Role of sebaceous glands in inflammatory dermatoses

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Skin is an important interface between the host and its environment. Inflammatory dermatoses often have disrupted skin barrier function, rendering patients more susceptible to allergenic triggers leading to an exaggerated immune response. The skin surface lipid film, an important component of the skin barrier, comprises a mixture of keratinocyte and sebaceous gland–derived lipids. Recent evidence demonstrated that defective keratinocyte lipid synthesis predisposes for the development of atopic dermatitis. However, the important role of sebaceous gland–derived lipids in skin inflammatory diseases may be underrecognized. This overview focuses on the importance of the contribution of sebaceous glands to barrier function. Sebaceous gland alteration may play a role in the pathogenesis of common skin diseases including acne vulgaris, atopic dermatitis, psoriasis, rosacea, and seborrheic dermatitis. (J Am Acad Dermatol 2015;73:856-63.)

Key words: acne; atopic dermatitis; eczema; psoriasis; rosacea; sebocytes; seborrheic dermatitis; sebum.

INTRODUCTION

Skin barrier and dysfunction

Skin provides a vital barrier against a harsh external environment and its barrier plays a critical role in modulation of skin permeability and hydration. Disruption of the skin barrier is characterized by increased skin pH and transepidermal water loss, and decreased epidermal hydration, and is associated with the development of inflammatory skin diseases such as atopic dermatitis (AD).[1]

The skin surface lipid film is composed of both sebocyte- and keratinocyte-derived lipids. Sebocyte lipids are synthesized by sebaceous glands and secreted to the surface of the stratum corneum. Keratinocyte lipids are synthesized by keratinocytes and incorporated within the layers of stratum corneum. The pathogenesis of inflammatory skin conditions caused by keratinocyte lipid defects has been intensely studied.[2-5] However, limited data exist regarding the role of sebaceous gland lipids and this review focuses on their role in the pathogenesis of common inflammatory dermatoses including acne, AD, rosacea, seborrheic dermatitis, and psoriasis.

Sebaceous glands

Sebaceous glands are holocrine glands that secrete via disintegration of the glandular cells into the upper portion of the hair follicles, which is then distributed onto the skin surface. Widely distributed in all areas except for palms, soles, and back of feet,[6] sebaceous gland are most concentrated on the face (especially the T-zone), followed by the back and chest.[6] The number and activity of sebaceous glands differ by anatomic location, age, and gender. Sebaceous gland function is responsive to stimulation by sex hormones and adrenal corticosteroids.[7] Recent data demonstrated that skin treated with α-bungarotoxin, an acetylcholine receptor antagonist, has markedly decreased sebum production and pore sizes, suggesting that local neuronal stimulation may regulate sebaceous function.[8]

Sebaceous gland lipid composition and function

The composition of sebum differs from keratinocyte lipids. Keratinocyte lipid composition is 65% triglycerides and free fatty acids, and 20% cholesterol whereas sebum lipid composition has been reported

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to be 57% triglycerides and free fatty acids, 26% wax esters, 12% squalene, and only 2% cholesterol.[9] Within the pilosebaceous glands, sebum is composed of squalene, wax esters, and triglycerides. Once secreted onto skin surface, bacterial and yeast lipases hydrolyze triglycerides into free fatty acids.[10] Squalene, characteristically found in sebum, is used as a marker to distinguish sebaceous from keratinocyte lipids.[9] Interestingly, sebaceous glands lack enzymes for squalene to cholesterol conversion,[6,9] therefore cholesterols isolated from sebum presumably originate from the epidermis rather than sebaceous glands.[6,9,11]

Sebum lubricates the skin and hair to protect against friction and trap moisture.[12] Sebum also acts as a delivery system for antimicrobial lipids[13,14] and antioxidants,[10,15] along with the generation of pheromones and body odor.[16] Antioxidants are delivered to the skin surface through sebum in the form of squalene, coenzyme Q10, and vitamin E.[15,17,18]

CAPSULE SUMMARY

- Sebaceous glands contribute to the skin surface lipids.
- Sebaceous lipid barrier perturbation may be a significant contributor to pathogenesis of acne vulgaris, atopic dermatitis, psoriasis, rosacea, and seborrheic dermatitis.
- Further research into the sebaceous gland contribution to skin surface lipids may uncover new therapeutic strategies for treating inflammatory dermatoses.

Sebum measurement

Several devices are available for measurement of skin biophysical properties related to sebum. Sebutape (CuDerm Corp, Dallas, TX), Sebufix (Courage+Khazaka electronic GmbH, Cologne, Germany), and Sebumeter (Courage+Khazaka electronic GmbH, Cologne, Germany) are now the most commonly used devices for sebum collection and measurement. Historic and recent advances in sebum measurements are summarized in Table I.[19-26]

SEBACEOUS GLAND–DERIVED LIPIDS IN INFLAMMATORY DERMATOSES

Acne vulgaris

Acne vulgaris is the most common inflammatory skin condition that affects up to 85% of adolescents, and frequently persists into adulthood.[27] The pathogenesis is multifactorial and includes sebaceous gland overactivity. Acne starts in early puberty, and parallels increased sebaceous production stimulated by rising androgen levels. Sebaceous gland function in acne is influenced by multiple hormones including androgens, corticotropin-releasing hormone,[28] vitamin D,[29] and insulin-like growth factor 1.[30] Lesional sebaceous gland have enhanced expression of 11-β-hydroxysteroid dehydrogenase type I, which converts cortisone into cortisol and plays a role in steroid and stress-related acne by modulating glucocorticoid-induced lipid synthesis.[31]

Because sebum excretion rate correlates with acne severity[32] and predicts acne outcome,[33] sebum hypersecretion was believed to be the main sebaceous disruption in acne.[34] However, the pathogenesis is likely more complex with data suggesting an abnormal sebum lipid composition. Skin surface lipids of patients with acne have low linoleate (C18:2) levels, whereas high levels prevent comedogenesis.[35] Squalene also appears important as subjects with acne have elevated levels of squalene.[36] Oxidized squalene induces the release of inflammatory cytokines in cultured keratinocytes[37] and leads to comedogenesis on rabbit ear skin.[38] Colonizing *Propionibacterium acnes* metabolize sebaceous triglycerides into free fatty acid on the skin surface, and the density of *P acnes* increases with increased sebum excretion rate.[39] Further research will be needed to understand how the local microflora and the lipid profiles modulate the composition of the other and how this may contribute in the pathogenesis of acne.

The clinical improvement in patients with acne treated with isotretinoin (13-*cis*-retinoid acid) and spironolactone is linked to their sebostatic effects. With isotretinoin treatment, profound dose-dependent reduction in sebum excretion rate and free fatty acid production rate are seen by 2 to 4 weeks of treatment.[40,41] Maximum glandular inhibition is achieved by 5 to 6 weeks[40] and maintained throughout the 16-week treatment course.[40,41] Pilosebaceous unit atrophy is observed within 3 weeks of treatment,[42] and is characterized by marked reduction in sebaceous gland alveoli size.[43] By 12 to 16 weeks, sebaceous gland size is markedly decreased to 90% of pretreatment value[42] and reduces the relative amount of squalene and wax esters in the skin surface lipids.[44] Interestingly, the use of isotretinoin in the treatment of acne leads to a high rate of cheilitis and dry skin,[45,46] further supporting the role of sebaceous gland hypofunction in the development of dry skin and dermatitis.

Spironolactone is a synthetic antiandrogenic agent. Despite its common use for hormonal acne, there are few clinical studies on the use of