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Understanding the role of CTD phosphorylation of RNA polymerase II in mRNA transcription

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Statement of the Problem: In eukaryotes, transcription in interphase is orchestrated through the regulation by kinases (Kin28, Bur1 and Ctk1) and phosphatases (Ssu72, Rtr1 and Fcp1) which act through the post-translational modification of CTD (carboxy terminal domain of the largest subunit of RNA Polymerase II). The CTD comprises of repeated Tyr1Ser2Pro3Thr4Ser5Pro6Ser7 motif with potential epigenetic modification sites. Despite the observation of transcription and periodic expression of genes during mitosis with entailing CTD phosphorylation and dephosphorylation, the associated CTD specific kinases and its role in transcription remains unknown. Furthermore, the phosphorylation of CTD serves as a signal for the binding of various transcription regulators for mRNA biogenesis. However the role of CTD-Ser7 phosphorylation in mRNA transcription remains largely unknown.

Methodology & Theoretical Orientation: We integrate the biochemistry, yeast genetics, proteomics and bioinformatics approach to identify the specific CTD kinase and understand the underlying mechanism of gene regulation.

Findings: Here we have identified Cdc15 as a potential mitotic CTD kinase whose inactivation causes reduction of global CTD phosphorylation during mitosis as well as affects the expression of genes undergoes complete transcription or whose transcript level peaks during mitosis. The phosphorylation of CTD by Cdc15 is independent of any prior Ser phosphorylations. We have also established the role of CTD-Ser7 phosphorylation in efficient mRNA capping which in turn influences the unconditional growth and mRNA transcription. CTD interact with mRNA capping enzyme in a specific pattern of Ser5PSer7PSer5P and our studies provides molecular insights into the capping enzyme CTD interaction and function.

Conclusion & Significance: Regulation of transcription is one of the most important steps that control cell growth and differentiation. Understanding transcription would help address and control the abnormal cellular behavior in cancer and other diseases and will eventually contribute towards more targeted treatment strategies.

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