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REVIEW

Roles of CREB-binding protein (CBP)/p300 in respiratory epithelium tumorigenesis

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CREB-binding protein (CBP) and its homologue p300 are transcriptional co-activators of various sequence-specific transcription factors that are involved in a wide array of cellular activities, such as DNA repair, cell growth, differentiation and apoptosis. Several studies have suggested that CBP and p300 might be considered as tumour suppressors, with their prominent role being the cross-coupling of distinct gene expression patterns in response to various stimuli. They exert their actions mainly via acetylation of histones and other regulatory proteins (e.g. p53). A major paradox in CBP/p300 function is that they seem capable of contributing to various opposed cellular processes. Respiratory epithelium tumorigenesis represents a complex process of multi-step accumulations of a gamut of genetic and epigenetic aberrations. Transcription modulation through the alternate formation of activating and repressive complexes is the ultimate converging point of these derangements, and CBP/p300 represents key participants in this interplay. Thus, illumination of their molecular actions and interactions could reveal new potential targets for pharmacological interventions in respiratory epithelium carcinogenesis.

***Keywords*:** CBP, p300, lung cancer, acetylation, transcription factor

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Introduction

cAMP response element-binding protein-binding protein (CBP) and p300 were originally identified as factors binding to the cAMP response element-binding protein (CREB) and the adenoviral E1A, respectively [1, 2]. The human *CBP* locus resides in the chromosomal region 16p13.3 and shows homology to 22q13, where p300 is located [3]. CBP/p300 proteins share several conserved regions, which constitute most of their known functional domains (Figure 1). CBP and p300 have interchangeable roles during embryonic development and in many processes govern cellular homeostasis [4, 5]. However, genetic and molecular evidence suggests that they also fulfil distinct functions [3]. Homozygous CBP–/– and p300–/– knockout mice were inviable due to severe developmental defects, albeit abnormal heart formation was noted only in p300–/– mice, thus suggesting that both proteins are necessary during embryogenesis with overlapping and unique functions [6]. Consistently, double heterozygous CBP+/– and p300+/– knockout mice are also embryonic lethal. However, only CBP+/– mice display features of Rubinstein-Taybi syndrome (RTS) [6, 7], while a more severe and penetrant RTS-like phenotype was found in mice in which one CBP allele was modified to express a truncated CBP protein [7].

Apart from other structurally defined regions, CBP/p300 have specific areas for interaction with a wide array of transcription factors and co-factors (Figure 1). The plethora of these interacting proteins indicates the unique involvement of CBP/p300 in transcriptional control as ubiquitous and versatile co-integrators. Many of the protein interactions with CBP/p300 are regulated by upstream signals. For example, phosphorylation of the transcription factor CREB modulates its interaction with CBP, while hormones can induce the binding of CBP/p300 to nuclear receptors [8]. Notably, in some cases CBP/p300 can stimulate diverse

