Transcriptional Initiation in Ribosomal Protein Genes in the Fission Yeast *Schizosaccharomyces pombe*  

Diego A. Rojas, Sandra Moreira-Ramos, Fabiola Urbina and Edio Maldonado

**Abstract**

Transcription of class II genes in eukaryotic organisms is carried out by the multi-subunit enzyme RNA polymerase II (RNA pol II) and includes the general transcription factors and the mediator. The region inside the promoters, which recruits and specifies the transcriptional machinery, is called “core promoter” and contains sub-regions called “core promoter elements,” which are necessary for transcription initiation, where the most studied and classic element is the TATA-box. Ribosome protein gene (RPG) promoters do not possess a TATA-box (TATA-less promoters), and those, in particular, in the fission yeast *Schizosaccharomyces pombe* have a TATA-box analog called the HomolD-box. The transcription of RPG promoters is dependent on the RNA pol II transcription system and the HomolD-box is recognized by the transcription factor Rrn7. In this chapter, the authors will describe the general mechanisms associated to the transcription of TATA-less promoters in eukaryotic organisms and how the transcription initiation is carried out in the RPG promoters from those organisms, particularly in *Schizosaccharomyces pombe*. Finally, the authors will analyze the role of the HomolD-box and the transcription factor Rrn7 in the coordination of transcription initiation from RPG promoters and other ribosome-related genes and the presence of transcriptional modules in their promoters, which could be coordinated and regulated by a discrete number of transcription factors.

**Keywords**: transcription, ribosomal protein gene (RPG), RNA polymerase, TATA-less promoter, *Schizosaccharomyces pombe*

**1. Introduction**

Protein synthesis in eukaryotic organisms includes several steps and requires many regulatory events [1, 2]. One of these critical steps is ribosome biogenesis, which includes ribosomal protein gene (RPG) transcription and rRNA synthesis. As in many other central events in the cell, ribosome biosynthesis must be a regulated and coordinated process. A typical coordinated regulation of gene and protein expression is the presence of common DNA elements in the promoters of related genes, which are co-regulated by a discrete number of transcription factors. Those genes under the control of a common DNA element form a transcriptional
module (regulon). In this chapter, the authors will describe the state of the art of several topics associated to the transcription initiation from TATA-less promoters in eukaryotic organisms, such as the transcriptional regulation of RPGs in metazoan cells and the description of a novel mechanism of regulation present in the RPG of the fission yeast Schizosaccharomyces pombe.

2. General features of transcription initiation in the eukaryotic organisms and TATA-less CPEs

Transcription in eukaryotic organisms is carried out by RNA polymerases (RNA pols), which are enzymatic complexes composed by at least 12 subunits. In general, eukaryotic genes are classified as class I, II, and III, where class I genes codify rRNAs; class II codify pre-mRNAs; and class III codify 5S rRNA, tRNAs, and snRNAs, respectively. Transcription of each class of genes is carried out by a different RNA pol. Class I genes are transcribed by RNA pol I, class II genes are transcribed by RNA pol II, and class III genes are transcribed by RNA pol III, respectively. This specific transcription is based on the recognition of specific DNA sequences in the promoters of each class of genes by different transcription factors (TFs) that are able to recruit each specific RNA pol. These sequences are named “core promoter elements” (CPEs) and are located inside the region of the promoter named “core promoter” (CP) that is able to direct the formation of a pre-initiation complex (PIC) and initiate specific transcription of the gene. The CPEs are recognized by TFs specific to each RNA pol, which are called “general transcription factors” (GTFs).

In summary, each RNA pol has a set of specific GTFs and these protein factors are able to recognize the CPEs associated to each class’ gene promoters.

