Histone acetyltransferases are crucial regulators in NF-κB mediated inflammation

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Post-translational modifications of proteins, such as acetylation, are important regulatory events in eukaryotic cells. Reversible acetylations of histones and non-histone proteins regulate gene expression and protein activity. Acetylation levels of proteins are regulated by a dynamic equilibrium between acetylation by (histone) acetyltransferases and deacetylation by (histone) deacetylases. Alterations in this equilibrium can result in pathological states. Inflammation is a physiological response that, under certain conditions, turns into a disease. This review focuses on the crucial regulatory roles of protein acetylation in NF-κB-mediated inflammation and the potential applications of small-molecule inhibitors of acetylation for the treatment of inflammatory diseases.

All cellular processes are regulated by a complex and dynamic network of signals and interactions that allows cells to respond to alteration in the cellular environment. This network is, among others, regulated by post-translational modifications such as acetylation, methylation phosphorylation and ubiquitination. These modifications alter protein–protein interactions, modulate enzyme activity and function as regulatory switches for many cellular processes. Histones are small proteins around which DNA is wrapped to form the basic packaging unit of DNA called the 'nucleosome'. Post-translational modifications of histones modify their interactions with DNA and with other proteins, and change the chromatin structure to expose promoter regions for binding of transcription factors.

Inflammation is a physiological response, triggered by physical, biological or chemical stimuli, which is necessary for cell survival. Under certain circumstances, however, the inflammatory response is inappropriate or excessive, which leads to pathological states. Abnormal and chronic inflammatory responses have been associated with various diseases including asthma, cancer, diabetes and neurodegenerative diseases.

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It has been demonstrated clearly that post-translational modifications of proteins play a crucial part in regulating the intensity, the duration and the specificity of inflammatory responses. This review focuses on the role of histone and non-histone protein acetylations by histone acetyltransferases (HATs) in nuclear factor κB (NF-κB)-mediated inflammation. Furthermore, we discuss the inhibition of acetylation by small-molecule HAT inhibitors as a potential therapeutic approach to control inflammation.

Protein acetylation

Reversible acetylation of histones and other proteins is modulated by the activity of HATs and histone deacetylases (HDACs). These enzymes catalyze, respectively, the introduction or removal of acetyl groups from ε-amino functionalities of specific lysine residues. HATs are classified based on their cellular localization in nuclear HATs (type A) and cytoplasmatic HATs (type B) [1]. Several nuclear HATs have been identified, whereas only one cytoplasmatic HAT (HAT 1) has been described so far. HATs have been divided into five families based on their primary structure homology. The three families that have been studied extensively are: the GNAT (GCN5-related *N*-acetyltransferase) family, represented by GCN5 (general control nonderepressible 5) and PCAF (p300/CBP associated factor); the p300/CBP family, including p300 and CBP

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(CREB-binding protein); and the MYST family, which includes Tip60 (TAT-interacting protein 60). The acronym MYST derives from the four founding members of this HAT family: mammalian MOZ, yeast Y bf2/Sas3 and Sas2, and mammalian Tip60.

Role of acetylation in NF-κB-mediated inflammation

The NF-κB transcription factors encompass a family of inducible transcription factors that play a crucial part in the expression of numerous genes that are involved in immune and inflammatory responses and in cell survival [2]. NF-κB transcription factors exist in homo- or hetero-dimeric complexes consisting of different members of the Rel family of proteins. The most prevalent and best studied of these complexes is the p50–p65 heterodimer. In resting cells, p50–p65 is present in the cytoplasm in an inactive form, bound to inhibitory proteins known as IκBs (Fig. 1). Upon stimulation by specific inducers such as inflammatory cytokines [tumor necrosis factor (TNF) and interleukin-1 (IL-1)], bacterial products (lipopolysaccharide) or oxidative stress (H_2O_2), the IκBs are phosphorylated, ubiquitinated and degraded. Degradation of IκBs results in the release of the p50–p65 dimer, which translocates into the nucleus, followed by specific upregulation of gene expression. Owing to the central role of NF-κB in inflammation, the NF-κB pathway has been recognized as a target for therapeutic intervention.

Acetylation of NF-κB complex

Several regulatory mechanisms control the NF-κB response to specific stimuli. Among these, post-translational modifications play an important role and regulate different functions of NF-κB. Post-translational modifications mutually influence each other, which results in a complex pattern of modifications that all determine the output and the duration of responses upon specific stimulations of NF-κB. In this review we focus on reversible acetylation of NF-κB and histones connected to its target genes. Recently, it has been described that acetylations of specific lysine residues of NF-κB subunits play distinct roles in the regulation of its transcriptional capacity, its DNA-binding ability and duration of its actions (Fig. 1).

