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Chapter 7

Subunits Common to RNA Polymerases

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Abstract

RNA polymerases are heteromultimeric complexes responsible of RNA synthesis. In yeast, as in the other eukaryotes, these complexes contain five common subunits (Rpb5, Rpb6, Rpb8, Rpb10 and Rpb12) that must have similar functions in the three RNA polymerases. However, some of these proteins have been shown to also have specific roles. In the last few decades, substantial progress has been made to understand the role of these common subunits in transcription, but their participation in the activity of each enzyme remains unclear. This review gives a comprehensive overview of current knowledge on the five common subunits of eukaryotic RNA pol, placing attention not only on their common roles in the activity of the RNA pols but also on describing specific roles for some of the complexes.

Keywords: RNA polymerases, transcription, protein complexes, common subunits, RNA

1. Introduction

Transcription is carried out by the RNA polymerases (RNA pol). While archaea and bacteria contain only one RNA pol, most eukarya contain three different enzymes responsible for the specific synthesis of different types of RNAs [1]. RNA pol I synthesises the precursor of the three largest rRNAs, whereas RNA pol III sy\nthesises mostly tRNAs and 5S rRNA, together with several short non-translated RNAs. Meanwhile, RNA pol II produces all mRNAs and many non-coding RNAs [1, 2]. Moreover, in plants, two additional polymerases, IV and V (or nuclear RNA polymerases D and E), reportedly synthesise small interfering RNAs (siRNAs), regulating methylation and participating in gene silencing, as well as long non-coding RNAs involved in development and response to environmental changes [3–5].

While bacteriophage T7 and some related enzymes that transcribe the mitochondrial genome or contribute to chloroplast transcription are single-subunit RNA polymerase [6], bacterial, archaeal and eukaryotic enzymes are heteromultimeric complexes (**Table 1**). As in other eukaryotes, yeast RNA pol I, II and III are composed of 14, 12 and 17 subunits, respectively. These contain a catalytic core formed by the two largest subunits, which are highly conserved through evolution (Rpb1 and Rpb2). Moreover, among all eukaryotic RNA pol subunits, five have bacterial homologues (Rpb1, Rpb2, Rpb3, Rpb6 and Rpb11) and others are common to archaea, but without bacterial homologues (Rpb4, Rpb5, Rpb7, Rpb8, Rpb9, Rpb10, and Rpb12) [1, 2, 6–9]. Finally, eukaryotic RNA pols contain five common subunits to the three enzymes (Rpb5, rpb6, Rpb8, Rpb10 and Rpb12), which have archaeal homologues (**Figure 1**) [10–12].

In the last few decades, substantial progress has been made to understand the role of the RNA pol common subunits in transcription, but their participation in the activity of each enzyme remains unclear. This review gives a comprehensive overview of current knowledge on the

Eukaryotes						
Bacteria	**Archaea**	**RNA pol I**	**RNA pol II**	**RNA pol III**	**RNA pol IV (plants)**	**RNA pol V (plants)**
β	Rpo1 (RpoA)	RPA190	RPB1	RPC160	NRPD1	NRPE1
β	Rpo2 (RpoB)	RPBA135	RPB2	RPC128	NRPD/E2	NRPD/E2
α	Rpo3 (RpoD)	RPAC40	RPB3	RPAC40	RPB3 [1]	RPB3 [1]
α	Rpo11 (RpoL)	RPAC19	RPB11	RPAC19	RPB11	RPB11
ω	Rpo6 (RpoK)	RPB6	RPB6	RPB6	RPB6 [1]	RPB6
	Rpo5 (RpoH)	RPB5	RPB5	RPB5	RPB5 [3]	NRPES5
	Rpb8 (RpoG)*	RPB8	RPB8	RPB8	RPB8 [1]	RPB8 [1]
	Rpo10 (RpoN)	RPB10	RPB10	RPB10	RPB10	RPB10
	Rpo12 (RpoP)	RPB12	RPB12	RPB12	RPB12	RPB12
	Rpo4 (RpoF)	RPA14	RPB4	RPC17	NRPD/E4	NRPD/E4
	Rpo7(RpoE)	RPA43	RPB7	RPC25	NRPD7 [1]	NRPE7
		RPA12	RPB9	RPC11	NRPD9b	RPB9
	Rpo13*					
		RPA49		RPC53		
		RPA34.5		RPC37		
				RPC82		
				RPC34		
				RPC31		