RNA pol II has been widely studied due to the enzyme that transcribes protein-coding genes. One of the first CPEs described in the promoters of class II genes was the so-called TATA-box [3–5]. This CPE is distributed in the promoters of most eukaryotic organisms and is located 25–40 bp upstream from the transcription initiation site. The formation of a PIC on the promoters containing a TATA-box has been extensively studied and characterized [6–8]. The formation of a PIC on the TATA-box starts with the recognition and binding of the transcription factor TATA-binding protein (TBP) to the TATA-box which in turn recruits the other GTFs and RNA pol II to form the PIC, which is able to initiate transcription upon the addition of the ribonucleotides [9, 10] (Figure 1). As it can be seen from the model, RNA pol II is integrated into the PIC in association with TFIIF when the promoter-TBP-TFIIB complex is formed. On the other hand, a fraction of RNA pol II can be purified from cell extracts in association with TFIIF and the mediator, and since those complexes are preformed inside the nucleus, a fast recruitment of the PIC to the promoter could be produced [11–13]. The multi-subunit complex named mediator (a general transcriptional coactivator) is also necessary for the transcription in vivo, in crude cell extracts, of class II genes [14]. In addition, recently, it has been demonstrated that another protein complex is recruited in vivo at most of the class II gene promoters in S. cerevisiae, where it plays a fundamental role in transcription. This multi-protein complex is named SAGA and is composed of several subunits including Gcn5, which have histone acetyltransferase (HAT) activity Spt gene products and TBP-associated factors (TAFs) that are shared with the complex TFIID [15].

In metazoan cells, the transcription factor TBP is tightly associated to TAFs and the TBP-TAF complex is named TFIID [16]. The role of TAFs seems to be the recognition of certain CPEs such as the Inr, motif ten element (MTE), and downstream promoter element (DPE) (see below). However, in yeast, this complex seems to be unstable, since it is possible to purify TBP free of TAFs from yeast cell extracts. Although TAFs are required for in vivo transcription of S. cerevisiae genes, the exact
mechanism of their function has not been identified yet. Interestingly, using an \textit{in vitro} approach using TFIID-depleted yeast cell extracts, it was found that transcription from both TATA-containing and TATA-less promoters is dependent on TFIID, but isolated recombinant TBP can only rescue the transcription of TATA-containing promoters, indicating that additional interactions are necessary to efficiently transcribe TATA-less promoters [17].

However, our vision of transcription initiation on TATA-box-containing promoters cannot explain the mechanisms of transcription initiation on all the class II genes, because the analysis of several other class II gene promoter sequences showed that...
in most of them the TATA-box is absent. Different studies have determined that only 10–15% of mammal core promoters contain a TATA-box element [18–20]. Those promoters that do not contain a TATA-box were named TATA-less promoters and they have also been studied and different CPEs have been characterized.

After the identification of TATA-box sequence, other conserved promoter elements were identified. One of them is the initiator element (Inr), identified as a conserved DNA element in the region near to the transcription start site [21]. This element can not only direct transcription initiation by itself if other CPEs are not present, but also act synergistically in the presence of a TATA-box [22]. The proteins TAF\textsubscript{II}150 and TAF\textsubscript{II}250 have been identified as the transcription factors that are able to recognize the Inr and allow the formation of the PIC in Inr-containing promoters [23, 24]. However, other Inr-containing promoters might be able to direct transcription initiation in a TAFs-independent manner. In those promoters, a few proteins have been identified as Inr-binding factors, such as TF\textsubscript{II}-I and YY1 [25, 26]. Also, in other reports, transcription initiation from the human DNA beta polymerase promoter and from the human dihydrofolate reductase (DHFR) promoter, both TATA-less and Inr-containing promoters, has been achieved using solely TBP, IIB, IIE, IIH, and RNA pol II [26, 27]. This suggests that in some TATA-less promoters, the formation of a functional PIC might follow a common pathway with those TATA-containing promoters.

Another CPE that has been described in TATA-less promoters is the downstream promoter element (DPE), identified first in Drosophila melanogaster [28]. This element is widely distributed in metazoan organisms and is located 28–32 bp downstream from the transcription start site and can be contained in the context of a TATA-box and/or an Inr. Studies in Drosophila have shown that proteins TAF\textsubscript{II}40 and TAF\textsubscript{II}60 might bind to the DPE to improve transcription initiation [29, 30]. Similar elements have not been found in yeast yet.