It has been shown that the p65 NF-κB subunit (also known as RelA) is acetylated at specific sites by different HATs. Chen *et al.* reported acetylation at lysine residues 218, 221 and 310 by the HATs p300 and CBP [3]. Acetylation at Lys 221 increases the binding affinity of the NF-κB complex to the DNA κB enhancer. Furthermore, acetylation at Lys 221, alone or in combination with Lys 218, impairs assembly of NF-κB with newly synthesized IκBα, which extends the duration of the NF-κB activity. By contrast, deacetylation by HDAC3 stimulates IκBα binding, which promotes NF-κB export from the nucleus to the cytoplasm [4]. Acetylation at Lys 310 is required for full transcriptional activity of p65, but does not affect the DNA binding or its assembly with IκBα. In a subsequent study, it was shown that acetylation on this position provides a binding site for binding of the bromodomain of the transcriptional coactivator Brd4 [5]. Recent work by Yang *et al.* showed that acetylation at Lys 310 enhances the transcriptional activity of p65 by impairing the methylation of lysine residues 314 and 315, which is important for the ubiquitination and degradation of chromatin-associated p65 [6]. The HDAC Sirtuin 1 (SIRT1) deacetylates p65 at Lys 310 and thus terminates NF-κB-dependent gene expression [7]. Thus, acetylations of NF-κB on residues 218, 221 and 310 increase its transcriptional activity.

By contrast, acetylation at other positions decreases the NF-κB transcriptional activity. Acetylations on the lysine residues 122 and 123 by p300 and PCAF reduce binding of NF-κB to the DNA κB enhancer and facilitate binding to IκBα and subsequent export from the cytoplasm [8]. Other acetylations have no direct effect on transcriptional activity. Acetylation at lysine residues 314 and 315 by p300 do not affect the general transcriptional activity of the NF-κB complex [9,10]. Nevertheless, these acetylations modulate the expression of specific sets of genes, which indicate that site-specific acetylations of p65 regulate the specificity of the NF-κB-dependent gene expression.

The p50 subunit of NF-κB is also subject to stimulus-induced acetylation. *In vitro*, p50 is acetylated at lysine residues 431, 440 and 441 [11]. It has been shown that acetylation by p300 increases binding of p50 to the DNA and enhances the transcriptional activation by NF-κB [12].

Further evidence for the importance of direct acetylations of NF-κB subunits as regulatory mechanisms is the observation that diverse cofactors can regulate NF-κB transactivation by modulating p50–p65 acetylation levels. For example, the transcriptional repressor Daxx impairs the transcriptional activity of NF-κB by binding to p65 and interferes with its acetylation [13]. By contrast, the transcription coactivator Stat3 maintains constitutive NF-κB activity in inflammation-induced cancers by promoting p300-mediated acetylation of the p65 subunit [14].

Taking these data together it is concluded that direct acetylation and deacetylation of specific lysine residues in the p50 and p65 subunits of NF-κB play a crucial part in the regulation of different NF-κB functions. Acetylations on different sites have different effects on NF-κB transcriptional activity and NF-κB-dependent gene expression. Several studies show that inhibition of deacetylation extends NF-κB transcriptional activity in response to specific stimuli, whereas other studies demonstrate that inhibition of deacetylation decreases NF-κB transcriptional activity [2,15,16]. This indicates that the resulting effect of both HAT and HDAC inhibition depends on the selectivity for specific NF-κB acetylation sites. The crucial role of NF-κB acetylation and deacetylation in the regulation of NF-κB-mediated gene expression raises the idea to modulate inflammatory responses by modulating NF-κB acetylation levels with HAT and HDAC inhibitors. It has been shown that NF-κB acetylations are mediated by the HATs such as p300, CBP and PCAF, which indicates that small-molecule inhibitors of these HATs will modulate NF-κB signaling via direct inhibition of NF-κB acetylation as well as via modulation of histone acetylation.

Acetylation of co-activators of NF-κB

Several cofactors that are involved in the regulation of the NF-κB transactivation are subject to direct acetylations by HATs. These acetylations modulate their interactions with the NF-κB subunits. Such acetylations have been described for poly(ADP-ribose) polymerase-1 (PARP-1), Signal Transducers and Activators of Transcription 1 (Stat1) and the glucocorticoid receptors. PARP-1 is a coactivator of NF-κB that has been demonstrated to have a role in inflammatory disorders. PARP-1 is acetylated upon inflammatory stimulation on specific lysine residues by p300 and CBP and deacetylated by HDACs 1–3 [17]. Acetylation of PARP-1 is required for the interaction with p50, which results in coactivation of NF-κB in response to inflammatory stimuli. Stat1 is a transcription factor

