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Commentary

Mucosal humoral immunity in cystic fibrosis - a tangled web of failed proteostasis, infection and adaptive immunity

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The central role of chronic endobronchial infection with *Pseudomonas aeruginosa (Pa)* in the pathophysiology of cystic fibrosis (CF) has long focused on defects in compartmental host defense as well as pathogen adaptability [1,2]. As the secretory IgA system (sIgA) is a central component of mucosal immunity [3], careful examination of its integrity is warranted. However, studies of sIgA are surprisingly sparse in the otherwise voluminous literature on respiratory host defense in relation to underlying genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and resulting functional defects in CFTR protein. In their *EBioMedicine* paper, Collin et al. have endeavored to address this gap with a multifaceted approach evaluating the sIgA system in CF spanning cellular, murine model and clinical components, with emphasis on sIgA antibody response to *Pa* [4]. Three main groups of findings emerge, the first of which is confirmatory of prior work, but the second and third offer some surprising and provocative results that bring a new perspective and raise unanswered questions to pursue.

First, Collin et al. utilized explanted end-stage lung tissue as well as sputum and serum from clinically stable CF patients, classified by *Pa* infection status, and controls to demonstrate increased lymphoid aggregates, IgA plasmacytes, epithelial polymeric immunoglobulin receptor (pIgR; necessary for IgA transcytosis into the airway lumen) and IgA, in adults with CF. Serum and sputum IgA were increased, while sIgA and secretory component (SC) were also present in sputum [4]. This validates studies demonstrating an intact and activated systemic and mucosal adaptive humoral immunity in CF. In addition, homozygosity for the F508del CFTR mutation was associated with higher IgA and SC, while *Pa* infection was associated with higher levels of systemic and local *Pa*-specific IgA antibodies.

However, when the sIgA system was interrogated at the cellular and murine animal model levels, using primary human bronchial epithelial cell cultures (HBECs) and homozygous F508del mice in the absence of *Pa* infection, down-regulation of pIgR mRNA and protein, SC and sIgA, were found in CF-derived cultures and murine BAL. In HBEC cultures this down-regulation was mimicked with CFTR inhibitors. Downregulation was not observed in lung homogenates, a finding the investigators attribute to dilutional effects in the whole lung milieu [4].

How is CFTR dysfunction linked to down-regulation of the sIgA system? Collin et al. hypothesize a role for endoplasmic reticulum (ER) stress induced by biosynthetic misfolding of F508del CFTR, resulting in activation of the unfolded protein response (UPR). In support of this hypothesis Collin et al. examined the CF UPR closely. They found, first, both CF-derived HBECs and F508del mice had increased levels of spliced X-box binding protein 1 (XPB1s) [4], a target of UPR activation via inositol-requiring transmembrane kinase/endonuclease α, one of several known pathways of UPR activation [5]. Second, transmission electron microscopy showed enlarged ER cavities in CF-derived HBECs. Third, in Calu-3 epithelial cells, which stably express high levels of pIgR, UPR activation *in vitro* (as shown by increased XPB1s as well as phosphorylated stress-induced eukaryotic initiation factor 2α) demonstrated reduced pIgR protein, IgA transcytosis and SC release [4].

In reconciling F508del CFTR-induced ER stress, UPR activation and downregulation of the sIgA system to the clinical findings of an upregulated system, infection seems to play an important role. (While the focus in Collin et al. is on *Pa* infection, the few patients in their sample population not infected with *Pa* were infected with other known CF bacterial or fungal pathogens). Here, murine endobronchial infection using *Pa*-coated beads resulted in upregulation of pIgR in the airway epithelium in wild type mice, as well as increased pIgR, total IgA and sIgA in bronchial lavage fluid from wild type and F508del mice, implicating sIgA upregulation by infection that overrides UPR-mediated suppression.

The mechanism of this infection-related reversal was explored first by direct exposure of CF HBECs to *Pa* supernatants, which did not upregulate the system. However, an indirect effect was observed when IL-17, known to upregulate pIgR in the bowel, was tested. Murine *Pa* infection via the bead method did induce IL-17A mRNA, and CF HBECs or Calu-3 cells stimulated with IL-17A showed increases in pIgR, IgA transcytosis and SC release. CF lung explants also showed increased retinoic acid receptor-related orphan receptor gamma *t*+ Th17 cells [4], consonant with prior studies [6, 7]. IL-17 did not independently activate the UPR.

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The provocative findings of Collin et al. raise questions requiring further study. Consistency across the various experimental platforms was not uniformly obtained, inviting external validation. For example, raised levels of IL-17 were not found in the CF patients in contrast to prior studies including young children [7-9]. The role of the UPR in CF remains unclear, with some studies implicating a direct effect of F508del misfolding while others find key UPR inducers come indirectly from the inflammatory milieu that may be variably induced by the many pathogens capable of transiently or chronically infecting the CF airway [5], or even by sterile inflammation prior to infection. The role of impaired autophagy implicated in CF on sIgA remains unexplored. Finally, and perhaps most importantly, the functional activity of sIgA in CF needs to be better elucidated. Secretory IgA, owing to its multimeric structure, has high antigen avidity, aiding immune exclusion [10]. The work of Collin et al. should be praised for finding new paths and providing new opportunities to understand and combat CF lung disease in the era of CFTR small molecule modulators.

Declaration of Competing Interest

Author has no conflicting interests to declare.

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