Fungal KATs/KDACs: A New Highway to Better Antifungal Drugs?

Karl Kuchler1,*, Sabrina Jenull1, Raju Shivarathri1, Neeraj Chauhan2,3,*

1 Department of Medical Biochemistry, Medical University Vienna, Max F. Perutz Laboratories, Austria, 2 Public Health Research Institute, 3 Department of Microbiology, Biochemistry and Molecular Genetics, New Jersey Medical School, Rutgers, The State University of New Jersey, Newark

* chauhan1@njms.rutgers.edu (NC); karl.kuchler@meduniwien.ac.at (KK)

Introduction

According to the World Health Organization, infectious diseases stand out as the major cause of death worldwide. Although bacterial, viral, and parasitic infections appear to constitute the major threat, the clinical relevance of fungal infections has not been adequately recognized. In fact, invasive fungal infections constitute a biomedical problem of epic proportions, because a handful of human fungal pathogens claim an estimated 1.5 million lives per year [1]. Importantly, invasive fungal diseases represent leading causes of morbidity and mortality in immunocompromised individuals, particularly in patients with hematological malignancies, bone-marrow and organ transplant recipients, intensive care unit patients, preterm neonates, and patients with inborn or acquired immune deficiencies such as AIDS [2].

The vast majority of fungal infections are caused primarily by Candida albicans, Aspergillus fumigatus, and Cryptococcus spp. [2]. The overall mortality rate of 35%–40% for candidemia alone exceeds all gram-negative acute bacterial septicemia [3]. Importantly, pronounced inherent clinical antifungal drug resistance, especially in species like Candida glabrata [4], promotes a dramatic increase of infections [5, 6]. The unsolved challenge of getting fast, reliable, and accurate pathogen-specific clinical diagnosis of fungi has remained as another major impediment to successful and efficient antifungal therapy [7].

A mere four chemical entities (polyenes, azoles, echinocandins, and flucytosine) constitute the armory of clinically relevant drugs [1]. A few variant azoles and echinocandins received recent United States Food and Drug Administration (FDA) approval, but new chemical entities are either missing or mainly experimental in nature [8]. Of note, vaccination against fungal infections is currently unavailable and heavily debated, although recent clinical trials may hold new promises as well as challenges ahead [9–11]. Interestingly enough, compelling evidence indicates that chromatin tightly controls fungal virulence and/or pathogen fitness in the host. Nucleosome remodeling and assembly pathways impact the dynamic interplay with host immune surveillance, facilitate immune evasion, as well as drive antifungal drug resistance [12]. For example, several lysine acetyltransferases (KATs) and lysine deacetylases (KDACs) control fungal virulence [13]. This suggests that KATs/KDACs modifying both histones and non-histone targets could aid in antifungal drug discovery [13, 14]. Here, we provide a comprehensive overview of chromatin modifications in human fungal pathogens, particularly those altering virulence (Table 1, Fig 1). However, owing to space constraints, we will focus our discussion on KDACs/KATs in Candida spp. In addition, we discuss how the modulation of KATs/KDACs in Candida spp. could pave the way for novel therapeutic strategies to combat fungal infections [13].
| Catalytic subunit Ca | Histone target | ** * Inhibitors /Activators* | Virulence/ Fitness (mouse) | Other Candida spp. | Other fungal pathogens | S. orthologue | Mammalian orthologue (s): modified residue | References |
|----------------------|----------------|-----------------------------|-----------------------------|--------------------|-----------------------|-------------|-------------------------------|------------|
| KDACs                |                |                             |                             |                    |                       |             |                                |            |
| Hos1/orf19.4411      | H4K12          | TSA, SB, SAHA               | -                           | Cg, Ct, Cp         | Host1                 | HDAC3/HDAC1: all four core histones | [14, 68–70] |            |
| Hos2/orf19.5377      | specific for H3, H4 including H4K16, H4K12; in vitro: no KDAC activity? | MGCD290 (specific), TSA, SB, SAHA | attenuated (Set3) | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Hos2        | HDAC3: all four core histones | [13–14, 28, 56, 68–74] |
| Hos3/orf19.2772      | H4K12, H2BK16  | -                           | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Hos3        | -                             | [14, 69, 75–77] |
| Rpd3/orf19.2834      | all four core histones, except H4K16; nonhistone: HSP90 | TSA, SB, SAHA, Apicidin, VPA | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Rpd3        | HDAC1/HDAC2: all four core histones | [31, 40, 69–70, 74, 78–86] |
| Rpd31/orf19.6801     | all four core histones, except H4K16 | TSA, SB, SAHA, Apicidin | attenuated | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Rpd3        | HDAC1/HDAC2: all four core histones | [31, 40, 69–70, 74, 78–82, 161] |
| Hda1/orf19.2606      | specific for H3, H2B including H3K9, H3K18, H2BK16; nonhistone: HS P90 | TSA, SB, SAHA, Apicidin | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Hda1        | HDAC6: all four core histones | [31, 74, 77, 84–91] |
| Hst1/orf19.4761      | H3, H4 including H4K5 | NAM                          | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Hst1        | SIRT1/SIRT3: H4K16, H5K9    | [82, 88, 92–96] |
| Hst2/orf19.2580      | H4K5, H4K12    | NAM                          | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Hst2        | SIRT3/SIRT2: H4K16, H3K9    | [82, 94, 96–100] |
| Hst3/orf19.1934      | H3K56          | NAM                          | decreased                   | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Hst3/Hst4   | SIRT3: H4K16                  | [25–26, 82, 96, 101] |
| Sir2/orf19.1992      | H4K16, H3K56   | Splitomycin (specific), NAM, Sirtinol | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn, Chr* | Hst1 (Blast Sir2 higher identity) | SIRT1: H4K16, H3K9 | [15, 69, 77, 83, 94, 100, 102–104] |
| orf19.2963           | (uncharacterized) | -                           | -                           | Cg, Ct, Cp         | Hc                   | Hst2        | -                             |            |
| HMTs                 |                |                             |                             |                    |                       |             |                                |            |
| Set1/orf19.6009      | H3K4           | -                           | decreased                   | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Set1        | SETD1a/SETD1b/H3K4           | [15, 27, 82, 105–106] |
| Set2/orf19.1755      | H3K36          | -                           | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Set2        | SETD2: H3K36                  | [27, 82, 107–108] |
| Dot1/orf19.7402      | H3K79          | -                           | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Dot1        | DOT1L: H3K79                  | [27, 82, 107–108] |
| Serine-Kinases       |                |                             |                             |                    |                       |             |                                |            |
| Cst20/orf19.4242     | H2BS10         | Hesperidin (developed for Mst1) | attenuated                   | Cg, Ct, Cp         | Af, Hc                | Ste20       | MST1: H2B14                   | [75, 109–112] |
| Mec1/orf19.1283      | H2AS129        | -                           | -                           | Cg, Ct, Cp         | Af, Hc, Chn           | Mec1        | ATM: H2A139                   | [113–114] |
| Tel1/orf19.5580      | H2AS129        | -                           | -                           | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Tel1        | ATR: H2A139                   | [113–115] |
| HDHP                 |                |                             |                             |                    |                       |             |                                |            |
| Pho15/orf19.4444     | H2A (in vitro) | -                           | competitive fitness normal  | Cg, Ct, Cp         | Af, Fo, Hc, Chn       | Pho13       | -                             | [27, 116–117] |
| KATs                 |                |                             |                             |                    |                       |             |                                |            |
| Gcn5/orf19.705       | H2BK6, H3(K4, K9, K14, K18, K23, K27), H4K8 | Garcinol, Anacardic acid, CPTH2 | decreased                   | Cg, Ct, Cd, Cp | Af, Fo, Hc, Chn       | Gcn5        | KAT2A and KAT2B: H3K9, H3K14, H3K18, | [41, 57, 74, 118–127] |
| Hat1/orf19.779       | H2AK8, H4(K5, K12) | -                           | decreased                   | Cg, Ct, Cd, Cp | Af, Fo, Hc, Chn       | Hat1        | HAT1/KAT1: H2AK5, H4K12     | [37, 127–132] |
| Elp3/orf19.7387      | H3K14, H4K8    | -                           | -                           | Cg, Ct, Cd, Cp | Af, Fo, Hc, Chn       | Elp3        | ELP3/KAT9: H3K14, H4K8     | [127, 133–134] |
| Hpa2/Hpa3/orf19.6323 | H3K14, H4(K5, K12) | Cl, Cd, Cp                  | Af, Fo, Hc, Chn             | Hpa2               | -                     | [135–136] | (Continued) |
| Catalytic subunit Ca | Histone target | ** Inhibitors/Activators* | Virulence/Fitness (mouse) | Other Candida spp. | Other fungal pathogens | Sc orthologue | Mammalian orthologue(s): modified residue | References |
|----------------------|----------------|--------------------------|--------------------------|-------------------|------------------------|--------------|------------------------------------------|------------|
| Hpa3/Hpa2/orf19.6323 | H4K8           |                          |                          |                   |                        | Hpa3        | -                                        | [135]      |
| Med5 (Nut1)/orf19.1808 | H4K16         | Cg, Ct, Cd, Cp           | Af, Fo, Cn               | Nut1              |                        | -            | [137–138]                                |            |
| Esa1/orf19.5416     | H2A(K5, K8), H2B(K11, K16), H2AZ(K3, K8, K10, K14), H4(K5, K12, K16, K20) | NU9056, MG149           | Cg, Ct, Cd, Cp      | Af, Fo, Hc, Cn       | Esa1                   | TIP60/KAT5: H3K14, H4K5, H4K8, H4K12, H4K16 [15, 17, 57, 130, 139–141] |
| Sas2/orf19.2087     | H4(K16, K20)   | Cg, Ct, Cd, Cp           | Fo                       | Sas2              | KAT8: H4K16, H4K5, H4K8 [139, 142–144] |
| Sas3/orf19.2540      | H3(K14, K23)   | Cg, Ct, Cd, Cp           | Af, Hc, Cn               | Sas3              | KAT6: H3K14 [15, 127, 145–146] |
| Nat4/orf19.4664     | H2A, H4        | Cg, Ct, Cd, Cp           | Af, Fo, Hc               | Nat4              | NAA40: H4, H2A [147–148] |
| Taf1/250 (Taf1)/orf15.7354 | H3, H4       | -                        | Af, Fo, Hc, Cn           | Taf1              | KAT4 [127, 149–150] |
| Rtt109/orf19.7491   | H3K56          | Anacardic acid, CPTH6, C646/CPTPB*, TTK21* | decreased               | Cg, Ct, Cd, Cp | Af, Hc, Cn | Rtt109 p300: H3K56 [25, 121, 125, 151–158] |
| orf19.7074          | H3(K9, K14, K18) | Cg, Ct, Cd, Cp           | Af                        | Sgf29             | SGF29: H3K14 [159] |
| Spt10/orf19.2361    | H3K56          | Cg, Ct, Cd, Cp           | Af, Cn                    | Spt10             | - [160] |

