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Life and death of transcriptional co-activator p300

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Transcriptional co-activator p300, which contains an intrinsic histone acetyltransferase activity, is required for an array of important cellular processes. Tight control of p300 function is critical to ensure precise histone acetylation and gene activation. Dysregulation of p300 has been implicated in many types of diseases and numerous studies have examined the functional requirement of p300 to act as a co-activator or as an acetyltransferase for other transcription regulators. Few, however, have tackled how p300 itself is regulated and if post-translational modification and spatial distribution are means of p300 regulation. In this article, we present a current view on the molecular mechanisms by which the activity and stability of p300 is regulated.

Introduction

Transcriptional co-activator p300 was first identified as an E1A binding protein due to its involvement in E1A function, particularly during cell cycle progression and cellular differentiation.[1-3] It serves not only as a histone acetyltransferase (HAT), but also as a factor acetyltransferase (FAT) for many transcription regulators through a hit-and-run mechanism.[4-11] Besides having an acetyltransferase domain, p300 also contains several conserved functional domains through which it interacts with other cellular proteins (**Fig. 1**).[12-15] Thus, the basic functional mode of p300 is to serve as a HAT or a FAT, and to act as a scaffold or bridge for transcription factors and other components of the basal transcription machinery to facilitate chromatin remodeling and to activate gene transcription (**Fig. 2**).[16,17] Transcriptional co-activator CBP, which was initially identified as a CREB binding protein and later found to be also an acetyltransferase,[18-22] may be regulated similarly to p300 given their structural and functional similarities.

Regulation of p300 by Acetylation

The list of proteins that can be acetylated by p300 is long and includes p300 itself. The autoacetylation of p300 was first observed in acetylation assays using purified cell free systems.[4,5,23] Detailed kinetic studies with multiple molecular approaches have later determined that p300 autoacetylation is predominantly achieved in an intermolecular manner.[24,25] To date, a total of 17 different autoacetylation sites have been identified in p300 HAT domain,[11,24,25] four of which have been validated in the endogenous p300 by mass spectrometry in a proteomics survey.[26]

Careful kinetic analyses have also provided significant insights into the molecular mechanisms by which the HAT activity of p300 is regulated. Many of the acetylated lysine residues are clustered in p300 HAT domain, which is sensitive to proteases, and the catalytic activity of p300 is stimulated by autoacetylation of some of these lysine residues.[25] Autoacetylation of these lysine residues appears to act as a reversible switch to control the HAT activity and, consequently, the potential of p300 to act as a transcriptional co-activator.[27-29] However, p300 harbors hundreds of lysine residues and about half of them are located in functional domains other than HAT. The extent of autoacetylation of the full length p300 and the influence of the cellular milieau are not known. In addition, it is still unclear if other cellular acetyltransferases can also acetylate p300 and play a role in the regulation of the catalytic activity of p300.

Regulation of p300 by Phosphorylation

Phosphorylation of p300 occurs abundantly during cell proliferation and differentiation.[30-33] Cyclin-dependent kinases are directly or indirectly involved in the regulation of p300 and CBP during cell cycle progression.[34-36] Site specific serine-threonine phosphorylation have been identified in p300 and coupled to the potential of p300 to act as a transcriptional co-activator in modulating target gene expression.[32,37-41] In addition, p300 phosphorylation is also functionally linked to DNA damage response.[42]

Akt/protein kinase B (PKB) is a critical factor of cell proliferation and survival, and the function of Akt is mediated through substrate phosphorylation at a consensus motif.[43,44] Transcriptional co-activator p300, which contains such an optimal motif at the C-terminal region, interacts with Akt and is a bona fide substrate for phosphorylation by Akt at this optimal motif.[45-49] The phosphorylation of p300 by Akt augments p300 HAT activity and induces the recruitment of p300 to its target promoters, leading to histone acetylation and transcriptional activation.[48,49] More importantly, Akt also contributes to p300 transcriptional activity by increasing the metabolic stability of p300, or maintaining the critical concentration of endogenous