Several other CPEs have been identified in TATA-less promoters but their contribution to transcription initiation is still poorly understood. Such is the case of motif ten element (MTE) [31]; TFIIB recognition element (BRE) [32]; X core promoter element 1 and 2 (XCPE1 and 2) [33, 34], both of which are able to direct transcription initiation; and the poly-pyrimidine initiator motif (TCT) motif [35]. The TCT motif element will be described in another section of this chapter.

However, using the information from the sequencing of the genomes of other organisms and the new bioinformatics technologies, it is expected that novel conserved CPEs will be identified and characterized and the transcription initiation mechanisms of TATA-less promoters will be revealed. Such is the case of the ribosomal protein genes (RPGs) in the fission yeast Schizosaccharomyces pombe, whose promoters do not contain a TATA-box; instead they possess a conserved sequence, acting as a TATA-analog to direct transcription initiation in those genes. In the next section, the RPG promoter of the fission yeast will be described and the transcription initiation mechanism will be discussed.

3. Characterization of ribosomal protein gene (RPG) promoters of Schizosaccharomyces pombe and their transcription initiation mechanism

3.1 The Schizosaccharomyces pombe RPG transcriptional module: the HomolD-box

The characterization of the promoter sequences of 14 RPGs from the fission yeast Schizosaccharomyces pombe showed discrete conserved modules, which were
named Homol A, B, C, D, and E (Table 1) [36–38]. These homology regions were completely different from those described in promoters of genes from other yeasts and mammals, such as TATA-box, Inr, or DPEs. The function of each Homol element was studied using a promoter-deletion mutant approach [37]. This work showed that the role of Homol A, B, C, and E is associated to the regulation of transcription initiation, and that they might have a upstream activation sequence (UAS)-like function. Only the HomolD sequence was able to function as an element that could direct transcription initiation in the same way as the TATA-box [36]. The conserved sequence of the HomolD-box is the octamer CAGTCACA/G; however, in several sequences, this element is found in the inverted form as TGTGACTG. The HomolD-box is located 39–52 bp upstream of the transcription start site in the same position as the TATA-box in the fission yeast promoters. In an *in vivo* approach, using reporter-gene assays in *S. pombe* cells, it was shown that the HomolD-box is necessary to direct and initiate transcription from the RPG and was postulated to act as a TATA-box analog; in the same work, using an electrophoretic mobility shift assay (EMSA), a novel protein complex that binds to the HomolD-box was identified [36]. In other studies using an *in vitro* approach, it was shown that point mutations in the HomolD-box sequence abolish completely the ability of this element to direct transcription initiation from the RPG [39].

Currently, we know that the genome of *Schizosaccharomyces pombe* contains 141 RPGs encoding the full set of 79 ribosomal proteins. Interestingly, the analysis of the promoter sequences showed that 140 RPGs contained a highly conserved HomolD-box in the region 49–104 bp upstream of the ATG start codon [40]. Additionally, other 59 non-RPGs also showed the presence of the HomolD-box in their promoters. In addition, using promoter databases, it was possible to find HomolD-box sequences in several promoters from other eukaryotic organisms, such as humans and plants, indicating the broad distribution of this novel CPE. Moreover, a functional HomolD-box was found in the human ATPV1H gene where RECQL/DDB1 complex binds to this sequence and is required for *in vitro* transcription [41].

Interestingly, HomolD-boxes in RPG promoters are broadly distributed in the Ascomycota fungus phylum [42]. However, in those organisms closely related to the yeast Saccharomyces cerevisiae, other CPEs, in the same position as the HomolD-box, are present in RPG promoters. These elements are named Rap1 and bind the transcription factor Rap1p [43]. It seems likely that Rap1 replaced the HomolD-box of *Schizosaccharomyces pombe* in Saccharomyces cerevisiae during evolution. Moreover, several other yeast species share both HomolD-box and Rap1 promoter elements [42]. Taking all those observations together, we suggest that RPGs from *S. pombe*, *S. cerevisiae*, Drosophila, and mammals form a transcriptional module that is under the control of the HomolD-box, Rap1-box, and TCT motif (*Drosophila* promoter element), respectively.

