

## **Review of Clinical Factors That Cause Acne Vulgaris**

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### **Abstract**

*Acne vulgaris is a common skin disorder caused by inflammation and/or blockage of the pilosebaceous follicle. This research is a literature review study that is descriptive in nature and seeks to compile information on the factors related to the etiopathogenesis of the clinical manifestations of acne vulgaris. A survey was conducted in the Web of Science database in the period from January to May 2020, using the keywords "acne vulgaris, etiopathogenesis and pathophysiology". The etiopathogenesis of acne vulgaris is multifactorial, but most studies list the following factors: like diet, daily habits, age, genetics, abnormalities in the production of sebum, follicular hyperkeratinization, increased colonization by Cutibacterium (formerly Propionibacterium) acnes, periglandular dermal inflammation, oxidative stress and immune reactions of the patient. Topical and/or systemic treatments for acne vulgaris, often includes retinoid-associated antibiotics. However, improper use of these can lead to bacterial resistance, in addition, it may trigger adverse effects at epidermis and dermis. The results obtained in this study are important in relation to the treatment of the pathogenesis of acne vulgaris. It is believed that this information - when analyzed together - can help with a better definition of the therapeutic protocol.*

**Key-words:** skin disorder, pilosebaceous follicle, etiopathogenesis, pathophysiology.

### **Financial Support**

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

### **Introduction**

Acne vulgaris is the most prevalent skin disease in the world, affecting proximately 650 million people or about 9.4% of the population globally.<sup>1</sup>

Although acne vulgaris is the most frequent disease in young people, little has been reported about the multifactorial aspect of the pathophysiology of acne vulgaris.<sup>2-4</sup> As such, this study sought to identify

the factors related to the etiopathogenesis of the clinical manifestations of acne vulgaris through a literature review of a descriptive nature. A survey was conducted in the *Web of Science* database in the period from January to May 2020, using the keywords "*acne vulgaris, etiopathogenesis, and pathophysiology*", articles with content relevant to the topic were selected.

### **Etiopathogenesis of Acne Vulgaris**

Acne vulgaris is a severe chronic inflammatory dermatosis and it manifests in the pilosebaceous follicle.<sup>5</sup> Its etiopathogenesis is multifactorial, but research points to the following factors: like diet, daily habits, age, genetics, abnormalities in the production of sebum, increased follicular keratinization, periglandular dermal inflammation, oxidative stress, assessments of immune systems to patients and changes in the microbial skin community, which are affected by innate immunity can lead to a chronic inflammatory condition.<sup>2,6</sup> This disease affects the quality of life and has psychosocial implications for affected individual.<sup>7,8</sup> It also generates other negative effects, such as unaesthetic characteristics, edema, tissue sensitization, and in some cases, scarring.<sup>9,10</sup>

It is often treated with antibiotics like tetracycline, erythromycin, and clindamycin, which are administered topically or systemically, in association with topical medications such as benzoyl peroxide, retinoids like isotretinoin or azelaic acid, or in the form of monotherapy with antiandrogens like flutamide.<sup>11,12</sup> Therapy with these products against the acne-promoting bacteria has led to the development of resistance to antimicrobials.<sup>2,5,6</sup>

Although they produce significant effects in the treatment of acne vulgaris, they may trigger intolerable adverse effects, such as severe dryness of the mucous membranes and the skin, itching, scaling, erythema, contact dermatitis, hepatic complications, toxicity to sebocyte, increased levels of triglycerides and cholesterol and teratogenesis.<sup>3,4,12</sup>

This pathology is classified as inflammatory and non-inflammatory in accordance with the predominant lesions, and can be graded from I to V according to the severity of the condition.<sup>13</sup> Grade I acne is comedonian, non-inflammatory, it features comedones formed by the accumulation of sebum and keratin in the pilosebaceous follicle. Inflammatory acne is responsible for the grade II, III, IV and V conditions. In grade II acne, there are papular-pustulous lesions in addition to the comedones. Cysts and nodules can be found in grade III acne. Grade IV or conglobate acne is a severe form of the disease with multiple inflammatory nodules and the formation of abscesses and fistulas in the tissue. Finally, grade V acne is rare and severe, occurring abruptly and accompanied by systemic manifestations (fever, leukocytosis and arthralgia).<sup>14,15</sup>

With the severity of the condition, the skin may develop scars, causing great concern to the patient regarding the unaesthetic characteristics of the image.<sup>3</sup> Post-acne scars can be formed through a sequence of abnormal wound healing after lesions that occurs in the pilosebaceous follicle.<sup>16</sup>

