UNIVERSITY OF PORTSMOUTH

The role of CFTR in normal human lung microvascular endothelial cells

By

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Abstract:

Cystic fibrosis is the most common hereditary lethal disease in the Western world, resulting from defects in the expression or function of cystic fibrosis transmembrane conductance regulator (CFTR), a chloride ion channel that controls the movement of salt and water through epithelial cells in multiple organs including airway, intestine and genitourinary system, and has anti-inflammatory and antioxidant properties.

The hypothesis tested in this research is that CFTR expressed in normal human lung microvascular endothelial cells protects the cells from inflammatory changes and oxidative stress.

A low level of stable CFTR, which was down-regulated by CFTR activity was found. Pharmacological inhibition of CFTR in endothelial cells results in a rapid increase in production of reactive oxygen species and a decrease in the abundance of the transcriptional factor Nrf2, both of which are characteristic of oxidative stress. An increase in production of vascular endothelial growth factor was a consequence of this oxidative stress. Furthermore, CFTR inhibition in endothelial cells results in an increase in IL-8 production through activation of the activator protein-1 pathway, which is mediated through activation of the epidermal growth factor receptor. Also inhibition of CFTR in neutrophils increased the expression of neutrophil elastase activity on the cells surface in response to opsonized zymosan, indicating a mechanism for the observation that neutrophil surface elastase activity correlates with decline in lung function in patients with CF.

Exposing endothelial cells to shear stress significantly enhanced the production of nitric oxide and reduced endothelin-1 release from vascular endothelia cells, and the responses were not influenced by CFTR function. In addition, CFTR inhibition increased F-actin polymerisation and influenced the distribution of F-actin, preventing the alignment of cells with the direction of shear flow.

Treatment of endothelial cells with antioxidant decreases both oxidative and inflammatory changes after CFTR inhibition by reducing reactive oxygen species production and reduced IL-8 production. The data indicates that endothelial CFTR may be a target for oral systemic potentiators and correctors that are in development for CF.

Declaration

Title of Report**: The role of CFTR in normal human lung microvascular endothelial cells**

Whilst registered as a candidate for the above degree, I have not been registered for any other research award. The results and conclusions embodied in this thesis are the work of the named candidate and have not submitted for any other academic award.

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Dedication:

This Thesis is dedicated to the memory of my son Sarmed, my father Mohsin Khalaf, my mother Raffeeah Hussein, who always believed in me, and my ability to be a successful person. You are gone but your faith in me made this journey possible.