Abbreviations: KDACs: lysine deacetylases; HMTs: histone methyltransferases; HDPH: histone dephosphorylase; KATs: lysine acetyltransferases; TSA: trichostatin A; SB: sodium butyrate; SAHA: suberoylanilide hydroxamic acid; VPA: valproic acid; NAM: nicotinamide; CPTH2: Cyclopentyldiene-[4-(4-chlorophenyl)thiazol-2-yl]hydrazine; CPTH6: 3-methylcyclopentyldiene-[4-(4`-chlorophenyl)thiazol-2-yl]hydrazine; NU9056: 5-(1,2-Thiazol-5-ylidene)-1,2-thiazole; MG149: 2-(4-Heptylphenethyl)-6-hydroxybenzoic acid; CTPB: N-[4-Chloro-3-(trifluoromethyl)phenyl]-2-ethoxy-6-pentadecylbenzamide; TTK21: N-(4-Chloro-3-trifluoromethyl-phenoxy)-2-n-propoxy- benzamide; Ca: Candida albicans; Cg: Candida glabrata; Ct: Candida tropicalis; Cp: Candida parapsilosis Af: Aspergillus fumigatus; Cn: Cryptococcus neoformans; Fo: Fusarium oxysporum; Hc: Histoplasma capsulatum. Source for orthologues in Candida spp.: Candida genome database (CGD) [33]; Source for orthologues in other fungal pathogens: blast performed at EnsembFungi [32]; Saccharomyces genome database (SGD) [31]; and CGD.

a: In ScSir2 is a paralog of Hst1. All blast hits from other fungal pathogens showed higher identity to CaHst1 than to CaSir2.

+ KAT activators.

* majority of targets are cytoplasmic [34].

** Most of the inhibitors/activators for respective mammalian KATs.

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Fig 1. Histone modification by lysine acetylation through writers (KATs) and erasers (KDACs). Much of the mechanistic knowledge about the role of chromatin modifications in gene expression regulation comes from the nonpathogenic baker’s yeast (for excellent recent reviews, see [65–67]). Although the precise mechanisms of the interplay between writers, readers, and erasers remain ill-defined in many cases, it is fair to speculate that histone modifiers may play pivotal roles in the adaption of fungal pathogens to host immune defense. The major nucleosome building blocks, histones H2A, H2B, H3, and H4, are subject to dynamic and reversible posttranslational modifications (PTMs) by several KATs and KDACs functioning as writers and erasers of epigenetic marks. KATs like the Rtt109, which is a fungal-specific writer, and the cognate Hst3 eraser recognize the lysine residue K56 on histone H3. The KAT Esa1 acts primarily on H2A/H2B and H2AZ, with Hda1 and Hos3 acting as erasers (Panel A). By contrast, Hat1 targets mainly, though not exclusively, newly synthesized cytoplasmic histone H4 for the purpose of nuclear nucleosome remodeling during DNA damage repair [37], as well as other processes demanding nucleosome exchange. The pleiotropic KAT Gcn5 acts mainly on histone H4 and H3. Each N-terminal histone lysine can be recognized by several redundant KATs/KDACs. Histone H3 and H4 are modified by several writers and erasers in C. albicans, creating extensive combinatorial complexity and many possibilities for gene regulation depending on the
Chromatin Modifications in Adaptive Gene Regulation and Virulence

The protein components of a eukaryotic chromosome include a wide variety of DNA-binding proteins required for fundamental cellular functions such as DNA replication, recombination, and repair, as well as adaptive gene regulation. Many proteins undergo reversible posttranslational modifications (PTM), among others, including acetylation, methylation, phosphorylation, sumoylation, or ubiquitination [15]. For instance, lysine residues in the amino tails of histones are frequently modified by either acetyl or methyl groups. These PTMs of histone tails constitute the epigenetic “histone code” recognized by reader and writer proteins that regulate gene expression [16]. Of note, histone modifications can also have nonepigenetic functions. In fact, there is accumulating evidence that histone modifications not only form a code but also modulate biological processes in a context-dependent manner through dedicated chromatin signaling pathways in physiology and pathology [17]. Indeed, proteomic approaches show that acetylation at ε-groups of lysine residues is a ubiquitous PTM in prokaryotes [18], plants [19], fungi [20], Drosophila melanogaster [21], and human cells [22], affecting chromatin function perhaps due to neutralization of the lysine charge [23]. The addition and removal of acetyl groups to lysine residues is catalyzed by evolutionary conserved KATs and KDACs, respectively (Fig 1). Although lysine acetylation was first reported for histones [18, 21, 24], it is now known to occur on non-histone proteins, including transcriptional regulators, and proteins involved in metabolism or stress signaling. Interestingly, the genetic and chemical manipulation of KAT/KDAC activities in C. albicans disclosed a function in fungal virulence [12–14].

