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Small molecule inhibitors of histone acetyltransferases and deacetylases are potential drugs for inflammatory diseases

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Abstract

Lysine acetylation is a reversible post-translational modification (PTM) of cellular proteins and represents an important regulatory switch in signal transduction. Lysine acetylation, in combination with other PTMs, directs the outcomes as well as the activation levels of important signal transduction pathways such as the nuclear factor (NF)-κB pathway. Small molecule modulators of the 'writers' (HATs) and 'erasers' (HDACs) can regulate the NF-κB pathway in a specific manner. This review focuses on the effects of frequently used HAT and HDAC inhibitors on the NF-κB signal transduction pathway and inflammatory responses, and their potential as novel therapeutics.

Introduction

Lysine acetylation is a reversible post-translational modification (PTM) of cellular proteins and represents an important regulatory switch in signal transduction cascades [1,2]. An increasing number of studies highlight the importance of lysine acetylation as a key PTM, directing the outcomes as well as the activation levels of important signal transduction pathways such as the nuclear factor (NF)-κB pathway. For example, acetylation of NF-κB transcription factors p65 and p50 plays an important part in their nuclear localization and transcriptional activity [3]. Similar phenomena have been observed for other pathways [4]. Next to this, acetylation of histones connected to specific genes has an important role in gene-specific transcription in the NF-κB pathway [3]. Furthermore, an increasing number of reports describe significant levels of crosstalk between lysine acetylation and other PTMs, such as ubiquitinylation, methylation and phosphorylation, in the NF-κB pathway. For example, competition between acetylation and ubiquitinylation on the same lysine residues is observed for transcription factor p65 [5]. This highlights the fact that acetylation is not a

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sole determining factor but, rather, is a regulator working in concert with other PTMs at multiple levels in signaling cascades.

Lysine acetylations are generally regulated by ‘writers’ and ‘erasers’, which are denoted as histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively, owing to their original discovery as histone-modifying enzymes. An important future challenge is to identify and quantify distinct HAT and HDAC activities in distinct signaling pathways such as the NF-κB pathway, as well as their aberrations in disease (models). Considering the importance of lysine acetylation in the NF-κB pathway (Fig. 1), small molecule modulators of HATs and HDACs have great potential to regulate this signaling cascade specifically, which is an important aim in drug discovery.

Focusing on the NF-κB pathway, here we summarize the effects of lysine acetylation of the p65 transcription factor as well as histones. In addition, we highlight the role of crosstalk between lysine acetylation and other PTMs such as methylation and phosphorylation. Furthermore, we discuss the effects of frequently used small molecule HAT and HDAC inhibitors on the NF-κB signal transduction pathway and inflammatory responses *in vitro* and *in vivo*.

Lysine acetylation as a regulator of the NF-κB pathway

In 2001, it was discovered that acetylation of p65 inhibits binding to the inhibitory complex IκBα, and thus stimulates gene transcription; whereas deacetylation promotes IκBα binding and nuclear export [6]. This study triggered intense interest in lysine acetylations of the seven lysine residues (122, 123, 218, 221, 310, 314, 315) of p65 that are subject to this PTM. These acetylations have specific roles in activation of the NF-κB pathway and have been previously reviewed [7,8]. Importantly: acetylation of lysines 122 and 123 decreases DNA binding [9]; acetylation at lysines 218 and 221 increases binding to κB enhancers; and acetylation at lysine 310 is essential for full transcriptional activity [10]. In addition, acetylations of specific lysine residues in histone H3 and H4 play an important part in NF-κB-mediated gene transcription as reviewed [3].

Lysine acetylation does not act alone: crosstalk between lysine acetylation and other PTMs

The acetylation of lysine residues in the NF-κB transcription factor and in histones (and numerous other cellular targets) can be dramatically affected by the PTM state of other constituent amino acids. These so-called ‘crosstalk’ mechanisms act, presumably, *via* increasing or decreasing the affinity of the substrate protein for the respective HAT or HDAC complexes involved in their acetylation. A recent review nicely illustrates the importance of crosstalk between PTMs on the NF-κB transcription factor [8]. In addition, previous reviews illustrate the importance of crosstalk between lysine acetylation and other PTMs in the histones [11–14]. Here, we highlight some specific examples that demonstrate the crucial involvement of crosstalk in NF-κB activation as well as in histones implicated in inflammation. The examples described below are limited to known cases of crosstalk within the same protein (*cis* crosstalk). In addition, a growing number of examples make it clear

that similar mechanisms also operate in modulating protein–protein interactions including those between the peptides tails of different histones (*trans* crosstalk).

