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The SMC loader Scc2 regulates gene expression

Comment on: Lindgren E, et al. Inactivation of the budding yeast cohesin loader Scc2 alters gene expression both globally and in response to a single DNA double strand break. Cell cycle 2014; 13(23):3645-58; http://dx.doi.org/10.4161/15384101.2014.964108

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Proper regulation of gene expression is fundamental for maintaining the integrity of the genome, a process essential for cell survival and cell cycle progression. Central to this process is the multi-subunit protein complex, cohesin. The importance of cohesin is seen in humans where mutations in the cohesin complex proteins result in a group of developmental diseases collectively termed "cohesinopathies." Cornelia de Lange syndrome (CdLS), the most common of the cohesinopathies, is caused mainly by mutations in Scc2 (also known as NIPBL). Mutations in cohesin have also been reported to cause cancer. The working model is that mutations in cohesin affect gene expression, most likely by disruption of enhancer-promoter communication, but additional mechanisms have also been proposed.

The role of the SMC loader Scc2 in regulating gene expression has been well studied in higher organisms. However, it is still not known whether the role of Scc2 in regulating gene expression is evolutionarily conserved from humans to budding yeast. Scc2 was previously reported in budding yeast to bind to active genes transcribed by RNA polymerases I, II, and III,[1] but the biological implications of Scc2 inactivation on these genes is still unknown. In this issue, Lindgren et al.[2] examine the role of Scc2 in gene expression in budding yeast.

The group examined the transcriptional program in WT and scc2 mutant (*scc2–4*) in the presence and absence of DNA damage. Analysis of the gene expression program showed that hundreds of genes were differentially expressed in the *scc2–4* mutant. Gene ontology (GO) analysis of up-regulated genes in the presence or absence of a break showed enrichment for genes important for mitochondrial processes, DNA repair and chromosome segregation. Among the down-regulated genes, the biological processes most affected were those important for ribosome biogenesis, tRNA processing, and RNA polymerases I and III transcription. This observation is in support of earlier studies in other cohesin mutants where mutations caused defects in ribosome biogenesis and translation.[3] Scc2 inactivation affected gene expression in both the presence or absence of DNA damage.

Interestingly, Lindgren et al. found that the changes in the gene expression profile were independent of cohesin binding. Cohesin was still found associated with cohesin associated regions (CARs) and double strand break (DSB) proximal genes in the loading mutant background. Earlier studies in CdLS patient cells indicated that mutations in the loader reduced cohesin binding but did not alter the overall pattern of binding observed. In patient cells, some of the changes in gene expression correlated with loss of binding, although whether this was a cause or consequence of transcriptional changes was not clear.[4]

In summary, the results support earlier findings in higher eukaryotes of the evolutionary role of Scc2 in regulating gene expression.[5] In addition, the observation that inactivation of Scc2 does not affect the cohesin binding pattern suggests that Scc2 could regulate gene expression independent of cohesin.[6] Budding yeast do not have enhancers, yet mutations in Scc2 still cause changes in gene expression, suggesting that loss of enhancer function alone cannot explain the etiology of CdLS. Scc2 could regulate gene expression in many other ways such as serving as a "chromatin adaptor" for recruitment of other factors that maintain a nucleosome free region as recently reported.[7] Despite the tremendous work done in examining cohesin's role in gene expression, the molecular mechanisms are yet to be elucidated. More work is still required to fully understand the etiology of "cohesinopathies." Because of the remarkable evolutionary conservation of Scc2 and cohesin, budding yeast may serve as a good model in which to identify the evolutionarily conserved functions of these proteins in gene expression.

References

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