The cohesin complex: sequence homologies, interaction networks and shared motifs

ABSTRACT

We have combined genomic and proteomic data into a comprehensive network of information to reach a better understanding of the function of the cohesin complex. We have identified new SMC homologs, created a new SMC phylogeny and identified shared DNA and protein motifs. The potential for Scc2 to function as a kinase - a hypothesis that needs to be verified experimentally - could provide further evidence for the regulation of sister-chromatid cohesion by phosphorylation mechanisms, which are currently poorly understood.

INTRODUCTION

Background Cohesin is a macromolecular complex that holds sister chromatids together at the metaphase plate during mitosis. The links between the sister chromatids are formed during DNA replication and destroyed during the metaphase to anaphase transition, when sister chromatids separate to opposite poles of the cell. In budding yeast, the 14S cohesin complex comprises at least two SMC (structural maintenance of chromosomes) proteins - Smc1 and Smc3 - and two SCC (sister-chromatid cohesion) proteins - Scc1 and Scc3. A recent development is the identification of a separate complex, comprising two further sister-chromatid cohesion proteins, Scc2 and Scc4, that function in the loading of cohesin macromolecules onto chromosomes. The Smc1 and Smc3 proteins belong to the conserved and well characterized SMC family, which also includes Smc2 and Smc4, components of the condensin macromolecular complex. The SMCs have a highly conserved structure comprising five domains arranged in a head-rod-tail architecture, including a Walker A motif in the amino-terminal domain and a DA-box (Walker B motif) in the carboxy-terminal domain (Figure 1a). Dimeric models of Smc1-Smc3 protein complexes have been proposed, in which the coiled-coil domains of each protomer interact in an antiparallel arrangement, bringing the Walker A and B motifs together at the termini of the structure, forming two complete ATP-binding sites (Figure 1b). In accordance with this model, an SMC homodimer has been observed by electron microscopy in Bacillus subtilis. A similar model is proposed for Smc1-Smc3 heterodimers in eukaryotes. A number of additional proteins are known to play key roles in the cohesion mechanism. Eco1 is involved in the establishment of cohesion during S phase of the cell cycle, but not for its maintenance during G2 or M phases. Esp1, a separin protein, is a protease that cleaves Scc1 at the metaphase-to-anaphase transition to trigger sister chromatid separation. This protein is complexed with the securin protein Pds1 for some of the cell cycle, which prevents the onset of anaphase when there has been DNA or spindle damage during DNA replication. When Esp1 is separated from Pds1, it undertakes the proteolytic cleavage of Scc1 (for review see). Here, we have combined available genomic and proteomic data into a comprehensive network of information to reach a better understanding of the function of the cohesion complex. We have searched for homologs of the SMC proteins, created a new evolutionary tree for these proteins and identified an interesting homology between SMC3 and Mmip1 in mouse. We have also created a cohesion interaction network of 17 proteins using two proteomic databases. A number of pairs of proteins within this network share sequence motifs that could represent common binding sites. In addition, the genes encoding a subset of six proteins in the network share a

common upstream regulatory element.

CONCLUSION

Conclusions We have combined available genomic and proteomic data into a comprehensive network of information to reach a better understanding of the function of the cohesin complex. We have identified a new sequence homolog to SMC that highlights the capability of a protein to conduct different functions in different cellular locations, and have created a new phylogeny for SMC proteins that includes a number of eukaryotic sequences (predominantly Rad18 homologs) within an ancestral family of SMC proteins. A complex network of interacting cohesion proteins was identified. Six of these networked proteins contain a known upstream regulatory sequence. In addition we have identified a number of protein pairs within the network that share protein motifs, which could indicate a common structural feature such as a binding site. In this way we discovered a motif shared by Scc2 and Chk1 that suggests Scc2 could have kinase activity. This hypothesis needs to be verified experimentally. The potential for Scc2 to function as a kinase could provide further evidence for the regulation of sister-chromatid cohesion by phosphorylation mechanisms, which are currently poorly understood.