The C. albicans genome harbors eight putative KATs and twelve KDACs [27], which have been evolutionary conserved in fungal species, including most major fungal pathogens such as A. fumigatus or Cryptococcus neoformans (Table 1). However, the progress in understanding their function in species other than C. albicans has been slow, primarily due to lack of tools or significant mechanistic data on KDACs/KATs. However, a plausible scenario indicates that fungal KATs/KDACs act in close cooperation with dedicated transcriptional regulators, thereby forming a dual-layer network of chromatin-mediated transcriptional control [27–30]. Indeed, the importance of lysine acetylation in host–pathogen interactions or fungal morphogenesis is beginning to emerge. For instance, inhibition of the KDACs Hda1 and Rpd3 in C. albicans blocks Hsp90-dependent antifungal resistance [31]. Likewise, genetic ablation of the KDAC Set3, a component of the SET3C complex, triggers hyperfilamentation of C. albicans but also strongly attenuates virulence [28]. Moreover, C. albicans cells lacking the KAT Rtt109

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[25, 26] and the KDAC Hst3 [26] are highly sensitive to genotoxic agents and antifungal echinocandins [26]. Furthermore, Hst3 [32], Hda1, and Rpd3 [33] are also intimately involved in morphogenetic changes such as white-opaque switching, which is thought to impact host-niche occupancy as well as antifungal susceptibility of C. albicans [34, 35].

The evolutionarily conserved KAT Hat1, a prototypical KAT, facilitates DNA damage repair of double strand breaks in mammals [36] and in C. albicans [37]. Interestingly, KATs also play important roles in the morphogenetic yeast to hyphae transition [28, 29], biofilm formation, and drug resistance [38–40], as well as virulence [38]. Likewise, genetic ablation of Gcn5, a highly conserved pleiotropic fungal KAT, strongly debilitates virulence [41]. Importantly, Hat1 recognizes a specific set of lysine residues on histones tails, the equivalent residues of which are either absent or not modified by mammalian orthologues, suggesting that fungal Hat1 inhibitors are unlikely to affect the mammalian Hat1, making it especially suitable as a potential antifungal target.

Non-histone Lysine Acetylation in Host-Pathogen Interactions

Interestingly, lysine acetylation of non-histone target proteins is increasingly recognized as a means to regulate cellular processes. Fungal acetylome data are just emerging [20], and it will be exciting to identify virulence modifiers from these genome-wide datasets. Interestingly, acetylation appears abundant in mitochondria [42]. However, it is not clear whether acetylation of mitochondrial proteins takes place in the cytosol before their mitochondrial import or inside mitochondria? How the acetylation status influences mitochondrial function and nuclear cross-talk or even two-component signaling pathways that regulate fungal virulence [43] remains open. Notably, mitochondria and intrinsic signaling pathways play key roles in fungal pathogenesis [43, 44], but a link of acetylation, mitochondria, and virulence remains to be discovered.

Notably, chromatin-related gene regulation contributes to Candida spp. survival in the human host [45] or even inside innate phagocytes. For example, during invasion of dendritic cells by C. albicans, both host and fungal chromatin experience complex modifications that regulate the magnitude of the inflammatory immune response but also the susceptibility of pathogens to immune defense [46]. Interestingly, prominent bacterial pathogens also exploit histone modifications to promote their intracellular replication or to evade host immune defense [47]. For example, Shigella flexneri induces its own uptake by modifying the host actin cytoskeleton [48]. Borrelia burgdorferi [49] and Mycobacterium tuberculosis [50] employ similar strategies to aid their persistence in human host cells.

Using KATs/KDACs Modulators as Novel Antifungal Drugs

A limited arsenal of antifungals inhibit pathogen growth through fungistatic and/or fungicidal mechanisms [8, 51] by interfering with plasma membrane function (amphotericin B), cell wall glucan biogenesis (echinocandins), DNA synthesis (flucytosine), or ergosterol metabolism (azoles). Antifungal therapies are also limited because of toxicity, increasing drug resistance, as well as adverse drug–drug interactions. The former “gold standard” drug amphotericin B invariably causes severe toxicity in patients, limiting its use and effectiveness. Triazoles remain as preferred drugs because of their excellent toxicity profiles, moderate costs, and ease of oral administration [8]. However, the majority of triazoles are fungistatic rather than fungicidal, promoting the emergence of resistance [6]. Furthermore, some non-C. albicans species, most notably C. glabrata, display marked intrinsic resistance to triazoles and in some cases even cross-resistance to echinocandins [5]. Nonetheless, the fungicidal echinocandins have been outstanding drugs, but their use is also limited due to poor oral bioavailability, its ineffectiveness against C. neoformans or invasive aspergillosis [6], as well as high cost. Furthermore, recent reports
indicate dramatically increasing prevalence of echinocandin-resistant *Candida* isolates [5, 52]. This is a serious matter of concern, especially because these species are increasingly recovered among bloodstream clinical isolates [5]. Remarkably, the incidence of echinocandin-resistant *C. glabrata* at certain medical centers in the US increased from 2%–3% in 2001 to more than 13% in 2010 [52]. Furthermore, the identification of multidrug-resistant (azoles and echinocandins) *C. glabrata* isolates [5] has set off the alarm bells, because treatment options for patients infected with such strains have become limited. Thus, the efficient antifungal therapy is hampered by a deadly combination of limited antifungal drug entities, increasing occurrence of bloodstream fungal infections, and emerging resistance, underscoring the critical need for discovering new types of antifungal drugs.

Of note, modulators of KATs/KDACs have received considerable attention as novel therapeutics in noninfectious disease settings, because protein acetylation is affected in several types of cancer and neurodegenerative diseases [53–55]. Hence, several KDAC inhibitors are currently in development as anticancer drugs or even in clinical use [53–55]. For example, MGCD290, a fungal KDAC inhibitor, proved active in combination with fluconazole and echinocandins against drug-resistant *Candida*, as well as filamentous fungi [56–57]. The best-known KDAC inhibitor trichostatin A (TSA) increases the susceptibility of *Candida* spp. to azole antifungals [31, 40, 58]. This synergy may arise from inhibitory effect of TSA on ergosterol biosynthesis or from the SET3C KDAC complex, because TSA is a regulator of Set3, which controls protein kinase A (PKA) signaling through Efg1 [28]. Hence, as outlined in Fig 1 and Table 1, exciting new data keep emerging. However, more efforts are needed to delineate the molecular mechanisms of drugs controlling activity of fungal KATs/KDACs.

