
The relevance of sebum composition in the etiopathogeny of acne

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ABSTRACT

Acne vulgaris is an inflammatory disease that develops around the hair follicle. Many are the interconnected etiopathogenic factors involved, among which we can mention the increase in levels of androgen hormones, sebum hypersecretion, follicular hyperkeratosis with microcomedo formation, the proliferation of the bacteria *Propionibacterium acnes* (*P. acnes*) and the resulting inflammatory response. The way this bacterial growth occurs and how it is connected with the development of the inflammatory process have been themes of many clinical and experimental trials. Modifications in the sebum composition lead to a greater proliferation and differentiation of keratinocytes that obstruct the follicular ostium and favor the formation of comedones. On the other hand, these modifications alter the follicular hydration and facilitate the proliferation of the *P. acnes*, which not only produces chemotactic factors but also releases lipase that oxidizes the squalene. The oxidized squalene induces the formation of pro-inflammatory cytokines and boosts the innate immunity of keratinocytes and sebocytes, thus

generating the inflammatory process. The aim of this study was to review the literature regarding the new concepts on the pathogenesis of acne.

Keywords: Acne; Sebum composition; Review.

1. INTRODUCTION

Acne vulgaris, with its many etiopathogenic factors involved, is a primary inflammatory pathology of the skin [1]. The induction of the inflammatory signaling in the pilosebaceous unit is an essential component in the developing process of the lesions [2, 3]. It commonly starts during puberty with the increase of androgen production, resulting in the increase of sebum production. The overproduction of the latter, associated with the abnormal shedding of keratinocytes, lead to the obstruction of the follicle opening and the formation of microcomedones [4].

The sebum accumulation in the follicular infundibulum stimulates the proliferation of the Gram-positive bacteria *Propionibacterium acnes* (*P. acnes*) in genetically predisposed individuals [5]. This increase in the bacterial population leads to the

release of not only cytokines such as interleukins IL-6 and IL-8 by the infundibular keratinocytes, but also IL-8, IL-12 and pro-inflammatory mediators by the macrophages, resulting in the development of the inflammation in the follicle and in the adjacent dermis [3].

Therefore, the key factors involved in the pathogenesis of acne are classically established as follows:

- (1) increase in levels of androgen hormones,
- (2) sebum hypersecretion,
- (3) follicular hyperkeratosis with microcomedo formation,
- (4) the proliferation of the bacteria *Propionibacterium acnes* (*P. acnes*), and
- (5) the resulting inflammatory response [4, 5].

The way this bacterial growth occurs and how it is connected with the development of the inflammatory process have been themes of many clinical and experimental trials, which have revealed the relation of the production of pro-inflammatory cytokines by the sebocytes and keratinocytes with the quantitative and qualitative variations of the lipid content of the sebum caused by the *P. acnes* in particular [3-6]. Some studies suggest that the deregulation in the sebum production along with the alterations in its composition play an essential role in the abnormal follicular proliferation and in the development of the inflammation that triggers comedonal lesions [7, 8].

Thus, the aim of this study was to review the literature regarding the new concepts on the pathogenesis of acne.

2. THE ROLE OF SEBUM IN THE PROLIFERATION OF *P. ACNES*

Human sebum is a holocrine secretion formed by the disintegration of sebocytes. It is composed of a nonpolar mixture which contains triglycerides (41%), free fatty acids (16%), squalene (12%), monoester waxes (25%), cholesterol ester and free cholesterol (4%) and vitamin E [6, 9]. Squalene participates in the antioxidant defense system of the skin by suppressing oxidized free radicals. Furthermore, it plays an important role not only in anti-inflammatory actions but also in the development of acne [10, 11].

On the cutaneous surface microorganisms and

oxygen transform the sebum produced by the glands. In normal skin, through the lysis of triglycerides, the formation of fatty acids occurs. The linoleic acid is one of them, which besides being the main constituent of acyl-glucosylceramides, acylceramides and acyclic lipids also contributes to the stratum corneum hydration and the integrity of the cutaneous barrier [10, 11]. Sebum lipids also promote photoprotection, especially against UVB irradiation, and they have lipophilic antioxidants. Linoleic acid is also directly related to the synthesis of squalene and monoester waxes [6, 9, 12]. Cutaneous surface lipids, especially those secreted by the sebaceous glands and transported through the follicular duct, are part of the skin innate immunity and contribute to the antimicrobial skin barrier, thus limiting bacterial colonization [6].

Recent studies have revealed that in patients with acne the amount of linoleic acid in the sebum is reduced, affecting the composition of sphingolipids in the follicle, which is associated with the increase in concentration of the sebaleic acid and squalene [12]. The greater permeability of the stratum corneum, resultant from the reduction in the linoleic acid levels and the consequent reduction in the sphingolipid generation, increases follicular hydration, which allows for the proliferation of the *P. acnes* in the comedo. In turn, it generates lipase, which plays an important role in the alteration of the lipid composition of the sebum [5, 13].

