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Review

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# Epigenetic Control of Oxidative Stresses by Histone Acetyltransferases in *Candida albicans*

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*Candida albicans* is a major pathogenic fungus in humans, and meets at first the innate immune cells, such as macrophages, in its host. One important strategy of the host cell to kill *C. albicans* is to produce reactive oxygen species (ROS) by the macrophages. In response to ROS produced by the macrophages, *C. albicans* operates its defense mechanisms against them by expressing its oxidative stress response genes. Although there have been many research studies explaining the specific transcription factors and the expression of the oxidative stress genes in *C. albicans*, the regulation of the oxidative stress genes by chromatin structure is little known. Epigenetic regulation by the chromatin structure is very important for the regulation of eukaryotic gene expression, including the chromatin structure dynamics by histone modifications. Among various histone modifications, histone acetylation is reported for its direct relationship to the regulation of gene expression. Recent studies reported that histone acetyltransferases regulate genes to respond to the oxidative stress in *C. albicans*. In this review, we introduce all histone acetyltransferases that *C. albicans* contains and some papers that explain how histone acetyltransferases participate in the oxidative stress response in *C. albicans*.

**Keywords:** *Candida albicans*, oxidative stress response, histone acetyltransferase

## Introduction

All organisms respond to changes in the external environment for their survival. The signal transduction mechanisms of the cells can transfer these external signals into the cells and subsequently cause various transcriptional changes. In other words, cells regulate their gene expression and produce necessary proteins for themselves to survive against the external signals [1, 2]. The signaling pathways connecting the external signals to the transcription factors have been studied for a long time and have now been revealed in many reports. Recent advances in next-generation sequencing technology have contributed to elucidating in detail the mechanisms by which specific genes are induced in specific environments [3, 4]. These signaling pathways also play important roles in host-pathogen interactions [5]. Therefore, it is very important to understand the pathways by which pathogens respond to host defense mechanisms, especially transcriptional regulation.

*Candida albicans* is an opportunistic pathogenic fungus in humans, and also uses a variety of signaling pathways to overcome the host defense mechanisms. Within a host, *C. albicans* is attacked by innate immune cells of the host, such as macrophages and neutrophils. These innate immune cells produce the reactive oxygen species (ROS), such as hydrogen peroxide and superoxide, to kill the pathogens. These ROS cause oxidative stress to *C. albicans* and induce irreversible damage to *C. albicans* by causing programmed cell death, forming protein-protein cross-link, or interacting with lipids and nucleic acids [6].

*C. albicans* expresses various antioxidant genes to protect itself from the oxidative stress. Some examples are the following: catalase (CAT1), which stimulates the degradation of hydrogen peroxide ($H_2O_2$) into water ($H_2O$) and oxygen ($O_2$); and glutathione peroxidase (GPX) and superoxide dismutase (SOD), which are peroxide scavenging enzymes.

The expression of genes encoding these proteins is critical to the virulence and pathogenesis of *C. albicans* [6–10]. There are many reports on the signal transduction pathways through which *C. albicans* regulates its transcription responding to ROS [6].

Since *C. albicans* is a eukaryotic organism, we have to consider the transcriptional regulation by the chromatin structure. DNA in all eukaryotic organisms is packaged into the regular structure of chromatin, which contains nucleosomes as its basic unit [11]. The nucleosome consists of the core histone containing two copies of H2A, H2B, H3, and H4 wrapped by 146 base pair DNA. For the transcription factors to access the regulatory sequences in DNA, the chromatin structure should be regulated into the open state. One of the important mechanisms for regulating the chromatin structure is the posttranslational modifications of histone proteins [12]. Because N-terminal tails of histone proteins are protruded outward from the nucleosomes, they are likely to be targeted for various chemical modifications, including methylation, ubiquitylation, phosphorylation, acetylation, and so on [13]. Since histone acetylation among various histone posttranslational modifications, can cause a change of the chromatin structure by neutralizing the basic amino acids of histones, the functions of histone acetylation relating to the chromatin structure and transcription have been revealed by many scientists [13, 14].

Histone acetylation by histone acetyltransferases (HATs) occurs in lysine residues of histones and these acetyl groups can be removed by histone deacetylases (HDACs) [15]. HAT, as a writer for the histone acetylation, is generally part of a complex containing various subunits and generates ε-*N*-acetyl lysine by acetylating the lysine residue of histone using acetyl-CoA as an acetyl group donor [16, 17]. HATs are classified into two types; type A and type B. Type A HATs are present in the nucleus, and type B HATs are in the cytoplasm. Type A HAT is responsible for acetylating the histones within the nucleosomes and is known to regulate transcription directly [13, 18].

