



## Role of Cytokines in the Pathogenesis of Acne

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### Abstract

**The aim** of this study was to investigate the role of cytokines in light of recently discovered aspects of acne immunopathogenesis.

**Materials and Methods:** The study included 276 patients aged between 16 to 44 years with various forms of acne vulgaris. Severe manifestations of the disease were identified in 126/45.6% patients; disease lasted 1 to 5 years in 157/56.9% patients. The serum levels of cytokines were determined by ELISA using standard kits. The cells were characterized using flow cytometry.

**Results:** The obtained data on an excessive secretion of pro-inflammatory cytokines (IL-1 $\alpha$ , IL-2) and VEGF on the background of decreasing the content of anti-inflammatory cytokines (IL-4, IL-10) indicate an insufficient activity of anti-inflammatory immune response. It was concluded that acne is a model of chronic immunodeficiency inflammatory dermatoses with the activation of innate immunity and the subsequent development of the adaptive T-cell immune response. (**Int J Biomed.** 2017;7(1):37-40.)

**Key Words:** acne vulgaris • cytokines • innate immunity • secondary immunodeficiency

### Introduction

Acne vulgaris, also known as acne, is a chronic relapsing inflammatory disease of the pilosebaceous units (hair follicles and their accompanying sebaceous glands).<sup>[1-4]</sup> Acne has a multifactorial pathogenesis, of which the key factor is genetic predisposition. Acne develops as a result of an interplay of the following factors: follicular epidermal hyperproliferation with hyperkeratosis, excess sebum production, the presence and activity of the commensal bacteria *Propionibacterium acnes* (*P.acnes*), androgen excess states, and inflammation.<sup>[1,5,6]</sup> Previously, it was reported that the release of the cytokine IL-1 $\alpha$  by keratinocytes of the sebaceous duct was pivotal in the life cycle of the comedone, mediating both its development and its spontaneous resolution.

There is clear evidence that *P.acnes* is responsible for the local inflammatory response of acne. After sebum production, *P.acnes* colonizes sebaceous follicles and releases lipase and proinflammatory mediators. *P.acnes* may trigger an innate

immune reaction via the activation of TLR2. Toll-like receptors (TLRs) are a component of the innate immune system involved in host defense against invading micro-organisms<sup>[7-9]</sup> and their activation ultimately triggers the expression of immune response genes, including those coding for various cytokines and chemokines that stimulate recruitment of host immune cells.<sup>[10]</sup> TLRs can activate innate immune responses through keratinocytes, neutrophils, monocytes/macrophages, natural killer cells, and dendritic cells. There are nearly a dozen different TLRs, but TLR2 and TLR4 appear to be specific for acne pathogenesis.<sup>[11]</sup>

Stimulation of TLR2 by *P.acnes* increases concentrations of IL-8 and IL-12.<sup>[4,12,13]</sup> *P.acnes* can activate several pathways that ultimately converge to activate nuclear factor (NF)- $\kappa$ B transcription factor. Downstream release of inflammatory cytokines (such as IL-1, IL-6, IL-8, IL-10, IL-12, and TNF- $\alpha$ ) mediate pathogen destruction via effector cells.<sup>[9,10]</sup>

Macrophages surrounding the pilosebaceous unit with TLR2 receptors were histologically described in biopsy material of patients with acne.<sup>[14]</sup>

In addition to innate immunity, also adaptive immunity, and especially the Th17 pathway, may contribute significantly to the inflammatory response in acne.<sup>[15,16]</sup>

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Several converging lines of evidence indicate that inflammation may be present throughout the development of acne lesions, both during the latter stages where inflammatory papules, pustules, and nodules are present, and also during the early stages of lesion development, in microcomedones and comedones.<sup>[7, 17]</sup>

It has been found that the delayed resolution of inflammatory acne lesions takes place due to opportunities of *P.acnes* to stimulate the production of antibodies and histamine vasoactive peptides, as well as their resistance to the neutrophilic and monocytic phagocytosis.<sup>[18,19]</sup> It has been shown that the inflammatory process in patients with acne is supported by polynuclear neutrophils, which produce a large number of free radicals, by prostaglandins, leukotrienes B4 and complement.<sup>[1,20]</sup>

It has also been revealed that *P.acnes* antigens activate the complement system and provide the migration of free radicals, neutrophils, and macrophages in PSUs with the following production of proteolytic enzymes, IL-1 $\alpha$ , IL-1 $\beta$ , IL-8, and TNF- $\gamma$ , which causes inflammation and a complex cascade of pathogenetic mechanisms of disease.<sup>[5,20-22]</sup> However, the role of cellular and humoral immunity and cytokine activity in acne is still a subject of studies.

