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MINIREVIEW

Protein Acetylation and Acetyl Coenzyme A Metabolism in Budding Yeast

Luciano Galdieri, Tiantian Zhang, Daniella Rogerson, Rron Lleshi, Ales Vancura

Department of Biological Sciences, St. John's University, Queens, New York, USA

Cells sense and appropriately respond to the physical conditions and availability of nutrients in their environment. This sensing of the environment and consequent cellular responses are orchestrated by a multitude of signaling pathways and typically involve changes in transcription and metabolism. Recent discoveries suggest that the signaling and transcription machineries are regulated by signals which are derived from metabolism and reflect the metabolic state of the cell. Acetyl coenzyme A (CoA) is a key metabolite that links metabolism with signaling, chromatin structure, and transcription. Acetyl-CoA is produced by glycolysis as well as other catabolic pathways and used as a substrate for the citric acid cycle and as a precursor in synthesis of fatty acids and steroids and in other anabolic pathways. This central position in metabolism endows acetyl-CoA with an important regulatory role. Acetyl-CoA serves as a substrate for lysine acetyltransferases (KATs), which catalyze the transfer of acetyl groups to the epsilon-amino groups of lysines in histones and many other proteins. Fluctuations in the concentration of acetyl-CoA, reflecting the metabolic state of the cell, are translated into dynamic protein acetylations that regulate a variety of cell functions, including transcription, replication, DNA repair, cell cycle progression, and aging. This review highlights the synthesis and homeostasis of acetyl-CoA and the regulation of transcriptional and signaling machineries in yeast by acetylation.

Protein acetylation at lysine residues is a posttranslational protein modification. Histones have been known to be acetylated for a long time; during the last 20 years it became clear that histone acetylation plays an important role in regulation of gene expression, DNA repair, silencing, and cell cycle progression (1, 2). More recently, genomic and proteomic approaches for bacteria, yeast, and higher eukaryotes identified many nonhistone proteins that are acetylated, suggesting that the role of acetylation extends beyond histones (3–6). Remarkably, some of these acetylations play important regulatory roles not only in chromatin-mediated processes but also in other aspects of cell physiology, including metabolism (7, 8). Histone/protein acetylation is catalyzed by lysine acetyltransferases (KATs), which utilize acetyl coenzyme A (CoA) as a substrate. Acetyl-CoA is a central metabolite at the junctions of key catabolic and anabolic pathways, and its cellular level reflects the metabolic state of the cell. Protein acetylation is dynamically regulated by a balance between KATs and histone deacetylases (HDACs) (2, 9). However, recent accumulating evidence shows that the level of acetyl-CoA in the nucleocytosol and mitochondrion regulates protein acetylation within the corresponding compartment (10–13). Acetylation of histones and nonhistone proteins thus reflects acetyl-CoA levels and connects metabolism with chromatin structure and signaling. In this review, we focus on the regulation of synthesis and homeostasis of acetyl-CoA and on the regulatory role of protein acetylation in the physiology of *Saccharomyces cerevisiae*.

ACETYLATION OF HISTONES

Histones are the main DNA-packaging proteins; the four core histones, H2A, H2B, H3, and H4, form an octamer, around which 147 bp of DNA are wrapped to form the nucleosome. Nucleosomes are assembled along the entire length of DNA and represent the basic building unit of chromatin. The packaging of DNA into chromatin poses a barrier for cellular processes that require access to DNA, and cells rely on complexes that acetylate histones to make the chromatin more accessible (1). Histone acetylation occurs on all four core histones (Table 1), affects chromatin assembly and structure, and regulates diverse cellular functions, such as gene expression and DNA replication and repair (2, 14). Histone acetylation affects chromatin structure by two mechanisms. First, acetylation neutralizes the charge of lysine and can alter histone-DNA and nucleosome-nucleosome interactions. Second, acetyllysines are recognized by bromodomain-containing proteins, which modify chromatin structure through a covalent or noncovalent mechanism.

Histone acetylation is associated with chromatin assembly. During S phase, replicated DNA must be immediately packaged with histones into nucleosomes in a process of replication-coupled nucleosome assembly. This process plays an important role in the inheritance of epigenetic states and the maintenance of genome integrity (15). The assembly of newly synthesized histones into nucleosomes requires histone chaperones CAF-1, Asf1p, and Rtt106p. These three proteins bind histones H3 and H4 and function coordinately in nucleosome assembly during the S phase of the cell cycle. Newly synthesized histones H3 and H4 are acetylated by KATs before being assembled into nucleosomes (16, 17). Histone H4 is acetylated at lysine residues 5 and 12 (acH4K5 and -12), an acetylation pattern that is conserved from yeast to humans. In yeast cells, this acetylation is performed by Hat1p (18). Patterns of acetylation on newly synthesized H3 are not as conserved among species. In budding yeast, newly synthesized H3 is acetylated at lysine 56 (acH3K56) by Rtt109p (19). This modification depends on Asf1p and is important for nucleosome assembly during DNA replication and DNA repair (20, 21). In addition to acH3K56, new H3 is acetylated on five lysine residues

Published ahead of print 17 October 2014

Address correspondence to Ales Vancura, vancuraa@stjohns.edu.

