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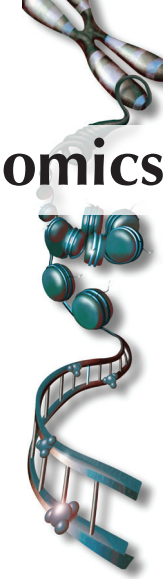

Functions of SAGA in development and disease

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Precise regulation of gene expression programs during embryo development requires cooperation between transcriptional factors and histone-modifying enzymes, such as the Gcn5 histone acetyltransferase. Gcn5 functions within a multi-subunit complex, called SAGA, that is recruited to specific genes through interactions with sequence-specific DNA-binding proteins to aid in gene activation. Although the transcriptional programs regulated by SAGA in embryos are not well defined, deletion of either Gcn5 or USP22, the catalytic subunit of a deubiquitinase module in SAGA, leads to early embryonic lethality. Here, we review the known functions of Gcn5, USP22 and associated proteins during development and discuss how these functions might be related to human disease states, including cancer and neurodegenerative diseases.

Keywords: ATAC complex • cancer • development • differentiation • Gcn5 • histone acetylation • neurodegenerative disease • PCAF • SAGA • stem cells • Usp22

Histone acetylation has long been linked to active gene transcription. This modification is actively regulated by the opposing actions of histone acetyltransferases (HATs) and deacetylases, which target a number of highly conserved residues in the amino-terminal tail regions of the histones. Gcn5 was identified as the first transcription-related HAT in 1996 [1], and since that time, we have learned much about its biochemical partners and its biological functions.

In yeast, Gcn5 is integrated into SAGA and ADA complexes [2,3], and the major subunits and structures of the Gcn5-containing complexes are highly conserved across evolution [4,5]. In metazoans, Gcn5 is also part of a second, distinct complex, termed ATAC [6]. This article will focus on recent advances made towards defining Gcn5 functions during mammalian development, as well as the role of particular SAGA and ATAC components in human diseases.

Structure & composition of SAGA

Several excellent reviews of SAGA composition and structure have been written recently, therefore we will provide a brief description here [7–9]. SAGA is organized into several functional submodules (Figure 1), including a histone acetylation center that contains Gcn5 (HAT) together with the Ada proteins, and a deubiquitination (DUB) module that contains Ubp8, in addition to Sgf73, Sgf11 and Sus1 or their mammalian orthologs (Table 1) [10–12]. The best-characterized substrates for SAGA include several acetylation sites in H3 and a ubiquitylation site in H2B. SAGA also contains two modules essential for its architectural integrity and its interactions with transcriptional machinery: the TAF module and the SPT module (Table 1). The composition of SAGA (also referred to as STAGA or TFTC) is largely conserved in mammalian cells (Table 1) [4,13–19]. In addition, Gcn5 is incorporated into a distinct but related complex, called ATAC, which is distinguished by its Ada2a subunit [20,21]. The functions of ATAC are less well defined than those of SAGA, but studies in flies and mice indicate ATAC is important for acetylation on H4K12, 16 [22,23], mitotic progression [24] and normal embryo development [21]. PCAF,