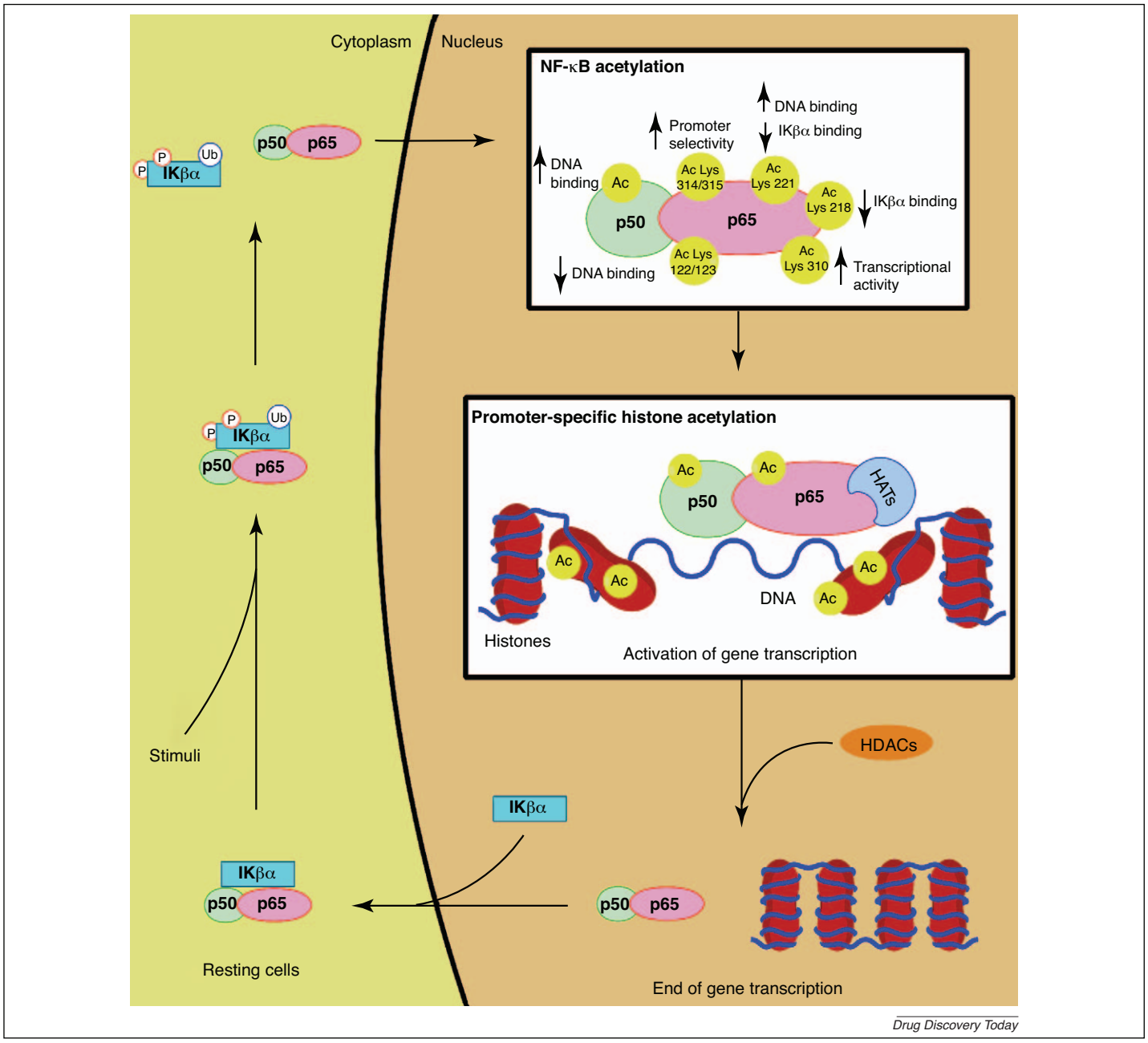

FIGURE 1

Importance of acetylation in NF-kB-mediated inflammation. In resting cells, p50–p65 subunits are present in the cytoplasm in an inactive form, bound to the inhibitory protein IκBα. Upon stimulation IκBα is phosphorylated, ubiquitinated and degradated. The p50–p65 dimer is released and translocates into the nucleus where both subunits are acetylated in different positions. Acetylations of p50–p65 regulate its transcriptional capacity, its DNA-binding ability and the duration of its action. p50–p65 subunits recruit HATs to the target gene. Gene-specific histone acetylations by HATs change the chromatin structure exposing promoter regions for binding of p50–p65.

that can modulate NF-κB activity. Acetylation of Stat1 by HATs, such as CBP, results in binding to the p65 subunit of NF-κB and consequently the reduction of NF-κB signaling [18]. The action of glucocorticoids involves acetylation of the glucocorticoid receptor. The deacetylated form of the glucocorticoid-bound glucocorticoid receptor can suppress NF-κB activity [19].