doi:10.1128/EC.00189-14

TABLE 1 Budding yeast HATs and HDACs

Catalytic subunit	Complex	Activity	Substrates	Reference(s)
Gcn5p	SAGA and others (SLIK/SALSA, ADA, HAT-A2, HATB3.1)	KAT	H3: K4, K9, K14, K18, K23	Histone acetylation reviewed in 2, 9, 14, 147
			H2B: K16	
			Rsc4p	47, 48
			Swi2p	49
			Spt7p, Ada3p, Sgf73p	12
			Ume6p	148
			Ifh1p	43
Esa1p	NuA4, Piccolo NuA4	KAT	H2A: K5, K8	Histone acetylation reviewed in 2, 9, 62, 63
			H2B: K11, K16	
			H4: K5, K8, K12, K16, K20	
			Htz1: K3, K8, K10, K14	35, 149
			Esa1p	50
			Sip2p	5
			Pck1p: K19, K514	5
			Yng2p	20
			Cdc3p, Cdc10p, Cdc12p, Shs1p	44
Rtt109p		KAT	H3: K9, K27, K56	
			Rtt109	51
Hat1p	Hat1p-Hat2p	KAT	H2A: K8	
			H4: K5, K12	60
Sas2p	SAS	KAT	H4: K16, K20	
			Sas2p	50
Sas3p	NuA3	KAT	H3: K14, K23	150
Elp3p	Elongator	KAT	H3: K14	151
			H4: K8	
Rpd3p	Rpd3(S), Rpd3(L)	HDAC	H2A: K5ac, K8ac	Histone deacetylation reviewed in 2, 14, 67
			H2B: K11ac, K16ac	
			H3: K9ac, K14ac, K18ac, K23ac	
			H4: K5ac, K8ac, K12ac	
			Swi4p	6
			Yng2p	20
			Rad53p	152
Hda1p	HDA	HDAC	H2B: K16ac	
			H3: K9ac, K14ac, K18ac, K23ac	
			Htz1p: K14ac	20
Hos1p		HDAC	H4	
			Smc3p	153
Hos2p	Set3C	HDAC	H3: K9ac, K14ac, K18ac, K23ac	
			H4: K5ac, K8ac, K12ac, K16ac, K20ac	
Hos3p		HDAC	H3, H4, H2A, H2B	154
Sir2p	Sir, RENT	HDAC	H4: K16ac, K20ac	155
			Ifh1p	43
			Pck1p	5
Hst1p	Sum1p/Rfm1p/Hst1p Set3C	HDAC	H4: K16ac, K20ac	155
Hst2p		HDAC		155
Hst3p/Hst4p		HDAC	H3: K56ac	155

(acH3K9, -14, -18, -23, and -27), and these modifications are important for nucleosome assembly. At least some of the acetylations on the H3 N terminus are carried out by Gcn5p (22).

Acetylation of chromatin histones is an integral part of transcriptional regulation. Acetylation of individual lysines within the tails of histone H3 and H4 and the recruitment of SAGA and NuA4 complexes to promoters strongly correlate with gene transcription (23–25). SAGA and NuA4 also acetylate histones within transcribed regions, thus promoting transcriptional elongation (26, 27). SAGA and NuA4 do not only acetylate histones in a targeted manner at specific genes, but also function globally and independently of transcriptional activators (28). A group of genes deviates from the general paradigm that increased acetylation of promoter histones results in increased transcription. These genes are normally repressed during exponential growth, when cellular levels of acetyl-CoA and global histone acetylation are high, and

are derepressed during a diauxic shift, when levels of acetyl-CoA and global histone acetylation decrease (29).

Histone acetylation is also involved in demarcation of heterochromatin. Yeast heterochromatin occupies ribosomal DNA, the silent mating-type loci *HMR* and *HML*, and chromatin domains adjacent to telomere ends (30). Silencing at the silent mating loci and telomeres is mediated by Rap1p and the SIR complex, which includes Sir1p, Sir2p, Sir3p, and Sir4p. The assembly of heterochromatin involves Sir2p-mediated deacetylation of histone H4 at K16 (acH4K16) and binding of Sir3p and Sir4p to deacetylated histone tails. The formation of boundary regions which prevent the spread of heterochromatin into adjoining euchromatin requires acetylation of histone H4 at K16 by Sas2p (31, 32). This acetylation allows for the incorporation of the histone variant Htz1p (33, 34), acetylation of which is also required for the efficient antisilencing function of the boundary regions (35). The antisilencing function of the boundary regions also requires Gcn5p- and Elp3p-mediated histone H3 acetylation (36). Thus, the balance between histone acetylation and histone deacetylation demarcates heterochromatin, and it appears that decreased cellular levels of acetyl-CoA and histone acetylation allow for the spread of heterochromatin into the telomere-proximal regions (37).

ACETYLATION OF NONHISTONE PROTEINS

A number of proteomic studies have shown that acetylation occurs at thousands of sites throughout eukaryotic cells and that the human proteome contains at least ~2,500 acetylated proteins (3, 4, 8, 13, 38–40). In comparison, similar analyses of human and mouse proteins identified ~2,200 phosphoproteins (41, 42). Thus, it appears that protein acetylation is as widespread as phosphorylation (38). In human cells, acetylated proteins are involved in the regulation of diverse cellular processes, including chromatin remodeling, the cell cycle, RNA metabolism, cytoskeleton dynamics, membrane trafficking, and key metabolic pathways, such as glycolysis, gluconeogenesis, and the citric acid cycle (4, 8).

Many acetylated nonhistone proteins have also been identified in *S. cerevisiae* (5, 6, 13). NuA4 was found to acetylate proteins involved in several processes, including metabolism, transcription, cell cycle progression, RNA processing, stress response, and cytokinesis (5, 43, 44). Many of the acetylated proteins are located in the nucleus or cytosol, and their acetylation is very likely regulated by the concentration of acetyl-CoA in the nucleocytosolic compartment. Indeed, the cytoplasmic proteins Sip2p, Cdc11p, Shs1p, and Pck1p were more acetylated in a strain with an increased level of acetyl-CoA than in wild-type cells (45). Many proteins that are acetylated by NuA4, including Pck1p and Sip2p, were identified via proteome microarrays (5). Pck1p encodes phosphoenolpyruvate carboxykinase, which catalyzes the conversion of oxaloacetate to phosphoenolpyruvate, the rate-limiting step in gluconeogenesis. Acetylation of Pck1p on K514 is required for enzymatic activity and the ability of yeast cells to grow on nonfermentable carbon sources (5). Sip2p, one of the three β-subunits of the SNF1 complex, is also acetylated by NuA4. This acetylation increases the affinity of Sip2p for the catalytic subunit Snf1p and inhibits SNF1 activity, resulting in a decreased phosphorylation of Sch9p and extended replicative life span (46).