A specific example of crosstalk in the NF-κB pathway involves the phosphorylations of p65 at serines 276 and 536, which serves to enhance the p300-mediated acetylation of lysine 310. This, in turn, leads to an overall transcriptional activation of the NF-κB pathway (Fig. 2a) [15]. In addition, it has been found that phosphorylation of serine 276 is required for binding of p65 to the coactivator CREB-binding protein (CBP), which promotes proinflammatory gene transcription.

Phosphorylation also has a major role in the crosstalk observed within histone proteins. One of the earliest reported and best-studied examples of crosstalk in histones involves the phosphorylation of serine 10 in histone 3 (H3S10) and its effect on lysine acetylation (Fig. 2b). Several kinases are known to phosphorylate H3S10. These include AuroraB and other members of the Aurora/Ipl 1 kinase family, as well as kinases implicated in transcriptional regulation such as the yeast non-specific serine/threonine protein kinase 1 (Snf1) and mammalian Proto-oncogene serine/threonine protein kinase 1 (Pim1), Ribosomal s6 kinase (Rsk), Mitogen and stress activated kinase 1 (Msk1), and Mitogen and stress activated kinase 2 (Msk2) kinases [16–18]. Phosphorylation of H3S10 leads to the stimulation of acetylation at lysine 14 (H3K14) with the prototypical histone acetyltransferase general control nonderepressible (Gcn)5 displaying an up to tenfold preference for acetylation of H3K14 when H3S10 is phosphorylated [19,20]. In contrast to the enhancement of acetylation at H3K14, phosphorylation of H3S10 completely blocks acetylation at the directly adjacent lysine 9 (H3K9) residue [21], clearly illustrating the varying crosstalk effects that the same PTM can impart.

In addition to serine phosphorylation, the methylation of lysine and arginine side chains is another common PTM known to impact lysine acetylation *via* crosstalk. The side chain of lysine can be mono-, di- or tri-methylated, often with varying crosstalk effects (Fig. 2c). For example, lysine methylation at lysine 4 in histone H3 (H3K4) leads to increased acetylation of H3K14 and other lysine residues in histone H3 by p300 and other acetyltransferases [22]. Further evidence suggests that the degree to which H3K4 is methylated directly influences the associated extent of H3 acetylation [23]. As a result, the trimethylation of H3K4 is generally seen as a marker for transcriptional activation given its direct role in promoting acetylation. Conversely, trimethylation of lysine 9 in histone 3 (H3K9) is linked to transcriptional repression and is associated with reduced histone H3 acetylation. *In vitro* studies have revealed that trimethylation of H3K9 leads to inhibition of H3 acetylation at lysines 14, 18 and 23 [23]. Given their opposing effects, it is perhaps not surprising that methylations of H3H4 and H3K9 appear to be mutually exclusive [22,24,25].

Likewise, the arginine side chain can be either mono-methylated or, more commonly, di-methylated to yield either asymmetric or symmetric dimethyl arginine. Interestingly, numerous examples of crosstalk between arginine methylation and lysine acetylation are known. A specific example involves the asymmetric dimethylation of arginine 3 in histone 4 (H4R3) by protein arginine N-methyltransferase (PRMT)1, which leads to increased histone 4 acetylation by p300, with the largest enhancement observed for acetylation at lysine 8 and

