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The Dynamics of Histones during DNA Replication Stress

Jean Sebastien*

Department of Biomedical Science, University of Lorraine, France

Editorial

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. The present state of knowledge about histone dynamics in replication stress is summarised below, with recent developments in the characterization of fork-protective mechanisms highlighted [1].

As replication forks traverse through the chromatin of eukaryotic cells, they will encounter a slew of impediments that must be repaired or avoided in order to maintain 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 are all examples of replication barriers (dNTPs). These barriers to replication fork advancement are possible replication stressors, and there is mounting evidence that cells have evolved specialised fork repair mechanisms to overcome each sort of stumbling block. Some barriers cause replication forks to pause, then resume without fork collapse, while others force replication forks to stall indefinitely until a convergent fork comes to mediate replication termination. The particular parameters that determine a replication fork's fate in response to a given impediment, however, are unknown [2].

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, along with newly produced histones, will be recycled into newly copied DNA. Anti-silencing factor 1 (ASF1), chromatin assembly factor 1 (CAF-1), promotes chromatin transcription (FACT), and RTT109 are some of the histone chaperones involved in this process. Following the chaperone-mediated assembly of nucleosomes, chromatin remodelers vary their compaction levels, locations, and even variant histone compositions [3]. 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 details of these processes have been extensively reviewed elsewhere; thus, except for histone modifications or variants, we will not repeat the information here. 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 'erase' histone marks. When replication barriers are encountered, PTM-containing histones help specialised repair or checkpoint proteins gain access to replicating chromatin [4].

Furthermore, replication stress response has been linked to differential histone variant exchange. Such interactions can create a microenvironment that encourages accessory fork factor recruitment across large chromatin domains. In this review, we discuss the current achievements in identifying the repair/checkpoint machineries that rescue cells from replication stress, emphasising the crucial roles of histone variations and PTMs in replication stress response.

DNA replication in eukaryotes begins at numerous replication origins, each of which requires the recruitment of the origin recognition complex, multiple additional proteins, and the loading of the MCM2-7 helicase. These elements come together to form pre-replicative complexes (pre-RCs). Replication origins in budding yeast are linked to AT-rich regions known as autonomously replicating sequence (ARS) consensus sequences (ACSs). Metazoans, on the other hand, lack a distinct origin sequence, with origin sites thought to be determined by a combination of DNA sequence and chromatin-associated factors. Furthermore, recent data suggests that epigenetic signals may play a role in origin recognition [5].

H2A.Z is abundant at replication origins and has been shown to play a functional role in recruiting the histone lysine methyltransferase enzyme SUV420H1; this action promotes H4K20me2 deposition at origins and regulates the licencing and activation of early replication origins via interactions between H4K20me2 and ORC1. Origins can be changed by sliding MCM2-7 complexes along chromosomes due to collisions with RNA polymerase, suggesting that eukaryotic origin location is more dynamic than previously thought.

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***Address for Correspondence:** Jean Sebastien, Department of Biomedical Science, University of Lorraine, France, E-mail:Jseastien@yahoo,com*

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