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Sebum, Inflammasomes and the Skin: current concepts and future perspective

Anne O. Oyewole and Mark A. Birch-Machin

Dermatological Sciences, Institute of Cellular Medicine, Newcastle University, UK

Corresponding author: Prof Mark A Birch-Machin, Dermatological Sciences, Institute of Cellular Medicine, Medical School, Framlington Place, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK, Tel: +44 191 222 5841, [Email: m.a.birch-machin@ncl.ac.uk](mailto:m.a.birch-machin@ncl.ac.uk)

Abstract

Increasing evidence has identified ultraviolet radiation (UVR) as the skin's most potent mutagen as over exposure results in sunburn, inflammation and DNA damage, thus contributing to a photo-ageing phenotype and possibly skin carcinogenesis.

The lipid-rich sebum secreted onto the surface of the skin plays an important physiological role in protecting the skin against external challenges. When skin is photosensitised by UVR, the lipid constituents of sebum are easily oxidised, generating several lipid photo-oxidative products (e.g. squalene peroxides). These photo-oxidative products have been shown to exert diverse toxicological, biological and immunological effects in the skin and have therefore been implicated in several detrimental skin alterations including premature skin ageing. The involvement of lipid peroxidation products in UVR-induced inflammatory responses has been inadequately studied and highly controversial. Furthermore, it is unclear to what extent these oxidative products contribute to the underlying mechanisms of skin photo-ageing. Therefore, this viewpoint essay will discuss the current knowledge on the effect of UVR exposure on skin surface lipids and how these may mediate UVR-induced inflammatory responses which may be key contributors to photo-damage in skin. This essay will also examine the potential role of inflammasomes (innate immune complexes) in the inflammatory response associated with UVR-induced lipid peroxidation. Limited evidence is available on the interactions between sebaceous lipids, downstream mediators and concomitant immune response in sun exposed skin and clearer elucidation may lead to novel biomarkers of photo-ageing and the incorporation of new molecules into current skin therapies which better target oxidised lipids and or downstream mediators/pathways.

Introduction

Sebum

Sebum is a highly specific mixture composed of lipids (1, 2) and plays an important physiological role in protecting the skin against external challenges such as pathogenic organisms, whilst also preventing water loss and facilitating the transport of antioxidants (e.g. vitamin E) to the surface of the skin (3-5). The individual components which characterise sebum include squalene, wax esters, free fatty acids, cholesterol esters and triglycerides (1). The synthesis and excretion of this heterogeneous mixture is thought to take approximately 1 week and pronounced sebum levels are correlated with developmental periods in life, for example adolescence (6, 7). The tight regulation of sebum has been shown to be important in protecting the skin; however an unbalance can have detrimental consequences (8-10). For example, an overproduction of sebum can lead to acne and other skin diseases, in contrast insufficient production and secretion can result in coarse, dry, cracked skin (8-11). The production of human "native" intracellular sebum, is accompanied by the colonisation and expression of microorganisms and xenobiotic, which in addition to oxygen, modify sebum prior to its secretion onto the surface of the skin (12, 13). This controlled modifications process reduces the reactivity of components of sebum and inhibits the growth of certain pathogens (13, 14), however there is clear evidence strongly supporting the premise that the absorption of UVR can further provoke structural modification of lipids (Figure 1) on the surface of the skin resulting in cellular damage via UVR-mediated lipid peroxidation (15-19).

Immunomodulatory effects of UVR-induced oxidised sebaceous lipids in skin

The photochemical reaction involving UVR and sebum has been shown by numerous investigators to induce the synthesis of several lipid photo-oxidative products such as squalene peroxides (e.g. squalene monohydroperoxide) (15-18, 20, 21). Oxidative degradation of squalene (the most abundant oxidisable component of sebum) has been shown to exert diverse toxicological, biological and immunological effects in the skin (5, 10, 12, 19). In a recent study, investigating the immunomodulatory effects of sebum on T cells, de Jong *et al.* (22) reported the ability of sebaceous lipids, in particular squalene to influence the activity of these inflammatory cells. These observation imply sebum may play a crucial role in regulating the inflammatory response in skin, and the authors propose a model whereby the breach of the skin barrier or trauma to this organ, could lead to the penetration of lipids deeper into the skin tissue, resulting in the activation of T cells through antigenicity (22).