12 (Fig. 2d) [26]. Given its role in promoting H4 acetylation, the asymmetric dimethylation of H4R3 by PRMT1 is generally associated with the activation of gene transcription. In a striking example of the subtleties at play in histone crosstalk, it has also been found that symmetric dimethylation at H4R3, as performed by PRMT5, antagonizes the crosstalk effects induced by PRMT1 (Fig. 2d). Counter to asymmetric dimethylation at H4R3, the PRMT5-mediated symmetric dimethylation of the same arginine residue is associated with deacetylation of H4 and leads to repressed transcription [27,28]. In addition, a recent report by Zheng and colleagues has shown that the acetylation of lysine 5 in histone 4 differentially affects methylation at H4R3 [29]. Acetylation of H4K5 was found to deactivate the asymmetric dimethylation of H4R3 by PRMT1 while enhancing symmetric dimethylation at the same arginine by PRMT5. From this, it is clear that crosstalk mechanisms play a significant part in acetylation of the p65 transcription factor and histones. Exploiting such mechanisms could provide avenues for the development of novel therapeutics designed to affect acetylation.

HATs in the NF-κB pathway

On the basis of their primary structure homology, HATs have been divided into five families. Three families that have been studied extensively are the Gcn5-related N-acetyltransferase (GNAT) family, represented by p300/CBP-associated factor (PCAF) and Gcn5; the p300/CBP family, including CBP and p300; and the MYST (the acronym MYST derives from the four founding members of this HAT family: mammalian MOZ, yeast Y bf2/Sas3 and Sas2, and mammalian Tip60) family including males absent on the first (MOF) and TAT-interacting protein 60 (Tip60) [30]. The HATs p300 and PCAF acetylate lysines 122 and 123 of p65 [9] and p300 has been described to acetylate lysines 310, 314 and 315 [31]. The role of HATs in acetylation of the NF-κB transcription factor as well as acetylation of the histones connected to κB promoters has been reviewed [3]. Interestingly, a recent study demonstrates that Tip60 is a co-activator of several NF-κB target genes and exerts its action *via* protein–protein interactions with p65. It appears that Tip60 binds earlier to the κB promoters than p65 and simultaneously promotes histone acetylation, which indicates that Tip60 could serve as a platform to promote NF-κB-mediated gene transcription [32].

HAT inhibitors mainly lead to inhibition of the NF-κB pathway

Several inhibitors of histone acetyltransferases are known and have been previously reviewed [3,33]. The natural product anacardic acid (Fig. 3, Table 1) is a small molecule inhibitor of HATs such as p300 and PCAF [34] and inhibits NF-κB-mediated gene transcription [35]. This inhibitor has been used as a starting point for the development of novel inhibitors such as the alkylidene malonates [36]. The novel anacardic acid derivative MG149 (Fig. 3, Table 1) demonstrates selectivity toward the MYST type of HATs: Tip60 and MOF [37], and this molecule effectively suppresses suberanilohydroxamic acid (SAHA)-induced hyperacetylation [38]. In addition, DNA microarrays demonstrated that MG149 inhibits the p53 and the NF-κB pathways, as well as a very limited number of other pathways [38].

Next to this, HTS identified the isothiazolones as HAT inhibitors [39]. However, attempts to optimize this class failed to give inhibitors with higher potency and selectivity [40–42], which could mainly be attributed to the exceptionally high reactivity of isothiazolones for thiolates [43]. Fortuitously, virtual screening enabled the identification of C646 (Fig. 3, Table 1) as the first potent, selective and cell-permeable p300 HAT inhibitor (K_i 0.4 μM) [44]. In addition, another recent virtual screening study describes the identification of a novel cell-permeable inhibitor (compound **2**, Fig. 3, Table 1) of p300, which is active at the same concentrations as C646 [45]. This demonstrates the strength of virtual screening as a strategy for identification of novel inhibitors for challenging targets such as HATs.

Regarding the use of C646 in cellular models, one study on prostate cancer cell lines demonstrated that siRNA-mediated and C646-mediated inhibition of p300 increase apoptosis, which is, among other things, caused by inhibition of the androgen receptor and the NF-κB pathway [46]. Another group demonstrated that p300 binds to the cyclooxygenase (COX)-2 promoter, and that inhibition of p300 activity by C646 diminished the p300 promoter binding and the expression of COX-2. Interestingly, this study was done in animal models in which C646 was administered *via* a lumbar intrathecal catheter, which demonstrates that HAT inhibitors can be administered locally in animal models [47]. Taken together these data demonstrate that C646 performs very well in cell-based studies and upon local administration in animal models. Inhibition of p300 by siRNA and the chemical inhibitor C646 leads to subsequent inhibition of, among others, the NF-κB pathway.

