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Gene expression of CD70 in patients with acne vulgaris

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Abstract
Background: Acne vulgaris is one of the most prevalent chronic inflammatory disorders of the pilosebaceous unit. It is detected by the accumulation of inflammatory papules, pustules, nodules, and cysts, as well as non-inflammatory comedones. Dendritic cells, natural killer cells, activated T cells, and B cells are the sole cells that express CD70, a member of the TNF family. The ligand for CD27. The dysregulation of CD27-CD70 complex signaling contributes to the pathogenesis of various immune-related illnesses; thus, investigating the gene expression of CD70 may be advantageous for understanding and managing acne vulgaris.
Objective: The current study assessed the gene expression of tissue CD70 in AV patients and correlate the gene expression with disease severity.
Conclusions: Lesional CD70 gene expression showed significant ability to predict acne vulgaris. Lesional CD70 gene expression is a novel candidate to be studied in acne pathogenesis.

Keywords: Acne vulgaris, gene expression, CD70

Introduction
A prevalent inflammatory pilosebaceous disease, acne vulgaris affects over 80% of young adults and adolescents. Acne primarily affects the face, chest, and back, and is characterized by open and closed comedones, as well as lesions that contain inflammatory nodules, pustules, and papules [1].
The conventional pathophysiology of acne vulgaris comprises four components, typically delineated sequentially, wherein elevated androgen levels or activity stimulate increased sebum production, accompanied by follicular hyperkeratinization that causes follicular obstruction. This facilitates the proliferation of the bacterium *Propionibacterium acnes* within the follicle, ultimately resulting in an inflammatory cascade and manifesting illness [2].
Cluster Differentiation (CD) 27 is a member of the Tumor Necrosis Factor (TNF) receptor family. There are numerous immune cells, including T helper cells, that express CD27. The TNF family includes CD70, which is exclusively found on activated T cells, B cells, natural killer cells, and dendritic cells. It acts as the ligand for CD27. Antigen receptor engagement, toll-like receptor stimulation, or CD40 signaling are the mechanisms by which T cell activation initiates CD70 expression. The interaction between CD70 on active Antigen Presenting Cells (APCs) and CD27 on T cells produces costimulatory signals that improve the activation, survival, proliferation, chemotaxis, and synthesis of cytokines, such as interleukin 2 and interferon-Ч, of cytotoxic T cells [3].

Materials and Methods
Data sources: The literatures on the causes, pathogenesis, clinical pictures of acne vulgaris, discuss role of CD70 expression in patients with acne vulgaris and its correlation with the disease's severity decline up to 2024 was sourced via a search of the Medline databases (Pub Med and Medscape).
Study selection: The inclusion of all studies was independently evaluated. They were included if they met the following criteria:
1. Written and published in the English vernacular.
2. Published in peer-reviewed journals.

3. Discuss the role of CD70 expression in patients with acne vulgaris and its correlation with the severity of the disease, as well as the causes, pathogenesis, and clinical images of acne vulgaris.

Data extraction: If the studies failed to satisfy the inclusion criteria, they were excluded. Considerations for evaluating the quality of a study included the acquisition of ethical approval, the specification of eligibility criteria, the implementation of suitable controls, and the provision of sufficient information and well-defined evaluation measures. In order to obtain information about the outcomes of interest, a data collection form was implemented to independently extract data from each eligible study.

Review of Literature

Acne vulgaris is a prevalent cutaneous disorder of the pilosebaceous unit in the general population at a high prevalence. With an estimated global prevalence of 9.38%, acne vulgaris was identified as the eighth most prevalent skin disease in a global burden of disease study [4].

Epidemiology

Acne prevalence estimates are subject to significant variation due to the absence of a universally accepted diagnostic or grading schema. In addition, the rate of acne is declining due to improved treatment options, which is resulting in fluctuations in estimates. Around 650 million individuals, or approximately 9.4% of the global population, are afflicted by acne vulgaris [5].

Pathogenesis of acne vulgaris

Under the influence of hormones, sebaceous glands secrete an excessive quantity of sebum. They are present on the entire body surface, with a greater concentration in the upper trunk, chest, and back. In regions where hair follicles are not present, such as the palm, sole, and dorsum of the feet, they are not present. An excessive quantity of sebum disrupts the follicular keratinization process, resulting in the obstruction of the sebaceous gland's pore. Consequently, acne develops. The following procedures are taken to conduct the pathogenesis.

- The excessive production of sebum from sebaceous glands
- hyperkeratinization, which results in the enlargement of microcomedos into comedos
- The colonization of the follicle by anaerobic bacteria, and
- The inflammatory responses [6]

1) Genetics

Genetics have been implicated in the development of acne, as evidenced by family and twin studies. Numerous genetic polymorphisms that influence gene expression and/or function have been investigated. the insulin-like growth factor (IGF1) (CA) 19 repeat polymorphism, the Pro12Ala polymorphism of peroxisome proliferator activated receptor gamma (PPARG124), the interleukin (IL6) 572 G/C polymorphism, and the IL1A 889 C/T polymorphism were all found to be associated with acne [7].

