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Research Week 2023

A Phosphorylation Code Coordinating Transcription Condensate Dynamics and DNA Replication

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Keywords

Biomolecular Condensates, DNA Replication, ATR, MED1, Histone Locus Body

Abstract

The intricate regulation of transcriptional programs and DNA replication processes in mammalian cells relies on dynamic nuclear protein organization. Biomolecular condensates, or biocondensates, are membrane-less compartments formed through liquid-liquid phase separation that play a pivotal role in the localization of transcriptional protein machinery and controlling chromatin organization. Given their relevance in these processes, dysregulation of biocondensate formation and function contributes to various human diseases, including cancer, neurodegeneration, and infectious diseases. Critically, the spatiotemporal regulation of nuclear biocondensates remains poorly understood, partly due to the lack of physiologically relevant models. ATR (ataxia-telangiectasia and rad3-related) is a well-studied kinase that functions as a cell cycle checkpoint kinase and master regulator of DNA damage response. Our work has uncovered a novel ATR-driven mechanism regulating histone gene transcription by controlling the dynamics of a transcriptional biocondensate that forms at the histone locus body (HLB) during DNA replication. Inhibition of ATR kinase activity results in an aberrant accumulation of MED1 (mediator subunit 1) at the HLB during S-phase, disrupting the balance in histone genes expression, and ultimately contributing to genomic instability. Moreover, we uncovered MED1 protein as a critical player in the cells' ability to sustain DNA replication stress and endure vulnerabilities in the DNA damage response of the cell. Importantly, our findings revealed a MED1-phosphorylation code orchestrating the dynamics of biocondensates in a cell cycle-dependent manner, demonstrating a previously unknown connection between transcription regulation and cell cycle progression. Our work stands as a pioneering effort, elucidating the impact of cell cycle-dependent phosphorylation signals on the formation and dynamics of nuclear condensates. Additionally, our study lays a crucial foundation for future research endeavors aimed at designing targeted interventions to modulate biocondensate dynamics, offering potential avenues for developing innovative therapeutics in various human diseases, including cancer, neurodegeneration, and infectious diseases.