Emerging Views on the CTD Code

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The C-terminal domain (CTD) of RNA polymerase II (Pol II) consists of conserved heptapeptide repeats that function as a binding platform for different protein complexes involved in transcription, RNA processing, export, and chromatin remodeling. The CTD repeats are subject to sequential waves of posttranslational modifications during specific stages of the transcription cycle. These patterned modifications have led to the postulation of the “CTD code” hypothesis, where stage-specific patterns define a spatiotemporal code that is recognized by the appropriate interacting partners. Here, we highlight the role of CTD modifications in directing transcription initiation, elongation, and termination. We examine the major readers, writers, and erasers of the CTD code and examine the relevance of describing patterns of posttranslational modifications as a “code.” Finally, we discuss major questions regarding the function of the newly discovered CTD modifications and the fundamental insights into transcription regulation that will necessarily emerge upon addressing those challenges.

1. Introduction

The transcription of DNA to RNA in eukaryotes is catalyzed by three structurally related RNA polymerases, with each acting on a different class of genes [1]. RNA polymerase I synthesizes most of the ribosomal RNA (rRNA) subunits while RNA polymerase III synthesizes tRNAs, 5S rRNA, and other small RNAs [2–4]. Two of these polymerases account for 75% and 15% of transcription in the cell, respectively [5]. However, the most studied polymerase is RNA Polymerase II (Pol II), which is responsible for the transcription of protein-coding genes, small nuclear RNA (snRNA), and small nucleolar RNA (snoRNA) [6–8]. In higher eukaryotes, Pol II generates long noncoding RNA (lncRNA) and microRNA (miRNA) [9, 10]. Pol II also transcribes cryptic untranslatable transcripts (CUTs) and stable unannotated transcripts (SUTs), which are degraded after synthesis [11–13]. The suppression of CUTs is important to prevent inappropriate transcription within ORFs, to enhance processivity during transcription elongation, and to prevent gene silencing via histone deacetylation [14–18].

Of the twelve Pol II subunits, five are common between the three polymerases [1, 19–21]. It is believed that the specific functions attributed to each polymerase arise from the combined action of remaining nonidentical subunits and other factors that associate with them. An especially unique feature of Pol II is the carboxy-terminal domain (CTD) of its large subunit Rpb1 (Figure 1(a)). The CTD serves as the primary point of contact for a wide variety of molecular machines involved in RNA biogenesis during the transcription cycle (reviewed in [8, 22–32]). This domain consists of a highly conserved heptapeptide repeat: Y1S2P3T4S5P6S7 [33–36]. The number of times this sequence is repeated varies among eukaryotic organisms, ranging from 15 repeats in amoeba, to 26 repeats in the budding yeast Saccharomyces cerevisiae, to 52 repeats in humans. When fully extended, the yeast CTD can span a distance of up to 650 Å, over 4 times the diameter of the core polymerase (Figure 1(b)) [24, 34, 35]. The ability of this repetitive sequence to interact with a wide range of nuclear factors stems from the dynamic plasticity of its structure and the diversity of binding surfaces generated by the multitude of post-translational...
Figure 1: RNA polymerase II structure. (a) Side view of the core Pol II crystal structure containing all twelve subunits and displaying the RNA exit channel (bold arrow) and the positioning of the CTD adapted from Armache et al. [71]. Cartoon in the upper right displays the color coding for the Pol II subunits used in the crystal structure. (b) Illustration of the relative length(s) between the CTD in various conformations and the core Pol II adapted from Meinhart et al. [72]. RNA positioning (red) upon exit of the Pol II and the positioning of the DNA template (blue) upstream and downstream of the core Pol II are also displayed. (c) Known modifications possible on the Pol II CTD are displayed. Glycosylation and phosphorylation are mutually exclusive modifications. Structural images of a heptad repeat in the cis- and trans-conformation are also shown [73–75]. G: β-O-linked N-acetylglucosamine [76]; P: O-linked phosphate.
Figure 2: The primary components of the RNA biogenesis machinery and their interactions with the RNA polymerase II C-terminal domain (CTD). Briefly, hypophosphorylated Pol II assembles at the preinitiation complex (PIC) with the Mediator and general transcription factors (GTFs), with TFIIH associating last. The TFIIH-associated kinase Kin28 phosphorylates Ser5 (shown in red) and Ser7 (shown in purple) on the CTD. Mediator-associated kinase Srb10 also contributes to the phosphorylation of Ser5-P. This mark enables promoter release and mediates interactions with the capping enzyme (CE) complex, Nrd1 component of termination machinery, and Set1 histone methyltransferase, which places trimethyl marks on histone H3K4. The Ser5-P mark also facilitates recruitment of Bur1 kinase. Bur1 places initial Ser2-P marks, which facilitate recruitment of Ctk1 kinase, and continues to replenish Ser7-P marks during elongation. Ctk1 is the primary Ser2 kinase, and its phosphorylation recruits splicing machinery (SP) through Prp40, as well as Set2 histone methyltransferase, which places di- and trimethyl marks on histone H3K36. Cleavage and polyadenylation (PA) machinery are recruited through many factors associating with the CTD. One of the factors, Pcf11, binds cooperatively to Ser2-P with Rtt103. The exonuclease complex (Exo) is also recruited through interaction between CTD and Rtt103 and through cooperative interaction between Rtt103 and Pcf11. Finally, the hypophosphorylated CTD is regenerated through three CTD phosphatases. Ser2-P is removed by the phosphatase Fcp1, while two phosphatases, Rtr1 and Ssu72, combine to remove Ser5-P marks during elongation and at termination, respectively. Upon dephosphorylation, Pol II is released with the assistance of a mechanism involving Pcf11 and can begin another cycle of transcription.
Table 1: Proteins known to bind RNA polymerase II C-terminal domain in *S. cerevisiae*.

| Protein/complex | Role in RNA biogenesis | Phospho-CTD bound | References |
|-----------------|-------------------------|-------------------|------------|
| TFIIIE          | Preinitiation complex   | Hypophosphorylated CTD | [63, 77]   |
| TFIIF           | Preinitiation complex   | Hypophosphorylated CTD | [77]       |
| TBP             | Preinitiation complex (TFIID) | Hypophosphorylated CTD | [78]       |
| Mediator Complex| Transcription activation/repression | Hypophosphorylated CTD | [48, 79]   |
| Ceg1            | Capping                 | Ser5-P            | [80–85]    |
| Abd1            | Capping                 | PCTD              | [83]       |
| Set1            | Histone methylation     | Ser5-P            | [86]       |
| Rpd3C(Rco1)     | Histone deacetylation   | Ser2-P + Ser5-P   | [87, 88]   |
| Spt6            | Histone chaperone       | Ser2-P            | [89]       |
| Nrd1            | Transcription termination/processing | Ser5-P | [90]       |
| Sen1            | Transcription termination/processing | Unknown | [91]       |
| Asr1            | Pol II ubiquitylation (Rpb4/7 Ejection) | Ser5-P | [92]       |
| Ess1            | Proline isomerase       | Ser2-P            | [93, 94]   |
| Set2            | Histone methylation     | Ser2-P + Ser5-P   | [95, 96]   |
| Prp40           | Splicing                | PCTD              | [97]       |
| Npl3            | Promotes elongation/prevents polyadenylation | Ser2-P | [98]       |
| Pcf11           | Cleavage/polyadenylation (CF1A) | Ser2-P | [99, 100] |
| Rna14           | Cleavage/polyadenylation (CF1A) | PCTD | [101]     |
| Rna15           | Cleavage/polyadenylation (CF1A) | PCTD | [101]     |
| Ydh1            | Cleavage/polyadenylation (CPF) | PCTD | [103]     |
| Yth1            | Cleavage/polyadenylation (CPF) | PCTD | [103]     |
| Pta1            | Cleavage/polyadenylation (CPF) | Ser5-P | [104]     |
| Rtt103          | 5′-3′ Exonuclease (Rat1) | Ser2-P | [105]     |
| Sus1            | mRNA export             | Ser5-P            | [106]      |
| Yra1            | mRNA export             | Hyperphosphorylated CTD | [107]     |
| Rsp5            | Pol II ubiquitylation (DNA damage response) | Ser2-P | [108, 109] |
| Hrr25           | DNA damage repair       | PCTD              | [24, 110]  |

CTD-interacting proteins, the processes they are involved in, the phosphorylation state of the CTD with which they associate, and where in the literature the interaction is documented. Ser2-P refers to phosphorylated serine 2, Ser5-P refers to phosphorylated serine 5, and PCTD refers to a mixed phosphorylation state generated by *in vitro* phosphorylation of a CTD peptide with cell extracts. Additional protein-CTD interactions are described [110] but have not been directly tested.

Displayed in Table 1. The focus of this paper is to highlight the recent advances in our understanding of the role of CTD in the early stages of the Pol II transcription cycle, expand on the concept of the CTD code hypothesis, and address the current questions and challenges within the field.

