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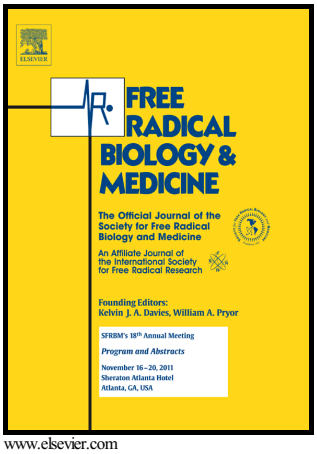

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Topical electrophilic nitro-fatty acids potentiate cutaneous inflammation.

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Abbreviations

subcutaneous (SC); nitro oleic acid (OA-NO_2), allergic contact dermatitis (ACD), contact hypersensitivity (CHS); nitro linoleic acid (LNO_2); conjugated nitro linoleic acid (CLA-NO_2); peroxisome proliferator-activated receptor-γ (PPAR-γ); nuclear factor E2-related factor 2 (Nrf2); nitro-fatty acid (NO_2-FA); antioxidant-response element (ARE); dendritic cells (DCs); histone deacetylase (HDAC); hypoxia inducible factor-1alpha (HIF-1α); imiquimod (IMQ)

Abstract

Endogenous electrophilic fatty acids mediate anti-inflammatory responses by modulating metabolic and inflammatory signal transduction and gene expression. Nitro-fatty acids and other electrophilic fatty acids may thus be useful for the prevention and treatment of immune-mediated diseases, including inflammatory skin disorders. In this regard, subcutaneous (SC) injections of nitro oleic acid (OA-NO_2), an exemplary nitro-fatty acid, inhibit skin inflammation in a model of allergic contact dermatitis (ACD). Given the nitration of unsaturated fatty acids during metabolic and inflammatory processes and the growing use of fatty acids in topical formulations, we sought to further study the effect of nitro-fatty acids on cutaneous inflammation. To accomplish this, the effect of topically applied OA-NO_2 on skin inflammation was evaluated using established murine models of contact hypersensitivity (CHS). In contrast to the effects of subcutaneously injected OA-NO_2, topical OA-NO_2 potentiated hapten-dependent inflammation inducing a sustained neutrophil-dependent inflammatory response characterized by psoriasiform histological features, increased angiogenesis, and an inflammatory infiltrate that included neutrophils, inflammatory monocytes, and γδ T cells. Consistent with these results, HPLC-MS/MS analysis of skin from psoriasis patients displayed a 56% increase in nitro-conjugated linoleic acid