Structural relationships between human transcriptional coactivators TFIID and SAGA

E Nogales[1], D Herbst[2], M Esbin[3], A Patel[4], R Louder[5]

[1]UC Berkeley [2]California Institute for Quantitative Biology (QB3), University of California, Berkeley, USA, [3]California Institute for Quantitative Biology (QB3), University of California, Berkeley, USA, [4]California Institute for Quantitative Biology (QB3), University of California, Berkeley, USA, [5]Department of Molecular and Cellular Biology, University of California, Berkeley, USA

enogales@lbl.gov

In eukaryotes, protein-coding genes expression involves the integration of cellular signals, chromatin modifications, and assembly of the transcription pre-initiation complex (PIC) that loads RNA polymerase II onto the promoter. PIC formation is initiated by recruitment of the TATA-binding protein (TBP) to the promoter by protein complexes containing TBP-associated factors (TAFs) that interact with activators, promoter DNA, and/or chromatin. Throughout evolution, these TAFs partitioned and specialized into two distinct coactivator complexes: the general transcription factor TFIID and the SAGA complex. Our structural studies on human TFIID (hTFIID) elucidated its molecular function as a chaperone for TBP deposition and initiation of PIC assembly. TFIID contains three large modules, A, B and C. Two of those, lobe A and B, are built on a core of histone fold-containing subunits and TAF5, with additional subunits conferring distinct arrangements of the modules within the full complex as well as distinct functions. In particular, lobe A includes TBP, which is kept in an inhibited state within TFIID by interaction with several TAFs. Following binding to downstream core promoter sequences, and with the help of TFIIA via its interaction with lobe B, TBP is ultimately deployed onto DNA, where it can initiate PIC assembly. The other TAF-containing transcriptional coactivator, SAGA, has been implicated in a multitude of cellular pathways, including serving as a regulatory hub in transcription. It contains several functional modules: a core of scaffolding histone fold-containing TAFs that parallels that found in TFIID's lobe A; a TRRAP module that binds activators such as c-Myc or p53; a histone acetyltransferase that deposits H3K9ac and H3K14ac at promoters of active genes; and a deubiquitinase that removes H2BK120 ubiquitination from active gene bodies. Studies of yeast SAGA have revealed its modular organization and structural details for some of its modules. We sought to elucidate the architecture of human SAGA and possible functional implications of its conserved and distinct characteristics from its yeast counterpart. Our cryo-EM structure reveals unexpected features and a divergent architecture that have functional implications in transcription and splicing with relevance in genetic diseases and cancer.