In a square, the RNA pol common subunits in a box. *Subunits RpoG and Rpo13 have been identified only in some archaeal species [6] [1]. The numbers in square brackets indicate the number of orthologues of RNA pol IV and RNA pol V subunits in plants.Different names for common subunits of yeast RNA pol: Rpb5: ABC27; Rpb6: ABC23 or Rpo26; Rpb8: ABC14.5; Rpb10: ABC10β; Rpb12: ABC10α.

Table 1. RNA polymerase (RNA pol) subunit composition.

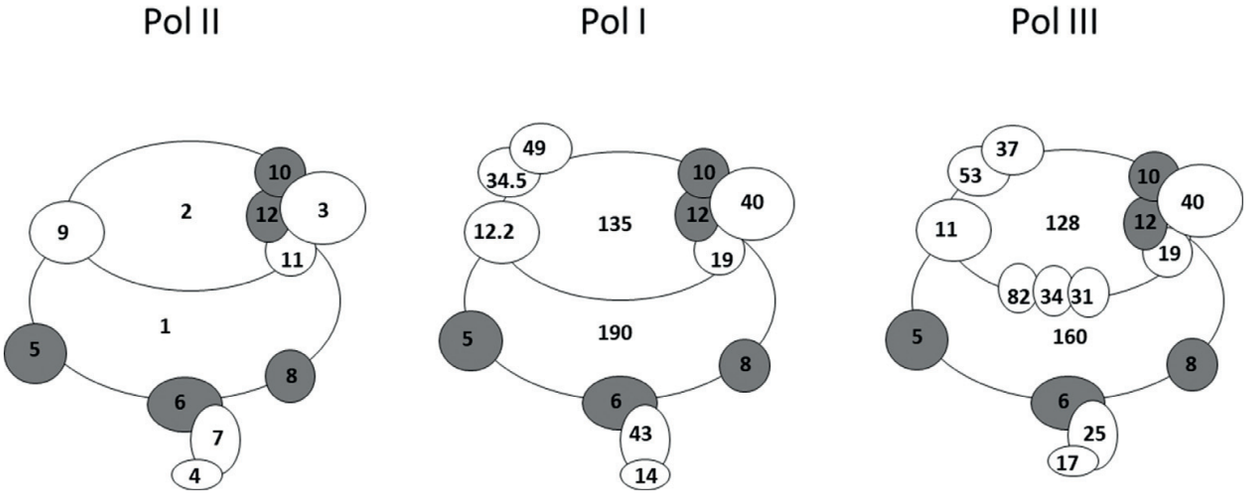

Figure 1. Schematic representation of structure of the RNA pols I, II and III. Each RNA pol common subunit is indicated in grey. The numbers correspond to each subunit are indicated in **Table 1**.

five common subunits of eukaryotic RNA pol, placing attention not only on their common roles in the activity of the RNA pols but also on describing specific roles for some of the complexes.

2. Rpb5

In budding yeast, the essential Rpb5 subunit, also known as ABC27, consists of 215 amino acid residues and has a molecular mass of 27 kDa [11, 13–15]. Contrary to other RNA polymerase common subunits, human Rpb5 homologue (RPB5), with 44% identity and 80% similarity to the yeast polypeptide, fails to complement the *RPB5* null allele in *Saccharomyces cerevisiae* [12]. Rpb5 shows homology not only with a small archaeal subunit called "H" but also with nuclear and cytoplasmic DNA viruses [16, 78]. Rpb5 have two paralogues in *Trypanosome brucei*, *T. cruzi* and *Leishmania major* [17]. Notably, it has been reported that along four distantly related eukaryotic lineages (the higher plant and protistan) Rpb5 shows different isoforms and as a result a diversification of its functions [17].