A number of proteins that play important roles in the regulation of chromatin structure and transcription are acetylated. Gcn5p acetylates the Rsc4p subunit of the RSC chromatin remodeling complex (47, 48). Surprisingly, this acetylation appears to create a binding site for one of the two Rsc4p bromodomains. This intramolecular binding inhibits binding of the other Rsc4p bromodomain to H3K14ac. The significance of this Rsc4p acetylation is not clear, as the mutation of the target lysine residue into a nonacetylatable arginine residue produces only modest phenotypes; however, Rsc4p acetylation is required when the acetylation of histone H3 is abolished (47). Gcn5p also acetylates the Swi2p subunit of the SWI/SNF complex. This acetylation promotes the dissociation of SWI/SNF from chromatin (49). Perhaps Rsc4p and Swi2p acetylation is a feedback mechanism that prevents excessive interaction of the RSC and SWI/SNF complexes with chromatin when the nucleocytosolic concentration of acetyl-CoA is high and histones are heavily acetylated.

Esa1p, the catalytic subunit of NuA4, autoacetylates at a conserved lysine residue *in vitro* and *in vivo*; this autoacetylation is required for catalytic activity of NuA4 (50). Yng2p, a subunit of the NuA4 complex, is acetylated by Esa1p and deacetylated by Rpd3p. This acetylation stabilizes Yng2p, and mutants that abolish this acetylation are hypersensitive to benomyl and methyl methanesulfonate, suggesting that Yng2p acetylation is required for normal function of NuA4 (20). Rtt109p, another KAT, autoacetylates at the active site lysine residue, and this acetylation is required for Rtt109p's enzymatic activity (51). Gcn5p acetylates Spt7p, Ada3p, and Sgf73p, subunits of the SAGA complex. This acetylation occurs on multiple lysine residues and coincides with SAGA recruitment to growth genes (12). Thus, it appears that the activity of KAT complexes is regulated by multiple autoacetylations; however, the significance of this regulation is not clear.

ACETYLATION OF MITOCHONDRIAL PROTEINS

In *S. cerevisiae*, about 4,000 lysine acetylation sites have been identified, many of them on mitochondrial proteins (13, 39). The acetylation of mitochondrial proteins correlates with acetyl-CoA levels in mitochondria, as demonstrated by the fact that acetylation of mitochondrial proteins is dependent on *PDA1*, which encodes a subunit of the pyruvate dehydrogenase (PDH) complex (13). The acetylation of mitochondrial proteins was also elevated by introducing the *cit1*Δ mutation. *CIT1* encodes mitochondrial citrate synthase; *cit1*Δ mutants are not able to utilize acetyl-CoA for citrate synthesis and probably have an elevated level of mitochondrial acetyl-CoA. These results suggest that most of the mitochondrial acetyl-CoA in exponentially growing cells is derived from glycolytically produced pyruvate that was translocated into mitochondria and converted to acetyl-CoA by the PDH complex. Inactivation of the PDH complex results in about a 30% decrease in cellular acetyl-CoA; this indicates that mitochondrial acetyl-CoA represents about 30% of the cellular pool. However, since mitochondria occupy only 1 to 2% of the cellular volume in *S. cerevisiae* (52), the mitochondrial acetyl-CoA concentration is about 20- to 30-fold higher than the concentration in the nucleocytosolic compartment and is probably within the millimolar range (12, 13, 53). Because of the extrusion of protons across the inner mitochondrial membrane, the pH of the mitochondrial matrix is higher than the pH in the cytosol or nucleus, at about 8.0 (53, 54). The high pH coupled with the high concentration of acetyl-CoA in the mitochondrial matrix create a permissive environment for nonenzymatic acetylation of mitochondrial proteins (13, 53). However, these considerations do not exclude the possibility that at

least some protein acetylation in the mitochondrion is catalyzed by KATs.

KATs AND HDACs

KATs are enzymes capable of transferring acetyl groups from acetyl-CoA onto the ε-amino group of lysine residues within histones and other proteins. HDACs hydrolyze the amide linkage between the acetyl group and amino group of lysine residues, yielding acetate. There are about 20 known KATs and HDACs in *S. cerevisiae* (Table 1). Despite being able to acetylate histones and many other proteins, KATs employ a common catalytic mechanism which involves the formation of a ternary complex of KAT–acetyl-CoA–histone and the deprotonation of the ε-amino group of lysine by a glutamate or aspartate residue within the active site of a KAT, followed by a nucleophilic attack on the carbonyl group of acetyl-CoA (51, 55, 56). Most kinetically characterized KATs have high catalytic efficiencies (k_{cat}/K_m, ~10^5 to 10^6 M^{-1} s^{-1}) and affinities (K_m or K_d, ~1 to 10 μM) for acetyl-CoA (51, 55). Since most KATs, including Esa1p and Gcn5p, have similar affinities for both acetyl-CoA and CoA and since CoA is a competitive inhibitor, the acetyl-CoA:CoA ratio may also be a significant regulatory factor. The kinetic and binding parameters also suggest that many KATs, including Esa1p and Gcn5p, should respond similarly to fluctuations in acetyl-CoA levels (51). The exception is Rtt109p, which has significantly lower affinity for CoA and thus probably exists in a more constitutively active state and is less dependent on the acetyl-CoA concentration (57).

