

Expression of members of the multi-protein SAGA chromatin modifying complex in blastocoel fluid-conditioned media from IVF-generated human embryos is associated with positive implantation status

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Introduction

Infertility affects approximately 1 in 8 couples trying to conceive. This leads many couples to seek fertility treatments to start their families, with in vitro fertilization (IVF) being a leading technology. Infertility causes many co-morbidities including anxiety, depression, and isolation. Additionally, the stigma around miscarriages and infertility is immense, and only furthers the co-morbidities experienced by persons trying to conceive. By improving infertility treatment outcomes, one could subsequently decrease the chronic mental and societal challenges that come with infertility.

Goal: This project seeks to improve the implantation rates of IVF through looking at the expression of various genes found in blastocoel fluid conditioned media. The information gained could potentially provide additional guidance in selecting the most viable embryo for implantation.

Methods

RNASeq data from blastocoel fluid-conditioned media from day-5 preimplantation euploid embryos had been previously obtained and used to identify a subset of genes for further expression analysis. The genes of interest (KAT2A, MYSM-1, USP22, USP28, USP34, and UBR5) were assessed for expression in a new set of media samples using RT-qPCR. Selection of media samples for this analysis was based on patient age, embryo ploidy status and implantation outcomes. The GAPDH housekeeping gene was also measured in all media samples in order to calculate negative ΔC_t (cycle threshold) values for each gene analyzed. The gene expression data was analyzed in regards to implantation outcomes of the embryo via Welch's t-test.

Results

- Statistically significant increased expression of MYSM-1, USP22, UPS28, and USP34 in media from embryos associated with a positive implantation status versus a negative implantation status ($p < 0.05$) was detected (Figure 1).
- UBR5 also showed significant expression in positive implantation status embryos ($p < 0.1$).
- KAT2A expression was also higher in positive implantation embryos

KAT2A EXPRESSION BY IMPLANTATION STATUS

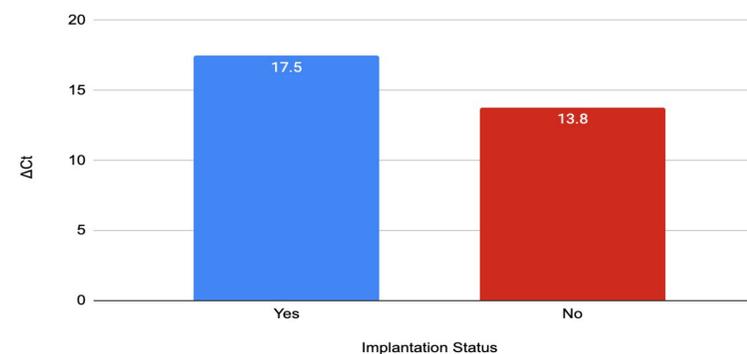


Figure 1: The average expression of KAT2A as measured by ΔC_t

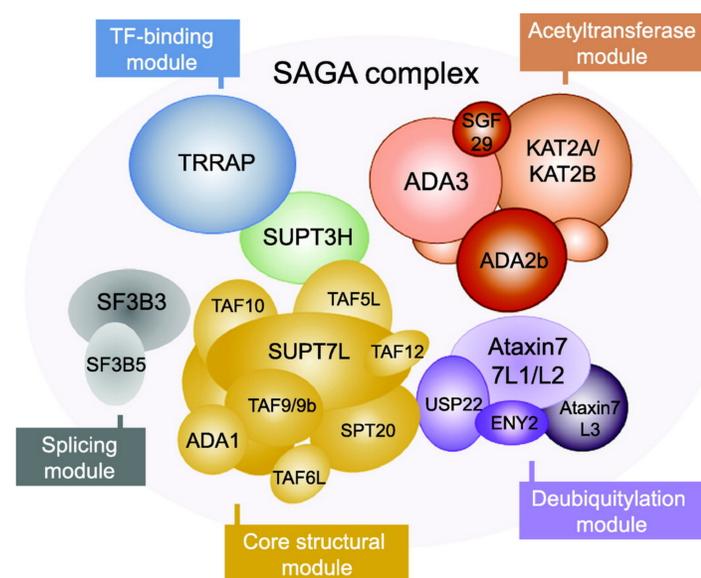


Figure 2: SAGA Complex

Bondy-Chorney, E., Denoncourt, A., Sai, Y., & Downey, M. (2019). Nonhistone targets of KAT2A and KAT2B implicated in cancer biology. *Biochemistry and Cell Biology*, 97(1), 30–45. <https://doi.org/10.1139/bcb-2017-0297>