1.1. RNA Pol II Transcription Cycle

1.1.1. Transcription Initiation. Initiation of transcription begins with the recruitment of gene-specific transcription factors (TFs), general transcription factors (GTFs), the Mediator complex, and Pol II. These factors self-assemble into a pre-initiation complex (PIC) at the promoters of Pol II-transcribed genes [29, 32]. Recognition of the promoter is only partially understood, but it is believed to occur via the recognition of the various cis-elements in the promoter region, such as the TATA box. Binding generally occurs within upstream nucleosome-free regions—the DNA centered over promoters flanked by well-positioned nucleosomes [42–45]. There are two main models for how these factors assemble at this region: the sequential model and the holoenzyme model (Figure 3). In both models, TFs first bind at the upstream activating/repressing sequences (UAS/URS) and recruit the transcriptional machinery. In the sequential model, TBP/TFIID/SAGA assembly at the promoter is accompanied by TFIIA, followed by TFIIB [46, 47]. Then, the Mediator complex arrives, connecting the PIC to transcription factors assembled at the UAS/URS [48–51]. This massive complex consists of three large modules known as the head, middle, and tail and an additional kinase module containing a cyclin-dependent kinase (Srb10 in yeast, Cdk8 in metazoans) [52–57]. The Mediator complex is important for basal transcription and plays a central role in facilitating communication between transcription factors bound to regulatory elements and the PIC [49–51, 56–60]. However, there are studies that suggest the Mediator is not present at most genes, and it only associates with a few UAS/URS in an activator- and stress-specific manner [61, 62]. Pol II is then recruited, followed by the last GTF, TFIIH, which is brought to the PIC by TFIIIE [63]. It is possible that several pathways of ordered recruitment exist for GTFs. Other components, including Pol II, TFIIE, and TFIIH, may
be recruited via interactions with the Mediator [64]. The holoenzyme model originated from the observation that Srb proteins, which are components of the Mediator, are tightly associated with core Pol II in the absence of DNA [65]. In this model, Pol II is associated with the Mediator and other general transcription factors as a massive holoenzyme supercomplex that is recruited immediately after TBP binds [66–68]. These complexes have been identified in yeast and mammalian systems [69]. Importantly, Pol II is fully able to activate transcription upon arrival in this state [68, 70].

Two complexes of the PIC, TFIIH and the Mediator, contain important kinases that phosphorylate the CTD. TFIIH is a ten-subunit complex containing two helicases, an ATPase, a ubiquitin ligase, a neddylation regulator, and a cyclin-dependent kinase (Kin28 in yeast, Cdk7 in metazoans) [111–118]. Both Kin28/Cdk7 and Srb10/Cdk8 have been shown to phosphorylate Ser5 (Ser5-P) in vivo, with Kin28/Cdk7 being the dominant kinase [24, 113, 119–124]. The 5’ enriched Ser5-P mark has been linked to a variety of chromatin-modifying and RNA processing events.

1.1.2. Transcription Elongation. Phosphorylation of Ser5 is involved in coordinating the placement of several key posttranslational modifications on chromatin that constitute the histone code [41] (reviewed in [125–127]). The structural properties of chromatin, such as the +1 nucleosome that resides immediately after gene promoters, are thought to provide a significant physical barrier to transcription. This barrier is weakened or removed through the combined action of posttranslational modifications on the flexible histone tails and chromatin remodeling complexes [127]. In this context, the Ser5-P mark recruits the yeast histone methyltransferase Set1. Trimethylation of histone H3K4 by Set1 and subsequent trimethylation of H3K79 by Dot1 are frequently associated with active transcription and have a reciprocal effect on H3K14 acetylation by SAGA and NuA3 [28, 86, 128, 129]. Ser5-P also recruits the histone deacetylase complexes Set3 and Rpd3C(S) [87], which are important for suppressing CUT initiation at promoters [87, 88].

An especially important role of Ser5-P is the recruitment of the capping enzyme complex. The capping complex places the m’G cap on the nascent transcript as it exits the core polymerase, stabilizing the mRNA by preventing its degradation by 5’-3’ exonucleases. The CTD repeats proximal to the core Pol II are ideally placed near the RNA exit tunnel to facilitate this capping reaction [130, 131]. The guanylyltransferase (Ceg1 in S. cerevisiae) and possibly the methyltransferase (Abd1 in cerevisiae) directly interact with both the Ser5-P and the core polymerase [80–85, 132, 133]. Although the recognition of the CTD is structurally different between yeast and mammalian capping enzymes, both complexes require Ser5-P for binding [81, 131]. A parallel line of experiments showed that inhibition of Kin28 kinase activity using a small-molecule inhibitor leads to a severe reduction in Ser5-P and 5’-capping of transcripts at gene promoters [134, 135]. In agreement with this, tethering the mammalian capping enzyme to the CTD rescues the null Ser5 to alanine mutants in the fission yeast Schizosaccharomyces pombe [136]. Interestingly, inactivation of Kin28 does not eliminate transcription: neither steady-state mRNA levels nor the ability to initiate transcription at the inducible GAL1 gene is significantly compromised by the inhibition [135]. A subsequent study using the same chemical inhibition system confirmed the earlier observations but incorrectly attributed small differences in transcript levels to inappropriate normalization of earlier microarray
The phosphorylation occurs at protein-Cdk7 is also the primary kinase that phosphorylates Ser7 by either Srb10 or residual Kin28, su
possible that extremely low levels of Ser5 phosphorylation, equilibrium binding of the small molecule to the kinase; it
inhibition is not an “all or none” phenomenon due to
only focused on chemical inhibition of Kin28 and that the
transcription. It is important to note that these studies
inactivating Kin28 does not significantly impact global
expression (Hein and Ansari, 2007, unpublished data)
[138]. These results strongly support the conclusion that
DNA-PK is required for RNA processing, passage through chromatin,
which are important for transcription activation [28, 86,
163]. Bur1 activity promotes the ubiquitylation of H2BK123
modifying enzymes and the phosphorylation of
CTD. Bur1 activity promotes the ubiquitylation of H2BK123
by the ubiquitin conjugating enzyme Rad6 and Bre1 [129,
163]. H2BK123Ub promotes Set1 trimethylation of histone
H3K4 and subsequent trimethylation of H3K79, both of
which are important for transcription activation [8, 86,
128, 129]. Bur1 also promotes transcription elongation
by coupling promoter-proximal CTN modifications with
promoter-distal marks. Bur1 is recruited to the transcription
complex by the Ser5-P marks placed at the promoter. It
then phosphorylates Ser2 (Ser2-P), priming the CTD for
the recruitment of Ctk1 (Cdk12), the major Ser2 kinase
[164]. Initial CTD phosphorylation also increases the activity
of Ctk1, thereby coupling sequential CTD modifications
(Figure 4(b)) [23, 159, 165, 166]. Interestingly, Bur1 travels
with Pol II and phosphorylates Ser7-P. Although the exact
role of this modification is unclear, it is likely a mark that

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**Figure 4**: Bur1 phosphorylation of the CTD facilitates the transition from initiation to elongation. (a) Ser5-P enhances recruitment and subsequent phosphorylation of Ser2 by Bur1. Bur1 also phosphorylates Spt5, which acts with the Paf1 complex to promote elongation. (b) CTD phosphorylation by Bur1 enhances the activity of Cdk1 on Ser2. The majority of the Ser2-P is maintained by competition between phosphorylation by Ctk1 and dephosphorylation by Fcp1. This increase in Ser2-P facilitates recruitment of many Ser2-P-binding proteins, such as Npl3. 

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The association of these elongation factors, which include Paf1, Spt16, Spt4, Spt5, Spt6, Spn1, and Elf1, occurs concur-
rently on all Pol II genes and is independent of gene length,
type, or expression [146]. The recruitment of these factors
is essential for transcription processivity (Spt4/5) [147–
149], histone regulation (Spt6/16, Spn1, Elf1) [150–156],
and gene activation/3′ processing (Paf1) [157]. Similarly,
mammalian P-TEFb complex is recruited to Pol II at this
stage of transcription [158–161]. This complex contains
a cyclin-dependent kinase (Cdk9) that phosphorylates the
DRB-sensitivity-inducing factor (DSIF), which allows Pol
II to overcome the promoter-proximal pausing induced
by the negative elongation factor (NELF) complex [23,
159]. It is unclear if promoter-proximal pausing occurs
in yeast, but it is known that Bur1 (the yeast homolog
of Cdk9) promotes elongation through post-translational
modification of Spt5 (DSIF) (Figure 4(a)) [162]. Bur1 also
improves transcription elongation through the recruitment
of histone-modifying enzymes and the phosphorylation of
CTD. Bur1 activity promotes the ubiquitylation of H2BK123
by the ubiquitin conjugating enzyme Rad6 and Bre1 [129,
163]. H2BK123Ub promotes Set1 trimethylation of histone
H3K4 and subsequent trimethylation of H3K79, both of
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We and others have recently demonstrated that Kin28/
Cdk7 is also the primary kinase that phosphorylates Ser7
(Ser7-P) [139–141]. The phosphorylation occurs at protein-
coding and noncoding genes and seems to be Mediator
dependent [142]. Cyclin-dependent kinases are thought to
prefer a substrate bearing Ser-Pro rather than Ser-Tyr dipep-
tides [143]. Additionally, while Kin28 has been localized to
promoters [83], Ser7-P marks were thought to be found only
at non-coding genes and at the 3′ end of protein coding genes
[144, 145]. The role of Ser7-P at promoters remains an active
area of investigation.

Following promoter clearance, transcription initiation
factors are exchanged for transcription elongation factors
required for RNA processing, passage through chromatin,
and suppressing cryptic transcripts. In budding yeast, this

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Figure 4: Bur1 phosphorylation of the CTD facilitates the transition from initiation to elongation. (a) Ser5-P enhances recruitment and subsequent phosphorylation of Ser2 by Bur1. Bur1 also phosphorylates Spt5, which acts with the Paf1 complex to promote elongation. (b) CTD phosphorylation by Bur1 enhances the activity of Cdk1 on Ser2. The majority of the Ser2-P is maintained by competition between phosphorylation by Ctk1 and dephosphorylation by Fcp1. This increase in Ser2-P facilitates recruitment of many Ser2-P-binding proteins, such as Npl3.
promotes elongation, as genes with uniformly high levels of Ser7-P are transcribed at significantly higher levels [138].

