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Preview

Selective Inhibition of CBP/p300 HAT

Vasiliki Sarli[1,*] and Athanassios Giannis[1,*]
[1] Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
*Correspondence: sarli@uni-leipzig.de (V.S.), giannis@uni-leipzig.de (A.G.)
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In this issue of *Chemistry & Biology*, Mantelingu and colleagues present the development of the garcinol derivative LTK-14, which is a specific and nontoxic inhibitor of histone acetyltransferase p300-HAT [1]. Interestingly, it blocks histone acetylation of HIV-infected cells resulting in inhibition of the multiplication of HIV in these cells.

In 1963 Jack H. Rubinstein and Hooshang Taybi described a childhood disease characterized by typical facial abnormalities, broad thumbs, broad big toes, growth and mental retardation, and an increased risk of neoplasia [2]. The molecular basis of the Rubinstein-Taybi Syndrome was later discovered to be disruption of one copy of the human CREB binding protein (CBP or CREBBP) gene that encodes the histone acetyltransferase CBP [3]. In addition to CBP, all mammals have a closely related factor, p300. In general, CBP and p300 are distinct but closely related proteins, which share extensive homology and perform not only overlapping but also unique functions [4]. Both CBP and p300 are able to acetylate specific lysine residues of histones H2A, H2B, H3, and H4, as well as nonhistone proteins, like p53. Through their acetyltransferase activity, as well as through their ability to interact with a large number of nuclear proteins, they are involved in a plethora of biological processes like transcription, differentiation, transformation, apoptosis, and embryonic development. For example, they participate in various tumor-suppressor pathways (i.e., wnt, p53) and they are also necessary for the actions of many cellular and viral oncogenes (i.e., *c-jun*, *c-fos*, *c-myb*, *v-myb*) [5]. Several viruses encode proteins such as the adenoviral E1A, the HTLV-1 Tax, and the simian virus 40 large T protein to specifically target CBP/p300 and to cause a loss of cell growth and enhance DNA synthesis. There is also evidence that the demand for CBP/p300 is greater than the supply, and the competition for these enzymes plays an important role in cell growth regulation [6]. In some instances, CBP and p300 can contribute to opposing cellular processes [5].

In eukaryotic cells, DNA is organized in a highly complex structure, chromatin, by both histone and nonhistone proteins. Acetylation of specific lysine residues in these proteins is a well-known posttranslational modification, which regulates chromatin structure and assembly, and trancription of many genes. Two classes of enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs), keep the balance of specific acetylation levels for proper cellular function. Dysregulation of either of these enzymes may lead to different diseases including cancer, diabetes, and AIDS. HATs are a diverse set of enzymes that are grouped into different family classes based on their catalytic domains. These include the GNAT, MYST, and the p300/CBP families [7]. In order to get insights into these CBP/p300-mediated biological effects cell-permeable small molecules acting as specific CBP/p300 inhibitors are necessary. These molecules can be also regarded as valuable tools in the area of epigenetics, as well as anticancer and antiviral drug candidates.

In this issue of *Chemistry & Biology*, Mantelingu and colleagues report on the development of the garcinol derivative LTK-14 (Figure 1), a specific inhibitor of p300-HAT. Contrary to the parent compound garcinol, LTK-14 was found to be nontoxic to T cells. Interestingly it inhibits histone acetylation of HIV infected cells resulting in inhibition of the multiplication of HIV in these cells. The SAR studies performed by the authors showed that the reason for the low toxicity of LTK-14 is the introduction of a methyl group at the aromatic moiety of garcinol. It is known that 1,2-dihydroxybenzene derivatives (catechols) are metabolized to afford the corresponding highly reactive ortho-quinones which display cell toxicity due to their ability to react with DNA affording depurinated adducts [8]. By alkylation of one of the two phenolic groups in garcinol an oxidation to ortho-quinones is no longer possible resulting in the observed lower toxicity. Furthermore, by introduction of a cyclization at the southeast part of garcinol, specificity was established: LTK-14 is an inhibitor of p300 and is inactive against PCAF, a member of the GNAT family.

The observation of the cytostatic and anti-HIV activity of phloglucinol derivatives is not new. Previously, a series of polyprenylated benzophenones (i.e., compounds **2** and **3**, Figure 1) from *Garcinia*, *Clusia*, and *Symphonia* species from the large plant family Guttiferae were reported to exhibit cancer chemopreventing and anti-HIV activities [9, 10].