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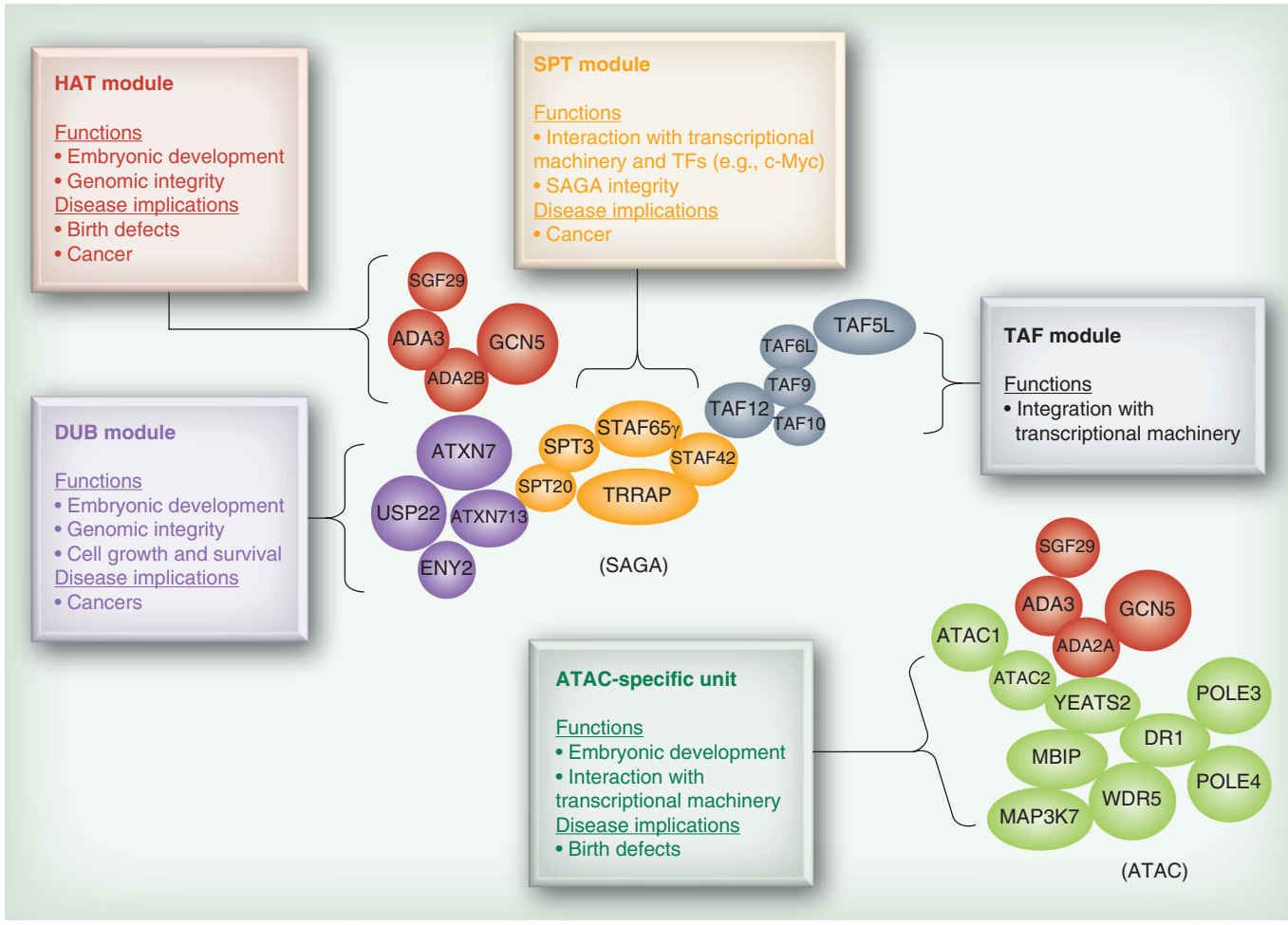

Figure 1. Schematics of mammalian Gcn5-containing complexes and their functions and implications in diseases. The modular structure and composition is based on a model of yeast SAGA [12]. In contrast to SAGA, the physical relationships between subunits in ATAC are less well defined. This figure only summarizes the presence of subunits, not their arrangement within ATAC. POLE3, POLE4 and MAP3K7 are included per [20]. The modules are indicated by the following color codes: red, HAT module; blue, DUB module; orange, SPT module; grey, TAF module; and green, ATAC-specific unit. The disease implications are based on studies using mammalian cells or mouse model systems, as well as from human patient samples, as described in the text.
DUB: Deubiquitination; HAT: Histone acetyltransferase; TF: Transcription factor.

which is highly related to Gcn5 [25], is a component of another multi-subunit complex similar to SAGA (Table 1) [26]. The increased complexity of mammalian SAGA and related complexes reflect their involvement in several diverse processes, including embryonic development, stress responses, cell growth, genome integrity, signaling pathways and metabolic control.

Developmental functions of Gcn5 & PCAF

Gcn5 and PCAF are highly similar (75% identical at the protein level) [25] and they are incorporated into similar complexes (Table 1) [26]. However, deletion of Gcn5 or PCAF has very different consequences in mice, indicating these proteins may have different functions *in vivo*.