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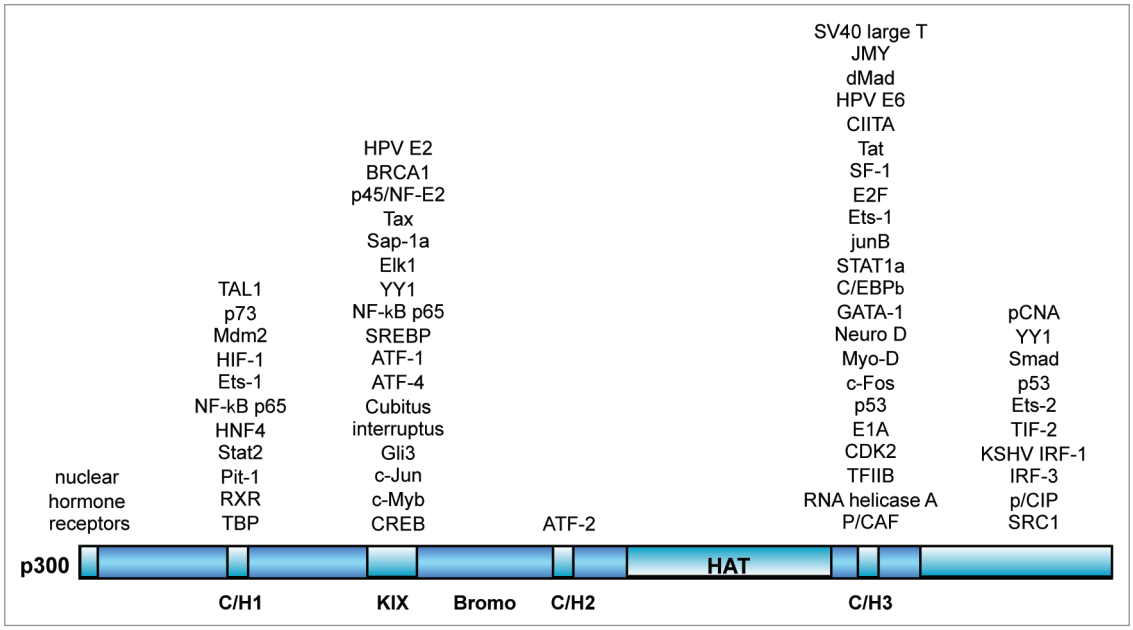

Figure 1. Listed are the examples of transcription factors, activators and co-activators associated with different functional domains of transcriptional co-activator p300. Indicated are the cysteine and histidine motif (C/H), the CREB-binding domain (KIX), the bromodomain (Bromo) and the histone acetyltransferase domain (HAT).

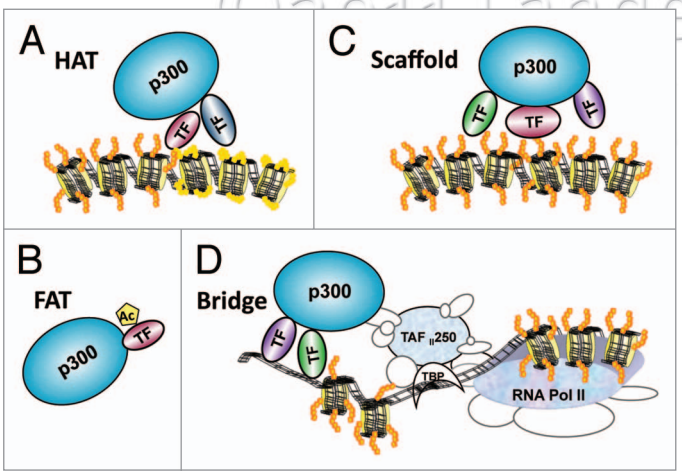

Figure 2. Transcriptional co-activator p300 regulates gene transcription by acting as: (A) a histone acetyltransferase (HAT); (B) a transcription factor acetyltransferase (FAT); (C) a scaffold for different transcription factors on chromatin; (D) a bridge to connect the transcription factors and the basal transcriptional machinery to activate gene transcription.

p300 protein in different cell systems.[47,50] Thus, Akt is also a critical regulator of p300 turnover.

