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TRANSCRIPTOMIC EVIDENCE OF SEXUAL DIMORPHISM IN EARLY HUMAN BLASTOCYSTS

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OBJECTIVE:

Although it is widely accepted that there are differences in early growth, development, and implantation between male and female embryos, few studies have yet to fully circumvent study design obstacles when evaluating the transcriptome of the human embryo (1). The objective of this study was to compare and contrast the transcriptome patterns of sibling male and female euploid blastocysts.

DESIGN:

Prospective cohort study on human embryos.

MATERIALS AND METHODS:

After receiving IRB consent, eleven sibling embryos were donated for research by an infertile couple. The embryos underwent embryo biopsy for preimplantation genetic testing for aneuploidy (PGT-A) by next generation sequencing (NGS) and vitrification. The blastocysts were thawed and underwent RNA Sequencing. Read counts per gene were summed across embryo cohorts and normalized using the median of ratios. Differential gene expression between embryo cohorts was calculated using DESeq2, in order to estimate variance-mean dependence and evaluate differential gene expression using a negative binomial distribution. A likelihood ratio test was used to account for heterogeneity due to batch. The adjusted threshold for significance was $p<0.05$.

RESULTS:

Of the 11 euploid blastocysts, differential gene expression was compared between 5 male and 6 female embryos. 21,417 genes were identified, 357 were up-regulated and 538 were down-regulated in male blastocysts. Of the 10 genes showing the lowest P value for significantly different expression levels between male and female blastocysts, 8 were located on the Y chromosome and 2 on the X. 7 of the 8 Y chromosome genes have paralog genes located on the X chromosome. The majority of the genes showing significantly different expression levels were located on the sex chromosomes, however there were a number located on autosomes. One example is the gene GCK located on chromosome 7. It showed a 7.97 Fold (log2) lower expression in male blastocysts, where $P<0.0003$. 1658 different molecular pathways were active in the two cohorts, while the ranking of the most active pathways was different between males and females, none showed statistical differences. Putative roles for these genes have been described in other tissues and include protein synthesis, cell proliferation, metabolism and cell differentiation.

CONCLUSIONS:

At a period in development when there are no obvious morphological or functional differences between males and females, 895 of the 21,417 (4%) of the active genes identified were expressed at significantly different levels in males compared to females. Many of the functions ascribed to the genes showing different levels of expression are related to processes in cellular proliferation and differentiation in adult stem cells and cancers. Most of the genes located on the sex chromosomes have homologous genes on the opposite sex chromosome, thereby correcting for a gene imbalance. Understanding transcriptomic events associated with mammalian sexual dimorphism may provide insights into the etiology of embryo morphokinetics, implantation, and maybe even later behavior patterning.

REFERENCES:

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