Deletion of *Gcn5* (*Gcn5l2*, renamed as *Kat2a*) results in early embryonic lethality in mice. *Gcn5*-null embryos show severe growth retardation by 8.5 days post coitum, as well as defects in maintenance of mesodermal lineages due to increased cell death. By contrast, deletion of *PCAF* (*Kat2b*) causes no obvious abnormal phenotypes [36,37]. This difference in phenotype may be partially due to differential expression levels and patterns of Gcn5 and PCAF during mouse development [25,36]. However, deletion of both *Gcn5* and *PCAF* results in a more severe phenotype than loss of *Gcn5* alone, indicating that PCAF does have some functions redundant to those of Gcn5 early in embryogenesis [36]. Gcn5 and PCAF also have redundant functions in mouse embryonic fibroblasts, which are distinct from those of the CBP/p300 HATs [38]. Although mice heterozygous for the *Gcn5*-null allele exhibit no defects, mice heterozygous for both *Gcn5* and *p300* have a more severe phenotype than

p300-single heterozygotes, indicating these HAT family proteins also have both shared and distinct functions during development [39].

Normal Gcn5 expression levels and activity are both required for proper development. Combination of a hypomorphic allele of *Gcn5* with a deletion allele in mice to reduce expression below 50% causes homeotic transformations in the skeleton, as well as exencephaly [40,41]. Mice homozygous for a catalytically inactive allele of *Gcn5* die in mid-gestation with severe neural tube closure defects [42]. The longer survival time of the *Gcn5*-hat mutants relative to the null mutants suggests that Gcn5 has functions early in development that are independent of its HAT activity. At least part of the increase in severity of phenotype in the *Gcn5*-null mice may be due to loss of USP22 and other DUB module components from SAGA upon loss of Gcn5, which gives rise to telomere defects, genome instability and increased cell death [33].

Use of a conditional allele of *Gcn5* that is deleted upon exposure to Cre recombinase allows definition of Gcn5 functions at particular stages of development or in particular tissues and lineages. For example, Nestin-Cre-mediated deletion of *Gcn5,* specifically in neural progenitor cell populations, results in a 25% reduction in brain mass with a microcephaly phenotype similar to that observed in Nestin-Cre-driven knockouts of *c-Myc* or *N-myc* [43–46]. Gene expression

Table 1. Components of SAGA and related complexes in yeast and human.

Component	Yeast		Human		
	ySAGA [2–3,5,7,12,27–30]	**yADA** [2,3]	**hSAGA** [7,13,14,16–18,20,31–33]	**hPCAF** [26,34]	**hATAC** [20,21]
HAT module	Gcn5	Gcn5	GCN5		GCN5/hPCAF
				PCAF	
	Ada2	Ada2		ADA2A/B	
			ADA2B		
					ADA2A
	Ada3	Ada3	ADA3	ADA3	ADA3
	Sgf29	Sgf29	SGF29	SGF29	SGF29
		Ahc1			
		Ahc2			
					ATAC1 (ZZZ3)
2nd HAT center					ATAC2
DUB module	Ubp8		USP22	?	
	Sgf73		ATXN7	?	
	Sgf11		ATXN7l3	?	
	Sus1		ENY2	?	
TAF module	Taf5		TAF5L	TAF5L	WDR5
	Taf6		TAF6L	TAF6L	MAP3K7†
	Taf9		TAF9	TAF9	
	Taf10		TAF10	TAF10	DR1 (NC2β)
	Taf12		TAF12	TAF12	POLE3†
SPT module	Tra1		TRRAP	TRRAP	POLE4†
	Spt8‡				
	Ada5/Spt20		p38IP/SPT20		MBIP
	Spt7		STAF65g		YEATS2
	Spt3		SPT3	SPT3	
			SAP130	SAP130	
	Ada1		STAF42		

†These factors were identified by [20] but not by [21].
‡Yeast has an alternative SILK complex that contains all SAGA components except for Spt8 [35].
?: These components have yet to be reported as part of the hPCAF complex; DUB: Deubiquitination; HAT: Histone acetyltransferase.

analysis indicates that about a sixth of the genes whose expression is affected by the loss of Gcn5 are N-myc targets, and Gcn5 is required for maintenance of histone acetylation at these target genes [46]. These findings indicate that Gcn5 is a key transcriptional cofactor for N-myc in neural progenitor cells in the developing brain.

