



Cystic Fibrosis Research News

Title:

Discovery of Dysregulated Circular RNAs in Whole Blood Transcriptomes from Cystic Fibrosis Patients – Implication of a Role for Cellular Senescence in Cystic Fibrosis

Lay Title:

A Search Begins for the Role of CircRNAs in Cystic Fibrosis

Authors:

Edward A. Salinas, Victor Macauley, Kim M. Keeling, Yvonne J.K. Edwards

Affiliations:

Heersink School of Medicine, University of Alabama Birmingham, Birmingham, AL 35294, USA

What was your research question?

- Are circular RNAs (circRNAs) dysregulated in the blood of people with cystic fibrosis (CF) compared to the blood of people without CF?
- Can we identify and characterize dysregulated circRNAs in blood due to reduced CFTR gene function?
- Can CF-dysregulated circRNAs be a springboard for further research or for developing novel biomarkers and therapeutics for people with CF?

Why is this important?

A circRNA is a gene that loops back on itself to form a closed ring-like structure. CircRNAs have distinct expression signatures and play critical roles in a variety of diseases. However, the role(s) of circRNA in relation to CF are unknown. This is the first publication to identify and characterize circRNAs dysregulated due to loss of CFTR gene function, thereby, allowing a better understanding of the roles circRNAs may play in altering pathways in the body that influence CF disease. This information can potentially be beneficial in the development of novel biomarkers or therapeutics for people with CF.

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cfresearchnews@gmail.com



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What did you do?

We had a study group comprised of 20 people with CF, who have two inherited copies of the same disease-causing CFTR mutation (p.Phe508del), and 20 people without CF matched for age and gender. At the time of sampling, the people with CF had clinically stable disease. We used blood gene expression sequencing data (also known as transcriptomes) which informs us of the levels of actively expressed genes. We compared the levels of circRNAs in people with CF to people without CF to identify dysregulated circRNAs due to the faulty CFTR gene. We then predicted the effects that dysregulated circRNAs may have on the development of CF symptoms. To help the analyses be reproducible, we developed and published a computational biology pipeline to analyze the gene expression sequencing data.

What did you find?

We discovered dysregulated circRNAs in the blood of people with CF compared to non-CF individuals. We found trends suggesting dysregulated circRNAs in CF samples are enriched for cellular senescence functions compared to the non-CF samples. Cellular senescence has both beneficial and detrimental effects on health. On one hand, cellular senescence is thought to suppress bacterial infection, facilitate tissue repair, and prevent the proliferation of potential cancer cells. Whilst, on the other hand, cellular senescence promotes a pro-inflammatory environment that causes tissue damage, leading to chronic CF-related inflammation.

What does this mean and reasons for caution?

One thing to note is our research is based on using blood samples. CF is a medical condition which affects multiple organs such as the lungs, intestines, pancreas, and other organs. It is possible that blood circRNA changes could be caused indirectly from the loss of function of the CFTR gene as blood circulates throughout all the major organs. Thus, any genomic or protein signals associated with the loss of function of the CFTR gene might be obscured as CF is most symptomatic in mucus membranes such as those in the lungs.

What's next?

We plan to validate data from our analyses in biological systems. We will determine whether dysregulated circRNAs identified in CF blood samples are also dysregulated in human CF cell lines and in CF animal models. We will then examine how changes in circRNAs affect cellular pathways that influence CF symptoms.

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Original manuscript citation in PubMed

<https://pubmed.ncbi.nlm.nih.gov/37142522/>

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