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EPIGENETICS

Histones pass the message on

> “H3K9 ... methylation can be inherited over > 50 generations after removal of the sequence-specific initiator”

Histone post-translational modifications can be epigenetically inherited in the fission yeast *Schizosaccharomyces pombe*, according to the results of a new study published in *Science*. Ectopically induced H3K9 (histone H3 lysine 9) methylation can be inherited over >50 generations after removal of the sequence-specific initiator, demonstrating that propagation of the marks can occur via the histones. Furthermore, the researchers characterized proteins that maintain or erase this mark.

Post-translational modifications of histones are associated with patterns of gene expression although, until now, it was unclear whether such epigenetic information could be transferred via histone modifications independently of DNA sequence or DNA methylation. To see whether histones can act as carriers of epigenetic information, the researchers engineered a Clr4 methyltransferase in which the usual chromodomain that recruits Clr4 to methylated H3K9 was replaced by a tetracycline repressor (TetR) domain to target the resultant fusion protein instead to genomically integrated *tetO* DNA sequences. The recruitment of this fusion protein (termed TetR–Clr4-I) is abolished in the presence of tetracycline, thus permitting the testing of initiator-independent maintenance.

To evaluate whether the Clr4 chromodomain is necessary for the establishment and/or maintenance of heterochromatin, Tet–Clr4-I strains were generated in the presence or absence of a wild-type (that is, chromodomain-containing) copy of Clr4. As a reporter, the *ade6* gene (the silencing of which results in the growth of red colonies) was inserted downstream of the *tetO* sites. Notably, the authors were able to show that the chromodomain of Clr4 is required for the maintenance of the silenced state, as initiator-independent silencing was abolished in cells lacking wild-type Clr4.

The researchers additionally constructed TetR–Clr4-I cells with deletions for several genes known to be involved in chromatin maintenance pathways. Notably, the deletion of *epe1* (which encodes a putative H3K9 demethylase) in the presence of tetracycline resulted in maintenance of the silenced state over >50 generations. The HP1 proteins (Swi6 and Chp2) and histone deacetylases (Clr3 and Sir2) are required for the maintenance of the silenced state in cells lacking Epe1 in *S. pombe*. The authors also show that a similar mechanism relying on the chromodomain of Clr4 is responsible for epigenetic inheritance of H3K9 methylation at native pericentromeric repeats.

The results from this study show that histones can act as carriers of epigenetic information independently of the underlying DNA sequence. The authors propose that maintenance of the silenced state is most likely determined by the balance between the rate of H3K9 methylation by the reader–writer Clr4 module and the rate of demethylation by an Epe1-dependent mechanism. H3K9 methylation is conserved from yeast to humans, and it will be interesting to see whether H3K9 methylation can be inherited independently of DNA sequence in mammalian cells.

Bryony Jones

ORIGINAL RESEARCH PAPER Ragunathan, K., Jih, G. & Moazed, D. Epigenetic inheritance uncoupled from sequence-specific recruitment. *Science* http://dx.doi.org/10.1126/science.1258699 (2014)

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