
**100 YEARS AGO**

**The best angle of traction on a rough or irregular surface is at an upward inclination to its general slope. This upward slanting pull can be applied to a two-wheeled vehicle, and to the fore-wheels of any vehicle, but not to the hind wheels — especially if they are far away. Consider, further, the summit of a hill, and let a waggon be so elongated that its hind wheels are still ascending while the horse is descending: his pull is exerted at a very bad angle on this part of the load… I should like to take this opportunity of saying that whether the traditional heavy draught of a long-bodied carriage is well founded or not, I am convinced that the ordinary hansom cab is badly balanced, and that a horse would be better with some load on his back, except when descending a hill… Nothing can be worse than a constant upward pressure on the chest of a horse: a pressure which at present automatically increases on an up grade, thus tending to deprive the animal of part of his own weight, on the existence of which the efficacy of every locomotive depends.** **Oliver Lodge**

From *Nature* 28 July 1904.

**50 YEARS AGO**

***The Papers of Wilbur and Orville Wright.*** **These two volumes give for the first time a full account by the Wright brothers of the history of the solution of the problem of human flight. In the introduction it is explained that they fully intended to write up the results of their work for publication, but that they became so preoccupied with their experiments and later with the marketing of their machines that they never did so. After Wilbur's death in 1912, Orville had the same good intention, but never carried it out. After his death in 1948, the voluminous correspondence of the brothers and their note-books eventually came into the possession of the United States Library of Congress, and it is from this material that the present volumes have been compiled… The second volume contains later experimental work; but is largely taken up with the efforts made by the brothers, sometimes separately and sometimes together, to obtain some reasonable financial recompense for all their work by selling their invention to governments or private companies, a matter in which they met with no small difficulty.**

From *Nature* 31 July 1954.

not responsible for their arrangement. Note that if the crossed pairs of interacting T-calixarenes are viewed as single entities, the arrangement still lacks inversion symmetry. It seems instead that the key to the micelle assembly is a non-planar linking of the T-shaped pairs, apparently mediated through coordinated hydrogen bonding. Once the pairs interlock, they become a curved building-block that imposes spherical geometry. The net effect is to exclude the formation of linear micelles or even membranes.

By adding moieties that prefer the local chemistry of the interlocking T-calixarenes, it should be possible to exploit the micelle's net polarity and make asymmetrically functionalized micelles with geometric accuracy. For instance, the four proteins that assemble into the histone octamer are subsequently involved in forming the complex three-dimensional structure that is the chromosome — an example that might prove fruitful for better understanding the physical principles in the packing of DNA. Other applications might include hierarchies of aggregates: precision micelles inside larger, perhaps less-ordered aggregates could deliver a targeted regimen of several therapeutic drugs. ■

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**Molecular biology**

# Cohesins slip sliding away

Karen E. Ross and Orna Cohen-Fix

Cohesin complexes have a central role in cell division, mediating the association between sister chromosomes. It now seems that cohesin binding is dynamic, adapting to changes in gene transcription.

Dividing cells face the monumental task of providing each progeny cell with a complete and accurate copy of the genome. During mitosis, the basic cell-division process, cells need to ensure that they send only one copy of every chromosome to each of the daughter cells. Cohesion between the two sister chromatids produced by chromosome duplication is essential to this process: following duplication, the sister chromatids are physically linked by an evolutionarily conserved, ring-shaped protein complex known as cohesin[1].

Cohesin binding serves three functions: it allows cells to keep track of the two sister chromatids, thereby ensuring their proper segregation in mitosis; it facilitates attachments between chromosomes and the spindle, the apparatus that segregates chromosomes into the two daughter cells; and it facilitates DNA repair by recombination. Cohesin-mediated cohesion between sister chromatids also has a vital role during meiosis, the specialized cell division that produces the reproductive cells.

