

Cystic Fibrosis Research News

Title:

Human epididymis protein 4 (HE4) levels inversely correlate with lung function improvement (delta FEV₁) in cystic fibrosis patients receiving ivacaftor treatment

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What was your research question?

Human epididymis protein 4 (HE4) is a member of whey acidic protein four-disulfide core (WFDC) family. Normally this protein is produced by bronchial epithelial cells at a small quantity and acts as an antiprotease in the frame of epithelial host defenses of the respiratory tract. In previous research, we found a correlation between increased HE4 levels

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and CF severity. In this study, we sought to confirm our previous finding of inverse correlation of HE4 levels with lung function parameter (FEV_1) in CF patients, and to assess the changes in HE4 levels with the administration of *ivacaftor*.

Why is this important?

Currently, there are no unambiguous blood-based biomarkers for monitoring the efficacy of CFTR modulating therapy. Hence, there is an unmet clinical need to establish a sensitive and easily reproducible biomarker, which is simply performed and accessible, ideally plasma or serum based.

What did you do?

We have retrospectively analyzed HE4 levels in plasma samples obtained from three independent clinical cohorts, which were monitored for FEV_1 , sweat chloride and BMI under *ivacaftor* treatment. In contrast to lung function evaluation and special sweat chloride measurement, this test needs only a simple blood sampling with a general laboratory immunoassay analysis.

What did you find?

In response to *ivacaftor* therapy and independently of baseline concentrations, HE4 levels were significantly lower already after 1 month of therapy, and remained that way through the end of respective study periods (up to 6 months). Plasma HE4 negatively correlates with lung function improvement, and markedly alters in both mild and severe CF lung disease reflecting to *ivacaftor*.

What does this mean and reasons for caution?

Plasma HE4 as a potential biomarker may be of value for routine clinical and laboratory follow-up of CFTR modulating therapy in CF individuals. However, further studies are required to validate HE4 as a surrogate endpoint biomarker for treatment efficacy in CF not only for *ivacaftor*, but also for other CFTR potentiators and correctors. The mechanism of how CFTR impacts on HE4 levels in pulmonary epithelial cells need to be investigated as well as the direct effect of CFTR modulators.

What's next?

We are going to investigate whether the beneficial effect of other CFTR specific therapy, such as *lumacaftor*, may be also monitored via measuring the plasma level of HE4 in CF.



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