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New partners for HP1 in transcriptional gene silencing

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summary

A new study in this issue of Molecular Cell demonstrates how chromatin assembly proteins HIRA/Asf1 help enforce transcriptional gene silencing in heterochromatin by bridging interactions between HP1 and histone deacetylase complexes.

The fundamental repeating unit of eukaryotic chromatin is the nucleosome: 146 bp of DNA wrapped around an octamer of the four core histone proteins. *In vivo*, chromatin assembly proteins bind nascent histones and ensure that they are deposited onto DNA at the right place and time. Many discoveries about the specialization of chromatin assembly proteins have been made in recent years. A principle division of labor is based on whether the assembly pathway is linked to the process of DNA replication, or is instead required for histone replacement during other events, such as restoring nucleosomes in the wake of RNA polymerase movement. In the latter case, the HIRA protein complex is implicated in DNA replication-independent deposition of histone isoform H3.3 (Tagami et al., 2004), and recent studies in human cells demonstrate that this role is important at subset of genome locations (Goldberg et al., 2010). Indeed, the critical roles of HIRA appear to be diverse in different organisms: in Drosophila, it is required for H3.3 deposition during sperm decondensation, but not in somatic tissues (Loppin et al., 2005); in budding yeast, HIRA acts in concert with histone binding protein Asf1 as a heterochromatin silencing factor (Green et al., 2005). In a new paper from the laboratory of Shiv Grewal (Yamane et al., this issue), the authors discover new interaction partners for fission yeast HIRA/Asf1, revealing how these proteins cooperate with both histone deacetylases and chromatin remodeling enzymes to exert transcriptional repression.

The heterochromatin of fission yeast has provided detailed views of the interplay between histone modifications and recruitment of multiple silencing proteins, including posttranscriptional silencing via Argonaute-containing RITS complexes and transcriptional gene silencing via the histone deacetylase (HDAC) and chromatin remodeling enzyme-containing SHREC complex (reviewed in (Grewal, 2010)). Central to these processes are recruitment events that require chromodomain-containing proteins that bind H3-K9me3 chromatin marks, notably the fission yeast Heterochromatin Protein 1 (HP1) homologs such as Swi6. The present studies were launched when mass spectrometric analysis of Swi6-associated proteins discovered peptides from HIRA complex subunits. Fission yeast HIRA also retains many of the characteristics of its budding yeast homologs, since it associates with Asf1 and contributes to heterochromatin silencing (Green et al., 2005). Indeed, the authors find that *S. pombe* mutants lacking HIRA/Asf1 display partial but significant defects

in gene silencing within the outer and inner pericentric heterochromatin, at the silent mating (*mat*) locus, and at retrotransposons, consistent with previous studies (Anderson et al., 2009). Notably, the HIRA/Asf1-Swi6 interaction appears to be a functionally conserved regulatory module important for genome stability: in human cells subject to a variety of genotoxic stresses, HIRA-mediated recruitment of HP1 and H3.3 to pericientric heterochromatin is required for maintaining normal kinetochore function (Zhang et al., 2007). Further, this discovery now places HP1 as a central hub in multiple chromatin assembly pathways, since it also interacts with the DNA synthesis-linked CAF-1 histone depostion complex in mammalian cells (Murzina et al., 1999).

To explore how HIRA/Asf1 support silencing in *S. pombe*, the authors tested recruitment dependency relationships. HP1(Swi6) and H3K9me3 localization is largely normal in cells lacking Asf1 or HIRA. In contrast, *swi6* mutants display altered localization of HIRA subunit Hip1; specifically, Hip1 recruitment to the heterochromatic *cenH* repeat within the *mat* locus is maintained, but wider localization across *mat* is reduced. Therefore, Asf1/HIRA spreading depends on Swi6, suggesting a role downstream of HP1 recruitment. This led to epistasis tests with other downstream silencing effectors. Double mutants lacking HIRA/Asf1 and RITS or SHREC subunits lead to increased silencing defects, indicating overlapping functionality. In contrast, double mutant combination with subunits of the Clr6-II complex, a silencing-related HDAC complex distinct from SHREC, produced no synergistic phenotypes, suggesting a common pathway with HIRA/Asf1. Indeed, the authors discovered that Asf1 physically interacts with the Clr6-II HDAC complex. This interaction is functionally relevant, because like mutants lacking the Clr6-II complex, *asf1*^{ts} mutants also display increased bulk and locus-specific H3K9ac levels, accompanied by increased cryptic antisense transcription. These results reveal a pivotal role for HIRA/Asf1 in the deacetylation of chromatin in the wake of RNA polymerase movement, consistent with budding yeast data demonstrating that these proteins are required to repress cryptic transcriptional initiation within ORFs (Cheung et al., 2008).

Additionally, in combination with mutations that eliminate the SHREC complex, *asf1*^{ts} mutations cause synergistic alterations in nucleosomal positioning and occupancy within heterochromatin. Therefore, HIRA/Asf1 appear to enforce silencing both by contributing to heterochromatic nucleosomal occupancy and by fostering histone deacetylation. As the repertoire of histone deposition complexes continues to grow (Campos and Reinberg, 2010), one expects that additional elegant networks of protein interactions that increase the functional specialization of chromatin remain to be discovered.

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