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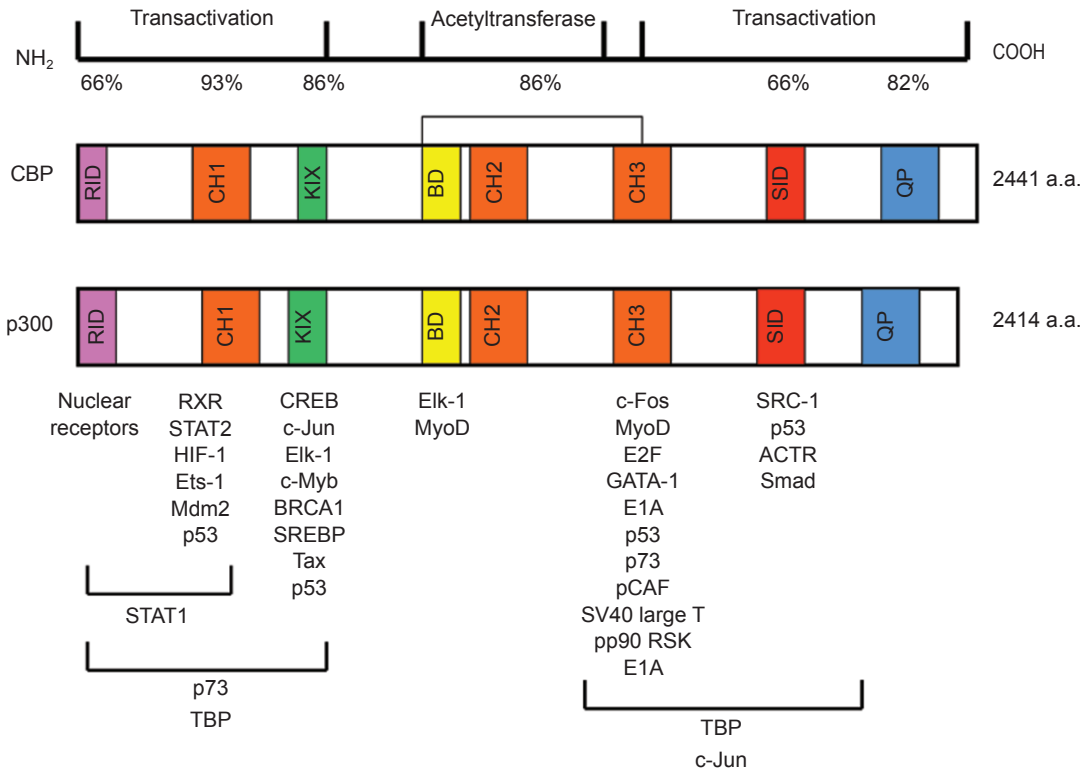

Figure 1 Schematic representation of CBP and p300 homologous regions and functional domains along with a selected list of proteins that bind to specific sites of CBP/p300. BD, bromodomain; CH1-3, cysteine and histidine-rich regions 1-3; KIX, binding site of CREB; QP, glutamine- and proline-rich domain; RID, receptor-interacting domain; SID, steroid receptor co-activator-1 interaction domain.

functions of certain transcriptional regulatory proteins [4, 5]. Nevertheless, the most intriguing feature of CBP/p300 is their stoichiometric function *in vivo* and their intrinsic enzymatic activities.

The importance of CBP/p300 is underscored by the fact that genetic alterations as well as their functional dysregulation are strongly linked to human diseases. Germline mutations of *CBP* were first reported in RTS, an autosomal-dominant disease characterised by mental retardation, skeletal abnormalities and a high malignancy risk, albeit such defects have not been associated with p300 so far [9, 10]. Nonetheless, mutations of the *p300* gene have been detected in human epithelial tumours, which is consistent with the general notion that p300 might possess tumour-suppressor activity [11, 12]. Although the tumour-suppressor function of CBP is still unclear, its involvement in chromosomal translocations associated with haematologic malignancies has been well-documented [13]. The critical involvement of CBP/p300 proteins in a variety of key molecular pathways provides the mechanistic rationale of their implication in respiratory epithelium tumorigenesis.

CBP/p300 transcriptional activity

The multifaceted role of CBP/p300 in transcription can be achieved by various mechanisms (Figure 2). CBP/p300 are thought to serve as a physical "bridge" between diverse gene-specific transcription factors (GSTFs) and components of the basal transcriptional machinery (BTM; e.g. TATA box-binding protein, TFIIB, TFIIE, TFIIF) thereby stabilising the transcription complex [4]. CBP/p300 might also act as a scaffold for the formation of multi-component complexes containing transcription factors and co-factors. A classical example of complex assembly involving multiple transcription factors and co-factors is the β-*interferon* gene promoter in response to viral infections [14]. The large size of CBP/p300 endows them with many different interaction surfaces, thus enabling them to bind concurrently to various proteins. By providing a platform for the assembly of transcription regulatory proteins, CBP/p300 might increase the relative concentration of these factors in the local transcriptional environment (Figure 2). Accordingly, cells can cooperatively utilise its repertoire

