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NEWS AND VIEWS

Nucleosome patterning evolution: steady aim despite moving targets

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Molecular systems are the scaffolding on which natural selection builds. Comparing the tendency of different molecular mechanisms to generate tolerable and useful raw genetic variation is a challenging interdisciplinary problem. Modulation of gene expression is thought to be an important source of interspecific phenotypic divergence, and as new mechanisms are revealed, their potential roles must be considered. In this issue of *Molecular Systems Biology*, Tirosh *et al* (2010) use an interspecies hybrid approach to examine the genetic basis of variation in nucleosome arrangement and its potential to explain differences in gene expression. They find that most nucleosome occupancy and position differences are explained by changes in nearby DNA, and these differences prove to be surprisingly poor predictors of gene expression differences between species.

If a gene differs in expression between two species, the causal genetic locus of variation could either be linked to the gene itself (*cis*) or located somewhere else (*trans*). With a few assumptions, whether the locus of change is in *cis* or *trans* can often be determined by examining gene expression in a hybrid of the two species (Wittkopp *et al*, 2004; Tirosh *et al*, 2009). In purely *trans* cases, the alleles of both species will be expressed identically in the hybrid, whereas alleles will retain the expression profile of their source species if all variation can be explained by *cis* changes. Although the proportion of *trans* variation is usually higher in crosses within a species (Brem *et al*, 2002), most gene expression differences between species are explained by variation that maps in *cis* (Wittkopp *et al*, 2004; Tirosh *et al*, 2009).

The new study addresses the molecular basis of these changes by examining the relationship between gene expression and how DNA is packaged into chromatin. In eukaryotes, nuclear DNA is wrapped around complexes of eight core histone proteins called nucleosomes. Nucleosome–DNA interactions respond to environmental conditions and can affect other regulatory proteins, which might serve as a potential mechanism to explain interspecific variation in gene expression. Using enzymatic digestion and next-generation DNA sequencing, Tirosh *et al* mapped the positions of nucleosomes in sister species of yeast (*Saccharomyces cerevisiae* and *Saccharomyces paradoxus*) as well as their interspecific hybrid. They then identified changes in nucleosome arrangement among these strains and found that ~10% of nucleosomes differed in either position or degree of occupancy.

Strikingly, ~70% of nucleosome arrangement alterations were encoded in *cis*, meaning that interspecific variation in nucleosome behavior was largely determined by differences in the nearby DNA sequence. Indeed, most *cis*-based differences could be directly explained by the tendency of AT-rich sequences to disfavor nucleosome occupancy (Iyer and Struhl, 1995). Indirect effects could also be traced as changes in nucleosome position propagated along the chromosome and affected adjacent nucleosomes, supporting the relevance of the statistical positioning model (Kornberg and Stryer, 1988) to explaining interspecific variation. The remaining ~30% of differences were presumably encoded by changes to *trans*-acting chromatin remodeling or transcription factors, suggesting that alterations to this machinery may usually be too pleiotropic and affect too many targets to be allowed by selection.

If differences in nucleosome positioning and occupancy are mostly encoded in the nearby DNA, could they explain differences in gene expression between species? Nucleosome remodeling and repositioning facilitate the association of DNA with transcription factors and the basal transcriptional machinery, so one might expect genes that are more highly expressed in one species would be depleted in nucleosomes (Figure 1). However, Tirosh *et al* find that differences in nucleosome arrangement tend to be excluded from functional elements in promoters. Furthermore, comparing gene expression with total nucleosome occupancy and mapped nucleosome changes shows that these differences are not substantial causative contributors to gene expression differences between species (Tirosh *et al*, 2010).

The lack of correlation between differences in nucleosome arrangement and gene expression suggests that nucleosome