Most Ser5-P marks are removed near the +1 nucleosome through the action of the newly characterized CTD phosphatase Rtr1 [167]. This phosphatase has been shown to specifically remove Ser5-P marks immediately after promoter clearance. The Ser2-P phosphatase Fcp1 also associates during elongation, but Ser2-P levels remain high across the transcript due to the opposing action of the Ser2-P kinase Ctk1 [168, 169]. It is thought that the Ubp8 component of SAGA travels with Pol II and promotes deubiquitylation of H2BK123Ub [170], which allows the association of Ctk1 and subsequent phosphorylation of Ser2 on the CTD [171].

Ser2-P is critically important for the interaction between the CTD and many histone modifying and RNA processing machines [75, 83, 132, 172–178]. Increasing levels of Ser2-P, in combination with the residual Ser5-P, promote the recruitment of the Set2 methyltransferase, which catalyzes the formation of H3K36me2 and H3K36me3 [95, 96, 179–181]. This leads to the recruitment of the histone deacetylase complex Rpd3S (and the removal of acetylation from histones H3 and H4, thereby resetting the transcription state of the nucleosomes and repressing cryptic transcription within ORFs [87, 182, 183]. Ser2-P is involved in the cotranscriptional and posttranscriptional processing of RNA. Cotranscriptional processing of introns via splicing involves the yeast protein Prp40, which preferentially associates with Ser2-P/Ser5-P marked CTD [97]. Ser2-P is also bound by the SR-like (serine/arginine rich) protein Npl3, which functions in elongation, 3′-end processing, hnRNP formation, and mRNA export [184–187]. Finally, increasing levels of Ser2-P, coupled with depletion of Ser5-P, leads to the recruitment of the termination and polyadenylation machinery (discussed below).

1.1.3. Transcription Termination. The role of CTD modifications in orchestrating transcription termination is better described in recent reviews [31, 188]. In essence, two models have been proposed to explain how Pol II termination occurs, with the emerging view being that it is likely a combination of the two models that best describes the mechanism. The first model, known as the “allosteric” or “antiterminator” model, proposes that transcription through the polyadenylation site leads to an exchange of elongation factors for termination factors, resulting in a conformational change of the elongation complex. Indeed, this model is supported by chromatin immunoprecipitation (ChiP) data of elongation factor exchange at the 3′ end of genes [146, 189]. The second model, known as the “torpedo” model, postulates that cleavage of the transcript at the cleavage and polyadenylation site (CPS) creates an entry site for the 3′-3′ exonuclease Rat1 (Xrn2 in mammals), which degrades the 3′ RNA and promotes Pol II release by “torpedoing” the complex [189–191]. In this model, recruitment of Rat1 is likely to be indirect, possibly through its partner Rtt103. Rtt103 has been shown to bind Ser2-P in a cooperative manner with Pcf11 [192], an essential component of the cleavage factor IA (CFIA) complex that also promotes Pol II release [193]. Interestingly, ChiP data shows Pcf11 at both protein-coding and noncoding genes, and mutating Pcf11 results in terminator read-through due to inefficient cleavage at both gene classes [75, 174, 193–196]. Pcf11 may play an important role in both the termination and processing of protein-coding and non-coding genes.

Processing of Pol II transcripts occurs via one of two distinct, gene class-specific pathways in yeast. Many small mRNAs (<550 bp), CUTs, snRNA, and snoRNA (non-coding genes) are processed via the Nrd1-Nab3 pathway (Figure 5), while longer mRNAs (protein-coding genes) are processed in a polyadenylation-dependent process (Figure 6) [8, 11, 12, 27, 31, 178, 195, 197–199]. The decision to proceed down a certain processing path is modulated by the phosphorylation state of the CTD. Nrd1 preferentially associates with Ser5-P, and its recruitment is also enhanced via histone H3K4 trimethylation by Set1 [90, 200]. Nrd1 and Nab3 can scan the nascent RNA for specific sequence elements (GUAA/G or UUGA for Nrd1, and UCUU or CUUG for Nab3) as it exits the core polymerase [90, 199, 201–207]. The helicase Sen1 (senataxin in humans), which exists in complex with Nrd1 and Nab3, resolves the DNA:RNA hybrids known as R-loops that form between the template DNA and the nascent RNA, keeping the specific sequence elements exposed and preserving genomic stability [208–210]. The involvement of Sen1 is dependent on the phosphatase Gcl7, which dephosphorylates Sen1 and is essential for the proper termination of snRNA and snoRNA transcripts [211]. Upon detecting its consensus sequence elements, the Nrd1 complex and the Rnt1 endonuclease cleave these short transcripts [195, 212–214], which are then trimmed at the 3′ end by the TRAMP complex and the exosome [6, 215–217]. Nrd1 then disengages from the transcription complex, with help from antagonizing Ser2-P marks [198]. Unlike snRNA/snoRNAs, which have protective structural elements in the RNA, Nrd1-terminated CUTs have no protective elements at their 3′ ends and are thus fully degraded by TRAMP after cleavage [8, 11, 12]. Nrd1 has been mapped to the 5′ end of transcribed regions, but a recent study has demonstrated that Nrd1 occupancy is maintained across the open reading frame of genes [196]. Although no homolog of Nrd1 has been found in mammalian cells, the Integrator complex that is involved in 3′ processing of snRNA transcripts is recruited by Ser7-P [218]. The association of this complex with Ser7-P CTD was demonstrated by the abolishment of this interaction upon mutation of Ser7 to alanine [145]. Subsequent analysis using a panel of CTD peptides determined that the Integrator prefers to bind a diphosphorylated CTD substrate spanning two heptad repeats in the S7-P-S2-P conformation [219]. It is possible that Ser7-P may serve as a similar scaffold for snRNA and snoRNA processing machinery in yeast.

The second pathway, used for the processing of most mRNA transcripts, involves the cleavage and polyadenylation factor (CPF) complex, cleavage factor IA and IB (CFIA and CFIB) complexes, and the exosome (Figure 6) [31, 195, 197]. Many of the termination and 3′ processing factors involved in this process are known to preferentially associate with Ser2-P or Ser2-P/Ser5-P enriched CTD including: Npl3, Rtt103, Rna14, Rna15, Ydh1, Yhh1, Pta1, and Pcf11. In this pathway, Rna15 competes with Npl3 for recognition of a
Figure 5: Nrd1-dependent termination pathway. The Nrd1-Nab3-Sen1 complex is recruited via interaction between Nrd1 and Ser5-P. This recruitment is facilitated by H3K4me3, which is placed by the Set1 histone methyltransferase. The mechanisms by which the Ssu72 and Glc7 phosphatases promote termination are still unclear, but it may be that the dephosphorylation of Sen1 by Glc7 and of the CTD by Ssu72 causes the polymerase to pause, and allowing the termination machinery to associate. During elongation, both Nrd1 and Nab3 scan the nascent RNA for their preferred sequences (see text for details). Upon finding their consensus sequences, Nrd1-Nab3-Sen1 complex is able to be associated with the RNA. The endonucleases Rnt1 and Ysh1 may contribute to the cleavage of the RNA, which is followed by 3′-5′ trimming the transcript by the TRAMP complex and by the degradation of the remaining RNA exiting Pol II by the 5′-3′ exonuclease Rat1 (Exo).

UA-rich site in the nascent RNA [98, 187]. This competition is removed upon phosphorylation of Npl3 by casein kinase 2 (CK2) [98]. Rna15 can then bind the nascent RNA and promote endonucleolytic cleavage followed by polyadenylation by the polyadenylate polymerase (Pap1) [197, 220]. Polyadenylation-binding proteins (PAB) then protect the mature transcript from exonucleolytic degradation (Figure 6) [221].

In both pathways, the CTD is hypophosphorylated by the combined action of two essential phosphatases at the end of transcription: Ssu72 and Fcp1. Ssu72 is a member of the Associated with Pta1 (APT) complex, which is present at both gene classes and is involved in 3′ processing of non-coding RNAs [222]. As such, Ssu72 is primarily localized at the 3′ end of transcripts [222], although there is one instance in which it has been found at promoters [223]. Temperature-sensitive mutants of Ssu72 exhibit read-through at both protein-coding and non-coding transcripts [224]. Ssu72 is the primary Ser5-P phosphatase [225], and its phosphatase activity is enhanced by the prolyl isomerase Ess1/Pin1 and by interacting with Pta1/symplekin [226–228]. Recently, crystal structures have shed light on the mechanism of Ssu72: the phosphatase binds to Ser5-P only when the adjacent Pro6 is in the cis-conformation [73, 74]. In contrast to Ssu72, Fcp1 associates with TFIIF during transcription and is found across the entire transcribed
Figure 6: The mRNA termination pathway. Rna15 competes with Npl3 for binding to the nascent RNA. CK2 phosphorylates Npl3, allowing Rna15 to find its preferred binding site (an A/U-rich region) in the RNA. The CPF and CFIA components assemble through interactions with the CTD and the Yth1 component of CPF cleaves the nascent RNA at the polyadenylation site, followed by polyadenylation by Pap1. Then the Rat1 exonuclease complex associates via cooperative interaction between Pcf11 and Rtt103 and leads to termination and dissociation of Pol II.

region [168, 169, 229, 230]. Although it has Ser5-P and Ser2-P phosphatase activity in vitro, Fcp1 is considered a Ser2-P-specific phosphatase in vivo [231, 232]. Fcp1 activity is enhanced upon phosphorylation of Fcp1 by CK2 [233]. Defects in Fcp1 also result in transcription read-through at Nrd1-dependent transcripts [198]. Though it is unclear which phosphatase removes Ser7-P, new data from our lab suggest that Ssu72 may be the phosphatase that removes Ser7-P at both the 5′ and 3′ ends of genes [234]. Removal of this mark may be even more important than its placement as mutation of Ser7 to alanine slows growth while mutating Ser7 to the phosphomimic glutamate is lethal [144].