The capability of embryonic stem (ES) cells to self-renew and differentiate makes them an excellent model for studying development *in vitro*. *Gcn5*-null ES cells survive and appear to grow normally, except for a delay in progressing through the G2/M phase of the cell cycle [47]. When stimulated to differentiate, *Gcn5*-null cells form endoderm, ectoderm and mesoderm within embryoid bodies, indicating they are capable of differentiation. However, expression of transcription factors essential for ES cell identity such as Oct4 and Nodal is prematurely lost at early stages of differentiation when Gcn5 is absent, suggesting that Gcn5 is required for maintaining ES cells in a pluripotent, self-renewing state [47]. Gcn5 may also be important in other stem cell-like states. For example, Gcn5 acetylates H1.4K34 in induced pluripotent stem cells, and this modification strongly marks both carcinoma *in situ* and invasive seminoma nuclei, both of which are precursors of type II testicular germ cell tumors [48]. H1.4K34ac is also dynamically regulated during spermatogenesis with the highest expression levels detected in immature germ cells (spermatogonia) and meiotic spermatocytes [48]. Gcn5, therefore, may also be important for normal sperm development.

Usp22 functions in differentiation & development

Usp22 is also essential for mouse embryonic development [49]. Usp22 and its yeast ortholog, Ubp8, are best characterized in terms for their activity towards H2B, but they also have other substrates [33,50,51]. The lethality of *Usp22*-null mice was linked to deubiquitylation and stabilization of the Sirt1 deacetylase, which in turn suppressed p53-mediated apoptosis. Although another group did not see any effects on Sirt1 levels upon depletion of *Usp22* [49,52]. The full range of Usp22 functions during mouse development are not yet clear.

In mouse ES cells, Usp22 represses the transcription of the pluripotency factor Sox2, thereby promoting differentiation [53]. Loss of Usp22 occupancy at the *Sox2* locus is associated with elevated levels of H2Bub and increased transcription of Sox2. Atxn7l3, another component of the DUB module, and Sirt1, also associate with the *Sox2* locus, providing a novel example of a HAT complex component that recruits a deacetylase to repress transcription of a target gene.

Developmental functions of ATAC

ATAC was first identified in flies [22], and a highly similar mammalian complex was subsequently defined [20]. ATAC contains a second HAT protein, Atac2, which is specific for lysines in H4, in contrast to Gcn5, which targets H3 and H2B. *Atac2*-null mice die early in gestation with a phenotype that resembles, but is less severe than, that of *Gcn5*-null embryos [21], as might be expected since Gcn5 loss affects both ATAC and SAGA. ATAC localizes to different regulatory elements and regulates target genes that are distinct from those of SAGA [54,55]. ATAC also acetylates nonhistone proteins, and in human cells, ATAC controls mitotic progression by acetylating cyclin A [24]. Additional studies are needed to understand how Gcn5 functions are proportioned between the SAGA and ATAC complexes and to define the full range of ATAC functions.

Disease connections

The genetic studies above clearly indicate that Gcn5 and USP22 have important roles during development, which may presage important functions for these proteins in human diseases. So far, findings from a number of laboratories indicate that Gcn5 and SAGA might contribute to both neurodegenerative diseases and to cancers.