Regulation of p300 by the Proteasome Pathway

Many transcriptional factors and activators are regulated by the 26S proteasome, which is one of the major proteolysis systems of the cell and localizes to both the cytoplasmic and nuclear compartments. It contains a 20S core particle capped at both ends by the 19S regulatory particles, which recognize the protein targets.[51,52] Prior to degradation, target proteins are generally covalently conjugated with polyubiquitin through a series of enzymatic reactions involving the ubiquitin-activating E1 enzymes, E2 conjugases and E3 (and in some cases E4) ligases.[53,54]

The protein level of transcriptional co-activator p300 is essential for normal cellular processes such as embryonic development and cell proliferation.[55] Dysregulation of p300 has been implicated in many types of diseases. Therefore, p300 needs to be tightly regulated to maintain normal cellular processes. So far, multiple signaling pathways have been identified in the regulation of p300 turnover. Ubiquitination of p300 is associated with unphosphorylated form,[56] and the conjugation of ubiquitin occurs at specific regions such as the bromodomain region.[57] Moreover, p300 can be modified by sumoylation near the bromodomain, which correlates with transcriptional repression.[58] Similar to p300, CBP is also degraded through the ubiquitin-proteasome pathway and promyelocytic leukemia (PML) nuclear bodies appear to be the nuclear sites involved in ubiquitin-dependent degradation of CBP.[59]

Reversible phosphorylation can selectively signal protein degradation through the 26S proteasome pathway. For example, MAP kinase p38 associates with p300, phosphorylates p300 and induces proteasome-mediated p300 degradation.[60] Interestingly, Ras signaling pathway has also been implicated in selective p300 turnover.[61] Nevertheless, phosphorylation of p300 by protein kinases can also play an important role in maintaining the metabolic stability of this co-activator, such as in the case of Akt (**Fig. 3**).[47,50] Consequently, dephosphorylation of p300 by phosphatase can serve as a signal to designate the co-activator for proteolysis. For example, the B56γ3 (PPP2R5C) regulatory subunit of protein phosphatase 2A (PP2A) is a negative regulator

of p300 activity by targeting p300 degradation through the 26S proteasome pathway (**Fig. 3**).[62] Many small molecules have been shown to induce p300 degradation through the activation of different signaling transduction cascades leading to reversible phosphorylation of p300, and p300 activity is dynamically regulated by these signaling pathways.[33,50,62-64]

