News from the secret world of the egg cell

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Scientists at the IMBA (Institute of Molecular Biotechnology) of the Austrian Academy of Sciences have discovered that the division of mammalian egg cells depends on cohesin proteins that embrace chromosomes before birth and are not renewed thereafter. The cohesin complex is remarkably long-lived but eventually lost irreversibly from chromosomes. The inability of egg cells to renew the ties that hold chromosomes together might contribute to maternal age-related chromosome missegregation and aneuploidy, leading to the production of trisomic fetuses. These insights provide a possible explanation for the molecular causes of the maternal age effect.

Maternal age is the single most important risk factor leading to the production of fetuses with trisomy, such as three copies of chromosome 21 or Down's Syndrome. Three copies of one chromosome can result from a failure to accurately segregate chromosomes in the egg cell, erroneously retaining two maternal copies and acquiring a paternal copy from sperm following fertilization. The causes for the increase in trisomic pregnancies in older mothers have remained elusive.

One key hypothesis focuses on a ring-like protein complex called cohesin. It embraces the replicated chromosomes, which is referred to as "cohesion" and holds them together until cell division. The precocious loss of cohesin prior to cell division can result in chromosome missegregation and aneuploidy.

"A few years ago, scientists observed that cohesin is lost from the chromosomes in ageing egg cells. It is assumed that the causes of genetic

disorders, such as Down's Syndrome, lie in cohesin loss and weakened cohesion", says Sabrina Burkhardt, doctoral candidate in the research group of Kikue Tachibana-Konwalski at the IMBA and first author of a study published in the journal *Current Biology* today. Burkhardt explains the background of the work: "Like every cell, also the egg cell undergoes an ageing process in a woman's body. Women are born already with a fixed number of egg cells, all captured in an arrested stage of the meiosis. When a woman enters puberty, the egg cells begin to ovulate one after the other. During the arrest, cohesin levels decrease and cohesion is thought to weaken over time."

"We are studying the mechanisms of how chromosomes are held together by the cohesin complex from birth until ovulation in egg cells", explains Kikue Tachibana-Konwalski. The study is based on her postdoctoral work carried out at the University of Oxford. There, she investigated whether cohesion is renewed in oocytes during the 2-3 weeks prior to ovulation. The researchers found no detectable turnover during this period, providing the first evidence that egg cell cohesin is long-lived, at least on the order of weeks. The finding was truly remarkable, as most proteins in body cells are exchanged within a few hours.

In the recent study Sabrina Burkhardt and colleagues provide further insights into the mysterious world of the egg cell. "The assay I developed as a postdoc can be taken as a proof-of-principle experiment that allowed us to address the key question, namely whether cohesion is renewed at all in adult oocytes or whether it is built exclusively before birth", says Kikue Tachibana-Konwalski. The research team carried out experiments to distinguish between two hypotheses: Either cohesin turns over and new cohesion is generated in adult oocytes, or cohesin builds cohesion in fetal oocytes and is maintained without turnover after birth.

Using a combination of mouse genetics, time-lapse microscopy and TEV

technology based on a plant virus, the team discovered that cohesin builds cohesion in fetal oocytes and is maintained for at least four months in adult mice.

"Our results support the hypothesis that cohesin is holding the chromosomes together for a very long time. We are therefore excited about the possibility that cohesin might be the most long-lived protein complex in a metabolically active cell studied to-date", says Tachibana-Konwalski. "The cohesin complex embraces replicated chromosomes for months without renewal in mouse eggs. If extended to the human, these results imply that cohesin might bind chromosomes in women's egg cells for decades without renewal. The loss of cohesin from chromosomes with age is therefore likely irreversible." The next step will be to investigate the molecular causes for the loss of cohesin from chromosomes in ageing oocytes.

The relevance of this study is represented in the statistics: the number of women who give birth to a child after the age of 35 continues to rise. In Austria, the average age of first-time mothers was 24 in 1985; by 2013, it had risen to 29. Today there is a clear trend towards late motherhood and the associated increased risk of trisomic pregnancies.

More information: Chromosome Cohesion Established by Rec8-Cohesin in Fetal Oocytes Is Maintained without Detectable Turnover in Oocytes Arrested for Months in Mice DOI: dx.doi.org/10.1016/j.cub.2015.12.073

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