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The Interactions of the Largest Subunit of RNA Polymerase II with Other Cellular Proteins: a Bioinformatic Approach

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Abstract

The function of a protein is governed by its interaction with other proteins inside a cell. Therefore, it is important to identify the interacting partners of a particular protein to decipher its function. The protein interaction networks are generally determined by bioinformatic as well as experimental methodologies such as yeast two hybrid, mass spectrometry, immunoprecipitation, and fluorescence resonance energy transfer assays. Here, we have analyzed bioinformatically the interactions of Rpb1p (the largest subunit of RNA Polymerase II) with other proteins in yeast, using *Cytoscape* software and *Biogrid/ Biomart* database. We find that Rpb1p interacts with a large number of proteins involved in mRNA synthesis, processing, export, and other cellular processes. These results validate the application of such bioinformatic approach to determine the interactome for other cellular proteins.

Keywords: bioinformatics, protein interactions, Rbp1, yeast, human.

Introduction

All cellular processes are carried out by the concerted actions of proteins through specific interaction networks. Therefore, protein function annotation has become an important area of research in post-genomic sequencing era. Thus, an understanding of various cellular processes demands elucidation of the protein-protein interaction networks within cell. Several experimental methodologies such as yeast two hybrid, mass spectrometry, immunoprecipitation, and fluorescence resonance energy transfer assays have been employed to decipher cellular protein-protein interactions. Based on these experimental studies, several bioinformatic tools have been developed to comprehensively analyze protein interaction networks of different cellular proteins. Here, we have used the Cytoscape software (Zhang *et al*., 2007) and Biogrid/ Biomart database to identify the interactions of the largest subunit of RNA Polymerase II (RNAPII), Rpb1, with other proteins in yeast. Such analysis has revealed a large number of primary interactions of Rpb1p with many proteins involved in the regulation of transcription, chromatin structure, DNA repair, and other cellular events as discussed below.

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Rpb1 and its interactions with other RNAPII subunits

The protein coding genes are transcribed into mRNA by RNAPII that is highly conserved from yeast to human. RNAPII is composed of 12 different subunits. These subunits are Rpb1, Rpb2, Rpb3, Rpb4, Rpb5, Rpb6, Rpb7, Rpb8, Rpb9, Rpb10, Rpb11, and Rpb12. Rpb1 is the largest subunit, and is essential to maintain the structural integrity of RNAPII. Moreover, it has Mg^{2+}-dependent polymerase activity. The Rpb1 and Rpb2 subunits are located at the core of RNAPII with smaller subunits at the surface (Cramer *et al*., 2001, 2008; Bushnell and Kornberg, 2003; Cramer, 2004). Thus, Rpb1 interacts with several RNAPII subunits as also observed in this bioinformatic analysis (Fig. 1).

An important feature of Rpb1 is its c-terminal domain (CTD) that consists of multiple heptapeptide repeats (YSPTSPS) (Buratowski, 2003; Egloff and Murphy, 2008). Serine-2 and serine-5 (S-2 and S-5) of the heptapeptide in the CTD are phosphorylated and dephosphorylated during transcription by different kinases and phosphatases. Such phosphorylation status of Rpb1-CTD plays an important role in integrating various nuclear events through a variety of proteins involved in mRNA synthesis, processing, and export (Buratowski, 2003; Egloff and Murphy, 2008; Pandit *et al*., 2008). In addition, Rpb1 interacts with Mediator, general transcription factors and activator, chromatin modifying and remodeling factors, and several other proteins to maintain normal cellular functions. These interactions are discussed below.

Interaction of Rpb1 with Mediator

The yeast Mediator complex comprises of a large number of subunits that include Srb (suppressor of RNA polymerase B) proteins (Srb2, Srb4, Srb5, Srb6, Srb7, Srb8, Srb9, Srb10, Srb11), Med proteins (Med1, Med2, Med4, Med6, Med7, Med8 and Med11), and several other polypeptides (Pgd1, Cse1, Nut2, Rgr1, Gal11, Sin4, Rox3 and Soh1) (Kornberg, 2005). The core of the Mediator complex (known as core mediator complex) lacking Srb8, Srb9, Srb10 and Srb11 (or the Srb8–11 module) has a