Structurally, Rpb5 has a bipartite organisation combining two globular modules separated by a short hinge: an N-terminal domain ("*jaw*" domain), found only in eukaryotes (positions 1–142 in *S. cerevisiae*), and a C-terminal globe largely conserved in all non-bacterial enzymes ("*assembly*" domain) [7, 16, 18–20]. Both modules are essential *in vivo* and are functionally exchangeable with their human homologues, except for a small central segment located between positions 121–146 in *S. cerevisiae* [10]. The eukaryotic module of Rpb5 has two highly conserved sequence blocks. One of them harbours the last 12 amino acids and the other, highly conserved (positions 11–30 in budding yeast), belongs to the long hydrophilic helix Rpb5-α1 and occupies the "*lower*" far-end of the DNA *Cleft* [7, 21, 22]. The C-terminal module (position 143–215) binds the largest subunit of RNA pol II (Rpb1) and their paralogues on the RNA pols I and III [10, 23]. Rpb5 does not belong directly to the catalytic domain of RNA pol II [7, 22, 24]. Nevertheless, some studies indicate that the N-terminal domain probably accounts for the Rpb5/DNA contacts found 15–20 nucleotides ahead of the

transcription fork in RNA polymerases III [25] and II [26]. In addition, the N-terminal module marks the far end of the DNA channel in the RNA pol II [7, 27] and probably also in the RNA pols I and III [28–30]. Notably, the *lower jaw* and the *assembly* domains of Rpb5 belong to the Shelf module, one of the four RNA pol II mobile modules (*core*, *jaw-lobe*, *shelf* and *clamp*) in *S. cerevisiae* [7, 18].

The periphery localization of Rpb5 on all three enzymes [7, 30, 31] would allow possible interactions with general transcription factors or specific gene regulators. It should be the basis of the interaction between Rpb5 and Rsc4, a subunit of RSC (chromatin remodeler complex) in *S. cerevisiae* [32]. The lack of this interaction affects the chromatin structure in the promoter region of some RSC-regulated genes, leading to impaired transcription. Rpb5 also interacts with TFIIE in *Schizosaccharomyces pombe* [33]. In human, RPB5 directly interacts with HBx (hepatitis B virus X protein), essential for HBV infection, and both RPB5 and HBx communicate with transcription initiation factor TFIIB but through different sites [34]. Human RPB5 also interacts with $hTAF_{II}68$ (human TATA-binding protein-associated factor II 68) identified by its homology to the proto-oncogenes EWS (Ewing's sarcoma) and TLS (Translocated in Liposarcoma; another member of the EWS gene family) [35–37]. *In vitro* studies have shown that RPB5 also interacts with the TATA-binding protein-interacting protein 120 (TIP120), which stimulates the transcription driven by RNA pols I and III [38]. Furthermore, RPB5 in human has been described to interact with the general transcription factor TFIIF and this association is critical for the interaction between TFIIF and the RNA pol II [39].

The HBx transactivation seems to be modulated by the protein URI/RMP (Unconventional Prefoldin Rpb5 Interactor) that specifically binds to RPB5 both *in vitro* and *in vivo* and negatively modulates transcription through binding to RPB5 [40]. Owing to RPB5-URI interaction, RPB5 could participate in regulating the androgen receptor in human cells [41]. This interaction also extends to *S. cerevisiae* and the correct association between Rpb5 and the URI orthologue, Bud27, is essential for the correct cytoplasmic assembly of the three RNA pols before their entry to the nucleus [42]. Notably, in mammals, RPB5 forms a complex with UXT, WDR92/Monad, PDRG1, URI, PFDN2 and PFDN6, which is thought to adopt a prefoldin-like structure and cooperates with the cochaperone R2TP complex to assembly of RNA pol II [43–45].

Furthermore, it has been proposed that Bud27 modulates the association between Sth1 (subunit of RSC complex) and the RNA pol II probably through Rpb5 interaction in *S. cerevisiae* [46].