Discussion

MYSM-1, USP22, UPS28, and USP34 are deubiquitinating enzymes (DUBs). DUBs often play a role in protein degradation, DNA repair, chromatin remodeling, cell cycle regulation among other functions. KAT2A is a histone acetyltransferase as part of the multi-protein complex SAGA.

The SAGA complex is a multi-protein chromatin modification complex that mediates acetylation and deubiquitylation of histones (Figure 2). KAT2A is a histone acetyltransferase and acts as a ubiquitination catalyst along with USP22. The silencing of USP22 has been shown to lead to the apoptosis of embryonic fibroblasts. USP22 also has been found to have an active role in regulation of cancer pathologies, as it can be overexpressed leading to tumorigenesis due to an unregulated rate of the cell cycle. Both decreased levels of USP22 and KAT2A have shown embryonic lethality in mouse models. It is possible that decreased expression of KAT2A could nullify the DUB subunit of SAGA. Therefore, assessing the levels of both USP22 and KAT2A (or other members of SAGA), could potentially serve as a molecular indicator of embryo viability. Measuring SAGA member expression levels in blastocoel fluid-conditioned media may serve to improve the selection criteria for IVF-embryo selection.

Conclusion

Our findings suggest that analysis of KAT2A and USP22 levels in more blastocoel fluid-conditioned media samples may allow us to determine the range of gene expression associated with successful implantation outcomes. This could further improve the criteria for IVF embryo selection.

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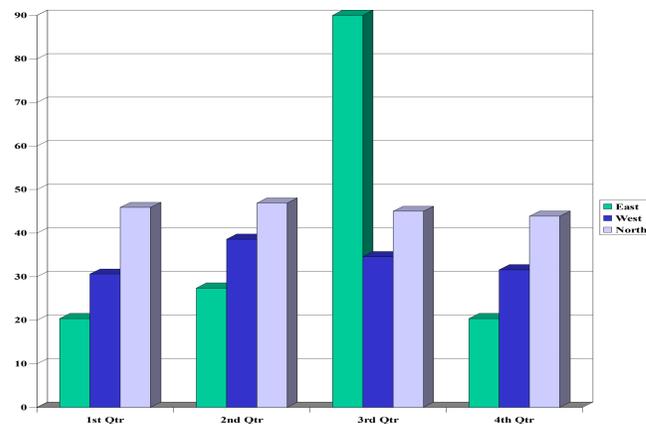
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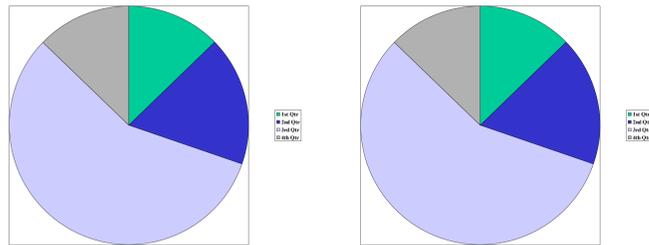
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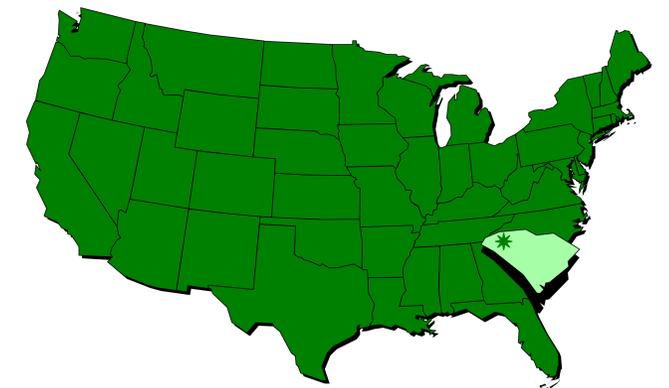
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