| Homol  | Consensus          | Binding TF                  | Function                                      | Reference |
|--------|--------------------|-----------------------------|-----------------------------------------------|-----------|
| HomolA | TCAGTAACGAA        | Unknown                     | UAS-like                                      | [48]      |
| HomolB | AAAAGCTATG         | Unknown                     | UAS-like                                      | [48]      |
| HomolC | AAGAGTAAATCT       | Unknown                     | UAS-like                                      | [48]      |
| HomolD | CAGTCACA/G         | Rrn7 (*S. pombe*) RECL/DDB1 (Human, *S. pombe*) | Transcription initiation and regulation of RPG expression | [36, 39, 48] |
| HomolE | AGGGTAGGGT         | Unknown                     | UAS-like                                      | [37, 48]  |

*Table 1.*

*Homol sequences identified in RPG promoters in *S. pombe*. *
3.2 The role of Rrn7 and CK2 in RPG transcription initiation in *Schizosaccharomyces pombe*

The HomolD-box present in the RPG promoters of the fission yeast is the target of a DNA-binding protein with biochemical features different from TBP. The identification of the HomolD-box-binding protein was achieved using DNA affinity chromatography with double-stranded tandem HomolD-boxes covalently attached to a resin. Proteins bound to the resin were eluted and analyzed by mass spectrometry. The result was that the transcription factor Rrn7 was identified in the protein DNA-bound fraction [39]. This factor is a member of the RNA pol I transcriptional machinery and its function is to transcribe rDNA in the nucleolus. In the rDNA promoter, this factor is able to bind to a conserved box, which is similar to a HomolD-box. Rrn7 showed a specific HomolD-box-binding activity and it is required for the specific transcription of RPGs containing a HomolD-box [39]. Moreover, the GTFs and RNA pol II were required for accurate transcription initiation of a HomolD-box-containing promoter.

Rrn7 is part of the Zn-ribbon protein family related to TFIIB, including the mammalian ortholog TAF1B [44]. It possesses a Zn-ribbon domain in the N-terminal region and two cyclin-like domains in the carboxy-terminal region, displaying domain conservation with the TFIIB family members [44]. Recently, it has been demonstrated that *Schizosaccharomyces pombe* Rrn7 is able to interact with casein kinase 2 (CK2) both *in vitro* and *in vivo*, leading to a functional phosphorylation of threonine 67 in the N-terminal domain. This modification modulates negatively the transcriptional activity of Rrn7, affecting HomolD-directed transcription and DNA-binding activity [45]. Studies in *S. pombe* cell cultures using the specific CK2 inhibitor 4,5,6,7-tetrabromobenzotriazole (TBB) have shown the potentiation of RPG expression during CK2 inhibition. Moreover, using chromatin immunoprecipitation assays, it has been found that CK2 is associated with RPG promoters, suggesting that this kinase has a role in the modulation of ribosomal protein abundance [45].

3.3 Preinitiation complex (PIC) formation on the RPG promoters in *Schizosaccharomyces pombe*

As stated before, RPGs that contain a HomolD-box are transcribed by the RNA pol II transcription apparatus [39]. The formation of the PIC on a HomolD-box-containing promoter was recently described [45, 46]. The first step in the formation of a PIC on these promoters is the binding of Rrn7 to the HomolD-box. As mentioned previously, this step in the PIC establishment might be regulated by phosphorylation of Rrn7 via CK2 protein kinase [45]. Upon the binding of Rrn7 to the HomolD-box, the general transcription factors TBP and TFIIB are able to recognize this DNA-protein complex [46]. After the binding of TBP/TFIIB to the complex, the RNA pol II/TFIIF complex is recruited, which in turn allows the TFIIE factor to be incorporated into the complex [46]. Finally, the mediator and the coactivator PC4 may be incorporated into the PIC and might modulate basal transcription through a putative HomolE-binding factor in those promoters that contain this DNA element. All the steps describing the pathway of complex formation are summarized in Figure 1.