HDAC classes

The HDACs are a highly homologous group of enzymes that are classified based on their primary and secondary structure. The zinc-binding HDACs are denoted class I (HDAC 1, 2, 3 and 8), class IIa (HDAC 4, 5, 7 and 9), class IIb (HDAC 6 and 10) and class IV (HDAC 11). In addition, there is a group of NAD^+-dependent HDACs, which are denoted class III (sirtuin 1–7) [48].

Inhibitors of zinc-dependent HDACs have ambiguous effects on the NF-κB pathway

Although HDAC inhibitors were initially discovered as anticancer agents, many studies indicate their ability to suppress inflammatory responses. In this respect, early evidence stems from a study demonstrating that phenylbutyrate and trichostatin A (Fig. 3, Table 1) inhibit tumor necrosis factor (TNF)α expression in inflamed tissues in a rheumatoid arthritis animal model [49]. Another early study demonstrates that HDAC inhibitor SAHA (Fig. 3, Table 1) inhibits lipopolysaccharide (LPS)-induced cytokine release *in vitro* and *in vivo* [50]. Interestingly, this anti-inflammatory effect was observed at much lower concentrations than tumor suppressive effects *in vitro*. The anti-inflammatory potency of HDAC inhibitors has been described in several reviews [51–53]. It was observed that HDAC inhibitors such as SAHA and Trichostatin A (TSA) delay and reduce NF-κB nuclear translocation and gene expression upon TNF*a* stimulation [54]. The potential of HDAC inhibitors to suppress inflammation is also nicely illustrated by compound **1**, recently described by Lee *et al.* (Fig. 3, Table 1) [55]. This novel HDAC inhibitor exhibits nanomolar HDAC inhibitory potency

and demonstrated a strong suppressive effect on inflammatory mediator expression in animal models. Most interestingly, a recent study applied the HDAC inhibitor givinostat (Fig. 3, Table 1) in a relatively small patient group suffering from systemic-onset juvenile idiopathic arthritis, and demonstrated a clear therapeutic benefit and excellent safety profile [56].

In contrast to inhibiting inflammation, other studies have also demonstrated that certain HDAC inhibitors can also lead to the stimulation of proinflammatory gene transcription. Initial studies on NF-κB acetylation reported that HDACs 1–3 (class I) can deacetylate p65 and negatively regulate gene transcription [6,57]. In addition, HDAC activity leads to histone deacetylation, which is generally associated with inhibition of gene transcription. Both factors imply that HDAC inhibitors stimulate proinflammatory gene transcription, which is supported by several studies. Indeed, it was demonstrated that SAHA [58], TSA [59,60], MS275 [58,61,62] and LBH589 [61] enhance NF-κB activation (Fig. 3, Table 1).

Toward elucidation and selective modulation of specific HDACs in the NF-κB pathway

Such contradictory findings can be explained by applications of different cell types and the lack of selectivity of the employed HDAC inhibitors. Most frequently, applied HDAC inhibitors target all zinc-dependent HDACs, because most rely on the strongly zinc-coordinating hydroxamic acid functionality (carried by pan-HDAC inhibitors; Fig. 3, Table 1) [62]. This hampers elucidation of the relevance of HDAC activity in specific disease models. However, over the past few years, more selective inhibitors have become available. An example includes entinostat/MS275 (Fig. 3, Table 1), which is HDAC1–3 (class I) selective [62]. Also, the first HDAC class IIa (HDAC 4, 5, 7 and 9) selective inhibitors with a trifluoromethyloxadiazole scaffold (TFMO; Fig. 3, Table 1) were recently identified [63]. Interestingly, this novel class of inhibitors lacks the usual hallmark of class I and class IIb inhibition: cell death or apoptosis. This is beneficial for applications in non-oncology areas such as inflammation.