Often, changes are observed in the sebum components of the skin of patients with this disease, especially in the levels of squalene and linoleic acid. Studies have reported that low concentrations of linoleic acid in the tissue influence glandular epithelial wall protection, which can then be affected by free fatty acids, obtained through the hydrolysis of triglycerides by the lipases of *Cutibacterium (formerly Probionibacterium) acnes (C. acnes)*, causing hyperkeratinization and dermal inflammation (Fig. 1).<sup>17,18</sup>

## Sebaceous Hyperactivity

In normal conditions, the activity of the sebaceous gland is of fundamental importance for transepidermal permeation. In addition to preventing desiccation of the skin's surface, lubricating the hair and forming a hydrolipidic layer in conjunction with the products secreted by the sudoriferous glands.<sup>19</sup>

Essential fatty acids play a crucial role in the pathogenesis of acne.<sup>13</sup> Linoleic acid is a natural constituent of sebum and animal model studies have shown that a significant reduction of linoleic acid concentrations in the sebum is correlated with the increase of comedogenesis.<sup>17</sup>

Individuals with acne vulgaris have lower concentrations of linoleate in the sebum, which increases the keratinization of the ductal wall and makes the comedo wall more permeable to the mediators of the inflammatory process.<sup>20</sup>

A pilot study using dietary supplementation with a total of 3 g per day of linoleic, linolenic and gamma-linolenic acids resulted in a quantitative reduction of the size of sebaceous glands, visualized by cutaneous biopsies after three consecutive months of supplementation.<sup>21</sup>

The hyperinsulinemia can directly stimulate the production of sebum, increasing androgen synthesis.<sup>17</sup>

The sebaceous glands develop and are stimulated by androgenic hormones.<sup>22</sup> Dihydrotestosterone (DHT), resulting from the local conversion of testosterone by the enzyme 5-alpha-reductase (5- $\alpha$ R), is the main androgen determining the increased production of sebum. The enzyme 5- $\alpha$ R is responsible for the conversion of testosterone into DHT, which in turn modulates sebaceous secretion. When in higher activity in the infundibular keratinocytes, it induces the greater capacity of these cells to produce active androgens, thus increasing the production of sebum.<sup>23</sup>

## Infundibular Hyperkeratinization

The primary function of the keratinocytes is to produce keratin, a fibrous protein with a three-dimensional structure conferring resistance, elasticity and impermeability to water. In normal conditions, the constant cell renewal in the epidermis causes the cells of the corneal layer to be gradually eliminated and replaced by others.<sup>24</sup>

However, follicular hyperkeratinization in the upper region of the hair follicle may contribute to the obstruction of the duct with byproducts generated in the sebaceous gland. The hydrolytic proteases produced by *C. acnes* can then act on the glandular epithelium, leading to rupture and subsequent expulsion of the sebaceous content to the dermis. With this, sebaceous lipids are injected into the dermis by *C. acnes*, and cornified epitheliocytes produce a humoral-type response, establishing the inflammation.<sup>17</sup>

## Infundibular Bacterial Colonization

Although it belongs to the normal bacterial flora of the skin and hair follicles, *C. acnes* is the main microorganism involved in the etiopathogenesis of acne vulgaris.<sup>21</sup> This bacterial hydrolyzes triglycerides, producing free fatty acids and glycerols that irritate the follicle wall induce keratinization, and the formation of comedogenic byproducts triggering an inflammatory process, which depending on the severity may form papules, pustules, nodules and cysts.<sup>17,23</sup>

*C. acnes* is able to modulate the proliferation and differentiation of keratinocytes by inducing

filaggrin and integrin expression.<sup>25</sup> Previous studies have shown a correlation between type I insulin-like growth factor (IGF-I) and the serum levels of the severity of acne in women,<sup>26</sup> and they showed that the IGF-1 levels are directly related to the quantity of sebum in the skin; the inhibition of the type I insulin-like growth factor receptor (IGF-1R) results in a reduction of the epidermis.<sup>27</sup>

Neutrophils are attracted by the presence of intrafollicular material in the dermis and phagocyte *C. acnes* without destroying it. As a consequence, the hydrolases destroy the tissue wall, and activation of the complement system occurs with the production of C5 $\alpha$ , another potent neutrophil chemotactic factor.<sup>17</sup>

