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Sub2: A TFIIB Interacting Protein with Pleiotropic Roles in mRNA Synthesis, Processing and Transport

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Perspective

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Abstract

The generally accepted view is that different steps of transcription, mRNA processing and mRNA trafficking are performed by dedicated accessory factors. The research during last couple of decades, however, has challenged this dogma. We recently showed that the general transcription factor TFIIB, in addition to its well established role in initiation, is also involved in termination of transcription. Mass spectrometry of purified TFIIB revealed Sub2 as one of its major interacting partners. Sub2 has already been implicated in elongation step of transcription, splicing and mRNA trafficking. Interaction of Sub2 with TFIIB implicates it in initiation and termination steps of transcription. Multiplicity of Sub2 biological roles may be responsible for its link with a number of human pathological conditions making it a potential drug target.

Keywords: mRNA Processing and mRNA Trafficking; Transcription of Protein; Mass Spectrometry

Abbreviations: GTF: General Transcription Factor; RNAPII: RNA Polymerase II; PIC: Preinitiation Complex; TREX: Transcription and Export.

Perspective

TFIIB is a conserved general transcription factor (GTF) required for transcription of protein encoding genes in eukaryotes and archaea [1]. The classical role of TFIIB is to bridge the gap between the promoter binding TFIID and the RNA polymerase II (RNAPII), essentially forming the preinitiation complex (PIC) [2]. However, recent studies have implicated TFIIB in steps beyond initiation of transcription. TFIIB not only occupies the 5' end of actively transcribed genes, but also their 3' ends [3-7]. The 3' end occupancy of TFIIB is due to a structural conformation of the transcription template called gene looping, where the 5' and 3' ends of an actively transcribed gene are juxtaposed, facilitating the hand-off of the RNAPII to the promoter for reinitiation [8]. Quantitative proteomic analysis of affinity purified TFIIB from the chromatin fraction revealed that TFIIB associates with two of the three yeast termination complexes, CF1 and Rat1 [9]. Interaction of promoter-linked TFIIB with CF1 and Rat1 complexes occupying the 3' end of a gene may be responsible for the gene assuming a looped formation.

Mass spectrometry of chromatin-eluted TFIIB revealed a novel interactor, Sub2, which associated with TFIIB at a consistently high level [9]. Sub2 is a splicing factor and a component of the TRanscription EXport (TREX) complex [10]. It has previously been thought to be recruited to the actively transcribed gene during elongation of transcription due to its association with the THO (transcription-dependent hyper recombination complex) complex, an elongation complex in yeast which is a part of the larger TREX complex [11]. The association of Sub2 with TFIIB indicates that it may be recruited to the gene earlier than we thought. Since TFIIB occupies both the promoter and terminator regions of

actively transcribing genes, we expected Sub2 to interact with initiation and termination factors like TFIIB. Preliminary results from our laboratory confirmed that Sub2 indeed associates with two termination complexes, the CPF and CF1 complexes (Dwyer and Ansari, 2024, unpublished results). These results strongly suggest that Sub2, in addition to its role in RNA trafficking, splicing and transcription elongation, may also be involved in initiation and termination steps of transcription.

Sub2 may be the factor that links transcription to RNA processing and RNA trafficking. It is an evolutionarily conserved protein with homologs present in humans, flies and worm. The human homolog of Sub2, called UAP56 (U2AF associated protein56; also known as DDX39B), could functionally substitute for Sub2 in budding yeast, thereby affirming the evolutionarily conserved nature of two proteins [12]. Both Sub2 and UAP56 possess RNA-dependent helicase activity. They have been implicated in multiple aspects of mRNA metabolism including mRNA splicing, export, and ribosome biogenesis [13]. Multiple studies have revealed the central role of UAP56 and Sub2 as components of the transcription and export (TREX) complex responsible for guiding mRNA from the nucleus to the cytosol [14-16]. Cryo-EM studies of yeast TREX complex found THO subunits Tho2 and Hpr1 intertwine to form the binding surface for Mft1, Thp2, and Tex1.The resulting complex homodimerizes with a Sub2 molecule to form the TREX complex [16]. During splicing, Sub2/UAP56 is necessary for proper assembly of the pre-spliceosome complex [17]. Spliceosome assembly is a well-coordinated process involving many proteins and ncRNAs [18]. Loss of Sub2 results in stalling of the pre-spliceosome assembly and therefore improper splicing [17].

Emerging research has indicated that the repertoire of Sub2/UAP56 physiological involvement extends well beyond their established functions in splicing and export. A number of studies have implicated the factor in telomere maintenance and in maintaining genomic integrity through suppression of co-transcriptional R-loop formation [19,20]. The RNA-DNA helicase activity of Sub2/UAP56 unwinds R-loops around actively transcribed regions of the genome [20]. This function may be responsible for Sub2/UAP56 facilitating transcription elongation by allowing RNAPII to proceed unobstructed through the coding region of the gene [21]. Depletion of Sub2/UAP56 also results in DNA damage at the telomeric regions [22]. Unpublished results from our laboratory suggest that Sub2 may have as yet unidentified roles in transcription cycle than previously thought. The research during the last couple of decades have demonstrated that different steps of transcription are interlinked and occur in a cooperative fashion with RNA processing and transport of mRNA out of the nucleus in cytoplasm [23]. In this context, the study of Sub2 may help us gain insight into how the various steps of gene expression from transcription initiation, splicing, termination to transport of mRNA to the cytoplasm are regulated to coordinate proper expression of a gene in response to external or internal environmental cues.

Probably due to these broadly encompassing roles, Sub2 has been linked to a number of human pathological conditions like cancer, neurodegenerative disorders and viral diseases [24]. Specifically, Sub2/UAP65 depletion affects the expression of the tumor suppressor gene BRCA1 [25]. It has also been implicated in viral RNA transport to the host cytosol for translation [26]. This makes Sub2 a suitable candidate for drug targeting for the above mentioned disorders. Further study of Sub2 is needed to establish the scope of its function in regulation of gene expression and the molecular mechanisms underlying these functions. This will open up the avenues for potential targeting of the protein for drugs to treat linked pathologies.

Author Contribution

AA conceptualized; EF prepared the original draft; AA edited the manuscript. All authors contributed to the article and approve the submitted version.

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