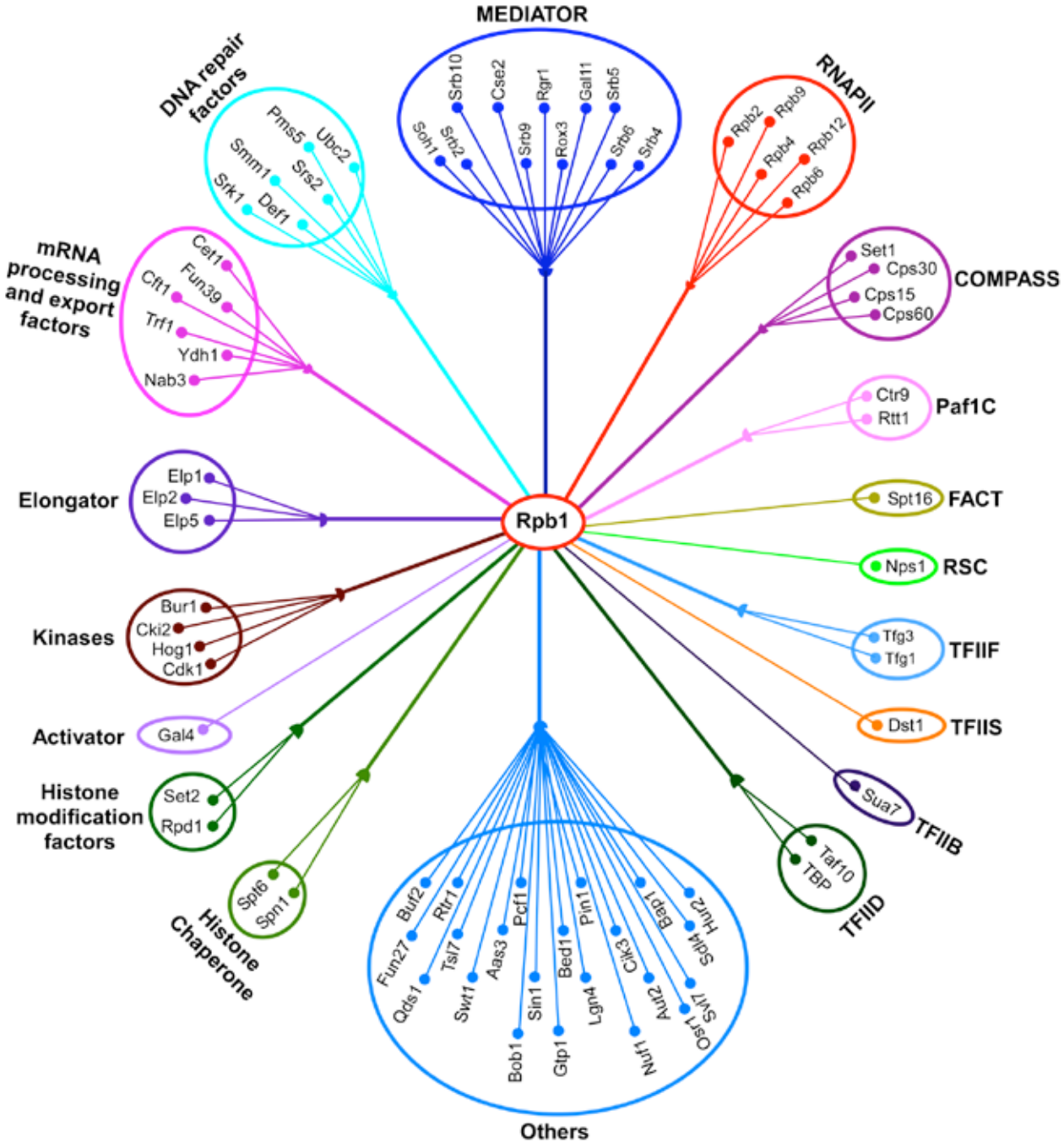

Fig. 1: The interaction of the largest subunit of RNAPII (Rpb1) with other cellular proteins in yeast as revealed by bioinformatic analysis.

stimulatory effect on transcription, whereas the whole Mediator complex represses transcription of a subset of genes (Borggrefe and Kornberg, 2002; Kornberg, 2005; Björklund and Gustafsson, 2005; Casamassimi and Napoli, 2007). Therefore, the Mediator complex plays an important role in transcriptional regulation as a co-activator or co-repressor through its interaction with several transcription factors. One important partner of Mediator in transcription machinery is RNAPII. Here, we have bioinformatically analyzed the interactions of the Mediator components with the largest subunit of RNAPII. This analysis shows that Rpb1 interacts with at least 11 subunits of the Mediator complex. These subunits are Cse2, Srb9, Rgr1, Gal11, Srb4, Srb5, Rox3, Srb2, Srb6, Soh1 and Srb10 as shown in Fig. 1. Likewise, Mediator components interact with other factors during transcription.

