The specific contributions of cohesin-SA1 to cohesion and gene expression: implications for cancer and development

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Cohesin is an evolutionarily conserved complex originally identified and named for its role in sister chromatid cohesion. Increasing evidence suggests that cohesin is also a major chromatin organizer of the interphase nucleus, and thereby affects many aspects of DNA metabolism including transcription, replication and recombination. Cohesin entraps two DNA segments within its ring-shaped structure either in trans, to hold the sister chromatids together, or in cis, to facilitate long-range DNA looping. Vertebrate somatic cells have two different versions of the cohesin that consist of Smc1, Smc3, Rad21 and either SA1 or SA2, but their functional specificity has been largely ignored. We recently generated a knock out mouse model for the gene encoding SA1 and found that this protein is essential to complete embryonic development. Cohesin-SA1 mediates cohesion at telomeres, which is required for their replication. Telomere defects in SA1 deficient cells provoke chromosome segregation errors resulting in aneuploidy despite robust centromere cohesion. This aneuploidy could explain why heterozygous animals have an earlier onset of tumourigenesis. In addition, the genome wide distribution of cohesin changes dramatically in the absence of SA1, and the complex shows reduced accumulation at promoters and CTCF sites. As a consequence, gene expression is altered leading to downregulation of biological processes related to a developmental disorder linked to cohesin function, the Cornelia de Lange Syndrome (CdLS).