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Review

Oxidative stress and antioxidant therapy in cystic fibrosis ☆,☆☆

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ABSTRACT

Cystic fibrosis is a lethal autosomal recessive condition caused by a defect of the transmembrane conductance regulator gene that has a key role in cell homeostasis. A dysfunctional cystic fibrosis transmembrane conductance regulator impairs the efflux of cell anions such as chloride and bicarbonate, and also that of other solutes such as reduced glutathione. This defect produces an increased viscosity of secretions together with other metabolic defects of epithelia that ultimately promote the obstruction and fibrosis of organs. Recurrent pulmonary infections and respiratory dysfunction are main clinical consequences of these pathogenetic events, followed by pancreatic and liver insufficiency, diabetes, protein-energy malnutrition, etc. This complex comorbidity is associated with the extensive injury of different biomolecular targets by reactive oxygen species, which is the biochemical hallmark of oxidative stress. These biological lesions are particularly pronounced in the lung, in which the extent of oxidative markers parallels that of inflammatory markers between chronic events and acute exacerbations along the progression of the disease. Herein, an abnormal flux of reactive oxygen species is present by the sustained activation of neutrophils and other cystic fibrosis-derived defects in the homeostatic processes of pulmonary epithelia and lining fluids. A sub-optimal antioxidant protection is believed to represent a main contributor to oxidative stress and to the poor control of immuno-inflammatory pathways in these patients. Observed defects include an impaired reduced glutathione metabolism and lowered intake and absorption of fat-soluble antioxidants (vitamin E, carotenoids, coenzyme Q-10, some polyunsaturated fatty acids, etc.) and oligoelements (such as Se, Cu and Zn) that are involved in reactive oxygen species detoxification by means of enzymatic defenses. Oral supplements and aerosolized formulations of thiols have been used in the antioxidant therapy of this inherited disease with the main aim of reducing the extent of oxidative lesions and the rate of lung deterioration. Despite positive effects on laboratory end points, poor evidence was obtained on the side of clinical outcome so far. These aspects examined in this critical review of the literature clearly suggest that further and more rigorous trials are needed together with new generations of pharmacological tools to a more effective antioxidant and anti-inflammatory therapy of cystic fibrosis patients. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.

1. Introduction

Cystic fibrosis (CF) is a lethal autosomal recessive disorder caused by a single gene defect. This was identified in 1989 to map on the chromosome 7 and to correspond to the gene coding for the transmembrane conductance regulator (CFTR) that is mainly expressed in the apical membrane of epithelial cells that line mucous membranes and submucosal glands [1]. Several mutations have been identified to cause this gene defect with the Phe508del, or ΔF508, as one of the most common mutations in Caucasians. The prevalence at birth varies in the different regions according with ethnic background, from roughly 1 in 3000 white Americans and northern

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Europeans to 1 in 350,000 in Japan. Mutations are grouped in 6 classes based on the type of defect caused on CFTR protein metabolism and function. Several physiological processes affected by these mutations are related to the role of CFTR as anion channel. This mainly regulates chloride efflux, but other and larger anions such as reduced glutathione cross the plasmalemma throughout this transmembrane protein widely expressed in diverse epithelial tissues. Other ion transport systems are under its influence, such as bicarbonate anion and sodium channels, so that a defective CFTR can impair several processes such as cell volume and pH regulation, transepithelial transport, membrane conductance, and the GSH-related antioxidant and detoxification activity in the extracellular milieu [2,3]. CFTR dysfunction is associated with an altered fluid and electrolyte composition of secretions, their increased viscosity and progressive obstruction and fibrosis of organs [4]. The severity of these CF symptoms varies independently of the type and number of mutations diagnosed, suggesting that CFTR gene and its mutations interact with other genes at the transcriptional and post-translational level to influence a wide series of physiological processes. Lung, pancreas and liver are severely affected by these events, and recurrent infections of the airways together with pancreatic insufficiency and diabetes are most common conditions secondary to CF [1].

The presence of a defective CFTR appears to produce a redox imbalance in epithelial cells and extracellular fluids and to cause an abnormal generation of reactive oxygen species (ROS). A constitutive defect of GSH metabolism together with a lowered intake and absorption of fat-soluble antioxidant vitamins (vitamin E and carotenoids) could contribute to a defective antioxidant protection, which is believed to exacerbate oxidative stress indices along with the progression of clinical status [5–7]. The development of inflammatory and degenerative lesions in target tissues such as lung, pancreas and liver further exacerbate the shift from normal to abnormal flux of ROS in several organs, thereby leading to develop systemic oxidative stress. This is a chronic-degenerative trait common to other and severe inflammatory diseases such as chronic kidney disease and some auto-immune syndromes (reviewed in [8,9]), which may conspire with further mechanisms to worsen the prognosis of this inherited disorder (recently reviewed in [10]).