Earlier work by Ryu and colleagues (2009) demonstrating the ability of UVR to promote squalene peroxidation through the generation of singlet oxygen, also found that keratinocytes treated with squalene peroxide exhibited enhanced secretory levels of prostaglandin E₂ (PGE₂). The authors also observed epidermal thickening and increased melanogenesis (e.g. hyperpigmentation) upon the application of squalene peroxide onto guinea pig skin. Further investigation using a cultured human epidermal melanocyte model revealed that increased melanogenesis was not a direct consequence of squalene peroxide topical application but rather likely to be mediated through the increased release of inflammatory mediators such as PGE₂ from keratinocytes which stimulate melanin synthesis (21). In a study conducted by Kostyuk *et al.* (16), the authors demonstrated that the constituents of sebum such as vitamin E (α -tocopherol) and squalene were dose-dependently degraded by UVR (16). Furthermore the authors observed that oxidised squalene derivatives extracted from sebum (collected from healthy volunteers), that was irradiated prior to application to a cultured skin model (consisting of human primary keratinocytes) mediated a significant ($P < 0.05$) increase in the mRNA (messenger ribonucleic acid) expression levels of inflammatory cytokines and receptors including IL-6, IL-8, TNF- α and IL-1R1 (16). It has long been known that lipids such as eicosanoids can potentiate inflammatory dysregulation (23), however mounting evidence now appears to show that photo-oxidised sebaceous lipids could also be involved in the mechanism underpinning the inflammatory response in skin and therefore could be a novel biomarker of photo-damage. Furthermore, the approach undertaken by investigators such as Capitanio *et al.* (10), de Jong *et al.* (22) and Kostyuk *et al.* (16) has highlighted the importance of identifying the inflammatory cytokines and receptors which may be involved in the downstream inflammatory cascade, which may directly or indirectly promote protein damage and apoptosis leading to premature skin ageing.

Potential role of Inflammasomes in UVR-induced oxidised sebaceous lipid mediated inflammation

Cellular insults are recognised by the body through the innate immune system which initiates an immediate, non-specific response against adverse physiological and pathological conditions (24-26). Inflammasomes are intracellular multiprotein complexes that form part of the skin's immune defence (24, 25, 27-33). The inflammasome is an essential entity for the induction of the inflammatory process and consists of 3 main components; the central effector protein procaspase-1, NLR protein and the adaptor apoptosis-associated speck-like protein containing a CARD (ASC) (Figure 2). Inflammasomes have been shown to play an important role in the induction of inflammatory mediators such as IL-1 β (28, 29) and these

mediators consequently activate a cascade of biological events including apoptosis and inflammation. To date investigators have identified several inflammasome complexes including; NALP1 (also known as NLRP1), NALP3 (also known as NLRP3) and NALP4 (also known as NLRC4 or IPAF) (24, 25). Among all the NLRs inflammasomes reported, NALP3 is the most studied and best characterised. Evidence appears to point to the involvement of both NALP1 and 3 in the production and secretion of pro-inflammatory mediators in the skin in response to UVR damage (26, 27, 29, 30, 32, 34). The mechanisms implicated in the activation of these molecular platforms that integrate cellular signals and promote the production of inflammatory mediators are proposed to involve the detection of a cornucopia of 'danger' signals including pathogenic signatures or stress signals (e.g. ROS and skin irritants) which activate the structural organisation of the inflammasome complex (26, 30, 32, 34-41). To the best of our knowledge, it has yet to be established whether oxidised sebaceous lipids are recognisable danger signals which are able to orchestrate the assembly of inflammasomes, and thus mediate the inflammatory process.