Several studies have already shed more light on the role of specific HDACs in the NF-κB pathway. A noteworthy recent study reports that HDAC3 deacetylates p65 on lysines 122, 123, 314 and 315, and that it is a positive regulator of inflammatory gene expression [64], which might seem contradictory to the previously mentioned initial studies [6,57] and studies using MS275 [58,61,62]. However, note that these concern not only HDAC3 but also HDAC1 and 2. This indicates that future studies should be aimed at developing more selective HDAC inhibitors that target, for example, HDAC3. Additionally, there have also been interesting reports on the role of SIRT type HDACs in the NF-κB pathway [65]. For example, HDAC SIRT1 deacetylates p65 at lysine 310 and thus inhibits the NF-κB transcriptional activity [66]. Interestingly, the small molecule SIRT1 activator SRTCX1003 (Fig. 3, Table 1) inhibits NF-κB activation *in vitro* and LPS-induced production of proinflammatory cytokines in BALB/c mice [67]. Also, SIRT2 interacts with p65, and deacetylates lysine 310, thereby inhibiting NF-κB transcriptional activity. Sirt2 knockdown results in increased expression of a subset of NF-κB target genes, indicating involvement of Sirt2 in the expression of a subset of NF-κB target genes [68]. This suggests that SIRT

activators have a good potential for further development into molecules that suppress NF-κB activation in inflammation.

Concluding remarks

Lysine acetylation is a key regulator of the NF-κB pathway, which works in concert with other PTMs *via* complex crosstalk mechanisms to determine the signaling output. Importantly, small molecule modulators of its writers (HATs) or erasers (HDACs) have been demonstrated to regulate NF-κB signaling, suggesting that these are potential drugs for inflammatory diseases. An ongoing challenge toward regulation of the NF-κB pathway is the development of highly potent molecules that selectively target specific HATs or HDACs. Fortuitously, this field has seen remarkable progress over the past few years. Several inhibitors now demonstrate specific effects in distinct disease models in cellular systems and animal studies, which is very promising for drug discovery. A noteworthy example is HAT inhibitor C646. Owing to its high selectivity and potency for p300, this inhibitor mainly leads to inhibition of pathways that are connected to NF-κB, the androgen receptor and the glucocorticoid receptor in cellular and animal models. Another promising example is HAT inhibitor MG149, which mainly inhibits expression related to the NF-κB and p53 pathways.

Additionally, some currently described HDAC inhibitors show encouraging effects in animal models and even patients; pan-HDAC inhibitor givinostat displayed promising therapeutic benefits in patients suffering from juvenile idiopathic arthritis. An important consideration in the development of such agents is the capacity for HDAC inhibitors to show either activation or inhibition of inflammatory responses. We presume that a main cause of these ambiguities is that different reports employed different cell types. In addition, we speculate that they could also be explained by HDAC (non) selectivity of the inhibitors used. In the light of this, it is interesting that a recent study demonstrated that HDAC3 is a positive regulator of inflammatory gene expression, which deacetylates p65 on four specific lysines. This suggests that HDAC3-specific inhibitors, and perhaps more specific inhibitors for other HDACs, could unambiguously suppress inflammatory responses. Also, the role of studied SIRT type HDACs seems to be mainly inhibition of NF-κB gene transcription and, in line with this, SIRT1 activator SRTCX1003 encouragingly reduced inflammatory responses in mice. This indicates that activators of SIRT type HDACs could be also be effective in suppressing inflammatory responses. However, it often remains unclear which specific HDACs need to be targeted by inhibitors or activators. Thus, a challenge lies ahead in determining whether specific HDACs target specific lysine acetylations in specific signaling cascades, or if their effects are (much) broader (a challenge which also still applies to HATs). Finally, in addition to the current approaches of pursuing modulators of HDACs and HATs, agents capable of inhibiting (or enhancing) the various enzymes that install PTMs that crosstalk with acetylation could also find use as drugs for modulating histone (de)acetylation.

Appendix A. Supplementary data

Refer to Web version on PubMed Central for supplementary material.

