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Inhibition of indoleamine 2,3-dioxygenase 1 alleviates atopic dermatitis-like symptoms

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Introduction & Objectives:

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by immune dysregulation and skin barrier dysfunction. The tryptophan metabolism, primarily through the tryptophan-indoleamine 2,3-dioxygenase 1 (IDO1)-kynurenine pathway, plays a key role in immune regulation and inflammation; however, its involvement in AD pathogenesis remains unclear. This study investigated the therapeutic effects of PF-06840003 (PF), a selective inhibitor for IDO1, in AD models.

Materials & Methods:

Human primary keratinocytes were stimulated with PF (100 ~ 400 μM) in the presence or absence of interleukin (IL)-4/IL-13 and the mRNA expression of inflammatory cytokines and chemokines was analyzed using real-time PCR. *In vivo*, an MC903-induced AD-like mice were administered with PF (5 ~ 15 mg/kg) or vehicle. Disease severity was evaluated by ear thickness, scratching behavior, and transepidermal water loss (TEWL). Skin biopsies were analyzed for inflammatory cytokines and skin barrier-related genes. Histological assessments included hematoxylin and eosin (H&E) staining for epidermal thickness and toluidine blue staining for mast cell infiltration.

Results:

In vitro studies revealed that PF dose-dependently suppressed the mRNA expression of *IL1α*, *IL6*, *IL8*, *CCL2*, and *CCL3* in human keratinocytes stimulated with IL-4/IL-13 cocktail. Moreover, *in vivo*, PF alleviated AD-like symptoms in mice, significantly reducing skin inflammation, ear thickness, scratching bouts, and TEWL in a dose-dependent manner. Meanwhile, PF suppressed the mRNA expression of *Tnf*, *Il4*, and *Il13*, and upregulated skin barrier-related genes such as *Tjp1* and *Cldn1* in AD skin lesion. Histologically, H&E staining and toluidine blue staining showed a significant decrease in epidermal thickness and mast cell infiltration, respectively, in PF-treated groups compared to the counterpart.

Conclusion:

PF exhibited potent anti-inflammatory and skin barrier-protective effects in both *in vitro* and *in vivo* models of AD, suggesting that IDO1 inhibition and regulation of tryptophan metabolism as a promising therapeutic strategy for skin inflammation such as AD.