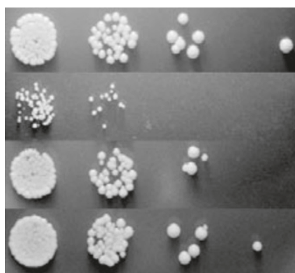
Global effects



Regulation of eukaryotic transcription involves combined action of sequence-specific transcription factors, which are important for recruiting chromatin-modifying enzymes to specific genes, and the general transcription factor complexes, which recruit the RNA polymerases to the basal promoters of virtually all genes. Thus, global transcription regulators, such as the Spt10 protein from *Saccharomyces cerevesiae*, are expected to affect the activity of the core basal promoters. How Spt10 exerts its regulatory effects has not been clear. To address this question, Eriksson *et al.* performed chromatin immunoprecipitation experiments and found that Spt10 is only associated with the promoters of genes encoding the major core histones. This observation suggests that Spt10 influences the expression of most genes indirectly, perhaps through reduction of the level of histone proteins in the cell. Consistent with this hypothesis, the organization of chromatin is globally defective in *spt10*Δ cells. Further, overexpression of histone proteins rescues the phenotype of *SPT10* deletion. Using *in vitro* binding experiments, the authors show that specific, high-affinity binding of Spt10 to the core histone promoters requires the presence of a pair of upstream activating sequences (UAS). Analysis of the yeast genome reveals that only the core histone promoters contain this arrangement of UAS pairs. These results indicate that Spt10 is a sequence-specific transcription factor that activates the transcription of core histones. The authors propose that the global regulatory effects associated with *SPT10* deletion are most likely mediated through the disruption of nucleosomes at the basal promoters of most genes. (*Mol. Cell. Biol.* **25**, 9127–9137, 2005) *HPF*

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Eluding surveillance

The faithful transmission of genetic information during mitosis requires not only accurate DNA replication but also repair. Cells have developed a surveillance system to check the integrity of chromosomes and to coordinate repair and cell-cycle progression. In yeast, this system has been termed the checkpoint response. One well-studied example is the block in mitosis caused by a single double-strand break (DSB) in the genome. This mitotic arrest depends on the highly conserved phosphorylation cascade initiated by Mec1, the yeast homolog of the human ATR kinase, and relayed through the Rad53 and Chk1 kinases. Interestingly, the ends of linear eukaryotic chromosomes do not elicit this response. This is because they are prevented from behaving like DSBs by specialized structures on their ends, called telomeres. But how do telomeres elude this DNA damage response despite the fact that DNA damage checkpoint proteins, such as Mec1, are present at telomeres? This puzzle has now been at least partially solved by Michelson *et al.*, who show that an internal tract of telomeric repeats can inhibit the checkpoint response. They find that the presence of this sequence shortens cell-cycle arrest to 1–2 hours (<20% of the normal arrest response). This shortened arrest is not due to repair of the DSB. Instead, they propose that the shortened arrest is likely due to the presence of an inhibitor, because checkpoint signaling is inhibited from a DSB on the same chromosome but not from a DSB on a different chromosome. The inhibitory activity requires all of the checkpoint genes but does not require telomerase or telomere-derived gene silencing. On the basis of these findings they suggest that the internal telomeric repeats act as anticheckpoints, most likely by recruiting proteins that then inhibit checkpoint signaling. Whether any known or new telomere-associated proteins are involved in the mechanism of anticheckpoint activity will require further study. (*Genes Dev.* **19**, 2546–2559, 2005) *BK*

Research highlights written by Hwa-ping Feng, Evelyn Jabri, Boyana Konforti and Michelle Montoya.

Guiding growth

In *Drosophila*, motor axon guidance decisions require a subset of the five neural receptor protein tyrosine phosphatases (RPTPs). Mutations in any one of these RPTPs result in only partially penetrant phenotypes because of their redundant functions. Despite their importance, extracellular ligands for the RPTPs are thus far unknown. LAR is an RPTP enriched in growth cones and involved in guiding axons at the entrance of target muscle fields. *Lar* loss-of-function (LOF) mutants are less able to innervate their muscle targets. Fox and Zinn now show that Syndecan (Sdc), a heparin-sulfated (HS) proteoglycan, is a ligand for LAR. Using a novel deficiency screen, in which a LAR extracellular domain–alkaline phosphatase (AP) fusion was used to stain the muscle of *Drosophila* wild-type and homozygous-deletion embryos, the authors identified a chromosomal deletion in the *Sdc* gene that eliminated the LAR-AP staining pattern at muscle attachment sites but not at CNS axons. Biochemical and genetic experiments revealed that LAR interacts with Sdc in an HS-dependent manner, Sdc is expressed at the appropriate time and place to influence LAR-expressing growth cones entering the muscle field, and *Lar Sdc* double mutants do not display any new motor axon–guidance phenotypes. These and other data suggest that Sdc is a positive regulator of LAR function. While these experiments identify Sdc as an *in vivo* ligand for LAR, they also suggest that there is at least one other unidentified ligand responsible for LAR-AP staining at CNS axons. The mechanism behind how Sdc binding to LAR promotes axon guidance also remains to be discovered. (*Curr. Biol.* **15,** 1701–1711, 2005) *MM*

Assigning a function

The biogenesis of the ribosome is a complex process during which precursor ribosomal RNAs (pre-rRNAs) are covalently modified, cleaved and then assembled with proteins into the distinct subunits of the ribosome. In budding yeast, more than 170 proteins and 70 small nucleolar RNAs (snoRNAs) are implicated in this process, but the functions of many of these factors are not clear. For example, there are 18 putative ATP-dependent RNA helicases, many of which are essential for viability, for which a precise role or RNA substrate is not known. These helicases could remodel pre-rRNAs, many of which have extensive secondary structures, to allow their incorporation into the ribosome. Alternatively, they could facilitate the separation of pre-rRNAs from snoRNAs after modification and cleavage of the pre-RNAs. Kos and Tollervey show that one of these helicases, Dbp4p, is required for the dissociation of two snoRNAs from the pre-rRNA. The authors screened a panel of putative helicases required in the maturation of the 18S rRNA for their role in the association or dissociation of pre-rRNA and snoRNA. They found that when Dbp4 was absent, the U14 and snR41 snoRNAs remained base-paired to pre-rRNA. Furthermore, point mutations in Dbp4 that affected its ATPase and unwinding activity prevented the release of U14, which is required for both site-specific modification of pre-rRNA and cleavage of pre-rRNA from pre-ribosomal complexes. These data assign a function for Dbp4p in unwinding pre-rRNA from the U14 and snR41 snoRNAs. The challenge remains to determine the roles of the other 17 helicases in ribosome biogenesis. (*Mol. Cell* **20**, 53–64, 2005) *EJ*