3. Rpb6

Rpb6 (also known as ABC23 or Rpo26) is an acidic 155-amino acid subunit with apparent and predicted molecular masses of 23 and 18 kDa, respectively [11, 47]. It is phosphorylated in all three RNA pols, mainly on serine and threonine residues [48–51]. Moreover, the *in vitro* phosphorylation of rat RPB6 by casein kinase II (CKII) has been demonstrated [52]. Eukaryotic RNA pols I, II and III subunit Rpb6 are homologous in sequence, structure and function to archaeal RNA pol subunit RpoK and bacterial subunit ω [53]. In addition, *S. cerevisiae* Rpb6 is functionally interchangeable with their human homologue *in vivo* [12, 54], demonstrating their structural and functional conservation.

S. cerevisiae RPB6 is an essential gene for cell growth [11, 55], and RNA pol I lacking Rpb6 is virtually inactive in RNA synthesis *in vitro* but regains activity upon the addition of Rpb6 [56].

A role for Rpb6 in transcription elongation has been proposed. In fact, some temperature-sensitive mutants in *S. pombe* are unable to grow in the presence of 6-azauracil and a functional and direct physical interaction of Rpb6 with transcription elongation factor TFIIS has been proposed [57]. Moreover, a recent study demonstrates that the C-terminus of RPAP2, the human homologue of the CTD phosphatase Rtr1 participating in the transition from transcription initiation to elongation, interacts directly with the RNA pol II subunit Rpb6 *in vitro* [58]. Rpb6 could also participate in transcription initiation, since the archaeal TFIIB and Rpb6 counterparts have been demonstrated to interact *in vitro* [59].

According to a global role of Rpb6 in transcription, the *RPB6* gene has also been identified as a dosage suppressor of the cold-sensitive phenotype of *tgs1Δ* cells, which lacks of the trimethylguanosine (TMG) caps of small nuclear (sn) RNA in *S. cerevisiae* [60].

Rpb6 was found to make contact with three small RNA pol subunits, Rpb5, Rpb7 and Rpb8, as well as with the foot of the RNA pol II, with its largest subunits Rpb1 and Rpb2 [7, 61]. Similarly, Rpb6 interacts on the crystal structure with the largest subunit of the RNA pol I, Rpa190 [30] and probably with its homologue in the RNA pol III, Rpc160. Notably, the contact between Rpb6 and Rpb7 involves the residue Gln^{100} of Rpb6 and Gly^{66} of Rpb7 on the RNA pol II core and the *rpb6Q100R* mutant leads to Rpb4/7 dissociation at high temperatures [21, 62].

While the C-terminal segment of Rpb6, from amino acids 72 to 155, is well organised on the crystal structure of yeast RNA pol II [7], the N-terminal domain 71-amino acid segment on the RNA pol II structure, as well as the N-terminal 54-amino acid segment on the RNA pol I structure is disordered [24, 28, 30]. Moreover, the segment from amino acids 55 to 71 of Rpb6 on the RNA pol I structure comprises an α-helix that provides additional contacts with Rpa43 and Rpa14 [28, 30]. The N-terminal region of Rpb6 seems to be dispensable for the functions of this subunit, explaining the lack of conservation of this region with its archaeal homologues and the low degree of similarity of the Rpb6 sequence among various eukaryotes [63]. However, a region of 13 amino acids in the C-terminal domain of Rpb6 is highly conserved in eukaryotes and archaea, suggesting an essential function [63]. Rpb6 is connected to the base of a flexible module containing portions of Rpb1 and Rpb2, called the clamp, through a set of five "switches" that control clamp movement [7]. In addition, the association of Rpb6 with Rpb4/Rpb7 dimmer suggest that these two subunits could modulate the clamp movement and may regulate the position of the clamp by signalling through Rpb6 [62].

Rpb6 and its bacterial homologue have been proposed to promote RNA pol II assembly and/or increase RNA pol stability, through specific interactions with the RNA pol II largest subunit, Rpb1, in the case of *S. cerevisiae* [53, 56, 63, 64]. It has been recently reported that mutations in foot conserved domain of Rpb1 cause an integrity defect of the RNA pol II, altering the association between Rpb1 and Rpb6, and the correct association of the dimer Rpb4/7. This assembly alteration causes a transcriptional defect, which affects the amount of enzyme associated with genes and its transcriptional activity [64]. In addition, the partial dissociation of Rpb4/Rpb7 dimmer leads to an increase in mRNA stability by loss of mRNA imprinting [65, 66]. Notably,

all these defects are overcome by *RPB6* overexpression and agree with previous data pointing to an important role of Rpb6 in RNA pol II integrity/assembly [47, 63–65].