**The aim** of this study was to investigate the role of cytokines in light of recently discovered aspects of acne immunopathogenesis.

## Materials and Methods

A study performed between 2010 and 2014 included 276 patients (86/31.1% men and 190/68.9% women) aged between 16 to 44 years with various forms of acne. Severe manifestations of the disease were identified in 126/45.6% patients; disease lasted 1 to 5 years in 157/56.9% patients. Written informed consent was obtained from all patients. An investigation of the dynamics of clinical and paraclinical parameters was carried out under the scheme developed by the individual protocol of clinical and laboratory examination (standard and special parameters), taking into account gender, age, onset and duration of the disease and the nature of its course. The acne severity was identified according to FDA guidance (2005). The serum levels of cytokines (IL-1 $\alpha$ , IL-2, IL4, IL-6, IL-8, IL-10, TNF- $\alpha$ , INF- $\gamma$  and VEGF) were determined by ELISA using standard kits (BioSource International, Inc. hIL-1-10 kit, Inc. INF- $\gamma$  kit, Inc. TNF- $\alpha$  kit, Inc. hVEGF kit) in the range of detectable concentrations (of 1 to 13 pg/ml) and test-system Bio-Plex Pro™ Human Cytokine 8-plex Assay (BenderMedSystems, Austria). The cells were characterized using flow cytometry. The statistical analysis was performed using the statistical software «Statistica». (v6.0, StatSoft, USA). The mean (M) and standard error of the mean (SEM) were calculated. For data with normal distribution, intergroup comparisons were performed using Student's t-test. Group comparisons with respect to categorical variables are performed using chi-square. Pearson's Correlation Coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A probability value of  $P < 0.05$  was considered statistically significant.

## Results and Discussion

Parameters of cellular immunity before treatment in patients with various forms of acne severity are shown in Fig. 1.

Analysis of parameters of cellular immunity showed that in all degrees of acne severity, there was a tendency to increase the content of neutrophils, lymphocytes; in severe forms of the disease, we found a tendency to increase in the content of white blood cells and reduction in lymphocyte level due to the chronic abscessed course of the disease. In patients with mild to moderate severity of acne, CD3+CD4+-T-cells were within normal range ( $42.9 \pm 3.9\%$ ), but their content significantly decreased in the severe form of acne ( $35.9 \pm 4.8\%$ ;  $P < 0.05$ ). We found a significant increase in the content of CD95+ lymphocytes in patients with mild to moderate degrees of the disease and a significant decrease in the content of CD95+ lymphocytes with severe degrees. The immunoregulatory index (CD4/CD8) decreased significantly in patients with a severe form of acne ( $1.38 \pm 0.3$ ;  $P < 0.05$ ).

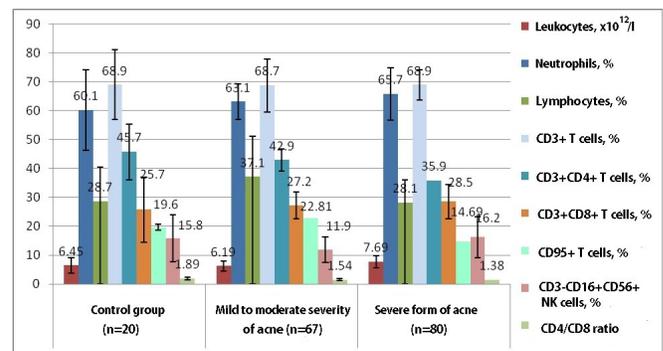


Fig. 1. Parameters of cellular immunity in patients with various forms of acne severity

The parameters of humoral immunity before treatment are presented in Figure 2. Thus, in various forms of acne severity, the initial levels of B-lymphocytes (CD19+) and immunoglobulin levels (IgA, IgM, IgG) were in the normal range. At the same time, we found a significant decrease in the content of large circulating immune complexes (CIC) for all degrees of acne severity; middle CIC were in the normal range, while the content of small CIC was significantly increased in all degrees of acne severity, ensuring the maintenance of the aseptic inflammation.