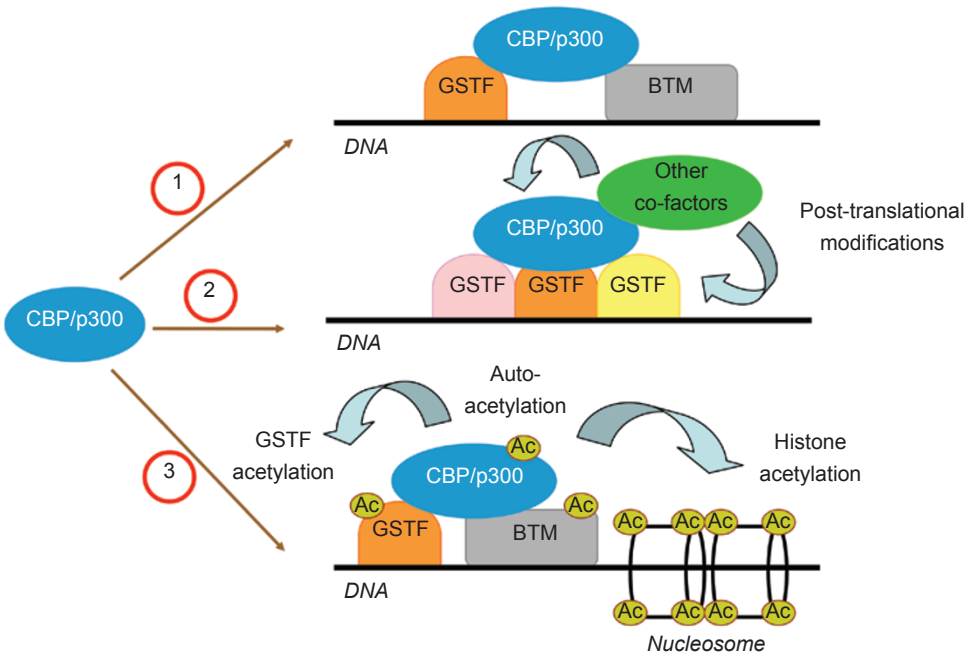

Figure 2 CBP/p300 participate in transcriptional control through various mechanisms. (1) "Bridging" GSTFs with the BTM. (2) Contributing to the formation of multi-protein complexes and directly and/or indirectly modulating the activation status of GSTFs through post-translational modifications. (3) Exhibiting acetyl-transferase activity on nucleosomes and certain GSTFs. Ac, acetyl group.

of proteins, so that the combinations of a few ubiquitous factors, and signal- and tissue-specific modulators, could create a broad spectrum of regulatory complexes.

Post-translational chromatin modifications modulate the activity of many genes by modifying both the core histones and non-histone transcription factors [15]. Acetylation of multiple sites in the histone tails has been directly associated with transcriptional upregulation, while de-acetylation correlates with transcriptional repression. Mechanistically, histone acetylation promotes the accessibility of DNA to transcription protein complexes, by facilitating the "unwiring" of the chromatin structure [16]. CBP/p300 can interact with chromatin nucleosomes via nucleosome assembly proteins, histone-binding proteins and possibly histones themselves [17, 18]. In addition to histones, CBP/p300 also modulate a variety of other proteins by acetylation [19, 20]. In most instances, acetylation of transcription factors has been shown to enhance their DNA-binding activity (e.g. p53, p73, retinoblastoma (Rb), E2F, Sp3, signal transducers and activators of transcription) [11, 21], although it seems plausible that acetylation also regulates protein-protein interactions, protein-DNA recognition [19], as well as nuclear transport and structure [22, 23]. Acetylation of components of the BTM (e.g. TFIIE, TFIIF) has been found to enhance DNA-binding activity and gene transcription [24]. Moreover, CBP/p300 can bind additional co-factors that possess acetyl-transferase activity (e.g. p300/CBP-associated factor (p/CAF)) [25], and also recruit proteins bearing other chromatin-modifying enzymatic activities (e.g. histone methyltransferases) [26].