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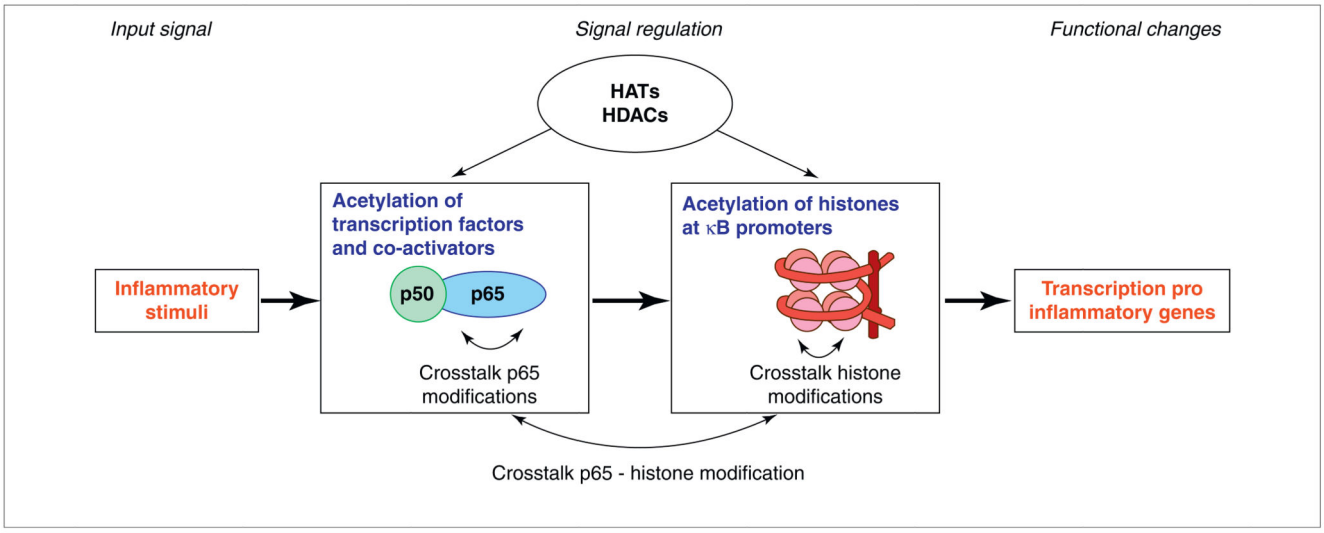

Figure 1.

Schematic representation of the diverse roles of lysine acetylation in the activation of the nuclear factor (NF)-κB pathway. Lysine acetylations of the transcription factors as well as their co-activators play an important part in the duration of the response and the signaling output. Lysine acetylation status of the histones works in concert with acetylation status of the transcription factors to enable or disable transcription of specific genes. Crosstalk of acetylation with other PTMs is an important component in the NF-κB pathway. Abbreviations: HATs, histone acetyltransferases; HDACs, histone deacetylases.

