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Epigenetics and Genomic Stability

Goal

To understand the role of chromatin and RNA surveillance mechanisms in genome organization and in the maintenance of genomic stability.

Background

Recent results have revealed another layer of complexity in the eukaryotic transcriptome. While previous expression analyses focused mostly on mRNA expression levels, new transcriptome profiling techniques provide unbiased genome-wide information about transcription activity. These studies have revealed that genomic regions previously thought to be silent, such as heterochromatic regions, intergenic regions and antisense portions of the genome, are actually transcriptionally active and produce a significant amount of non-protein-coding RNA (ncRNA) transcripts. Although a growing number of examples show that some of these ncRNAs can affect key nuclear events, the majority of these transcripts, so-called cryptic unstable transcripts (CUTs) are rapidly degraded by the RNA surveillance machinery. The general function of this widespread, pervasive transcription is not understood, but its level is strictly controlled by the chromatin structure. Defects in this repressive chromatin structure or impairment of the RNA surveillance system can lead to strong accumulation of cryptic transcripts and to genomic instability.

The main focus of the research in our laboratory is:
(i) to understand the role of chromatin in the repression of pervasive transcription;
(ii) to reveal the molecular mechanisms responsible for the recognition and degradation of CUTs;
(iii) to understand the link between ncRNA accumulation and genomic instability and how it contributes to cancer development.

Research Highlights

Chromatin compacts and protects the genome, but it also restricts direct access of macromolecules to the DNA. Chromatin modifying activities can open the chromatin structure and provide regulated access to specific genomic loci. Chromatin characteristics, such as position, occupancy and turnover-rate of nucleosomes, incorporation of histone variants, histone modifications and other epigenetic mechanisms, establish an elaborate genomic indexing mechanism, which is responsible for defining functional units in the genome. To identify factors that have a role in repress-

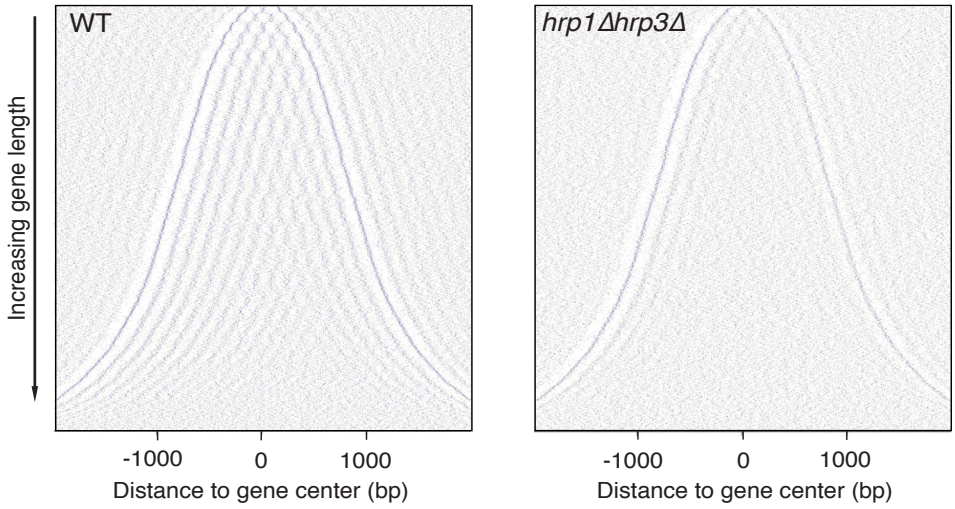

Fig. 1: The regularly organized nucleosome arrays in gene coding regions are disrupted in the hrp1Δhrp3Δ strain. *Two-dimensional plots of nucleosomes along 3,778 genes in WT and hrp1Δhrp3Δ strains. Each row represents a gene; genes were sorted vertically (shortest at the top and longest genes at the bottom) according to the distance between the first and last nucleosome of the gene and were aligned at the mid point. Blue dots correspond to the centre of identified nucleosomes.*

ing cryptic transcription activity in *S. pombe*, we screened a deletion library for chromatin-related factors and tested their effect on cryptic transcription. We found that deletion of the *S. pombe* Chd1 chromatin remodelers, hrp1 and hrp3, results in a dramatic increase in cryptic transcription. To determine the underlying molecular mechanism, we mapped genome-wide nucleosome position and histone acetylation patterns in the Chd1-deficient strain. These experiments uncovered a specific role for Chd1 remodelers in maintaining the highly ordered nucleosome structure within transcription units (Figure 1).

We extended our analysis to other mutations also known to enhance cryptic transcription activity. Although these mutants accumulate cryptic transcripts very similarly to the Chd1-deficient strain, our data showed that the underlying mechanisms are remarkably different.

Another important mechanism to inhibit the accumulation of ncRNAs is their rapid degradation by the nuclear exosome. However, the way that these cryptic RNA transcripts are recognized and targeted to the exosome is not fully understood. We recently identified a multi-subunit complex in *S.pombe* that specifically binds to CUTs and targets them to the nuclear exosome for degradation. Phylogenetic analysis of the subunits shows high similarity to subunits of the human Nuclear EXosome Targeting (NEXT) complex. Deletion or mutation of *S.pombe* NEXT-like (spNEXT) complex subunits leads to dramatic accumulation of CUTs and other aberrant RNAs. spNEXT physically interacts with the nuclear exosome, and with various RNA binding and processing complexes, including the cap-binding, spliceosome, cleavage and poly-adenylation complexes. These results suggest that spNEXT plays a central role in RNA quality control by coupling RNA processing to the RNA degradation machinery.

Selected Publications 2011 - 2013

Zhu, J.*, Zhou, Y.*, Schermann, G., Ohle, C., Bendrin, K., Sugiyama, T., and Fischer, T. (2013). *Schizosaccharomyces pombe* NEXT-like (spNEXT) complex is a central component in RNA quality control. Submitted (* These authors contributed equally)

Hennig, B.P., and Fischer, T. (2013). The great repression: Chromatin and cryptic transcription. Transcription 4, 97-101.

Hennig, B.P., Bendrin, K., Zhou, Y., and Fischer, T. (2012). Chd1 chromatin remodelers maintain nucleosome organization and repress cryptic transcription. EMBO Rep 13, 997-1003.

Zhang, K., Fischer, T., Porter, R.L., Dhakshnamoorthy, J., Zofall, M., Zhou, M., Veenstra, T., and Grewal, S.I. (2011). Clr4/Suv39 and RNA quality control factors cooperate to trigger RNAi and suppress antisense RNA. Science 331, 1624-27.

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