such a scaffold could bind simultaneously without steric conflict. Even more intriguing is the possibility that the ribosome itself may 'sense' the nascent chain before it exits the ribosomal tunnel and thus recruit the appropriate proteins at the right time to take care of the nascent chain[17,18].

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1. Ramakrishnan, V. *Cell* **108**, 557–572 (2002).
2. Keenan, R.J., Freymann, D.M., Stroud, R.M. & Walter, P. *Annu. Rev. Biochem.* **70**, 755–775 (2001).
3. Nissen, P., Hansen, J., Ban, N., Moore, P.B. & Steitz, T.A. *Science* **289**, 920–930 (2000).
4. Hartl, F.U. *Nature* **381**, 571–579 (1996).
5. Frydman, J. *Annu. Rev. Biochem.* **70**, 603–647 (2001).
6. Bukau, B., Deuerling, E., Pfund, C. & Craig, E.A. *Cell* **101**, 119–122 (2000).
7. Frydman, J. & Hartl, F.U. *Science* **272**, 1497–1502 (1996).
8. Thulasiraman, V., Yang, C.F. & Frydman, J. *EMBO J.* **18**, 85–95 (1999).
9. Kramer, G. *et al. Nature* **419**, 171–174 (2002).
10. Hesterkamp, T., Hauser, S., Lutcke, H. & Bukau, B. *Proc. Natl. Acad. Sci. USA* **93**, 4437–4441 (1996).
11. Deuerling, E., Schulze-Specking, A., Tomoyasu, T., Mogk, A. & Bukau, B. *Nature* **400**, 693–696 (1999).
12. Teter, S.A. *et al. Cell* **97**, 755–765 (1999).
13. Houry, W.A., Frishman, D., Eckerskorn, C., Lottspeich, F. & Hartl, F.U. *Nature* **402**, 147–154 (1999).
14. Hartl, F.U. & Hayer-Hartl, M. *Science* **295**, 1852–1858 (2002).
15. Pool, M.R., Stumm, J., Fulga, T.A., Sinning, I. & Dobberstein, B. *Science* **297**, 1345–1348 (2002).
16. Beckmann, R. *et al. Cell* **107**, 361–372 (2001).
17. Liao, S., Lin, J., Do, H. & Johnson, A.E. *Cell* **90**, 31–41 (1997).
18. Nakatogawa, H. & Ito, K. *Cell* **108**, 629–636 (2002).

picture story

The origin of silence

At eukaryotic telomeres and centromeres, DNA is condensed into a transcriptionally silent structure known as heterochromatin. Here, the lack of gene expression can 'spread' randomly into nearby active DNA and, as it can be inherited from generation to generation, may give rise to epigenetic effects whereby individuals with the same genes display different phenotypes. The yeast *Saccharomyces cerevisiae* also packages its chromosomal mating loci into heterochromatin to maintain mating type, but here silencing is maintained unambiguously. In a recent paper, Zhang *et al.* (*EMBO J.* **21**, 4600–4611; 2002) studied the structure and function of the yeast Orc1 protein, a subunit of the origin recognition complex (ORC), revealing a mechanism by which the silencing machinery can be recruited to mating loci.

In *S. cerevisiae*, each of the two chromosomal loci, dubbed HML and HMR, contain silencing elements bound by the replication complex ORC. Four silent information regulator (ySir) proteins are also needed to silence these chromosomal regions; ySir2p is an NAD-dependent histone deacetylase, while ySir3p and ySir4p bind to histone tails lacking acetyl groups. Efficient silencing may thus involve recruitment of ySir2p and histone deacetylation, which lowers gene expression and nucleates a ySir3p/ySir4p repressive structure. Similar processes underlie silencing at telomeres.

But how is it that silencing contained at mating loci, while it spreads at regions bordering telomeres? ORC may provide a clue, as the yeast Orc1 (yOrc1) protein subunit can bind directly to ySir1p *via* its N-terminal domain (NTD). Recruitment of ySir1p to the HML and HMR silencer elements *via* the ORC complex could thus bring about binding of the remaining Sir proteins and strengthen their association with the mating loci.

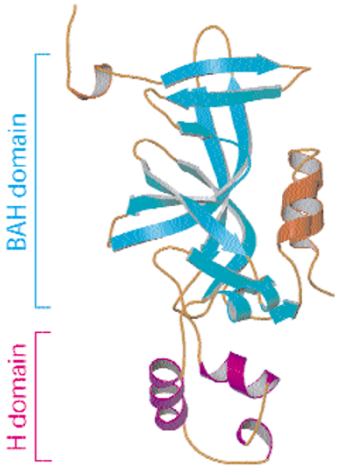

Figure courtesy of R.-M. Xu. Modified with permission from Zhang *et al.*

Zhang *et al.* found two domains in the structure of the conserved yOrc1p NTD: a bromodomain-adjacent homology (BAH) domain comprised mostly of β-strands, and a smaller helical H domain (left). The core BAH domain is relatively common based on sequence alignment, while the H domain is found in yOrc1p and ySir3p as well as in metazoan counterparts of Orc1. The authors found the yOrc1 H domain to be necessary for silencing (right, wild type, pink). Replacing the yeast Orc1 H domain with that from the human protein, which does not bind ySir1p well, abolishes silencing (right, ΔH domain, white). Chromatin immuno-precipitation experiments were used to probe ySir proteins distribution on the mating loci, and removing the yOrc1 H domain was found to reduce recruitment of ySir2p, ySir3p and ySir4p, as well as ySir1p. At telomeres, however, deletion of the H domain in yOrc1p did not affect Sir protein recruitment, consistent with exclusive function at mating loci.

The yOrc1p H domain is thus necessary to recruit all Sir proteins to mating loci. Similar interactions between ORC1 and silencing components may occur in other metazoans: in *Drosophila melanogaster*, for example, Orc1 interacts with the chromatin modifier HP1. Zhang *et al.* were also able to pinpoint mutations in the BAH domain that suppress the silencing phenotype of histone mutants, offering insight into additional functions of this motif. The roles of BAH domains in DNA methyltransferases, histone deacetylases and ATP-dependent chromatin remodeling factors remain to be established, but are likely to reveal interesting links between nuclear processes.

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