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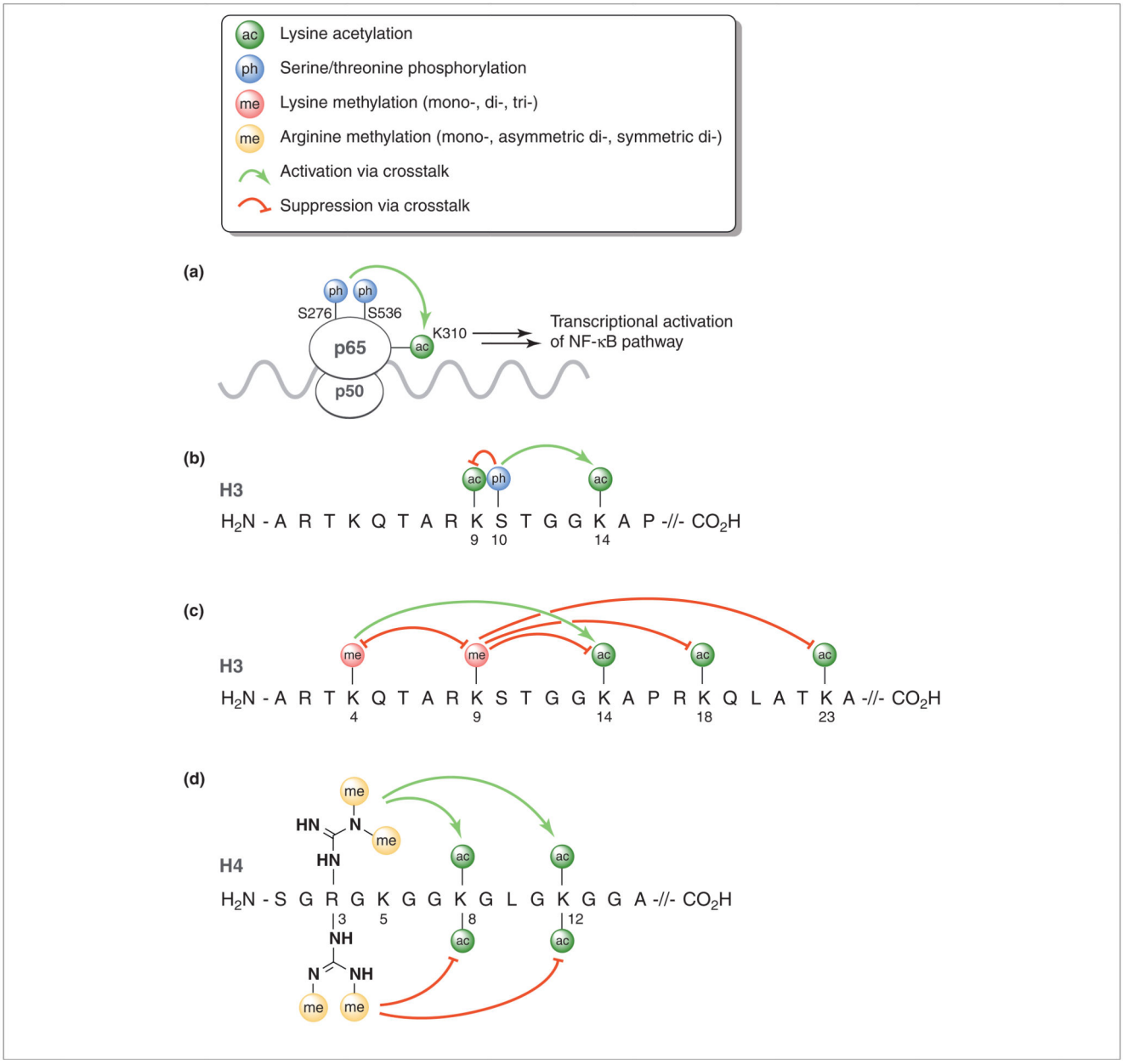

Figure 2.

Examples of various post-translational modifications (PTMs) and their crosstalk interactions with lysine acetylation in the p65 transcription factor and histone proteins. Abbreviation: NF-κB, nuclear factor κB.