Neurodegenerative diseases

The neural tube defects observed in the *Gcn5*-hat mutant mice and in mice bearing hypomorphic alleles of *Gcn5* suggest that Gcn5 or SAGA may be particularly important in neural functions. Indeed, a component of the SAGA DUB module, Atxn7, is implicated in a human neural degenerative disease, spinal cerebellar ataxia type 7 (SCA7). Polyglutamine expansions in ataxin7 (polyQ-Atxn7) are associated with SCA7, which is characterized by both cerebellar and retinal degeneration. Mouse models of SCA7 bearing polyQ-Atxn7 alleles confirm that the polyQ expansions contribute to the pathogenesis of the disease [56]. Reduction of polyQ-Atxn7 expression restores motor function and prevents cerebellar synaptic reorganization in a conditional mouse model [57], suggesting a causative role for polyQ-Atxn7 in the development of SCA7. PolyQ-Atxn7 incorporates into SAGA [19,58,59] and has been reported to inhibit Gcn5 HAT activity, resulting in a dominant-negative effect on SAGA transcriptional activity as a coactivator of photoreceptor genes regulated by the cone-rod homeobox transactivator in SCA7 transgenic mice [19]. Another group reported that polyQ-Atxn7 altered the recruitment of SAGA to photoreceptor genes, leading to changes in chromatin structure and deregulation of these genes, contributing to a subsequent progressive loss of rod photoreceptor function [60].

Gcn5 depletion in SCA7 mice accelerates cerebellar and retinal degeneration, even though cerebellar deletion of *Gcn5* in the absence of polyQ-Atxn7 caused only mild ataxia [61]. These findings indicate that loss of Gcn5 may contribute to the time of onset and severity of human SCA7, but is not sufficient to drive disease formation. Loss of Gcn5 impairs the deubiquitinating activity of Usp22 [33], which partners with Atxn7 in the DUB module. Gcn5 loss, then, may exacerbate the SCA7 phenotype by compromising Usp22 functions. PolyQ-Atxn7 may also inhibit USP22 activity *in vivo*. Additional USP22 mouse models are needed to determine if loss of DUB activity leads to neurodegeneration as seen in SCA7.

PCAF appears to have important neural functions as well. Even though *PCAF*-null mice are viable without any overt physical phenotypes [36,37], subsequent studies have revealed behavioral alterations in these mice. At a young age, *PCAF*-null mice exhibit impaired short-term memory, with deficits in learning abilities, spatial memory and recognition memory. As the animals age, contextual long-term memory becomes affected as well [62]. These memory deficits are likely due to morphological changes observed in the hippocampus, a region in the brain that is crucial for multiple forms of memory [63,64]. *PCAF*-null mice also develop an exaggerated response to acute stress, indicating that PCAF may have a role in controlling emotional states. Interestingly, PCAF involvement in stress response seems to vary among different mouse genetic backgrounds [65], suggesting *PCAF*-null mice could be potentially valuable for research into genetic variables that affect emotional behaviors and disorders [66,67]. Moreover, mice lacking *PCAF* develop a resistance to amyloid toxicity [65], such as is associated with human dementias. Although a role for PCAF has not yet been confirmed in human cognitive diseases, these observations indicate that modulating acetyltransferase activity may offer a new way to develop therapies for dementias.

Cancer implications

Several studies using different cell model systems have demonstrated the involvement of Gcn5, USP22 and several other SAGA components in processes that are closely linked to the hallmarks of cancer, including DNA damage repair, cell cycle regulation and post-translational regulation of both oncoproteins and tumor suppressors.

DNA damage response & maintenance of genome integrity

Chromatin compaction can be a barrier to DNA repair [68]. Various factors that modify histones or remodel nucleosomes facilitate repair [69], including Gcn5.

A large-scale screen for DNA damage-responsive histone modifications in human cells revealed that H3K9ac and H3K56ac are rapidly and reversibly reduced in response to DNA damage [70]. The reduction of these two modifications might be caused by enhanced activities of histone deacetylases, or by histone eviction coupled with degradation in response to DNA damage. Gcn5, known to deposit the acetyl mark on H3K9, was reported to also acetylate H3K56 in human cells [70]. Another group, however, found that H3K56Ac is mediated by p300/CBP [71], and that H3K56Ac forms foci at sites of DNA damage in human cells. These different observations might reflect different dosages of DNA-damaging reagents used by the two groups. In any case, these data indicate that these HATs are important to the DNA damage response, whose failure leads to genomic instability that is central to carcinogenesis [72].

Other studies also indicate that Gcn5 is involved in multiple types of DNA repair. After UV-induced DNA damage, Gcn5 is recruited to damage sites by direct association with E2F1, and acetylation of H3K9 by Gcn5 facilitates nucleotide excision repair [73]. In response to γ-irradiation-induced double-strand breaks, cross-talk between serine-139 phosphorylation in H2AX (forming γ-H2AX) and Gcn5-mediated H3 acetylation aids the recruitment of SWI/SNF complexes to facilitate double-strand break repair [74].