On the other hand, type B HAT is known to be responsible for acetylating free histones newly synthesized within the cytoplasm, and the histone acetylated by type B HAT in the cytoplasm is transported into the nucleus. The histones acetylated by type B HAT in the cytoplasm can be incorporated into the nucleosomes after their transport into the nucleus and then be deacetylated by the HDAC complex within the nucleosomes [18].

Type A and B HATs are well conserved in *C. albicans*, and recent studies have reported the functions of HATs regulating the expression of oxidative stress-responsive genes in *C. albicans* responding to ROS. They suggested that various HATs of *C. albicans* are critical to the virulence and pathogenesis of the fungus by regulating chromatin structure and transcription [19–21]. However, the mechanisms of how HATs regulate the oxidative stress-responsive genes are not identical, even if their enzymatic activities are identical in how they acetylate the lysine residues of histones. Whereas the SAGA complex of *C. albicans*, a type A HAT, induces an open chromatin state and interacts with the transcription factors for the expression of oxidative stress-responsive genes [19], Rtt109 and the NuB4 complex of *C. albicans*, type B HATs, repress the oxidative stress-responsive genes [20, 21]. Here in, we review the conserved HATs of *C. albicans* and how the SAGA complex, NuB4 complex, and Rtt109 regulate the oxidative stress-responsive genes and virulence in *C. albicans*.

## Histone Acetyltransferases in *C. albicans*

*C. albicans* contains HATs that are conserved in mammals and other eukaryotes, including fungi (Table 1). Like various proteins with HAT activity in other organisms, the function of each protein bearing HAT activity in *C. albicans* varies largely depending on the other subunits in the complex [22]. As described above, HATs are classified into Type A existing in the nucleus and Type B functioning in the cytoplasm, and can also be classified according to the sequence homology of the HAT domain existing in the catalytic subunit. According to the latter classification, HATs are classified into the Gcn5 family, the MYST family including Moz/Ybf2(Sas3)/Sas2/Tip60, and others [22]. Fig. 1 shows various conserved HATs in *C. albicans* by searching the Candida Genome Database (http://candidagenome.org) and Interpro (https://www.ebi.ac.uk/interpro/). In *C. albicans*, whereas only Gcn5 is present as the Gcn5 family, Esa1, Sas2, and Sas3 are present as the MYST family. In addition, Rtt109, which is a fungal-specific HAT, and Hat1, Elp3, and Hpa3 are conserved in *C. albicans*. Each component of HAT complexes conserved in *C. albicans* and their known targets are listed in Table 1, based on the information from *Saccharomyces cerevisiae*.

Gcn5 of *C. albicans*, which is required for filamentous and invasive growth, is known to be essential for hyphal elongation under the serum-induced condition [23]. *C. albicans* can grow in a filamentous form depending on the external environment. *C. albicans*, which recognizes hypha-inducing signals, such as serum, grows as a hyphal form by inducing expression of various hypha-specific genes [24]. For this signaling, the NuA4 complex containing one HAT of the

**Table 1.** Histone acetyltransferases (HATs) conserved in *C. albicans*.

| HAT complex | Catalytic subunit | Core components | Known targets in *S. cerevisiae* | Known targets in *C. albicans* | References |
|---|---|---|---|---|---|
| SAGA/ SLIK/ ADA | Gcn5 (*orf19.705*) | Ada2, Ada3, Sgf29, Ada1, Tra1, Spt3, Spt7, Spt8, Spt20, Taf5, Taf6, Taf9, Taf10, Taf12, Ubp8, Sus1, Sgf11, Sgf73, Chd1 | H3K9ac<br>H3K14ac<br>H3K18ac<br>H3K23ac<br>H3K27ac<br>H3K36ac<br>H4K16ac<br>H2BK11ac<br>H2BK16ac<br>H2A.ZK14ac | H3ac | [23, 37, 49–52] |
| NuA4 | Esa1 (*orf19.5416*) | Epl1, Yng2, Tra1, Yaf9, Act1, Arp4, Swc4, Eaf1, Eaf3, Eaf5, Eaf6, Eaf7 | H4K5ac<br>H4K8ac<br>H4K12ac<br>H4K16ac<br>H2A.ZK14ac | H4K5ac<br>H4K12ac<br>H4K16ac | [51, 53–55] |
| SAS | Sas2 (*orf19.2087*) | Sas4, Sas5 | H4K16ac | H4K16ac | [26, 56] |
| NuA3a/b | Sas3 (*orf19.2540*) | Eaf6, Taf14, Nto1, Yng1, Pdp3 | H3K14ac | | [57–59] |
| NuB4 | Hat1 (*orf19.779*) | Hat2 | H4K5ac<br>H4K12ac | H4K5ac<br>H4K12ac | [31, 60] |
| Elongator | Elp3 (*orf19.7387*) | Elp1, Elp2, Elp4, Elp5, Elp6 | H3K14ac<br>H4K8ac | | [61] |
| | Hpa3[a] (*orf19.6323*) | | H4K8ac | | [62] |
| | Rtt109 (*orf19.7491*) | | H3K56ac | H3K56ac | [20, 63] |