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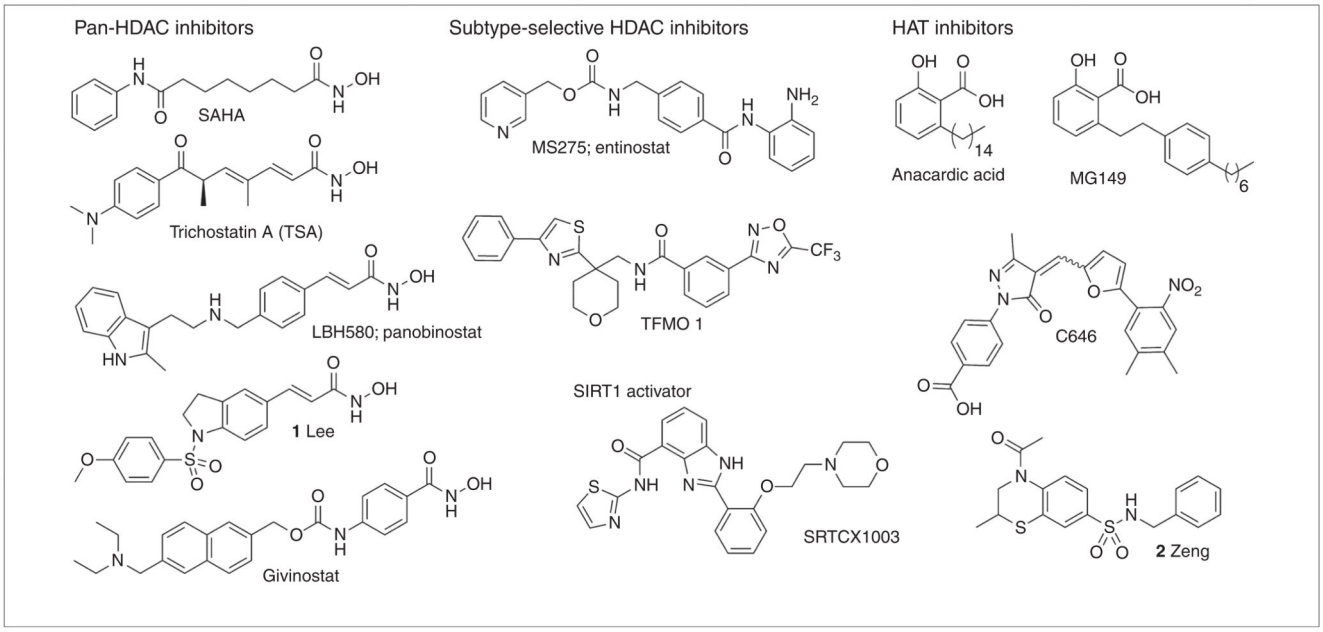

Figure 3.

Structures of small molecules that interact with writers (histone acetyltransferases; HATs) or erasers (histone deacetylase; HDACs) of lysine acetylations.

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Table 1

Small molecules that interfere with writers (HATs) or erasers (HDACs) of lysine acetylations, and their selectivity and effects on disease models for NF-κB-mediated inflammation

Compound	Selectivity	Effects in disease models	Refs
HAT inhibitors			
Anacardic acid	p300 and PCAF inhibitor	Inhibits the NF-κB pathway	[35]
MG149	Tip60 and MOF selective inhibitor	Inhibits SAHA-induced hyperacetylation	[37,38]
		Inhibits the NF-κB and p53 signaling pathways	
C646	p300 selective inhibitor (K_i 0.4 μM)	Increases apoptosis by inhibition of the androgen receptor and NF-κB pathway	[44,46,47]
		Repression of gene expression	
		Inhibition of COX-2 expression	
Compound 2 (Fig. 3)	p300 HAT inhibitor (IC_{50} 3.4 μM)	–	[45]
HDAC inhibitors or activators			
SAHA	Pan-HDAC inhibitor	Suppression of LPS-induced cytokine release *in vitro* and *in vivo*	[50,62]
Trichostatin A (TSA)	Pan-HDAC inhibitor	Inhibition of TNFα *in vitro*	[49,62]
LBH580 (panobinostat)	Pan-HDAC inhibitor	Enhances NF-κB activation	[61,62]
ITF2357 (givinostat)	Pan-HDAC inhibitor	Therapeutic benefit in patients suffering from juvenile idiopathic arthritis	[56,62]
Compound 1 (Fig. 3)	Unknown	Inhibition of IL6, PGE2, TNFα and NO in RAW 264.7 macrophages	[55]
		Anti-inflammatory in paw edema mouse model	
MS275 (Entinostat)	HDAC1-3 selective inhibitor	Enhances NF-κB activation	[58,62]
TFMO 1	Class IIa selective inhibitor	–	[63]
SRTCX1003	SIRT1 activator	Inhibits NF-κB activation	[67]

COX, cyclooxygenase; HDAC, histone deacetylase; IL, interleukin; LPS, lipopolysaccharide; MOF, males absent on the first; NF-κB, nuclear factor κB; NO, nitric oxide; PCAF, p300/CBP associated factor; PGE, prostaglandin E; RAW, Abelson murine leukemia virus transformed; SAHA, suberanilohydroxamic acid; SIRT, Sirtuin; Tip60, TAT-interacting protein 60; TNF, tumor necrosis factor.