The ability of so many proteins to interact with CBP/p300 suggests that competition for the rather limited intracellular pool of CBP/p300 might account for the observation that unrelated transcription factors inhibit each other without direct interference [27, 28]. In this vein, sequestration of CBP/p300 by the adenoviral protein E1A [29], human papilloma virus protein E6 [30] and other viral proteins [3] is probably a means by which oncogenic viruses suppress many cellular transcription factors, and thereby may contribute to cellular transformation.

Given the multiple activities of CBP/p300, it is of paramount importance to enlighten their own regulatory principles. CBP/p300 are thought to be modulated by phosphorylation via cyclin/cyclin-dependent kinase (Cdk) complexes in G_1/S [31], whereas various kinases, such as protein kinase A, protein kinase C, phosphatidylinositol-3 kinase/AKT and mitogen-activated protein kinases (MAPK), have been shown to phosphorylate CBP *in vitro*

[19, 32]. Furthermore, CBP/p300 are also targets of other post-translational modifications, such as methylation [33] and sumoylation [34]. Recent data have indicated the existence of an auto-regulatory loop, whereby the acetyl-transferase activity of p300 is considered to be intrinsically weak [35], and its auto-acetylation, or possibly acetylation via other proteins, might stimulate its acetyl-transferase activity [35]. De-acetylases (e.g. histone deacetylase 1 (HDAC1)) or other proteins (e.g. p53) could associate with p300 to keep it in a catalytically inactive state [36, 37]. On the other hand, it has been shown that p300 can also inactivate HDAC1 via acetylation. Thus, two positive feedback loops (activation through auto-acetylation and inhibition of an inhibitor) ensure maximal p300 activity. A recent study has suggested that p300 auto-acetylation serves as a switch to regulate its arrival and departure during pre-initiation complex assembly [38]. In addition, there is evidence that p300 also functions in elongation [39]. Therefore, the activity of CBP and/or p300 and their capacity to bind with certain transcriptional regulatory proteins are subjected to regulation by diverse mechanisms, hence contributing to transcriptional specificity and plasticity.

Implication of CBP/p300 in respiratory epithelium tumorigenesis

Most of the described tumour-related mutations in CBP/p300 result in truncation of the p300 protein. In majority of the cases, the second allele was inactivated through deletion (loss of heterozygosity (LOH)), silencing (hemizygosity) or a different mutation (compound heterozygosity). These findings have qualified p300 as a classical tumour-suppressor gene, but with a low detected mutation rate in cell lines [40]. It is currently less clear whether CBP should also be classified as a tumour-suppressor gene. However, the high prevalence of malignant tumours among RTS patients along with the fact that both CBP and p300 proteins are targets of transforming viruses suggest that disruption of CBP function contributes to carcinogenesis [11]. In lung cancer, LOH has been frequently detected in diverse chromosomal regions, albeit relatively few targeted tumour suppressor genes (including *p53*, *Rb*, *p16* and *FHIT*) have been identified [41]. Recently, it was shown that the *CBP* gene is genetically altered in almost 15% of lung cancer cell lines and 5% of primary lung tumours [42]. Thus, point mutations and homozygous deletions of the *CBP* gene might be involved in the pathogenesis of a subset of lung carcinomas (Figure 3). Interestingly enough, these *CBP* mutations are not clustered in the catalytic (acetyl-transferase) region but are dispersed throughout the entire gene, indicating that the biological effects of such mutations are diverse [42]. Another important aspect is the observed

