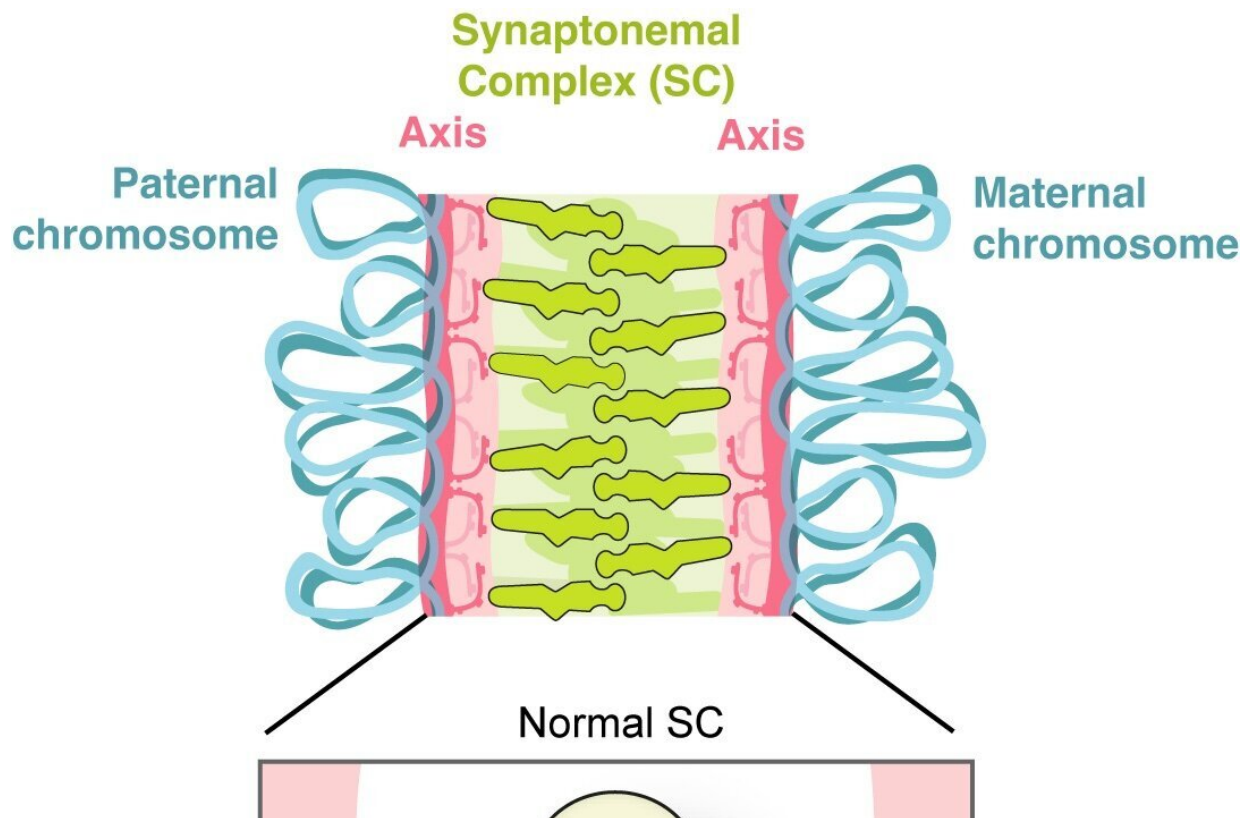


Nematode proteins shed light on infertility

January 3 2024, by Lisa Potter



A cartoon of paired homologous chromosomes (blue) with the synaptonemal complex (SC, green) assembled between them. Below, from top to bottom, are cartoons depicting the localization of proteins in a normal SC, in the SC of the researcher-bred infertile nematodes, and in the SC of the nematodes with the suppressor-mutation. Credit: Lisa Kursel and Maria Diaz de la Loza

In a [new study](#) published in the *Proceedings of the National Academy of*

Sciences, University of Utah (the U) biologists have developed a method for illuminating the intricate interactions of the synaptonemal complex in the nematode *C. elegans*.

The authors identified a trio of protein segments that guide chromosomal interactions, and pinpointed the location where they interact with each other. Their novel method uses a technique known as genetic suppressor screening, which can serve as a blueprint for research on large cellular assemblies that resist traditional structural analysis.