It is not known how cohesins link sister chromatids together; cohesin might bind to chromosomes directly, bridging the two sister chromatids, or, given its ring-like structure, it might form a ring that encircles one or both sisters[2]. Regardless of the mechanism, the presence of cohesin is likely to cause a logistical problem: when behemoth enzyme complexes such as RNA polymerase, which transcribes genes into RNA, slide along cohesin-bound chromosomes, they have to contend with these complexes in their path. Lengronne *et al.*(page 573 of this issue[3]) and Glynn *et al.* (writing in *PLoS Biology*[4]) have created high-resolution maps of cohesin-binding sites throughout the genome of budding yeast, and have thereby gained tantalizing insight into how the transcription machinery and cohesins coexist.

The importance of cohesin has generated great interest in identifying cohesin-binding sites on chromosomes. DNA-binding proteins often show a preference for particular DNA sequences, but, curiously, no such sequences had been identified for cohesin. Previous work revealed that cohesins are present at centromeres, the sites on chromosomes that mediate attachments to the spindle, and along chromosome arms, where they are bound with an average spacing of 10 kilobases[5–7]. Chromosome-arm binding sites tend to be in regions between genes — intergenic regions — that are rich in adenine (A) and thymine (T) nucleotides. However, these previous studies did not examine large portions of the genome at high resolution. Therefore, Lengronne *et al.*[3] and Glynn *et al.*[4] set out to create a more complete picture of cohesin-binding sites, hoping to uncover the underlying principles that govern cohesin localization.

Both groups generated their cohesin maps using a technique called ChIP–chip,

for chromatin immunoprecipitation followed by analysis on a microarray, or 'gene chip' (Fig. 1). Yeast cells were first treated with chemical crosslinkers to attach cohesins covalently to their chromosomal binding sites. The DNA was then sheared, and antibodies against one of the cohesin subunits were used to precipitate cohesin complexes and their associated DNA. This DNA was then amplified, labelled and incubated with a microarray consisting of DNA fragments of known sequence that represented much of the yeast genome. The labelled DNA bound to matching sequences on the array, thereby identifying the sequences corresponding to cohesin-binding sites in living cells.

The new maps for cohesin-binding sites revealed that, along chromosome arms, cohesins did not bind randomly to intergenic regions. Rather, cohesin-site preference was influenced by the orientation of the neighbouring genes. Genes have a defined polarity: they are transcribed from one end (head) to the other (tail). Neighbouring genes can be found in various arrangements relative to each other: head to head, head to tail, or tail to tail. Of more than 1,000 cohesin-association sites that map to chromosome arms, the vast majority occur between genes that are arranged tail to tail, where transcription of the two genes converges (Fig. 2a). It might be that a specific feature of the nucleotide sequence or a particular chromatin modification attracts cohesins to these zones of convergent transcription. However, an intriguing possibility raised in both reports is that RNA polymerase, as it moves along the chromosome, acts like a snowplough and shoves cohesins along the DNA, causing them to pile up where RNA polymerases travelling in opposite directions meet.

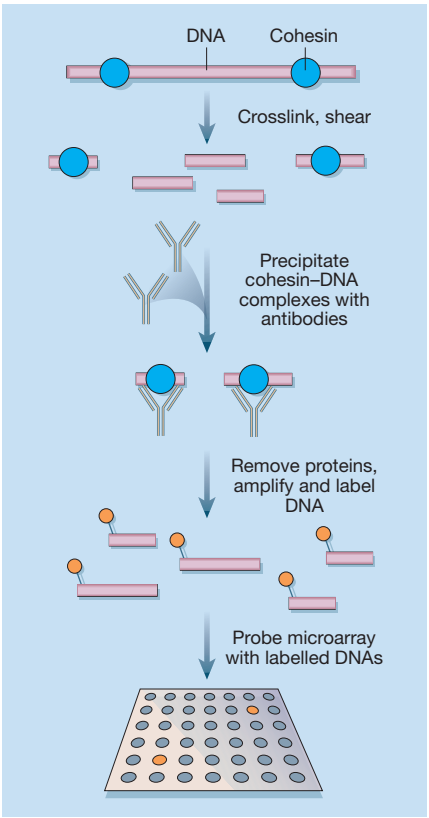


Figure 1 **The ChIP–chip technique used by Lengronne *et al.*[3] and Glynn *et al.*[4]. Chemical crosslinkers link cohesins (blue) to their chromosomal binding sites. The DNA (pink) is sheared into fragments of 0.2–1 kilobases, and antibodies against one of the cohesin subunits (Y-shaped structures) precipitate the cohesin complexes and their associated DNA. This DNA is amplified, labelled and incubated with a microarray containing known yeast DNA sequences at designated spots, represented by circles. The orange circles indicate places on the microarray where the precipitated DNA bound to a matching sequence.**