### Follicular and Underlying Dermal Inflammation

The inflammation can occur both by an irritating action of the sebum, which overflows to the dermis when there is rupture of the follicular wall, and through the presence of chemotactic factors and pro-inflammatory mediators produced by *C. acnes*.<sup>27</sup> Studies on *C. acnes* have demonstrated some properties that contribute to the local inflammatory response, such as the production of enzymes that facilitate follicular rupture, the existence of surface proteins that stimulate cellular and humoral immune response, thus damaging the adjacent tissues to inflammation.<sup>17,28</sup>

The body's first line of defence against infectious diseases is the innate immune response of the organism.<sup>29</sup> *C. acnes* cooperates in the activation of this response.<sup>30</sup> The components of this bacterium can activate the toll-like receptors (TLR-2 -2).<sup>17</sup> These receptors are able to mediate the response to standard molecules associated with pathogens.<sup>31</sup>

Signs of intracellular cytokines activate monocytes and macrophages, which release the tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), interleukin-6 (IL-6), reactive oxygen species (ROS), prostaglandin eicosanoid type 2 (PGE2) and nitric oxide (NO), all inflammatory mediators (Fig. 2).<sup>29</sup> The mitogen-activated protein kinases (MAPKs) include the extracellular-signal-regulated kinases (ERKs), protein 38 (p38) and the *c-jun N-terminal kinase* (JNK). These mediators play a crucial role in regulating cellular responses to pro-inflammatory molecules.<sup>27</sup>

The main function of IL-1 $\beta$  and TNF- $\alpha$  is to trigger the innate inflammatory response and act as a co-stimulatory molecule of the immune response.<sup>32</sup> Besides, TNF- $\alpha$  also plays an essential role in the tissue remodelling process after an injury, since it acts as an angiogenic factor and fibroblast growth factor.<sup>33</sup>

The production of cytokines and inflammatory mediators, in association with the irritating effects of the elements resulting from hydrolysis through *C. acnes* action, attract inflammatory cells, which subsequently determine the rupture of the follicle through lysosomal action.<sup>34</sup> The production of cytokines by the ductal keratinocytes also seems to be relevant. Interleukin-1 alpha (IL-1 $\alpha$ ), which induces comedogenesis, is present at high levels in many comedones.<sup>23</sup>

Other mediators may be involved in hyperkeratinization.<sup>27</sup> *In vitro* models have shown the ability of the epidermal growth factor to rupture the comedo ducts, forming inflammatory acne lesions with the consequent activation of the nuclear transcription factor kappa B (NF-kB), which is important for the positive regulation of many pro-inflammatory cytokines and cell proliferation genes.<sup>35</sup>

Due to its importance in the expression of inflammatory genes, NF-kB is a target for the treatment of various inflammatory diseases, and most anti-inflammatory agents have demonstrated to block the expression of inflammatory cytokines, inhibiting the activation via NF-kB. It has been shown that the

inhibition of the production and biological activity of nitric oxide synthases (iNOS), cyclooxygenase-2 (COX-2), TNF- $\alpha$  and IL-1 $\beta$  by selective inhibitors results in significant improvements in the development of several inflammatory diseases (Fig. 3).<sup>36</sup>

As a result, TNF- $\alpha$  and IL-1 $\beta$  are activated. These primary cytokines cause inflammation, acting on endothelial cells and preparing adhesion molecules, facilitating the recruitment of all inflammatory cells in the skin. TNF- $\alpha$  and IL-1 $\beta$  can help to stimulate the proliferation of secondary cytokines, such as interleukin-8 (IL-8).<sup>37</sup>

When they are activated by microbial ligands, the TLR produce an intracellular response that can lead to the translocation of NF- $\kappa$ B, with the consequent modulation of the expression of immune response genes.<sup>35</sup>

Researchers have reported that *C. acnes* has a soluble factor, which, in the presence of lymphocyte CD14 (a marker for monocyte populations), can activate TLR-2 and TLR-4<sup>17</sup> and synthesize proinflammatory factors.<sup>31</sup>

Other studies have shown that, in response to the inflammation by *C. acnes*, human keratinocytes secrete beta-2 defensin ( $\beta$ D-2) and IL-8 and that these molecules are potent chemotactic factors of leukocytes and neutrophils infiltration, in addition to acting on the growth and differentiation potential of keratinocytes at the site of the *C. acnes* infection.<sup>38</sup> This evidence suggests that the maintenance of the inflammatory process of acne vulgaris is caused by *C. acnes*. The ideal treatment could, therefore, be a single product capable of suppressing the inflammatory response, reducing keratinization and the proliferation of *C. acnes*.<sup>11,39</sup>