3. MODIFICATION OF THE SEBUM COMPOSITION AND THE INFLAMMATION

It has been demonstrated that, besides hyperseborrhea, lipid peroxidation and alterations in the lipid composition of the sebum, which are caused by the proliferation of the *P. acnes* and defined as disseborrhea, are essential etiopathogenic factors in the acne process. Such factors play a key role in the induction of the inflammation and in comedogenesis [14]. Moreover, low levels of linoleic acid also lead to an alteration in the cutaneous barrier function due to the increase in the permeability of the comedo wall to inflammatory substances [3].

The accumulation of peroxidized lipids, especially peroxidized squalene, can induce the production of the pro-inflammatory cytokines IL-1 α , IL-6 and IL-8 as well as the activation of

peroxisome proliferator-activated receptors (PPARs), which are nuclear transcription factors involved in the control of lipid metabolism and the control of the inflammation [9, 15, 16]. This accumulation in the comedones is positively correlated to the grading of acne severity [17, 18].

Keratinocytes and sebocytes also act as immune active cells since innate immunity molecules, like toll-like receptors TLR-2 and TLR-4, CD1 and CD14, are expressed in human keratino-

cytes. Besides, antimicrobial peptides, like defensin 1, defensin 2 and cathelicidin, are also expressed and they can be activated in the sebaceous gland. Such molecules can be activated by the *P. acnes* and by the altered lipid content in the sebum, thus producing pro-inflammatory cytokines through the activation of nuclear transcription factor (NF), which, in turn, can induce lipogenesis (Figure 1) [3, 7].

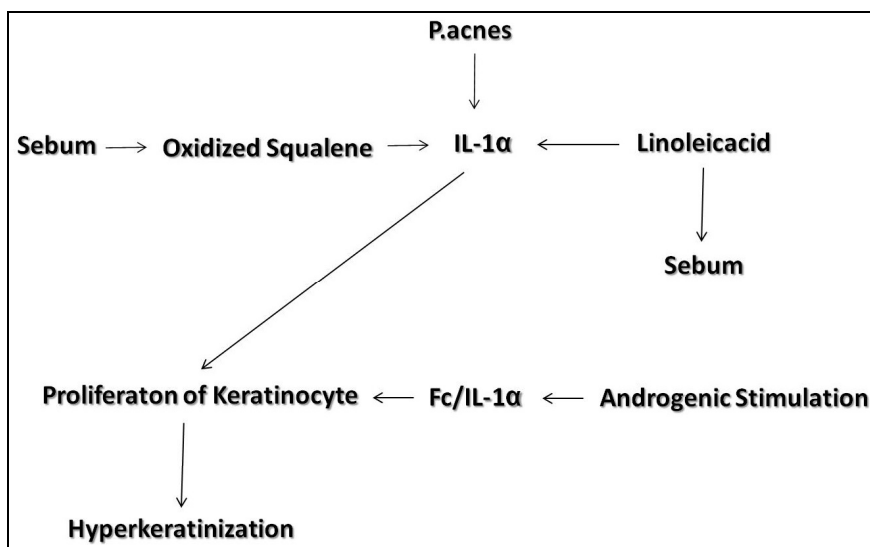


Figure 1. Representative scheme of the triggering of the inflammatory process. Adapted from Reynolds [7].

Prostaglandins are other pro-inflammatory mediators thought to be involved in the acne lesion development [19]. Studies conducted with rats revealed that the increase in the expressions of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) induces hyperplasia of the sebum glands and an increase in sebum production [20].

Other studies have also shown the relation between the modifications in the sebum composition due to oxidation and the progression of the inflammatory condition. The concentration of peroxidized lipids and IL-1 α is significantly higher in the comedones when compared with the concentration in the stratum corneum, which is determined/explained by the proliferation of the existing bacterial flora and the *P. acnes* in the comedo. Such proliferation leads to the rupture of the glandular wall with the propagation of the inflammatory reaction in the dermis and in the dermal vascular component/network. *P. acnes* stimulates the secre-

tion of the comedogenic cytokine IL1- α , which, besides playing a critical role in the pathogenesis of acne, also stimulates vascular endothelial cells to produce inflammatory markers [8, 9, 20], thus aggravating the clinical condition.

4. MODIFICATION OF THE SEBUM AND FOLLICULAR HYPERKERATOSIS

Recent studies have shown that the amount of linoleic acid in the sebum is reduced in patients with acne, thus affecting the composition of the sphingolipids in the follicle [9, 12, 14]. The abnormal distribution of fatty acids affects the proliferation and differentiation of keratinocytes, with the resultant development of follicular hyperkeratosis and the comedo [12].