Consistent with this model, Lengronne *et al.*[3] and Glynn *et al.*[4] show that when transcriptional activity changes, the pattern of cohesin-binding sites also changes. Cohesins appear on genes whose transcription is turned off and disappear from genes whose transcription is turned on (Fig. 2b). The observed relocation of cohesin was rapid, in one case occurring within 15 minutes of the start of transcription[3]. In this experiment, an increase in transcription was associated not only with the loss of cohesin from the gene-coding region, but also with accumulation of cohesin near the gene's tail (Fig. 2b). This rearrangement could come about in one of two ways: cohesin could dissociate and rebind, or it could slide along the DNA, piling up at the end of the gene as a result of the movement of the RNA polymerase. The second possibility is attractive given cohesin's ring structure, but it would mean that this rearrangement is independent of the factors necessary for loading cohesin onto DNA[8] — which has yet to be proven.

Not all cohesin was found in regions of convergent transcription. Glynn *et al.*[4] examined several cohesin-binding sites within genes and found them to be AT-rich, suggesting that along chromosome arms AT-richness and convergent transcription may be two independent determinants of cohesin binding. Consistent with previous reports, the region surrounding the centromere was also thickly coated with cohesin. Binding of cohesin to this region depends on chromosome-associated proteins that mediate the attachment of the chromosome to the spindle[9]. In animal cells, cohesin is also found near centromeres, and in this case it is recruited by factors in heterochromatin, a specialized, highly compact chromatin structure[10].

Cohesins are also associated with zones of convergent transcription in fission yeast[3], but it remains to be seen whether the same is true in multicellular organisms. Unlike yeast genes, which are generally small, the genes of multicellular organisms can be huge, and zones of convergent transcription may be too widely spaced to provide sister chromatids with sufficient cohesion. Interestingly, vertebrates have two types of cohesin complex with different subunit compositions[1], raising the possibility that they differ in their binding-site preference. Thus, the rules that govern cohesin localization in other organisms await further investigation.

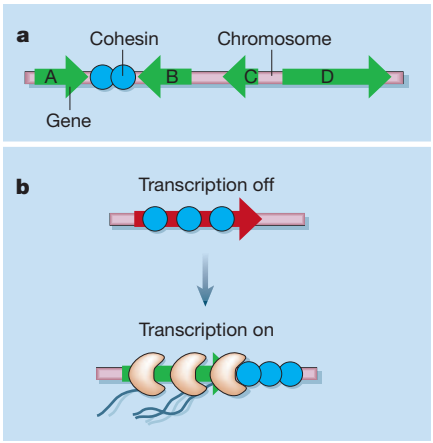


Figure 2 **Cohesins associate with zones of convergent transcription.** a, **Genes occur in several orientations along the chromosome; green arrows indicate the direction of transcription. Genes A and B are arranged tail to tail; genes B and C are head to tail; and genes C and D are head to head. Cohesins are generally found in the spaces between genes that are arranged tail to tail.** b, **Transcription leads to cohesin rearrangement. When transcription of a gene switches from off (red) to on (green), cohesins are lost from the coding region and instead associate near the end of the gene. RNA polymerase is shown in beige and the newly synthesized RNAs are shown as thin black lines.**

The creation of a genome-wide map of cohesin-binding sites in budding yeast suggests that sister chromosome cohesion is much more dynamic than previously imagined, adapting to the immediate transcriptional needs of the cell. Cohesin rearrangement could occur by a surprisingly simple mechanism — in the face of RNA polymerase, cohesins may go slip sliding away. ■

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