### **Hormonal Influence: Adjuvant Factor in the Etiopathogenesis of Acne Vulgaris**

On the skin surface, the microbial community is mostly constituted by bacteria belonging to the three main genera of *Corynebacteria*, *Propionibacteria* and *Staphylococci*.<sup>40</sup> Interplay between members of this cutaneous microbiota at pilosebaceous unit is essential for the maintenance of a healthy skin.<sup>18</sup>

In addition to expressing androgen receptors, the sebaceous glands also have functional receptors for neuropeptides, such as the corticotropin-releasing hormone (CRH), melanocortins,  $\beta$ -endorphins, vasoactive intestinal peptides (VIP), neuropeptides  $\gamma$  (NP $\gamma$ ) and substance P. These receptors control the proliferation, differentiation and androgen metabolism of sebocytes, in addition to the production of cytokines and lipogenesis.<sup>41</sup>

DHT is the main androgen involved in the gland, positively stimulating its development and the production of sebum.<sup>42</sup> Individuals with acne vulgaris usually have increased sebaceous glands that produce more sebum than individuals with healthy skin because the conversion rate of testosterone into DHT through the action of 5- $\alpha$ R is approximately thirty times greater in affected individuals (Fig. 4). However, the increase in the production of sebum in isolation is insufficient to explain the development of acne vulgaris.<sup>43</sup> The lipid composition of the sebum plays an important role in the pathogenesis of acne.<sup>20</sup> The levels of linoleic acid in the sebum of individuals with acne are known to be lower than those of individuals not affected by the pathology.

Deficiencies in linoleic acid, squalene and androgens have been implicated as causal factors of follicular hyperkeratinization and comedogenesis.<sup>44,45</sup> Some studies, therefore, highlight the importance of

ROS as inflammatory mediators produced by phagocytes in the development of acne. Low levels of linoleic acid increase free radical production, so that superoxide dismutase (SOD) and catalase (CAT) decrease whereas xanthine oxidase (XO) and lipid peroxidation increase.<sup>46</sup>

The presence of lipoperoxides in the sebum of individuals with acne is mainly due to the peroxidation of squalene and decreased levels of vitamin E, the predominant antioxidant in the sebum.<sup>47</sup> In conjunction with monounsaturated fatty acids (MUFAs), lipoperoxides are capable of generating inflammatory reactions, which start hyperkeratinization at the acroinfundibulum level of the pilosebaceous follicle.<sup>48,49</sup>

### **Oxidative Stress in Acne Vulgaris**

In normal physiological conditions, the skin has two endogenous defence systems against oxidative stress: antioxidant enzymes (CAT, SOD and glutathione peroxidase (GPX)) and non-enzymatic molecules (vitamin E, beta-carotene, ubiquinone and reduced glutathione (GSH)).<sup>50-52</sup> However, sometimes the endogenous defence system against ROS is insufficient.<sup>53,54</sup>

When oxidizing species overcomes the skin's natural antioxidant system, the cellular redox imbalance leads to alterations in the cellular homeostasis and the generation of degenerative processes.<sup>55</sup> The oxidants produced by lipid peroxidation induce hyperkeratinization, increasing comedogenesis, forming advanced glycation end products through the formation of such byproducts as 4-hydroxy-2-nonenal and malondialdehyde (MDA), which may reticulate proteins and alter the rigidity of keratin, increasing follicular impaction. In addition, the lipid peroxides sensitize the walls of the follicles in the inflammatory response, making them more susceptible to rupture.<sup>20</sup>

The implications of the impairment of the antioxidant defence system in inflammatory skin diseases were confirmed by a study that reported that N-acetyl-L-cysteine (NAC), known as the precursor of GSH, causes a negative regulation of interleukin-4 (IL-4), interleukin-5 (IL-5) and gamma interferon (INF- $\gamma$ ) in T-helper cells type-2 (Th2), with subsequent superactivation of the response in T-helper cells type-1 (Th1). This study also revealed that NAC works as a therapeutic agent in the treatment of diseases related to Th2.<sup>56</sup>

The interaction between superoxide ( $O_2^{\cdot-}$ ) and nitric oxide (NO) leads to the formation of highly reactive peroxynitrites (ONOO $\cdot$ ). In order to revert the overproduction of ROS, the skin activates antioxidant mechanisms such as SOD, which converts  $O_2^{\cdot-}$  to hydrogen peroxide ( $H_2O_2$ ), which is converted by CAT and GPx to water,<sup>57</sup> which is partially used for bactericidal action in polymorphonuclear leukocytes (PMN).<sup>55</sup>