The propagation of the inflammatory response, in particular the involvement of oxidised sebaceous lipids and inflammasomes has been widely studied in skin disorders including acne (10, 42), however much of the research up to now has not focused on normal skin, acutely or chronically exposed to sunlight. Inflammasomes play an essential role in the skins first line of defence against harmful environmental stimuli, and there is substantial evidence demonstrating the ability of NALP3 to regulate the inflammatory response against UVR. However, the excessive up-regulation of cytokine mediators and enhanced activation and recruitment of inflammatory cells could potentially cause damage to healthy skin tissue and also contribute to the underlying pathology of skin diseases such as acne. Thus, it is important to establish whether sebum (and subsequent modification of its constituents by UVR), plays a pivotal role in the development and progression of photo-oxidative skin damage via an inflammasome dependent pathway. Another avenue which also warrants further investigation, is the ability of squalene to cross-talk with the adaptive immune response through the direct activation of T cells, as recently described by de Jong (22). Further analysis of oxidised skin lipids, and their interactions with the immune system, will undoubtedly help to uncover the pathways that may lead to skin photo-damage as well as novel targets which can be harnessed for therapeutic treatments.

Paradox of oxidized sebaceous lipids

The compelling evidence provided by Capitanio *et al.* (10), Ryu *et al.* (21) and others (16, 18) appears to demonstrate the potential role of sebum as an exogenous photosensitiser, which further develops our current understanding and also implicates sebum in skin

alteration/ageing mediated by UVR. However, the induction of inflammatory lipid mediators, cytokines, and receptors at sites of exposure may also reflect the importance of oxidised lipids as an important biological mediator in orchestrating events crucial for a defensive strategy. Kostyuk and colleagues (2012) propose that oxidised squalene derivatives at low level may act as endogenous signalling molecules to initiate a protective and immunological response against UVR. Chronic UVR exposure however, may result in heightened levels of these reactive by-products leading to excessive inflammatory mediators ensuing prolonged inflammatory reaction. The existing accounts fail to resolve the contradiction between the role of sebaceous oxidised lipids in contributing to the host defence and propagating skin damage. We therefore propose a paradoxical hypothesis whereby sebaceous lipids upon oxidation by UVR play a positive role in the skins defence through contributing to the immediate regulation of specific mediators. The relationship during excessive exposure (e.g. prolonged or intense) perturbs the immunomodulatory impact of these oxidised lipids resulting in tissue damage through unremitting inflammation. Addressing the biological role of human sebum (in particular squalene) and its peroxidised derivatives products are warranted. There is currently a deficiency in recent data being published on this area; therefore an extensive more systematic research approach will enable us to draw clearer inferences on the involvement of these reactive lipid products in the initiation and progression of ageing and pathological conditions.

Conclusion and future perspectives

UVR is associated with the decomposition of sebaceous lipids, increased formation of ROS, antioxidant depletion and dysregulation of cytokine production (by both the innate and adaptive immune cells) which collectively perturb skin homeostasis and promote skin damage. Although studied and analysed extensively in immune cells such as macrophages and langerhans cells, many NLR inflammasome complexes, also expressed in human epithelial tissue such as the skin have not received as much attention. Growing evidence has identified that the skin contains components of inflammasomes and also produces and secretes pro-inflammatory markers. Inflammasomes have been shown to be a vital immune complex in the initiation of the innate immunological response and may also act as an early biomarker for photo-damage in skin. Furthermore, inflammasomes are able to regulate the expression levels of key cytokine mediators which promote pro-survival signalling mechanisms including apoptosis, cellular repair and recruitment of DNA repair machinery. Further work is still required to fully elucidate the possible molecular mechanism involved in oxidised lipid mediated inflammasome formation as a consequence of cellular stress/injury. This may provide research tools to investigate further, the physiological function of NLRs

and may also enable greater protective strategies to be developed in order to minimise the phototoxic effects of UVR induced lipid peroxidation (in sebum) and the associated photo-damage.