4. Regulation of RPG expression in *Schizosaccharomyces pombe*

The expression of genes containing the HomolD-box in their promoters is almost unknown. However, data from analysis of the RPG expression profiles during
several biological processes in *S. pombe*, for example, the switch from vegetative to meiotic growth and growth under stress conditions, have revealed a tightly coordinated expression for all 141 RPGs. For example, during the switch from vegetative to meiotic growth, transcription of RPG is down-regulated, but then, within a short time, strong reactivation of RPG expression is observed at the beginning of meiosis. The same co-regulation profile is observed in 32 of the 59 non-RPGs that contain a HomolD-box in their core promoter [40]. Many, but not all, of these non-RPGs encode components whose homologs in other organisms are involved in protein biosynthesis and signal transduction [40].

Several promoters of *Schizosaccharomyces pombe* RPGs have been isolated and characterized [47–50], showing that individual ribosomal proteins are encoded by two or three related genes whose promoters contain a HomolD-box. Interestingly, in each gene family, at least one promoter possesses a tandem repeat ACCCTACCCT or the inverted form (AGGGTAGGGT) upstream of the HomolD-box. This sequence corresponds to the HomolE-box, which is considered a proximal UAS-like sequence for HomolD-box-containing promoters, since the presence of this element strongly increases *in vivo* transcription directed by the HomolD-box. Both promoter elements HomolD- and HomolE-boxes must be in the same orientation to be functional. The distance between the boxes is critical in transcription modulation of RPGs, and it has been described that the smaller the distance between HomolD and HomolE, the higher the transcription activity. This distance ranges from 0 to 32 nucleotides.

Now that the complete genome of *Schizosaccharomyces pombe* is available and searchable, it is known that of the 141 RPG promoters, 140 promoters contain a HomolD-box and 62 contain a HomolE-box upstream of the HomolD-box. In contrast, only 5 of the 59 non-RPG promoters containing a HomolD-box contain a HomolE-box [40].

The activity of the HomolE-box must be related to a transcriptional activator in the same manner as the IFH1 element is recognized by a TF (Ifh1p) in *Saccharomyces cerevisiae* RPGs [51, 52]. This element has been identified upstream of the Rap1 sequence in RPG promoters. It is likely that a member of the same family of Ifh1p recognizes the HomolE-box in *S. pombe*. However, the gene encoding this protein has not been identified yet.

The modular architecture of the *Schizosaccharomyces pombe* RPG promoters where the HomolE-box is always found upstream of HomolD indicates that some of the promoters are under the control of the HomolE-box. This fact suggests that there must be a mechanism that regulates RPG transcription through the HomolE-box under specific growth conditions.

Further investigations must be performed to understand how RPG expression is regulated and which are the mechanisms involved in the coordination between HomolD- and HomolE-boxes during RPG transcription. Despite the fact that there are several factors and mechanisms studied in RNA pol II-directed transcription, most of the promoters studied possess a TATA-box, whereas RPG promoters are TATA-less. Moreover, transcriptional initiation and activation from TATA-less promoters are poorly understood both in metazoan and yeast cells. Thus, the RPG promoters and the arrangement of HomolE-HomolD could provide a model to study transcription in TATA-less promoters using a promoter element such as HomolD that is analogous to the TATA-box.

5. Coordinated regulation of the expression of ribosomal components in *Schizosaccharomyces pombe*

Ribosome biogenesis is one of the most complicated processes in eukaryotic cells, requiring coordinated expression of all ribosome components, which are
essential for accurate translation activity. The coordinated regulation and expression of the RPG with other ribosomal components is still poorly understood. However, in the fission yeast *Schizosaccharomyces pombe*, it is known that rRNAs, RPGs, and box C/D snoRNAs contain in their promoters a HomolD-box [39, 53], which might be able to control the expression of those genes. Moreover, the Rrn7 transcription factor, which is the HomolD-box-binding protein in RPG, was found to be responsible for the control of the gene expression of box C/D snoRNAs and RPGs in vivo in *Schizosaccharomyces pombe* cells [53]. Interestingly, the yeast orthologs of the human RECQL/DDB1 complex may recognize the HomolD-box and down-regulate RPG expression [53]. Taking all these results together, we propose a model, in which the HomolD-box is bound by Rrn7 and co-regulates the transcription of RPG, box C/D snoRNA and rRNA genes in the fission yeast. This model is summarized in Figure 2.

