Title:
SPX-101 is stable in and retains function after exposure to cystic fibrosis sputum

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What was your research question?
We wanted to understand the stability of SPLUNC1 and SPX-101 in CF sputum.

Why is this important?
SPLUNC1 (short, palate, lung, and nasal clone 1) is a protein and a natural regulator of the epithelial sodium channel (ENaC) in the airways. ENaC is important because it regulates how much sodium (salt) is absorbed from the liquid on the surface of the airways; a proper balance of fluid in the lungs allows for any particles e.g. dust particles to be easily moved up out of the lungs. If too much sodium is absorbed, the fluid is thicker than it should be and there are problems clearing the lungs of sticky secretions leaving the lungs open to infection. In CF, a loss of SPLUNC1 function leads to hyperactivation of ENaC and increased sodium absorption. Therefore, inhibiting ENaC activity could potentially hydrate CF airways with the advantage of not being affected by the CFTR mutation. In this study, we wanted to find out whether proteases (enzymes which break down proteins) which are found in the sputum of people with CF stop SPLUNC1 from working properly and whether this contributes to high levels of ENaC activity. SPX-101 is a peptide mimetic of SPLUNC1 which is being developed to replace the lost function of SPLUNC1 in the airways.

What did you do?
We measured the amount of SPLUNC1 in sputum of 18 healthy people (no diagnosis of lung disease) and 26 people with a diagnosis of CF. We also incubated SPLUNC1 and SPX-101 in sputum from people with CF and then looked at their stability. Furthermore, we measured the ability of SPX-101 to regulate ENaC, in the presence of and after exposure to sputum proteases, by investigating internalisation of ENaC, airway surface liquid height and impact on survival of an animal model of CF.
What did you find?
We found that the amount of SPLUNC1 was reduced or absent in sputum from people with CF as compared to sputum from healthy participants. In fact, only two of 25 CF sputum samples had appreciable level of SPLUNC1. We further found that SPLUNC1 is rapidly corrupted by CF sputum in as little as 15 minutes. Several proteases enriched in CF sputum, including neutrophil elastase, cathepsin G, trypsin, and matriptase are all well able to stop SPLUNC1 from working properly. In contrast, SPX-101 was very stable in CF sputum with less than 10% corruption of the protein over the course of the experiment. Importantly, SPX-101 that had been incubated with CF sputum retained its ability to regulate ENaC.

What does this mean and reasons for caution?
SPX-101 is different from SPLUNC1 as the protein is stable in CF sputum and is, therefore, suitable for investigation as a treatment. By restoring the lost SPLUNC1 regulatory function to the lungs of people with CF, it may be possible to increase airway hydration, promote the clearance of debris from the airways and recover lost lung function. Beyond CF, SPX-101’s potential to increase airway hydration could prove to be beneficial in other diseases associated with mucociliary clearance defects and high levels of sputum proteases, such as non-CF bronchiectasis, COPD, and severe asthma.

What’s next?
SPX-101 is currently in Phase II clinical development for the treatment of CF.

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