Global dephosphorylation of the CTD facilitates the release of Pol II from DNA, which can then recycle to promoters for the next cycle of transcription [224, 235, 236]. It has been proposed that transcription termination and subsequent dephosphorylation of the CTD is coupled to transcription reinitiation through gene looping, by which the promoter and terminator regions are brought together, allowing Pol II to associate more rapidly with the PIC [237, 238]. Intriguingly, Ssu72 and the GTF TFIIB have been shown to be essential in gene looping [223, 239]. Taken together, the phosphorylation and dephosphorylation of the CTD is intimately involved in every phase of transcription, from initiation, to elongation, to termination, and possibly reinitiation.

1.1.4. Other Regulatory Roles of the CTD. In addition to its many roles in transcription initiation, elongation, and termination, the CTD has been implicated in a variety of transcription-extrinsic processes, such as mRNA export and stress response. mRNA export (reviewed in [240–242]) requires the packaging of the mRNA into export-competent messenger ribonucleoprotein (mRNP) via association with the
Figure 7: Sus1 in TREX2 and SAGA complexes coordinates mRNA export. (a) Subunit compositions of TREX2 and SAGA complexes are shown, highlighting Sus1 (asterisk). (b) mRNA export coordinated by Sus1. Sus1 binds Ser2-P and Ser2-P/Ser5-P CTD, connecting the CTD to the SAGA histone acetyltransferase complex. Sus1 also interacts with Yra1 component of the THO/TREX complex on the RNA. Mex67-Mtr2 are recruited by interaction with Yra1 and help form the export-competent mRNP. At the nuclear pore complex (NPC), Mlp1-Mlp2 interact with the polyA mRNA-binding protein Nab2 and Mex67 interacts with Sac3 of the TREX2 complex. This interaction brings the export-competent mRNP to the NPC in preparation for export to the cytoplasm. Sus1 is a component of both TREX2 and SAGA and serves to tether actively transcribed gene promoters to the NPC.

Mex67:Mtr2 heterodimer [243]. This heterodimer is brought to the mRNA by Yra1 and Sub2, components of the THO subunit of the TREX1 complex [242]. The process of mRNP export is coordinated by the protein Sus1. This central protein directly interacts with Ser5-P and Ser2-P/Ser5-P of the CTD, Ub8 subunit of the SAGA complex, Yra1 subunit of the TREX1 complex, and Sac3 subunit of the TREX2 complex at the nuclear pore (Figure 7) [106, 244].

The CTD is also involved in stress response. The ubiquitin ligase Rsp5 binds the CTD and ubiquitylates Pol II in response to DNA damage [245, 246]. Similarly, UV-induced DNA damage in mammalian fibroblasts results in hyperphosphorylation of the CTD by the mammalian positive transcription elongation factor b (P-TEFb), which then regulates Pol II ubiquitylation and subsequent degradation [247]. Under conditions not well understood, Ser5-P can...
also recruit the Asr1 ubiquitin ligase, which ubiquitylates the Rpb1 and Rpb2 subunits of Pol II. This ubiquitylation promotes ejection of the Rpb4/7 heterodimer from the core polymerase and inactivates Pol II, which may provide a mechanism for stopping polymerases engaged in abortive or cryptic transcription [92].

2. The CTD Code Controversy: Is It a Code?

The concept of the CTD code was first proposed due to the enormous amount of information that can be encoded via post-translational modification of the CTD repeats [40, 248]. The code would coordinate the assembly of complexes that “read, write, and erase” the code during transcription. Historically, the Ser5-P and Ser2-P marks have been the best characterized, with the canonical distribution of Ser5-P being enriched at the 5’ end of genes and Ser2-P enriched towards the 3’ end. Recently, our lab and several others have been able to map the phospho-CTD occupancy profiles across the yeast genome [135, 138, 139, 146, 196]. There are interesting discrepancies between the observations made by various groups. For example, Mayer et al. find the canonical profile to be present at every gene with Ser7-P profiles overlapping with Ser5-P [146], while we find clusters of genes with noncanonical CTD profiles for Ser2-P, Ser5-P, and Ser7-P [138]. We observe gene-specific phosphorylation profiles, with Ser2-P levels being significantly lower at non-coding genes and Ser7-P profiles diverging from Ser5-P profiles only at protein-coding genes. The distinct patterns of CTD marks at these two gene classes reflect the different mechanisms of transcription termination and 3’ end processing machinery that act on these two classes of RNA. Similarly, Kim et al. also observe differences in phospho-CTD profiles at snoRNAs and at introns [196]. However, the positions of the Ser5-P and Ser7-P peaks in Kim et al. are offset from Tietjen et al. and Mayer et al. Importantly, all three genome-wide analyses reveal an unexpected degree of cooccurrence of CTD marks, suggesting a bivalent or even multivalent mode of recognition by docking partners. In support of this idea, the Set2 histone methyltransferase and the Integrator complex have been shown to prefer a bivalent mark rather than a single phosphorylated residue [95, 96, 219].

In addition to the various phosphorylation marks, the isomerization state of the CTD also contributes to the complexity of the code. For example, Pcf11 binds the CTD in the trans-conformation while Ssu72 prefers a cis-CTD as substrate [73–75]. Many in the transcription field have made the argument that the CTD code is not a true code because it does not convey biological information via a rigorous decoding key. However, research in the last several years has demonstrated that specific phosphorylation marks and proline isomerization are important for conveying information from cis-elements encountered by Pol II to the protein complexes necessary for successful progression through the transcription cycle. Further investigation into the mechanism of this information transfer will resolve the controversy over the existence of a CTD code.

3. Future Directions

Extraordinarily rapid progress has been made over the last several years in the field of CTD research; however, many important questions remain unanswered. Although the profiles of Ser7-P have been mapped and several of its kinases discovered, its function at protein coding genes remains unclear. Additionally, most of the kinases identified are established members of the transcription initiation or elongation complexes. One could expect to find new enzymes that could modulate the CTD in response to signals, as post-translational modifications are often used as a mechanism for cells to respond to external stimuli. The recent discovery of Ser7-P at elongating Pol II has also prompted the question of whether Tyr1 and Thr4 phosphorylation (Tyr1-P and Thr4-P) occurs? Tyr1 can be phosphorylated by c-Abl in mammals, but no homolog is present in yeast [249]. In addition, both Tyr1-P and Thr4-P has been detected in S. pombe [250]. Interestingly, Tyr1-P and Thr4-P were found in both the hyperphosphorylated and hypophosphorylated states of Pol II, opening the possibility of CTD function independent of transcription. However, neither the profile nor function of these potential modifications have been extensively characterized.

The role of non-canonical residues and their modification states on mammalian CTD remain to be explored. In mammals, the Ser7 residue is only weakly conserved in polymerase-distal repeats of the CTD, often changed to lysine or arginine [144]. Interestingly, Arg1810 of rpb1 in the human CTD is methylated by the coactivator-associated methyltransferase1 (CARM1) [39]. This methylation occurs prior to both transcription initiation and phosphorylation of Ser2 or Ser5, and mutation of this residue results in the improper expression of a variety of snRNAs and snoRNAs. In addition to methylation, the CTD may also be subject to glycosylation. Recent studies suggest O-GlcNac are transferred to Ser5 and Ser7 by O-GlcNac transferase and removed by O-GlcNac amidinase during PIC assembly. This cycling of O-GlcNac may be important for preventing aberrant CTD phosphorylation by TFIIF [251].

Besides the characterization of novel marks, significant structural challenges remain for understanding the known phosphomarks. One limitation of ChIP is its inability to identify the exact phosphorylation patterns across individual CTD repeats in vivo at different points during the transcription cycle. Recent mutational analysis suggests that the minimal functional unit of the CTD consists of three consecutive Ser-Pro dipeptide residues in a S2-S5-S2 configuration [36], but it is unclear if all three serines can be phosphorylated on one functional unit or if phosphorylation alternates between repeats. The lack of positively charged amino acids makes the phoshpo-CTD patterns difficult to decipher via mass spectrometry. Additionally, the highly repetitive nature of the CTD makes it difficult to distinguish between the first repeat and the twenty-first. Consequently, the position along the CTD where interacting partners associate remains a mystery. Mutation of Ser2 to glutamate in the core-distal repeats and mutation of Ser5 to glutamate in the core-proximal repeats are lethal [252]. However, this
does not directly demonstrate whether the proteins that bind these phosphorylated residues are located at these repeats. Characterizing the phosphorylation patterns and protein occupancies at individual repeats will help determine the existence of a “CTD recognition” code, and this promises to be one of the most exciting and important challenges in the future of CTD research.

