SQUALENE OXIDATION PRODUCTS ISOLATED FROM PHOTO-OXIDISED HUMAN SKIN SURFACE LIPIDS INDUCE METABOLIC AND INFLAMMATORY RESPONSES CHARACTERISTIC FOR SOLAR UV IRRADIATION IN HUMAN KERATINOCYTES

V. A. KOSTYUK[1,2], A. I. POTAPOVICH[1,2], A. STANCATO[1], CH. DE LUCA[1], D. LULLI[1], P. FIDANZA[1], S. PASTORE[1], L. G. KORKINA[1]

[1]Tissue Engineering & Skin Pathophysiology Laboratory, Dermatology Research Institute (IDI IRCCS), Rome 00167, Italy;
[2]Physiology Department, Belarusian State University, Minsk, Belarus
kosty-vladimir@yandex.ru

Aims: To identify endogenous extracellular mediators and evaluate mechanisms underlying metabolic and inflammatory responses of human keratinocytes to solar UV irradiation.

Results: Physiologically relevant doses of solar simulated UVA+UVB were applied ex vivo to human skin surface lipids (SSL) or *in vitro* to primary cultures of normal human epidermal keratinocytes (NHEK). The decay of photo-sensitive lipid-soluble components, such as alphatocopherol, squalene (Sq), and cholesterol in SSL was analysed and products of squalene photooxidation (SqPx) were quantitatively isolated from irradiated SSL. When administered directly to NHEK, low-dose solar UVA+UVB induced distinct time-dependent, sometimes bi-modal inflammatory and metabolic responses through activation of aryl hydrocarbon (AhR) and epidermal growth factor (EGFR) receptors. To mimic UVA+UVB action, NHEK were exposed to intact or photo-oxidised SSL, Sq or SqPx, 4-HNE, and the product of tryptophan photo-oxidation 6- formylindolo[3,2-b]carbazole (FICZ). FICZ strongly activated metabolic responses characteristic for UVB, such as nuclear translocation of AhR and AhR nuclear translocator (Arnt) and downstream CYP1A1/CYP1B1 gene expression. Unlike UVA+UVB, FICZ inhibited EGFR/ERK pathway and did not affect inflammatory cytokines/enzymes. 4-hydroxy-2-nonenal, known to mediate UVB-induced EGFR nuclear translocation, affected ERK and Akt1 phosphorylation in a bi-phasic manner and slightly stimulated IL-6, COX-2, and iNOS gene expression. SqPx induced the majority of metabolic and inflammatory responses characteristic for UVA+UVB acting via AhR-, EGFR-, and G-protein coupled receptor (G2A)-connected pathways.

Conclusion: Squalene, a major component of human skin surface lipids, could be a universal sensor of solar UV irradiation and products of its photo-oxidation mediate metabolic and inflammatory responses of keratinocytes to UVA+UVB.