Acetylation of histones in NF-κB-mediated gene transcription

Dynamic acetylations and deacetylations play an important role in the regulation of gene transcription resulting from activation of the NF-κB pathway. Upon DNA binding the NF-κB subunits can recruit HATs and HDACs to the target gene promoter to change the acetylation profiles of the histones. It has been shown that the transcriptional activation domain of p65 interacts with the N-terminal and C-terminal domain of the HATs CBP and p300 [20]. These HATs function as co-activators for gene transcription. It has been demonstrated that the presence of HATs, such as CBP, p300 and PCAF, at the gene promoter is essential for NF-κB-mediated gene expression [21]. By contrast, it has also been shown that p65 interacts with HDACs, such as HDAC-1 and SIRT6, that function as

TABLE 1

Promoter-specific hyperacetylation of NF-κB-dependent genes

Gene	Stimulus	Cell type	Acetylation site	HAT involved	Ref.
GM-CSF	IL-1β	A549	Histone H4 Lys 8, 12	Unknown	[24]
Eotaxin-1	TNF-α	HASMC	Histone H4 Lys 5, 12	PCAF	[26]
Interleukin-8	Legionella	Human lung epithelial	Histone H3 Lys 14, Histone H4	p300/CBP	[31]
	Listeria	HUVEC	Histone H3 Lys 14, Histone H4 Lys 8	CBP	[32]
	LPS	HUT-78 and Jurkat and monocytes	Histone H4	Unknown	[33]
	H_2O_2 and PM_{10}	A549	Histone H4	Unknown	[34]
Interleukin-6	TNF-α	L929sA HEK293T	Histone acetylation	p300/CBP	[27]
ELAM	TNF-α	L929sA HEK293T	Histone acetylation	p300/CBP	[27]
CXCL10	TNF-α and INF-γ	ASM	Histone H4	CBP	[28]
E-selectine	TNF-α	HUVECs	Histone H3 Lys 9, 14, Histone H4 Lys 5, 8, 12	PCAF p300	[29]
Cox-2	Bradykinin	ASM	Histone H4 Lys 5, 8, 16	Unknown	[30]
	IL-1β	ASM	Histone H4 Lys 8	Unknown	[30]

repressors of gene transcription by deacetylating histones at promoters of NF-κB target genes [22,23].

The importance of promoter-specific histone acetylation by HATs has been demonstrated for many NF-κB target genes (Table 1). HATs are involved in gene transcription of granulocyte-macrophage colony-stimulating factor (GM-CSF), which is a protein that is involved in physiological and pathological inflammatory processes. IL-1β stimulates GM-CSF production through activation of the NF-κB pathway. The GM-CSF production is associated with increased acetylation at Lys 8 and Lys 12 of histone H4 connected to the GM-CSF promoter [24]. Another example is CCL11 (also known as eotaxin-1), which is an eosinophil chemoattractant with relevance in allergic diseases such as asthma. CCL11 transcription is increased upon stimulation with TNF-α. NF-κB is the key transcription factor for CCL11. In the TNF-α-induced CCL11 transcription, PCAF is recruited, upon phosphorylation, to the CCL11 promoter. PCAF increases histone H4 acetylation at Lys 5 and Lys 12, which promotes p65 association with DNA and the transcription of the CCL11 gene. Histone H4 acetylation is markedly reduced after treatment with β_2-agonists and glucocorticoids. This suggests that one of the mechanisms of actions of these medicines is the indirect decrease of histone acetylation, which inhibits inflammatory gene transcription [25,26].

IL-6 is another important mediator of inflammatory responses. Overexpression of CBP and p300 potentiates basal and TNF-α-induced IL-6 promoter activation via interactions with the NF-κB subunit p65. A similar mechanism is proposed for the endothelial leukocyte adhesion molecule (ELAM), which is another NF-κB-dependent promoter [27]. Interferon-γ-inducible protein-10 (CXCL10) is a chemokine implicated in the pathophysiology of asthma and COPD (chronic obstructive pulmonary disease). Stimulation of asthmatic airway smooth muscle cells with TNF-α or interferon (IFN)-γ induces recruitment of CBP and acetylation of histone H4, but not H3 at the CXCL10 promoter, which consequently increases its transcriptional activity [28]. Another gene that is expressed upon inflammatory stimulation is E-selectin. E-selectin is an adhesion molecule that is rapidly expressed by endothelial cells activated upon inflammatory stimulation. Induction of E-selectin gene expression by TNF-α is associated with hyperacetylation of histones H3 and H4 connected to the E-selectin promoter by the HATs PCAF and p300 [29]. Another gene where expression is induced in response to inflammation is cyclooxygenase 2 (COX-2). Transactivation of COX-2 gene expression involves selective hyperacetylation of histone H4 connected to the COX-2 promoter in a stimulus-specific manner. Stimulation with bradykinin causes acetylation at Lys 5, 8 and 16, whereas stimulation with IL-1β causes only acetylation at Lys 8 [30]. This demonstrates that specific stimuli induce a distinct histone acetylation pattern, which regulates distinct gene transcription patterns in response to specific inflammatory stimuli.

