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Sodium influx modulates innate immune inflammation and metabolism in cystic fibrosis.

Thomas Scambler[1], Chi Wong[1], Shelly Pathak[1], Samuel Lara Reyna[1, 2], Jonathan Holbrook[1 ,2], Heledd Jarosz-Griffiths[1], Fabio Martinon[3], Sinisa Savic[1, 4], Daniel Peckham[2, 5] and Michael F. McDermott[1].

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

Objective: This study aimed at understanding the relationship between increased sodium flux with metabolism and NLRP3 inflammasome signalling in CF.

Methods: Blood samples were taken from patients with stable CF, active CF, autoinflammatory patients, non-CF bronchiectasis (NCFB) and healthy controls (HC) for monocyte and serum studies. Human bronchial epithelial cell (HBEC) lines were also studied. ELISAs were performed to detect extracellular and intracellular proteins. Flow cytometry was used to detect M1-type and M2-type and ASC specks. Fluorescent probes for sodium and potassium were used to measure ion flux.

Results:
Serum levels of IL-1β, IL-18, IL-1Ra and ASC specks were elevated in CF samples compared to HC and patients with NCFB, with significantly less anti-inflammatory M2-type macrophages from patients with CF. Furthermore, we observed elevated sodium influx and decreased intracellular potassium upon ATP stimulation in CF cells, known activators of the NLRP3 inflammasome. To understand the impact that increased sodium and potassium flux has on glycolysis, we measured ATP, glucose, succinate and lactate, which we found to be all elevated in CF monocytes and HBECs. Finally, we stimulated monocytes and HBECs for NLRP3 inflammasome activation. We found that CF monocytes and HBECs were hyper-responsive to NLRP3 inflammasome activation and inhibiting ENAC with amiloride reduces this hyper-responsiveness.

Conclusions:
Collectively, our findings reveal novel intrinsic mechanisms behind the excessive degrees of inflammation, independent of infection, that are observed in CF. We demonstrate that CF monocytes and macrophages are skewed towards a proinflammatory phenotype and that increased Na+ influx, via ENaC, contributes to metabolic reprogramming and NLRP3 activation in cells with CF-associated mutations. Finally, we show that amiloride is capable of regulating these proinflammatory and metabolic perturbations of the innate immune response in vitro.

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