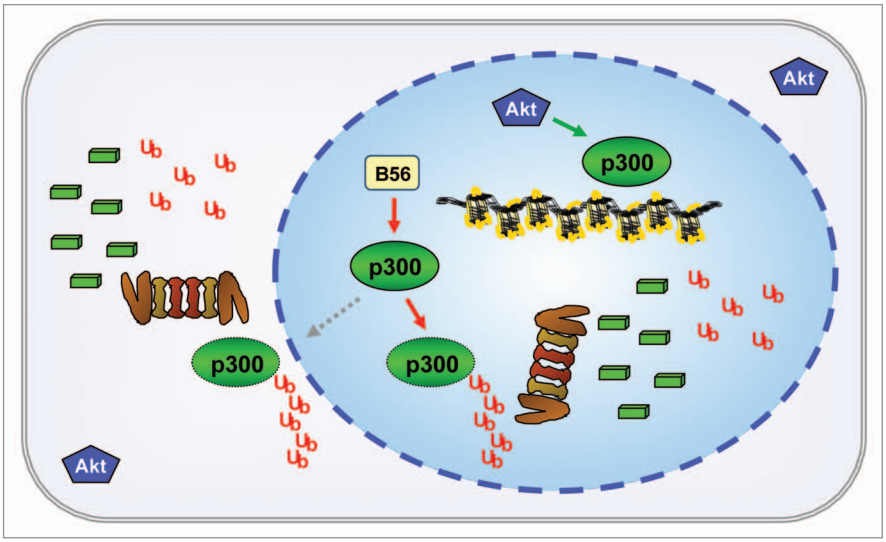

Figure 3. Nuclear Akt is important for maintaining p300 stability, suggesting a role for Akt in the regulation of gene transcription through the control of p300 activity. There is also a functional interaction between p300 and the B56 regulatory subunit of PP2A, which targets p300 degradation through the 26S proteasome in the nucleus. Additionally, p300 is a substrate of the cytoplasmic-ubiquitin proteasome pathway.

Regulation of p300 by Cellular Distribution

Tight regulation of nuclear p300 activity is critical to ensure precisely controlled histone acetylation and transcriptional activation. Nucleo-cytoplasmic shuttling has been implicated in the control of the availability and activity of this co-activator. In response to cellular stimuli, p300 distributes to the cytoplasm, which coincides with its ubiquitination and subsequent degradation (**Fig. 3**).[57] The spatial control of p300, removing it from the site of nuclear action, may be an integral mechanism to regulate the function of the co-activator in response to cellular challenge, limiting its opportunity to interact with sequence-specific transcription factors, to acetylate histones or transcription factors, and to coordinate transcriptional activation.

Aggresome can be formed as a consequence of overwhelmed proteasome system in response to toxic proteins.[65] The formation of aggresome is a cellular protective mechanism to sequester cytoplasmic protein aggregates or to deliver them for disposal through the alternative autophagosome pathway. Many nuclear proteins including p300 are substrate of aggresome and undergo cytoplasmic degradation, which is an integral part of the normal cellular regulatory process.[57] Interestingly, p300 is differentially recruited to aggresome in breast cancer and in normal cells.[66] Moreover, p300 localizes in the cytoplasm of oocytes within primordial follicles and distributes to the nucleus during different stages of oocyte growth.[67]

Besides being degraded through the aggresome system, p300 also appears to play a functional role in the cytoplasm. Particularly, it contains a cytoplasmic E4 ubiquitin ligase activity.[68-70] Thus, p300 is able to regulate p53 through multiple molecular pathways. It not only acetylates p53 and acts as its transcriptional co-activator, but also contributes to p53 ubiquitination through the intrinsic E3/E4 activities.[68-70] The function of p300 is required for endogenous p53 polyubiquitination and rapid turnover. Moreover, the intrinsic E4 ligase activity of p300 is exclusively localized to the cytoplasm.[68] This compartmentalization of p300 separates its activity as ubiquitin ligase in the cytoplasm from as acetyltransferase required for p53-mediated gene transcription in the nucleus, which resolves effectively the opposite function of p300 on p53 with respect to proteolysis and activation.

Perspectives

Increasing evidence has provided functional implications of p300 modification and metabolic stability in epigenetic regulation, and shed molecular insights into the roles of cellular trafficking and spatial distribution in gene transcription through p300 regulation. Activation of gene expression requires concerted action of sequence-specific transcription factors, co-activators and the transcription machinery at target enhancers and promoters. Direct competition for a limited amount of p300 in a particular cellular environment or rapid removal of p300 from a specific chromatin locus is essential to synchronize the activation or repression of gene sets, which often share overlapping binding sites or require the function of p300 as an integrator. The key determinants or specificities are not just residing in the transcription regulators, which recruit p300 to the loci, but also in the regulation of p300 by the cellular milieu per se. Deciphering the molecular basis for the regulation of p300 by post-translational modifications and spatial distribution will help us understand how p300 responds to signaling cascades and exerts its diverse functions.

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