Histone acetylation in IL-8 gene expression

Histone acetylation has an important role in the activation of IL-8 gene expression in immune responses triggered by bacterial infections. For example, IL-8 expression in *Legionella pneumophila* infected lung cells involves increased recruitment of p300 and CBP, as well as enhanced acetylation of histones H3 and H4 at the IL-8 gene promoter [31]. The same is observed upon infection by intracellular *Listeria monocytogenes*, which also induces acetylation of histone H3 and H4 at the IL-8 promoter, consequently increasing IL-8 expression. By contrast, *Listeria*-induced IFN-γ gene expression does not require changes in the histone acetylation at the IFN-γ promoter. Furthermore, the HDAC inhibitor trichostatin A increases *Listeria*-induced expression of IL-8, but not of IFN-γ-induced IL-8 expression. This demonstrates that histone acetylation regulates the gene expression patterns in response to specific stimuli [32]. Another stimulus that increases IL-8 expression is lipopolysaccharides (LPS). LPS-induced IL-8 gene transcription is associated with acetylation of histone H4 at the IL-8 promoter. Interestingly, glucocorticoids suppress IL-8 expression, which is accompanied by the reduction of histone acetylation of the IL-8 promoter [33]. By contrast, IL-8 expression and release is also increased upon oxidative stress induced by H_2O_2 and environmental particulate matter (PM_{10}). It has been shown that H_2O_2 and PM_{10} augment the intrinsic HAT activity in alveolar epithelial cells leading to increased histone H4 acetylation at the IL-8 gene

promoter [34]. These findings demonstrate that IL-8 expression is positively correlated with histone acetylation.

Role of acetylation in disease

Asthma and COPD

Inflammatory lung diseases such as asthma and COPD are associated with the expression of multiple inflammatory genes in the lungs. Increasing evidence demonstrates that the balance between HAT and HDAC activity is altered in these diseases. A recent study showed significant reduction of HDAC activity and increased HAT activity in peripheral blood mononuclear cells from children with allergic asthma. The intensity of these alterations was positively correlated to bronchial hyper-responsiveness [35]. In another study, it has been shown that bronchial biopsies from subjects with asthma contain reduced HDAC1 and HDAC2 expression and decreased HDAC activity. By contrast, HAT activity was increased, although no difference in expression of HATs (PCAF and CBP) was found [36]. Furthermore, it has been found that HAT activity is increased and HDAC activity is decreased in alveolar macrophages of subjects with asthma compared with healthy subjects [37]. The HAT activity was reduced to normal levels in patients that were treated with glucocorticoids, which indicates that glucocorticoids regulate inflammatory responses indirectly by the reduction of HAT activity.

The inflammatory lung disease COPD is also characterized by a disturbed HAT/HDAC balance. A study with lung tissue samples of COPD patients showed reduced HDAC activity and expression, and increased histone H4 acetylation at the IL-8 promoter. In contrast to asthma, HAT activity in COPD patients was not increased in comparison with healthy subjects [38]. The reduced HDAC expression and activity measured in COPD are also responsible for the steroid resistance associated with this disease [19]. Taken together, these findings indicate that a shift of the HAT/HDAC balance towards HAT activity could underlie the increased expression of inflammatory genes in inflammatory lung diseases, which is a mechanism that has been described in several review articles [39–41]. This demonstrates that inhibition of HAT activity has potential for the treatment of such inflammatory diseases.

Diabetes

Inflammatory processes have a role in the pathogenesis of diabetes. This has been shown in experiments with high glucose conditions that mimic diabetes. These experiments demonstrated activation of NF-κB-dependent gene transcription of inflammatory genes in monocytes *in vitro*. This activation proceeds through recruitment of p65 and HATs to the TNF-α and COX-2 promoters, with concomitant increases in histone H3 and H4 acetylation. Furthermore, increased histone H3 acetylation at TNF-α and COX-2 promoters has been found in human blood monocytes from type 1 and type 2 diabetic subjects in comparison with non-diabetic subjects [42]. A study in endothelial cells and vascular tissue demonstrated that glucose causes upregulation of p300 accompanied by increased histone acetylation and expression of extracellular matrix proteins and vasoactive factors. These proteins are responsible for alterations of endothelial and vascular structure and function in organs, which are affected by chronic diabetic