**Conclusions and Outlook**

Fungal infections are associated with astronomical annual Medicare costs, exceeding billions in Europe or the US, thus causing enormous economic burdens to already strained healthcare systems. Hence, current efforts in drug discovery are obviously lagging behind the need for improved antifungals. Unfortunately, the fundamental roles of KATs/KDACs in fungal pathophysiology, gene regulation, and/or adaptive genetic/epigenetic changes have not yet attracted enough attention in antifungal drug discovery. Moreover, among other roadblocks on the antifungal innovation highway, the academic setting has been struggling with insufficient funding from public and private bodies, thus further impairing the translation from basic science to application. For instance, grant support for fungal pathogen research falls several orders of magnitude below the levels of prominent bacterial or parasitic pathogens (http://www.gaffi.org/ and https://gfinder.policycures.org/PublicSearchTool/). Importantly, major pharma companies no longer entertain large-scale targeted antifungal discovery, partly because of high costs, limited number of validated targets, and high propensity of adverse toxicity owing to the eukaryotic nature of fungal pathogens. Importantly, the long-standing hesitation to exploit nonessential fungal genes as antifungal targets needs a careful reevaluation. Actually, a genetic argument predicts that essential genes may in fact even be poorer targets due to risks of drug resistance development, particularly in prophylactic settings or when overused. In fact, any gene affecting fungal fitness or adaptive changes in the host, irrespective of whether a fungal or a host gene could serve as a proper antifungal target [59]. Of note, all antifungal drugs target fungal growth in the host. However, there is increasing and compelling evidence that modulating the amplitude and magnitude of the host inflammatory immune response can be beneficial for the outcome of invasive fungal diseases [60–62]. Thus, chromatin-mediated adaptive changes during fungal pathogen host interplay opens new windows of opportunities and may hold great promises for future antifungal drug discovery.
Targeting fungal KATs/KDACs as a therapeutic strategy could also offer decisive advantages. First, fungal KATs/KDACs are structurally less well conserved, and some of the modifications are exclusively found in fungi, minimizing the risk of immune toxicity (Table 1, Fig 1). Second, the expansion of genome-scale genetic technologies, especially CRISPR/Cas9 approaches [63], makes it feasible to use dual-systems biology approaches to decipher the dynamic underlying host–pathogen relations [64] but also to better understand molecular mechanisms of KDAC/KAT functions under host immune surveillance. Of course, potential risks exist as well, because drug-mediated KDAC/KAT modulation may also lead to hyper-virulence phenotypes. For instance, blocking fungal KATs/KDACs can debilitate drug resistance but could otherwise lead to hypervirulence, owing to fitness gain in vivo due to inefficient recognition by immune surveillance [38]. Of note, virulence data on the role of other important chromatin or histone regulators mediating reversible phosphorylation and/or methylation of histones are unavailable for most fungal pathogens (Table 1). Thus, it is tempting to speculate that these genes will most likely expand the potential pool of suitable antifungal drug targets. Finally, another underexplored area is the role of non-chromatin, non-histone proteins modified by KDACs/KATs or other chromatin modifiers (Table 1). Interestingly, recent evidence indicates that non-histone targets of KATs may also play fundamental roles in fungal virulence and drug resistance [14], opening yet another new window of opportunity in antifungal drug discovery.

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References

1. Brown G.D., et al., Hidden killers: human fungal infections. Sci Transl Med, 2012. 4(165): p. 165rv13. doi: 10.1126/scitranslmed.3004404 PMID: 23253612
2. Pfaller M.A. and Diekema D.J., Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev, 2007. 20(1): p. 133–63. doi: 10.1128/CMR.00029-06 PMID: 17223626
3. Kett D.H., et al., Candida bloodstream infections in intensive care units: analysis of the extended prevalence of infection in intensive care unit study. Crit Care Med, 2011. 39(4): p. 665–70. doi: 10.1097/CCM.0b013e318206c1ca PMID: 21169817
4. Healey K.R., et al., Prevalent mutator genotype identified in fungal pathogen Candida glabrata promotes multi-drug resistance. Nat Commun, 2016. 7: p. 11128. doi: 10.1038/ncomms11128 PMID: 27020939
5. Pfaller M.A., et al., Frequency of decreased susceptibility and resistance to echinocandins among fluconazole-resistant bloodstream isolates of Candida glabrata. J Clin Microbiol, 2012. 50(4): p. 1199–203. doi: 10.1128/JCM.06112-11 PMID: 22278842
6. Perlin D.S., Echinocandin resistance, susceptibility testing and prophylaxis: implications for patient management. Drugs, 2014. 74(14): p. 1573–85. doi: 10.1007/s40265-014-0286-5 PMID: 25255923
7. Perrioth J., Choi B., and Spellberg B., Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Med Mycol, 2007. 45(4): p. 321–46. doi: 10.1080/13693780701218689 PMID: 17510856
8. Widerhold N.P. and Patterson T.F., What’s new in antifungals: an update on the in-vitro activity and in-vivo efficacy of new and investigational antifungal agents. Curr Opin Infect Dis, 2015. 28(6): p. 539–45. doi: 10.1097/QCO.0000000000000203 PMID: 26374950
9. Datta K. and Hamad M., Immunotherapy of Fungal Infections. Immunol Invest, 2015. 44(8): p. 738–76. doi: 10.3109/08941939.2015.1093913 PMID: 26575463
10. Levitz S.M., et al., Exploiting fungal cell wall components in vaccines. Semin Immunopathol, 2015. 37(2): p. 199–207. doi: 10.1007/s00281-014-0460-6 PMID: 25404118
11. Nanjappa S.G. and Klein B.S., Vaccine immunity against fungal infections. Curr Opin Immunol, 2014. 28: p. 27–33. doi: 10.1016/j.coi.2014.01.014 PMID: 24583636
12. Rai M.N., et al., Functional genomic analysis of Candida glabrata-macrophage interaction: role of chromatin remodeling in virulence. PLoS Pathog., 2012. 8(8): p. e1002863. doi: 10.1371/journal.ppat.1002863 PMID: 22916016

13. Hnisz D., Tscherner M., and Kuchler K., Targeting chromatin in fungal pathogens as a novel therapeutic strategy: histone modification gets infectious. Epigenomics, 2011. 3(2): p. 129–32. doi: 10.2217/epi.11.7 PMID: 22122275

14. Lamoth F., Juwadi P.R., and Steinbach W.J., Histone deacetylation inhibition as an alternative strategy against invasive aspergillosis. Front Microbiol, 2015. 6: p. 96. doi: 10.3389/fmicb.2015.00096 PMID: 25762988

15. Kouzarides T., Chromatin modifications and their function. Cell, 2007. 128(4): p. 693–705. doi: 10.1016/j.cell.2007.02.005 PMID: 17320507

16. Jennewein T. and Allis C.D., Translating the histone code. Science, 2001. 293(5532): p. 1074–80. doi: 10.1126/science.1063127 PMID: 11498575

17. Elia E. and Shiota A., The chromatin signaling pathway: diverse mechanisms of recruitment of histone-modifying enzymes and varied biological outcomes. Mol Cell, 2010. 40(5): p. 689–701. doi: 10.1016/j.molcel.2010.11.031 PMID: 21145479