Interaction of Rpb1 with COMPASS

COMPASS is a histone methyltransferase in yeast (Miller *et al*., 2001). It methylates histone H3 on lysine-4 (H3K4) for transcriptional activation (Miller *et al*., 2001; Santos-Rosa *et al*., 2002; Liu *et al*., 2005; Shilatifard, 2006). COMPASS consists of 7 proteins (Cps60, Cps50,

Cps40, Cps35, Cps30, Cps15 and Set1). The Set1 component of COMPASS boasts the enzymatic activity (Miller *et al*., 2001). Other COMPASS subunits play structural and functional roles to direct Set1 to perform its histone methylase activity (Shilatifard, 2006). COMPASS is recruited to the active genes by RNAPII, and thus methylates histone H3K4 in a transcription-dependent manner (Hampsey and Reinberg, 2003; Shilatifard, 2006). Consistent with these results, this bioinformatic analysis reveals that Rpb1 interacts with four subunits of COMPASS. These subunits are Set1, Cps15, Cps30 and Cps60 (Fig. 1).

Interaction of Rpb1 with PAF

Paf1C is a RNAPII-associated complex. In yeast, Paf1C is composed of Paf1, Cdc73, Ctr9, Rtf1, and Leo1 (Mueller and Jaehning, 2002; Hampsey and Reinberg, 2003). Basically, Paf1C interacts with histone methyltransferase, COMPASS, and histone H2B ubiquitinating enzymes (e.g. Rad6 and Bre1), and thus regulates histone covalent modification for stimulated transcription (Krogan *et al*., 2003a; Rosonina and Manley, 2005). Paf1C is co-transcriptionally recruited to active genes by RNAPII (Krogan *et al*., 2003a; Xiao and Strahl, 2005; Rosonina and Manley, 2005). Consistently, this bioinformatic analysis shows the interactions of the Ctr9 and Rtt1 subunits of Paf1C with the largest subunit of RNAPII (Fig. 1). In addition, Paf1C regulates mRNA 3′ end formation through its interaction with mRNA cleavage and polyadenylation factors (Nordick *et al*., 2008).

Interaction of Rpb1 with FACT

FACT (Facilitates Chromatin Transcription) was identified as a factor required for transcription on chromatin template (Orphanides *et al*., 1998, 1999). FACT is composed of two subunits, namely, Spt16 and Pob3 in yeast. Lately, FACT has been implicated as an important elongation factor as a histone chaperone (Belotserkovskaya *et al*., 2003; Belotserkovskaya and Reinberg, 2004). Accordingly, FACT has been shown to travel with elongating RNAPII, and subsequently alters chromatin structure, thereby facilitating transcription (Belotserkovskaya *et al*., 2003; Belotserkovskaya and Reinberg, 2004; Saunders *et al*., 2003; Reinberg and Sims, 2006). These results are corroborated with this bioinformatic analysis for the interaction of FACT with the largest subunit of RNAPII (Fig. 1). In addition to its role in transcriptional elongation, FACT is recruited to gene promoter, and regulates transcriptional initiation (Mason and Struhl, 2003). Further, FACT has been shown to participate in regulation of DNA repair and replication (Wittmeyer and Formosa, 1997; Wittmeyer *et al*., 1999; Schlesinger and Formosa, 2000; Heo *et al*., 2008). Thus, FACT plays an important role in various cellular events.

Interaction of Rpb1 with RSC

RSC (remodels the structure of chromatin) is an abundant Swi/Snf-like chromatin remodeling complex with multiple subunits in yeast (Cairns *et al*., 1996). Unlike Swi/Snf, RSC is essential for cellular viability. It has been implicated to activate as well as repress transcription (Moreira and Holmberg, 1999; Sudarsanam and Winston, 2000; Angus-Hill *et al*., 2001). Further, this bioinformatic analysis shows that the Nps1 component of RSC interacts with the largest subunit of RNAPII (Fig. 1). Thus, RSC appears to regulate transcription via its interaction with RNAPII. In addition to its role in transcription, RSC has been shown to play important role in DNA repair (van Attikum and Gasser, 2005; Chai *et al*., 2005; Shim *et al*., 2005).