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References
[1] P. Cramer, K. J. Armache, S. Baumli et al., “Structure of eukaryotic RNA polymerases,” Annual Review of Biophysics, vol. 37, pp. 337–352, 2008.
[2] I. Grummt, “Life on a planet of its own: regulation of RNA polymerase I transcription in the nucleolus,” Genes & Development, vol. 17, no. 14, pp. 1691–1702, 2003.
[3] J. Russell and J. C. B. M. Zomerdijk, “RNA-polymerase-I-directed rDNA transcription, life and works,” Trends in Biochemical Sciences, vol. 30, no. 2, pp. 87–96, 2005.
[4] G. Dieci, G. Fiorino, M. Castenuvolo, M. Teichmann, and A. Pagano, “The expanding RNA polymerase III transcription,” Trends in Genetics, vol. 23, no. 12, pp. 614–622, 2007.
[5] M. Werner, P. Thuriaux, and J. Soutourina, “Structure-function analysis of RNA polymerases I and III,” Current Opinion in Structural Biology, vol. 19, no. 6, pp. 740–745, 2009.
[6] F. Wyers, M. Rougemaille, G. Badis et al., “Cryptic Pol II transcripts are degraded by a nuclear quality control pathway involving a new poly(A) polymerase,” Cell, vol. 121, no. 5, pp. 725–737, 2005.
[7] C. A. Davis and M. Ares, “Accumulation of unstable promoter-associated transcripts upon loss of the nuclear exosome subunit Rrp6 in Saccharomyces cerevisiae,” Proceedings of the National Academy of Sciences of the United States of America, vol. 103, no. 9, pp. 3262–3267, 2006.
[8] S. Lykke-Andersen and T. H. Jensen, “Overlapping pathways dictate termination of RNA polymerase II transcription,” Biochimie, vol. 89, no. 10, pp. 1177–1182, 2007.
[9] M. Faller and F. Guo, “MicroRNA biogenesis: there’s more than one way to skin a cat,” Biochimica et Biophysica Acta, vol. 1779, no. 11, pp. 663–667, 2008.
[10] M. Guitman, I. Amit, M. Garber et al., “Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals,” Nature, vol. 458, no. 7235, pp. 223–227, 2009.
[11] J. T. Arigo, D. E. Eyler, K. L. Carroll, and J. L. Corden, “Termination of cryptic unstable transcripts is directed by yeast RNA-binding proteins Nrd1 and Nab3,” Molecular Cell, vol. 23, no. 6, pp. 841–851, 2006.
[12] M. Thiebaut, E. Kisseleva-Romanova, M. Rougemaille, J. Boulay, and D. Libri, “Transcription termination and nuclear degradation of cryptic unstable transcripts: a role for the nrd1-nab3 pathway in genome surveillance,” Molecular Cell, vol. 23, no. 6, pp. 853–864, 2006.
[13] S. Y. Ying and S. L. Lin, “Intron-mediated RNA interference and microRNA biogenesis,” Methods in Molecular Biology, vol. 487, pp. 387–413, 2009.
[14] C. D. Kaplan, L. Laprade, and F. Winston, “Transcription elongation factors repress transcription initiation from cryptic sites,” Science, vol. 301, no. 5636, pp. 1096–1099, 2003.
[15] J. Camblong, N. Iglesias, C. Fickentscher, G. Diepopo, and F. Stutz, “Antisense RNA stabilization induces transcriptional gene silencing via histone deacetylation in S. cerevisiae,” Cell, vol. 131, no. 4, pp. 706–717, 2007.
[16] F. De Santa, I. Barozzi, F. Mietton et al., “A large fraction of extragenic RNA Pol II transcription sites overlap enhancers,” PLoS Biology, vol. 8, no. 5, Article ID e1000384, 2010.
[17] U. A. Örom, T. Derrien, M. Beringer et al., “Long noncoding RNAs with enhancer-like function in human cells,” Cell, vol. 143, no. 1, pp. 46–58, 2010.
[18] F. Sato, S. Tsuchiya, S. J. Meltzer, and K. Shimizu, “MicroRNAs and epigenetics,” FEBS Journal, vol. 278, no. 10, pp. 1598–1609, 2011.
[19] R. A. Young, “RNA polymerase II,” Annual Review of Biochemistry, vol. 60, pp. 689–715, 1991.
[20] N. Woychik and R. Young, “Exploring RNA polymerase II structure and function,” in Transcription: Mechanisms and Regulation, R. C. Conaway and J. W. Conaway, Eds., pp. 227–242, Raven Press, New York, NY, USA, 1994.
[68] A. Barberis, J. Pearlberg, N. Simkovich et al., "Contact with a component of the polymerase II holoenzyme suffices for gene activation," *Cell*, vol. 81, no. 3, pp. 359–368, 1995.

[69] D. M. Chao, E. L. Gadbois, P. J. Murray et al., "A mammalian SRB protein associated with an RNA polymerase II holoenzyme," *Nature*, vol. 380, no. 6569, pp. 82–85, 1996.

[70] A. J. Koleske and R. A. Young, "The RNA polymerase II holoenzyme and its implications for gene regulation," *Trends in Biochemical Sciences*, vol. 20, no. 3, pp. 113–116, 1995.

[71] K. J. Armache, H. Kettenberger, and P. Cramer, "Architecture of initiation-competent 12-subunit RNA polymerase II," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 12, pp. 6964–6968, 2003.

[72] A. Meinhart, T. Kamenski, S. Hoepfner, S. Baumli, and P. Cramer, "A structural perspective of CTD function," *Genes & Development*, vol. 19, no. 12, pp. 1401–1415, 2005.

[73] K. Xiang, T. Nagaike, S. Xiang et al., "Crystal structure of the human symplekin-Ssu72-CTD phosphopeptide complex," *Nature*, vol. 467, no. 7316, pp. 729–733, 2010.

[74] J. W. Werner-Allen, C. -J. Lee, P. Liu et al., "cis-proline-mediated ser(P)5 dephosphorylation by the RNA polymerase II C-terminal domain phosphatase Ssu72," *Journal of Biological Chemistry*, vol. 286, no. 7, pp. 5717–5726, 2011.

[75] A. Meinhart and P. Cramer, "Recognition of RNA polymerase II carboxy-terminal domain by 3′-RNA-processing factors," *Nature*, vol. 430, no. 6996, pp. 223–226, 2004.

[76] W. G. Kelly, M. E. Dahmus, and G. W. Hart, "RNA polymerase II is a glycoprotein. Modification of the COOH-terminal domain by O-GlcNAc," *Journal of Biological Chemistry*, vol. 268, no. 14, pp. 10416–10424, 1993.

[77] M. E. Kang and M. E. Dahmus, "The photoactivated cross-linking of recombinant C-terminal domain to proteins in a HeLa cell transcription extract that comigrate with transcription factors IIE and IIF," *Journal of Biological Chemistry*, vol. 270, no. 40, pp. 23390–23397, 1995.

[78] A. Usheva, E. Maldonado, A. Goldring et al., "Specific interaction between the nonphosphorylated form of RNA polymerase II and the TATA-binding protein," *Cell*, vol. 69, no. 5, pp. 871–881, 1992.

[79] L. C. Myers, C. M. Gustafsson, D. A. Bushnell et al., "The Med proteins of yeast and their function through the RNA polymerase II carboxy-terminal domain," *Genes & Development*, vol. 12, no. 1, pp. 45–54, 1998.

[80] E. J. Cho, T. Takagi, C. R. Moore, and S. Buratowski, "mRNA capping enzyme is recruited to the transcription complex by phosphorylation of the RNA polymerase II carboxy-terminal domain," *Genes & Development*, vol. 11, no. 24, pp. 3319–3326, 1997.

[81] C. Fabrega, V. Shen, S. Shuman, and C. D. Lima, "Structure of an mRNA capping enzyme bound to the phosphorylated carboxy-terminal domain of RNA polymerase II," *Molecular Cell*, vol. 11, no. 6, pp. 1549–1561, 2003.

[82] C. K. Ho and S. Shuman, "Distinct roles for CTD Ser-2 and Ser-5 phosphorylation in the recruitment and allosteric activation of mammalian mRNA capping enzyme," *Molecular Cell*, vol. 3, no. 3, pp. 405–411, 1999.

[83] P. Komarnitsky, E. J. Cho, and S. Buratowski, "Different phosphorylated forms of RNA polymerase II and associated mRNA processing factors during transcription," *Genes & Development*, vol. 14, no. 19, pp. 2452–2460, 2000.

[84] S. McCracken, N. Fong, E. Rosonina et al., "5′-Capping enzymes are targeted to pre-mRNA by binding to the phosphorylated carboxy-terminal domain of RNA polymerase II," *Genes & Development*, vol. 11, no. 24, pp. 3306–3318, 1997.

[85] S. C. Schroeder, B. Schwer, S. Shuman, and D. Bentley, "Dynamic association of capping enzymes with transcribing RNA polymerase II," *Genes & Development*, vol. 14, no. 19, pp. 2435–2440, 2000.

[86] H. H. Ng, F. Robert, R. A. Young, and K. Struhl, "Targeted recruitment of Set1 histone methylase by elongating Pol II provides a localized mark and memory of recent transcriptional activity," *Molecular Cell*, vol. 11, no. 3, pp. 709–719, 2003.

[87] C. K. Govind, H. Qiu, D. S. Ginsburg et al., "Phosphorylated Pol II CTD recruits multiple HDACs, including Rpd3C(S), for methylation-dependent decetylation of ORF nucleosomes," *Molecular Cell*, vol. 39, no. 2, pp. 234–246, 2010.

[88] S. Drouin, L. Laramée, P. E. Jacques, A. Forest, M. Bergeron, and F. Robert, "DSIF and RNA polymerase II CTD phosphorylation coordinate the recruitment of Rpd3S to actively transcribed genes," *PLoS Genetics*, vol. 6, no. 10, Article ID e1001173, pp. 1–12, 2010.