18. Wang Q., et al., Acetylation of metabolic enzymes coordinates carbon source utilization and metabolic flux. Science, 2010. 327(5968): p. 1004–7. doi: 10.1126/science.1179687 PMID: 20167787

19. Wu X., et al., Lysine acetylation is a widespread protein modification for diverse proteins in Arabidopsis. Plant Physiol, 2011. 155(4): p. 1769–78. doi: 10.1104/pp.110.165852 PMID: 21311030

20. Zhou X., et al., Systematic Analysis of the Lysine Acetylation in Candida albicans. J Proteome Res, 2016.

21. Weinert B.T., et al., Proteome-wide mapping of the Drosophila acetylome demonstrates a high degree of conservation of lysine acetylation. Sci Signal, 2011. 4(183): p. ra48. doi: 10.1126/scisignal.2001902 PMID: 21791702

22. Zhao S., et al., Regulation of cellular metabolism by protein lysine acetylation. Science, 2010. 327(5968): p. 1000–4. doi: 10.1126/science.1179689 PMID: 20167786

23. Yang X.J. and Seto E., Lysine acetylation: codified crosstalk with other posttranslational modifications. Mol Cell, 2008. 31(4): p. 449–61. doi: 10.1016/j.molcel.2008.07.002 PMID: 18722172

24. Kouzarides T., Acetylation: a regulatory modification to rival phosphorylation? EMBO J, 2000. 19(6): p. 1176–9. doi: 10.1093/emboj/19.6.1176 PMID: 10716917

25. Lopes da Rosa J., et al., Histone acetyltransferase Rtt109 is required for Candida albicans pathogenesis. Proc Natl Acad Sci U S A, 2010. 107(4): p. 1594–9. doi: 10.1073/pnas.0912427107 PMID: 20080464

26. Wurtele H., et al., Modulation of histone H3 lysine 56 acetylation as an antifungal therapeutic strategy. Nat Med, 2010. 16(7): p. 774–80. doi: 10.1038/nm.2175 PMID: 20601951

27. Hnisz D., Schwarzmuller T., and Kuchler K., Transcriptional loops meet chromatin: a dual-layer network controls white-opaque switching in Candida albicans. Mol Microbiol, 2009. 74(1): p. 1–15. doi: 10.1111/j.1365-2958.2009.06772.x PMID: 19555456

28. Hnisz D., et al., The Set3/Hos2 histone deacetylase complex attenuates cAMP/PKA signaling to regulate morphogenesis and virulence of Candida albicans. PLoS Pathog, 2010. 6(5): p. e1000889. doi: 10.1371/journal.ppat.1000889 PMID: 20485517

29. Hnisz D., et al., A histone deacetylase adjusts transcription kinetics at coding sequences during Candida albicans morphogenesis. PLoS Genet, 2012. 8(12): p. e1003118. doi: 10.1371/journal.pgen.1003118 PMID: 23236295

30. Lu Y., Su C., and Liu H., A GATA transcription factor recruits Hda1 in response to reduced Tor1 signaling to establish a hyphal chromatin state in Candida albicans. PLoS Pathog, 2012. 8(4): p. e1002663. doi: 10.1371/journal.ppat.1002663 PMID: 22536157

31. Robbins N., Leach M.D., and Cowen L.E., Lysine deacetylases Hda1 and Rpd3 regulate Hsp90 function thereby governing fungal drug resistance. Cell Rep, 2012. 2(4): p. 878–88. doi: 10.1016/j.celrep.2012.08.035 PMID: 23041319

32. Stevenson J.S. and Liu H., Regulation of white and opaque cell-type formation in Candida albicans by Rtt109 and Hst3. Mol Microbiol, 2011. 81(4): p. 1078–91. doi: 10.1111/j.1365-2958.2011.07754.x PMID: 21749487

33. Srikantha T., et al., The histone deacetylase genes HDA1 and RPD3 play distinct roles in regulation of high-frequency phenotypic switching in Candida albicans. J Bacteriol, 2001. 183(15): p. 4614–25. doi: 10.1128/JB.183.15.4614-4625.2001 PMID: 11443097
34. Lohse M.B. and Johnson A.D., White-opaque switching in Candida albicans. Curr Opin Microbiol, 2009. 12(6): p. 650–4. doi: 10.1016/j.mib.2009.09.010 PMID: 19853498

35. Morschhauser J., Regulation of white-opaque switching in Candida albicans. Med Microbiol Immunol, 2010. 199(3): p. 165–72. doi: 10.1007/s00430-010-0147-0 PMID: 20390300

36. Yang X., et al., Histone acetyltransferase 1 promotes homologous recombination in DNA repair by facilitating histone turnover. J Biol Chem, 2013. 288(25): p. 18271–82. doi: 10.1074/jbc.M113.473199 PMID: 23653357

37. Tscherner M., et al., The histone acetyltransferase Hat1 facilitates DNA damage repair and morphogenesis in Candida albicans. Mol Microbiol, 2012. 86(5): p. 1197–214. doi: 10.1111/mmi.12051 PMID: 23075292

38. Tscherner M., et al., The Candida albicans Histone Acetyltransferase Hat1 Regulates Stress Resistance and Virulence via Distinct Chromatin Assembly Pathways. PLoS Pathog, 2015. 11(10): p. e1005218. doi: 10.1371/journal.ppat.1005218 PMID: 26473952

39. Nobile C.J., et al., A histone deacetylase complex mediates biofilm dispersal and drug resistance in Candida albicans. MBio, 2014. 5(3): p. e01201–14. doi: 10.1128/mBio.01201-14 PMID: 24917598

40. Kim S.C., et al., Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. Mol Cell, 2006. 23(4): p. 607–18. doi: 10.1016/j.molcel.2006.06.026 PMID: 16916647

41. Chang P., Fan X., and Chen J., Function and subcellular localization of Gcn5, a histone acetyltransferase in Candida albicans. Fungal Genet Biol, 2015. 81: p. 132–41. doi: 10.1016/j.fgb.2015.01.011 PMID: 25656079

42. Adam T., et al., Cytoskeletal rearrangements and the functional role of T-plastin during entry of Shigella flexneri into HeLa cells. J Cell Biol, 1995. 129(2): p. 367–81. PMID: 7721941

43. Seider K., et al., The facultative intracellular pathogen Candida glabrata subverts macrophage cyto- kine production and phagolysosome maturation. J Immunol, 2011. 187(6): p. 3072–86. doi: 10.4049/jimmunol.1003730 PMID: 21926328

44. Rupp J., et al., Chlamydia pneumoniae hides inside apoptotic neutrophils to silently infect and propagate in macrophages. PLoS One, 2009. 4(6): p. e6020. doi: 10.1371/journal.pone.0006020 PMID: 19547701

45. Cowen L.E., et al., Mechanisms of Antifungal Drug Resistance. Cold Spring Harb Perspect Med, 2015. 5(7): p. a019752.

46. Alexander B.D., et al., Increasing echinocandin resistance in Candida glabrata: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis, 2013. 56(12): p. 1724–32. doi: 10.1093/cid/cit136 PMID: 23487382

47. Bolden J.E., Parmigiani R.B., and Marks P.A., Histone deacetylase inhibitors: molecular mechanisms of action. Oncogene, 2007. 26(37): p. 5541–52. doi: 10.1038/sj. onc.1210620 PMID: 17694093

