

CDK11 binds chromatin and mRNAs of replication dependent histones regulating their expression.

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1. Abstract

Expression of canonical, replication-dependent histones (RDH) is highly regulated during the cell cycle echoing their main role during cell division and epigenetic inheritance. RDH genes produce the only non-polyadenylated transcripts and for their correct expression recruit a battery of alternative 3' end processing factors. Exploiting metaplots, positional heat maps and computational methods, we decipher CDK11 binding along RDH mRNA and DNA identifying it as key player in the molecular regulation of RDH biogenesis.

Applying ChIP-seq, we described CDK11 binding to RDH gene body that triggers RNAPII C-terminal repeat domain phosphorylation on the serine2 (Ser2) residues. This Ser2 phosphorylation is required for RNAPII to continue transcription elongation on RDH genes. Using nucleotide resolution crosslinking immunoprecipitation (iCLIP), we identified CDK11 binding along RDH transcripts with accumulation upstream of stem loop, an RNA structure formed at the 3' end of RDH transcripts. This RNA-CDK11 interaction is complementary to the DNA-CDK11 interaction on the RDH and both are required for the correct expression of RDH. Thus, CDK11 knockdown exhibits a strong decrease in RDH expression measured by RNA-seq and a small proportion of unprocessed RNAs read-through after the stem-loop. CDK11 stem loop binding is required to recruit RDH processing factors that will cleave the transcripts just downstream of the stem loop. Therefore in the absence of CDK11, this process becomes deficient.

CDK11 is an essential gene for growth of several cancers and is of potential clinical importance as a druggable player to improve cancer prognosis by yet unknown molecular mechanism.

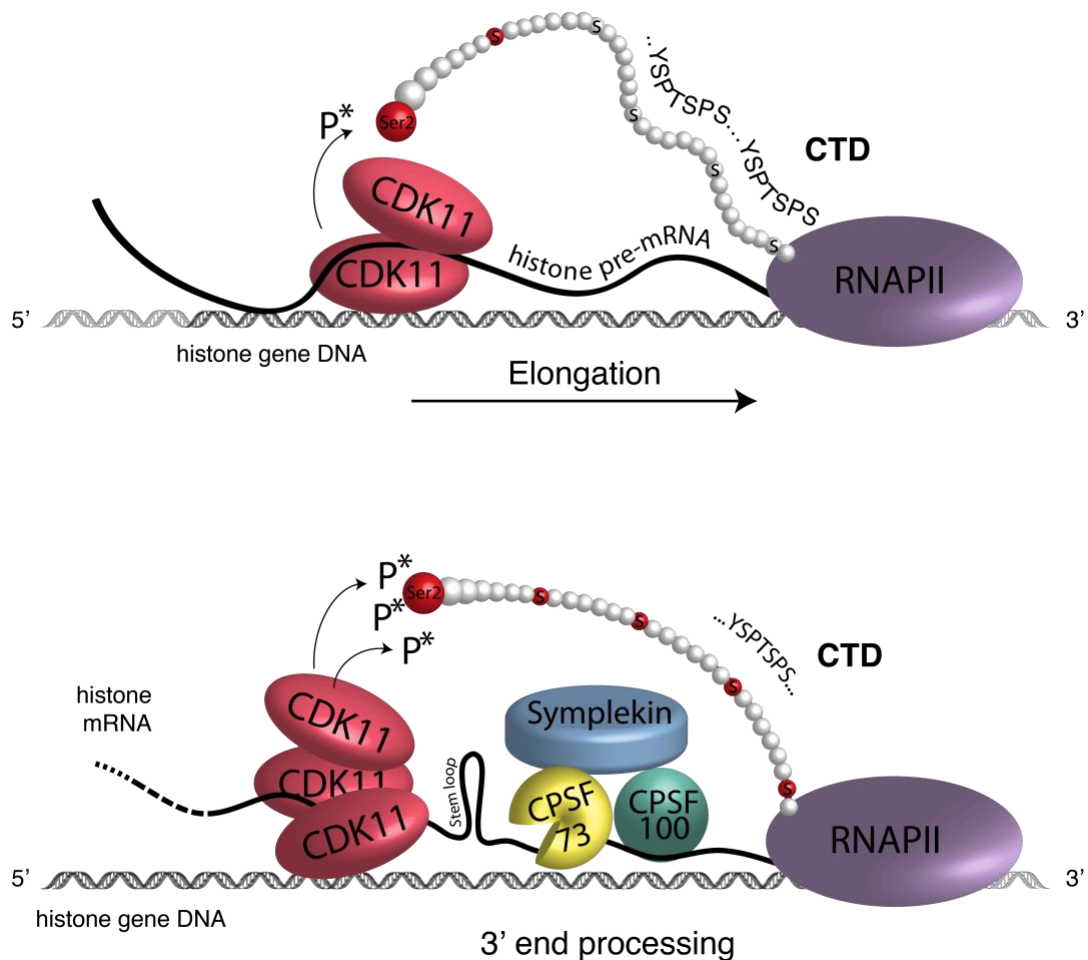


Figure 1 Schematic working model. CDK11 regulates transcription elongation of RDH genes and contributes to their 3' end processing. CDK11 (red oval) binds collaboratively with nascent RDH mRNAs (black line) to chromatin of RDH genes (grey double helix) and phosphorylates (arrow) Ser2 (red ball) in the CTD (red and grey balls) of RNAPII (violet oval). The Ser2 phosphorylation promotes the RNAPII elongation on RDH genes. CDK11 is bound abundantly at the 3' end of RDH mRNAs and this binding likely occurs on or in the close vicinity of RDH chromatin. CDK11-dependent phosphorylation of Ser2 contributes to the recruitment of 3' end processing HCC complex (SYMPLEKIN (blue oval), CPSF100 (green circle) and CPSF73 (yellow circle) allowing CPSF73 to cleave nascent RDH mRNA (black line).