KATs have historically been classified into nuclear (A-type) and cytoplasmic (B-type) KATs (58). The B-type KAT in *Saccharomyces cerevisiae* is Hat1p, which acetylates histone H4 at lysines 5 and 12, sites known to be modified in newly synthesized histone H4 (59). However, despite this specificity, inactivation of Hat1p did not reveal Hat1p's role in chromatin assembly (60). Yeast A-type KATs include Gcn5p, Esa1p, Sas2p, Sas3p, Rtt109p, and Elp3p (Table 1). Gcn5p, Hat1p, and Elp3p belong to the GNAT group (Gcn5-related N-acetyltransferase) of KATs, while Esa1p, Sas2p, and Sas3p belong to the MYST group (named after its founding members, MOZ, Ybf2/Sas3, Sas2, and Tip 60) (58, 61). Most of the KATs and HDACs function as multisubunit complexes (14, 58, 61). Gcn5p is the catalytic subunit of several complexes, with SAGA being the largest and best characterized (62, 63). Esa1p, the catalytic subunit of NuA4 and Piccolo NuA4, is the only yeast KAT that is essential for viability (64, 65). While NuA4 is involved in targeted histone acetylation, the smaller complex Piccolo NuA4 plays a role in global histone acetylation (66).

As in other organisms, budding yeast HDACs are classified as class I HDACs (Rpd3p, Hos2p, and Hos1p), class II HDACs (Hda1p and Hos3p), or class III HDACs, also called sirtuins (Sir2p, Hst1p, Hst2p, Hst3p, and Hst4p) (Table 1). The central catalytic domains of class I and II HDACs are similar, unlike type III HDACs, which are NAD (NAD^+) dependent (67, 68). Similar to KATs, HDACs are also recruited to specific genomic loci and regulate expression of corresponding genes (23, 24, 69, 70). The NuA4 and SAGA complexes are the major KAT activities that are counteracted by the HDAC activities of the Hda1p and Rpd3 complexes (20). The NuA4, SAGA, Hda1p, and Rpd3p complexes provide the bulk of the control over the dynamic balance of global histone acetylation and deacetylation. Since the mutations in the Hda1p complex display the most prominent alleviating interactions with the mutations in the NuA4, SAGA, and Elongator complexes, it appears that the Hda1p complex removes the largest amount of acetyl groups (20).

SYNTHESIS OF ACETYL-CoA

Acetyl-CoA is a central metabolite that connects metabolism and signaling with the chromatin structure and transcription. In eukaryotes, there are two possibilities for synthesis of cytoplasmic acetyl-CoA. In animals, plants, and algae, acetyl-CoA is generated from citrate by ATP-citrate lyase (ACL). ACL, a key enzyme in fatty acid biosynthesis, utilizes citrate exported from the mitochondrion and converts it into acetyl-CoA and oxaloacetate. ACL-encoding genes are also present in many fungi; however, with the exception of *Yarrowia lipolytica*, members of the *Saccharomycotina* subphylum do not contain ACL-encoding genes (71). In *Saccharomyces cerevisiae* and most other members of *Saccharomycotina*, nucleocytosolic acetyl-CoA is synthesized by acetyl-CoA synthetase (10, 71, 72).

The preferred sources of carbon and energy for the yeast *Saccharomyces cerevisiae* are fermentable sugars, such as glucose. When yeast cells are grown in liquid cultures of rich medium containing glucose under aerobic conditions, the cells metabolize glucose predominantly by glycolysis, producing pyruvate (Fig. 1). The majority of this pyruvate is converted into acetaldehyde by pyruvate decarboxylase, encoded by the *PDC1*, *PDC5*, and *PDC6* genes. *PDC1* is responsible for the majority of the pyruvate decarboxylase activity (73). *PDC1*, unlike *PDC5*, is strongly expressed in rich glucose medium; however, expression of *PDC1* is repressed by ethanol (74). Expression of both *PDC1* and *PDC5* is autoregulated. *PDC5* becomes strongly expressed in *pdc1*Δ mutants, and promoter activity of *PDC1* is upregulated in mutants lacking the coding region of *PDC1* (75). In addition, thiamine represses *PDC5* and thus under thiamine limitation, both *PDC1* and *PDC5* are expressed (76).

In cells grown in medium with a high concentration of glucose, the majority of the acetaldehyde is converted into ethanol by alcohol dehydrogenase (77, 78). Budding yeast have 5 genes that encode alcohol dehydrogenases *ADH1* to *ADH5*. Adh1p, Adh3p, Adh4p, and Adh5p catalyze the reduction of acetaldehyde into ethanol, while Adh2p oxidizes ethanol into acetaldehyde (79–84). Adh1p is the cytosolic enzyme that generates the majority of ethanol.

A relatively small fraction of acetaldehyde is converted to acetate by acetaldehyde dehydrogenase (77, 78). The yeast genome encodes five aldehyde dehydrogenases: *ALD2* to *ALD6*. Ald2p and Ald3p are cytosolic proteins involved in the synthesis of coenzyme A (85); their expression is repressed by glucose. Ald6p is also cytosolic but is constitutively expressed. Ald4p and Ald5p are mitochondrial; Ald4p, the major mitochondrial form, is repressed by glucose, while Ald5p is expressed constitutively. When cells are grown in rich medium with glucose, the majority of acetate is produced by Ald6p in the cytosol (86, 87). On nonglucose carbon sources that do not repress the expression of *ALD4*, acetaldehyde is also converted to acetate in the mitochondrion by Ald4p (88–90).

Cytosolic acetate is subsequently converted to acetyl-CoA by acetyl-CoA synthetase (10, 91). *ACS1* and *ACS2* encode two yeast acetyl-CoA synthetases which catalyze the ligation of acetate and CoA to yield acetyl-CoA. On glucose-containing medium, *ACS2* is essential and *ACS1* is repressed (10, 92, 93). On nonfermentable carbon sources, the *acs2*Δ mutant is viable but grows slowly (10,