[89] S. M. Yoh, H. Cho, L. Pickle, R. M. Evans, and K. A. Jones, "The Spt6 SH2 domain binds Ser2-P RNAIP to direct Iws1-dependent mRNA splicing and export," *Genes & Development*, vol. 21, no. 2, pp. 160–174, 2007.

[90] L. Vasiljeva, M. Kim, H. Mutschler, S. Buratowski, and A. Meinhart, "The Nrd1-Nab3-Sen1 termination complex interacts with the Ser5-phosphorylated RNA polymerase II C-terminal domain," *Nature Structural & Molecular Biology*, vol. 15, no. 8, pp. 795–804, 2008.

[91] J. S. Finkel, K. Chinchilla, D. Ursic, and M. R. Culbertson, "Sen1p performs two genetically separable functions in transcription and processing of U5 small nuclear RNA in Saccharomyces cerevisiae," *Genetics*, vol. 184, no. 1, pp. 107–118, 2010.

[92] A. Daunly, F. Geng, M. Muratani, J. M. Geisinger, S. E. Salghetti, and W. P. Tansey, "Modulation of RNA polymerase II subunit composition by ubiquitylation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 50, pp. 19649–19654, 2008.

[93] D. P. Morris, H. P. Phatnani, and A. L. Greenleaf, "Phospho-carboxy-terminal domain binding and the role of a prolyl isomerase in pre-mRNA 3′-end formation," *Journal of Biological Chemistry*, vol. 274, no. 44, pp. 31583–31587, 1999.

[94] X. Wu, C. B. Wilcox, G. Devasahayam et al., "The Ess1 prolyl isomerase is linked to chromatin remodeling complexes and the general transcription machinery," *The EMBO Journal*, vol. 19, no. 14, pp. 3727–3738, 2000.

[95] K. O. Kizer, H. P. Phatnani, Y. Shibata, H. Hall, A. L. Greenleaf, and B. D. Strahl, "A novel domain in Set2 mediates RNA polymerase II interaction and couples histone H3 K36 methylation with transcription elongation," *Molecular and Cellular Biology*, vol. 25, no. 8, pp. 3305–3316, 2005.

[96] E. Vojnic, B. Simon, B. D. Strahl, M. Satllter, and P. Cramer, "Structure and carboxy-terminal domain (CTD) binding of the Set2 SR1 domain that couples histone H3 Lys36 methylation to transcription," *Journal of Biological Chemistry*, vol. 281, no. 1, pp. 13–15, 2006.

[97] D. P. Morris and A. L. Greenleaf, "The splicing factor, Prp40, binds the phosphorylated carboxy-terminal domain of RNA Polymerase II," *Journal of Biological Chemistry*, vol. 275, no. 51, pp. 39935–39943, 2000.

[98] J. L. Dermedy, J. M. Dreyfuss, J. Villén et al., "Unphosphorylated SR-like protein Npl3 stimulates RNA polymerase II elongation," *PLoS One*, vol. 3, no. 9, Article ID e3273, 2008.
C. G. Noble, D. Hollingworth, S. R. Martin et al., “Key features of the interaction between Pcf11 CID and RNA polymerase II CTD,” *Nature Structural & Molecular Biology*, vol. 12, no. 2, pp. 144–151, 2005.

D. Hollingworth, C. G. Noble, I. A. Taylor, and A. Ramos, “RNA polymerase II CTD phosphopeptides compete with RNA for the interaction with Pcf11,” *RNA*, vol. 12, no. 4, pp. 555–560, 2006.

D. Barilla, B. A. Lee, and N. J. Proudfoot, “Cleavage/polyadenylation factor IA associates with the carboxyl-terminal domain of RNA polymerase II in Saccharomyces cerevisiae,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 2, pp. 445–450, 2001.

A. Kyburz, M. Sadowski, B. Dichtl, and W. Keller, “The role of the yeast cleavage and polyadenylation factor subunit Ydh1p/CTrp2 in pre-mRNA 3′-end formation,” *Nucleic Acids Research*, vol. 31, no. 14, pp. 3936–3945, 2003.

B. Dichtl, D. Blank, M. Sadowski, W. Hubner, S. Weiser, and W. Keller, “Yihlp/CTrp directly links poly(A) site recognition and RNA polymerase II transcription termination,” *The EMBO Journal*, vol. 21, no. 15, pp. 4125–4135, 2002.

C. R. Rodriguez, E. J. Cho, M. C. Keogh, C. L. Moore, A. L. Greenleaf, and S. Buratowski, “Kin28, the TFIIH-associated carboxy-terminal domain kinase, facilitates the recruitment of mRNA processing machinery to RNA polymerase II,” *Molecular and Cellular Biology*, vol. 20, no. 1, pp. 104–112, 2000.

M. Kim, N. J. Krogan, L. Vasiljeva et al., “The yeast Rat1 exonuclease promotes transcription termination by RNA polymerase II,” *Nature*, vol. 432, no. 7016, pp. 517–522, 2004.

P. Pascual-Garcia, C. K. Govind, E. Queralt et al., “Sus1 is recruited to coding regions and functions during transcription elongation in association with SAGA and TREX2,” *Genes & Development*, vol. 22, no. 20, pp. 2811–2822, 2008.

A. L. MacKellar and A. L. Greenleaf, “Cotranscriptional association of mRNA export factor Yra1 with C-terminal domain of RNA polymerase II,” *Journal of Biological Chemistry*, vol. 286, no. 42, pp. 36385–36395, 2011.

A. Chang, S. Cheang, X. Expanol, and M. Sudol, “Rsp5 WW domains interact directly with the carboxyl-terminal domain of RNA polymerase II,” *Journal of Biological Chemistry*, vol. 275, no. 27, pp. 20562–20571, 2000.

B. P. Somesh, J. Reid, W. F. Liu et al., “Multiple mechanisms confining RNA polymerase II ubiquitination to polymerases undergoing transcriptional arrest,” *Cell*, vol. 121, no. 6, pp. 913–923, 2005.

H. P. Phatnani, J. C. Jones, and A. L. Greenleaf, “Expanding the functional repertoire of CTD kinase I and RNA polymerase II: novel phosphoCTD-associating proteins in the yeast proteome,” *Biochemistry*, vol. 43, no. 50, pp. 15702–15719, 2004.

J. Q. Svejstrup, W. J. Feaver, J. LaPointe, and R. D. Kornberg, “RNA polymerase transcription factor I IH holoenzyme from yeast,” *Journal of Biological Chemistry*, vol. 269, no. 45, pp. 28044–28048, 1994.

J. Q. Svejstrup, Z. Wang, W. J. Feaver et al., “Different forms of TFIIH for transcription and DNA repair: holo-TFIIH and a nucleotide excision repairosome,” *Cell*, vol. 80, no. 1, pp. 21–28, 1995.

C. J. Hengartner, V. E. Myer, S. M. Liao, C. J. Wilson, S. S. Koh, and R. A. Young, “Temporal regulation of RNA polymerase II by Srb10 and Kin28 cyclin-dependent kinases,” *Molecular Cell*, vol. 2, no. 1, pp. 43–53, 1998.

V. E. Myer and R. A. Young, “RNA polymerase II holoenzymes and subcomplexes,” *Journal of Biological Chemistry*, vol. 273, no. 43, pp. 27757–27760, 1998.

F. Tirode, D. Busso, F. Coin, and J. M. Egly, “Reconstitution of the transcription factor TFIIH: assignment of functions for the three enzymatic subunits, XBP, XPD, and cdk7,” *Molecular Cell*, vol. 3, no. 1, pp. 87–95, 1999.

W. H. Chang and R. D. Kornberg, “Electron crystal structure of the transcription factor and DNA repair complex, core TFIIH,” *Cell*, vol. 102, no. 5, pp. 609–613, 2000.

Y. Takagi, C. A. Masuda, W. H. Chang et al., “Ubiquitin ligase activity of TFIIH and the transcriptional response to DNA damage,” *Molecular Cell*, vol. 18, no. 2, pp. 237–243, 2005.

G. Rabut, G. Le Dez, R. Verma et al., “The TFIIH subunit Tfb3 regulates cullin neddylation,” *Molecular Cell*, vol. 43, no. 3, pp. 488–495, 2011.

M. E. Dahmus, “Reversible phosphorylation of the C-terminal domain of RNA polymerase II,” *Journal of Biological Chemistry*, vol. 271, no. 32, pp. 19009–19012, 1996.

O. Bensaude, F. Bonnet, C. Cassé, M. F. Dubois, V. T. Nguyen, and B. Palancade, “Regulated phosphorylation of the RNA polymerase II C-terminal domain (CTD),” *Biochemistry and Cell Biology*, vol. 77, no. 4, pp. 249–255, 1999.

B. Palancade and O. Bensaude, “Investigating RNA polymerase II carboxy-terminal domain (CTD) phosphorylation,” *European Journal of Biochemistry*, vol. 270, no. 19, pp. 3859–3870, 2003.

W. J. Feaver, J. Q. Svejstrup, N. L. Henry, and R. D. Kornberg, “Relationship of CDK-activating kinase and RNA polymerase II CTD kinase TFIIH/TFI1K,” *Cell*, vol. 79, no. 6, pp. 1103–1109, 1994.

P. Rickert, J. L. Corden, and E. Lees, “Cyclin C/CDK8 and cyclin H/CDK7/p36 are biochemically distinct CTD kinases,” *Oncogene*, vol. 18, no. 4, pp. 1093–1102, 1999.

