Impact of secondhand smoke on cystic fibrosis: is there a link to fatty acid metabolism?

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Cystic fibrosis (CF) is an autosomal recessive disease caused by genetic mutations of the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene leading to viscous secretions, chronic respiratory infections and airway inflammation. Although survival of patients has been markedly improved due to better care and new treatment options, lung failure is still the major cause of mortality.

Thus, controlling respiratory infection and excessive airway inflammation is an important goal in the treatment of CF lung disease. Interestingly, heterogeneity in disease severity has been noted for a long time and airway inflammation may already be present in young children even in the absence of infection.[1] Multiple factors have been proposed to explain the variety of disease severity even in young patients. These factors include differences in *CFTR* mutations, poor compliance with treatment, external factors like early viral infections and environmental factors like secondhand smoke exposure (SHSe). Many clinicians believe that SHSe is a major contributing factor for disease progression, although the mechanisms associated with increased inflammation and infection due to SHSe in infants and young children with CF is not fully elucidated. Kopp *et al*[2] in this issue are the first who were able to close this important gap. They could clearly demonstrate that SHSe is highly prevalent in young children with CF and results in alterations of arachidonic acid (AA) metabolism and inflammatory gene expression, which in turn impairs bacterial clearance.

Since the famous study of Freedman *et al*,[3] which was published in 2004, it is well known that patients with CF suffer from a disturbed lipid metabolism. This includes an altered lipid constitution with low amounts of linoleic and docosahexaenoic acid and an altered cholesterol and sphingolipid metabolism. However, Kopp *et al*[2] were able to show that SHSe aggravates these findings and demonstrate why SHSe is especially detrimental to children with CF. In order to examine whether SHSe alters the endogenous biosynthesis of lipid mediators derived from AA, they determined lipid mediator profiles of patients' serum and found that SHSe decreased AA-derived prostaglandin (PG) D_2 and leukotriene (LT) C_4 lipid mediators as well as their monohydroxy precursors in patients with CF. Of note, the authors analysed secondhand smoke by longer-term exposure measures in the hair of patients and controls, which is much more representative than measures in saliva or urine.

Kopp *et al*[2] particularly found decreased PGD_2 serum levels which could be associated with impaired clinical outcome, such as hospitalisation for pulmonary exacerbation in infants with CF and children exposed to SHS. Furthermore, they demonstrated a dose-dependent decrease of PGD_2 with increasing concentrations of cigarette smoke extract (CSE) in *in vitro* experiments with CSE-exposed macrophages. This finding is surprising since the physiological role of PGD_2 remains controversial. Many studies have reported that PGD_2 is a key player of the TH-2-driven inflammatory response in asthma, mediating bronchoconstriction and eosinophilia. Therefore, PGD_2 is a promising new therapeutic target in asthma.[4] In contrast, other groups have reported that PGD_2 facilitates resolution of inflammation through the PRKAR2A-mediated suppression of JAK2/STAT1 signalling by inhibiting the recruitment of dendritic cells and neutrophils.[5] At present, the pro-inflammatory and/or anti-inflammatory effects of PGD_2 are difficult to understand. Although the paper of Kopp *et al*[2] does not provide a definite answer, it is important to note that not only PGD_2 was downregulated. The manuscript's findings are especially interesting since CFTR itself seems to be involved in the regulation of the PGD synthase-PGD_2-15d-PGJ_2 pathway.[6]

Further lipidomics analysis revealed a decrease of lipoxin (LX) A_4, LTE_4 and PGE_2 in CF compared with non-CF macrophages *in vitro*. Thereby, the authors demonstrated that the COX-2-dependent and also the 5-lipoxygenase-dependent endogenous biosynthesis of lipid mediators derived from AA is impacted by cigarette smoke in a decreasing manner. Especially regarding pro-resolving actions, specialised pro-resolving mediators, such as LXA_4, are described to orchestrate resolution processes, such as clearance of microbes and cellular debris by macrophages.[7–10] Moreover, the administration of 1 nM LXA_4 has been shown to have protective effects against *Pseudomonas aeruginosa* bacterial challenge together with a delaying action against bacterial invasion in CF airway epithelial cells from patients with CF.[7]

Taken together, Kopp *et al*[2] showed for the first time that infants and children with CF and SHS exposure biosynthesize significantly lower amounts of AA-derived lipid mediators, have dysregulated inflammatory gene expression and have impaired bacterial clearance. By correlation of PGD_2 levels with clinical outcome, the authors could show the high impact of altered AA-dependent lipid mediator pathways in infants and children with CF, particularly by SHSe.

Since the biosynthesis of pro-inflammatory as well as pro-resolving lipid mediator pathways were negatively affected by SHSe, further clarification would be valuable to identify specific functions of distinct AA-derived lipid mediators in smoke-exposed patients with CF.

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