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Abstract Title
Profiling Circular RNAs in Amniotic Fluid and Fetal Lungs from Congenital Diaphragmatic Hernia Cases: Insights into Potential Prognostic and Diagnostic Applications

Background
Circular RNAs (circRNAs) are stable, closed-loop RNAs formed by backsplicing. Because of their stability, circRNAs in amniotic fluid (AF) may serve as useful diagnostic and prognostic markers for Congenital Diaphragmatic Hernia (CDH).

Objective
The objective of this study was to examine AF circRNA expression in CDH pregnancies to explore any potential relationships with survival outcomes and CDH pathways.

Methods
AF samples were collected from CDH pregnancies treated with fetoscopic endoluminal tracheal occlusion (FETO) (n=8; 4 survivors, 4 non-survivors). CircRNAs were measured using the Arraystar Human circRNA Array V2. Differential expression was analyzed with limma in R and compared with our previously published CDH lung data. The parental genes of the significant circRNAs were assessed with gene ontology and KEGG pathway analyses, and selected circRNAs were validated by sequencing their backsplice junctions.

Results
We detected 10,760 circRNAs in AF, 514 of which were differentially expressed (FDR < 0.05). These included 24 that overlapped with differentially expressed circRNAs in late-gestation lung and 4 associated with CDH-related genes. Two of the identified circRNAs (hsa_circRNA_103415 and hsa_circRNA_103361) was experimentally validated in both CDH and control AF samples. Parental genes of the significant circRNAs were found to be enriched within functional groups involved in molecular modifications, metabolism, and nucleoside binding, as well as within nuclear and cytoskeletal cellular components. They were also linked to signaling pathways involved in focal adhesion, FcγR-mediated phagocytosis, HPV infection, and endometrial cancer.

Conclusion
This study suggests a link between AF circRNA expression and CDH outcome through distinct expression profiles between CDH survivors and CDH non-survivors, and connections with genes and pathways important for fetal development. These findings highlight the diagnostic and prognostic potential of circRNAs, as well as provide direction for the study of their functional roles in CDH pathogenesis.

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