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Title:

CHARACTERIZING MEIOTIC AND MITOTIC ERRORS IN THE INNER CELL MASS AND TROPHECTODERM OF POOR QUALITY PREIMPLANTATION EMBRYOS

Authors:

Christine Briton-Jones, PhD, HCLD[1,2], Lucky Sekhon, MD[1,2], Ethan Ellis, BS[2], Joseph A. Lee, BA[1], Eric Schadt, PhD[2], Robert P. Sebra, PhD[3] and Alan B Copperman, MD[1,2,3]

Affiliations:

1. Reproductive Medicine Associates of New York, 635 Madison Ave 10th Floor New York, New York, United States, 10022

2. Icahn School of Medicine at Mount Sinai, Klingenstein Pavilion 1176 Fifth Avenue 9th Floor New York, New York, United States, 10029

3. Sema4, a Mount Sinai Venture, Stamford, CT

Objective:

Human blastocysts that undergo trophectoderm (TE) cell biopsy for pre-implantation genetic testing for aneuploidy (PGT-A) are capable of achieving normal morphological development despite having gains or losses in chromosome copy number. Occasionally in clinical embryo culture we see nonviable blastocysts with morphology of few or no inner cell mass (ICM) cells and good quality TE cells. Also the reverse is seen, a blastocyst with good quality ICM but few elongated TEs. These embryos are not suitable for biopsy or clinical use. However, these morphologically abnormal blastocysts provide a novel glimpse at the very earliest stages of human cell differentiation. The aim of the study was to compare rates of meiotic and mitotic errors resulting in loss, gain or mosaicism of chromosomes in cells from poor quality blastocysts.

Design:

Experimental study on human embryos donated for research.

Materials and Methods:

The study included embryos donated by patients from fresh cycles between January and June of 2016. Embryos reaching the blastocyst stage of development but ineligible for TE biopsy (<4CC, Modified Gardners), were biopsied and 5-6 cells were evaluated for aneuploidy by NGS. Ploidy status including mosaicism was identified based on bioinformatical interpretation of chromosome copy number falling within disomic (between 1.8 - 2.2), aneuploid thresholds (less than 1.2 and more than 2.8) and mosaic (between 1.2-1.8 and 2.2-2.8). The mean number of monosomy, trisomy and mosaic calls was determined and compared for each study group. Kruskal Wallis was used to determine statistically significant differences, where $p<0.05$.

Results:

Of the 15 blastocysts, with isolated poorly graded ICM (n=9) or trophectoderm (n=6), that underwent NGS. Of the embryos with poor ICM and good TE: 7 were euploid; 2 were mosaic and 1 was aneuploid. Of the embryos with good ICM and poor TE grade: 2 were euploid and 4 had complex aneuploidy. Blastocysts with good ICM grade but poor TE grade had significantly higher incidence of mosaicism and aneuploidy ($p<0.0001$).

Conclusion:

As embryo development reaches the blastocyst stage, the incidence of aneuploidy is significantly reduced. The reason for this reduction in incidence of aneuploid calls between cleavage stage and blastocyst stage embryos is believed to be that the burden of aneuploidy leads to embryonic arrest. This study showed that embryos with many copy number variants are still capable of growing a morphologically normal ICM. In contrast the blastocysts with morphologically normal trophectoderm had fewer aneuploid calls, despite having none or few ICM cells present. Our study's findings suggest that the consequence of aneuploidy is less severe in ICM cells compared to TE cells, as at this specific time point in embryonic development, ICM cells are more closely related to the cleavage stage blastomeres than the differentiated trophectoderm. Our current work is focused on identifying differential gene expression in these embryos, which allow a unique opportunity to study the roles of ICM and TE cells largely independent of each other.