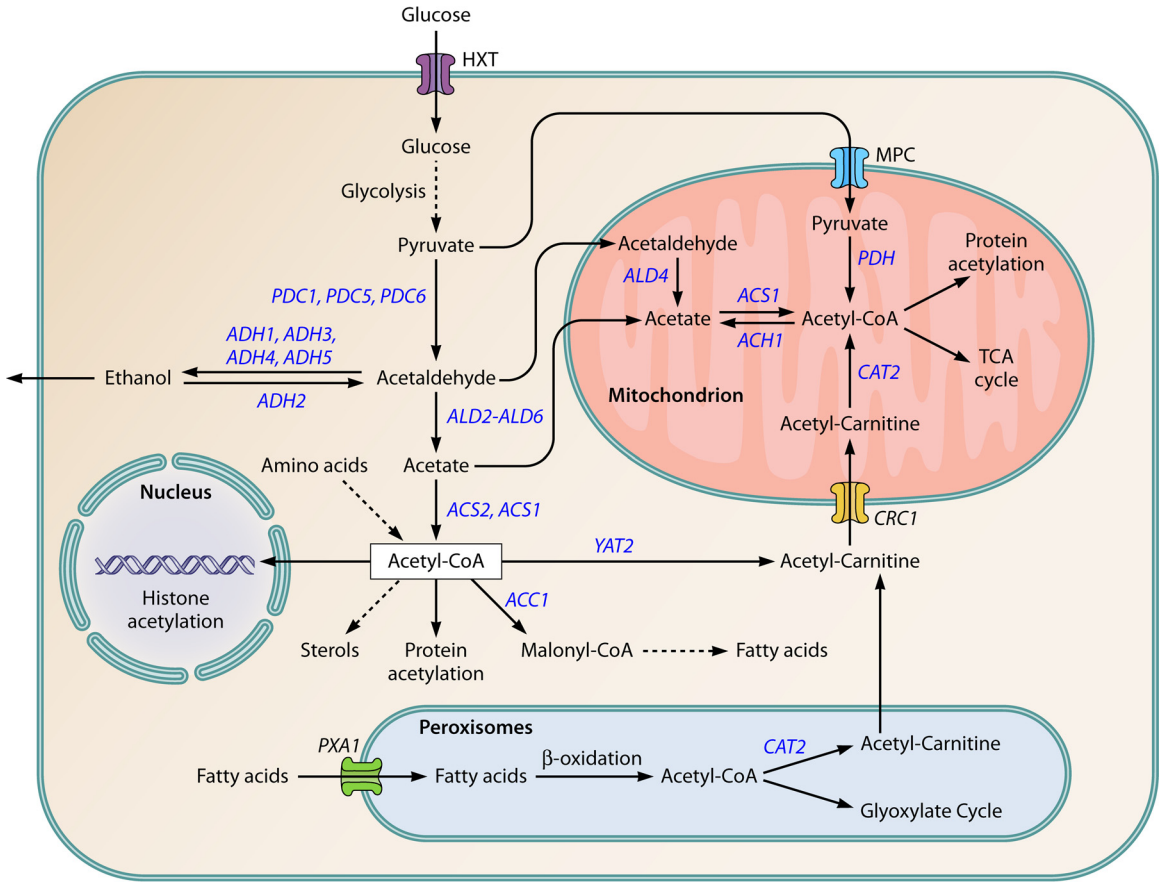

FIG 1 Acetyl-CoA metabolism in budding yeast. Multistep pathways of glycolysis and fatty acid synthesis are indicated by dashed lines.

94). Upon glucose exhaustion, the expression of *ACS1* is activated by the transcriptional factors Cat8p and Adr1p (95, 96). The glucose repression of *ACS1* is mediated by at least two mechanisms. First, Ume6p represses *ACS1* in a glucose-dependent manner (96). Second, expression of *CAT8* is repressed by Mig1p/Mig2p in the presence of glucose (97). The K_m of Acs1p for acetate is about 30-fold lower than that of Acs2p (92). Therefore, even a small increase in *ACS1* expression would be expected to have a significant impact on the cellular level of acetyl-CoA. There is some uncertainty regarding the subcellular distribution of Acs1p and Acs2p. Acs1p was found in the mitochondrion (98, 99), nucleus, and cytoplasm (100), while Acs2p was found in the cytosol, nucleus, and perhaps the endoplasmic reticulum (10, 100, 101). When *Salmonella enterica* ACS was targeted to different cell compartments in *S. cerevisiae*, only cytoplasmic or nuclear localization, but not mitochondrial localization, was able to complement loss of Acs2p activity for growth on glucose (10). This finding indicates that acetyl-CoA cannot be transported out of the mitochondrion in *S. cerevisiae*.

Since glucose represses the tricarboxylic cycle and respiration in *S. cerevisiae*, only a relatively small fraction of glycolytically produced pyruvate is translocated into mitochondria and converted to acetyl-CoA by the PDH complex (13, 77, 78). However, the mitochondrial pool of acetyl-CoA is biochemically isolated and cannot be used for protein acetylation in the nucleocytosolic compartment (10). The assumption that the mitochondrial pool of acetyl-CoA is relatively small in *S. cerevisiae* cells grown in glucose medium becomes problematic when cells exhaust glucose and switch metabolism from fermentation to oxidative metabolism (the diauxic shift) or are grown on nonfermentable carbon sources. Under these conditions, the glucose repression of genes required for mitochondrial biogenesis and oxidative metabolism is relieved, and mitochondrial biogenesis and metabolism are upregulated.

Acetyl-CoA, produced by both Acs1p and Acs2p under glucose-derepressed conditions, can be transesterified by carnitine acetyl-CoA transferase Yat2p into acetyl-carnitine in the cytosol. Acetyl-carnitine is transported into the mitochondrion by the Crc1p transporter. When cells are grown on fatty acids as a source of carbon and energy, peroxisomes proliferate and genes involved in fatty acid β-oxidation are induced. The acetyl-CoA generated in the peroxisomes by β-oxidation is converted into acetyl-carnitine by the carnitine acetyl-CoA transferase Cat2p and subsequently exported into the cytosol and mitochondrion (Fig. 1).

