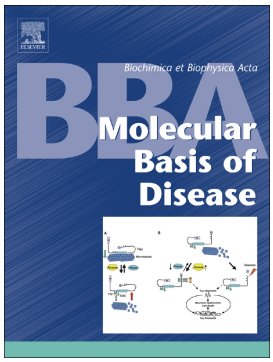

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Modulation of cellular membrane properties as a potential therapeutic strategy to counter lipointoxication in Obstructive Pulmonary Diseases

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Abstract

Maintaining the equilibrium between saturated and unsaturated fatty acids within membrane phospholipids (PLs) is crucial to sustain the optimal membrane biophysical properties, compatible with selective organelle-based processes. Lipointoxication is a pathological condition under which saturated PLs tend to accumulate within the cell at the expense of unsaturated species, with major impacts on organelle function. Here, we show that human bronchial epithelial cells extracted from lungs of patients with Obstructive Pulmonary Diseases (OPDs), *i. e.* Cystic Fibrosis (CF) individuals and Smokers, display a characteristic lipointoxication signature, with excessive amounts of saturated PLs. Reconstitution of this signature *in cellulo* and *in silico* revealed that such an imbalance results in altered membrane properties and in a dramatic disorganization of the intracellular network of bronchial epithelial cells, in a process which can account for several OPD traits. Such features include Endoplasmic Reticulum-stress, constitutive IL8 secretion, bronchoconstriction and, ultimately, epithelial cell death by apoptosis. We also demonstrate that a recently-identified lipid-like molecule, which has been shown to behave as a "membrane-reshaper", counters all the lipointoxication hallmarks tested. Altogether, these insights highlight the modulation of membrane properties as a potential new strategy to heal and prevent highly detrimental symptoms associated with OPDs.

Keywords: Lipointoxication, Endoplasmic-Reticulum stress, Apoptosis, Cystic Fibrosis, Chronic Obstructive Pulmonary Disease