Early embryos can correct genetic abnormalities during development

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Professor William G. Kearns told the annual meeting of the European Society of Human Reproduction and Embryology that a three-day-old embryo (called a cleavage stage embryo) with an incorrect number of chromosomes (known as "aneuploidy") was capable of undergoing "a dynamic process of genetic normalisation" so that by day five, when it had developed to the blastocyst stage, it had become euploid, with the correct number of chromosomes.

The findings have significant implications not just for preimplantation genetic screening (PGS) during fertility treatment, but also for future, cell-based, stem cell treatments for conditions ranging from haematological disorders to neurological damage.

Prof Kearns, senior author of the study, who is an associate professor in the department of gynecology and obstetrics, at the Johns Hopkins Medical Institutions in Baltimore (USA) and the director of the Shady Grove Center for Preimplantation Genetics, LabCorp in Rockville (USA) explained: "There has been mounting evidence that PGS using cells from the outer layer of the blastocyst, the trophectoderm, at day five results in higher pregnancy rates than evaluating a blastomere at the cleavage stage on day three. There are also good data to suggest that there are a substantial number of genetically different cells existing in many cleavage stage embryos – a condition known as 'mosaicism'. Additionally, tests performed on pregnant women to determine if genetic abnormalities exist in the developing foetus show that aneuploid cells of placental origin are relatively common in foetal blood. These

observations led to our hypothesis that mechanisms may exist in the developing embryo that could cause mosaic embryos to marginalise abnormal aneuploid cells and preserve normal cells, and thus 'genetically correct' to a genetically normal embryo.

"Preimplantation genetic screening (PGS) refers to the removal of a cell from a developing embryo and evaluating this cell for all chromosome abnormalities. If the results of this screening show that the embryo is normal, then either it undergoes uterine transfer or is frozen for future use. In cases where PGS evaluation yields a biopsied cell that is chromosomally abnormal, standard practice is to discard the corresponding embryo."

From April 2010 onwards, Prof Kearns and Dr Paul Brezina, an obstetrics and gynaecology doctor and an infertility fellow at the Johns Hopkins Medical Institutions, and their colleagues recruited 12 women who required PGS by microarrays of all 23 pairs of chromosomes and, after undergoing in vitro fertilisation (IVF), there were 126 embryos that they were able to biopsy at day three. (Microarrays are a method of rapidly scanning large amounts of DNA).

In a statement before the conference, Dr Brezina explained: "In the IVF laboratory, all embryos that undergo PGS on day three are cultured to the blastocyst stage of development at day five, at which time the PGS results are available. In this study we evaluated all embryos that developed to the blastocyst stage with documented chromosomal abnormalities not compatible with a live birth from a cell taken from the embryo on day three. At the blastocyst stage, the embryo has developed into two parts; the inner cell mass (ICM), which has cells that will form the foetus, and the trophectoderm (TE), which has cells that will form the placenta. Instead of taking a biopsy from either of these cell types, we dissected the entire embryo and captured as much of the ICM and TE cells as possible. These ICM and TE cells were isolated into two separate

groups. Using microarrays we tested these groups for chromosomal abnormalities. We had the potential to detect mosaicism (the presence of several different cell lines within a single embryo) at a rate of approximately five percent, but we did not see mosaicism in any of the ICM or TE samples evaluated.

"This underscores the importance of our methodology, as mosaicism could not be ruled out with a biopsy of a single cell from each cell type at the blastocyst stage. Incredibly, a high proportion (64%) of embryos showed complete genetic correction in both the ICM and TE cell populations. In other embryos, either the ICM or TE, but not both, showed genetic correction. In still others, both the ICM and TE remained abnormal. Interestingly, in all samples, the type of abnormalities that were documented at day three were different to the abnormalities observed at the later, blastocyst stage."

Out of the 126 embryos, 62 (49.2%) were euploid and 64 (50.8%) were aneuploid at day three; of these 43 (69.4%) of the euploid embryos developed to the blastocyst stage, while only 25 (39.1%) of the aneuploid embryos did. Of the 25 aneuploid day-five embryos, 68% possessed a euploid ICM and 76% possessed a euploid TE, with 64% having both a euploid ICM and TE. Therefore, 16 of the 25 had correction in both the TE and ICM cells.

Prof Kearns said: "These results suggest that there is a dynamic process of genetic normalisation that occurs in the developing human embryo. It is likely that there is considerable cellular mosaicism in many cleavage stage embryos and that there are mechanisms in place that cause marginalisation of abnormal cells while allowing growth of normal cells. The exact mechanisms that allow this, however, at this time are still unknown. The existence of such a process has significant implications for furthering numerous scientific fields."

For fertility treatment, the discovery that a large percentage of embryos deemed to be abnormal at day three could become normal at day five suggests that during PGS, day five is the better time to predict the ultimate chromosomal status of the embryo, rather than day three. In addition, if a day-three embryo was found to be aneuploid, then these findings suggest that it would be worth waiting and testing the trophectoderm at day five before making the final decision about whether to implant the embryo or discard it.

The findings also have implications outside the field of reproductive medicine. Prof Kearns said: "The applications to other fields are numerous. Based on these results, it is likely that some level of aneuploid mosaicism is extremely common, and possibly a normal part of embryogenesis. A current challenge within stem cell biology is the high rate of acquired aneuploidy that is observed with cell colonies in extended culture. Dissecting the mechanism underlying the normalisation observed in this study in a stem cell system would be highly useful and may be applied to cell-based therapeutic approaches using stem cells. An understanding of such in vitro reparative mechanisms could potentially add to current strategies for gene repair and stem cell transplant therapy. Stem cell therapies have been suggested for a wide swath of medical diseases, ranging from haematological disorders to neurological damage."

Determining the mechanisms that govern the process of genetic normalisation in the developing human embryo is the next stage of research for Dr Brezina and Prof Kearns and their colleagues.

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