



Quorum sensing molecules and pathways in airway epithelial cells during chronic infection in patients with cystic fibrosis

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Abstract:

Introduction: Cystic fibrosis (CF) is a severely underdiagnosed genetic disorder in several areas of the world, especially Asia, which disrupts the respiratory, digestive and reproductive systems via the production of abnormally thick mucus linings or biofilms leading to fatal lung infections. In CF, a mutant strain of *Pseudomonas aeruginosa* form biofilms that sustain chronic infections. Quorum sensing (QS) mechanisms are intimately involved in

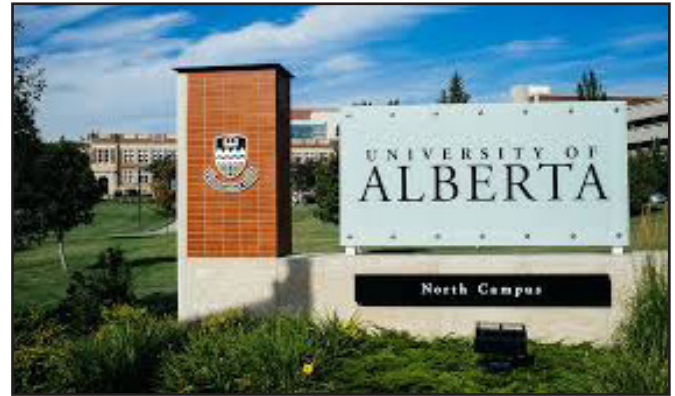
intercellular communication in bacterial networks that regulate density detection and biofilm formation. The objectives of this review are to (i) evaluate the unprecedented role of QS signaling molecules in signaling pathways of airway epithelial cells that enhance *P. aeruginosa* biofilm survival and chronic infection and (ii) identify strategies for therapeutic intervention based on current understandings of these pathways. Of the

three QS intercellular signaling pathways in *P. aeruginosa*, *las* and *rhl* signaling, the

inducers are N-acylhomoserine lactones (AHLs) while QS mechanisms for *pqs* employ 2-alkyl-4-quinolones (AQs) as inducers. Although there is a complex interplay and ample crosstalk between genes and gene products, little is understood about the mechanisms.

Recently, the cytotoxic effects of the AHL, N-3-oxo-decanoyl-L-homoserine lactone (C12), in altering integrity of the epithelium and decreasing gap junctional intercellular communication between epithelial cells was demonstrated. This can impair the polarity of airway epithelial cells by promoting the imbalance of ions between the apical and basolateral surfaces and thereby result in increased vulnerability of cells and diminished response to infection. Additionally, it was

determined QS inducers decrease nuclear factor erythroid 2-related factor (NRF2)-bound antioxidant response element. Based on this cellular characterization, a number of effective therapeutic strategies can be considered.



First, it is now conceivable that utilizing Src tyrosine and ROCK inhibitors or targeting the activation of PON2 degradation of C12 may alleviate detrimental effects on the epithelium in CF patients. The potentiation of NRF2 activity is another promising intervention, which could counteract the biofilm activity and respond to detrimental QS signals affecting the host. Alternatively, Nrf2-Keap1 dissociation can be activated or polyubiquitination and degradation of the complex can be blocked. Another possible form of treatment may be to enhance the activity of HO-1 and NADH quinone dehydrogenase to enhance the clearance of reactive molecules and enhance the immune response. Nevertheless, characterization of complex signaling pathways involved in *P. aeruginosa* QS-mediated mechanisms is integral to the development of novel therapeutics to address pathologies such as CF. However, more clinical studies are warranted prior to adopting these strategies.

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