In *S. cerevisiae*, assembly of the RNA pols occurs in the cytoplasm prior their entry to the nucleus, and Rpb6 and Rpb5 assemble in a process dependent on the prefoldin-like Bud27 [42]. Similarly, cytoplasmic RNA pol I assembly has been previously proposed in human [44]. In accordance with the role of Rpb6 in RNA pols assembly, the lack of Bud27 alters the correct cytoplasmic assembly of Rpb5 and Rpb6 to the three RNA polymerases, leading to a more instable RNA pol II [42]. Intriguingly, of the five shared subunits, both Rpb6 and Rpb5 have two paralogues in *Trypanosome brucei*, *T. cruzi* and *Leishmania major* [17]. One is identical in domain organisation to the canonical eukaryotic subunit, called RPB6, whereas the other differs in domain organisation, RPB6z. The highly charged N-terminal domain of RPB6 is absent in RPB6z, making it seems similar in structure to the archaeal subunit. Moreover, the trypanosomatid RPB6z subunit also differs from the canonical RPB6 because of a short insertion in the C-terminal domain [17].

4. Rpb8

Rpb8 (also known as ABC14.5) is an essential subunit of 16.5 kDa conserved among eukaryotes and thought to be restricted to them [11, 12, 67]. However, recently, the Rpb8 archaeal orthologues, called G or Rpo8, has been identified in *Sulfolobus acidocaldarius* (18% identity) and other 15 of the 17 Crenarchaea. This protein presumably appeared at an early step in eukaryotic evolution [6, 68]. This Rpo8 subunit (15.1 kDa; 132 residues) is located at peripheral positions, similar to eukaryotic Rpb8, and interacts with subunit Rpo1N, equivalent to the interaction of Rpb8 with Rpb1 in eukaryotes [69].

Rpb8 crystal structure in RNA pol II contains nine closely packed β-strands forming a double OB-fold [7]. Rpb8 interacts with the largest subunit of the RNA pol II, Rpb1, and shows a subunit interface between Rpb3 and Rpb11. Two-hybrid analyses identified similar binding of Rpb8 to the Rpb1-like subunits of RNA pol I (Rpa190) and RNA pol III (Rpc160) [61]. In addition, mutational analysis of *S. cerevisiae* Rpb8 demonstrated a functional interaction with Rpb6 [67].

As opposed to the Rpb8 human orthologue, *S. pombe* Rpb8 cannot replace *S. cerevisiae* protein. A region of 21 amino acids (residues 68–88) of Rpb8 is absent in *S. pombe.* On the contrary, in human, only six of those residues are missing from the sequence. However, overexpression of Rpc160 in *S. cerevisiae* allows *S. pombe* Rpb8 to functionally replace Rpb8, suggesting a specific interaction between the *S. cerevisiae* Rpb8 and Rpc160 subunit [70]. Notably, *S. pombe* Rpb8 selectively affects RNA polymerase III but not RNA polymerase I complex assembly [70].

5. Rpb10

Rpb10, also called AB10β in yeast, is one of the smallest polypeptides (70-aminoacid polypeptide in *S. cerevisiae* and 71 in *S. pombe*) shared by all three RNA polymerases with a molecular

weight of around 10 kDa [71, 72]. Rpb10 has a strong conservation along eukaryotic sequences with 41 identical amino acid positions in fungal, plant and human sequences [73]. In addition, Rpb10 shows a close homology to the N subunit of archaeal enzyme [12, 54, 74] and is loosely related to the smallest enzyme of cytoplasmic DNA viruses [73, 75, 76]. *In vivo* studies in budding yeast have demonstrated that Rpb10 can be functionally replaced by its human homologue (RPB10) [12]. Nevertheless, the N subunit of archaeal cannot replace Rpb10 *in vivo* [73]. However, yeast/archaeal chimeras are largely interchangeable, pointing to a conserved function in their respective transcription complexes [12].

