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Shushing histone turnover: It’s fun protecting epigenome-genome

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Epigenetic modifications organize the genome into open ("euchromatin") and closed ("heterochromatin") chromatin domains, which drive translation of genetic information into specific outputs in different cell types. The post-translational modifications of histones have emerged as a critical component of epigenetic marking systems. Histone modifications not only dictate the organization of chromatin into distinct domains, but also transmit epigenetic memory during cell division. However, DNA replication poses a challenge for preserving epigenetic memory, requiring chromatin associated histone modifications to be restored following chromatin disruption.

Histone modifications, such as histone 3 lysine 9 methylation (H3K9me) that marks heterochromatin, have been widely studied including in the fission yeast Schizosaccharomyces pombe. The H3K9 methyltransferase Clr4/Suv39h is recruited by DNA sequence- or RNA-dependent mechanisms to establish heterochromatin. Once established, heterochromatin itself provides additional epigenetic specificity ("epigenetic-template") that can propagate heterochromatic structures in a self-templating manner in cis, a role more evident when de novo nucleation mechanisms to establish heterochromatin. Once established, heterochromatin itself provides additional epigenetic specificity ("epigenetic-template") that can propagate heterochromatic structures in a self-templating manner in cis, a role more evident when de novo nucleation mechanisms are impaired. We have shown that the ability of Clr4/Suv39h to methylate H3K9 ("write") and also bind to H3K9me ("read") establishes an elegant feedback loop critical for epigenetic inheritance of heterochromatin. Importantly, parental histones are carriers of epigenetic memory and must be faithfully segregated upon cell division, yet the mechanisms have remained unclear.

Indeed, few components involved in the inheritance of epigenetic states have been uncovered. Using a specially designed genetic screen, we recently identified the SNF2 family ATP-dependent chromatin remodeler, Fft3 (Fission Fun Thirty), as required for heterochromatin maintenance in dividing cells, but dispensable for de novo assembly. Fft3 is a homolog of SMARCAD1 (human) and FUN30 (budding yeast) implicated in heterochromatin assembly and Clr3 recruitment maintains silencing in the absence of Fft3. Indeed, the peri-centromeric region active for de novo assembly and Clr3 recruitment maintains silencing in the absence of Fft3. Fft3 also localizes to highly transcribed genes and genes containing internal repeats. Moreover, Fft3 was recently reported to interact with transcription machinery, whether its localization to genetic regions is transcription-dependent is unclear. Remarkably, Fft3 facilitates replication fork progression through these sites, and suppresses nucleosome turnover to prevent RNA-DNA hybrid
accumulation (Fig. 1). Cells lacking Fft3 experience replication stress, DNA damage and genotoxin sensitivity. Clr4/Suv39h is also required for replication progression through specific euchromatic sites. In absence of Fr3, these regions accumulate R-loops, which causes genome instability.

Replication and transcription require unwrapping and rebuilding nucleosomes. Chromatin remodelers and histone chaperones are needed to manipulate DNA–histone contacts. Like Fft3, the histone chaperone FACT suppresses nucleosome turnover at highly transcribed genes and aids in redepositing displaced nucleosomes behind the RNA polymerase. FACT also contributes to replication-coupled nucleosome assembly, like Asf1 and CAF-1. Similar to Fft3, FACT also facilitates heterochromatin maintenance and interacts with Swi6. Fr3 may work in conjunction with histone chaperones such as FACT to preserve epigenetic memory by displacing and redepositing nucleosomes in the wake of DNA/RNA polymerases (Fig. 1). A new paradigm also emerges in which suppression of nucleosome turnover prevents formation of structural barriers to promote proper replication and protect genome integrity.

 Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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