We have two copies of each chromosome in every cell in our bodies, except in our reproductive cells. Sperm and egg cells contain a single copy of each chromosome with a unique mix of genes from our parents, an evolutionary trick to give our offspring [genetic variability](#). The sperm and egg are made during meiosis, the process by which cells with two chromosome copies reduce their chromosome numbers to one. For meiosis to work, the two [chromosomes](#) must align perfectly and exchange the correct amount of genetic information. Any deviation puts fertility at risk.

Enter the synaptonemal complex (SC), a zipper-like protein structure that lines up and anchors the two parental chromosomes together, end-to-end, to facilitate successful genetic exchanges. Failure to regulate this exchange is a leading cause of age-related infertility in humans and could compromise fertility across the tree of life.

Humans, fungi, plants, worms and anything that reproduces sexually uses the SC to make [reproductive cells](#), known as gametes. Despite its importance, we don't understand how proteins within the SC regulate chromosomal interactions because this multi-step process happens in internal organs and has been impossible to recreate in a lab.

"This is a way to lock in on systems in cells that are too 'loosey-goosey'

to use methods that rely on crystallization," said Ofer Rog, associate professor of biology at the U and senior author of the study. "A lot of the interactions in cells are loosely bonded together. The problem is that you can't look at it under an electron microscope because nothing is stable enough—everything is constantly moving. Our approach allows you to study even the interactions that are relatively weak or transient."

The birds and the bees, and the nematodes

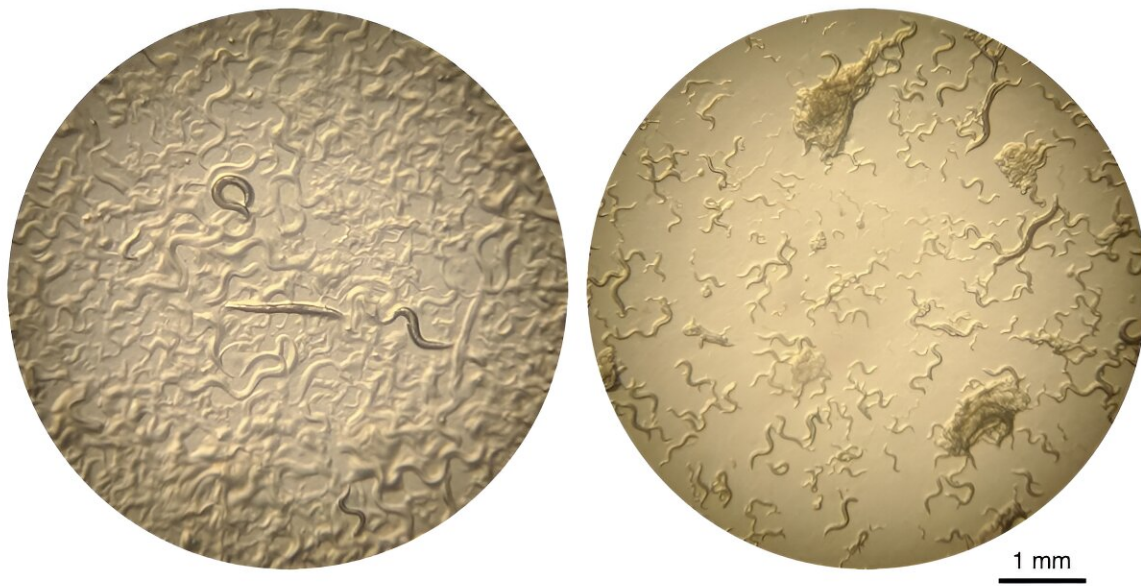
Let's dig into meiosis. Chromosomes are thread-like structures made of DNA that carry genetic information when cells divide and from generation to generation. Regular cells have a certain number of chromosomes; humans have 46 and *C. elegans* have 12. Chromosomes come in pairs called [homologous chromosomes](#) that carry the genes we inherited from each of our parents—one from our mom, one from our dad.

When meiosis begins, homologous chromosomes arrange themselves into elongated structures organized along a backbone called the axis. The axes of homologous pairs are aligned lengthwise to each other while at the same time, the synaptonemal complex (SC) forms between the parallel axes. The homologous pairs have matching genes arranged in the same order, with small variations within the genes—these are the variations that make each individual unique.

