How Promiscuous Transcription Activators Find the Right Fit

February 20, 2012

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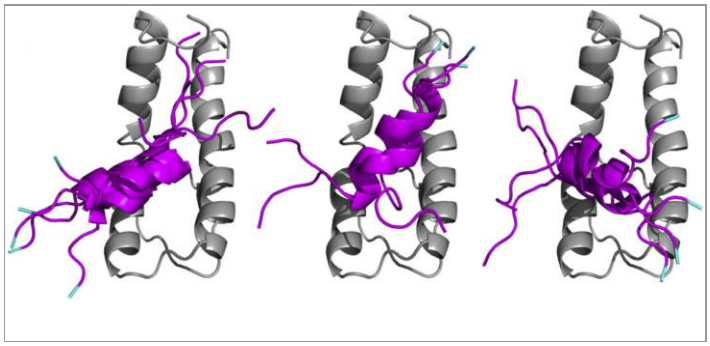
Transcription activators enhance transcription by recruiting coactivator complexes that remodel chromatin and/or directly engage transcription machinery. As each activator is integral to the transcription of many genes, it is important to understand what defines a functional activation domain and how this activation domain interacts with various coactivator complexes, particularly as many activators and coactivators have multiple binding partners. Traditional mutagenesis studies have failed to elucidate the minimal requirements that define a functional activation domain, and previously described structures of different activator-coactivator complexes exhibit key differences. Moreover, known activation domains have variable primary sequences and often exhibit disordered structures in the absence of binding partners, both of which preclude the identification of a conserved element.

Postdoctoral fellow Dr. Clemens Heikaus and colleagues in the lab of Dr. Steven Hahn, Basic Sciences Division, and members of Dr. Rachel Klevit's lab at the University of Washington took an innovative approach to address these questions by first considering how an activation domain interacts with multiple coactivator subunits. Explicitly, they examined the binding interface between the central activation domain of the yeast activator Gcn4 and the activator-binding domain of two unrelated coactivator complexes. To do this, the authors utilized a combination of NMR spectroscopy, computational biology and mutagenesis studies. They found that in the presence of either activator-binding domain, the structurally disordered central activation domain of Gcn4 forms an alpha helix. Aromatic residues within this alpha helix mediate contacts with a hydrophobic cleft in the activator-binding domain of the coactivator subunit Gal11. These aromatic residues were also shown to be critical for Gcn4-Gal11 binding affinity and for the transcription of Gcn4 target genes. In contrast, acidic residues on Gcn4 that surround this hydrophobic interface appear to be dispensable for Gcn4-mediated transcription. This finding is surprising because other transcription activators appear to use acidic residues for binding and transcription activation (e.g., p53 and herpes simplex virus activator Vp16). At the same time, such activators also form an analogous alpha helix with key aromatic residues upon coactivator binding. The authors propose that this helix motif represents the minimal requirement for a functional activation domain. Remarkably, docking calculations performed

with NMR structure-based constraints predict that the Gcn4-Gal11 interface adopts multiple orientations, thus suggesting how this conserved motif can support multiple, low affinity interactions with unrelated coactivators.

Brzovic PS, Heikaus CC, Kisselev L, Vernon R, Herbig E, Pacheco D, Warfield L, Littlefield P, Baker D, Klevit RE, Hahn S. 2011. The acidic transcription activator Gcn4 binds the mediator subunit Gal11/Med15 using a simple protein interface forming a fuzzy complex. *Molecular Cell* 44:942-53.



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A conserved binding motif within the central activation domain of yeast transcription activator Gcn4 appears to adopt multiple orientations to facilitate its interactions with numerous unrelated coactivator complexes. (The Gcn4 domain is shown in purple and coactivator domain in gray.)