Another enzyme that likely plays a role in the regulation of acetyl-CoA homeostasis is acetyl-CoA hydrolase/transferase Ach1p. Ach1p catalyzes the hydrolysis of acetyl-CoA or the transfer of CoA from short-chain acyl-CoAs onto acetate, yielding acetyl-CoA. *ACH1* is repressed by glucose (102), and the *ach1*Δ mutation is not lethal; this mutation causes growth defects on acetate, but not on other nonfermentable carbon sources or on glucose (102, 103). Deletion of Ach1p results in mitochondrial

damage, accumulation of reactive oxygen species, and decreased chronological life span (104). In addition, deletion of *ACH1* results in an increased extracellular level of acetate and increased acetylation of histones, presumably due to an increased nucleocytosolic level of acetyl-CoA (105). Conversely, nucleocytosolic depletion of acetyl-CoA stimulates autophagy and prolongs life span (105).

REGULATION OF ACETYL-CoA HOMEOSTASIS

The pools of acetyl-CoA in the nucleocytosolic and mitochondrial compartments are separate; the concentration of acetyl-CoA in the nucleocytosolic compartment affects protein acetylation in the nucleus and cytosol (10, 45, 106), while the concentration of acetyl-CoA in mitochondrion affects acetylation of mitochondrial proteins (13). In cells exponentially growing on glucose, the mitochondrial pool of acetyl-CoA represents about 30% of the total cellular pool (13). It is not clear if this ratio of nucleocytosolic and mitochondrial acetyl-CoA is maintained as cells progress through the diauxic shift into stationary phase and whether there is a cross talk mechanism coordinating and regulating the levels of acetyl-CoA in both compartments. However, mitochondrial metabolism is required to maintain cellular levels of acetyl-CoA and histone acetylation in stationary phase; interestingly, this requirement is bypassed by simultaneous activation of the *SNF1* and retrograde pathways (107). This bypass upregulates synthesis of the storage carbohydrate trehalose, which is subsequently metabolized to provide acetyl-CoA (107).

It appears that pyruvate, acetaldehyde, and acetate can be transported from the cytosol to the mitochondrion, where they give rise to mitochondrial acetyl-CoA. The mitochondrial pyruvate carrier was recently identified (108, 109). However, unlike in organisms that possess ACL, *Saccharomyces cerevisiae* does not seem to have a mechanism for export of mitochondrial acetyl-CoA into the cytosol. In this context, it is important to note that pyruvate dehydrogenase complex in mammalian cells can be translocated from the mitochondrion to the nucleus and thus can redirect pyruvate metabolism to provide acetyl-CoA for histone acetylation during the G_1-to-S phase transition (110). It is unknown if a similar mechanism exists in budding yeast.

Since current methods do not allow accurate measurements of acetyl-CoA separately in the nucleocytosolic and mitochondrial compartments, the total cellular level of acetyl-CoA is very often used to approximate the nucleocytosolic level. Cellular levels of acetyl-CoA and histone acetylation are highest during exponential growth of yeast cells when glucose in the medium is abundant. As glucose is exhausted and cells enter the diauxic shift, they switch their metabolic mode from glycolysis to respiration, and cellular levels of acetyl-CoA and global histone acetylation decrease (12, 111–113).

The nucleocytosolic level of acetyl-CoA is regulated by both the synthesis and utilization of acetyl-CoA. Inactivation of Acs2p results in rapid histone hypoacetylation (10), indicating that Acs2p is the main source of acetyl-CoA in the nucleocytosolic compartment when cells are grown on glucose. Activity of Acs2p and the cellular concentration of acetate would thus be two key factors regulating the synthesis of acetyl-CoA in the nucleocytosolic compartment. Interestingly, the activity of acetyl-CoA synthetase in bacteria (114–116) and mammals (117, 118) is regulated by acetylation. Acetylation of a conserved lysine residue (lysine 609) of *Salmonella enterica* acetyl-CoA synthetase results in almost complete inactivation of the enzymatic activity (114). Deacetylation, resulting in reactivation of the enzyme, is catalyzed by HDAC enzymes that belong to the sirtuin family. In mammals, this sirtuin is SIRT3 (117–119). In *S. cerevisiae*, the lysine residue that is acetylated in *Salmonella enterica* is conserved in Acs2p. In addition, deletion of two sirtuins, *HST3* and *HST4*, results in a growth defect on acetate, suggesting that the enzymatic activity of Acs2p and/or Acs1p is compromised in the absence of *HST3* and *HST4* (115). However, direct evidence that *S. cerevisiae* Acs1p and/or Acs2p is regulated by acetylation has not been reported.

The nucleocytosolic level of acetyl-CoA is also regulated by *de novo* synthesis of fatty acids, which utilizes nucleocytosolic acetyl-CoA as a precursor (120, 121). Protein acetylation in the nucleocytosolic compartment and synthesis of fatty acids thus compete for the same acetyl-CoA pool. The first and rate-limiting reaction in *de novo* synthesis of fatty acids is carboxylation of acetyl-CoA to form malonyl-CoA, a reaction that is catalyzed by acetyl-CoA carboxylase (Acc1p) (120). Decreased flux of acetyl-CoA through the fatty acid synthesis pathway by reducing *ACC1* expression results in an increased cellular level of acetyl-CoA, globally increased histone acetylation, and altered transcriptional regulation (45, 106). It is interesting that hypomorphic *ACC1* mutations were isolated in a genetic screen for suppressors of inositol auxotrophy caused by low expression of the *INO1* gene in *snf1*Δ cells (122). Inositol auxotrophy of *snf1*Δ cells was suppressed by the *tetO*$_7$*-ACC1* allele via inhibition of the enzymatic activity of Acc1p with the ACC inhibitor soraphen A or by inhibiting Acc1p by providing long-chain fatty acids in the medium (122). The *ACC1* gene was also recovered in a genetic screen for mutations that allow constitutive expression of the *PHO5* gene in medium with a high phosphate concentration (123). The expression of both *INO1* and *PHO5* is affected by global histone acetylation (28, 124). Global histone acetylation, as opposed to targeted acetylation, functions over large chromosomal regions irrespective of promoters, coding regions, or sequence-specific transcription factors (14). Thus, it is likely that the hypomorphic *ACC1* mutations were recovered in both genetic screens because decreased enzymatic activity of Acc1p leads to an increased nucleocytosolic pool of acetyl-CoA and globally increased histone acetylation (45, 106).