2) Hormonal factors

Sebum secretion is elevated during puberty as 5-alpha reductase converts testosterone to more potent DHT, which bonds to specific receptors in the sebaceous glands, thereby increasing sebum production, under the influence of androgens. This results in the retention of sebum, which is a consequence of the follicular epidermis's increased hyperproliferation. Pro-inflammatory compounds are released into the dermis as a result of the rupture of distended follicles, which induces inflammation. Staphylococcus epidermis, C. acnes, and Malassezia furfur increase inflammation and promote the proliferation of follicular epidermis [8].

The production of female sex hormones, particularly estrogens, oestradiol, and oestrone, appears to be amplified during menstrual cycles and pregnancy, which in turn affects acne vulgaris. Most frequently, DHEA levels are elevated [9]. In contrast, there is no discernible difference in the levels of 17α hydroxyprogesterone between women with and without acne. In addition, in women, elevated levels of oestradiol have a protective effect [10].

3) Diet

The central line of the endocrine pathway of sexual maturation is the insulin-like growth factor signaling that is induced by hyperglycemic foods. This signaling plays a primary role in the development of acne. The large quantities of glycemic carbohydrates, saturated fats, and dairy products in the western diet facilitate sebaceous lipogenesis and sebum secretion. Consumption of dairy products contributes to the progression of acne vulgaris. The prevalence of acne was found to be positively correlated with the consumption of full-fat, condensed, and low-fat milk. The reduction of acne is significantly supported by the regular consumption of low glycemic index diets and omega-3 fatty acids [11].

Hyperglycemic carbohydrates, milk and dairy products, and saturated fats, including trans-fats and deficient ω-3 Polyunsaturated Fatty Acids (PUFAs), are the three primary dietary classes that contribute to acne. The impact of aberrant nutrigenomics on sebaceous gland homeostasis is revealed by the superimposition of diet-induced insulin/insulin-like growth factor (IGF-1)-signaling on elevated IGF-1 levels during puberty [12].

4) Role of linoleic acid

Linoleic acid is a crucial fatty acid that is present in the organic composition of sebums. The hair follicle barrier is compromised by a deficiency of linoleic acid, which allows other free fatty acids generated by bacterial lipases to enter. These foreign fatty acids will lead to further deficiency of linoleic acid creating a vicious circle ending with production of abnormal thick sebum that obstructs the sebaceous gland duct [12].

Evidently, the sebaceous gland selectively utilizes fatty acids, while linoleic acid appears to be subjected to β-oxidation exclusively. Acetyl-CoA is produced by converting it into precursors (two carbon units), which are then incorporated into various metabolic pathways, including the biosynthetic pathway that leads to the synthesis of squalene and wax esters. The follicle's sphingolipid composition is influenced by the reduced linoleic acid content of the sebum. Sphingolipids in the human epidermis serve as a protective barrier between the human body and the environment. It has been postulated that the sphingolipids with reduced linoleic acid facilitate follicular hyperkeratosis, a critical component of comedo formation [13].

5) Role of inflammation

Inflammation is a critical factor in the initiation, progression, and resolution of acne vulgaris. IGF-1 and virulent *P. acnes* are the most critical factors in the induction of aninflammatory response in acne. IGF-1 is sufficient to stimulate the expression of pro-inflammatory cytokines in primary human sebocytes. A rise in the expression of NF-κB, IL-1β, IL-6, IL-8, and TNF-α was observed in cultured sebocytes following stimulation with IGF-1 [14].

Androgen may have comparable effects to IGF-1, as it has the ability to elevate the level of IGF-1 in the serum of healthy men. sebocytes release cytokines and Matrix Metalloproteinases (MMPs) and recruit inflammatory cells into the pilosebaceous unit following IGF-1 stimulation. MMPs have the capacity to rupture the follicular membrane, resulting in the dissolution of the extracellular matrix and the leakage of fatty acids into the dermis [12].

6) Bacterial factor

P. acnes is a rod-shaped, gram-positive, facultative, and anaerobic bacteria that is a primary inhabitant of the human epidermis. It comprises 87% of the clones, which are also shared with other Staphylococcus, Corynebacterium, Streptococcus, and Pseudomonas species. Before puberty, *P. acnes* remains quiescent. But androgenic hormones increase the concentration of sebum, which activates the bacteria and promotes their proliferation. It is fundamentally sustained by the fatty acids in sebum, which are secreted by sebaceous glands. Sebum, cellular debris, and metabolic by-products from the adjacent skin tissue are the primary sources of energy and nutrients for microbes in the follicles. Consequently, the follicle's obstruction can create an environment that is favorable for the proliferation of microorganisms [15].