[a] *S. cerevisiae* contains both Hpa2 and Hpa3 with high sequence homology, but with different target residues, whereas *C. albicans* contains only one conserved *S. cerevisiae* Hpa3.

MYST family, Esa1, functions to induce hypha-specific genes by binding to the promoters of these genes with the help of Efg1, which is a key transcription factor for hyphal formation, and by acetylating nucleosomal H4 around these regions [25]. Another MYST family, Sas2, which is a catalytic subunit of the SAS HAT complex (Sas2-Sas4-Sas5), is known to be able to acetylate free histones and nucleosomal histones [26–28]. Sas2 is known to acetylate histone H4 lysine 16 and plays a critical role in the transcriptional regulation by antagonizing the function of Sir2, which is a histone deacetylase [29, 30]. As for the last MYST family member of *C. albicans*, Sas3, little known about its function relating to gene expression or virulence in *C. albicans*.

In addition to the GCN5 family and MYST family, Hat1, a well-known HAT of *C. albicans*, is a catalytic subunit of the NuB4 complex. The report that the deletion of the *Hat1* gene causes increasing DNA damage and the induction of pseudohyphal growth in *C. albicans* suggests the possibility to develop the Hat1 protein as an antifungal therapeutic target [31]. As will be discussed in detail later, the Hat1-deleted mutant of *C. albicans* increases the resistance to oxidative stress compared with its wild-type [21].

Rtt109 is the first HAT known about its physiological function in *C. albicans* [20]. Rtt109 was first identified to acetylate histone H3 lysine 56 in *S. cerevisiae* [32]. The catalytic domain of Rtt109 has no sequence homology with that of other HATs (Fig. 1). H3K56 acetylation mediated by Rtt109 is specific for the S phase and plays a critical role in the genome stability [33]. Rtt109 has been also reported for its role in the oxidative stress response in *C. albicans* and we will discuss this later in detail [20].

Although the specific roles of Elp3 and Hpa2, which are two other HATs in *C. albicans*, have not been elucidated yet, their functions in *C. albicans* can be deduced from their

