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Autophagy and Cystic Fibrosis: When Recycling Goes Bad

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In today's environmentally conscious climate, recycling and reusing essential elements is of upmost importance to preserve our delicate ecosystem. This same mantra can be examined in terms of host-pathogen relationships in chronic respiratory disease. Cystic Fibrosis is a disease characterized for years in terms of defective mucociliary clearance of lung mucus and pathogens leading to a cycle of chronic respiratory infections obtained from the environment. Today, we know that innate immune defects also contribute to the heavy burden of respiratory infection in CF. However, when it comes to host-pathogen interactions in CF, autophagy-mediated recycling of essential proteins has gone awry. Autophagy is a conserved, physiologic process whereby host cells degrade cytoplasmic material via lysosomes. Autophagy functions can range from recycling of large organelles and molecules to clearance of intracellular pathogens [1]. Triggers of autophagy are varied, including starvation, stress, infection, and immune signaling among others. Over the last few years, several groups have demonstrated defects in autophagy in relation to CF, including Cystic Fibrosis Transmembrane Regulator (CFTR) associated sequestration of essential autophagy molecules [2,3] and inflammatory signaling related to defective autophagy [4]. Without proper autophagy recycling of proteins, essential autophagy molecules such as Beclin-1 accumulate in aggresomes, rendering subsequent autophagy interactions ineffective. Additionally, recent studies in CF have demonstrated defects in bacterial clearance of *Burkholderia cenocepacia* [5] and *Pseudomonas aeruginosa* [6] due to defective autophagy. Without essential autophagy flux, patients with CF are unable to mount effective autophagy-mediated responses against specific pathogens, but it is unknown if this affects all pathogen interactions in CF.

Immunomodulation in CF is a difficult task considering the polymicrobial milieu that most patients possess. However, innate immune responses must be considered seriously in the face of a global dearth of new antibiotic development combined with rising antibiotic resistant strains. While much attention has rightfully focused on mucus clearance and antibiotic-mediated killing of bacteria in CF as measures to treat chronic respiratory infections, the fact remains that chronic respiratory infections continue to be the leading cause of death in CF. With so many environmental pathogens such as *B. cenocepacia* and *P. aeruginosa* causing virulence in CF, it is vital that we overcome host immune deficiencies to provide better outcomes for patients. To date, there is no standard of care regimen for *B. cenocepacia,* and even the use of continuous inhaled antibiotic regimens such as the recent inhaled aztreonam trial fail to demonstrate benefit in this population [7].

The full interaction of CFTR, autophagy pathways, and immune responses in CF remains to be elucidated, however current evidence suggests that some form of manipulation of autophagy in CF would be beneficial. A key question remains, how will autophagy stimulators affect other essential host functions in CF and host-pathogen interactions? While rapamycin has been an effective autophagy inducer in CF in vitro and in vivo studies, side effects have been noted in transplanted CF populations and associations with interstitial lung disease in other populations [8,9]. However, other autophagy inducers may have less side effects, and synthesis and testing of novel compounds is under way. Additionally, will it be enough to target nebulized autophagy inducers for pathogen clearance, or will the sequestration systemically of autophagy molecules in CF warrant systemic-based therapies? Answers to these questions will be sought over the coming years with further research into autophagy in CF and the eventual translation to clinical trials. As the popular environmentally-friendly slogan states, it's time for us to help CF patients "Go Green", and improve their own host defense through autophagy-mediated clearance of bacteria without having to rely on ineffective antibiotics.

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