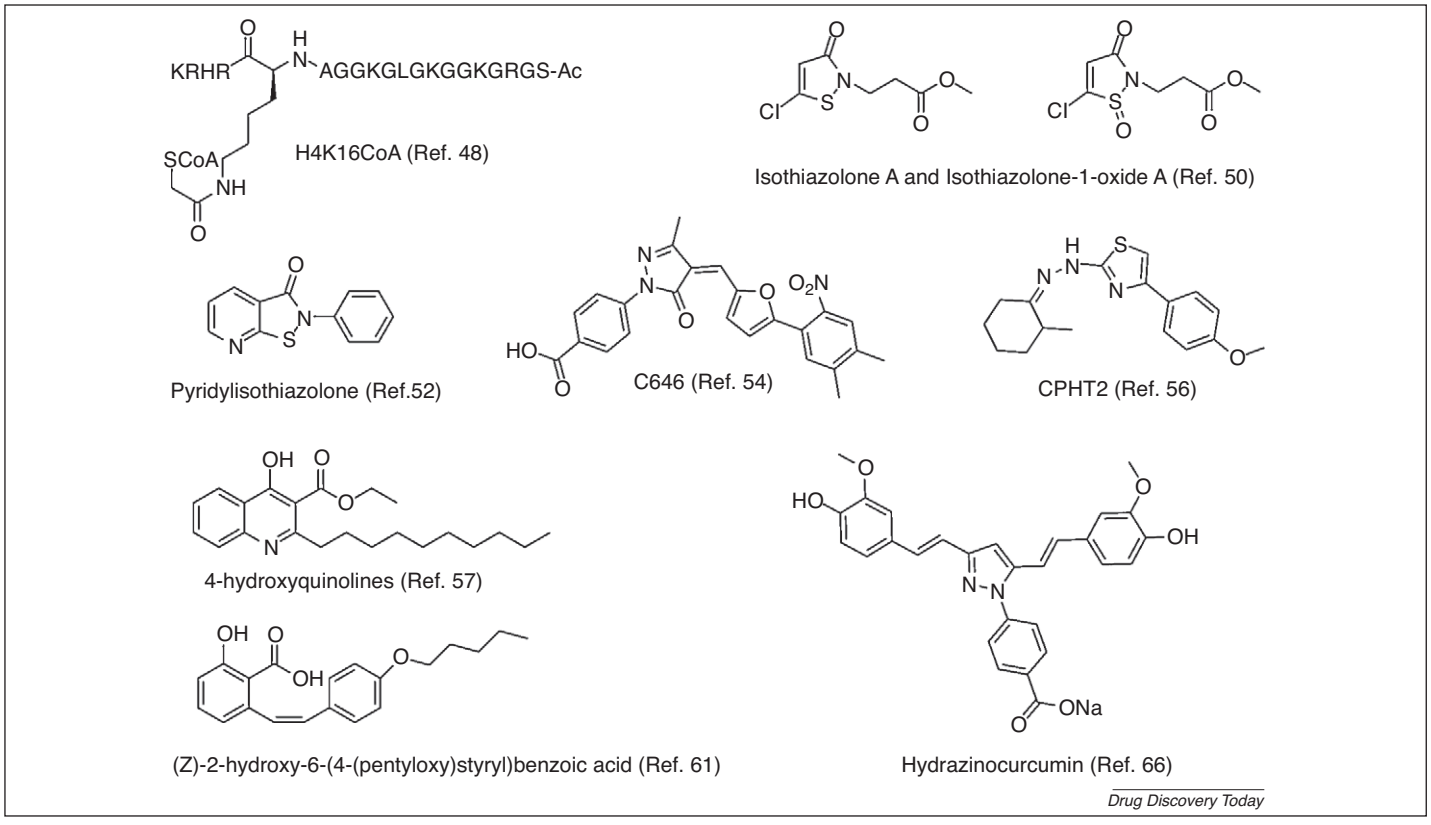

FIGURE 2

Recent small molecule inhibitors of histone acetyltransferases.

complications [43]. These results suggest that inhibition of histone acetylation might be a valuable strategy to suppress inflammatory responses in diabetes.

Neurodegenerative diseases

Neurodegenerative diseases, such as Alzheimer's and Parkinson's disease and amyotrophic lateral sclerosis, are characterized by slow and progressive dysfunction and loss of neurons in the central nervous system. Several findings support the theory that inflammation contributes to the development of the neurodegeneration by activating chronic immune responses, in particular by microglia and astroglia. Highly activated glial cells express pro-inflammatory cytokines and chemokines that increase excitotoxicity on neurons and are responsible for neuronal apoptosis [44,45]. The inflammatory response of glial cells involves the activation of different signaling pathways, including NF-κB, which is accompanied by histone hyperacetylation [46–48]. There are many examples in the literature of small molecules that provide protection against glial-cell-induced neurodegeneration by blocking the NF-κB pathway [49,50]. These findings raise the idea that HAT inhibitors could also find a therapeutic application in this field.