This interpretation, at least in the case of *INO1* expression, was recently challenged by an elegant study by Kohlwein's group. Their study showed that Acc1p regulates the relative proportions of C_{16} and C_{18} fatty acids in membrane phospholipids. The transcriptional repressor Opi1p, which shuttles between the endoplasmic reticulum and nucleus and regulates the *INO1* promoter, preferentially binds to C_{16} over C_{18} phospholipid species. Decreased Acc1p activity favors C_{16} fatty acids and thus sequesters Opi1p in the endoplasmic reticulum and derepresses *INO1* (125).

The nucleocytosolic level of acetyl-CoA is also regulated by the SNF1 complex (106). SNF1 is the budding yeast ortholog of mammalian AMP-activated protein kinase (AMPK). SNF1 and AMPK are highly conserved in eukaryotes and serve as cellular energy sensors and master regulators of metabolism (126, 127). Snf1p phosphorylates and inactivates Acc1p (128, 129). Inactivation of SNF1 thus results in increased Acc1p activity, increased conversion of acetyl-CoA into malonyl-CoA, a reduced pool of nucleocytosolic acetyl-CoA, and globally decreased histone acetylation (106). The yeast SNF1 complex consists of the catalytic α-subunit Snf1p, one of three different regulatory β-subunits, Sip1p, Sip2p, or Gal83p, and the stimulatory γ-subunit Snf4p (130). Sip2p, one

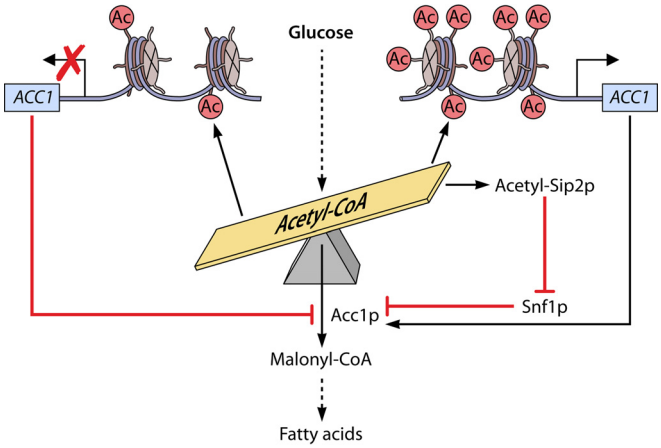

FIG 2 Model of the role of Acc1p and SNF1 in regulation of acetyl-CoA homeostasis.

of the regulatory β-subunits of the SNF1 complex, is acetylated (5). The level of Sip2p acetylation depends on the nucleocytosolic level of acetyl-CoA (45) and is decreased in *snf1*Δ cells (106). The acetylation of Sip2p increases its interaction and inhibition of Snf1p (46). It is tempting to speculate that Sip2p acetylation and consequent inhibition of Snf1p forms a regulatory loop with Acc1p, which contributes to the regulation of acetyl-CoA homeostasis (Fig. 2). Increased acetyl-CoA levels would promote Sip2p acetylation and inhibition of Snf1p. Decreased activity of Snf1p would result in lower Snf1p-mediated phosphorylation and inhibition of Acc1p, and thus in increased conversion of acetyl-CoA to malonyl-CoA. On the other hand, decreased acetyl-CoA levels would result in hypoacetylation of Sip2p and increased activity of Snf1p. This, in turn, would lead to increased phosphorylation and inhibition of Acc1p and decreased conversion of acetyl-CoA to malonyl-CoA (Fig. 2). This homeostatic mechanism would maintain the nucleocytosolic level of acetyl-CoA within certain limits and would prevent gross hypoacetylation or hyperacetylation of chromatin histones, a condition that might alter the regulation of chromatin-based processes, such as transcription or DNA replication and repair. However, regulation of nucleocytosolic acetyl-CoA homeostasis is probably more complex and most likely involves additional mechanisms. For example, transcription of *ACC1* is decreased in *gcn5* cells (131) and in cells expressing the nonacetylatable version of histone H4 (H4K5, -8, -12, and -16R) (132). Decreased histone acetylation due to low nucleocytosolic acetyl-CoA concentration would thus diminish *ACC1* transcription and likely also the conversion of acetyl-CoA to malonyl-CoA, which would elevate acetyl-CoA levels (Fig. 2). In addition, since the acetyl-CoA synthetase reaction involves hydrolysis of ATP into AMP and pyrophosphate, synthesis of acetyl-CoA by both Acs1p and Acs2p is likely regulated by ATP levels (116).

Another possible mechanism that is likely to regulate acetylation of histones and perhaps other nuclear proteins is the nucleus-localized biosynthesis of acetyl-CoA which may result in a locally increased concentration of acetyl-CoA. The nuclear localization of citrate lyase (11), translocation of pyruvate dehydrogenase from mitochondria to nucleus in mammalian cells (110), and nuclear localization of Acs2p in budding yeast (10) all fit into this paradigm. Interestingly, the enzyme producing *S*-adenosylmethionine, a substrate for protein methyltransferases, is targeted to certain promoters in mammalian cells, and by stimulating local production of *S*-adenosylmethionine the enzyme promotes histone methyltransferases that establish transcriptionally repressive chromatin (133).

The connection between metabolism and protein acetylation has another dimension, which involves the activity of NAD^+-dependent protein deacetylases called sirtuins (116, 134). The dependence of sirtuins on NAD^+ indicates that their enzymatic activity depends on the metabolic state of the cell through the cellular level of NAD^+ and/or nicotinamide or the NAD^+/NADH ratio. When glucose is abundant and the metabolite flux through glycolysis is high, the majority of cytosolic NAD^+ is converted into NADH, the activity of sirtuins is low, and global protein acetylation is high. The involvement of sirtuins in global protein acetylation in mammalian cells is supported by studies that show that the activity of SIRT1, a major cytosolic NAD^+-dependent HDAC, is low when glucose is abundant and high during energy limitation (135). However, an abundance of glucose is also associated with increased synthesis of acetyl-CoA (11, 12, 136), and thus it is difficult to differentiate between the effect of acetyl-CoA level and the activity of sirtuins on protein acetylation. Interestingly, it seems that yeast sirtuins regulate synthesis of NAD^+; in the absence of *HST1*, one of the yeast sirtuins, the synthesis of NAD^+ is upregulated (137).