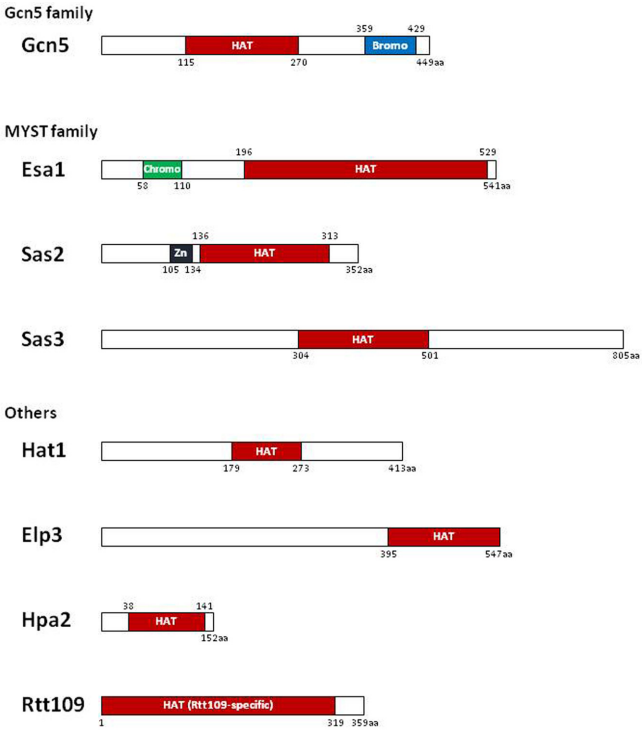


**Fig. 1.** Various histone acetyltransferases (HATs) conserved in *Candida albicans*.

We searched HATs that have conserved catalytic domain sequences by using the Candida Genome Database (http://candidagenome.org) and Interpro (https://www.ebi.ac.uk/interpro/) and classified these HATs into the GCN family, MYST family, and others. In *C. albicans*, GCN5 is an only HAT in the GCN family and has a Bromo-domain. The MYST family has three HATs; Esa1, Sas2, Sas3. These HATs have a conserved HAT domain, but Sas3 is a little known HAT with regard to gene expression. On the other hand, Esa1 can bind to the promoter of hyphal-specific genes and contribute to their induction. Sas2 can acetylate free histones and nucleosomal histones. As for the HATs not classified to the GCN or MYST family, both Hat1 and Rtt109 are well-known HATs in *C. albicans*. Hat1 can acetylate H4 K5 and K12 by forming a complex with Hat2. Rtt109 has a catalytic domain that shows no sequence homology with other HATs, but Rtt109 is well known to acetylate H3K56.

roles in *S. cerevisiae*. Elp3 is one of the six subunits composing the Elongator complex, which is important to transcription elongation as a major component of RNA polymerase II holoenzyme [34, 35]. Hpa2, which is a member of the Gcn5-related *N*-acetyltransferase superfamily, is known to contain D-amino acid *N*-acetyltransferase activity and acetylating activity specific to the lysine residues of histones H3 and H4 in *S. cerevisiae* [36].

HATs form a complex by interacting with other proteins, and their functions vary depending on the proteins they are binding to, as with most other histone modifiers. Besides their acetylating activity, HAT complexes can regulate the gene expression responding to the external signals by interacting with other transcription factors or changing the chromatin structure. Because *C. albicans* defends itself against the attack of the host by regulating gene expression responding to the host-producing signals, HATs of *C. albicans* are likely to be the target of therapeutic drugs. Therefore, studies about the functions of HATs are necessary to understand the pathogenesis and defense mechanisms of *C. albicans*.

## HAT Module of the SAGA Complex: Its Positive Regulation of Oxidative Stress-Responsive Genes by Interacting with Other Transcription Factors

The first reported HAT-related protein contributing to the oxidative stress response in *C. albicans* was Ada2. Nantel's group reported that Ada2 depletion in *C. albicans* causes a severe decrease of histone acetylation levels on numerous genes and increases the sensitivity to oxidative stressors, such as menadione and $H_2O_2$ [19]. Ada2 is a component of the Spt-Ada-Gcn5-acetyltransferase (SAGA) coactivator complex, which is the first isolated nuclear HAT complex, a type A HAT, in *S. cerevisiae* [37]. In the SAGA complex, Ada2 interacts with Gcn5 bearing the active site of HAT activity, and this interaction between Ada2 and Gcn5 is critical for Gcn5's HAT enzymatic activity [38]. Because the SAGA complex interacts with TATA-binding protein, the SAGA complex is known to be an important coactivator for the transcription initiation [22]. Nantel's group performed Ada2-chromatin immunoprecipitation (ChIP) microarray and found that Ada2 associates with 200 promoters of stress-responsive genes, including oxidative stress-responsive genes [19]. Moreover, they observed the decreased acetylation level of histone H3 lysine 9 on two selected promoters of Ada2 binding regions in Ada2-depleted *C. albicans*. Whereas the SAGA complex containing Ada2 interacts with the upstream regions of promoters and acetylates histones on the same region in *S. cerevisiae* [39], Ada2 of *C. albicans* and the histones acetylated by Ada2 are abundant in the promoter regions in *C. albicans*.

