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Epidemiology, Pathogenesis, and Vaccine Development of Acne

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Abstract:

Acne is a widespread and chronic inflammatory disease of the pilosebaceous glands affecting millions of people worldwide, particularly among adolescents. The current treatment method is mainly oral and smear medication, combined with a variety of physical and chemical therapy used as adjuvant therapy, alternative therapy or sequelae treatment. However, due to antibiotic resistance and bacteria evolve over time, need a vaccine as a new alternative treatment, in recent years, with the rapid development of molecular biology and immunology, based on specific antigen antibody technology acne vaccine has made significant progress, but there is still no successful development of acne vaccine. This paper analyzes the main four pathogenesis of acne and the current treatment, including oral and daub anti-inflammatory drugs and antibacterial drugs, supplemented by physical and chemical therapy, focus on the development of acne vaccine, present situation, challenges and future trend, hope to further promote the research and development of acne vaccine provide certain theoretical basis and reference value, and provide new ideas and methods for the prevention and treatment of acne. And acne pathogenesis complex and cannot determine the vaccine clinical trial effect these two problems are not solved, pathogenic mechanism involves multiple complex factors, a single vaccine may not have enough protective effect, difficult to completely prevent or cure acne, therefore, the next step need to consider targeting multiple pathogens and virulence factors combination of multivalent vaccine, and need for long-term clinical trials and observation.

Keywords: Acne; acne inflammation; acne pathogenesis; cutibacterium acnes; vaccine.

1. Introduction

Acne vulgaris, commonly known as acne, is a high incidence of pilosebaceous gland inflammation chronic skin disease, is also a big worry for many people in adolescence, its pathogenesis is not completely clear, Cutibacterium acnes (C. acnes, formerly called propionibacterium acnes) is considered to be a very key factor [1]. Approximately 85% of adolescents worldwide are affected by acne, some of which may persist until adulthood [2]. Acne may appear as non-inflammatory (acne) and inflammatory (papules, pustules, cysts, nodules). Acne has been recognized as a chronic disease, the clinical symptoms of acne is not limited to papules or acne, serious will leave disfiguring scars on the face, leading to discomfort, emotional stress, damage, even permanent skin scarring, cause poor self-esteem, anxiety, social fear and depression, largely reduces the patients' physical health and quality of life, bringing huge economic costs and psychological burden to individual and social. Acne treatment is not limited to the skin disease itself, but also involves psychology, psychiatry, etc.

Since the last century, scientists have been working on acne vaccines. The early acne vaccines were prepared based on the inactivated pathogens of C. acnes, and then turned their research to the specific antigen of C. acnes in an effort to develop a safer and more effective vaccine. In recent years, with the rapid development of molecular biology and immunology disciplines, significant progress has been made in acne vaccines based on specific antigen antibody technology. Over the years, some studies and practices has been carried out at home and abroad on the pathogenic mechanism, course and treatment of acne. However, in the past 40 years, there has been no breakthrough innovation in acne treatment, it is widely believed that acne products are irritating, whether traditional acne products are really effective, etc., and antibiotic resistance is increasing. Most of the current isoretinotes, hormones, and antibiotics can only provide short-term effects, many methods and products do not fundamentally treat acne, and are not applicable to all patients, and may cause other hazards [3].

Based on the research breakthrough of skin surface microorganisms such as C. acnes in recent years, it provides further explanation for the pathogenesis of acne, that is,

it provides more enlightenment and feasibility for the scientific scheme of acne prevention and treatment, and vaccine is also recognized as an important research and development direction. This paper will analyze the pathogenesis and treatment methods of acne, It aims to provide a certain theoretical basis and reference value for further promoting the research and development of acne vaccine and to provide new ideas and methods for for acne prevention.

2. Pathogenesis

Although acne is a common skin disease, its etiology and pathogenic mechanism have not been determined. At present, the four recognized acne physiopathological factors include increased sebum secretion affected by androgen, abnormal keratosis of sebaceous glands, excessive proliferation of microorganisms such as acnes and inflammatory reactions caused by bacterial antigens and cytokines; in addition, genetic, environmental changes, diet, stress and hormonal factors may also cause or aggravate acne [4].

