Commentary

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Histone Dynamics During Dna Replication Stress

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Abstract

Not just for genome stability, but also for cell viability, accurate and full genome replication is required. Cells, on the other hand, are constantly threatened by spontaneous DNA alterations and DNA lesions from both endogenous and exogenous sources, which provide a persistent threat to the replication process. Replication stress is defined as any hurdle that delays replication forks or disrupts replication dynamics, and we've learned a lot about how cells respond to and resolve such obstacles in the last decade. Furthermore, new research has discovered linkages between replication stress response deficiencies and genomic instability or illnesses like cancer. Histone dynamics are important in controlling fork progression and replication stress responses because replication stress occurs in the presence of chromatin.

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Introduction

A vast number of difficulties will be encountered as replication forks move through the chromatin of eukaryotic cells, and these impediments must be repaired or bypassed to ensure accurate DNA duplication and genomic integrity. Secondary structures formed by specific DNA sequences, difficult-to-replicate genome regions, DNA lesions, chemically modified nucleotide bases, proteins tightly bound to DNA, DNA/RNA hybrids, or deficiencies in Deoxyribonucleotide Triphosphates (dNTPs) are all examples of replication barriers [1,2]. These obstacles to replication fork advancement can cause replication stress, and evidence is mounting that cells have evolved specialised fork repair mechanisms to overcome each type of obstacle [3]. Some barriers cause replication forks to pause, then resume without fork collapse [4], while others force replication forks to stall indefinitely until a converging fork comes to mediate replication termination [5,6]. The particular parameters that determine a replication fork's fate in response to a given impediment, however, are unknown.

Eukaryotic DNA replication occurs in the setting of chromatin, which is significant. The nucleosome, which is made up of a piece of DNA wrapped around a core of histone proteins, is the most basic unit of chromatin. The nucleosome and the replisome multi-protein molecular machinery responsible for DNA replication) are known to interact physically. According to current thinking, an active replisome will evict parental histones ahead of the machinery, and the evicted histones, together with newly produced histones, will be recycled into newly copied DNA [7]. Anti-Silencing Factor 1 (ASF1), Chromatin Assembly Factor 1 (CAF-1), Promotes Chromatin Transcription (PCT), and RTT109 are some of the histone chaperones involved in this process [8]. Following the chaperone-mediated assembly of nucleosomes, chromatin remodelers alter their compaction levels, positions, and even variant histone compositions. Furthermore, histone, chaperones and chromatin remodelers are required for genome maintenance and stress tolerance as important mediators of effective cellular responses to replication stress. The molecular specifics of these processes have already been fully discussed elsewhere [9-11], so we won't go through them again here, save in terms of histone modifications and variations.

PTMs on parental and newly produced histones flanking replication forks have been found to coordinate with essential components of various repair mechanisms or checkpoint machineries. Histone PTMs are regulated by histone writers, readers, and erasers, which are protein machines that 'write, read, and delete' histone marks [12]. When replication barriers are met, the PTM (Post-Translational Modifications) containing histones help specialist repair or checkpoint proteins gain access to replicating chromatin. Furthermore, replication stress response has been linked to differential histone variant exchange. Such interactions can create a milieu that encourages accessory fork factor recruitment over vast chromatin domains. The recent achievements in describing the repair/checkpoint machineries that rescue cells from replication stress are discussed in this review, with a focus on the importance of histone variations and PTMs in replication stress response.

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