On the other hand, the relation between oxidized lipids and antioxidants on the surface of the skin has been considered of extreme importance in

the etiopathogenesis of the acne. Some components of this complex mixture of molecules are clearly cytotoxic or irritating, and they cause a reactive follicular hyperkeratosis. Again, the accumulation of peroxidized lipids, especially peroxidized squalene, can induce not only the production of pro-inflammatory cytokines but also the activation of PPARs. The enzymes involved in the expression/formation of the PAARs, including 5-LOX, have been related to inflammatory disease of the skin characterized by the hyperproliferation of keratino-

cytes [3, 7, 10].

Therefore, the inflammatory process triggered by lipid peroxidation seems to be the promoting factor of abnormal keratinization and comedogenesis [19]. Some studies in animals show that peroxidized squalene induces epithelial hyperkeratosis in the follicular infundibulum and sebaceous hyperplasia in the ears of rats and rabbits [21, 22]. Furthermore, patients with acne have increased levels of IL-1 α in the stratum corneum, with higher concentrations in comedogenic areas (Figure 2) [18].

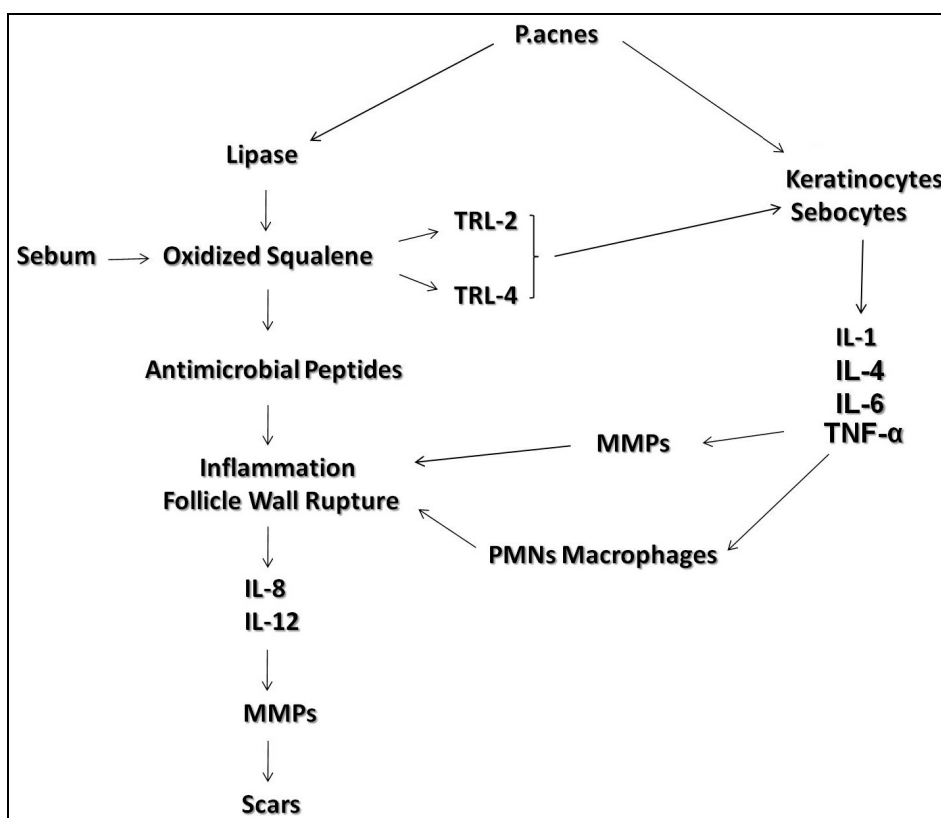


Figure 2. Representative scheme of the process of hyperkeratinization.

5. CONCLUSION

The linoleic acid reduction promotes a greater proliferation and differentiation of keratinocytes that obstruct the follicular ostium and favor the formation of comedones. On the other hand, this reduction alters the follicular hydration and facilitates the proliferation of the *P. acnes*, which not only produces chemotactic factors but also releases lipase that oxidizes the squalene. The oxidized squalene induces the formation of pro-inflammatory cytokines and boosts the innate immu-

nity of keratinocytes and sebocytes, thus generating the inflammatory process.

In conclusion, through many distinct mechanisms, the resulting compounds of sebum oxidation play a fundamental role both in the pathogenesis as well as in the maintenance of the inflammatory process of the acne.

AUTHORS' CONTRIBUTION

MGC: Conception and design, Development of methodology, Acquisition of data, Administrative,

technical, or material support. FD: Acquisition of data, Analysis and interpretation of data, Administrative, technical, or material support. CDAMF: Acquisition of data. GLV: Writing, review and/or revision of the manuscript. FF: Study supervision, Analysis and interpretation of data, Writing, review and/or revision of the manuscript. The final manuscript has been approved by all authors.

TRANSPARENCY DECLARATION

The authors declare that there is no conflict of interest regarding the publication of this article.

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