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PPAR agonists upregulate filaggrinm expression and improve lipid composition and organization in a filaggrin knock down skin model

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Loss-of-function mutations in the gene encoding for filaggrin (FLG) are the major predisposing factor for atopic dermatitis (AD). As for today, therapeutic options for FLG associated skin diseases only alleviate the symptoms such as dry and itchy skin or reduce the inflammation. No therapy exists preventing the development of these symptoms or restoring the disturbed skin barrier function. Peroxisome proliferator-activated receptor (PPAR) agonists are not only important therapeutics for the treatment of lipid disorders and diabetes but also exhibit beneficial effects in patients suffering from inflammatory skin diseases like AD. PPAR agonists are known to increase the expression of FLG in skin and positively influence the skin barrier homeostasis, skin barrier recovery and stratum corneum (SC) integrity (1). In order to study the effects caused by a lack of FLG in vitro we established a FLG knock down skin model (2, 3). In this study, we evaluated the effects of the PPAR agonists' docosahexaenoic acid (DHA) and clofibrate (CLF) in a FLG deficient (FLG-) skin model in terms of FLG expression, skin lipid organization and composition and skin permeability. We detected an about 18.96-fold upregulation of FLG in DHA treated normal skin models (FLG+). FLG expression increased significantly about 2.69-fold in FLG- models upon DHA treatment even exceeding the FLG expression of DHA untreated FLG+ samples. These results were confirmed on the protein level. Histological examination revealed a thickening of the SC upon DHA treatment (FLG-/DHA- 8 ± 1.2 µm vs. FLG-/DHA+ 12.8 ± 1.5 µm). In terms of skin lipid composition, a treatment with DHA normalized the pathologically increased free fatty acid (FFA) levels: FFA amounts were reduced from 22.0 ± 2.7 µg/mg to 15.3 ± 1.0 µg/mg in FLG- models following DHA treatment (FLG+ 13.3 ± 1.5 µg/mg). Furthermore, the skin lipid organization was significantly improved in FLG- constructs as determined by ATR-FTIR. Interestingly, skin absorption studies did not show an improvement of the skin barrier after DHA treatment. The beneficial effects on the skin barrier homeostasis are undoubted but further studies are necessary to completely understand the effects of PPAR agonists on the skin barrier function.

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