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Re-SET for Transcription

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Buffering dosage imbalance of early- and late-replicating genes is important for dividing eukaryotic cells. Voichek et al. (2018) described critical roles of H3K4 methylation and Paf1C in this process, which was regulated by the S phase checkpoint and H3K56 acetylation.

Coordinating transcription and replication is a fundamental challenge in both prokaryotes and eukaryotes. An important aspect is how gene dosage imbalance introduced during replication is addressed. The bias toward early replicating genes is especially prominent under replication stress, when replication fork progression is slowed or stalled (e.g., by hydroxyurea treatment depleting the dNTP pool). Prokaryotic cells take advantage of this bias by positioning genes involved in DNA damage responses for early replication, as a strategy to alleviate replication stress. In eukaryotes, this bias is generally buffered by transcription regulation, as large-scale gene dosage imbalance often leads to serious problems. In a study published in this issue, Barkai and colleagues systematically searched for genes required for expression homeostasis during replication in budding yeast (Voichek et al., 2018). They analyzed the transcription profiles of over 1,000 deletion mutants, winnowing down to a short list with increased expression of early replicating genes. These mutants were then closely examined for changes in transcription as cells synchronized in the G1 phase were released into the S phase in the presence of hydroxyurea. Using this approach, they identified and characterized an important buffering role of histone H3 lysine 4 methylation (H3K4me), which is catalyzed by the Set1-containing histone methyltransferase (HMT) complex, and regulated by the RNA polymerase II associating factor (Paf1)-containing complex (Paf1C) (Rao and Dou, 2015). This study extends their previous work that histone H3 lysine 56 acetylation (H3K56ac) preferentially suppresses transcription from the nascent chromatin (Voichek et al., 2016), and further sheds light on the molecular circuit underlying expression homeostasis during replication.

In eukaryotes, transcription occurs in the chromatin landscape, which is shaped by numerous histone post-translational modifications (PTMs). Among them, H3K4me exhibits stereotypical distribution patterns along the transcribed genes, most notably the enrichment of H3K4me3 around transcription start sites (TSS) and 5′ end of the gene body (Rao and Dou, 2015). The level of H3K4me3 is tightly associated with high transcription activity and is subject to regulation by co-transcriptional mechanisms (Soares et al., 2017). Histone H3K4me3 level oscillates with the cell cycle. Distribution of H3K4me1/2/3 along the gene body is also dynamically and differentially regulated in the cell cycle (Bar-Ziv et al., 2016). During replication, newly deposited histones have no PTMs and the kinetics for post-replication recovery of histone PTMs are variable (Zee et al., 2010). Specifically, recovery of H3K4me3 is slow at both the global level and the gene-specific level, while recovery of H3K4me1/2 is much faster on nascent chromatin (Zee et al., 2010). Thus, H3K4me2 and H3K4me3, just like H3K56ac (Voichek et al., 2016), differentially mark the nascent and the mature chromatins. Barkai and colleagues show that expression homeostasis is compromised in cells deficient in either *set1*Δ or *paf1*Δ cells (Voichek et al., 2018). Furthermore, low H3K4me3 level on the nascent chromatin contributes partly to the function of H3K56ac in buffering gene dosage imbalance. These results strongly suggest that the distinct patterns of H3K4me and H3K56ac on the nascent chromatin may underpin the reduced transcription therein relative to the mature chromatin (Figure 1).

H3K56ac is a deposition-related histone acetylation, peaks in the S phase, and is quickly removed thereafter; it only persists at high levels in cells under replication stress (Masumoto et al., 2005). The replication stress activates the S phase checkpoint, which promotes origin firing, stabilizes forks, and promotes restart (Cimprich and Cortez, 2008). The S phase checkpoint is also involved in coordinating replication and transcription (Poli et al., 2016). It stabilizes H3K56ac while reducing transcription by inducing phosphorylation of Paf1 and subsequent eviction or degradation of Pol II. Barkai and colleagues show that the S phase checkpoint is essential for buffering persistent gene dosage imbalance caused by replication stress and further delineate the regulatory pathway. The ability of the S phase checkpoint to regulate H3K56ac and Paf1 leads to slow conversion of H3K4me2 to H3K4me3 on the nascent chromatin, which suppress transcription activity (Kim and Buratowski, 2009). On the other hand, high H3K4me3 on the un-replicated, mature chromatin ensures higher transcription activity through the positive feedback regulation between transcription and H3K4me3. The S phase checkpoint therefore not only clears Pol II from the nascent chromatin, but also thwarts the recovery of the chromatin landscape that is associated with and conducive to transcription. Extrapolating from these results, the authors posit that as post-replication recovery of epigenetic marks can both affect and be affected by transcription, these feedback loops may be critical for expression homeostasis during replication.