PROTEIN ACETYLATION AND YEAST METABOLIC AND CELL CYCLES

The eukaryotic cell division cycle can be divided into the sequential G_1 (gap 1), S (synthesis), G_2 (gap 2), and M (mitotic) phases. In *S. cerevisiae*, cells increase in size during G_1 until they reach a checkpoint at which they need to make a decision. When external conditions are favorable and nutrients are abundant, cells commit to cell division in a process called START. When nutrients are restrictive, the cells arrest growth and enter a quiescent state called G_0. At the end of the G_1 phase, cells decide whether or not to pass START and commit to cell division. The transcript levels of several genes increase during late G_1, promoting the initiation of DNA replication and other events of the G_1/S transition. Transcription during G_1 is dominated by MBF and SBF complexes, each composed of two subunits. The MBF complex consists of Mbp1p and Swi6p, and the SBF complex consists of Swi4p and Swi6p. The Mbp1p and Swi4p proteins are the DNA-binding components of MBF and SBF, respectively, while Swi6p plays a regulatory role in both complexes. The acetylation of Swi4p was shown to be critical for allowing the interaction with Swi6p and the formation of the SBF complex (6). Moreover, the acetylation of Swi4p depends on the cellular concentration of acetyl-CoA, and the acetylation status of Swi4p affects expression of the histone genes (106).

The SBF and MBF complexes drive expression of about 200 genes (138), including genes involved in DNA synthesis and repair. In early G_1 phase, the inhibitor Whi5p binds to and represses promoter-bound SBF and MBF. This repression is relieved by the phosphorylation of Whi5p by Cln3-Cdc28 (139, 140). Cln3p is a rate-limiting activator of START (141). The transcriptional induction of *CLN3* is triggered by SAGA-mediated acetylation of histones in the promoter region of *CLN3* (142). The recruitment of SAGA to the *CLN3* promoter depends on the autoacetylation of SAGA subunits. Other KATs, including NuA4, SAS2, and SAS3, cannot substitute for SAGA for induction of *CLN3* transcription

(142). These results suggest a model in which acetyl-CoA levels affect two events that regulate START, and it is possible that intracellular levels of acetyl-CoA are one of the key factors which determine whether a cell commits to cell division.

Continuous growth of yeast in a chemostat under glucose-limited conditions results in metabolic oscillations, termed yeast metabolic cycles (143–145). Under these conditions, cells cycle through three metabolic phases: OX (oxidative), RB (reductive, building), and RC (reductive, charging). The oxygen consumption, mitochondrial activity, and induction of genes required for growth, such as ribosomal and amino acid biosynthesis genes, peak during the OX phase. The OX phase is followed by the RB phase, when cell division occurs. Many genes that are expressed during the diauxic shift and stationary phase in batch culture are expressed during the RC phase, prior to the next OX phase. Using this experimental approach, Tu's laboratory discovered that the intracellular concentration of acetyl-CoA peaks during the transition between the OX and RB phases (12). This increased acetyl-CoA concentration is associated with increased recruitment of the SAGA complex to the promoters of growth genes and with increased Gcn5p/SAGA-catalyzed acetylation of histone H3 at K9, K14, K18, K23, and K27 and histone H4 at K5, K8, and K12 in the corresponding promoters. Under these conditions, Gcn5p also acetylates three subunits of the SAGA complex: Spt7p, Ada3p, and Sgf73p. This acetylation occurs on multiple lysine residues, and the acetylation of Spt7p and Sgf73p depends on Ada3p. It appears that acetylated SAGA preferentially binds to growth genes during the OX phase and that the activity of the NuA4 complex is to some extent regulated by SAGA (12).

CONCLUSION

Protein acetylation in eukaryotes has emerged as a dynamic modification that links metabolism with chromatin structure/function and cell signaling. Much of our understanding of the significance of protein acetylation comes from studies in budding yeast; however, it appears that despite the differences in the synthesis of acetyl-CoA between budding yeast and higher eukaryotes, the connection between metabolism, protein acetylation, chromatin structure, and signaling is conserved throughout evolution. Proteomic surveys have identified many acetylated proteins, some of them containing more than one acetylated lysine residue; the major challenge will be to identify which acetylations are regulatory and how they regulate the activity of a particular protein. A related question is whether all KATs and all acetylation sites are affected by acetyl-CoA fluctuations to the same extent, or whether the acetylation status of different lysine residues differs in responsiveness to acetyl-CoA fluctuations. Future work is also needed to advance our understanding of the regulation of acetyl-CoA homeostasis in nucleocytosolic and mitochondrial compartments and what factors regulate acetyl-CoA partitioning between the two compartments under different physiological and nutritional conditions. Another interesting area is the role of protein acetylation in the regulation of cell cycle progression and aging. Two events that regulate cell cycle progression from G_1 to S phase depend on protein acetylation: the assembly of the SBF complex requires Swi4p acetylation (6), and the transcription of *CLN3* is induced by the acetylation of promoter histones (142). Combined with strong evidence implicating that the intracellular level of acetyl-CoA is a gauge of the metabolic state of the cell (146), these results suggest that acetyl-CoA may be one of the factors connecting metabolism with the cell cycle. It is likely that future work exploring the role of acetyl-CoA homeostasis and protein acetylation will bring to light surprises beyond our expectations.

ACKNOWLEDGMENTS

We apologize to any scientists whose work could not be cited in this review due to space limitations.

Research in the Vancura lab is supported by a grant from the NIH (GM106324).

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