Two cytoplasmic enzymes, SOD and myeloperoxidase (MPO), protect the cell contents against oxidant activation.<sup>55</sup> SOD reduces both oxidative stress and the activation of inflammatory response mediators, while the GPx-GSH system performs the buffering of acute oxidative stress. The oxidative degeneration process of poly-unsaturated fatty acids known as lipid peroxidation induced by ROS leads to the formation of highly reactive aldehydes, such as MDA, which is related to damage to proteins, apoptosis or the release of pro-inflammatory mediators.<sup>58</sup>

Previous studies have reported that the sebum components, particularly squalene, show an increased comedogenicity when they are oxidized, and oxidized squalene and its metabolites are found in much higher levels in patients with acne vulgaris than in healthy controls.<sup>49</sup>

It has also been established that comedogenesis seems to be related to high levels of bioactive IL-1 $\alpha$  derived from the hyperkeratinocytes of the pilosebaceous unit.<sup>59</sup> When the oxidative damage blocks and alters the pilosebaceous unit, bacteria that colonize the site proliferate rapidly, producing toxins that irritate the skin. The immune system attacks the bacteria, and this increases the tissue inflammation exponentially.<sup>60</sup>

Other studies have revealed that acne vulgaris is mediated by the increased generation of ROS, which can be attributed to low levels of antioxidant enzymes such as CAT, SOD, and total antioxidant capacity (TAC).<sup>54</sup> Lipidic peroxidation of fatty acids and unsaturated triterpenes like squalene generates intracellular and extracellular ROS.<sup>48</sup>

The production of organic peroxides of squalene also reduces tissue levels of GSH and stimulates the production of inflammatory cytokines, positively regulating lipoxygenase (LOX) activity.<sup>49</sup> Another important discovery revealed that the activity of LOX and leukotriene B4 (LTB4) had been implicated in the promotion of inflammation in acne even in the absence of *C. acnes*. LTB4 is a chemoattractor capable of recruiting neutrophils, and its inhibition proved to reduce acne.<sup>61,62</sup>

When the keratinocytes are exposed to *C. acnes*, the surface proteins immediately generate ROS, most notably O<sub>2</sub><sup>-</sup>. SOD converts O<sub>2</sub><sup>-</sup> into H<sub>2</sub>O<sub>2</sub>, and GPx then converts it into water. In this sense, SOD and GPx may undergo an intense reduction due to the oxidative stress load in the more severe forms of acne vulgaris.<sup>55</sup>

## CONCLUSION

The etiopathogenesis of acne vulgaris is multifactorial, and prior analysis of the possible causes is a determining factor for the adequate therapeutic choice.

Significant findings highlight that the initial factor is related to the oxidation of the sebum. Multifactorial events, like diet, stress, daily habits, age, genetics and hormones, generate conditions for the oxidation of the sebum. Squalene is one of the constituent fatty acids in the sebum. Despite its importance for the health of the skin, it is transformed into squalene hydrogen peroxide when it undergoes oxidative damage, which is potentially comedogenic. The oxidative breakdown of squalene and other lipids of the skin are not only consequences of the acne process but can be directly linked to the pathogenesis of acne. It is therefore believed that the inflammation of acne vulgaris is a secondary event to lipid peroxidation. That is, the equilibrium in the sebum components of the follicular unit may regulate and control the oxidative stress of the skin, avoiding the homeostatic imbalance of keratinization and sebaceous production, as well as sebaceous hyperplasia, conditions that can reduce bacterial colonization in the infundibulum, preventing tissue inflammation and possible formations of unaesthetic scars and characteristics.

Knowing the factors that promote acne, makes it possible to develop an effective treatment protocol for the clinical manifestations of acne vulgaris.

