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Epigenetics and Genomic Stability

Goal

To understand how epigenetic mechanisms contribute to genome organization, maintenance of genomic stability and chromosome segregation.

Background

A large portion of the eukaryotic transcriptome consists of non-protein-coding RNA transcripts (ncRNAs or cryptic transcripts), but the function and significance of this widespread ncRNA transcription is not understood. The majority of these cryptic transcripts are recognized and quickly degraded by the RNA surveillance machinery. Defects in the recognition and degradation of cryptic transcripts or increased transcriptional activity outside of transcription units can lead to toxic accumulation of these transcripts. But how do genomic indexing mechanisms define transcription units and their transcripts? The answer to this question lies in chromatin structure and its modifying activities. Combinations of epigenetic marks provide a complex indexing mechanism for defining transcription units. Defects in such epigenetic indexing could lead to cryptic transcript accumulation and to genomic instability.

The main focus of the research in our laboratory is:

- to understand the role of chromatin and its modifying activities in genomic indexing;
- to understand the link between cryptic transcript accumulation and genomic instability and how it contributes to cancer development.

Research Highlights

Recently developed techniques give detailed and sensitive genome-wide maps of transcription activity, including the intergenic and antisense portion of the genome. We are using high resolution tiling arrays in combination with high-throughput sequencing technology to obtain an unbiased picture of eukaryotic transcriptional activity throughout the genome. With the help of these techniques we have identified mutations in the fission yeast *S. pombe* that lead to cryptic transcript accumulation. Currently we are focusing on these mutations and trying to understand the molecular mechanisms behind the observed phenotypes. (Figure)

We have found that accumulation of ncRNAs is associated with genomic instability and sensitivity to DNA damage. Furthermore, we discovered that RNase H, an enzyme that degrades DNA-RNA hybrids, is important for the maintenance

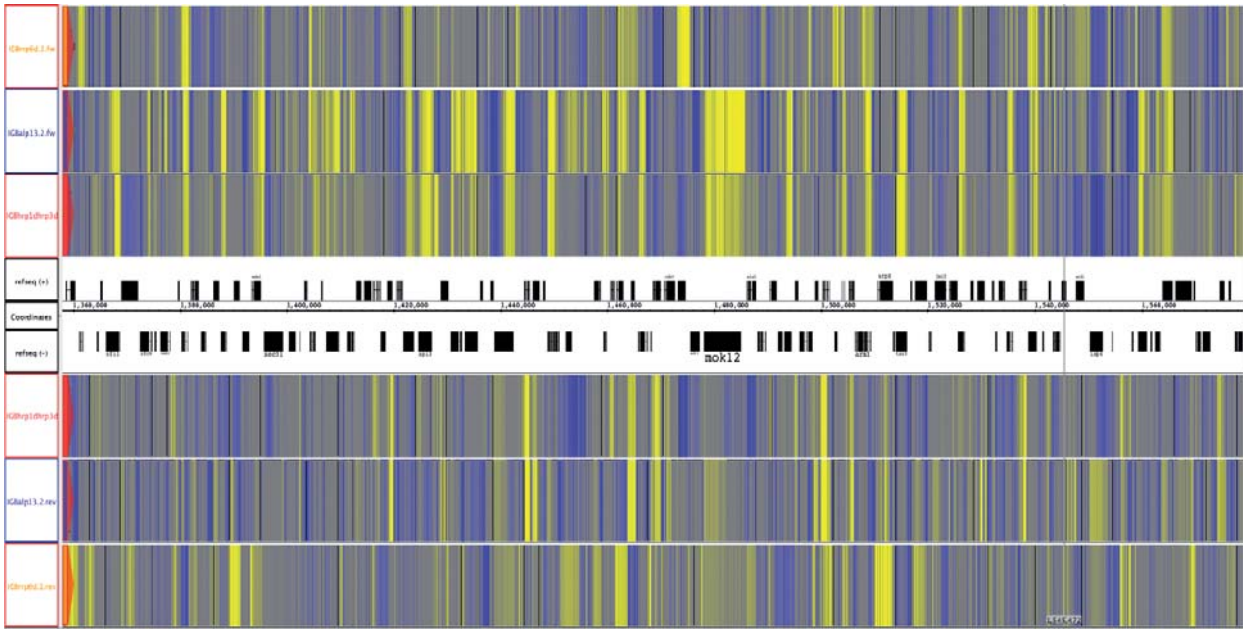

Fig. 1: Genomic view of ncRNA-accumulating S. pombe mutants. Yellow bars represent increased RNA levels compared to wild type expression levels, while blue bars represent a decrease.

of genomic stability, and essential in the isolated ncRNA-accumulating mutants. These results suggest that ncRNAs form DNA-RNA hybrids with their DNA template, which can lead to replication fork collapses and consequently to DNA lesions and genomic instability. We would like to further study the molecular mechanisms leading to genomic instability, and the in vivo function of RNase H in eukaryotic genome organization.

RNA may play a more significant role in nuclear processes than previously imagined. These studies will increase our general understanding of genomic organization, transcriptional regulation and the biological significance of ncRNAs in the eukaryotic cell. Mutations leading to genomic instability are a major cause of cancer development, which highlights the importance of studying the molecular mechanisms behind this process.

Selected Publications 2008 - 2010

Zofall, M.*,T. Fischer*, K. Zhang, M. Zhou, B. Cui, T.D. Veenstra, S.I. Grewal. (2009). “Histone H2A.Z cooperates with RNAi and heterochromatin factors to eliminate antisense RNAs.” Nature 461(7262):419-22 (*These authors contributed equally).

Fischer, T., B. Cui, J. Dhakshnamoorthy, M. Zhou, C. Rubin, M. Zofall, T.D. Veenstra, S.I. Grewal. (2009). “Diverse roles of HP1 proteins in heterochromatin assembly and functions in fission yeast.” PNAS 106(22):8998-9003.

Roguev, A., S. Bandyopadhyay, M. Zofall, K. Zhang K, T. Fischer, S.R. Collins, H. Qu, M. Shales, H.O. Park, J. Hayles, K.L. Hoe, D.U. Kim, T. Ideker, S.I. Grewal, J.S. Weissman, N.J. Krogan. (2008). “Conservation and Rewiring of Functional Modules Revealed by an Epistasis Map in Fission Yeast.” Science 322(5900):405-410.

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