Gcn5, Usp22 and SAGA are also important to maintaining the integrity of telomeres. Shelterin proteins protect telomeres from inappropriate recombination. Two shelterin components, TRF1 and Pot1a are regulated by Usp22, which limits their ubiquitination and subsequent turnover by the proteasome. Loss of Gcn5 leads to depletion of Usp22 and the DUB module from SAGA, compromising Usp22 activity, leading to telomere fusions [33].

Regulation of cell growth, proliferation & survival

Several connections have been made between Gcn5, SAGA and the regulation of cell growth and proliferation. For example, SAGA has been defined as a co-activator for the c-Myc oncoprotein in a number of *in vitro* cell systems [75–77]. TRRAP, STAF65g and GCN5 itself have been reported to interact directly with Myc, thereby recruiting SAGA to Myc target genes [75,77]. The catalytic activity of Gcn5 is required for activation of Myc target genes [77,78]. Gcn5 and other HATs acetylate the Myc protein, increasing its stability [79]. Mouse model systems indicate that Myc induces widespread changes in chromatin structure, including increased acetylation [80], and that Gcn5 and N-Myc share a number of transcriptional targets [46]. Myc often cooperates with other transcription factors, including E2F1, for full activation of its target genes. A recent study of non-small-cell lung

cancers revealed that GCN5 is highly expressed in these tumors, compared with matched normal tissues, and that it specifically potentiates lung cancer growth by directly promoting the expression of E2F1, cyclin D1 and cyclin E1 in an E2F1-dependent manner [81].

The Sgf29 component of SAGA contains tandem Tudor domains that serve as 'readers' for H3K4 di- or tri-methylation (H3K4me2/3). These interactions are required for recruitment of the SAGA complex and H3 acetylation at target gene promoters [82]. Interestingly, studies in rat hepatoma cell lines indicate that Sgf29 acts downstream of Sry and promotes c-Myc-mediated gene transcription and malignant transformation [31,83], providing yet another link between SAGA functions and Myc.

Gcn5 and PCAF also acetylate the p53 tumor suppressor at Lys320, and this acetylation promotes activation of p53 target genes such as p21 [84]. The involvement of Gcn5 in the functions of both the Myc oncogene and the p53 tumor suppressor indicate that it may both promote and inhibit cancer growth.

Usp22 has strong links to oncogenesis. Usp22 was first identified in microarray screens as part of an 11-gene 'death from cancer' signature for highly aggressive, therapy-resistant tumors [85]. This signature includes the Bmi1 polycomb group protein, and several Bmi1 target genes, suggesting that this molecular signature is related to stem cell-like characteristics [86]. Usp22 was later shown to act as an oncogene [87], regulating cell cycle progression, proliferation and apoptosis [50,81]. Increased expression of Usp22 has now been associated with poor prognosis in several additional cancers, including liver cancers, colorectal cancers, breast cancers, esophageal squamous cell carcinoma and oral squamous cell carcinoma [88–90]. If an increase in Usp22 DUB activity can be linked to these cancers, then DUB inhibitors may provide attractive prospects for new therapy development.

Developmental signaling pathways linked to malignancies

Aberrations in signaling pathways that are essential to embryonic development or to stem cell properties are often observed in cancer. These altered pathways may help to sustain populations of cancer-initiating cells (i.e., cancer stem cells), which share many characteristics with ES cells [91,92]. Components of Gcn5 complexes and PCAF may be involved in these signaling pathways. PCAF, for example, is required for Hedgehog-Gli-dependent transcription that drives cell proliferation in medulloblastomas and glioblastomas, and silencing of PCAF reduces the tumor-forming potential of neural stem cells [93]. ADA2a and ADA3 are required for acetylation of β-catenin, which promotes transcriptional functions of β-catenin in lung and colon cancer cell lines [94].

