Researchers further illuminate pathway for treatment of cystic fibrosis

13 January 2016, by Jamie Williams

It is well established that people with cystic fibrosis (CF) have two faulty copies of the CFTR gene, but debate continues on the question of whether certain symptoms of the airway disease are caused by the mutation or if the genetic defect precedes, but does not directly lead to some of the worst symptoms patients face.

Carla Ribeiro, PhD, associate professor of medicine, and her colleagues at the UNC Marsico Lung Institute/Cystic Fibrosis Research Center fall into the latter camp. A paper from this group, published in the *American Journal of Critical Care Medicine*, suggests new targets for therapy and further bolsters the case for inflammation as an acquired response unrelated to the CFTR genetic mutation.

"By studying alveolar macrophages, which provide our airways with a crucial defense against pathogens, we are able to more fully understand the larger picture of CF symptoms and continue progress towards targeted treatment for patients," Ribeiro said.

Alveolar macrophages are the body's first line of defense, and in healthy people these cells work to flush inhaled pathogens out of the airways. But, because in CF patients airway dehydration leads to mucus obstruction and persistent bacterial infection, the macrophages' heightened response to such pathogens causes a "snowball effect," resulting in hyper-inflammation, over-production of mucus, and chronic infection.

Ribeiro and colleagues Bob Lubamba, PhD, research specialist Lisa Jones, Wanda O'Neal, PhD, and Richard Boucher, MD, showed that CF alveolar macrophages are key contributors to the inflammation of CF airways, and that the overabundance of a protein called XBP-1 in these cells mediates their inflammatory effect. Ribeiro said she has focused much of her work in the past few years on trying to understand the role of this protein in CF airways disease.

To conduct the research, they harvested alveolar macrophages from human CF lungs and healthy lungs and showed that CF alveolar macrophages exhibit an increased basal inflammatory response when compared to healthy macrophages. When stimulated with factors present in CF airways, both sets of macrophages responded – but the inflammatory response of CF macrophages was larger. And, in both sets of cells, the inflammatory response was coupled to activation of XBP-1, but the activation was greater in CF macrophages.

They then over-expressed the activated XBP-1 protein in normal macrophages and reproduced the hyper-inflammatory phenotype found in CF macrophages. In contrast, decreasing the XBP-1 levels blunted the inflammatory response. These findings led the researchers to surmise that the XBP-1 pathway was implicated in the hyper-inflammatory response of CF alveolar macrophages. Because inhibition of CFTR function did not elicit a CF-like response in the macrophages harvested from healthy lungs, the research indicated that this particular immune response was not directly due to the CFTR mutation but was, instead, acquired.

"Our work has shown that the alveolar macrophage plays a key role in the pathogenesis of CF airway inflammation," Ribeiro said. "And that activation of XBP-1 mediates the secretion of inflammatory factors by alveolar macrophages. This is all helping to make a stronger case for why this pathway may be an important target for therapy."

Ribeiro added that this work could have implications in airway diseases beyond CF, including COPD and asthma.

In an editorial published along with the article, the potential therapeutic impact was forecast:

"Interventions aimed at XBP-1 or other molecules associated with sustaining the proinflammatory phenotype in the CF lung, in combination with antimicrobials and CFTR modulators, may provide improved resolution of infection and inflammation."

Provided by University of North Carolina at Chapel Hill School of Medicine