2.1 The Role of C. acnes in Acne Pathogenesis

Studies have shown that the pathogenesis of acne is most mainly attributed to the changes in the skin microbiome [5], among which the biggest impact is P.acnes, and the overgrowth and reproduction of E. acnes can trigger inflammation, which leads to acne. Specifically, C. acnes is the main bacterium associated with acne, and its overgrowth is strongly linked to acne pathogenesis. C. acnes participates in the development of skin inflammation by exossome vesicles and related inflammatory factors [6]. The typing of C. acnes revealed that different strains induce immune responses and have significant differences between proteomes, and that strains can induce different immune responses; Acne-related strains trigger proinflammatory cytokines such as IFN γ and IL-17, while healthy-related strains promote anti-inflammatory IL-10 production [7], and modulation of immune responses induced by specific C. acnes phylotypes may help control inflammatory responses in acne pathogenesis and explore new treatment options [8]. It is a complex process, involving many links. Other pathogenic mechanisms include increased sebum secretion, excessive keratosis of pilosebaceous glands, inflammatory response, genetic and environmental factors.

The environment is a crucial factor in the growth of acne. Acne is a gram-positive, rod anaerobic bacteria commonly found in the human skin, rich in lipid glands and hair follicles [9],can also exist in the nasal cavity, oral cavity, intestinal tract, etc. Studies have shown that the surface of human skin contains a large amount of acne [10], but under normal circumstances, the sebaceous duct and hair follicle hole are open to the outside world, will not form an anaerobic environment, the growth of acne is inhibited, does not cause inflammatory response, when the sebaceous gland secretion of sebum increases or abnormal keratosis of hair follicles, it will cause the sebaceous gland tube mouth and hair follicle hole blockage, leading to the formation of an anaerobic environment conducive to the survival and reproduction of Acnes, resulting in a large number of hyperplasia, leading to inflammation.

The complete genome of C. acnes has been sequenced, providing some clues about its pathogenic potential and its strategy to survive in the harsh environment of human skin. Metagenomic studies have revealed the existence of prominent gene sets in acne or health-related Chlamydia acne strains [11]; Metagenomics can capture more sample diversity, and the study shows that C. acne strains are structurally different from healthy individuals, and further analysis can achieve finer resolution, some of which may become important targets and techniques in future acne treatment research.

For example, comparative genomic analysis of C. acnes provides a reliable method for genetic diversity and typing applications, opening up new avenues for studying the mechanisms that drive virulence and pathogenicity[12]. Recent advances in distinguishing phylotypes of C. acnes have demonstrated a strong association between acne and the C. acnes ribotype 4 (RT4) strain and ribotype 5 (RT5) strains, and their genomes contain a specific site encoding a virulence effector that could be explored for targeted therapeutics to restore natural commensal population structure[13]. Using a meta-analysis of genome-wide association studies (GWAS) of acne, the researchers identified 29 new acne susceptibility loci and identified putative causal genes, including LAMC2, TGFB2, WNT10A, LGR6, FGF2 and GLI2, which may provide researchers with more novel targets for the development of novel acne therapies [14].

2.2 The Remaining Three Pathogenic Mechanisms

The increased sebum secretion is also a pathogenic factor of acne.Studies have found that the incidence and severity of acne is linked to increased liposuction [15]. Those hormonal factors, such as androgens, especially testosterone and insulin growth hormone (IGH-1), can increase sebum synthesis and secretion [7,15], and increase the severity of acne. In addition to local hormone effects on fatty glands, systemic hormone disorders play a key role in triggering adult acne [4].

In addition, abnormal corrosion of the follicle is also a pathogenic factor of acne, normal follicles are an import-

ant component of the skin, responsible for the liposuction, protection and moisturization of skin, healthy follics often flow single-cell corneal forming cells into the skin cavity, eventually removed.Due to excessive proliferation of coronary cells in acne patients, can not normally fall off, causing follicle conduction blockage and abnormal coronation of the follicles, and forming blackheads, further aggravating the development of acne [4].