In view of these aspects, the CF patient is assumed to have a higher antioxidant demand. This has provided the rationale for the systematic investigation of antioxidant levels in blood and targeted tissues of CF patients, mainly the epithelium and lining fluids of the airways, and to plan for antioxidant interventions that might rescue specific defects of these patients. These also include the use of anti-inflammatory agents and nutritional formulations which can produce an "antioxidant effect", i.e. the lowering of oxidative stress indices, as a result of their direct or indirect action. Despite a number of promising in vitro and pre-clinical observations, antioxidants used as oral supplements or directly administered in the CF airways have failed to provide convincing evidence at the clinical level. Future efforts are required to identify more advanced agents and therapeutic strategies that may enhance secondary prevention and chemotherapy of airway inflammation and oxidative stress in CF patients. Advances in the approaches capable of improving nutritional status and antimicrobial therapy are of main relevance to further ameliorate quality of life and survival rates in CF.

These aspects will be discussed in this manuscript with the aim of providing an updated review of the literature as well as of strategies and future directions of antioxidant therapies in CF patients.

2. Inflammatory pathways and oxidative stress in CF

2.1. Progressive inflammatory damage in CF lungs and the contribution of oxidants

Evidence supporting the occurrence of oxidative stress in CF is by now established and extensive [6,10–12]. As introduced above, CF-related defects of the pulmonary epithelium and a sustained PMN activation by recurrent infections create the conditions for an abnormal flux of reactive oxygen species (ROS) in the CF lung (Fig. 1) between events of acute and chronic inflammation. Abnormalities of markers of ROS activity and inflammation are most evident during acute respiratory exacerbations and show improvement with the

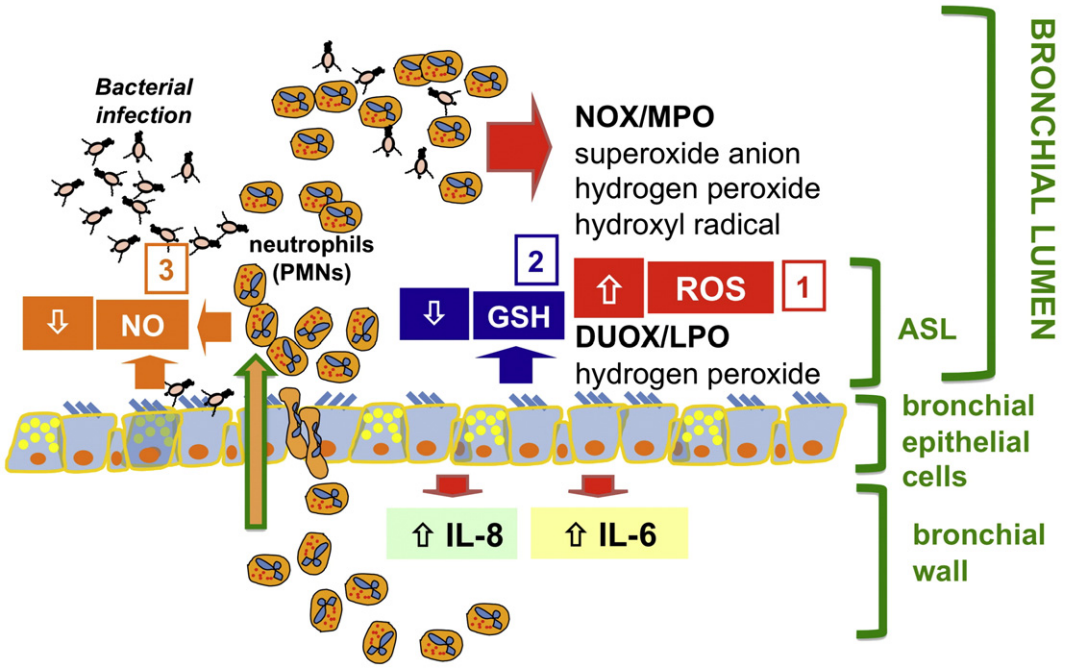

Fig. 1. Oxidative unbalance in conductive airways of patients affected by cystic fibrosis. airway surface liquid (ASL) in CF bronchi is characterized by 1. increased concentration of reactive oxygen species (ROS), 2. lowered levels of glutathione (GSH) and 3. reduced nitric oxide (NO). The net increase of pro-oxidative species in ASL, as a result of derangements of both neutrophils and bronchial epithelial cells, contributes to the progressive lung tissue damage and to the amplification of the inflammatory response in CF airways. This is characterized by the release of chemokines and cytokines (e.g. IL-8 and IL-6, respectively). NOX, NADPH oxidase; MPO, mieloperoxidase; DUOX, dual oxidase; LPO, lactoperoxidase, IL, interleukin.