Interaction of Rpb1 with activator and general transcription factors

In transcriptional activation, the activator stimulates formation of the pre-initiation complex (PIC) assembly which subsequently initiates transcription (Roeder, 2005; Thomas and Chiang, 2006). PIC is formed by the assembly of general transcription factors (e.g. TFIIA, TFIIB, TFIID, TFIIE, TFIIF, TFIIH, RNAPII, etc.). RNAPII is an important component of the PIC assembly, which initiates transcription in the presence of TFIIH. Further, previous studies (Smale and Kadonaga, 2003; Roeder, 2005; Thomas and Chiang, 2006) have implicated the interaction of RNAPII with activator and various general transcription factors during transcriptional initiation or activation as also seen in this bioinformatic analysis (Fig. 1).

Interaction of Rpb1 with Elongator

RNAPII associates with a variety of proteins/protein complexes during transcription elongation. (Shilatifard *et al*., 2003; Buratowski, 2003; Cramer, 2004; Buratowski, 2005; Shilatifard, 2006; Svejstrup, 2007). Elongator is one such component with six different subunits, namely Elp1, Elp2, Elp3, Elp4, Elp5 and Elp6 (Otero *et al*., 1999; Krogan and Greenblatt, 2001; Winkler *et al*., 2001; Li *et al*., 2001; Svejstrup, 2007). The Elp3 subunit has histone H4 acetyltransferase activity which facilitates transcriptional elongation following RNAPII-dependent association of Elongator with the body of gene (Wittschieben *et al*., 1999). These results are corroborated with this bioinformatic analysis that reveals that interacts of the Elp1, Elp2 and Elp5 subunits of Elongator with the largest subunit of RNAPII (Fig. 1). In addition to its role in transcriptional elongation, Elongator participates in cytoplasmic kinase signaling, exocytosis and tRNA modification (Holmberg *et al*., 2002; Rahl *et al*., 2005; Esberg *et al*., 2006; Jablonowski *et al*., 2006; Huang *et al*., 2005).

Interaction of Rpb1 with Set2 and HDAC

Histone covalent modifications have been associated with transcriptional regulation. Elongating RNAPII has been found to be associated with several covalent modification factors such as Set1 (COMPASS) and Elp3 (Elongator) as mentioned above. Further, elongating RNAPII has been implicated to regulate histone H3 K36 methylation at the body of gene by Set2 histone methylase (Li *et al*,, 2002; Krogan *et al*., 2003b; Hampsey and Reinberg, 2003; Keogh *et al*,, 2005; Carrozza *et al*., 2005). Set2 associates with the S-2 phosphorylated form of RNAPII that occurs towards the 3′ end of the coding sequence, hence leading to histone H3 K36 methylation. Intriguingly, methylated-K36 on histone H3 leads to the recruitment of repressive Rpd3(S) complex with multiple

subunits (e.g., Rpd3, Eaf3, Ume1, Sin3, Sap30, Sds3, Pho23, and Cti6/Rxt1) (Keogh *et al*,, 2005; Carrozza *et al*., 2005; Joshi and Struhl, 2005; Yang and Seto, 2008; Lee and Shilatifard, 2007). The chromodomain of Eaf3 is responsible for such recruitment (Joshi and Struhl, 2005; Carrozza *et al*., 2005; Keogh *et al*,, 2005). Rpd3 has a histone deacetylase (HDAC) activity that preferentially deacetylates acetylated-K on histone H4 (Keogh *et al*,, 2005; Carrozza *et al*., 2005; Joshi and Struhl, 2005). Such deacetylation has been implicated to repress cryptic transcriptional initiation. Thus, RNAPII regulates transcription by a fine tuning of acetylation/methylation marks via its interaction with Set2 and HDAC (Fig. 1).