48. Pfaller M.A., et al., Activity of MGCD290, a Hos2 histone deacetylase inhibitor, in combination with azole antifungals against opportunistic fungal pathogens. J Clin Microbiol, 2009. 47(12): p. 3797–804. doi: 10.1128/JCM.00618-09 PMID: 19794038
57. Pfaffer M.A., et al., In vitro activity of a Hos2 deacetylase inhibitor, MGCD290, in combination with echinocandins against echinocandin-resistant Candida species. Diagn Microbiol Infect Dis, 2015. 81(4):259–263. doi: 10.1016/j.diagmicrobio.2014.11.008 PMID: 25600842

58. Lamoth F., et al., Identification of a key lysine residue in heat shock protein 90 required for azole and echinocandin resistance in Aspergillus fumigatus. Antimicrob Agents Chemother, 2014. 58(4): p. 1889–96. doi: 10.1128/AAC.02286-13 PMID: 24395240

59. Li X., et al., Potential Targets for Antifungal Drug Discovery Based on Growth and Virulence in Candida albicans. Antimicrob Agents Chemother, 2015. 59(10): p. 5885–91. doi: 10.1128/AAC.00726-15 PMID: 26195510

60. Majer O., et al., Type I interferons promote fatal immunopathology by regulating inflammatory monocytes and neutrophils during Candida infections. PLoS Pathog, 2012. 8(7): p. e1002811. doi: 10.1371/journal.ppat.1002811 PMID: 22911155

61. Zwolanek F., et al., The non-receptor tyrosine kinase Tec controls assembly and activity of the noncanonical caspase-8 inflammasome. PLoS Pathog, 2014. 10(12): p. e1004525. doi: 10.1371/journal.ppat.1004525 PMID: 25474208

62. Wirnsberger G., et al., Inhibition of CBLB protects from lethal Candida albicans sepsis. Nat Med, 2016.

63. Min K., et al., Candida albicans Gene Deletion with aTransient CRISPR-Cas9 System. mSphere, 2016. 1(3).

64. Tierney L., et al., Systems biology of host-fungus interactions: turning complexity into simplicity. Curr Opin Microbiol, 2012. 15(4): p. 440–6. doi: 10.1016/j.mib.2012.05.001 PMID: 22717554

65. Harr J.C., Gonzalez-Sandoval A., and Gasser S.M., Histones and histone modifications in perinuclear chromatin anchoring: from yeast to man. EMBO Rep, 2016. 17(2): p. 139–55. doi: 10.15252/embr.201541809 PMID: 26792937

66. Waters R., van Eijk P., and Reed S., Histone modification and chromatin remodeling during NER. DNA Repair (Amst), 2015. 36: p. 105–13.

67. Dahlin J.L., et al., Histone-modifying enzymes, histone modifications and histone chaperones in nucleosome assembly: Lessons learned from Rtt109 histone acetyltransferases. Crit Rev Biochem Mol Biol, 2015. 50(1): p. 31–53. doi: 10.3109/10409238.2014.978975 PMID: 25365782

68. Xiong B., Lu S., and Gerton J.L., Hos1 is a lysine deacetylase for the Smc3 subunit of cohesin. Curr Biol, 2010. 20(18): p. 1660–5. doi: 10.1016/j.cub.2010.08.019 PMID: 20797861

69. Robyr D., et al., Microarray deacetylation maps determine genome-wide functions for yeast histone deacetylases. Cell, 2002. 109(4): p. 437–46. PMID: 12086601

70. Yang X.J. and Seto E., The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. Nat Rev Mol Cell Biol, 2002. 2(4): p. 289–99. doi: 10.1038/nrm7218 PMID: 11640970

71. Rundlett S.E., et al., HDA1 and RPD3 are members of distinct yeast histone deacetylase complexes that regulate silencing and transcription. Proc Natl Acad Sci U S A, 1996. 93(25): p. 12965–6. doi: 10.1073/pnas.93.25.12965 PMID: 8825324
81. Bernstein B.E., Tong J.K., and Schreiber S.L., Genomewide studies of histone deacetylase function in yeast. Proc Natl Acad Sci U S A, 2000. 97(25): p. 13708–13. doi: 10.1073/pnas.250477697 PMID: 11095743

82. Brosch G., Loidl P., and Graesssl S., Histone modifications and chromatin dynamics: a focus on filamentous fungi. FEMS Microbiol Rev, 2008. 32(3): p. 409–39. doi: 10.1111/j.1574-6976.2007.00100.x PMID: 18221488

83. Mai A., et al., Discovery of uracil-based histone deacetylase inhibitors able to reduce acquired antifungal resistance and trailing growth in Candida albicans. Bioorg Med Chem Lett, 2007. 17(5): p. 1221–5. doi: 10.1016/j.bmcl.2006.12.028 PMID: 17196388

84. Robert T., et al., HDACs link the DNA damage response, processing of double-strand breaks and autophagy. Nature, 2011. 471(7336): p. 74–9. doi: 10.1038/nature09803 PMID: 21368826

85. Kurdistani S.K. and Grunstein M., Histone acetylation and deacetylation in yeast. Nat Rev Mol Cell Biol, 2003. 4(4): p. 276–84. doi: 10.1038/nrm1075 PMID: 12671650

86. Wu J., et al., TUP1 utilizes histone H3/H2B-specific HDA1 deacetylase to repress gene activity in yeast. Mol Cell, 2001. 7(1): p. 117–26. PMID: 11172717

87. Klar A.J., Srikantha T., and Soll D.R., A histone deacetylation inhibitor and mutant promote colony-type switching of the human pathogen Candida albicans. Genetics, 2001. 158(2): p. 919–24. PMID: 11404352

88. Vogelauer M., et al., Global histone acetylation and deacetylation in yeast. Nature, 2000. 408(6811): p. 495–8. doi: 10.1038/35044127 PMID: 11100734

89. Robert F., et al., Global position and recruitment of HATs and HDACs in the yeast genome. Mol Cell, 2004. 16(2): p. 199–209. doi: 10.1016/j.molcel.2004.09.021 PMID: 15494307

90. Ekwall K., Genome-wide analysis of HDAC function. Trends Genet, 2005. 21(11): p. 608–15. doi: 10.1016/j.tig.2005.08.009 PMID: 16153738

91. Weber J.M., Irlbacher H., and Ehrenhofer-Murray A.E., Control of replication initiation by the Sum1/Rfm1/Hst1 histone deacetylase. BMC Mol Biol, 2008. 9: p. 100. doi: 10.1186/1471-2199-9-100 PMID: 18990212

92. Jing H. and Lin H., Sirtuins in epigenetic regulation. Chem Rev, 2015. 115(6): p. 2350–75. doi: 10.1021/cr500457h PMID: 25804908

93. Madsen C.T., et al., Biotin starvation causes mitochondrial protein hyperacetylation and partial rescue by the SIRT3-like deacetylase Hst4p. Nat Commun, 2015. 6: p. 7726. doi: 10.1038/ncomms8726 PMID: 26158509

94. Saavedra A., The conserved role of sirtuins in chromatin regulation. Int J Dev Biol, 2009. 53(2–3): p. 303–22. doi: 10.1387/ijdb.082675sav PMID: 19378253

95. Michan S. and Sinclair D., Sirtuins in mammals: insights into their biological function. Biochem J, 2007. 404(1): p. 1–13. doi: 10.1042/BJ20070140 PMID: 17447894

