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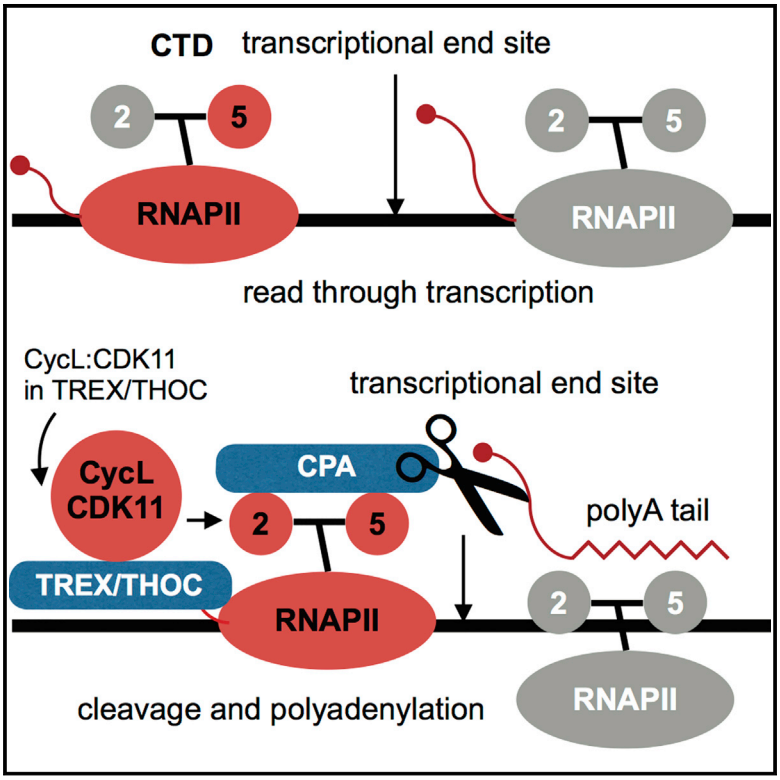
CDK11 in TREX/THOC Regulates HIV mRNA 3′ End Processing

Graphical Abstract



Highlights

- The cyclin-dependent kinase CDK11 increases HIV gene expression as part of TREX/THOC
- CDK11 is recruited by TREX/THOC to elongating RNAPII and phosphorylates its CTD
- RNAPII phosphorylation by CDK11 promotes cleavage and polyadenylation factor recruitment
- CDK11 regulates proper 3′ end processing of HIV for optimal viral gene expression

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In Brief

The role of the transcriptional cyclin-dependent kinase CDK11 in HIV replication is unclear. Pak et al. report that CDK11 functions in the transcription/export and THO complex (TREX/THOC) to phosphorylate RNAPII and promote assembly of cleavage and polyadenylation factors at the HIV 3′ end, which ensures optimal HIV gene expression.

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CDK11 in TREX/THOC Regulates HIV mRNA 3′ End Processing

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SUMMARY

Transcriptional cyclin-dependent kinases play important roles in eukaryotic gene expression. CDK7, CDK9 (P-TEFb), and CDK13 are also critical for HIV replication. However, the function of CDK11 remained enigmatic. In this report, we determined that CDK11 regulates the cleavage and polyadenylation (CPA) of all viral transcripts. CDK11 was found associated with the TREX/THOC, which recruited this kinase to DNA. Once at the viral genome, CDK11 phosphorylated serines at position 2 in the CTD of RNAPII, which increased levels of CPA factors at the HIV 3′ end. In its absence, cleavage of viral transcripts was greatly attenuated. In contrast, higher levels of CDK11 increased the length of HIV poly(A) tails and the stability of mature viral transcripts. We conclude that CDK11 plays a critical role for the cotranscriptional processing of all HIV mRNA species.

INTRODUCTION

The human immunodeficiency virus (HIV) is a retrovirus of the lentivirus family that integrates into the host genome, where it behaves similarly to other human genes. Its transcription and replication have been studied extensively, and lessons learned from HIV have contributed greatly to the understanding of eukaryotic biology (Peterlin and Price, 2006). For example, studies of its transcriptional transactivator (Tat) revealed that the control of RNA polymerase II (RNAPII) elongation is an important step in gene expression (Kao et al., 1987). It is now known that most if not all genes have RNAPII already engaged at their promoters and that extracellular cues can release it, thereby promoting diverse cellular processes, which include activation, proliferation, differentiation, and reprogramming (Rahl et al., 2010). Further steps in cotranscriptional processing, 5′ capping, mRNA splicing, and 3′ end formation, which include cleavage and polyadenylation (CPA), have also profited greatly from studies of HIV (Karn and Stoltzfus, 2012; Valente et al., 2009). Importantly, all these events involve RNAPII, especially its C-terminal domain (CTD). It contains 52 heptapeptide repeats (YSPTSPS), which contain five residues that can be phosphorylated by various kinases for specific functions (Adelman and Lis, 2012).

In association with their respective cyclins (Cycs), transcriptional cyclin-dependent kinases (CDKs) phosphorylate different serines (Ser2P, Ser5P, or Ser7P) and the threonine (Thr4P) in the CTD (Drogat et al., 2012; Loyer et al., 2005). These modifications play critical roles for 5′ capping, mRNA splicing, and CPA of primary transcripts (Blazek et al., 2011; Drogat et al., 2012; Loyer et al., 2005). Indeed, differentially phosphorylated forms of RNAPII provide binding platforms for complexes that execute these early and late events in transcription. They ensure that nascent RNA species mature into functional mRNAs, which can be exported into the cytoplasm for translation (Huang and Carmichael, 1996; Müller-McNicoll and Neugebauer, 2013; Proudfoot, 2011; Wahle and Rüegsegger, 1999).

For HIV, the involvement of CDK7, CDK9, CDK11, and CDK13 has been documented. Tat potentiates the role of CycH:CDK7 in 5′ capping of all viral transcripts (Zhou et al., 2003). Tat also recruits its coactivator, CycT1:CDK9, which forms the positive transcription elongation factor b (P-TEFb), for the transition from initiation to elongation of HIV transcription (Peterlin and Price, 2006). P-TEFb exists in two states, the active free form and the inactive 7SK snRNP, from which it must be released to target the HIV long terminal repeat (LTR) (Peterlin and Price, 2006). CycK:CDK13 affects mRNA splicing so that the overexpression and depletion of CDK13 decreases and increases the production of HIV Gag and Env proteins and the production of new viral particles, respectively (Berro et al., 2008). The role of CycL:CDK11 is less well defined, especially since the depletion and overexpression of CDK11 decreased levels of HIV replication, albeit in greatly different contexts (Valente et al., 2009; Yu et al., 2008).

The transcription/export (TREX) complex connects transcription and cotranscriptional processes. In yeast, TREX couples transcription, mRNA processing, and mRNA nuclear export (Strässer et al., 2002). Suppressors of the transcriptional defects of Hpr1Δ by overexpression complex (THOC) is required for transcription elongation (Li et al., 2005; Rehwinkel et al., 2004). THO proteins are also found in the TREX complex, hence the name TREX/THOC (Masuda et al., 2005). TREX is found at the coding and 3′ ends of genes (Kim et al., 2004; Strässer et al., 2002). In addition to RNAPII and TREX/THOC, the human 3′ end processing complex contains cleavage and polyadenylation specificity factors (CPSFs), cleavage-stimulatory factors (CstFs), the