Transcriptomic analysis of CFTR-impaired endothelial cells reveals a pro-inflammatory phenotype


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CFTR-impaired endothelial cells have a pro-inflammatory phenotype that can attract and reinforce leukocyte extravasation. Endothelial cells possibly contribute to the excessive inflammatory phenotype observed in cystic fibrosis. https://bit.ly/2GRijq8


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ABSTRACT Cystic fibrosis (CF) is a life-threatening disorder characterised by decreased pulmonary mucociliary and pathogen clearance, and an exaggerated inflammatory response leading to progressive lung damage. CF is caused by bi-allelic pathogenic variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a chloride channel. CFTR is expressed in endothelial cells (ECs) and EC dysfunction has been reported in CF patients, but a role for this ion channel in ECs regarding CF disease progression is poorly described.

We used an unbiased RNA sequencing approach in complementary models of CFTR silencing and blockade (by the CFTR inhibitor CFTRinh-172) in human ECs to characterise the changes upon CFTR impairment. Key findings were further validated in vitro and in vivo in CFTR-knockout mice and ex vivo in CF patient-derived ECs.

Both models of CFTR impairment revealed that EC proliferation, migration and autophagy were downregulated. Remarkably though, defective CFTR function led to EC activation and a persisting pro-
inflammatory state of the endothelium with increased leukocyte adhesion. Further validation in CFTR-knockout mice revealed enhanced leukocyte extravasation in lung and liver parenchyma associated with increased levels of EC activation markers. In addition, CF patient-derived ECs displayed increased EC activation markers and leukocyte adhesion, which was partially rescued by the CFTR modulators VX-770 and VX-809.

Our integrated analysis thus suggests that ECs are no innocent bystanders in CF pathology, but rather may contribute to the exaggerated inflammatory phenotype, raising the question of whether normalisation of vascular inflammation might be a novel therapeutic strategy to ameliorate the disease severity of CF.