The effect of UVR exposure on sebum and its constitutive lipids, and how these may mediate UVR-induced inflammatory responses has been inadequately studied in normal sun exposed skin and highly controversial. Cutaneous lipids are acknowledged as playing an integral role in the skin defence and there is compelling evidence demonstrating the protective effects of sebum in skin. Nevertheless it appears that sebum may have a dual role; firstly as ROS scavenger (due to its antioxidative properties) and secondly as inflammatory mediator. Whether the latter role modulates skin photo-damage requires further investigation as to date little or no work has been conducted in sun exposed skin. It is highly necessary that previous work is built upon using current technology in order to improve our understanding. For example, in 1999 Chiba *et al.* (20) reported that squalene-monohydroperoxide but not squalene-monohydroxide induced skin damage in hairless mice. It would be highly interesting to identify in human skin which oxidised lipid by-products are central regulators, converting skin stress signals into an inflammatory response. Physiological skin models (e.g. skin equivalent model) are useful tools that should be employed in future work, in order to close the gap in knowledge regarding the role and effect of lipid by-products at sub epidermal and dermal layers as currently the majority of the data generated are derived from 2-dimensional skin (keratinocyte) culture models or animal models.

Despite the identification of the pivotal role of inflammasomes in skin homeostasis, it has yet to be established, firstly whether oxidised lipids are able to instigate the assembly of these immune complexes. Secondly, the specific cell type in which this assembly may occur requires further evaluation. The ability of inflammasomes to influence the inflammatory response in acne has been investigated by Kistowska and colleagues (42). The authors observed that *P. acnes* selectively induced inflammasome activation in myeloid cells. The authors showed that IL-1 β secreted from myeloid cells in a NLRP3 inflammasome-dependent manner, was responsible for the induction of a neutrophilic inflammatory response *in vivo*. The evidence provided by Kistowska *et al.* along with work presented by Capitanio *et al.* showing that acne patients had significantly higher levels of oxidised squalene in their sebum (10) is interesting, as phototherapy is a mode of treatment used in some cases of acne and other skin disorders such as psoriasis and eczema. The etiology of acne, psoriasis and eczema are complicated, involving the complex interplay between environmental stimuli, cell types, cytokine mediators, receptors and their regulators. Current methodologies should therefore be applied to study the reduction of squalene in acne and other skin conditions by phototherapy treatment. Furthermore, the UVR absorption spectrum

of sebum should be measured, as it is possible that the oxidative degradation of sebaceous lipids occurs at a specific wavelength. Due to the complexity of skin diseases, differential cellular targets and varying responses to treatment in patients, the development of new therapeutic treatments is always paramount. Capitanio *et al.* (10) recently demonstrated the ability of the topical acne treatment Retinsphere (combination of retinoid and vitamin E), to effectively retard squalene oxidation and show clinical improvements in acne. Other investigators have also reported the beneficial effect of sunscreen (43) and Astaxanthin (a carotenoid, with antioxidative properties) (44) to ameliorate UVR-induced skin damage by significantly decreasing the recruitment of dendritic cells, facilitating the suppression of mediators (such as PGE₂ and IL-1β) that drive inflammation.

Collectively the findings highlight the need for further investigative work to be conducted into the ability of oxidised lipids to interact with inflammasomes and mediate inflammation. The full elucidation of the extensive crosstalk and interactions between mediators and concomitant immune response; the diverse biochemical and molecular events involved at different cellular levels, may lead us to better understand the contribution of these reactive by-products to the skins defence and photo-damage. New molecular insights may enable novel biomarkers of photo-damage to be developed as well as improved therapeutic strategies which better target oxidised lipids and or downstream mediators/pathways involved in photo-ageing.

Author contribution

Dr Anne Oyewole wrote the paper and Prof Mark Birch-Machin contributed to writing the paper and is senior author.

Conflict of interest

The authors have declared no conflicting interests.

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Figure 1

Figure 1. Chemical structures of squalene and oxidised by-products

Structural alteration of squalene, (the most predominate and easily oxidised component of sebum) by UVR stimulates formation of squalene photo-oxidation products (e.g. squalene epoxide) (19).

Figure 2

Figure 2. Mechanism of NALP3 Inflammasome Activation

A plethora of stimuli such as UVR, ROS, endogenous signals and potentially oxidised sebaceous lipids activate the NLR member protein NALP3, resulting in the formation of an inflammasome complex. The assembled complex consists of NALP3, ASC and pro-caspase 1 connected through N-terminal interactive motifs (PYD or CARD) and modulates the induction of caspase 1 which consequently generates pro-inflammatory cytokines such as IL-1. Secretion of these cytokines induces inflammation.