When the human immune system detects C. acnes, the immune response is triggered, and the inflammatory response begins [15]. The pathogenesis of acne is a complex interaction between the innate immune system and the adaptive immune system[16]. At the same time, the above increase in sebum secretion and excessive keratinization of the follicle sebaceous glands are also the trigger factors of the inflammatory response, which is based on the occurrence of acne, and the infection of E. acnes eventually causes the inflammatory response.

Alternatively, the occurrence of acne is also related to genetic and environmental factors, genes influence several aspects of acne pathogenesis, including sebum secretion, the keratinization process, and the response of the immune system to Chlamydia acnes [5]. For example, DNA methylation has been shown to play an important role in the mechanism of onset and development of inflammatory skin diseases [17]. In addition,environment, smoking, diet, stress and other factors may also be acne pathogenesis factors.

3. Therapies

3.1 Current Treatment

At present, the main treatment plan for acne is drug treatment, through oral and application of anti-inflammatory drugs and antibacterial drugs, such as vitamin A, isovitamin A, androgen receptor inhibitors, antibiotics, salicylic acid, benzoyl peroxide and hormone drugs, to control sebum secretion, follicle cortex, propionibacterium infection; with optical therapy, cryotherapy, chemical stripping and other physical and chemical therapy, used as adjuvant therapy, alternative therapy or sequelae treatment.

Antibiotics have been used in the treatment of acne for more than 40 years and are generally considered to inhibit chlamydia acne and play anti-inflammatory effects. Oral antibiotics are integral for moderate to severe acne, especially ineffective or refractory to topical drugs [18-20].

3.2 Acne Vaccine Development Progress

Since the last century, scientists have been working on acne vaccines. The early acne vaccines were prepared based on the inactivated pathogens of C. acnes, and then turned their research to the specific antigen of C. acnes in an effort to develop a safer and more effective vaccine. In recent years, with the rapid development of molecular biology and immunology disciplines, significant progress has been made in acne vaccines based on specific antigen antibody technology.

3.2.1 Inactivated Acne Vaccine

in 1979, Goldman et al. prepared an acne multivalent inactivated vaccine, used for cystic severe acne patients, the results show that more than 50% of patients' conditions significantly improved, but the subsequent experiments confirmed that only to control inflammation, not completely kill acnes, limited efficacy and may cause a nonspecific immune response, cause the body flora disorder [21]. In a paper published by Nakatsuji et al. in 2008, the study described the nasal immunization of mice with an acne bacterium antifungal vaccine that stimulates specific antibodies against C.acnes, the immunization with the active vaccine produced protective immunity against the attack of acne and facilitated the reduction of inflammation in the ear in mice, which effectively mitigated the cell toxicity of this vaccine, and weakened the production of the inflammatory cell factor IL-8 in human psoriaticSZ95 cells, while the use of antiviral vaccine based on acne in the nose provides a simpler way to develop the acne vaccine. Inactivated vaccines [22]. The advantage of inactivated vaccines is their lower cost, but they may induce nonspecific immune responses, thereby disrupting host bacterial balance, and may also lead to allergic reactions.

3.2.2 Sialidase-specific Vaccine

C.acnes specifically encodes a variety of proteins, of which sialidase is the first specific antigen used for the preparation of acne vaccines. Sialidases are involved in the adhesion of the pathogens to the host cells, and the bacterial adhesion process occurs during the early stages of the infection and is essential for their colonization. Alternatively, sialidases alter the sensitivity of their host cells to pathogens. Therefore, vaccination targeting C. acnes sialidase may be an effective approach to prevent early infection of C. acnes. In the study by Nakatsuji et al., mice were immunized with recombinant sialidase, vaccinated with sialidase antibodies that effectively suppressed acnes-induced inflammation, and anti-sialidase serum in vitro neutralized the cytotoxicity of IL-8 production induced by acne in human sebum cells, implying that sialidase-based vaccines may have the potential to treat acne [23]. In addition, sialidase specific vaccine mice in the body provide a protective immunity against acnes, prevent the mouse ear inflammation and proinflammatory macrophage inflammation protein (MIP-2) cytokines release, the results show that if acne sialidase antibodies

can strongly induced in patients with acne, can effectively prevent the development and development of acne and recurrence. Although sialidase-specific vaccines have been shown to reduce inflammation induced by C. acnes, they may not have the ability to neutralize virulence factors secreted by C. acnes.

