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Silent decision: HP1 protein escorts heterochromatic RNAs to their destiny

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Heterochromatin is classically perceived to be refractory to transcription because of its compact structure. However, Keller *et al* (2012) now demonstrated that heterochromatic transcripts can accumulate even when heterochromatin is normally packaged. By tracking down the fate of these heterochromatic RNAs, they revealed a new post-transcriptional mechanism of silencing in heterochromatin that involves the dynamic turnover of HP1^{Swi6} between its free, chromatin-bound and RNA-bound forms. The latter form escorts heterochromatic RNA to degradation.

In eukaryotes, chromatin can be classified into two states: euchromatin, which is loosely packed and actively transcribed, and heterochromatin, which remains condensed during interphase. The compact structure of heterochromatin is critical for its widespread roles in chromosome integrity, stability and transposon silencing around centromeres and in other repeat-rich regions, such as subtelomeric regions.

Heterochromatin is relatively devoid of coding sequences, and reporter genes embedded are tightly repressed under most situations. The compact structure of heterochromatin was generally thought to be inert and refractory to transcription (Gasser and Cockell, 2001). However, HP1 (heterochromatin protein 1), which binds the conserved heterochromatin mark, histone H3 lysine 9 methylation (H3K9me) and serves as the structural basis for the condensed state of heterochromatin, undergoes very active turnover between the chromatin-bound and -free states (Cheutin *et al*, 2003; Maison and Almouzni, 2004). Furthermore, heterochromatin is not as 'silent' as initially thought, and undergoes substantial transcription. But the transcripts are quickly processed by RNA interference (RNAi), which utilizes 20- to 30-nt small RNA to guide cleavage or translational inhibition of target transcripts (Carmell and Hannon, 2004), and to release RNA polymerase II (Zaratiegui *et al*, 2011). RNA degradation also participates in this process, and its role is newly interpreted by Keller *et al* (2012).

Although the detailed mechanisms underlying the establishment and maintenance of heterochromatin vary in different species, the principles are conserved from yeast to human. Much work has been done in the fission yeast *Schizosaccharomyces pombe* to understand how the enzymes responsible for the deposition of heterochromatic marks are recruited to specific regions of the genome, and has revealed a complicated network of mechanisms both dependent and independent of RNAi (Buhler *et al*, 2007; Grewal and Jia, 2007). The involvement of RNA turnover in this network is known but not well understood.

Keller *et al* (2012) set out to understand the role of RNA degradation by tracking down the fate of heterochromatic transcripts. They used a *cid14* mutant, which has defects in polyadenylation-assisted RNA turnover (Wang *et al*, 2008) and observed accumulation of transcripts from reporter genes embedded in heterochromatic regions. Interestingly, such derepression is not accompanied by heterochromatin decondensation. They also found a discrepancy between mRNA and protein levels, suggesting that these reporter gene transcripts are assembled into translation-incapable

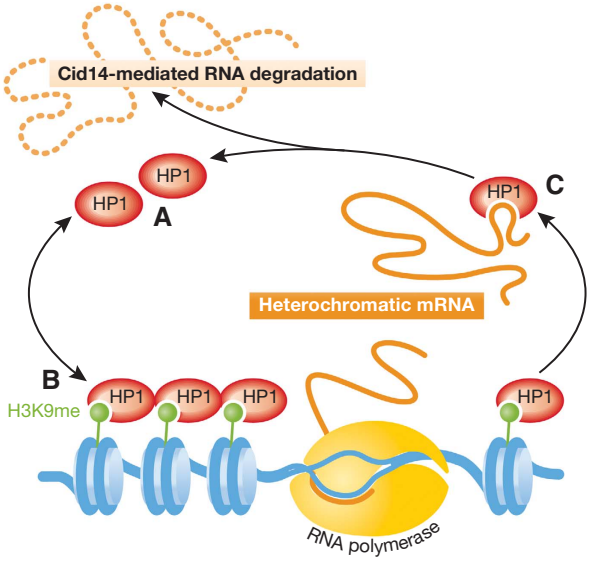

Figure 1 HP1^{Swi6} undergoes rapid turnover between its (**A**) free, (**B**) H3K9me-bound and (**C**) heterochromatic RNA-bound forms. The major structural component of heterochromatin, H3K9me-bound HP1^{Swi6} (**B**) exchanges dynamically with its free ensemble (**A**). Contrary to the classical view, RNA polymerase can get access to heterochromatin, but the transcripts are captured by HP1^{Swi6} (**C**) and escorted to Cid14-mediated RNA degradation. RNA competes with H3K9me for binding with HP1^{Swi6} and causes structural change to HP1^{Swi6}. Thus, both heterochromatin and HP1^{Swi6}–RNA association contributes to the tight repression of genes within heterochromatin.

ribonucleoprotein particles. The authors then hypothesized that Swi6, an HP1 homologue in *S. pombe*, may be central to these particles by targeting and escorting heterochromatic RNA for degradation, because of its dual affinity for both H3K9me and RNA (Motamedi *et al*, 2008). Keller *et al* (2012) confirmed $HP1^{Swi6}$–RNA association and further explored the structural basis of both interactions. They found that overlapping regions of $HP1^{Swi6}$ were important for both interactions, and demonstrated alternation between them and induced structural change of $HP1^{Swi6}$ after binding to either partner. Such alternation and structural change are important for $HP1^{Swi6}$ targeting RNA from heterochromatic regions, and may prevent $HP1^{Swi6}$ binding non-specifically to euchromatic mRNA. To explore the function of the newly identified $HP1^{Swi6}$–RNA association, the creation of a separation-of-function mutant was necessary, as $HP1^{Swi6}$ also has a structural role in heterochromatin. Guided by the structural information obtained for these interactions, the authors designed a mutant that abolishes RNA-binding, while not affecting heterochromatin structure, and indeed, observed that heterochromatic transcripts were no longer degraded, nor were they inhibited from being translated.

In summary, Keller *et al* (2012) have revealed another level of tight repression of heterochromatic genes through uncovering the dynamic turnover of $HP1^{Swi6}$ between its free, H3K9me-bound and RNA-bound forms (Figure 1). The structural component of heterochromatin, $HP1^{Swi6}$ serves as the unidentified link to capture heterochromatic transcripts onsite and escort them towards eventual degradation. Because of the high conservation of HP1, it is possible that a similar mechanism contributes to the tight repression of heterochromatin in higher eukaryotes.

Conflict of interest

The authors declare that they have no conflict of interest.

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