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Short Communication

Trophectoderm RNA: A Potentially Predictive Tool for Assessing Human Blastocyst Competency?

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Since its origins in late 1970s assisted reproductive technology (ART) has been accompanied by incremental improvements in *in vitro fertilization* (IVF) success rates [1]. Rates, however, of successful IVF treatment have remained relatively static in the past years [2]. This could in part be explained by the methods used to determine the 'best' embryos for transfer, which have remained relatively unchanged in recent years. For example, improvements in implantation and pregnancy rates arising through compliance with morphological criteria applied to pre-transfer embryos have already plateaued [3]. Other criteria that could aid the determination of the 'best' embryo for transfer, include metabolomics and morphokinetics (time-lapse) [4-6], with real-time live imaging being used for ART [4,7,8]. However, the required algorithms of these technologies are complex and still under development. The concurrent use of both time-lapse imaging and aneuploidy detection screening has led to increased efficiency in the selection of competent blastocysts for transfer [9]. However, reports are equivocal with some demonstrating the efficacy of aneuploid screening on blastocyst implantation in older mothers [10] and others failing to show such an effect [11,12]. Morphological criteria and preimplantation genetic testing for aneuploidy (PGT-A) are the main established technologies currently used in ART, with morphology assessment potentially improving the selection of the most competent embryos when combined with more recent-omics approaches [6].

Although the most frequent cause of early embryo implantation failure is chromosomal in nature [13,14], decreased delivery rates in women over 35 years can occur even when the embryo is euploid [15], with women over 40 years of age experiencing significantly lower implantation and pregnancy rates [12]. The reduced implantation potential of euploid blastocysts as a consequence of female ageing is not well understood [16] but could involve failures in DNA repair mechanisms, for example. The embryonic genome, therefore, alongside histone modifications, DNA methylation and post-transcriptional modifications may affect the embryonic transcriptome and could have an impact on implantation and delivery rates [12,15,17-24].

Trophectoderm gene expression can now be explored with quite high accuracy, opening up new molecular biologically based investigations into trophectoderm cells that have the potential to usefully predict implantation competence among embryos developed to the blastocyst stage. Two studies on animal models have attempted to correlate trophectoderm RNA expression with blastocyst implantation potential. The first study analysed pooled bovine embryos [25] and reported differentially expressed transcripts that were related to implantation, signal transduction and growth factors. A second study was conducted on 70 single mouse blastocyst transfers with successful implantation reported for 40 (28 of which developed to term). B3gnt5 (glycolipid metabolism) and Eomes (transcriptome activator during embryo development) transcripts along with Wnt/β-catenin signaling members, showed significant down-regulation in the non-implanted blastocysts [26]. Studies to assess trophectoderm gene expression profiles and implantation competency in the

human, have used either microarray or RNA sequencing technologies [18,24,27]. Jones., *et al*. examined single or pooled blastocyst gene expression, using a microarray approach, revealing only wider ontological descriptions of competent and incompetent differential gene expression analysis, while Kirkegaard., *et al*. using an RNA sequencing approach on single blastocyst biopsies with full term delivery being the primary outcome, reported several differentially expressed transcripts, including WEE2-AS1 and EFNB1. Ntostis., *et al*. employed RNA sequencing alongside a consideration of the ploidy status of transferred embryos to eliminate aneuploidy as a confounding factor in data analysis. Metabolism- and steroidogenesis-related transcripts, including HSD17B1 and CYP11A1, were found significantly down-regulated in the non-implanted blastocysts.

The embryonic transcriptome must indicate an important role during implantation and pregnancy and perturbations thereof could help explain some idiopathic infertility. Through the development of an algorithm based on molecular biomarkers, RNA could be used as a predictive tool for more confidently assessing likely implantation competency within a cohort of blastocysts per cycle, that leads to implantation success. The transcriptome could also reveal gene ontologies indicating roles for embryonic factors in maternal fetal communication and/or 'normal' embryo development. The molecular signatures of these ontologies could be also tested in parallel with the above biomarkers, perhaps predicting embryo implantation potential with even higher confidence.

An indirect way to measure molecular biomarkers that predict successful implantation, would be to apply a differential gene expression analysis on trophectoderm derived from the embryos of younger and advanced maternal age women. Advanced maternal age is an unavoidable natural process that compromises female fertility, due mainly to oocyte deficiencies including chromosomal aneuploidies [28,29] that increase the probability of miscarriage [30,31]. Younger women, however, (< 35 years old) normally have higher rates of implantation, pregnancy and delivery [32,33], with a few studies showing reduced implantation and delivery rates of aged euploid blastocysts [12,15]. Gene expression anomalies are linked to recurrent miscarriage [30,31,34] and changes in embryonic gene expression altering the transcriptome of human blastocysts are likely to be critical factors in advancing maternal age [35-38].

Euploid blastocyst transfer leads to implantation rates of between 50 and 80% [12,15,39], while idiopathic female infertility accounts for 14% - 26% of implantation failures [40]. If the causality was better understood, the proportion of women experiencing successful implantation could be improved. Based on the above evidence and arguments, trophectoderm RNA could be a tool with high potential to predict human blastocyst implantation competency and potentially helping couples achieve a viable and successful pregnancy.

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