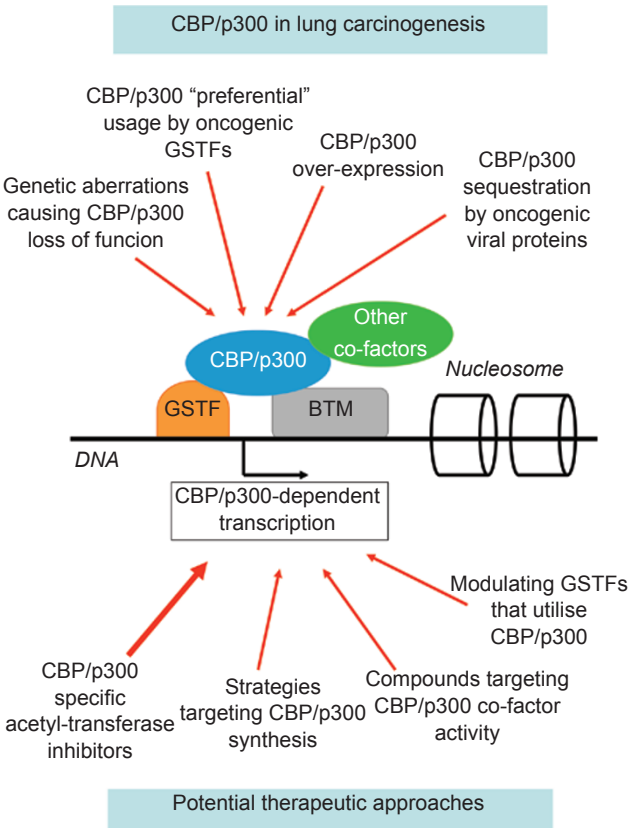

Figure 3 CBP/p300 may contribute to respiratory epithelium carcinogenesis via multiple routes. Potential strategies for therapeutic interventions are indicated (currently tested regimens mostly target CBP/p300 acetyl-transferase activity; thicker arrow). BTM, basal transcriptional machinery; GSTF, gene-specific transcription factor.

coexistence of CBP and p53 mutations, which suggests that *CBP* gene alterations might contribute to lung carcinogenesis by distorting pathways other than those engaging p53. Regarding p300, somatic mutations have been identified in several types of cancers [43], but their prevalence in lung cancer is unknown. The notion that CBP and p300 might play different roles in diseases such as lung tumorigenesis is supported by the observation that reintroduction of p300 but not CBP was able to suppress the growth of p300-deficient carcinoma cells [44].

Since mutations in CBP/p300 are relatively uncommon, CBP/p300 might contribute to lung carcinogenesis through alternative mechanisms (Figure 3). The cell-cycle apparatus acts as a dominant controller "supervising" the cell fate, and its deregulation represents an imperative step during malignant transformation. CBP/p300 are shown to associate

with the cyclin E/Cdk2 complex [45]. Although the precise role of CBP/p300 in regulating cell proliferation remains elusive, existing evidence suggests that they are negative modulators of the cell cycle. The fact that these proteins are targets of viral oncoproteins also suggests their importance in cell-cycle regulation, such as the control of DNA synthesis and S-phase progression [46]. For example, it has been shown that the p300/CBP-p/CAF protein complex can arrest cell cycle and might regulate target genes that are involved in the control of the G_1/S transition, such as *p21* [46]. *In vitro* models have also suggested that sequestration of CBP/p300 by viral oncoproteins has the general effect of modulating transcription through affecting transcription factors that normally utilise these co-activators [46], while the recently recognised link between CBP/p300 and the anaphase-promoting complex/cyclosomeE3 ubiquitin ligase has provided new insights into the roles of these proteins in the control of both cell cycle and transcription [45].

CBP/p300 are cardinal transcriptional co-regulators responsible for the proper function of a gamut of signalling cascades. To this end, the growth-suppressing effect of CBP/p300 might be well explained by their ability to augment p53-mediated transcription [47]. The *p53* tumour suppressor gene is the most commonly mutated gene in human cancers and is frequently found to be dysregulated in lung pre-malignant and malignant lesions [48]. A major function of p53 is to activate genes engaged in the response to DNA damage, such as *murine double minute 2* (*mdm2*), *p21*, *cyclin D1* and *Bax* [47]. Following DNA damage, p53 is activated by kinase-mediated phosphorylation as well as by acetylation at specific residues by CBP/p300 [49], resulting in increased stability of the p53-CBP/p300-DNA complex. Furthermore, CBP/p300 is required for p53-mediated transactivation of target genes through their co-activator function and through local histone acetylation [50]. It has also been suggested that the association of p53 with CBP/p300 might account for p53-mediated negative regulation of genes whose promoters lack a suitable p53 binding site [51]. Interestingly, CBP/p300 also contribute to controlling p53 stability by regulating its ubiquitination and degradation, through both Mdm2-dependent and Mdm2-independent mechanisms. Degradation of p53 is known to be mediated by a ternary complex comprising p53, Mdm2 and CBP/p300 [52]. Recently, the CH1 domain of CBP/p300 was found to display ubiquitin ligase activity towards p53, and therefore, CBP/p300 could also play a direct role in p53 degradation [53].

