Scientists reveal cause for frequent inherited diseases

Age-dependent deterioration of the chromosome glue protein cohesin responsible for chromosome missegregation in oocytes

Researchers at the Institute for Physiological Chemistry of the Medical Faculty Carl Gustav Carus of the TU Dresden determined a key trigger for many embryonal chromosome defects. Before girls are born, their ovaries contain all oocytes, which will later develop into mature eggs. Within the oocytes, cohesin proteins keep chromosomes together in pairs for proper distribution into the mature eggs. These cohesins are produced already during embryogenesis of the developing girl. After birth, the oocytes remain quiescent until ovulation, which may happen decades later. During this long period of arrest, cohesin may deteriorate within the oocytes. Using mouse models, it became clear now, that loss of cohesins or their weakening indeed happens and causes aberrant chromosome distribution and thus inherited diseases such as trisomies, wich increase dramatically in humans with increasing age of the mothers. These results are published in the current issue of the internationally renowned journal "Current Biology.

With advancing maternal age, the frequency of inherited syndromes like trisomie 21 (Down Syndrome) increases dramatically: at the mothers' age of 40, more than one-third of all embryos show chromosome defects. These are trisomies and other aneuploidies, i.e. the wrong distribution of chromosomes during maturation of the oocytes. As nowadays women have their babies at more advanced age, the age-dependent increase in aneuploidies becomes an even more serious problem.

In human oocytes, chromosomes are kept in pairs together over a period of up to 50 years to undergo the final cell divisions upon oocyte activation during ovulation. The cohesin proteins "glue" chromosomes together and ensure thereby their correct segregation. A few years ago, the group of Prof. Dr. Rolf Jessberger showed that loss of a cohesin protein in mice causes chromosomal abnormalities and age-dependent increase in aneuploidies, very similar to that increase in humans. These results were published in 2004 and 2005 in the top-notch journals Nature Cell Biology and Nature Genetics.

A remaining key question was, whether continuous production of cohesin during the long period of oocyte arrest is required to keep the chromosomes together. In the current publication (Current Biology, 2010), the Jessberger group shows that only the cohesin is required, that is produced in the embryonal oocyte, before birth of the female mouse. Together with two additional publications in the same issue of the journal, one with participation of Prof. Jessberger, it

became clear that this initially produced cohesin becomes weaker with increasing age of the mice. For example, a cohesin protection protein disappears in older mice as was shown in cooperation with the research group of Prof. Mary Herbert at the Univ. of Newcastle, UK.

In summary, these publications reveal the long sought-for cause of age-dependent aneuploidies: the slow deterioration of cohesin leading to chromosomes to fall apart and to be wrongly distributed in maturing oocytes.