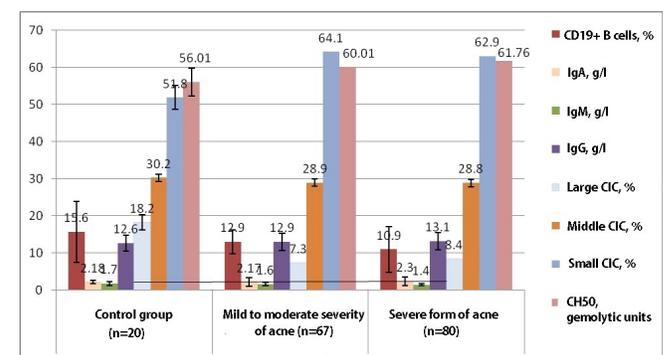
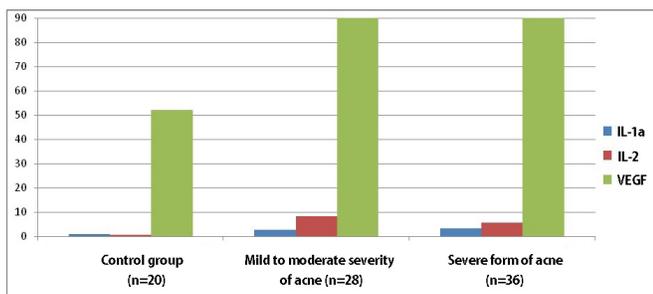
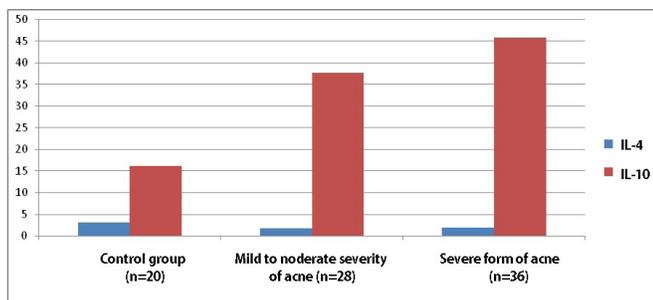


Fig. 2. The parameters of humoral immunity in patients with various forms of acne severity.

The serum levels of cytokines in patients with various forms of acne severity are shown in Figures 3 and 4. The serum level of IL-1 $\alpha$  tended to increase with mild to moderate severity, while the serum level of IL-1 $\alpha$  significantly increased in the severe form of acne. It should be noted that serum IL-1 $\alpha$  level exceeded the reference values more than 3 times. These changes directly correlated with the acne severity and clinical symptoms of severe skin inflammation ( $r=+0.88$ ). Serum IL-2 level in patients was also significantly elevated in all degrees of acne severity, but more significant in mild to moderate severity. This fact is due to the maximum functional activity of IL-2 in the early stages of the inflammatory process and less pronounced increase during chronic inflammation. Serum VEGF level was also significantly elevated in all monitored patients regardless of the severity compared to control values.



**Fig. 3.** Serum levels of IL-1 $\alpha$ , IL-2 and VEGF (pg/ml) in patients with various forms of acne severity



**Fig. 4.** Serum levels of IL-4 and IL-10 (pg/ml) in patients with various forms of acne severity

Serum IL-4 level was significantly reduced in all degrees of severity, indicating the suppression of anti-inflammatory cytokine secretion. Serum IL-10 level was increased in all degrees of severity, indicating the prolonged activation of inflammatory systems but was insufficient to provide the regression of clinical symptoms of the disease. Thus, the obtained data on an excessive secretion of pro-inflammatory cytokines (IL-1 $\alpha$ , IL-2) and VEGF on the background of decreasing the content of anti-inflammatory cytokines (IL-4, IL-10) indicate an insufficient activity of anti-inflammatory immune response. Clinically, these changes correlated ( $r=+0.89$ ) with the persistent torpid course of acne.

## Findings:

- In all patients with acne, regardless of the disease

severity, there is a pronounced secondary immunodeficiency with the predominant deficiency in T-cell immunity that is manifested on the background of significant changes in the level of large and small CIC, which indicates an imbalance in humoral immunity, underlying the recurrent protracted nature of acne.

- An excessive secretion of pro-inflammatory cytokines (IL-1 $\alpha$ , IL-2) and VEGF on the background of decreasing the content of anti-inflammatory cytokines (IL-4, IL-10) indicates an insufficient activity of anti-inflammatory immune response.

- It can be assumed that acne is a model of chronic immunodeficiency inflammatory dermatoses with the activation of innate immunity and the subsequent development of the adaptive T-cell immune response.

- The revealed immune-related markers of acne pathogenesis are a scientific basis for the development and introduction of innovative technologies with the universal corrective mechanism of action, including photodynamic therapy in combination with low-level laser therapy.

## Competing interests

The authors declare that they have no competing interests.

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