M. M. Gebara, M. H. Sayre, and J. L. Corden, “Phosphorylation of the carboxy-terminal repeat domain in RNA polymerase II by cyclin-dependent kinases is sufficient to inhibit transcription,” *Journal of Cellular Biochemistry*, vol. 64, no. 3, pp. 390–402, 1997.

A. Munshi, G. Shaﬁ, N. Aliya, and A. Jyothy, “Histone modiﬁcations dictate speciﬁc biological readouts,” *Journal of Genetics and Genomics*, vol. 36, no. 2, pp. 75–88, 2009.

J. S. Lee, E. Smith, and A. Shilatifard, “The language of histone crostalk,” *Cell*, vol. 142, no. 5, pp. 682–685, 2010.

J. L. Workman, “Nucleosome displacement in transcription,” *Genes & Development*, vol. 20, no. 15, pp. 2009–2017, 2006.

S. Nakashima, B. W. Sanderson, K. M. Delventhal, W. D. Bradford, K. Staehling-Hampton, and A. Shilatifard, “A comprehensive library of histone mutants identiﬁes nucleosomal residues required for H3K4 methylation,” *Nature Structural & Molecular Biology*, vol. 15, no. 8, pp. 881–888, 2008.

A. Wood, J. Schneider, J. Dover, M. Johnston, and A. Shilatifard, “The Paf1 complex is essential for histone monoubiquitination by the Rad6–Bre1 complex, which signals for histone methylation by COMPASS and Dot1p,” *Journal of Biological Chemistry*, vol. 278, no. 37, pp. 34739–34742, 2003.

P. Cramer, D. A. Bushnell, and R. D. Kornberg, “Structural basis of transcription: RNA polymerase II at 2.8 ångstrom resolution,” *Science*, vol. 292, no. 5523, pp. 1863–1876, 2001.

A. Ghosh, S. Shuman, and C. Lima, “Structural insights to how Mammalian capping enzyme reads the CTD code,” *Molecular Cell*, vol. 43, no. 2, pp. 299–310, 2011.

F. Dong and D. L. Bentley, “Capping, splicing, and 3′ processing are independently stimulated by RNA polymerase
[163] A. Wood, J. Schneider, J. Dover, M. Johnston, and A. Shilatifard, “The Buri/Bur2 complex is required for histone H2B mono-ubiquitination by Rad6/Bre1 and histone methylation by COMPASS,” Molecular Cell, vol. 20, no. 4, pp. 589–599, 2005.

[164] J. C. Jones, H. P. Phtannani, T. A. Haystead, J. A. MacDonald, S. M. Alam, and A. L. Greenleaf, “C-terminal repeat domain kinase I phosphorylates Ser2 and Ser5 of RNA polymerase II C-terminal domain repeats,” Journal of Biological Chemistry, vol. 279, no. 24, pp. 24957–24964, 2004.

[165] J. B. Kim and P. A. Sharp, “Positive transcription elongation factor B phosphorylates IsPT5 and RNA polymerase II carboxyl-terminal domain independently of cyclin-dependent kinase-activating kinase,” Journal of Biological Chemistry, vol. 276, no. 15, pp. 12317–12323, 2001.

[166] H. Qiu, C. Hu, and A. G. Hinnebusch, “Phosphorylation of the pol II CTD by KIN28 enhances BUR1/BUR2 recruitment and Ser2 CTD phosphorylation near promoters,” Molecular Cell, vol. 33, no. 6, pp. 752–762, 2009.

[167] A. L. Mosley, S. G. Pattenden, M. Carey et al., “Rtr1 is a CTD phosphatase that regulates RNA polymerase II during the transition from Serine 5 to Serine 2 phosphorylation,” Molecular Cell, vol. 34, no. 2, pp. 168–178, 2009.

[168] M. S. Kobor, J. Archambault, W. Lester et al., “An unusual eukaryotic protein phosphatase required for transcription by RNA polymerase II and CTD dephosphorylation in S. cerevisiae,” Molecular Cell, vol. 4, no. 1, pp. 55–62, 1999.

[169] E. L. Cho, M. S. Kobor, M. Kim, J. Greenblatt, and S. Buratowski, “Opposing effects of Ctk1 kinase and Fcp1 phosphatase at Ser 2 of the RNA polymerase II C-terminal domain,” Genes & Development, vol. 15, no. 24, pp. 3319–3329, 2001.

[170] K. W. Henry, A. Wyce, W. S. Lo et al., “Transcriptional activation via sequential histone H2B ubiquitination and deubiquitination, mediated by SAGA-associated Ubp8,” Genes & Development, vol. 17, no. 21, pp. 2648–2663, 2003.

[171] A. Wyce, T. Xiao, K. A. Whelan et al., “H2B ubiquitination acts as a barrier to Ctk1 nucleosomal recruitment prior to removal by Ubp8 within a SAGA-related complex,” Molecular Cell, vol. 27, no. 2, pp. 275–288, 2007.

[172] D. Bentley, “Coupling RNA polymerase II transcription with pre-mRNA processing,” Current Opinion in Cell Biology, vol. 11, no. 3, pp. 347–351, 1999.

[173] D. Bentley, “The mRNA assembly line: transcription and processing machines in the same factory,” Current Opinion in Cell Biology, vol. 14, no. 3, pp. 336–342, 2002.

[174] D. D. Licatalosi, G. Geiger, M. Minet et al., “Functional interaction of yeast pre-mRNA 3′ end processing factors with RNA polymerase II,” Molecular Cell, vol. 9, no. 5, pp. 1101–1111, 2002.

[175] N. J. Proudfoot, A. Forger, and M. J. Dye, “Integrating mRNA processing with transcription,” Cell, vol. 108, no. 4, pp. 501–512, 2002.

[176] S. H. Ahn, M. Kim, and S. Buratowski, “Phosphorylation of Serine 2 within the RNA polymerase II C-terminal domain couples transcription and 3′ end processing,” Molecular Cell, vol. 13, no. 1, pp. 67–76, 2004.

[177] D. L. Bentley, “Rules of engagement: co-transcriptional recruitment of pre-mRNA processing factors,” Current Opinion in Cell Biology, vol. 17, no. 3, pp. 251–256, 2005.

[178] S. Buratowski, “Connections between mRNA 3′ end processing and transcription termination,” Current Opinion in Cell Biology, vol. 17, no. 3, pp. 257–261, 2005.

[179] J. Li, D. Moazed, and S. P. Gygi, “Association of the histone methyltransferase Set2 with RNA polymerase II plays a role in transcription elongation,” Journal of Biological Chemistry, vol. 277, no. 51, pp. 49383–49388, 2002.

[180] N. J. Krogan, M. Kim, A. Tong et al., “Methylation of histone H3 by Set2 in Saccharomyces cerevisiae is linked to transcriptional elongation by RNA polymerase II,” Molecular and Cellular Biology, vol. 23, no. 12, pp. 4207–4218, 2003.

[181] B. Li, L. Howe, S. Anderson, J. L. Yates, and J. L. Workman, “The Ser2 histone methyltransferase functions through the phosphorylated carboxyl-terminal domain of RNA polymerase II,” Journal of Biological Chemistry, vol. 278, no. 11, pp. 8897–8903, 2003.

[182] M. J. Carrozza, B. Li, L. Flores et al., “Histone H3 methylation by Set2 directs deacetylation of coding regions by Rpd3S to suppress spurious intragenic transcription,” Cell, vol. 123, no. 4, pp. 581–592, 2005.

[183] M. C. Keogh, S. K. Kurdistani, S. A. Morris et al., “Cotranscriptional set2 methylation of histone H3 lysine 36 recruits a repressive Rpd3S complex,” Cell, vol. 123, no. 4, pp. 593–605, 2005.

[184] W. Gilbert, C. W. Siebel, and C. Guthrie, “Phosphorylation by Sky1p promotes Npl3p and mRNA dissociation,” RNA, vol. 7, no. 2, pp. 302–313, 2001.

[185] E. P. Lei, H. Krebber, and P. A. Silver, “Messenger RNAs are recruited for nuclear export during transcription,” Genes & Development, vol. 15, no. 14, pp. 1771–1782, 2001.

[186] M. E. Bucheli and S. Buratowski, “Npl3 is an antagonist of mRNA 3′ end formation by RNA polymerase II,” The EMBO Journal, vol. 24, no. 12, pp. 2150–2160, 2005.

[187] M. E. Bucheli, X. He, C. D. Kaplan, C. L. Moore, and S. Buratowski, “Polyadenylation site choice in yeast is affected by competition between Npl3 and polyadenylation factor CFI,” RNA, vol. 13, no. 10, pp. 1756–1764, 2007.

[188] N. J. Proudfoot, “Ending the message: poly(A) signals then and now,” Genes & Development, vol. 25, no. 17, pp. 1770–1782, 2011.

[189] M. Kim, S. H. Ahn, N. J. Krogan, J. F. Greenblatt, and S. Buratowski, “Transitions in RNA polymerase II elongation complexes at the 3′ ends of genes,” The EMBO Journal, vol. 23, no. 2, pp. 354–364, 2004.

[190] S. Connelly and J. L. Manley, “A functional mRNA polyadenylation signal is required for transcription termination by RNA polymerase II,” Genes & Development, vol. 2, no. 4, pp. 440–452, 1988.

[191] S. West, N. Gromak, and N. J. Proudfoot, “Human 5′ → 3′ exonuclease Xm2 promotes transcription termination at cotranscriptional cleavage sites,” Nature, vol. 432, no. 7016, pp. 522–525, 2004.