Involvement in metabolic energy pathways in cancer

Normal cells depend primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes. By contrast, most cancer cells switch to aerobic glycolysis, even in the presence of oxygen, to meet the soaring need for energy to support increased proliferation and growth [95]. Such reprogramming of energy metabolism is termed the 'Warburg effect' [72]. Under hypoxia, HIF-1α upregulates glycolytic enzymes to promote glycolysis, whereas p53 inhibits glycolysis and increases oxidative phosphorylation by activating *TIGAR* and *SCO2* gene expression. PCAF mediates differential recruitment of HIF-1α and p53 to the promoters of *TIGAR* and/or *SCO2* genes, thereby tuning the energy needs of the cells to different environmental conditions [96]. Although it is not yet clear whether PCAF is a rate-limiting factor for the glycolysis switch during tumor growth, these findings indicate that PCAF may provide an attractive target for controlling tumor growth and survival.

Conclusion & future perspective

Gcn5, Usp22 and a few other subunits of SAGA have been linked directly or indirectly to neurodegenerative diseases and to cancer. The essential developmental functions of Gcn5 and Usp22 in mouse indicate these factors may also be important for preventing human birth defects, such as exencephaly. PCAF has also been linked to cancer, as well as to energy metabolism, cognitive capacities and psychological behaviors. Clearly, understanding the full range of functions of these factors, and development of ways to modulate those functions, is important to human health.

One area that needs further investigation is definition of the relative distribution of Gcn5, in time and in space, between SAGA and ATAC during mammalian development, and the exact roles of these two complexes in embryogenesis. If Gcn5 levels are limiting *in vivo*, then changing the balance of its association between these complexes might have significant consequences for developmental programs. Loss or gain of individual subunits of the SWI/SNF ATP-dependent chromatin remodeler complex, for example, leads to a switch in lineage commitment during development [97]. Would the same be true for SAGA and ATAC? If so, might that also impact the functions of Gcn5 in cancer or other diseases?

Another open question is whether alterations in levels or activity of Gcn5, PCAF or Usp22 are sufficient to impact cancer development. Would inhibition of Gcn5,

for example, reduce the oncogenic properties of c-Myc overexpression? Is overexpression of USP22, such as is seen multiple human cancers, enough to initiate or drive cancer formation? It will also be important to determine how Gcn5 and USP22 functions are linked in cancer and in other diseases, such as SCA7.

Finally, the connections observed between PCAF and SAGA components and neural processes are fascinating, and may foreshadow discovery of a greater role for these proteins in both neural development and neural functions in adults. It is not clear, for example, how polyQ-Atxn7 affects the activity of USP22, or whether such effects contribute to SCA7. Another question is whether Gcn5 might affect cognitive abilities or emotional state as does PCAF, and if so, whether these two HATs are involved in the same or separate pathways.

Although we have learned a lot about the biochemical activities of these HATs over the last 18 years, we obviously still have a lot to learn about their biological functions. This knowledge will not only advance our understanding of chromatin regulation, but will also advance our understanding of human disease pathways.

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Executive summary

SAGA in transcription

- Gcn5 is the first transcription-related histone acetyltransferase (HAT) to be described, linking SAGA to gene transcription.
- SAGA is organized into functional modules and harbors both HAT (Gcn5) and deubiquitination (Usp22) activities, and the modularity of SAGA is conserved from yeast to humans.
- Identification of the second enzymatic activity of SAGA, the deubiquitinase Usp22, broadens the substrates of SAGA and revealed new roles of SAGA in gene regulation, as well as other processes.

Functions of SAGA in mammals & implications in human diseases

- Both Gcn5 and Usp22 are essential for mouse embryogenesis, indicating these factors may also be important for preventing birth defects in humans.
- Several subunits of SAGA are involved in pathogenesis of neurodegenerative diseases, for instance, polyQ expansion in Atxn7 causes spinal cerebellar ataxia type 7, and *Gcn5* deletion accelerates the disease progression in spinal cerebellar ataxia type 7 mice. This provides potential new targets for the development of therapeutic strategies for such diseases.
- SAGA interacts with transcription factors such as Myc to regulate gene transcription, cell growth and survival. Several key subunits are indicated in such processes, including TRRAP, Usp22 and Gcn5. The close interactions with Myc link SAGA to an array of human cancers that are driven by this oncoprotein.

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