HAT inhibitors in inflammation

Small-molecule HAT inhibitors that are subtype-selective and cell-permeable are essential tools to evaluate the role of HATs in inflammation. Several classes of HAT inhibitors have been reviewed previously [51,52]. The most potent and selective HAT inhibitors are the so-called bisubstrate inhibitors, which include the histone peptide and CoA (Fig. 2). These inhibitors are remarkably selective and potent but their lack of cell permeability limits their applicability [53,54]. High-throughput screening led to the identification of isothiazolones as potent HAT inhibitors [55,56]. Unfortunately, the high reactivity has limited their applications in cell-based studies [57,58]. Nevertheless, this class of covalent inhibitors provides opportunities for activity-based protein profiling of HATs in cell lysates [59]. Recently, a promising HAT inhibitor was discovered using virtual ligand screening [60]. This compound is a potent and selective inhibitor of p300 and it can reduce histone acetylation and cancer cell growth. Another group used phenotypic screening for the identification of new HAT inhibitors [61–63]. Nevertheless, none of the described compounds has been used to investigate the effect of small-molecule inhibition of acetylation on inflammation.

The screening of natural products has led to the identification of several HAT inhibitors (Fig. 3). Interestingly, these compounds originate from plants known in traditional medicine to have anti-inflammatory effects. For example, anacardic acid (AA) has been described as an inhibitor of the HATs p300/CBP and PCAF [64]. Interestingly, AA has anti-inflammatory properties. Sung *et al.* reported that AA inhibits acetylation of p65, and suppresses inducible and constitutive NF-κB activation with consequent reduction of NF-κB-dependent gene expression. The downregulation of p300 by siRNA abrogated the effects of AA on the NF-κB pathway, which suggests that the HAT inhibitory effect is essential for the anti-inflammatory properties of this compound [65]. Because of its promising characteristics, AA has been used to design new HAT inhibitors [66–68].

Another natural product that has recently been described to inhibit the HAT p300 [69] is plumbagin. Plumbagin also suppresses NF-κB activation induced by different inflammatory stimuli and downregulates NF-κB-dependent gene expression [70]. Interestingly, the intensively investigated natural product curcumin is an inhibitor of p300/CBP [71]. Its synthetic derivative, hydrazinocurcumin, also inhibits HATs [72]. Curcumin reduces NF-κB activation induced by a variety of stimuli and downregulates NF-κB-dependent expression of many inflammatory genes via suppression of TNF-α-induced p65 acetylation [73]. Furthermore, the natural products gallic acid and epigallocatechin-3-gallate also possess anti-inflammatory properties. Recently, these compounds were described as non-selective inhibitors of HATs [74,75]. They suppress p65 acetylation and abrogate NF-κB activation in response to different inflammatory stimuli. It should, however, be noted that epigallocatechin-3-gallate also inhibits phosphorylation of several proteins such as MAP kinases [76]. Finally, the natural product garcinol is a potent inhibitor of p300 and PCAF and also possesses anti-inflammatory properties [77]. It has been shown that garcinol inhibits constitutive and induced NF-κB activity and downregulates NF-κB-dependent genes [78]. Microarray analysis showed that garcinol inhibited the expression of many disease-related genes [79]. Taking these data together it is tempting to speculate that the anti-inflammatory and HAT inhibitory properties of these natural products are directly connected. Nevertheless, it should be noted that many HAT inhibitors also influence other protein targets that could cause their activity. In conclusion, the development of selective inhibitors for HAT (iso)-enzymes that specifically downregulate expression of distinct genes remains a major challenge.

Conclusions

Acetylations and deacetylations are crucial regulators in inflammation

Recent studies clearly demonstrate that inflammation requires acetylation of histone and non-histone proteins. The crucial regulatory role of acetylation has been extensively demonstrated for the NF-κB pathway. Acetylation regulates the function of many proteins that are involved in the NF-κB pathway. Direct acetylation and deacetylation of the NF-κB subunits p50 and p65 regulate their signaling output. Furthermore, it has been demonstrated that acetylation of co-activators of the NF-κB pathway is required for transcriptional activation. Finally, it has been shown that acetylation of the histones that are connected to NF-κB target genes exposes promoter regions for NF-κB binding. This allows transcriptional activation of pro-inflammatory genes. It should, however, be noted that the regulatory machinery of inflammation is incredibly complex and many questions remain to be answered. It is, for example, not always clear which HATs are required for which acetylations in the NF-κB pathway. Moreover, the relative importance of the different acetylations by different HATs for activation of the NF-κB remains to be investigated.

