Press Release

EMBL

Fishing games gone wrong

Trial-and-error behind important cause of female infertility

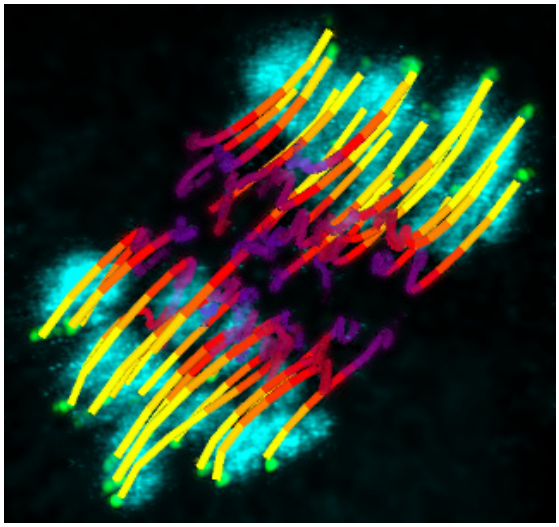
Heidelberg, 19 August 2011 – When an egg cell is being formed, the cellular machinery which separates chromosomes is extremely imprecise at fishing them out of the cell's interior, scientists at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, have discovered. The unexpected degree of trial-and-error involved in this process could explain why errors in the number of chromosomes in the egg cell are the leading cause of miscarriages and severe congenital diseases such as trisomies like Down's syndrome, as well as an important cause of female infertility. The findings are published online today in *Cell*.

Our cells have two copies of each chromosome, one inherited from our mother and the other from our father. An oocyte, the cell that matures into an egg cell, has to discard half of its chromosomes, keeping only the maternal or paternal copy of each. To do so, fibres called microtubules act like fishing lines, attaching themselves to chromosomes and reeling them in to opposite sides of the cell. However, the EMBL scientists discovered that these microtubules are much worse fishermen than expected, often incorrectly hooking onto a chromosome and having to let it go again.

"We saw that they have to go through several tries before getting the connection right," says Jan Ellenberg, who led the work at EMBL: "overall, 90% of all chromosomes get connected in the wrong way, and therefore the pathway that corrects these errors is heavily used."

The difficulty in the oocyte is that two fishing lines cast from opposite sides of the cell have to attach themselves to the maternal and paternal copies of the same chromosome. Each of those chromosome copies has a protein structure called a kinetochore, which acts like the magnet in a toy fish, providing the spot for the microtubule 'fishing lines' to attach themselves. The EMBL scientists were the first to track the movement of all kinetochores throughout the whole 8 hours of the first round of cell division in mouse egg cells, which are very similar to human ones.

"We were able to get very high resolution images for extended periods of time," explains Tomoya Kitajima, who carried out the work, "because our lab developed a microscope that automatically searches for chromosomes, zooms in, and scans only the area they are in, doing very little damage to the cell".



The coloured lines chart the movement (purple to yellow) of kinetochores (green dots) as microtubules hook onto them to separate the chromosomes (cyan).

Children playing magnetic fishing games often accuse others of cheating, using their fishing rod to move a fish into a position that makes it easier to catch. Ellenberg and Kitajima's time-lapse videos show that fishing microtubules also 'cheat' in this way. At earlier stages of cell division, before they start attaching themselves to kinetochores, microtubules interact with the arms of the chromosomes, nudging them into position in a 'belt' around the centre of the spindle.

But not even this chromosome belt, which had never been observed before, is enough to ensure that microtubules fish out the chromosomes correctly. The EMBL scientists' results show that kinetochore attachment is much more error-prone in this type of cell division, called meiosis, than in mitosis, the simpler form of cell division through which other cells in our body split in two. This is probably because the egg cell precursor is an inordinately large cell, and because in meiosis microtubules emanate from around 80 different places in the cell, rather than stemming only from two poles as they do in mitosis.

"Our findings provide a very plausible explanation for the high rate of errors during egg formation. They form the basis to focus our future work on age-related female infertility, as it seems very likely that a component of the pathway that corrects these errors will be involved" Ellenberg concludes. ●

Source Article

Kitajima, T.S., Ohsugi, M. & Ellenberg, J. Complete kinetochore tracking reveals error-prone homologous chromosome biorientation in mammalian oocytes. *Cell*, 19 August 2011.

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About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 20 member states (Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom) and associate member state Australia. Research at EMBL is conducted by approximately 85 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology; to train scientists, students and visitors at all levels; to offer vital services to scientists in the member states; to develop new instruments and methods in the life sciences and to actively engage in technology transfer activities. Around 190 students are enrolled in EMBL's International PhD programme. Additionally, the Laboratory offers a platform for dialogue with the general public through various science communication activities such as lecture series, visitor programmes and the dissemination of scientific achievements.