Recently, Balasubramanyam and colleagues were able to shed light on the mechanism of the action of these naturally occurring compounds [11]. They identified garcinol to be a histone acetyltransferase inhibitor which represses chromatin transcription. They reported that garcinol inhibits histone acetyltransferases p300 with an IC_{50} =7 μM and PCAF with an IC_{50} =5 μM.

In light of this evidence, Mantelingu and colleagues developed derivative LTK-14 for investigation of the role of CBP/p300 protein in global gene expression [1]. Microarray analysis

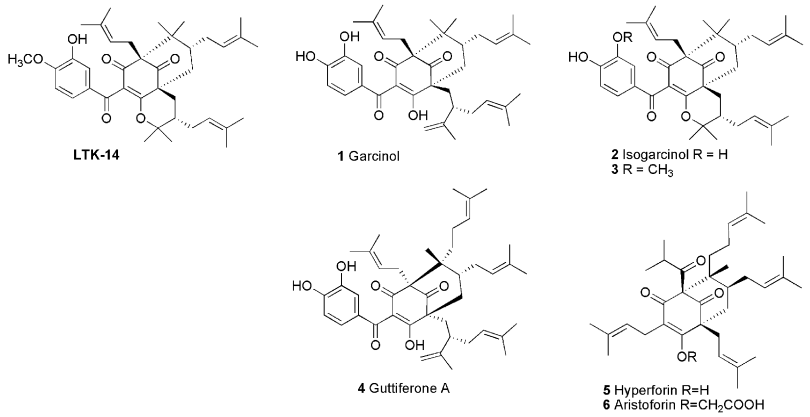

Figure 1. Structures of Phloroglucinol Derivatives

showed that inhibition of p300-mediated acetylation by LTK-14 downregulates 118 genes and upregulates 6 genes. Furthermore, they showed that derivative LTK-14 inhibited HIV replication in SupT1 cells. How can this be explained? Upon infection of susceptible cells, the RNA genome of the human immunodeficiency virus type 1 (HIV-1) is reverse transcribed into double-stranded DNA by the enzyme HIV-1 reverse transcriptase (HIV-1 RT), which is then inserted and integrated into the host genome by the HIV-1 integrase (HIV-1 IN). It has been showed that p300 acetylates three lysines in the carboxy terminus of IN, which is important for DNA binding. This modification increases IN affinity to DNA and also its enzymatic activity. After integration, the viral long term repeat (LTR) promoter is almost silent when integrated into the cellular genome. Histone acetylation at the LTR promoter plays an important role in the activation of HIV transcription. Activation of LTR requires the virally encoded transactivator of transcription (Tat), which induces the association of p300 and the CBP with the LTR promoter [12].

LTK-14 will be a valuable tool to study histone and nonhistone protein acetylation, as well as an experimental anti-HIV agent. However several important and critical caveats remain. How specific are these garcinol derivatives? In the light of the very recent discovery that similar phloglucinols like Hyperforin and Aristoforin (Figure 1) are potent inhibitors of Sirtuins SIRT1 and SIRT2 [13], it is necessary to investigate if LTK-14 has similar properties. Furthermore, due to the fact that CBP/p300 is involved in tumor suppression (for example inhibition of wnt pathway) and the observation that patients with Rubinstein-Taybi Syndrome have a higher incidence of hematologic malignancies it is rather unlikely that LTK-14 will find application in cancer therapy. A possible neurotoxicity of CBP/p300 inhibitors should be also taken into consideration. It is known that loss of function of CBP protein underlies several neurological disorders [14]. Finally, in a recent study, the mechanism of hepatoxicity of the antihypertensive drug todralazine was investigated. After long-term administration this drug is known to cause liver failure [15]. It was shown that histone acetylation was significantly impaired in patients treated with this drug. In vitro experiments showed that todralazine and analogs inhibit histone acetylation in a dose-dependent manner.

Despite these facts it is important to emphasize that LTK-14 is an interesting tool in the area of epigenetics [16] and may also find application in experimental antiviral therapy and in the study of processes like cancer, ageing, neurodegenerative diseases, obesity, and diabetes. In the light of other recent discoveries that similar naturally occurring phloroglucinols are able to modulate the acetylation status of histone and nonhistone proteins [13], it will be interesting to investigate the ability of other members of the phloroglucinol class of natural products to influence the activity of histone-modifying enzymes [17].

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