Proceedings Paper:
Holbrook, J, Scambler, T, Lara Reyna, S orcid.org/0000-0002-9986-5279 et al. (5 more authors) (2018) The effect of cysteamine and epigallocatechin gallate on the inflammatory phenotype in cystic fibrosis. In: Pediatric Pulmonology. 32nd Annual North American Cystic Fibrosis Conference, 18-20 Oct 2018, Denver, CO, USA. Wiley , p. 245.

https://doi.org/10.1002/ppul.24152

The effect of cysteamine and epigallocatechin gallate on the inflammatory phenotype in cystic fibrosis

Objectives: The self-degradative process, termed autophagy, is defective in cystic fibrosis (CF), as a result of abnormal function and production of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. In CF the accumulation of defective CFTR in the cytosol and a lack of expression of functional CFTR on the cell membrane, leads to perturbation of autophagy, resulting in amplified inflammation. In this study, the anti-inflammatory effect of pre-treating human bronchial epithelial cells (HBECs) and primary monocytes with the proteostasis regulator, cysteamine, and the flavonoid, epigallocatechin gallate (EGCG) was investigated.

Methods: HBEC lines Beas-2b (WT), IB3-1 (CF - ΔF508/W1282X), CUFI-1 (CF - ΔF508/ΔF508), CUFI-4 (CF - ΔF508/G551D) and CF patients' monocytes were studied. ELISAs were performed to measure IL-6, TNF and IL-10. Small molecule drugs, cysteamine (250μM) and EGCG (100μM), were used to treat both epithelial cell lines and patients' monocytes *in vitro.* LPS (10ng/ml) was used to stimulate both HBECs and monocytes. Western blots were used to demonstrate defective autophagy in the cell lines and in CF patient monocytes.

Results: Autophagy proteins were shown to be deficient in CF monocytes compared to HCs, and cysteamine was successfully shown to recover the proteins. The epithelial cell lines and CF patients' monocytes presented with a hyperinflammatory response to LPS, with raised levels of IL-6 and TNF. The levels of IL-6 and TNF were greatly reduced upon addition of cysteamine and EGCG. IL-10 levels were shown to be reduced in CF monocytes compared to HCs. Cysteamine and EGCG reduced the quantity of inflammatory cytokines secreted in HBECs and CF monocytes.

Conclusion: These data show that CF has an exaggerated inflammatory response and a deficient anti-inflammatory response to LPS stimulation in comparison to HC, showing an inherent inflammatory state in CF. The results show that the combination of cysteamine and EGCG is considerably more potent a treatment than when they are used separately.

Character Count: 1727

Keywords: autophagy, inflammation, cystic fibrosis, cytokines

Holbrook J[1,2,3], Scambler T[1], Lara-Reyna S[1,2], Wong C[1,2,3], Jarosz-Griffiths HH[1,2,3], Savic S[1,3,5], Peckham D[2,3,6†] and McDermott MF[1]

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, [2]Leeds Institute of Biomedical and Clinical Sciences, [3]Leeds Cystic Fibrosis Trust Strategic Research Centre,[4]Department of Biochemistry, University of Lausanne, Switzerland, [5]Department of Clinical Immunology and Allergy, St James's University Hospital, [6]Adult Cystic Fibrosis Unit, St James' University Hospital