Nantel's group also found that the increased sensitivity of Ada2-depleted *C. albicans* to oxidative stress results in the decrease of virulence, using a mouse model [19]. Since the oxidative stress produced by macrophages is the first defense mechanism of the host against *C. albicans*, the deficiency of Ada2 in *C. albicans* caused the attenuation of virulence in the mouse. *C. albicans* normally synthesizes

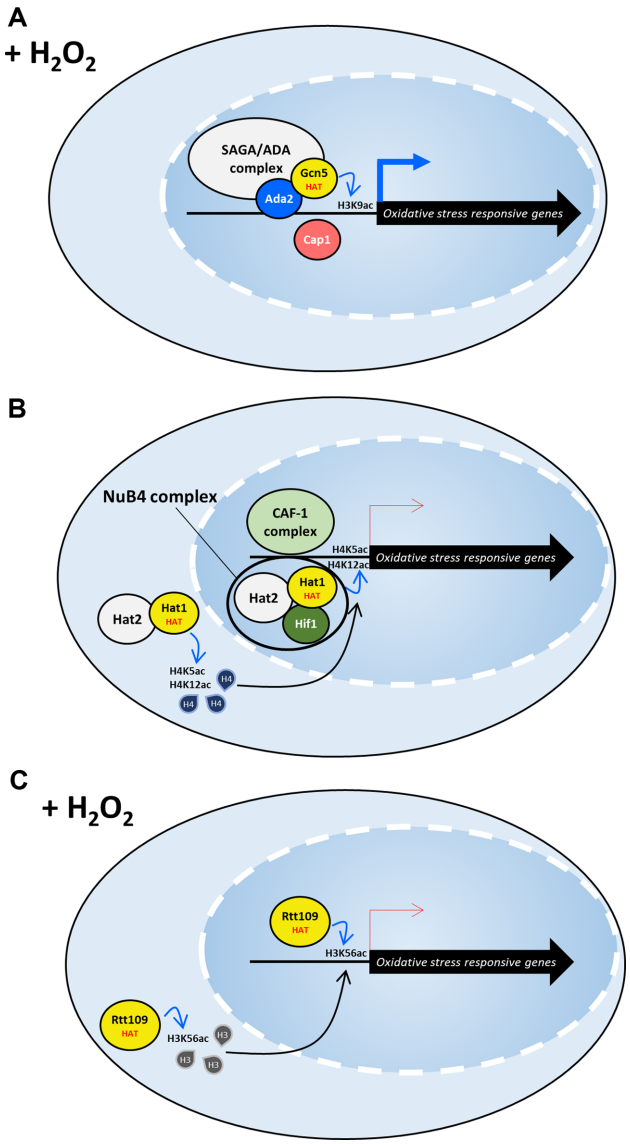


**Fig. 2.** Functional mechanisms of acetyltransferses for the regulation of oxidative stress responsive genes responding to the external oxidative signals in *C. albicans.*

(**A**) When host cells produce reactive oxygen species (ROS), the SAGA complex containing Ada2 regulates the oxidative stress responsive genes by interacting with Cap1 transcription factor and by acetylating these genes' promoters. (**B**) In the cytoplasm, the Hat1-Hat2 complex can acetylate H4K5 and K12 and these acetylated histones are transported into the nucleus. Hat1 and Hat2 form the NuB4 complex with Hif1, and the NuB4 complex can acetylate H4 K5 and K12 in the promoter of oxidative stress responsive genes. These acetylated nucleosomal histones repress the oxidative stress responsive genes. (**C**) Responding to the ROS, Rtt109 can acetylate H3K56 of free histones in the cytoplasm and the same site of nucleosomal histones around promoter regions of oxidative stress responsive genes in the nucleus. The blue arrows indicate the activation of transcription or acetylation. The red arrows indicate the repression of transcription.

antioxidant enzymes, such as glutathione reductase, thioredoxin reductase, and SOD, to evade the host defense mechanisms, and the expressions of the genes encoding these antioxidant enzymes are known to be mainly regulated by Cap1 [40]. Cap1 is a homolog of Yap1 of *S. cerevisiae*, a basic leucine zipper transcription factor classified into the AP-1 family, which is required for the oxidative stress response [41]. Jiang's group found 76 Cap1-regulated genes, including oxidative stress-responsive genes, by performing microarray using Cap1-depleted *C. albicans* under the $H_2O_2$-treated condition [40]. Nantel's group also found that Ada2-depleted *C. albicans* cannot express some Cap1-regulated genes under the oxidative stress condition, and that Ada2's recruitment to the promoter of Cap1-regulated genes is Cap1-dependent [19]. The way by which Ada2 regulates gene expression in a Cap1-dependent manner is consistent with the regulatory mechanism of the drug-resistant genes by Ada2 and Cap1 in *C. albicans* [19, 42]. Although the mechanisms of how Ada2 regulates the oxidative stress-responsive genes remain to be elucidated in *C. albicans*, the HAT module of the SAGA complex containing Ada2 regulates some Cap1-regulated genes by interacting with Cap1 transcription factor and by acetylating these genes' promoters in *C. albicans* (Fig. 2A). The regulation by the SAGA complex including Ada2 plays a critical role in the virulence and pathogenesis of *C. albicans*.

