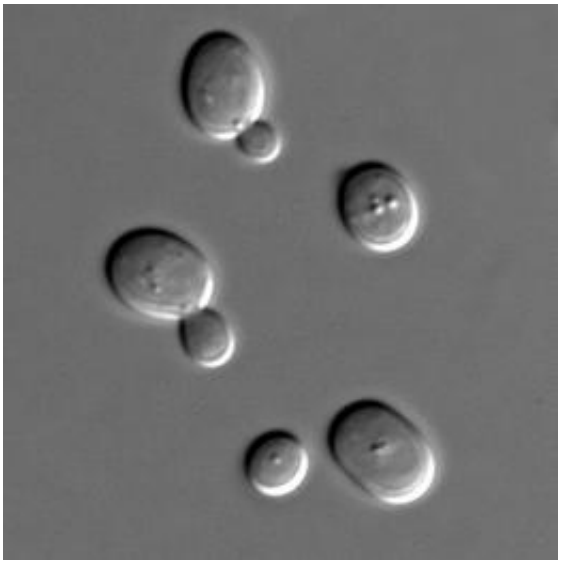
How yeast cells detect genetic infections

October 11 2018



Sacharomyces cerevisiae cells in DIC microscopy. Credit: Wikipedia.

ETH researchers studying yeast cells have discovered a new mechanism for detecting foreign genetic material from pathogens or environmental contamination, and rendering it harmless.

Over the course of their long history, bacteria have developed an effective immune system to detect and fend off intruding genetic material from viruses or competing bacteria. One element of this "innate" immune defence in single-cell organisms is the CRISPR-Cas system, which stores genetic material from intruders to recognise pathogens and fight them off in the event of a subsequent infection.

In contrast, it was not known whether eukaryotes ("higher" life forms) have comparable mechanisms acting as an effective autonomous immune defence system at the cellular level. Researchers assumed that simple eukaryotic cells could feature such mechanisms, but they didn't know which ones; until now, this has not been the subject of closer study.

Unusual defence mechanism

Now a team of researchers led by Yves Barral, Professor for Biochemistry at ETH Zurich, have found what they were looking for in yeast cells. These unicellular fungi, they discovered, feature a hitherto unknown defence mechanism located at a surprising spot within the cell: the chromosomes' centromere. The scientists have published their findings in the latest issue of the journal *Cell*.

The centromere is where the two halves of a chromosome, called chromatids, connect. It is also where a protein complex called the kinetochore assembles. During cell division, what are known as spindle fibres attach to the kinetochore in order to separate the sister chromatids, pull them apart, leave one chromatid in the mother cell and propel the other into the daughter cell. This ensures that genetic material is distributed evenly between the mother and daughter cells.

Foreign DNA does not condense

Barral and his colleagues have now demonstrated that the centromere plays a key role in chromosome condensation. It determines when and how a chromosome condenses, especially in its immediate vicinity. The centromere also sends out molecular signals to optimise chromosome compaction at its far ends.

In contrast, foreign genetic material—such as the virus-like DNA or DNA circles that enter a cell from time to time, or chromosomes without a centromere—cannot condense. As a result, no kinetochore can assemble and hence there is no attachment site for spindle fibres.

During cell division, non-condensed genetic material is recognised and actively retained in one of the two future daughter cells, which the researchers call the mother cell. In this way, foreign DNA is confined within the mother cell, while the daughter cell contains only characteristic DNA, namely half of all the chromatids as is to be expected.

Getting rid of DNA in and with the mother cell

This asymmetric division sees the mother cell collect DNA that is worthless for the organism, which causes it to age and die more quickly. This is how the yeast cells ensure that potentially harmful genetic material does not linger in the population. The daughter cells can divide again and again to build up a population that contains only reliable DNA.

In recent years, research has made the surprising discovery that centromeres vary greatly from species to species. "One would expect such a central and important structure to have hardly changed over the course of evolution and therefore to be quite similar across species," Barral says.

The ETH research team has now offered a possible explanation for this: "This rapid rate of evolution in centromeres might be driven by the arms race between host and pathogen," he explains. Pathogens would very quickly learn how to circumvent the control that the centromere exercises over chromosome condensation. This could increase pressure on the host organism to constantly change the centromere in order to prevent the passing on of foreign genetic material.

"Our discovery that the centromere is a part of the cell's autonomous defence against foreign DNA might explain why this part of the chromosome differs so greatly between species," Barral says.

Does the centromere promote the emergence of new species?

These findings might also have a bearing on how new species emerge. If, for instance, a population is divided by a geographical barrier, each of the two halves of the population might be exposed to different pathogens. As a result, the centromere would evolve differently in the two groups.

Should individuals from these two groups then meet at a later point in time, it could be that procreation is prevented by the fact that the centromeres are no longer compatible. "This is merely speculation, but we can well imagine that the two population groups no longer recognise each other as an identical species. So this mechanism might play an important role in speciation," Barral suspects.

Searching for viruses in yeast

He and his working group are currently studying fission yeast, a distant relative of baker's yeast. Fission yeast chromosomes are similar to those of animals. The researchers want to find out whether they, too, have a defence mechanism at the cellular level. Barral is also looking for viruses that attack fungi. "There's nothing to be found on this in the literature," he says, "but since yeasts are fungi and feature the immune mechanism we have now described, I'm assuming that viruses also attack fungi and infiltrate them with their DNA." He says it is only a matter of time until they find such viruses.

Barral and his colleagues worked on this study for four years. The idea that yeasts have a defence mechanism first came to them ten years ago, while they were researching the aging process in these microorganisms. "There is apparently a link between aging and defence against pathogens," Barral says. Their DNA is disposed of like superfluous proteins in the aging mother cell. "This new work suggests that the various parts of the puzzle we've worked on in recent years really do fit together."

More information: Kruitwagen T, Chymkowitch P, Denoth-Lippuner A, Enserink J, Barral Y. Centromeres License the Mitotic Condensation of Yeast Chromosome Arms. *Cell* (2018), Vol. 175; Issue 3. DOI: 10.1016/j.cell.2018.09.012

Provided by ETH Zurich