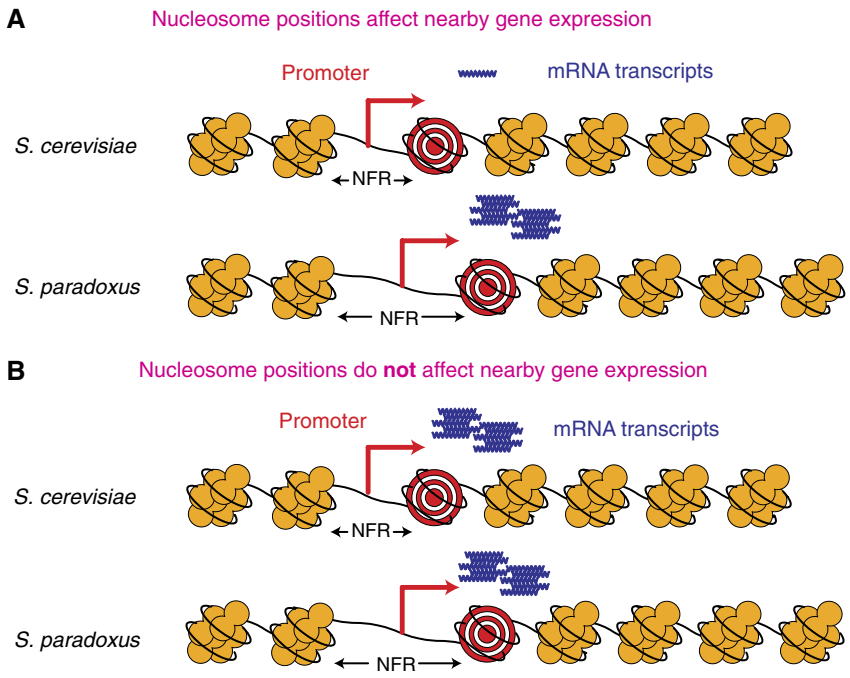

Figure 1 Hypothetical relationships between 'target' nucleosomes and gene expression. (**A**) Orthologous loci exhibit altered patterns of nucleosome deposition resulting from a shift in a 'target' nucleosome (e.g. the +1 nucleosome near a promoter). This nucleosome arrangement could cause a change in gene expression from the two promoters by increasing the nucleosome-free region (NFR). (**B**) Nucleosome positions are altered with no corresponding change in gene expression. Tirosh *et al* (2010) present evidence that this situation is the most common, in which changes in nucleosome position and occupancy between species do not result in gene expression changes.

arrangement evolves primarily through genetic drift and purifying selection. Nucleosomes may be predominantly localized by the establishment of barrier nucleosomes that give rise to ordered arrays of nucleosomes (Mavrich *et al*, 2008), which are in turn established by the association of transcription factors or the presence of AT-rich sequences that disfavor nucleosome positioning (Iyer and Struhl, 1995). Given the degeneracy of nucleosome-tolerant sequences, network-scale correlations between long-term evolutionary changes in gene expression and nucleosome occupancy (Field *et al*, 2009) might be better explained as a neutrally accumulated consequence of transcription factor-dependent network rewiring.

Many questions remain regarding the molecular nature of nucleosomes that differ between species. In particular, histone replacement and chemical modification have been associated with specific genomic positions or transcriptional states. For example, replacement of histone H2A in nucleosomes with the variant H2A.Z is associated with nearly all euchromatic promoters in *S. cerevisiae* (Raisner and Madhani, 2006). It would be interesting to determine how interspecific differences in nucleosome arrangement affect the pattern of H2A.Z deposition or nucleosome modification, and whether any of these 'marked' nucleosomes correlate better with recently evolved differences in gene expression.

It is widely accepted that changes in gene regulation have a central function in the evolution of phenotypic differences between species (Stern and Orgogozo, 2008). However, the balance and variety of mechanisms deployed to accomplish these changes remain contentious. The work of Tirosh *et al* suggests that upstream genetic changes in *trans*-acting chromatin-remodeling factors are disfavored by natural selection, whereas acceptable differences in nucleosome arrangement seem to have little effect. Instead, it seems likely that nucleosome arrangement evolves neutrally from one allowable configuration to another as the evolution of gene expression is directed by other players. The hunt for these factors continues.

Conflict of interest

The authors declare that they have no conflict of interest.

References

Brem RB, Yvert G, Clinton R, Kruglyak L (2002) Genetic dissection of transcriptional regulation in budding yeast. *Science* **296:** 752–755

Field Y, Fondufe-Mittendorf Y, Moore IK, Mieczkowski P, Kaplan N, Lubling Y, Lieb JD, Widom J, Segal E (2009) Gene expression divergence in yeast is coupled to evolution of DNA-encoded nucleosome organization. *Nat Genet* **41:** 438–445

Iyer V, Struhl K (1995) Poly(dA:dT), a ubiquitous promoter element that stimulates transcription via its intrinsic DNA structure. *EMBO J* **14:** 2570–2579

Kornberg RD, Stryer L (1988) Statistical distributions of nucleosomes: nonrandom locations by a stochastic mechanism. *Nucleic Acids Res* **16:** 6677–6690

Mavrich TN, Ioshikhes IP, Venters BJ, Jiang C, Tomsho LP, Qi J, Schuster SC, Albert I, Pugh BF (2008) A barrier nucleosome model for statistical positioning of nucleosomes throughout the yeast genome. *Genome Res* **18:** 1073–1083

Raisner RM, Madhani HD (2006) Patterning chromatin: form and function for H2A.Z variant nucleosomes. *Curr Opin Genet Dev* **16:** 119–124

Stern DL, Orgogozo V (2008) The loci of evolution: how predictable is genetic evolution? *Evolution* **62:** 2155–2177

Tirosh I, Reikhav S, Levy AA, Barkai N (2009) A yeast hybrid provides insight into the evolution of gene expression regulation. *Science* **324:** 659–662

Tirosh I, Sigal N, Barkai N (2010) Divergence of nucleosome positioning between two closely related yeast species: genetic basis and functional consequences. *Mol Syst Biol* **6:** 365

Wittkopp PJ, Haerum BK, Clark AG (2004) Evolutionary changes in cis and trans gene regulation. *Nature* **430:** 85–88