α-Lipoic acid as a potential treatment for Cystic Fibrosis

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Cystic Fibrosis is (CF) is the most common inherited autosomal recessive lethal disease in Caucasian population due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) [1]. This leads to airway obstruction, thick mucus, increased susceptibility to respiratory bacterial infections, chronic lung inflammation and progressive pulmonary insufficiency [2]. Among CFTR mutations, the most common deletion of Phe at position 508 (ΔF508), encodes a misfolded protein that is retained in the ER and fails to traffic to the plasma membrane [3]. Defective CFTR function increases intracellular ROS driving tissue transglutaminase (TG2) SUMOylation, in turn activating TG2 which crosslinks several proteins, among which BECN1, provoking defective autophagy [4]. TG2 can function as a rheostat of cellular homeostasis and a key regulator of the post-tranlastional network. αLipoic acid (αLA) is a dietary bioactive molecule because of its recognized therapeutic potential on several inflammatory diseases. αLA exerts antioxidant functions, and inhibits NF-kB [5]. In CF, NF-kB persistent activation is well known and linked to an exaggerated inflammatory mediator production [6]. Thus, NF-kB blockade may be crucial for limiting chronic lung inflammation in CF. Also the PPARs transcription factors have essential roles in the regulation of cellular differentiation, development and metabolism [7]. Noteworthy, αLA has been shown to modulate the PI3K/Akt pathway, and promote mitochondrial metabolism via PPAR coactivators stimulation [8]. We previously reported that the autophagic machinery is dysregulated in CF, contributing to inflammation [9]. In the present study we investigated the effects of αLA in two CF animal models, the homozygous DF508 ($CFTR^{dF508}$) and the Scnn1b-Tg CF mice. Injection of αLA by i.p. in $CFTR^{dF508}$ mice reduced, in lung homogenates, MIP2 levels, TNFα mRNA expression, VCAM1 and L-selectin expression as well as MPO and NF-kB activity. Similar results were observed in Scnn1b-Tg mice. In addition, resident CD68 positive cells decreased after αLA administration in $CFTR^{dF508}$ mice. It is well known that defective CFTR induces a remarkable up-regulation of TG2, in turn leading to functional sequestration of the anti-inflammatory PPARγ and increased inflammation. Therefore, we investigated the effects of αLA on TG2. Interestingly, we found that αLA inhibited TG2, thus increasing PPARγ expression in lungs isolated from both CF animal models. Moreover, similar results were obtained from trachea freshly isolated cells. αLA antiinflammatory effect on epithelial cells was confirmed in vitro by testing the molecule on human bronchial CF epithelial cell lines (IB3-1 and CFBE, carrying ΔF508/W1282X and ΔF508/ΔF508 CFTR mutations, respectively) and control cell lines (C38 isogenic of IB3-1 stably rescued with functional CFTR or 16HBE carrying WT-CFTR). Incubation of CF cells with αLA determined a reduction in TG2 protein expression and activity, TG2 SUMOylation, and increased PPARγ levels. αLA did not exert any effect on control cells (either C38 or 16HBE). Moreover, αLA determined a reduction in NF-kB activity. Our results show that αLA, may control TG2 activity, thus impacting on the unbalance of the dysregulation of the autophagic machinery taking place in CF cells. In conclusion, our results indicate that αLA may represent a new therapeutic tool in CF therapy.

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