[192] B. M. Lunde, S. L. Reichow, M. Kim et al., “Cooperative interaction of transcription termination factors with the RNA polymerase II C-terminal domain,” Nature Structural & Molecular Biology, vol. 17, no. 10, pp. 1195–1201, 2010.

[193] Z. Zhang, J. Fu, and D. S. Gilmore, “CTD-dependent dismantling of the RNA polymerase II elongation complex by the pre-mRNA 3′-end processing factor, Pcf11,” Genes & Development, vol. 19, no. 13, pp. 1572–1580, 2005.

[194] M. Sadowski, B. Dichtl, W. Hubner, and W. Keller, “Independent functions of yeast Pcf11p in pre-mRNA 3′ end processing and in transcription termination,” The EMBO Journal, vol. 22, no. 9, pp. 2167–2177, 2003.

[195] M. Kim, L. Vasiljeva, O. J. Rando, A. Zhelkovsky, C. Moore, and S. Buratowski, “Distinct pathways for snoRNA and mRNA termination,” Molecular Cell, vol. 24, no. 5, pp. 723–734, 2006.
[196] H. Kim, B. Erickson, W. Luo et al., “Gene-specific RNA polymerase II phosphorylation and the CTD code,” *Nature Structural & Molecular Biology*, vol. 17, no. 10, pp. 1279–1286, 2010.

[197] C. E. Birse, L. Minvielle-Sebastia, B. A. Lee, W. Keller, and N. J. Proudfoot, “Coupling termination of transcription to messenger RNA maturation in yeast,” *Science*, vol. 280, no. 5361, pp. 298–301, 1998.

[198] R. K. Gudipati, T. Villa, J. Boulay, and D. Libri, “Phosphorylation of the RNA polymerase II C-terminal domain dictates transcription termination choice,” *Nature Structural & Molecular Biology*, vol. 15, no. 8, pp. 786–794, 2008.

[199] E. J. Steinmetz, N. K. Conrad, D. A. Brow, and J. L. Corden, “RNA-binding protein Nrd1 directs poly(A)-independent 3′-end formation of RNA polymerase II transcripts,” *Nature*, vol. 413, no. 6853, pp. 327–331, 2001.

[200] N. Terzi, L. S. Churchman, L. Vasiljeva, J. Weissman, and S. Buratowski, “H3K4 trimethylation by Set1 promotes efficient termination by the Nrd1-Nab3-Sen1 pathway,” *Molecular and Cellular Biology*, vol. 31, no. 17, pp. 3569–3583, 2011.

[201] E. J. Steinmetz and D. A. Brow, “Repression of gene expression by an exogenous sequence element acting in concert with a heterogeneous nuclear ribonucleoprotein-like protein, Nrd1, and the putative helicase Sen1,” *Molecular and Cellular Biology*, vol. 16, no. 12, pp. 6993–7003, 1996.

[202] E. J. Steinmetz and D. A. Brow, “Control of pre-mRNA accumulation by the essential yeast protein Nrd1 requires high-affinity transcript binding and a domain implicated in RNA polymerase II association,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 12, pp. 6699–6704, 1998.

[203] N. K. Conrad, S. M. Wilson, E. J. Steinmetz et al., “A yeast heterogeneous nuclear ribonucleoprotein complex associated with RNA polymerase II,” *Genetics*, vol. 154, no. 2, pp. 557–571, 2000.

[204] K. L. Carroll, D. A. Pradhan, J. A. Granek, N. D. Clarke, and J. L. Corden, “Identification of cis elements directing termination of yeast nonpolyadenylated snoRNA transcripts,” *Molecular and Cellular Biology*, vol. 24, no. 14, pp. 6241–6252, 2004.

[205] K. L. Carroll, R. Ghirlando, J. M. Ames, and J. L. Corden, “Interaction of yeast RNA-binding proteins Nrd1 and Nab3 with RNA polymerase II terminator elements,” *RNA*, vol. 13, no. 3, pp. 361–373, 2007.

[206] F. Hobor, R. Pergoli, K. Kubicek et al., “Recognition of transcription termination signal by the nuclear polyadenylated RNA-binding (NAB) 3 protein,” *Journal of Biological Chemistry*, vol. 286, no. 5, pp. 3645–3657, 2011.

[207] W. Wlotzka, G. Kudla, S. Granneman, and D. Tollery, “The nuclear RNA polymerase II surveillance system targets polymerase III transcripts,” *The EMBO Journal*, vol. 30, no. 9, pp. 1790–1803, 2011.

[208] D. Ursic, K. L. Himmel, K. A. Gura, and D. J. Corden, “The yeast Sen1 gene is required for the processing of diverse RNA classes,” *Nucleic Acids Research*, vol. 25, no. 23, pp. 4778–4785, 1997.

[209] K. Skourti-Stathaki, N. Proudfoot, and N. Gromak, “Human senataxin resolves RNA/DNA hybrids formed at transcriptional pause sites to promote Xrn2-dependent termination,” *Molecular Cell*, vol. 42, no. 6, pp. 794–805, 2011.

[210] H. E. Mischo, B. Gómez-González, P. Grzegorzyk et al., “Yeast Sen1 helicase protects the genome from transcription-associated instability,” *Molecular Cell*, vol. 41, no. 1, pp. 21–32, 2011.

[211] E. Nedea, D. Nalbant, D. Xia et al., “The Glc7 phosphatase subunit of the cleavage and polyadenylation factor is essential for transcription termination on snoRNA genes,” *Molecular Cell*, vol. 29, no. 5, pp. 577–587, 2008.

[212] G. Chanfreau, P. Legrain, and A. Jacquier, “Yeast RNase III as a key processing enzyme in small nucleolar RNAs metabolism,” *Journal of Molecular Biology*, vol. 284, no. 4, pp. 975–988, 1998.

[213] G. Chanfreau, G. Rotondo, P. Legrain, and A. Jacquier, “Processing of a dicistronic small nucleolar RNA precursor by the RNA endonuclease Rnt1,” *The EMBO Journal*, vol. 17, no. 13, pp. 3726–3737, 1998.

[214] C. Allmang, J. Kufel, G. Chanfreau, P. Mitchell, E. Petfalski, and D. Tollery, “Functions of the exosome in rRNA, snoRNA and snRNA synthesis,” *The EMBO Journal*, vol. 18, no. 19, pp. 3599–3610, 1999.

[215] J. LaCava, J. Houseley, C. Saveanu et al., “RNA degradation by the exosome is promoted by a nuclear polyadenylation complex,” *Cell*, vol. 121, no. 5, pp. 713–724, 2005.

[216] D. E. Egecioglu, A. K. Henras, and G. F. Chen, “Contributions of Trf4p- and Trf5p-dependent polyadenylation to the processing and degradative functions of the yeast nuclear exosome,” *RNA*, vol. 12, no. 1, pp. 26–32, 2006.

[217] L. Vasiljeva and S. Buratowski, “Nrd1 interacts with the nuclear exosome for 3′ end processing of RNA polymerase II transcripts,” *Molecular Cell*, vol. 21, no. 2, pp. 239–248, 2006.

[218] D. Baillat, M. A. Hakimi, A. M. Näää, A. Shilatifard, N. Cooch, and R. Shiekhattar, “Integrator, a multiprotein mediator of small nuclear RNA processing, associates with the C-terminal repeat of RNA polymerase II,” *Cell*, vol. 123, no. 2, pp. 265–276, 2005.

[219] S. Egloff, S. A. Szczepaniak, M. Dienstbier, A. Taylor, S. Knight, and S. Murphy, “The integrator complex recognizes a new double mark on the RNA polymerase II carboxy-terminal domain,” *Journal of Biological Chemistry*, vol. 285, no. 27, pp. 20564–20569, 2010.

[220] L. Minvielle-Sebastia, P. J. Preker, and W. Keller, “RNA14 and RNA15 proteins as components of a yeast pre-mRNA 3′-end processing factor,” *Science*, vol. 266, no. 5191, pp. 1702–1705, 1994.

[221] M. J. Moore, “From birth to death: the complex lives of eukaryotic mRNAs,” *Science*, vol. 309, no. 5740, pp. 1514–1518, 2005.

[222] E. Neeva, X. He, M. Kim et al., “Organization and function of APT, a subcomplex of the yeast cleavage and polyadenylation factor involved in the formation of mRNA and small nucleolar RNA 3′-ends,” *Journal of Biological Chemistry*, vol. 278, no. 35, pp. 33000–33010, 2003.

[223] A. Ansari and M. Hampsey, “A role for the CPF 3′-end processing machinery in RNAP II-dependent gene looping,” *Genes & Development*, vol. 19, no. 24, pp. 2969–2978, 2005.

[224] E. J. Steinmetz and D. A. Brow, “Ssu72 protein mediates both poly(A)-coupled and poly(A)-independent termination of RNA polymerase II transcription,” *Molecular and Cellular Biology*, vol. 23, no. 18, pp. 6393–6394, 2003.

[225] S. Krishnamurthy, X. He, M. Reyes-Reyes, C. Moore, and M. Hampsey, “Ssu72 is an RNA polymerase II CTD phosphatase,” *Molecular Cell*, vol. 14, no. 3, pp. 387–394, 2004.

[226] S. Krishnamurthy, M. A. Ghazy, C. Moore, and M. Hampsey, “Functional interaction of the Ess1 prolyl isomerase with components of the RNA polymerase II initiation and termination machineries,” *Molecular and Cellular Biology*, vol. 29, no. 11, pp. 2925–2934, 2009.