"You can think of it like a zipper," Rog explained. "The axes of the chromosomes are like the two sides of your shirt. The [synaptonemal complex](#) is kind of like the teeth of the zippers that lock onto each other and can pull and align the two sides of the shirt correctly."

Scientists previously knew that the SC of *C. elegans* formed between homologs, but the U biologists are the first to pinpoint the exact position where the SC interacts with itself to facilitate genetic exchanges.

"When you exchange information between the chromosomes, you want to make sure that at the end you still have two complete chromosomes," said Rog. "The way the cell does it is that the two chromosomes are perfectly aligned. So, when you exchange segments between them, you're not losing any information in the process."



Two agar plates with nematodes and bacteria. The left agar plate contains a few adult worms that did not have suppressor mutations and remained sterile. These nematodes died off before they could clean their plate, allowing the bacteria to flourish. The right agar plate had worms with the suppressor mutation that allowed them to reproduce. The plate contains lots of nematodes and very little bacteria as the progeny ate them all. Credit: Lisa Kursel

How to analyze loosey-goosey structures

The researchers bred 50,000 nematodes that had temperature-sensitive defects in the SC. At high temperatures, the worms were unable to form the SC protein zipper needed to join the chromosomes together. Without the zipper, the gene exchanges during meiosis either didn't happen at all or didn't occur at the right number. Lisa Kursel, postdoctoral researcher and lead author of the study, ran the experiments.

"We grew the worms at the permissive cooler temperature, then exposed them to a chemical that caused millions of [mutations](#) along their chromosomes and watched to see if any of the mutated worms could reproduce at the warmer temperature," Kursel said. The chemically induced mutations that corrected the nematode's infertility are known as suppressor mutations. "Then we'd know if the suppressor mutations restored their fertility."

To identify the animals with mutations that made them fertile again, the researchers put the nematodes on agar plates filled with yummy bacteria. The agar plates that had fertile nematodes were soon empty as their progeny ate the food. The sterile worms on agar plates died off before they could clean their plates, allowing the bacteria to flourish.

Once the team had fertile nematodes, they could test if the mutation "fixed" the protein zipper. They then screened every single base pair on the DNA—100 million base pairs—and identified which mutations restored the worms' ability to reproduce. They found that all the helpful mutations occurred in short segments of three proteins, SYP-1, SYP-3, SYP-4. Moreover, the mutations carried distinct signatures of interaction. For example, while the original mutations changed the electric charge from positive to negative, the helpful mutations flipped the charge back.

"This was a strong indication that SYP-1, SYP-3 and SYP-4 interact with each other like magnets, with positive and negative regions attracted to each other," said Rog. Such "sticky" interactions could also help tether the chromosomes together.

Jesus Aguayo Martinez, a senior biology major and co-author of the study, looked at the behavior of the suppressor mutation in nematodes without the original SC-disrupting mutation.

"We thought that since the original mutation alone produced a fertility defect, then the nematodes with the suppressor mutation alone would also have a fertility defect. That wasn't the case," said Aguayo Martinez. "Surprisingly, normal worms and worms with only the suppressor mutations produced similar numbers of progeny."

Next steps

Uncovering the SC's role in meiosis may help to better understand fertility in humans. The SC has a similar role across all eukaryotes, from nematodes to fungi to plants to humans. Previous [research](#) by the Rog Lab at the University of Utah showed that the structure itself looks the same and acts similarly to bring in parental chromosomes to facilitate exchanges.

However, the actual sequences of the protein components are different between organisms. Such a pattern is unusual: Most cellular structures that carry essential, basic functions like cell division, genome duplication or metabolism are highly conserved, and could in fact be swapped between different organisms.

"A question that we think a lot about is 'What is special about the SC? Why can it do the same thing and look the same way, but consist of different building blocks?'" Rog explained.

Kursel, Aguayo Martinez, Rog and other members of the lab are doing more analysis on the evolution of the SC across species, and of other cellular structures that defy the common wisdom of evolution.

More information: Lisa E. Kursel et al, A suppressor screen in *C. elegans* identifies a multiprotein interaction that stabilizes the synaptonemal complex, *Proceedings of the National Academy of Sciences* (2023). [DOI: 10.1073/pnas.2314335120](https://doi.org/10.1073/pnas.2314335120)

Provided by University of Utah

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