Environmental stress protection and inflammaging prevention: A novel synergic antioxidant blend

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We present an efficient approach to slowing the progression of skin damage using a multi-mechanistic antioxidant blend suitable for cosmetic formulations and validate its performance in vitro. Three different mechanisms were targeted simultaneously: scavenging reactive oxygen species (ROS), mitigating intracellular ROS and reducing ROS-induced inflammaging markers. Using a Design of Experiment approach, a novel, non-phototoxic synergistic blend of antioxidants was identified and characterized in vitro for its ability to quench free radicals (DPPH assay) and intracellular ROS generated by UVA (DCFH assay). Further, we demonstrated that use of the blend results in a mitigation of markers correlated with inflammaging (photaging and hyperpigmentation) caused by environmental oxidative stress (PGES, IL-8, MMP-1). These results support the notion that a multi-mechanistic antioxidant blend may effectively alleviate environmentally induced skin damage and be easily incorporated into skin care formulations providing an anti-inflammaging benefit. Brewer, M.S. “Natural Antioxidants: Sources, Compounds, Mechanisms of Action and Potential Applications.” Comprehensive Reviews in Food Science and Food Safety, vol. 10, 2011; McMullen, Roger L. Antioxidants and the Skin. Allured Books, 2013; Oswald, T., Crane, C.M., Dueva-Koganov, O., Bianchini, R. Design of Experiments to Optimize a Novel Anti-oxidant Blend [conference presentation]. Innovations in Dermatological Sciences, Rutgers, NJ 2018.

The clock protein BMAL1 maintains the diploid status of human keratinocytes via a functional interaction with c-myc

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A diverse array of biological processes is under the control of the circadian clock composed of four core proteins, including BMAL1, CLOCK, PER1, and CRY1. These core circadian oscillators are present in major cell types within different skin compartments and regulate diverse aspects of skin homeostasis at the local level. We found that loss of BMAL1 promoted differentiation in human keratinocytes. This effect was accompanied by a significant increase in the cell population with polyplody and strong induction of t(3;14), a marker for DNA damage. These results indicate that BMAL1 is crucial for maintaining genome stability and proliferation potential in human keratinocytes. Mechanistic studies showed that loss of BMAL1 enhanced the expression of c-myc, a pro-oncogene with the pro-differentiation function in keratinocytes. More importantly, co-depletion of c-myc with BMAL1 genes could reverse premature differentiation and polyplody caused by the loss of BMAL1. These data suggest that the clock protein BMAL1 plays an essential role in maintaining the diploid stem cell potential by suppressing the expression and activity of c-myc in human keratinocytes.

Optimization of the barrier function of a tissue-engineered skin model through supplementation of cell culture media with docosahexaenoic acid

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Percutaneous absorption studies showed that tissue-engineered skin models are more permeable than normal human skin. These observations were partly explained due to the lower levels of polyunsaturated fatty acids, such as docosahexaenoic acid (DHA), found in the epidermal phospholipids of the skin model. In this study, we investigated the impact of a supplementation of the culture media with DHA on the barrier function of a reconstructed skin model. To this end, tissue-engineered human skin substitutes were produced according to the self-assembly method using culture media supplemented with 10 mM DHA and compared with their respective counterparts. The skin substitutes produced with or without DHA presented similar skin morphology, as they both displayed a differentiated epidermis. Moreover, the supplementation with DHA did not influence the skin substitute thickness. Percutaneous absorption of testosterone assayed using a Franz cell diffusion system was significantly decreased in skin substitutes produced with DHA, showing that addition of DHA into the culture media can affect skin impermeability in vitro. The incorporation of DHA into the phospholipid fraction of the epidermis was evaluated using gas chromatography analyses. According to these analyses, higher levels of DHA were measured in the epidermal phospholipids of the skin substitutes compared to the successful incorporation of eicosapentaenoic acid. Furthermore, retroconversion of DHA was measured in the epidermis after DHA supplementation. Taken together, these results showed that the addition of DHA into the culture media modulates the lipid profile of the skin models, leading to an improved skin barrier function.

Heterochromatin maintenance is crucial for terminal keratinocyte differentiation and inhibition of inflammatory responses in the epidermis

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Decreased skin barrier function may aggravate or even initiate psoriasis, and aiding barrier reestablishment using emollients helps improve the psoriatic symptoms, but the mechanisms for these changes have remained unclear. Herein, we showed that epidermal homoeostasis and inflammatory responses were disturbed in psoriasis and that Flg-deficient psoriasis mouse model exhibited severer psoriasis-like inflammation when treated with IMQ. In turn, topical application with a barrier reestablishment agent, such as emollients, rescued the epidermal barrier injury and skin inflammation. Moreover, silencing NLRC4 also markedly reduces the psoriasis-like inflammation in vivo. Through RNA-seq and ChIP-seq analyses we show that the epidermis from Flg-deficient mice over-expresses the pattern recognition receptor FPR1, activating which will up-regulate NLRC4, IL1B, IL1F, and other immune-related genes. In in vitro experiments, we further show that UnK regulates the PRR-ER stress pathway to modulate NLRC4 expression and activation, thus contributing to the immune responses of keratinocytes. Importantly, FPR1 antagonist also attenuates the skin symptoms and normalizes the barrier dysfunction in Flg-deficiency mouse skin. Taken together, these findings suggest that FPR1 antagonists aggravate inflammation by activating FPR1-ER stress-NLRC4 in keratinocytes, which is responsible for the feed-forward amplification of inflammatory responses in psoriasis. This work identifies FPR1 or NLRC4 as a novel potential therapeutic target for psoriasis and other inflammatory skin diseases involving the skin-barrier homoeostasis.