Unlike *Schizosaccharomyces pombe* in the case of *Saccharomyces cerevisiae*, there is accumulated evidence that show a putative coordinated model to regulate biogenesis of ribosome components. In this model, CK2 protein kinase is part of protein complexes that regulate RPG expression and rRNA synthesis [54] and interact with the protein Fhl1p that is associated to Ifh1p, which binds to the IFH1 element near to the Rap1 sequence. CK2 and Ifh1p are part of the complex CURI associated to rRNA processing and RPG transcription [55]. Also, in *S. cerevisiae*, another protein has been identified and named protein HmoI, which is associated with the transcription regulation of RPGs and rRNAs [56].

In addition to the role of CK2 to modulate Rrn7 function in *Schizosaccharomyces pombe* during HomolD-box directed transcription, there might be another points of regulation related to protein complexes, such as those described in the yeast *Saccharomyces cerevisiae*.

6. The TCT-motif module in metazoan RPG

The analyses of insect and mammalian RPG promoters have shown the presence of a common core promoter element that is part of the poly-pyrimidine initiator (TCT)-motif family, which is a novel core promoter element necessary to initiate transcription in those genes [35, 57]. In these promoters, the transcription start site (TSS) involves the TCT motif and is positioned around −2 to +6 relative to TSS, competing with exactly the same position as the Inr. However, the features of
the TCT-containing promoters are dissimilar to those Inr-containing promoters. The function of a TCT motif cannot be replaced by an Inr, and the TFIID complex cannot bind to the TCT motif [57]. Recently, studies in Drosophila RPG promoters, which contain a TCT motif, have shown the dependence on a TBP-related factor 2 (TRF2) but not TBP. Using a TRF2-depleted Drosophila whole cell extract, it was shown that human TRF2 [58, 59] and Drosophila TRF2 [60] were able to support TCT-dependent transcription. The TATA-binding protein TBP was unable to support TCT-dependent transcription. However, whether or not the TBP factor is required for TCT-dependent transcription remains to be determined. The proteins able to recognize this element are still unknown, because TRF2 is unable to bind directly to the TCT motif. It is possible that TRF2 interacts with other members of the RNA pol II basal transcription machinery and forms a PIC associated with the TCT motif. In addition, TRF2 is able to bind to the vicinity of the TSS of other genes, since it can be crosslinked and immunoprecipitated from that region, but whether or not this factor binds directly to the Inr motif is still unknown [61].

7. Conclusions

The fission yeast Schizosaccharomyces pombe provides an excellent biological model to study the coordinated expression of ribosome components. The finding that rDNAs, RPGs, and box C/D snoRNAs genes contain a HomolD-box, which is most likely bound by Rrn7, provides the starting point to investigate this issue. The most important questions to answer are: (i) to determine whether or not box C/D snoRNA genes are transcribed by the same transcription apparatus that transcribes RPG; (ii) to identify the signal that activates transcription of HomolD-box containing genes, and (iii) to identify the HomolE-binding protein. The resolution of all these issues would contribute to understand the regulation of RPG transcription in the fission yeast and most likely could be extrapolated to metazoan organisms.

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Conflict of interest

The authors do not have any conflict of interest.

Abbreviations

CP core promoter
CPE core promoter element
DPE downstream promoter element
GTF general transcription factor
Inr initiator
PIC pre-initiation complex
RNA pol RNA polymerase
| Abbreviation | Full Form |
|--------------|-----------|
| RPG          | ribosomal protein genes |
| rRNA         | ribosomal RNA |
| snoRNA       | small nucleolar RNA |
| TAF          | TBP-associated factor |
| TBP          | TATA-binding protein |
| TCT          | poly- pyrimidine initiator motif |
| TF           | transcription factor |
| TRF          | TBP-related factor |
| TSS          | transcription start site |

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