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## Illustrations

Figure 1

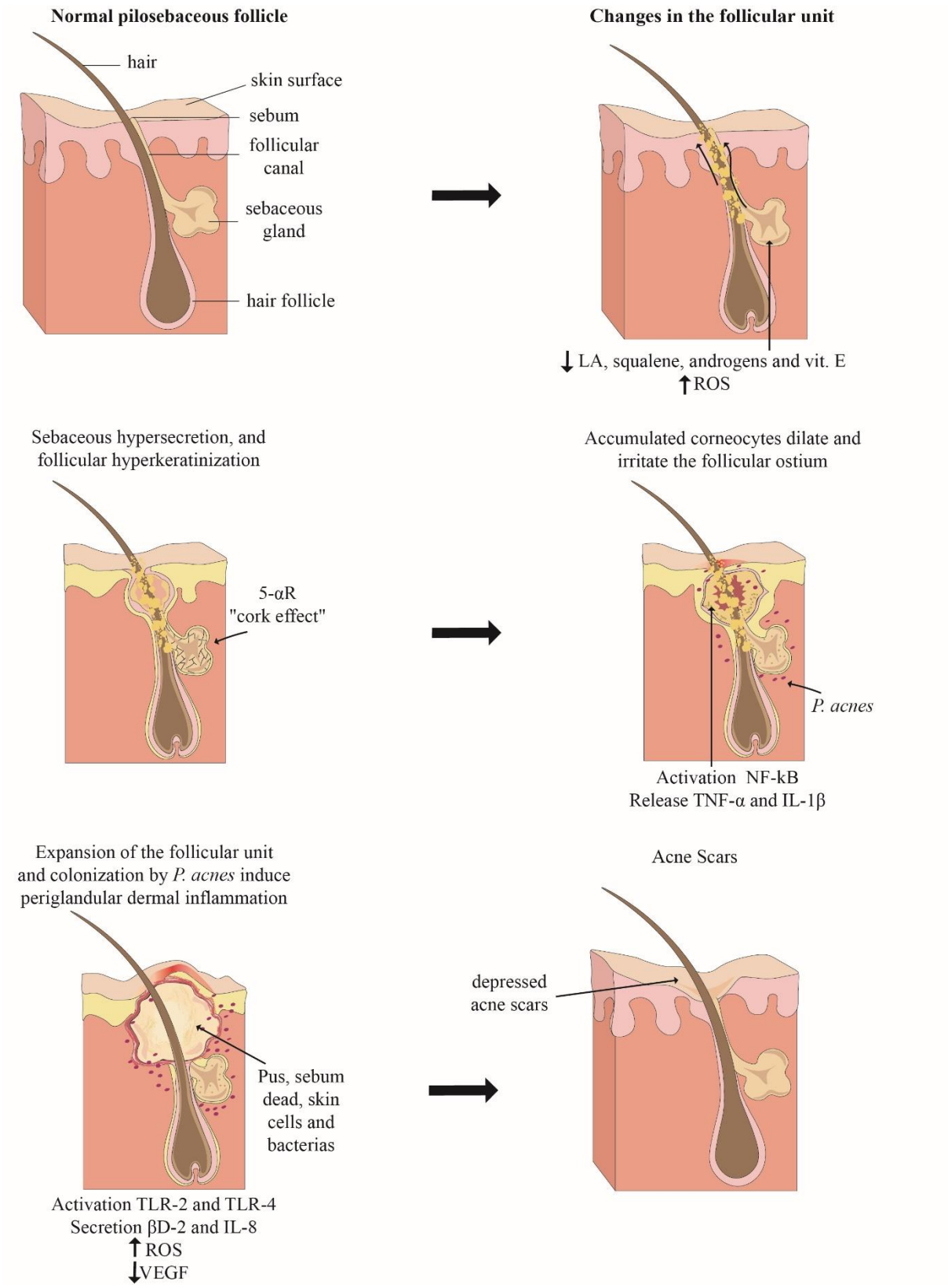


Figure 2

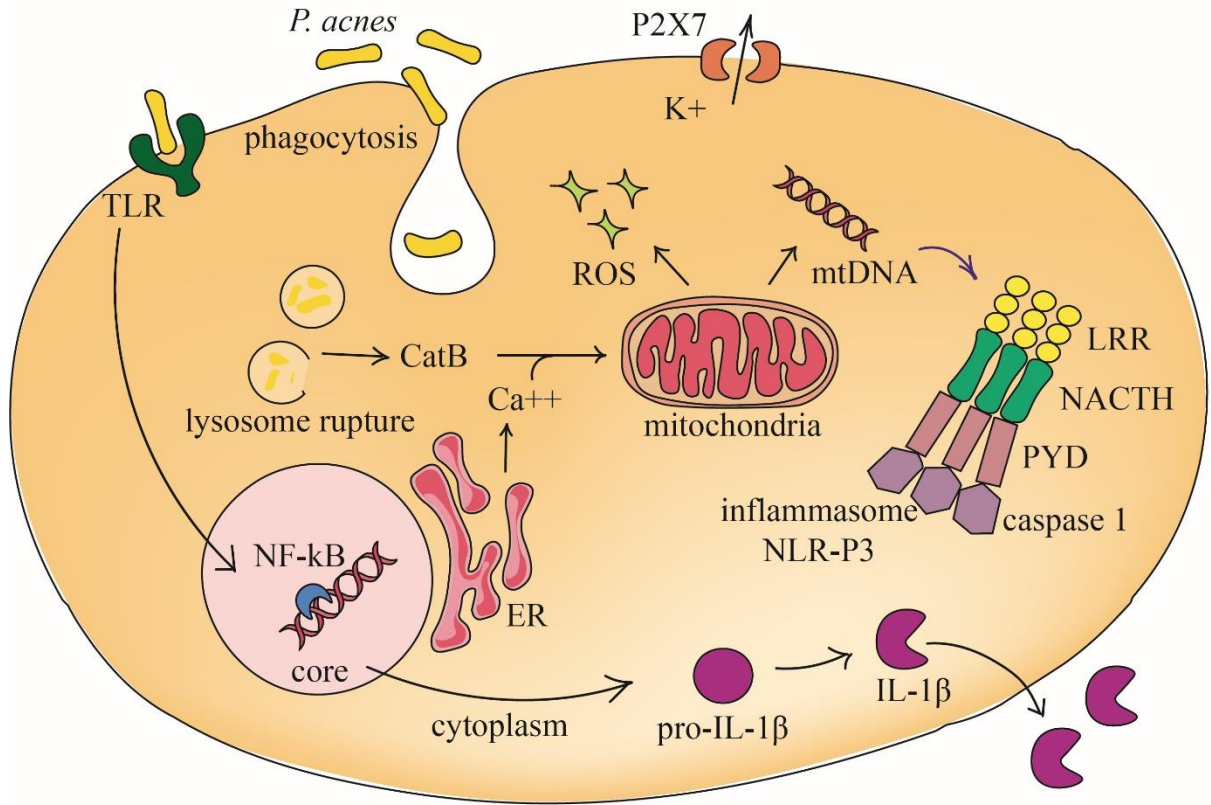


Figure 3

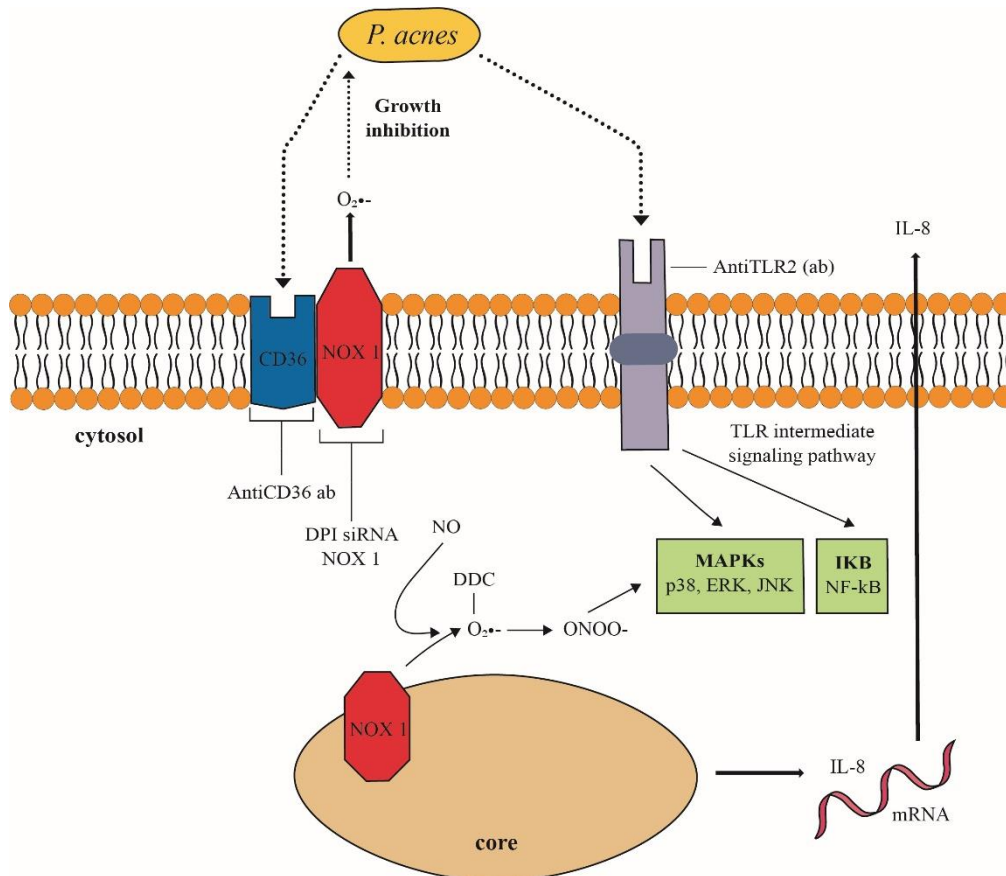
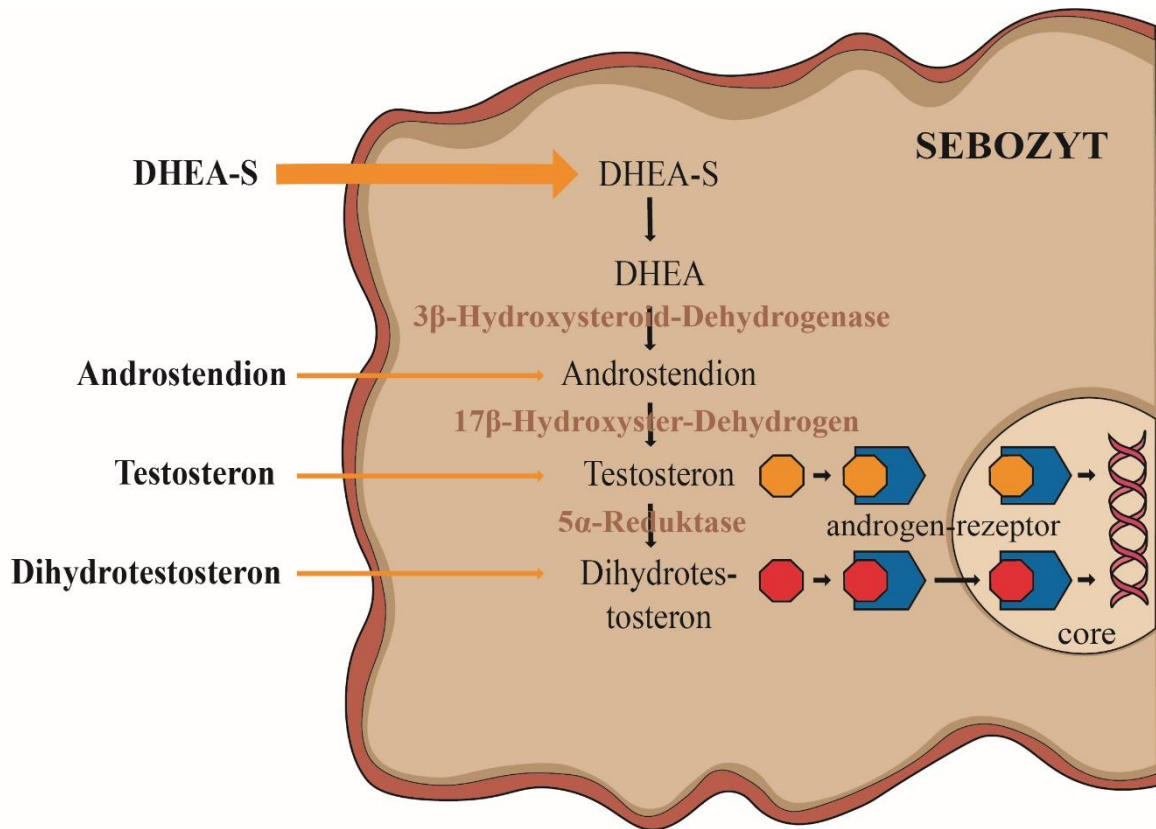


Figure 4



Legends to figures:

**Figure 1** Schematic of the formation of acne vulgaris: the healthy pilosebaceous follicle undergoes changes in the follicular unit.

Source: Authors.

**Figure 2** Schematic representation of *C. acnes* in contact with cells of myeloid origin, producing a sequence of molecular events.

Source: Adapted from Ribeiro et al. (2015).<sup>(63)</sup>

**Figure 3** Receptors of the subpopulation expressed in platelets, monocytes and macrophages (CD36) and TLR-2 recognize *C. acnes*.

Source: Adapted from Grange et al. (2009).<sup>(55)</sup>

**Figure 4** Dehydroepiandrosterone sulfate regulates the primary production of sebum.

Source: Adapted from Degitz et al. (2007).<sup>(64)</sup>