The E2F family of transcription factors play a pivotal role in regulating cell cycle progression and apoptosis [54]. In mammals, the E2F family has six different members. The best-characterised member is E2F-1 and its over-expression has been shown to be strongly associated with lung carcinogenesis [55]. The ability of E2F-1 to stimulate transcription appears to be subjected to multiple regulations including co-activation by CBP/p300 and reversal of Rb-mediated repression through Rb phosphorylation [55]. At a molecular level, the Cdk-stimulated interaction of CBP/p300 with E2F-1 may be involved in irreversibly committing cells to cell-cycle progression [56]. Interestingly, although E2F-1 has been shown to be acetylated *in vitro* by both p/CAF and CBP/p300 at the same lysine residues, a specific role for p/CAF in acetylation-induced stabilisation of E2F-1 in response to DNA damage was recently reported [57].

One of the major tasks of CBP/p300 is the cross-coupling of distinct gene-expression programs in response to various stimuli [28]. However, CBP/p300 levels *in vivo* are considered stoichiometric and apparently cannot simultaneously support its various functional activities. Thus, CBP/p300 over-expression or their preferential usage by certain "hyperactive" transcription factors, or a combination of both, could contribute to unopposed cellular proliferation as well as apoptosis inhibition during lung carcinogenesis. Recently, CBP over-expression at the very early stages of respiratory epithelium carcinogenesis has been documented [28]. This observation has led to a "step-wise" model in which CBP over-expression accompanied by upregulation of members of the activator protein-1 (AP-1) family and a gradual downregulation of the retinoid acid receptor β might favour lung tumour progression and proliferation [58].

This model is in accordance with clinical observations that have identified cyclin D1 over-expression, which is AP-1 dependent, as a frequent event in human lung tumours [59]. Intriguingly, recent studies have demonstrated that cyclin D1 could control transcription factor activity by directly interacting with and repressing the transactivation capacity of p300 [60]. Nevertheless, the mechanisms by which cyclin D1 regulates a variety of cellular functions are not fully understood. Another gene that merits discussion in consideration of lung carcinogenesis is cyclooxygenase-2 (COX-2). It has been shown that growth factor-induced COX-2 transcription is mediated through the Ras-MAPK signalling pathway and through subsequent activation of AP-1 [61]. COX-2 is an inducible enzyme during carcinogenesis, and many experimental and clinicopathological studies have revealed that COX-2 over-expression is associated with respiratory epithelium tumorigenesis through proliferation enhancement, apoptosis inhibition and triggering of angiogenesis [62]. In this respect, it is important to note that CBP/p300 are the predominant co-activators in COX-2 transcriptional activation [63].

Collectively, the accumulating evidence indicates that CBP/p300 function as general co-regulators of a variety

of transcription factors that could have either tumour-suppressing or tumour-enhancing properties. The abundance of CBP/p300 and the specific interaction mode between CBP/p300 and these various factors as dictated by the specific cell type and cellular context are likely of critical importance in determining how CBP/p300 might modulate cell physiology/pathology and regulate disease pathogenesis such as lung carcinogenesis.

The potential of modulating CBP/p300 in lung cancer therapeutics

In theory, CBP/p300-mediated signal propagation during respiratory epithelium tumorigenesis could be modulated by diverse strategies (Figure 3). For instance, in the case when their over-expression constitutes the problem, antisense oligodeoxynucleotides and RNA interference approaches could be used to reduce their production [64, 65]. Targeting protein-protein interfaces has emerged as a promising anticancer approach, although many theoretical caveats have to be tackled [66]. Moreover, new technologies have recently emerged to selectively block the function of critical transcription factors (e.g. structure-based rational design of decoy oligonucleotides) [67].