## Hat1 of the NuB4 Complex: Its Negative Regulation of Oxidative Stress-Responsive Genes by Interacting with Histone Chaperones

Hat1, one of the type B HATs, is an enzyme that acetylates histone H4 lysine 5 and 12 by forming a protein complex with the chaperone Hat2 in the cytoplasm. After acetylating histone H4 lysine 5 and 12 in the cytoplasm, the Hat1-Hat2 complex enters into the nucleus and forms the NuB4 complex by adding Hat1-interacting factor 1 (Hif1) [43]. Hif1 is a histone chaperone. The NuB4 complex is known to be critical for histone deposition into the DNA-damaged site [44].

The oxidative stress-responsive genes of *C. albicans* are repressed under normal conditions, but their expression levels are induced when *C. albicans* recognizes oxidative stress signals. The NuB4 complex in *C. albicans* has functions to repress the expression of the oxidative stress-responsive genes as opposed to the HATs discussed above [22]. In 2015, Kuchler's group found that the deletion of Hat1, which is a catalytic subunit of the NuB4 complex,

caused the increased expression of the oxidative stress-responsive genes and subsequently increased resistance against oxidative stress and innate immune cells of the host in *C. albicans* [21].

Because the NuB4 complex has a function for histone deposition, the histone chaperones are very important for the function of the NuB4 complex. When the NuB4 complex regulates the expression of various stress-responsive genes negatively, NuB4 forms a complex by interacting with histone chaperones, such as HIR and CAF-1 [21, 45]. Kucheler's group showed that the deletion of Cac2, one of the CAF-1 components, causes increased oxidative stress resistance like as the deletion of Hat1. Moreover, they confirmed that the transcription profiles of Hat1- and Cac2-deleted mutants are similar [21]. According to their results, the oxidative stress-responsive genes were more highly expressed in these two mutants than in a wild type. From these results, the Kuchler group has reported that the NuB4 complex, including Hat1, inhibits the expression of these oxidative stress-responsive genes by the increase of nucleosome occupancy as a result of its function of nucleosome deposition around the promoter regions of these genes, with the help of the CAF-1 complex [21] (Fig. 2B). They also found that the inhibition by the NuB4 complex with the histone chaperone CAF-1 is limited in *C. albicans* or CTG clade species among fungal species. Therefore, the deletion of Hat1 in *S. cerevisiae* does not cause the increased resistance against oxidative stress.

Recently, the functions of Hat1 related to the oxidative stress response were reported in humans. In humans, oxidative stress is a risk factor for the formation of renal cell carcinoma. The expression of the *HAT1* gene is greatly reduced in human kidney epithelial cells transformed by oxidative stress [46]. From the results of *C. albicans*, Hat1 blocks the expression of genes necessary for repairing oxidative stress, but these genes must be expressed when oxidative stress is applied. Therefore, we can conclude that the expression of Hat1 should be decreased because Hat1 inhibits the expression of oxidative stress-responsive genes.

## Rtt109: A Fungal-Specific HAT Contributing to DNA Stability and the Resistance against Oxidative Stress

Rtt109, a fungal-specific HAT, is classified as a type B HAT, which acetylates histones in the cytoplasm. Rtt109 is only detected in the fungal kingdom and is also found in *C. albicans* [20]. Kaufman's group reported that Rtt109 is required for the resistance against oxidative stress and virulence in *C. albicans* [20].

Rtt109 was initially identified as a DNA-damage response factor from *S. cerevisiae* [47] and it was reported that Rtt109 is required for genome stability by acetylating the lysine 56 of histone H3 (H3K56ac) [33]. In *S. cerevisiae*, H3K56ac plays roles to assemble proper nucleosomes and to regulate gene transcription [48]. Because the nucleosome must be assembled properly as the genes are transcribed, DNA replication-independent nucleosome assembly is important for the regulation of transcription. Moreover, the acetylated H3K56 mediated by Rtt109 in *S. cerevisiae* is known to associate with the elongating form of polymerase II, and it was reported that a high level of H3K56ac is observed on the transcriptionally active puff sites of *Drosophila* polytene chromosome [32].

