



# Cystic Fibrosis Research News

**Title:** Global assessment of the integrated stress response in CF patient-derived airway and intestinal tissues

**Authors:**

Giovana B. Bampi<sup>1</sup>, Robert Rauscher<sup>1,a</sup>, Sebastian Kirchner<sup>2,a,b</sup>, Kathryn E. Oliver<sup>3,4</sup>, Marcel J.C. Bijvelds<sup>5</sup>, Leonardo A. Santos<sup>1</sup>, Johannes Wagner<sup>1</sup>, Raymond A. Frizzell<sup>6</sup>, Hugo R. de Jonge<sup>5</sup>, Eric J. Sorscher<sup>3,4</sup>, Zoya Ignatova\*<sup>1</sup>

**Affiliations:**

<sup>1</sup>Biochemistry and Molecular Biology, Department of Chemistry, University of Hamburg, Hamburg, Germany

<sup>2</sup>University of Potsdam, Potsdam, Germany

<sup>3</sup>Emory University School of Medicine, Atlanta, Georgia, USA

<sup>4</sup>Children's Healthcare of Atlanta, Atlanta, Georgia, USA

<sup>5</sup>Gastroenterology and Hepatology Erasmus MC University Medical Center, Rotterdam, The Netherlands

<sup>6</sup>Pediatrics and Cell Biology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

<sup>a</sup>Contributed equally

<sup>b</sup>Current address: Wellcome Centre for Integrative Parasitology, Institute of Infection, Immunity and Inflammation, University of Glasgow, UK

\*Corresponding author. E-mail: [zoya.ignatova@uni-hamburg.de](mailto:zoya.ignatova@uni-hamburg.de)

**What was your research question?**

Our goal was to determine whether immune-related responses are activated in CF patients' cells when the most common mutation in the cystic fibrosis transmembrane conductance regulator (CFTR), F508del, is present alone and/or in combination with bacterial infection.

**Why is this important?**

The F508del mutation results in dysfunction of the chloride channel (CFTR), which leads to accumulation of thick mucus that establishes a favorable environment for bacteria to attach and multiply. Human cells have evolved various defense response (stress response programs) to deal with these burdens. Because CF patients suffer from prolonged exposure to recurring infections and inflammation, irreversible damage can occur in airway and intestinal tissues (among others). Thus, an overarching question we addressed was whether these immune-

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related stress responses result from only F508del-induced CFTR dysfunction, infections, or both.

## What did you do?

We utilized a technique called next generation RNA-sequencing (RNA-seq) to precisely identify stress programs activated in CF cells in the lab. RNA-seq is a cutting-edge technology that shows comprehensive pictures of gene expression patterns. Because previous studies have established specific genes associated with distinct stress responses, this allowed us to determine which pathways were uniquely affected by the presence of F508del-CFTR versus bacteria. Two types of CF patient-derived materials were compared: (1) airway cells extracted from lung transplants – i.e. tissues exposed to long-term lung infection and inflammation, and (2) intestinal organoids (“mini-guts”), which were collected from infection-free rectal biopsies.

## What did you find?

We made the following observations:

- 1) CF airway cells display clear activation of stress responses associated with CFTR dysfunction and tissue damage. Considering that these cells experienced prolonged exposure to pulmonary infection and inflammation, these results were not unexpected. However, the degree to which distinct pathways were stimulated was variable among different patient samples.
- 2) CF intestinal organoids also showed signs of stress activation triggered by mutant CFTR and inflammation, even though these samples originated from a comparatively infection-free environment.
- 3) The effects of cellular stress that occur in people can be detected in the laboratory.

## What does it mean and reason for caution?

These results suggest that F508del-CFTR alone can contribute to tissue dysfunction, regardless of whether bacterial pathogens are present. In addition, RNA-seq can be a useful tool for capturing unique variations in CF disease progression among age groups, genders, CFTR mutation status, etc. Moreover, this technique has the potential to inform personalized approaches to clinical intervention through matching an individual’s stress response profile to specific therapies. Caution should be taken, however, due to the small numbers of CF patients with CF that were assessed. Larger groups will be needed to determine whether additional data support these conclusions.



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## **What's next?**

We intend to replicate this study with broader representation of patients with different CFTR mutations (e.g. individuals with F508del or other rare defects), ethnic/racial backgrounds, genders, and disease severity. These parameters can then be utilized to stratify stress response signatures and draw conclusions relevant to subsets of groups of people with CF.

## **Original manuscript citation in PubMed**

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[cfresearchnews@gmail.com](mailto:cfresearchnews@gmail.com)