Interaction of Rpb1 with histone chaperone proteins

Chromatin presents a structural hindrance for the passage of elongating RNAPII. Therefore, molecular chaperones, which alter chromatin organization, become the rate limiting factors during transcriptional elongation. These chaperones are not only required to clear up the path for RNAPII during elongation, but also maintain the normal chromatin organization after transcription is completed. RNAPII has been shown to associate with molecular chaperones like FACT and Spt6 during transcriptional elongation (Krogan *et al*., 2002). Consistently, this bioinformatic analysis shows that histone chaperones interact with the largest subunit of RNAPII (Fig. 1). Further, this analysis reveals that Rpb1 interacts with Spn1 that is essential for the recruitment of Spt6 (Zhang *et al*., 2008). Intriguingly, Spt6 has also been shown to repress transcription of several genes (Compagnone and Osley, 1996). In addition, Spt6 has been implicated in mRNA processing, and export (Bucheli and Burtowski, 2005).

Interaction of Rpb1 with mRNA processing and export factors

Once the transcription is initiated, there are several proteins, which play a significant role in the processing of mRNA. Events, both at the 5′ end (such as capping) as well as 3′ end (e.g. mRNA cleavage and polyadenylation) involve several proteins. The recruitment as well as function of these proteins is tightly regulated. These proteins are shown to be co-transcriptionally recruited to the active genes by the elongating form of RNAPII (Zorio and Bentley, 2004; Bird *et al*., 2004; Buratowski, 2005; Mandel *et al*., 2008). In addition, RNAPII co-transcriptionally recruits mRNA export factors (Masuda *et al*., 2005; Buratowski, 2005). Consistently, this bioinformatic analysis shows the interaction of Rpb1 with the proteins involved in mRNA capping (Cet1), 3′ end formation (Ctf1, Fun39, Nab3 and Ydh1) and export (Trf1) (Fig. 1). Thus, RNAPII appears to regulate mRNA processing and export via its interaction with proteins involved in these processes.

Interaction of Rpb1 with DNA repair factors

Genomic DNA is constantly challenged by internal as well as external genotoxic agents. An extremely cytotoxic ramification is the lesion at the coding region of active gene which inhibits the passage of RNAPII, and subsequently leads to transcription coupled repair through its interaction with DNA repair and related factors (Lainé and Egly, 2006) as also revealed in this bioinformatic analysis (Fig. 1).

Interaction of Rpb1 with protein kinases

Biological processes in the cell are always tightly regulated. Phosphorylation/ dephosphorylation of proteins is one of the major ways the cell synchronize important cellular processes. The phosphorylation status of proteins is maintained by several distinct classes of kinases. Therefore, kinases play a critical role in regulation of many cellular events such as replication, transcription, cell cycle, protein degradation, etc. Further, kinase regulates transcription in a RNAPII-dependent manner. For example the largest subunit of RNAPII interacts with a number of protein kinases such as Cki2, Cdk1, Hog1 and Bur1 as shown in Fig. 1 . These kinases are involved in diverse biological processes such as endocytic trafficking (Cki2), cell cycle regulation (Cdk1), osmoregulation (Hog1), and transcription (Bur1) (Hicke *et al*., 1998; Alepuz *et al*., 2003; Keogh *et al*., 2003; Harvey *et al*., 2005).

Interaction of Rpb1 with other cellular proteins

In addition to the above interactions, Rpb1 is correlated with several other processes through its interaction with various proteins, which are grouped as “others” in Fig. 1 . For example, Rpb1 interacts with proteins involved in replication (e.g., Buf2, Bob1 and Sld4), cytoskeleton organization (e.g., Lgn4, Nuf1 and Gtp1), and protein sorting (e.g., Svl7, Bed1 and Qds1). Further, Rpb1 interacts with some transcriptional regulatory factors such as CCR4-NOT (Fun27), proline isomerase (Pin1), Rtr1, Sin1, Aas3 and Bap1.

Concluding remarks

The function of a protein is dictated by its interaction with other cellular proteins, and, thus, understanding of the protein interaction networks is very crucial for protein function annotation. Several bioinformatic tools have been developed based on experimental data to analyze protein-protein interactions. One such bioinformatic tool is *Cytoscape* software. Using this software, we have analyzed the interactions of the largest subunit of RNAPII with other proteins in yeast to test the validity of this tool for cellular protein-protein interactions in general. We find that the largest subunit of RNAPII interacts with a large number of proteins involved in various stages of transcription, chromatin modification and remodeling, DNA repair, and other biological processes, consistent with experimental studies. Thus, our study validates the general applicability of this bioinformatic approach to analyze cellular protein-protein interactions.

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