96. Gaglio D., D’Alfonso A., and Camilloni G., Functional complementation of sir2Delta yeast mutation by the human orthologous gene SIRT1. Proc Natl Acad Sci U S A, 2000. 97(25): p. 13708–13. doi: 10.1073/pnas.250477697 PMID: 11095743
104. Bedalov A., et al., Identification of a small molecule inhibitor of Sir2p. Proc Natl Acad Sci U S A, 2001. 98(26): p. 15113–8. doi: 10.1073/pnas.261574398 PMID: 11752457

105. Raman S.B., et al., Candida albicans SET1 encodes a histone 3 lysine 4 methyltransferase that contributes to the pathogenesis of invasive candidiasis. Mol Microbiol, 2006. 60(3): p. 697–709. doi: 10.1111/j.1365-2958.2006.05121.x PMID: 16629671

106. Boa S., Coert C., and Patterson H.G., Saccharomyces cerevisiae Set1p is a methyltransferase specific for lysine 4 of histone H3 and is required for efficient gene expression. Yeast, 2003. 20(9): p. 827–35. doi: 10.1002/yea.995 PMID: 12845608

107. Greer E.L. and Shi Y., Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet, 2012. 13(5): p. 343–57. doi: 10.1038/nrg3173 PMID: 22473383

108. Pokholok D.K., et al., Genome-wide map of nucleosome acetylation and methylation in yeast. Cell, 2005. 122(4): p. 517–27. doi: 10.1016/j.cell.2005.06.026 PMID: 16122420

109. Ahn S.H., et al., Sterile 20 kinase phosphorylates histone H2B at serine 10 during hydrogen peroxide-induced apoptosis in S. cerevisiae. Cell, 2005. 120(1): p. 25–36. doi: 10.1016/j.cell.2004.11.016 PMID: 15652479

110. Cheung W.L., et al., Apoptotic phosphorylation of histone H2B is mediated by mammalian sterile twenty kinase. Cell, 2003. 113(4): p. 507–17. PMID: 12757711

111. Leberer E., et al., Signal transduction through homologues of the Ste20p and Ste7p protein kinases can trigger hyphal formation in the pathogenic fungus Candida albicans. Proc Natl Acad Sci U S A, 1996. 93(23): p. 13217–22. PMID: 8917571

112. Xiong W., et al., Structure-Based Screen Identification of a Mammalian Ste20-like Kinase 4 (MST4) Inhibitor with Therapeutic Potential for Pituitary Tumors. Mol Cancer Ther, 2016. 15(3): p. 412–20. doi: 10.1158/1535-7163.MCT-15-0703 PMID: 26721946

113. Rossetto D., Avvakumov N., and Cote J., Histone phosphorylation: a chromatin modification involved in diverse nuclear events. Epigenetics, 2012. 7(10): p. 1098–108. doi: 10.4161/epi.21975 PMID: 22948226

114. Rando O.J. and Winston F., Chromatin and transcription in yeast. Genetics, 2012. 190(2): p. 351–87. doi: 10.1534/genet.111.132266 PMID: 22345607

115. Ward I.M. and Chen J., Histone H2AX is phosphorylated in an ATR-dependent manner in response to replicational stress. J Biol Chem, 2001. 276(51): p. 47759–62. doi: 10.1074/jbc.C100569200 PMID: 11673449

116. Noble S.M., et al., Systematic screens of a Candida albicans homozygous deletion library decouple morphogenetic switching and pathogenicity. Nat Genet, 2010. 42(7): p. 590–8. doi: 10.1038/ng.605 PMID: 20543849

117. Cieniewicz A.M., et al., The bromodomain of Gcn5 regulates site specificity of lysine acetylation on histone H3. Mol Cell Proteomics, 2014. 13(11): p. 2896–2910. doi: 10.1074/mcp.M114.038174 PMID: 25106422

118. Agalioti T., Chen G., and Thanos D., Deciphering the Transcriptional Histone Acetylation Code for a Human Gene. Cell, 2002. 111(3): p. 361–392. PMID: 12419248

119. Grant P.A., et al., Yeast Gcn5 functions in two multisubunit complexes to acetylate nucleosomal histones: characterization of an Ada complex and the SAGA (Spt/Ada) complex. Genes Dev, 1997. 11(13): p. 1640–50 PMID: 9224714

120. Balasubramanyam K., Altal M., and Varier R.A., Polyisoprenylated benzophenone, garcinol, a natural histone acetyltransferase inhibitor, represses chromatin transcription and alters global gene expression. J Biol Chem, 2004. 279(32):33716–26 doi: 10.1074/jbc.M402839200 PMID: 15157575

121. O’Meara T.R., et al., Cryptococcus neoformans Histone Acetyltransferase Gcn5 Regulates Fungal Adaptation to the Host. Eukaryot Cell, 2010. 9(8): p. 11931202.

122. Dekker F.J., and Haisma H.J., Histone acetyl transfersases as emerging drug targets. Drug Discov Today, 2009. 14(19–20): p. 942–948. doi: 10.1016/j.drudis.2009.06.006 PMID: 19577000

123. Ruotolo R., et al., Chemogenomic profiling of the cellular effects associated with histone H3 acetylation impairment by a quinoline-derived compound. Genomics, 2010. 96(5): p. 272–280. doi: 10.1016/j.ygeno.2010.08.005 PMID: 20732410
126. Chimenti F., et al., A novel histone acetyltransferase inhibitor modulating Gcn5 network: cyclopenetyl-dene-[4-(4'-chlorophenyl)thiazol-2-yl]hydrazone. J Med Chem, 2009. 52(2): p. 530–536. doi: 10.1021/jm800885d PMID: 19099397

127. Jeon J., Kwon S., and Lee Y.H., Histone acetylation in fungal pathogens of plants. Plant Pathol J, 2014. 30(1): p. 1–9 doi: 10.5423/PPJ.RW.01.2014.0003 PMID: 25288980

128. Kleff S., et al., Identification of a gene encoding a yeast histone H4 acetyltransferase. J Biol Chem, 1995. 270(42): p. 24674–24677. PMID: 7559580

129. Sobel R.E., et al., Conservation of deposition-related acetylation sites in newly synthesized histones H3 and H4. Proc Natl Acad Sci U S A, 1995. 92(4): p. 1237–1241. PMID: 7862667

130. Shah P., et al., The Aspergillus Genome Database (AspGD): recent developments in comprehensive multispecies curation, comparative genomics and community resources. Nucleic Acids Res, 2012. 40: p. D653–9 doi: 10.1093/nar/gkr875 PMID: 22080559

131. Tafrova J.I. and Tafrov S.T., Human histone acetyltransferase 1 (Hat1) acetylates lysine 5 of histone H2A in vivo. Mol Cell Biochem, 2014. 392(1–2): p. 259–272. doi: 10.1007/s11010-014-2036-0 PMID: 24682716

132. Makowski A.M., Dutnall R.N., and Annunziato A.T., Effects of acetylation of histone H4 at lysines 8 and 16 on activity of the Hat1 histone acetyltransferase. J Biol Chem, 2001. 276(47): p. 43499–43502. doi: 10.1074/jbc.C100549200 PMID: 11585814

133. Winkler S.G., et al., Elongator is a histone H3 and H4 acetyltransferase important for normal histone acetylation levels in vivo. Proc Natl Acad Sci U S A, 2002. 99(6): p. 3517–3522. doi: 10.1073/pnas.022042899 PMID: 11904415