Kaufman's group found that Rtt109-deleted mutants cannot form colonies well on the $H_2O_2$-containing media compared with the wild-type and lost their virulence in a mouse model. However, they observed the increased expression levels of oxidative stress-responsive genes, especially the gene of SOD, under the treatment of $H_2O_2$ in the Rtt109-deleted mutant in contrast to the Ada2-deleted mutant [19, 20]. Despite the increased expression levels of oxidative stress-responsive genes, *C. albicans* without Rtt109 showed high sensitivity to $H_2O_2$. These results are different from the previous results that H3K56 acetylation is associated with transcription activation. Although the relationship between H3K56 acetylation and the regulation of gene expression has to be further studied, Rtt109 can acetylate H3 lysine 56 of free histones in the cytoplasm and the same site of nucleosomal histones in the nucleus, and subsequently regulates the expression of some oxidative stress genes, perhaps negatively (Fig. 2C) [20].

In summary, we have reviewed the conserved HATs of *C. albicans* and the recent studies about the functions of some HATs related to the oxidative stress response in *C. albicans*. In general, many lysine residues of histone proteins are acetylated by HATs, and one organism contains several HATs. These various HATs have their specific acetylating lysine residues within histones. In *C. albicans*, there are at least eight conserved HATs containing HAT domains (Fig. 1). HATs can acetylate both free histones and nucleosomal histones, unlike other histone modifiers. Therefore, HAT can be classified into type A as the nuclear HAT and type B as the cytoplasmic HAT. Gcn5 of *C. albicans* is a type A HAT whose function is known, and a component of the SAGA complex. When *C. albicans* recognizes oxidative signals, such as $H_2O_2$, the SAGA complex containing Gcn5 and Ada2 is recruited to the promoter regions of the

oxidative stress-responsive genes by interacting with Cap1 (Fig. 2A) [19]. After recruitment of the SAGA complex to the promoter regions of these genes, histone H3 lysine 9 on these promoter regions is acetylated by the complex and then subsequently changes the chromatin structure to promote the transcription of oxidative stress-responsive genes. Whereas the SAGA complex of *C. albicans* regulates oxidative stress-responsive genes positively, type B HAT Hat1 of *C. albicans* regulates these genes negatively, even if these two enzymes' activities are identical. Hat1 is a component of the NuB4 complex, and has functions for both cytoplasmic free histones and nucleosomal histones by acetylating histone H4 lysines 4 and 12 (Fig. 2B) [21]. In the absence of oxidative stress, the NuB4 complex regulates the expression of oxidative stress-responsive genes with the help of the histone chaperone CAF-1 complex, since no antioxidant enzymes to remove ROS are needed (Fig. 2B).

*C. albicans* also has conserved Rtt109, which is a fungal-specific HAT. The function of Rtt109 for regulating oxidative stress-responsive genes has not been defined yet. In *C. albicans*, Rtt109 is responsible for the acetylation of histone H3 lysine 56 in both cytoplasmic free histones and nucleosomal histones, and Rtt109-depleted mutants show increased sensitivity against oxidative stress. However, under $H_2O_2$ treatment, Rtt109-depleted mutants express a high level of oxidative stress-responsive genes (Fig. 2C) [20]. Therefore, the mechanism of how Rtt109 regulates the expression of oxidative stress genes and the response to oxidative stress should be studied by interacting with HDACs or other histone modifiers.

Most histone modifiers are linked to transcriptional machineries for the regulation of gene expression. The transcriptional regulation by histone modification is one of the important epigenetic regulations, which means the regulation of gene expression by chromatin structure change without DNA sequence changes. To understand gene expression, the last step of the signaling pathways related to the response against the external stress, especially oxidative stress, studies on the regulation by histone modifications must be carried out. In addition, since these histone modifiers can be developed as targets of therapeutic agents for pathogenic fungi, it is important to understand the mechanism of action of histone modifiers in pathogenic fungi. However, the fact that histone modifiers are essential in the host limits the development of fungal therapeutic agents targeting histone modifiers. From this viewpoint, Rtt109, which exists only specifically in fungi, can be developed as a very important therapeutic drug target. In addition, understanding the mechanisms that other histone modifiers, as well as HATs including Rtt109, use to respond to the host's defense mechanisms is also highly needed to elucidate the overall epigenetic regulation in *C. albicans*.

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