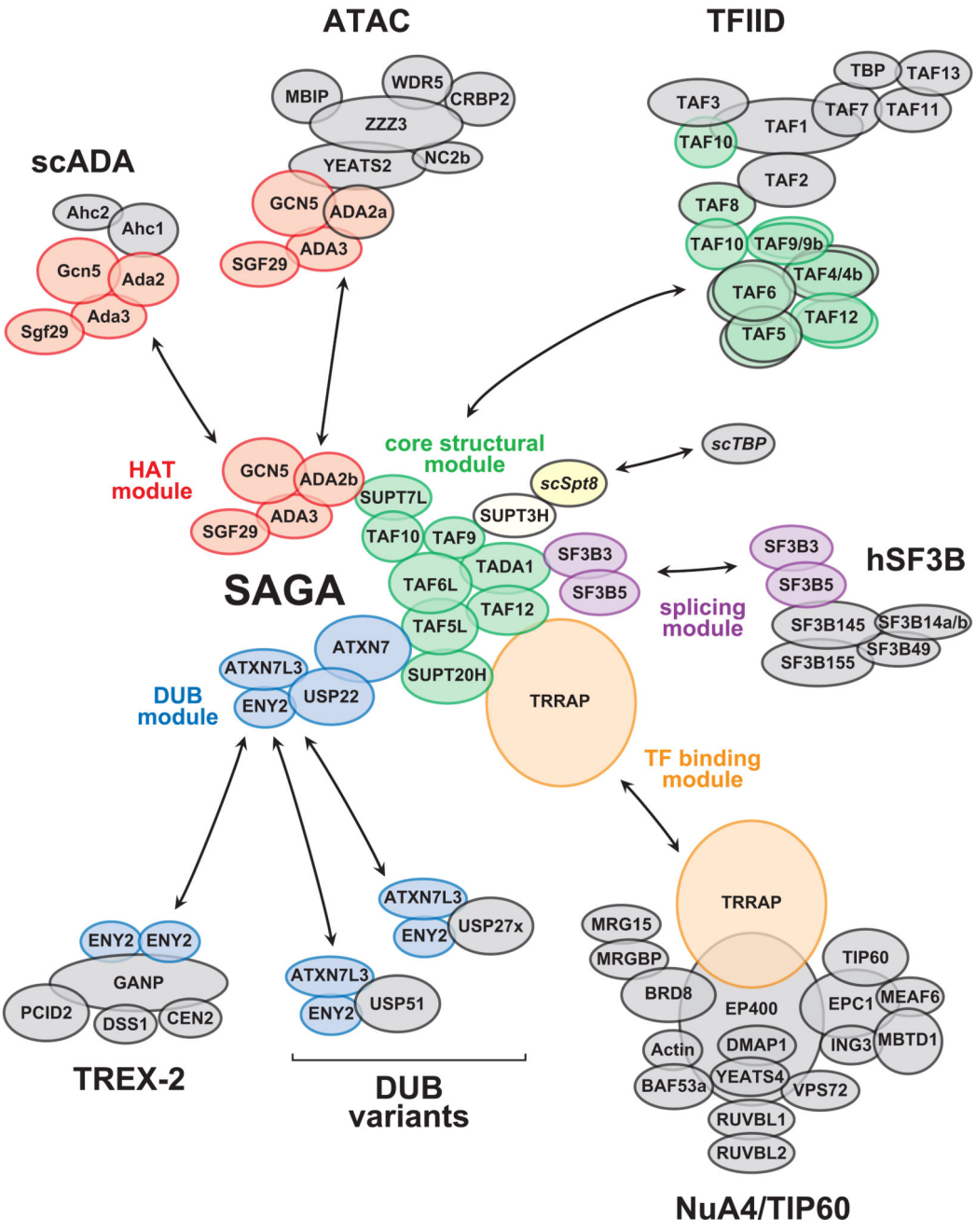

Figure 1. Schematic illustration of the composition of SAGA and the sharing of its components with other regulatory complexes.