134. Li F., et al., The Elp3 subunit of human Elongator complex is functionally similar to its counterpart in yeast. Mol Genet Genomics, 2005. 273(3): p. 264–272. doi: 10.1007/s00438-005-1120-2 PMID: 15902492

135. Sampath V., et al., Biochemical characterization of Hpa2 and Hpa3, two small closely related acetyltransferases from Saccharomyces cerevisiae. J Biol Chem, 2013. 288(30): p. 21506–21513. doi: 10.1074/jbc.M113.486274 PMID: 23775086

136. Angus-Hill M.L., et al., Crystal structure of the histone acetyltransferase Hpa2: A tetrameric member of the Gcn5-related N-acetyltransferase superfamilly. J Mol Biol, 1999. 294(5): p. 1311–1325. doi: 10.1006/jmbi.1999.3338 PMID: 10600387

137. Lorch Y., et al., Mediator-nucleosome interaction. Molecular cell, 2000. 6(1): p. 197–201. PMID: 10949041

138. Zhu X., et al., Mediator influences telomeric silencing and cellular life span. Mol Cell Biol, 2011. 31(12): p. 2413–2421. doi: 10.1128/MCB.05242-11 PMID: 21482672

139. Wang X., et al., Distinct and redundant roles of the two MYST histone acetyltransferases Esa1 and Sas2 in cell growth and morphogenesis of Candida albicans. Eukaryot Cell, 2013. 12(3): p. 438–449. doi: 10.1128/EC.00275-12 PMID: 23355007

140. Allard S., et al., NuA4, an essential transcription adaptor/histone H4 acetyltransferase complex containing Esa1p and the ATM-related cofactor Tra1p. EMBO J, 1999. 18(18): p. 5108–5119. doi: 10.1093/emboj/18.18.5108 PMID: 10487762

141. Coffee K., et al., Characterisation of a Tip60 specific inhibitor, NU9056, in prostate cancer. PloS One, 2012. 7(10).

142. Kimura A., Umehara T., and Horikoshi M., Chromosomal gradient of histone acetylation established by Sas2p and Sir2p functions as a shield against gene silencing. Nat Genet, 2002. 32(3): p. 370–377. doi: 10.1038/ng993 PMID: 12410229

143. Suka N., Luo K., and Grunstein M., Sir2p and Sas2p opposin gly regulate acetylation of yeast histone H4 lysine16 and spreading of heterochromatin. Nat Genet, 2002. 32(3): p. 378–383. doi: 10.1038/ng1017 PMID: 12379856

144. Su J., et al., The Functional Analysis of Histone Acetyltransferase MOF in Tumorigenesis. Int J Mol Sci, 2016. 17(1): p. 99.

145. Rosaleny L.E., et al., The Sas3p and Gcn5p histone acetyltransferases are recruited to similar genes. Genome Biol, 2007. 8(6): p. 119.

146. Howe L., et al., Histone H3 specific acetyltransferases are essential for cell cycle progression. Genes Dev, 2001. 15:3144 doi: 10.1101/gad.931401 PMID: 11731478

147. Song O.-K.K., et al., An Nalpha-acetyltransferase responsible for acetylation of the N-terminal residues of histones H4 and H2A. J Biol Chem, 2003. 278(40): p. 38109–38112. doi: 10.1074/jbc.C300355200 PMID: 12915400
148. Hole K., et al., The human N-alpha-acetyltransferase 40 (hNaa40p/hNatD) is conserved from yeast and N-terminally acetylates histones H2A and H4. PloS One, 2011. 6(9): p. e24713. doi: 10.1371/journal.pone.0024713

149. Mizzen C.A., et al., The TAF(II)250 subunit of TFIIID has histone acetyltransferase activity. Cell, 1996. 87(7): p. 1261–1270. PMID: 8980232

150. Kimura A., Matsubara K., and Horikoshi M., A decade of histone acetylation: marking eukaryotic chromosomes with specific codes. J Biochem, 2005. 138(6): p. 647–662. doi: 10.1093/jb/mvi184

151. Driscoll R., Hudson A., and Jackson S.P., Yeast Rtt109 promotes genome stability by acetylating histone H3 on lysine 56. Science, 2007. 315(5812): p. 649–652. doi: 10.1126/science.1135862

152. Han J., et al., Rtt109 acetylates histone H3 lysine 56 and functions in DNA replication. Science, 2007. 315(5812): p. 653–655. doi: 10.1126/science.1133234

153. Schneider J., et al., Rtt109 Is Required for Proper H3K56 Acetylation A chromatin mark associated with the elongating RNA polymerase II. J Biol Chem, 2006. 281(49): p. 37270–4. doi: 10.1074/jbc.C600265200

154. Das C., et al., CBP/p300-mediated acetylation of histone H3 on lysine 56. Nature, 2009. 459(7243): p. 113–117. doi: 10.1038/nature07861

155. Balasubramanyam K., et al., Small molecule modulators of histone acetyltransferase p300. J Biol Chem, 2003. 278(21): p. 19134–19140. doi: 10.1074/jbc.M301580200

156. Carradori S., et al., Evaluation of a large library of (thiazol-2-yl)hydrazones and analogues as histone acetyltransferase inhibitors: enzyme and cellular studies. Eur J Med Chem, 2014. 80: p. 569–578. doi: 10.1016/j.ejmech.2014.04.042

157. Chatterjee S., et al., A novel activator of CBP/p300 acetyltransferases promotes neurogenesis and extends memory duration in adult mice. J Neurosci, 2013. 33(26): p. 10698–10712. doi: 10.1523/JNEUROSCI.5772-12.2013

158. Bowers E.M., et al., Virtual Ligand Screening of the p300/CBP Histone Acetyltransferase: Identification of a Selective Small Molecule Inhibitor. Chem Biol, 2010. 17(5): p. 471–482. doi: 10.1016/j.chembiol.2010.03.006

159. Schram A.W., et al., A dual role for SAGA-associated factor 29 (SGF29) in ER stress survival by coordination of both histone H3 acetylation and histone H3 lysine-4 trimethylation. PloS One, 2013. 8(7): p. e70035. doi: 10.1371/journal.pone.0070035

160. Xu F., Zhang K., and Grunstein M., Acetylation in histone H3 globular domain regulates gene expression in yeast. Cell, 2005. 121(3): p. 375–385. doi: 10.1016/j.cell.2005.03.011

161. Lee J-EE, Oh J-HH, Ku M, Kim J, Lee J-SS, et al. Ssn6 has dual roles in Candida albicans filament development through the interaction with Rpd31. FEBS Lett, 2015. 589: 513–20. doi: 10.1016/j.febslet.2015.01.011

162. Davie J.R., Inhibition of histone deacetylase activity by butyrate. J Nutr, 2003. 133: 2485S–2493S. PMID: 12840228

163. Scholz C., Acetylation site specificities of lysine deacetylase inhibitors in human cells. Nat Biotech, 2015. 33: 415–423.

164. Grozinger C.M., Identification of a class of small molecule inhibitors of the sirtuin family of NAD-dependent deacetylases by phenotypic screening. J Biol Chem, 2001. 276: 38837–38843. doi: 10.1074/jbc.M106779200

165. Dekker F.J., van den Bosch T. and Martin N.I., Small molecule inhibitors of histone acetyltransferases and deacetylases are potential drugs for inflammatory diseases. Drug Discov Today, 2014. 19: 654–660. doi: 10.1016/j.drudis.2013.11.012