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Keywords: Antibiotic resistance, drug design, PrfA, structure-activity relationship

MS06 molecular machines and big complexes

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MS06-O1

Unveiling (class III) transcription through integrative structural biology

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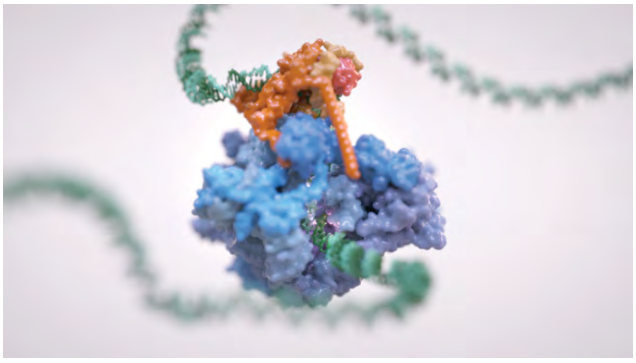
RNA Polymerase (Pol) III is the eukaryotic nuclear enzyme devoted to the transcription of essential non-coding RNAs, including the entire pool of tRNAs, the 5S ribosomal RNA and the U6 spliceosomal RNA. Yeast Pol III comprises 17 subunit and accounts for approximately 750 kDa in mass.

Initiation of gene transcription by RNA Pol III requires the activity of TFIIIB, a complex formed by Brf1, TBP and Bdp1. TFIIIB is required for recruitment of Pol III and to promote the transition from a closed to an open Pol III pre-initiation complex (PIC), a process stimulated by the activity of the Bdp1 subunit. Here we present two cryo-EM reconstruction of an open RNA Pol III PIC at 3.8Å and 3.3 Å, and a reconstruction of RNA Pol III at 3.0 Å.

The structures presented unravel the molecular mechanisms underlying RNA Pol III transcription initiation, highlighting the specific features of this highly efficient essential machinery but also the general conserved mechanisms of gene transcription initiation.

We also present the crystal structures of a vertebrate specific TFIIIB complex, containing the Brf2 subunit, a protein overexpressed in lung and breast cancers. Brf2 encompasses a redox-sensing switch, capable of turning on and off transcription of target genes in a redox dependent manner. Integrating structural and biochemical and functional data in living cells we discovered Brf2 to act as a master switch of the oxidative stress response and establish a mechanistic link between Brf2-dependent Pol III transcription and cancer.



Keywords: RNA Polymerase III, x-ray crystallography, cryo-EM