Being one of the key enzymes involved in post-translational modifications, the acetyl-transferases CBP/p300 hold crucial roles in the causal relationship between dysfunction of the acetylation/deacetylation equilibrium and respiratory epithelium carcinogenesis. During the last decade, a number of HDAC inhibitors have been identified that induce apoptosis in cultured tumour cells and have entered clinical testing [68]. Pharmacologic inhibition of HDACs might restore the distorted epigenetic network and have therapeutic effect throughout the carcinogenesis process. A proof of principle of this assumption was the recent approval of the HDAC inhibitor suberoylanilide hydroxamic acid for patients with progressive, persistent or recurrent forms of cutaneous T-cell lymphoma [68].

Although substantial progress has been made in the study of HDAC inhibitors, very little has been achieved in the area of acetyl-transferase inhibitors. Long before, polyamine-CoA conjugates were found to inhibit the acetyl-transferase activity of cell extracts [69]. Availability of recombinant acetyl-transferases (p300 and p/CAF) rendered it possible to synthesise and test more targeted and specific inhibitors, Lys-CoA for p300 and H3-CoA for p/CAF [70]. The major problem with these compounds was their lack of cellular permeability. In an effort to overcome this limitation, truncated derivatives were designed, synthesised and assessed as p300 inhibitors, with, however, disappointing results [71]. Two substituted derivatives that show about four-fold increased potency compared to the parental compound Lys-CoA have recently been identified and are currently being evaluated [72].

High-throughput screening of random chemical libraries for specific inhibitors of CBP/p300 acetyl-transferase activity is another way of identifying compounds that could then be further modified by medicinal chemistry methodologies to develop drugs suitable for clinical application. Recently, the first naturally occurring acetyl-transferase inhibitor, anacardic acid, was found. This substance inhibits very effectively, in a non-competitive manner, the activity of both p300 and p/CAF [73], and it has been also shown to increase *in vitro* the sensitivity of tumours to radiation therapy [74]. By using this molecule as a synthon, a synthetic amine derivative of anacardic acid (CTPB) has been generated [75]. However, again cells were impermeable or poorly permeable to both anacardic acid and CTPB. Nevertheless, these and other natural products might offer valuable "probes" for identifying potential clinically effective remedies. For example, curcumin was recently shown to exert a specific inhibitory activity towards CBP/p300 [76]. The first cell permeable acetyl-transferase inhibitor has also been reported. It is garcinol, a polyisoprenylated benzophenone derivative of *Garcinia indica* fruit rind, and has demonstrated potent inhibitory activity towards histone acetyl-transferases (HATs) both *in vitro* and *in vivo* [77]. In addition, a series of isothiazolone-based acetyl-transferase interfering agents were recently reported as being potential small-molecular-mass inhibitors for acetyl-transferases [78].

Conclusion

Developing an integrated picture of the role of CBP/p300 in lung carcinogenesis is a challenging task that awaits further exploration. CBP/p300 are considered multi-functional transcriptional co-activators participating in a broad spectrum of intracellular processes under normal and pathologic conditions. However, many questions remain unanswered. Further genetic and functional studies of CBP/p300 would aid at unravelling their prominent activities, thus generating new options for intervention during the formation of lung tumours.

Acetylation is a feature of active genes and its inhibition *in vivo* would repress majority of the genes, including those that are aberrantly expressed. Therefore, a systematic investigation of the effect of compounds targeting acetyl-transferase activity on normal and cancerous cell lines is a prerequisite to define their potential utility in lung cancer therapeutics. Further modifications of these compounds in conjunction with continued research for new molecules could lead to the development of potential novel agents targeting acetyl-transferases. Since acetylation and other

post-translational modifications (e.g. methylation, phosphorylation) are highly co-regulated and functionally interdependent, the effect of acetyl-transferase modulators should also be evaluated in this vein. The resulting information could be very useful to design combinatorial therapeutics targeting both HATs and other important enzymatic activities.

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