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Cystic Fibrosis Research News

Title:
TLR5 signalling is hyper-responsive in porcine cystic fibrosis airways epithelium

Lay Title:
Do cystic fibrosis patients have an abnormal innate immune response to pathogens?

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What was your research question?
We asked whether the cells from the lung epithelium, the cells that line the inner surface of the airways, respond normally to pathogen (germs that cause disease). These cells are important in the early immune response called the innate immune system.

Why is this important?
The innate immunity system is the first arm of the body against a pathogen. Under normal circumstances, it triggers an inflammatory response that calls blood immune cells to get rid of the pathogen. This response then resolves once the pathogen is gone. However, CF patients show a large and recurrent inflammation in the lungs. We do not know the reason behind this problem, but it could be related to a defect in how lung cells recognise pathogens. Understanding the mechanisms leading to this excessive inflammation is important to develop novel therapies that prevent lung damage in people with CF.

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What did you do?

We performed our study in a pig model of CF, as this animal model is one of the most relevant to study CF disease in the lungs.

We collected cells from the lung epithelium of CF and healthy pigs at birth to study whether innate immune receptors have a normal function. We studied two receptors called TLR4 and TLR5, which are responsible to detect specific parts of the bacteria. We treated the lung cells from CF and healthy pigs with different molecules that specifically activate either TLR4 or TLR5. Then we evaluated whether the lung cells from CF pigs produced a higher number of inflammatory molecules to call blood immune cells.

What did you find?

The most important finding is that CF lung epithelial cells have an exaggerated TLR5 response. We observed that when we activate TLR5 in CF lung cells, there is an increased expression of genes that are responsible for the attraction of a particular blood immune cell, the neutrophil. Excessive neutrophils in the lungs are a hallmark of CF and they associate with worse disease outcomes. We also found alterations in some genes that are responsible to stop the inflammatory process. We did not find alterations in the TLR4, suggesting that the defect is specific to TLR5.

What does this mean and reasons for caution?

Our results show that the excessive inflammation that is characteristic of CF lungs could be caused by an excessive TLR5 response. This means that new drugs could be produced targeting this receptor to reduce inflammation. However, the data must be taken with caution. We studied only lung epithelial cells on their own in the laboratory and the isolated response of single receptors. Cells use many receptors to understand their environment and sense pathogens. Therefore, we are missing the complex interactions that occur in the lungs in real life.

What's next?

Further studies are needed to determine whether the observed TLR5 alteration in the lung epithelial cells also occurs *in vivo* in the lungs during a bacterial infection.

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