Small-molecule inhibitors of HATs as tools to suppress inflammation

Inappropriate or excessive inflammatory responses that underlie many diseases are often accompanied by hyperacetylation of proteins that are involved in the NF-κB pathway. HATs are crucial

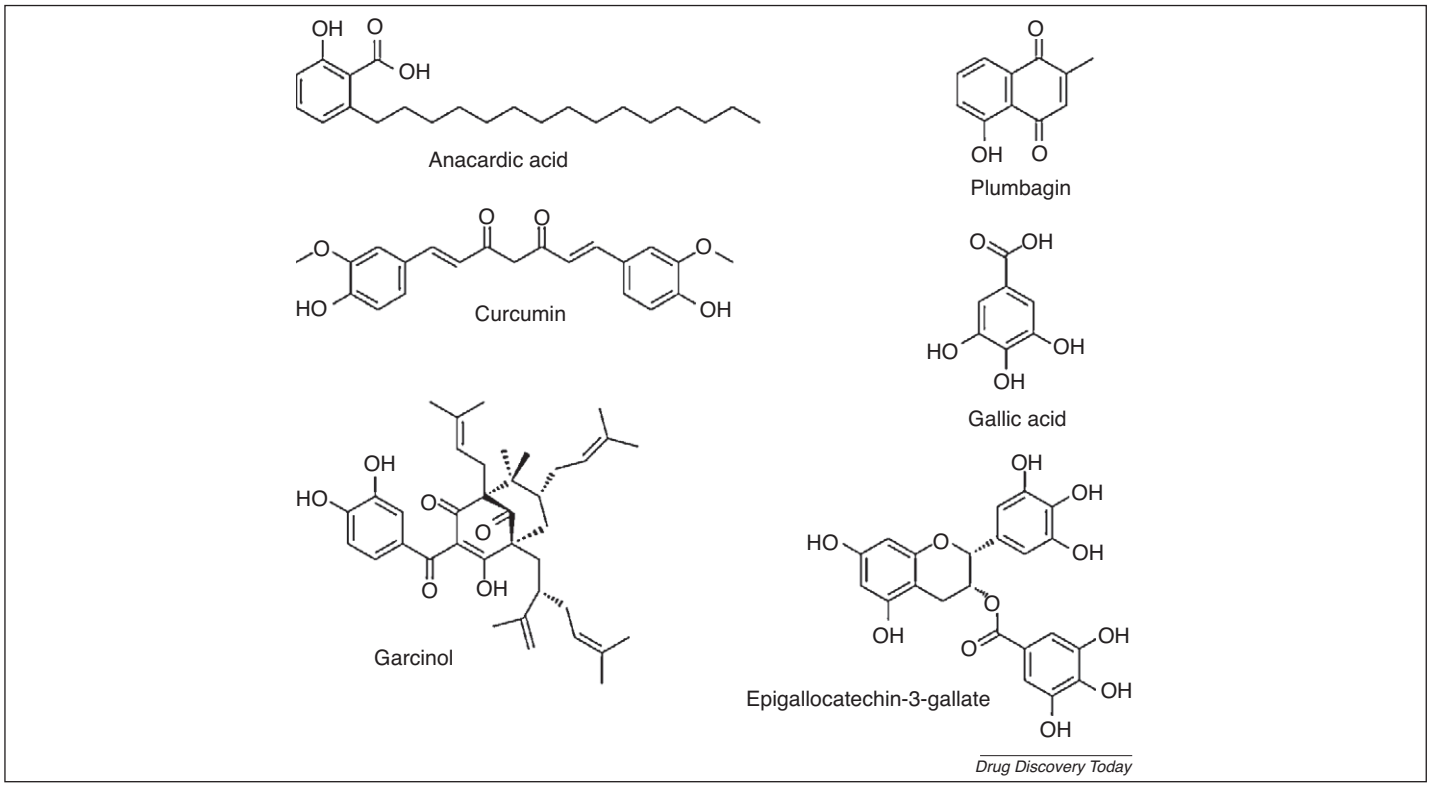

FIGURE 3

Natural product inhibitors of histone acetyltransferases.

for acetylation of many proteins that are involved in the NF-κB pathway. The commonly observed hyperacetylation in inflammation demonstrates that small-molecule inhibitors of HATs have potential to suppress inflammation. In addition, HAT inhibitors are valuable tools in pharmacological studies on inflammation. The number of HAT inhibitors has been constantly growing in recent years; however, their selectivity and potency is still limited. The development of novel HAT inhibitors with improved potency and selectivity is therefore urgently required to develop these compounds as anti-inflammatory drugs.

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