

GSH inhalation therapies in CF: how useful, how safe? Set-up of a CF murine model for monitoring of inflammation in vivo and assessment of convenient alternatives

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Background. Inhalation treatments with glutathione (GSH) have gained interest among CF patients. GSH is a primary antioxidant whose levels are significantly decreased in lungs during inflammatory processes. However the results attained so far remain disappointing. One of the possible reasons may lie in the fact that CF lungs often present with increased levels of gammaglutamyltransferase (GGT), an enzyme secreted by inflammatory cells, capable of degrading GSH.

Hypothesis and objectives. The hypothesis to be verified was whether the different levels of airways GGT in CF patients might modulate the effects of GSH-based therapies. It is of importance to clarify whether GSH inhalation therapies are truly beneficial, useless or even – in selected conditions – potentially dangerous.

Methods. Sputum samples from CF patients undergoing GSH inhalation treatments have been analyzed for GGT content and clinical and biochemical responses were correlated with GGT activity. In vitro experiments were performed with a CFTR-mutated cell line and a CF mouse model transiently transgenized with a human IL-8 promoter/luciferase reporter gene was set up.

Results. The analysis of approx. 190 samples confirmed the presence of heterogeneous levels of GGT in CF sputum. GGT activity correlates with neutrophil elastase and with the products of GGT-mediated GSH catabolism. GSH treatment did significantly reduce sputum levels of IL-8, TNF- α and IL-1 β but only in subjects presenting with a regression of inflammation. An increase in GGT levels during GSH therapy was associated with higher levels of an oxidative stress marker (protein carbonyls). The latter effect could be mediated by sputum GGT. Experiments in vitro confirmed the potential role of GGT in promoting

prooxidant reactions, whereas the in vivo model allowed us to study the activation status of NF- κ B factor. Further studies will likely allow to elucidate the exact role of GGT in airway inflammation.

Spin-off for research & clinical purposes. Our data demonstrate that sputum GGT activity correlates with neutrophilic inflammation in CF airways. Differentiating patients with increasing/decreasing GGT activity may discriminate subjects with resolving inflammation – more likely profiting from inhaled GSH – from those with exacerbation of inflammation – in which GSH might even produce aggravation of the damage. Future studies should consider the actual inflammatory status of the airways when anti-inflammatory treatments are targeted.

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