All the eukaryotic forms of Rpb10 share an invariant HVDLIEK motif (located between positions His-53 and Pro-65 in *S. cerevisiae*) critical for the biological activity of Rpb10 [73]. The Rpb10 sequence also harbours an atypical and invariant metal-binding domain $CX_2C…CC$ with Zn^{2+} binding properties *in vitro* [71, 73] that is conserved in eukaryotic, archaeal and viral polypeptides and that is strictly essential for yeast growth, as shown in site-directed mutagenesis experiments [73]. Curiously, mutations out of the metal-chelating domain sequence are fairly tolerant to amino acid replacements [73].

Rpb10 is localised in the periphery of all three RNA polymerases [7, 30, 31]. In budding yeast, Rpb10 was described to interact not only with two essential subunits of the RNA pols I and III, Rpac40 and Rpac19 (homologous to Rpb3 and Rpb11, respectively, in the RNA pol II) but also with the two largest subunits of RNA pol I (Rpa190 and Rpa135) and their homologues in RNA pol III (Rpc160 and Rpc128) [23, 72].

Rpb10 has been found to be involved in the assembly of RNA polymerases in eukaryotes as part of the assembly platform. In fact, it has been proposed that Rpb10 and Rpb12 form a stable complex with Rpb3-Rpb11 (homologous to the bacterial α-subunit homodimer) [77]. Rpb10 and Rpb12 fill concave depressions of Rpb2 and thereby act as structural adaptors between Rpb2 and Rpb3 (reviewed in [1]). Notably, mutations of the invariant HVDLIEK motif lead to a complete depletion of the largest RNA pol I subunit (Rpa190) and decrease the accumulation of mature rRNA species transcribed by RNA pol I [73]. However, Rpb10 could have additional functions beyond RNA polymerases assembly. In accordance, Rpb10 is localised in proximity to TBP in the structural model of the DNA-TBP-TFIIB-RNA pol II transcription initiation complex [79].

6. Rpb12

The eukaryotic subunit Rpb12, also designated as ABC10α [71, 80], together with Rpb10 are the smallest common subunits to the RNA pols. The corresponding gene is essential for growth in *S. cerevisiae* and the lethal phenotype of a yeast *RPB12* null mutant is complemented by expression of its homologous counterparts from *S. pombe* and *Homo sapiens* [12, 81]. A zinc-ribbon motif is conserved in this subunit between eukaryotes and *archaea*. The equivalent to Rpb12 in archaea is the P subunit (RpoP) that shows sequence similarities in their N-terminal zinc ribbon and some highly conserved residues in the C-terminus and that can complement a null RPB12 mutant strain. Mutational analysis of Rpb12 showed that only the first cysteine in the zinc-ribbon motif was essential for viability, whereas the mutation of other three cysteine

residues resulted in temperature-sensitive strains [80]. In the crystal structure of RNA pol II from yeast, Rpb12 contacts subunits Rpb2 and Rpb3 [7].

The importance of Rpb12 in transcription is extrapolated from studies on the archaeal P subunit. The P subunit is involved in promoter opening. The ΔP enzyme is unable to form stable open complexes and its activity can be rescued by the addition of Rpb12 or subunit P to transcription reactions. Notably, mutation of cysteine residues in the zinc ribbon impairs the activity of the enzyme in transcription reactions. The conserved zinc ribbon in the N-terminus seems to be important for proper interaction of the complete subunit with other RNA polymerase subunits, and a 17-amino acid C-terminal peptide is sufficient to support all basic RNA polymerase functions *in vitro* [82].

The contact between *S. cerevisiae* RNA pol III and the assembly factor TFIIIC involves the common subunit Rpb12 and the TFIIIB-assembling subunit of TFIIIC, t131. Moreover, thermosensitive mutation in the conserved C-terminal region Rpb12, which weakens this interaction, can be recovered by overexpression of a variant form of t131 [83].

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