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Properties of airway mucus in cystic fibrosis: their modification by changes in the activity of CFTR and after application of bicarbonate

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Background. Mucins are mucus glycoproteins that are kept compact inside mucous cells because their poly-anionic part are shielded by counter-ions. When mucus is secreted towards the airways, mucins expand to permit an efficient mucociliary clearance. This function, that requires rapid removal of cations, seems to depend on the presence of bicarbonate. In CF patients, the defective ion transport across mutated protein causes a simultaneous reduction of fluid, Cl^- and bicarbonate secretion leading to a viscous mucus phenotype with frequent infections and bacterial colonization of the airways.

Hypothesis and objectives. We have hypothesized, and aimed to demonstrate, that the consequence of the defective fluid and bicarbonate secretion in CF is an inappropriate structure of the mucus network with deficient rheological properties, and that pharmacological correction of the mutated CFTR may lead to recover the properties of mucus. In addition, we intended to determine whether inhalation of bicarbonate by CF patients can improve the properties of sputum.

Methods. The micro-rheology of mucus from CF and non-CF bronchial epithelium, and of untreated and bicarbonate-treated CF sputum, have been analysed using Multiple Particle Tracking, a technique that consists in following the movement of fluorescent beads inside the medium to be studied. The statistical analysis of the movement of the beads permits to calculate the diffusion coefficient and other parameters that give insights about mucus viscoelastic properties.

Results. We have determined that in CF mucus nano-beads have lower diffusion coefficient, and the elastic and viscous moduli are higher than in non-CF mucus. Also, we have found that 25% correction of F508del mutation with lumacaftor is enough to improve significantly CF mucus properties. Surprisingly, also incubation with amiloride, a compound that reduces fluid absorption but not the secretion of bicarbonate, improved CF mucus properties. Regarding inhalation of bicarbonate by CF patients, we have designed a pilot clinical trial that is still going on.

Spin-off for research and clinical purposes. In conclusion, CF mucus properties can be recovered in vitro either improving the hydration of the airways or increasing the activity of the mutated protein with a corrector compound, probably by increasing bicarbonate secretion. The results of our clinical trial will permit to determine whether bicarbonate, a low cost and mutation-independent treatment, can improve the properties of CF sputum.

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