European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:

Defective BACH1/HO-1 regulatory circuits in cystic fibrosis bronchial epithelial cells

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What was your research question?

Toxic substances called free oxygen radicals can cause tissue damage and are normally counteracted by various mechanisms in order to prevent tissue damage. Within the body's cells, proteins such as Hemeoxygenase-1 (HO-1) reduce these toxic free oxygen radicals. Therefore, we studied the role of HO-1 in modifying imbalances in the toxic free radicals in CF.

Why is this important?

We previously found reduced HO-1 protein levels in CF cells, but the reasons for this were not clear. In the current study, we found an increase in the levels of a protein that inhibits HO-1 called BACH1 in CF cells. In the absence of oxidative stress, the production of the HO-1 protein is restricted by BACH1. Oxidative stress leads to destruction of the BACH1 protein and an increase in HO-1 protein levels. Oxidative stress also causes an increase in a non-coding RNA called micro RNA 155 (miR-155), which negatively regulates production of the BACH1 protein, a mechanism that indirectly favors increased HO-1 protein production.

What did you do?

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We hypothesized that by blocking BACH1 production, we could rescue HO-1 production in CF cells. Alternatively, we sought to increase miR-155 to stop the production of BACH1. We also analyzed BACH1 protein stability by inhibiting global protein synthesis using anisomycin, a compound that blocks the production of new proteins. Further, to study the role of defective CFTR in increased BACH1 protein levels we overexpressed defective CFTR in healthy cells.

What did you find?

Our study showed that decreasing the levels of BACH1 increased HO-1 protein levels only in healthy control cells, while it failed to do so in CF cells. *Vice versa*, increasing the levels of BACH1 only restricted HO-1 levels in healthy controls but not in CF cells, suggesting that this regulatory pathway is defective in CF. We also observed in CF cells that high levels of miR-155 did not restrict the production of BACH1. While these experiments showed two defective regulatory pathways in CF cells, a reason explaining the observed increase in BACH1 levels at the molecular level was revealed in further experiments. These studies showed an increased BACH1 protein stability in CF cells and intriguingly this altered protein stability was also reproduced by simple overexpression of the defective CFTR in healthy cells.

What does this mean and reasons for caution?

These findings have two important implications: (1) CF cells have defective regulatory circuits, which might be due to errors, and changes in the "hardware" and probably in the "software" used in cells. (2) The increased protein stability of BACH1 in CF cells supports the concept of defective protein homeostasis (proteostasis) in CF cells.

What's next?

This concept implies that CF cells show dysfunctional components of regulatory networks balancing the protein composition (proteome), potentially enabling new therapeutic options in the future.

Original manuscript citation in PubMed

https://pubmed.ncbi.nlm.nih.gov/32534959/