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# Cystic Fibrosis Research News

## Title:

Inactivation of *CFTR* by CRISPR/Cas9 alters transcriptional regulation of inflammatory pathways and other networks

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## What was your research question?

We were trying to work out which properties of CF cells are affected by things that happen because a cell is missing CFTR from those that are affected because a cell is exposed to a CF environment in organs that are quite inflamed, such as the lungs or intestines.

## Why is this important?

Appropriate treatment depends on us knowing what is causing the clinical disease effects in people with CF. For example, if heightened inflammation is in-built in CF cells, then correcting CFTR may be the only way to reduce inflammation. If, on the other hand, it is the result of being in a lung or intestine that is filled with bacteria, then we may have other options.

## What did you do?

We used cells derived from the colon of a person who does not have CF, so these cells had never been in to a CF environment, and used a genome editing technique called CRISPR/Cas9 to create new cells in which we mutated the CFTR within them so as to make them like CF cells. We compared these new cells to ones in which CFTR remained intact and functional. We studied them without any outside stimulation and also with some causes of inflammation, including bacterial products and molecules made by the body to initiate inflammation. These

cells were examined using a technique called RNA seq that allows us to compare all of the genes, several thousand, which are active in those cells.

### What did you find?

We found that without stimulation, there was no difference in the inflammation gene profile between cells with and without CFTR. However, when they were exposed to an inflammatory molecule, tumour necrosis factor-$\alpha$, the cells without CFTR had a more active *CXCL8* gene. The *CXCL8* gene codes for a potent inflammatory molecule, IL8. When all the genes of these cells were examined, results suggested that there are genes that act differently simply by removing CFTR, others that require provocation to show CFTR-dependent differences and many genes that are unchanged by CFTR status.

### What does this mean and reasons for caution?

The results suggest that the absence of CFTR can affect many other genes in a cell and any of these could contribute to aspects of the disease. However, there may be other treatments, besides repairing or correcting CFTR, to cope with issues like inflammation. Caution is needed, as the cells that we used were derived from a tumour and thus we must first see how non-cancer cells behave under similar conditions.

### What's next?

Our next steps are to determine how native cells and tissues react. If they behave similarly, we will examine them for ways to suppress or reverse the effects of an absence of CFTR.

### Original manuscript citation in PubMed

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