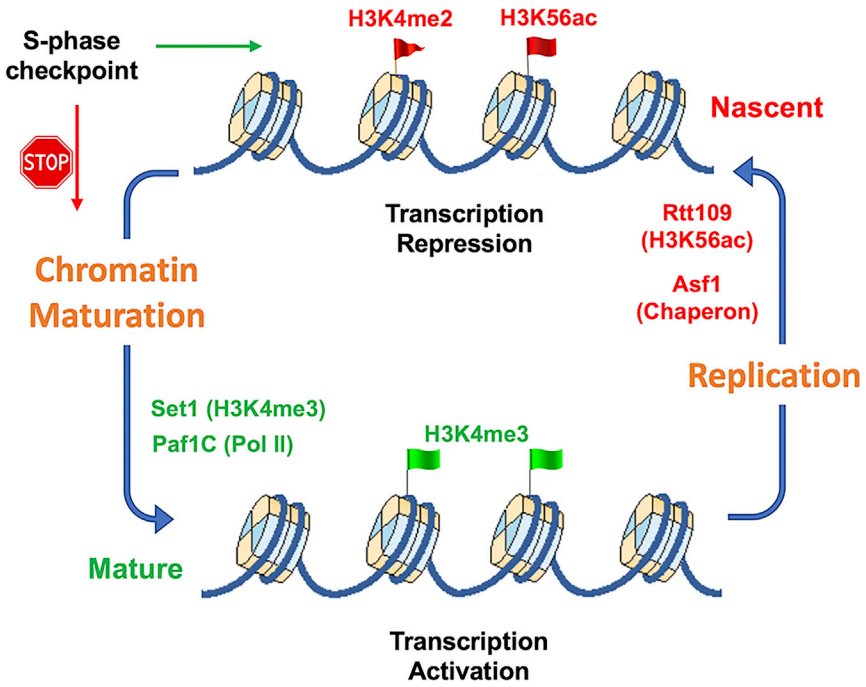

Figure 1. The S Phase Checkpoint Thwarts Post-replication Chromatin Maturation that Is Associated with and Conducive to Enhanced Transcription

The nascent chromatin is marked by H3K56ac, which prevents H3K4me3. Under replication stress, the S-phase checkpoint is activated. On one hand, it stabilizes H3K56ac on nascent chromatin; on the other hand, it phosphorylates Paf1, evicts RNA Pol-II, and reduces H3K4me3. Distinct H3K4me patterns on nascent and mature chromatin contribute to expression homeostasis.

This study, together with the previous work from Barkai and colleagues, provides a refreshing perspective on epigenetic mechanisms that coordinate replication and transcription. It also raises more questions: since additional deposition-related histone acetylation (e.g., H4K5/12ac) at highly conserved sites is also part of the conspicuous aspect of chromatin maturation (Sobel et al., 1995), do they play a role in the buffering and the S phase checkpoint as well? If other deposition-related acetylation plays a role in this process, is the transcription effect still channeled through the Paf1C-Set1 pathway? Can the S phase checkpoint affect other histone PTMs associated with transcription? Ultimately, the buffering effect of the S phase checkpoint may simply reflect the necessity to prevent transcription from DNA template that is still under replication or post-replication repair, which will otherwise lead to genome instability. More research is needed to address these questions and to fully understand the complex and conserved circuits that coordinate replication and transcription, and how their conflicts impact the stability and fate of the replisome, the transcription machinery, and the chromatin landscape.

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