7) Role of sebum

The pilosebaceous, which is composed of sebaceous glands and hair follicles, is primarily responsible for the production of sebum. An altered quantity and composition of sebum is associated with skin diseases such as acne vulgaris and AD, which are the result of changes in their lipid metabolism. Additionally, sebocytes are capable of eliciting inflammatory responses by secreting pro-inflammatory cytokines, chemokines, and antimicrobial peptides in response to pathogen activation (e.g., various *P. acnes* strains) and pathogen-associated molecular pattern recognition receptor ligands (e.g., TLR2 and TLR4) [16].

Clinical picture and grading of acne vulgaris

The comedon, which can be either open or confined, is the primary lesion in acne. Black-head comedons are open, while white-head comedons are closed. Pustules and/or nodules may also be present in acne lesions. The sebaceous gland-rich regions of the face, upper back, chest, and shoulders comprise the typical distribution. Scarring, post-inflammatory hyperpigmentation, or erythema are all examples of secondary lesions [17].

Grading of acne

Simple grading based on clinical examination, lesion enumeration, and those that necessitate complex instruments, such as photography, fluorescent photography, polarized light photography, video microscopy, and sebum production measurement, are all methods of assessing the severity of acne vulgaris. The two most frequently employed metrics are lesion enumeration and grading. In 1956, Pillsbury, Shelley, and Kligman published the first known grading system. Numerous systems were subsequently implemented, with the Global Acne Grading System (GAGS) being one of the most prevalent [18].

Global Acne Grading System (GAGS): To evaluate the severity of acne, the GAGS employs a quantitative scoring system. Doshi and his associates initially devised it in 1997. Six regional sub-scores are combined to calculate the total severity score. The most heavily weighted lesion within each region is multiplied by the factors -2 for the forehead, 2 for each check, 1 for the nose, 1 for the jawline, and 3 for both the chest and back. The formula is as follows: 1 for ≥ one comedon, 2 for ≥ one papule, 3 for ≥ one pustule, and 4 for ≥ one nodule [19].

Role of CD70 in inflammatory diseases and possible role in acne

The tumor necrosis factor receptor family includes Cluster Differentiation (CD) 27. CD27 is found on various cell types, including hematopoietic stem cells, cT cells, natural killer cells, and T helper (Th) cells. The tumor necrosis factor family includes CD70, an exclusively expressed ligand of CD27, which is found on activated T cells, B cells, natural killer cells, and dendritic cells. In response to antigen receptor attachment, toll-like receptor activation, or CD40 signaling, T cells begin to express CD70 [20].

Th and cT cells are stimulated, survive, proliferate, chemotaxis, and produce cytokines like interleukin 2 and interferon-ϐ through the costimulatory signals generated by the interaction of CD70 on stimulated Antigen Presenting Cells (APCs) and CD27 on T cells. In addition, the chemotaxis of further activated cT cells is enhanced by the production of CXCL10 chemokine by activated cT cells, which is induced by CD27-CD70 interaction [21].

It was also discovered that CD70, unrelated to interleukin 12, promoted Th1 cell differentiation. The surface of activated T cells can be stripped by matrix metalloproteinases, allowing soluble CD27 to be released into the bloodstream. The activation of T cells and antigen-primed B cells, as well as the production of immunoglobulin G, could be improved by serum soluble CD27, according to reports. Curiously, it was suggested that CD70 signaling caused by unaroused, premature APCs can invariably result in tolerance impairment and the development of autoimmunity. A number of immune-related diseases have been linked to abnormalities in the CD27-CD70 complex signaling, according to substantial evidence [22].

Psoriatic arthritis patients' CD4+ T lymphocytes isolated from synovial fluid showed an upregulation of CD70 expression [23]. Patients with RA also had elevated CD70 expression in their synovium and PBMCs (peripheral blood mononuclear cells) [24], systemic lupus erythematosus (SLE) [25], systemic sclerosis [26], and Sjogren's syndrome [27]. T cell activation triggers CD70 expression, but this is not suppressed because the CD70 gene promoter area is hypo- or demethylated, which is associated with this expression [20].

A number of in vivo investigations have hinted that monoclonal antibodies focusing on the CD27-CD70 complex may hold promise as a treatment option for inflammatory and autoimmune disorders. In a study on collagen-induced arthritis in mice, anti-CD70 antibodies

reduced antibody titers and ameliorated joint disease [28]. More so, when T cells were isolated from SLE patients, anti-CD70 antibodies inhibited the secretion of immunoglobulin by B cells [25]. In a mouse model of colitis, the administration of anti-CD70 antibodies prevented the disease and reduced Th1 cytokines associated with it [22].

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