Pseudomonas Aeruginosa, Thiocyanate and Thiosulfate Anions and their Roles in Cystic Fibrosis Airway Disease

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ABSTRACT:

Pseudomonas aeruginosa colonization plays a central role in cystic fibrosis airway disease. This pathogen, once colonized, is extremely difficult to clear and is well-known for its ability to develop resistance to antibiotics. In the normal lung, the first line of defense against these types of opportunistic pathogens is the fluid that lines the airways, the mucus layer that lies above it, and the cilia which extend through it, comprising the mucociliary transport system. This system is faulty in CF lung disease as a result of a mutation in an ABC transport protein, CFTR, which is responsible for the movement of anions onto the surface of the airways. The possibility of the transport of thiosulfate anion by the CFTR protein and the probable function of this anion is discussed, in terms of how its lack of transport could affect this system.
Discussion

Cystic Fibrosis is an autosomal recessive disease caused by the lack of function, due to various mutations, of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) which is responsible for the movement of anions to the airway surface. These anions contribute to the innate defense system of the airways, and are a part of the SOL, or periciliary layer that underlies the mucus, or gel layer. There is little doubt that the SOL contributes to airway defense, and the lack of this defense is directly responsible for the pathology seen in CF airways.

There has been much debate as to the means by which CF airway surface liquid (ASL) affects the pathology seen in the disease. It has been argued that the high salt content of CF ASL alters the bactericidal activity of CF ASL [1] Coakley et al argued that the absence of CFTR transported HCO3- caused changes in the surface pH of CF ASL which altered normal airway defense. [2] Matsui et al proposed that the increased activity of epithelial sodium channels in the airways caused a decrease in the volume and the hydration of this fluid. [3]

All of these propositions are likely, but provide only a piecemeal explanation of the lack of antimicrobial defense and the increased inflammatory cascade characteristic of CF airways. Our understanding of these characteristics can only be furthered by the determination of other CFTR substrate anions and their role in airway immunity.

To that end, it is illuminating to look at other proteins that share the ATP binding cassette (ABC) sequence motif, particularly the multidrug resistance associated (MRP) proteins, which are 50% homologous to the CFTR protein and likely to share similar function, if not exactly the same substrates. Indeed, Lellemann proposed, in 1997, that the induction of these proteins by antitumoral drugs comprised a novel therapy for the treatment of CF. [4] And, in 2003, Hurbain et al found that expression levels of MRP1 and MRP5 positively correlated with the increased chloride transport not attributable to the CFTR channel activity and milder lung disease in CF patients. Moreover, Hurbain attributed this correlation to an increased glutathione transport by these proteins to the interstitium, where it then was diffused into the SOL via paracellular pathways. [5]

Other MRPs are known to transport amphipathic anion compounds and glutathione, glucuronide and sulfate conjugates [7,8] In fact, there is much evidence to support the notion that substrates of the MRP proteins share similarities with the CFTR protein. For instance, Lindsell found that the CFTR was permeable to glutathione and Gao et al found abnormal glutathione transport in CF airway epithelia. [6, 9] As well, MRP proteins have been shown to move sulfate conjugates out of the cell, and it has been shown that expression of the CFTR protein is associated with increases in permeation by the adenine nucleotide and universal sulfate donor in cells, adenosine 3′-phosphate 5′-phosphosulfate. [10, 11] In fact, this observation has been suggested to explain the diminished glycoprotein sialylation seen in this disease. [13, 14] If, like glutathione, sulfates are trapped inside of the cell without a functional CFTR protein to transport them to the SOL,
it is little wonder that high molecular weight glycoconjugates generated by CF airway epithelial cells are oversulfated. [12]

Although the products of these processes affect the composition of the SOL, as well as the gel layer that overlies it in the airways, their genesis is of an intracellular nature. Just as glutathione, trapped in the cell, interacts intracellularly with hydrogen peroxide in this disease, to diminish the amount of this oxidant necessary in the SOL, which in turn interferes with the lactoperoxidase system, tasked with generating the bactericidal hypothiocyanate, the lack of transport of certain sulfates in the SOL would also have deleterious effects.

Of particular interest in this regard is the thiosulfate anion. Although there are no studies, as yet, that address the question of whether this anion is transported by the CFTR to the SOL, because of recent findings of high concentrations of hydrogen cyanide in the breath condensate of cystic fibrosis patients, it warrants particular attention. [15] This is certainly so, since cyanide production has been suggested to be a virulence factor in CF lung disease and epidemiological studies have deemed this pathogen as the most important pathogen in progressive, severe CF lung disease. [16, 17] Moreover, thiosulfate, itself, plays a role in the transformation of cyanide into thiocyanate.

Recent work linking thiocyanate concentrations in CF airways with disease severity highlighted the role of the lactoperoxidase system of innate immunity in CF airways. [18] Lorentzen et al suggested that the correlation between thiocyanate concentrations and lung function in CF patients might also reflect a beneficial role for this compound [19]. And, thiocyanate has been shown to act as a buffer for the enzymatic action of myeloperoxidase with Cl-, even at low concentrations. [20] Indeed, Chandler et al found that thiocyanate is cytoprotective against HOCl- and MPO mediated cell injury as well as effective against infection-mediated neutrophilic lung inflammation and P. aeruginosa infection and associated morbidity. [21]

Clearly, thiocyanate plays an important role in CF airway disease, and particularly in respect to P. aeruginosa infection. Indeed, it is a normal component of human airway lining fluid and has been found in high concentrations in the SOL. However, although airway epithelial cultures have been shown to secrete thiocyanate in a CFTR-dependent manner, this does not account for the high concentrations of it found in the airway lining fluid. [22]

It has been suggested that rhodanese, a mitochondrial enzyme which detoxifies cyanide by converting it into thiocyanate, and its actions on isothiocyanate-containing foods is the source of the non-CFTR-mediated thiocyanate in the airway epithelial lining fluid, but it is hardly likely that such a system, so central to the sterility of the airways, would be left to the vagaries of the human diet. Instead, another mechanism, of which thiosulfate anion plays a central role, in that it is used by the enzyme, rhodanese, to convert cyanide to thiocyanate, is a more likely explanation.
Currently, there are several therapies, for the treatment of cystic fibrosis, in the pipeline, that utilize thiocyanate because of both its antibacterial and anti-inflammatory properties. Thiosulfate anion, or one of its salts, such as sodium thiosulfate, which has already been used for the treatment of cyanide poisoning, should be considered as an aerosolized therapy for the treatment of cystic fibrosis, along with bicarbonate (as a buffer and to replace the HCO3- normally transported by the CFTR protein), and other substrates of the CFTR protein, either in their conjugated or non-conjugated forms. Not only will thiosulfate, as a substrate for rhodanese, utilize cyanide produced by Pseudomonas aeruginosa pathogen that inevitably target CF airways, but this process will provide thiocyanate for utilization in the lactoperoxidase system of airway immunity, as well as act as a buffer necessary to decrease inflammation associated with infections by this pathogen.

Such a formulation can be combined with long-lived oxidants, such as sorbitol or betaine, in order to draw water into the periciliary layer in order to adjust the level of this layer to normal. It can also be used to ameliorate airway bacterial, viral and fungal colonizations in other airway disease such as Bronchiolitis obliterans in lung transplant and pulmonary fibrosis patients.
CITATIONS:


