CDK9 inhibitors define elongation checkpoints at both ends of RNA polymerase II-transcribed genes.

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Abstract

Transcription through early-elongation checkpoints requires phosphorylation of negative transcription elongation factors (NTEFs) by the cyclin-dependent kinase (CDK) 9. Using CDK9 inhibitors and global run-on sequencing (GRO-seq), we have mapped CDK9 inhibitor-sensitive checkpoints genome wide in human cells. Our data indicate that early-elongation checkpoints are a general feature of RNA polymerase (pol) II-transcribed human genes and occur independently of polymerase stalling. Pol II that has negotiated the early-elongation checkpoint can elongate in the presence of inhibitors but, remarkably, terminates transcription prematurely close to the terminal polyadenylation (poly(A)) site. Our analysis has revealed an unexpected poly(A)-associated elongation checkpoint, which has major implications for the regulation of gene expression. Interestingly, the pattern of modification of the C-terminal domain of pol II terminated at this new checkpoint largely mirrors the pattern normally found downstream of the poly(A) site, thus suggesting common mechanisms of termination.

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