# The machinery for recombination is part of the chromosome structure

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During the development of gametes, such as egg and sperm cells in humans, chromosomes are broken and rearranged at many positions. Using state of the art technology, the research group of Franz Klein, professor for genetics at the Max F. Perutz Laboratories of the University of Vienna, has analyzed this process at high resolution. The surprising observations regarding the mechanism of meiosis are now published in the scientific journal *Cell*.

Without meiosis there would be no sexual reproduction, as germ cells have to be generated in this specialized cell division. Meiosis results in daughter cells containing a single, complete set of chromosomes, while body cells contain two sets. During fertilization, when sperm and egg fuse, their sets of chromosomes are combined to form a diploid embryo to close the cycle.

## Enigmatic meiosis

There are 46 chromosomes in every human cell, 23 maternal and 23 paternal ones. When germ cells are produced, one aspect of the reduction in chromosome numbers comes from merging maternal and paternal chromosomes to form a single daughter chromosome – a mechanisms called recombination. "The more we learn about meiosis, the more mysterious it becomes", says Franz Klein from the Department for Chromosome Biology of the University of Vienna. "It is surprising that maternal and paternal chromosomes find each other at all. Because

at the time of interaction all chromosomes have generated a sister and are tightly connected with her like a Siamese twin. Normally, in non-meiotic cells, chromosomes only interact and exchange with the sister chromosome. However, during the development of germ cells, only the exchange between parental chromosomes can guarantee the production of daughter cells with the right number of chromosomes", explains Klein.

## Nano-view of the chromosome

Franz Klein and his research team have analyzed components of the protein machinery, which initiates recombination by DNA-breakage. They created a high resolution map of the chromosomes and marked the interaction sites with those proteins. "Thanks to DNA microarray-technology, we get a resolution in the nanometer range, with insights unimaginable before", says Klein. The researchers were surprised to find the DNA-breaking machine tightly associated with chromosomal axis regions, instead of being soluble - an observation with far reaching consequences.

## Disposable machines

One of the many riddles in meiosis was how breaks on chromosomes impede the occurrence of other breaks in their vicinity. Earlier research had shown that each individual DNA-breakage complex only works a single time. "As we now know that these machines are anchored, we understand why there is preferentially a single break per region. The locally bound machine has fired and other machines can't get there as they are anchored to other chromosomal regions", explains Klein.

## When chromosomes are out of shape

Healthy chromosomes can form DNA loops, which are, in meiosis, connected by a protein axis. Defective genes can cause chromosomes to lose this shape. "No one could understand why the shape of chromosomes influences the function of the DNA-break machines. Now we know that these machines have to anchor between loops on the chromosome axis. If their loop-environment changes they anchor in different regions or lose functionality altogether", says Klein.

## Hyperactive sister

Sister chromosomes are connected like Siamese twins along the chromosome axis, where the DNA-break machines are anchored. It was very mysterious, how the sister chromosome is prevented to take part in the repair of DNA breaks during meiosis, despite being so close to the damage. A special feature of meiosis is the formation of a zone along the chromosome axis that inhibits recombination.

Franz Klein concludes: "We think that the DNA-break machines are anchored at the axis to position the breaks right within the recombination inhibiting zone. This may attract the sister chromosome loop, which remains trapped in the recombination inhibiting zone by one of the two ends flanking the break, while the second end docks off to form a search tentacle for finding the paternal chromosome. We have evidence for many details of this scenario – but most importantly, the inhibition of the involvement of the sister breaks down, if the anchoring of the DNA-break machines is defective. This indicates that anchoring may be indeed a key mechanism to control the sister. The result of a sister, hyperactive for DNA-break repair in meiosis is the death or severe impairment of the developing embryo."

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