For simplification, only human subunit names are shown, unless otherwise indicated (scSpt8 and scTBP). SAGA subunits are organized into structurally and functionally distinct modules that are shared with other regulatory complexes. Shared subunits are drawn identical between distinct complexes. Related subunits are drawn using the same colour, but with a black edge. The histone-acetyltransferase (HAT) module, depicted in red, is shared with the *S. cerevisiae* ADA complex (scADA) and the metazoan ATAC complexes. Several components of the core structural module, in green, form the core of the general

transcription factor IID (TFIID). In *S. cerevisiae*, Spt3 and Spt8 recruit TBP to SAGA, but it is unclear whether such a functional module exists in metazoans, in which SUPT3H might rather be part of SAGA core structural module. The splicing module, in purple, is shared with the human SF3B complex, which associates with the U2 snRNP to initiate splicing. The transcription factor (TF) binding subunit TRRAP, in orange, recruits both the SAGA and yNuA4/hTIP60 complexes to promoters. Finally, the deubiquitinase (DUB) module, in blue, shares both ATXN7L3 and ENY2 with either of the two USP22 paralogous deubiquitinases, USP27x and USP51. In addition, the DUB module component ENY2 is shared with the mRNA export factor TREX-2.

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Table 1

SAGA is a conserved transcriptional co-activator complex organized into well-defined structural and functional modules.

Shown are the names of each subunit from *Saccharomyces cerevisiae (sc)*, *Saccharomyces pombe (sp)*, *Drosophila melanogaster* and *Homo sapiens*, according to the official nomenclature. Names in brackets are alternative, commonly used names. Paralogous subunits are separated with a "/" sign and are indicated if they have been described as part of SAGA. In most cases, paralogous subunits are mutually exclusive within SAGA complexes. Individual module subunits are coloured according to the code used in Figure 1. *The TBP binding module comprises both Spt3 and Spt8 in *S. cerevisiae*. In metazoans, no ortholog of scSpt8 has been found and the histone-fold domains of SUPT3H might rather contribute to SAGA structural core. #The bromodomain is found in *S. cerevisiae* Spt7, but not in its metazoan orthologs. @In *S. pombe*, there are two paralagous genes, *tra1* and *tra2*, but only Tra1 is found in SAGA whereas Tra2 is specific for the NuA4 co-activator complex. Bromo: bromodomain; HFD: histone fold domain.

Functional tools	Orthologous SAGA complexes				Chromatin "reader" domains	Structural domains
	S. cerevisiae	*S. pombe*	*D. melanogaster*	*H. sapiens*		
HAT module	Gcn5	Gcn5	KAT2 (GCN5)	KAT2A/KAT2B (GCN5/PCAF)	Bromo	
	Ada2	Ada2	Ada2b	TADA2b	SANT SWIRM	
	Ngg1 (Ada3)	Ngg1 (Ada3)	Ada3	TADA3		
	Sgf29	Sgf29	Sgf29	SGF29	Tudor (x2)	
DUB module	Ubp8	Ubp8	dNonstop	USP22 (UBP22)		
	Sgf11	Sgf11	dSgf11	ATXN7L3	Nucleosome binding	
	Sgf73	Sgf73	dATXN7	ATXN7/ATXN7L1/L2		
	Sus1	Sus1	dE(y)2	ENY2		
Core structural module	Taf5	Taf5	WDA/TAF5L	TAF5L		WD40
	Taf6	Taf6	SAF6/TAF6L	TAF6L		HFD
	Taf9	Taf9	TAF9	TAF9/TAF9b		HFD
	Taf10	Taf10	TAF10b	TAF10		HFD
	Taf12	Taf12	TAF12	TAF12		HFD
	Spt7	Spt7	Spt7	SUPT7L (STAF65G)	Bromo#	HFD
	Hfi1 (Ada1)	Hfi1 (Ada1)	Ada1	TADA1		HFD
	Spt20	Spt20	Spt20	SUPT20H		
TBP binding*	**Spt3**	**Spt3**	**Spt3**	**SUPT3H**		**HFD (x2)**
	Spt8	**Spt8**	-	-		**WD40**
TF binding module	Tra1	Tra1@	Nipped-A(Tra1)	TRRAP		
Splicing module	-		SF3B3	SF3B3		
	-		SF3B5	SF3B5		