3.2.3 C. acnes CAMP Factor-specific Vaccine

Studies have shown that the virulence factor CAMP (Christie-Atkins-Munch-Peterson) secreted by Bacillus acnes, it is a secreted protein with hemolytic activity with sphingomyelinase and can be cytotoxic to specific keratinocytes and macrophages., which are the two main targets of acne; moreover, CAMP factors can induce cell death and trigger inflammation in sebaceous cells in the sebaceous glands. moreover, CAMP factors can induce cell death and trigger inflammation in sebaceous cells in the sebaceous glands.Studies have shown that the CAMP factor in C. acnes involved in inflammation induced by acetyl acetate [24]. Nakatsuji T et al. vaccinated mice with CAMP factor vaccine, resulting in protective immunity against C. acnes-induced ear inflammation, indicating that CAMP factors are immunogenic and secreted toxins and involved in C. acnes-induced inflammation [25]. We note that the use of vaccination and specific antibody injection to inhibit bacterial CAMP factors and host ASMase, respectively, achieved a combined action and effective relief of inflammation caused by C. acnes. These findings suggest a new infection mechanism where the CAMP factor can cooperate with host ASMase to enhance bacterial toxicity to degrade host cells without disturbing the human skin microbial ecosystem.

3.2.4 Acne Hyaluronic Acid Lyase Vaccine

In a recent study, the researchers identified that hyaluronidase produced by C. acnes had two variants, the HylA variant was produced entirely by the acne-associated acnes, and HylB was produced by the acnes associated with healthy skin [25]. When studying structural and genetic differences, the team found that HylA aggravates acne by causing inflammation, and HylB seemed to reduce inflammation and promote skin health; When studying the differences in the skin, we found that HylA produced larger hyaluronic acid fragments lead to a stronger inflammatory response, while HylB produced smaller anti-inflammatory fragments. After a genetic knockout of hyaluronidase, C. acnes is no longer inflammatory. Based on the findings, the researchers developed an acne vaccine targeting HylA, which is effective in reducing inflammation and alleviating acne pathology in a mouse model. The functional differences between HylA and HylB are the main driving force behind Chlamydia acnes health and acne phenotypes, and suggest HylA as an approach to acne treatment.

3.3 Challenges and Perspectives for Acne Vaccines

Despite significant progress in the development of an acne vaccine, there are still many challenges and problems. First of all, the pathogenesis of acne is not fully clear and involves many complex factors,a single vaccine may not have enough protective effect, and it is difficult to completely prevent or cure acne, therefore, the next step needs to consider targeting multiple pathogens and virulence factors combined with multivalent vaccine; Secondly, for C. acnes, there are problems such as a wide variety of strains and complex action mechanism, and the development of vaccines needs in-depth research on different types of strains; In addition, there is no ideal animal model of acne, the existing animal model is not able to fully copy the clinical manifestations of human acne and pathological changes, animal sebaceous glands secretion sebum composition is different from human, acne animal model of acne and inflammatory reaction mechanism and human have different so cannot determine the vaccine clinical trial effect [26]. In addition, the study of immune persistence and recurrence mechanism of acne vaccine is a very complex topic. Although the vaccine has achieved some results in animal experiments and clinical trials, it is still necessary to ensure the safety and efficacy of the vaccine through long-term clinical testing and observation.

In the prevention and control of diseases, vaccines are recognized by the vast majority of professionals and the public as an efficient tool. Advances in vaccine development have made it possible to withstand more pathogens and provide more possibilities to solve the problem of bacterial resistance. Vaccines targeting the bacterial pathogens of acne can not only reduce the use of unnecessary antibiotics, but also hope to work through multiple mechanisms to effectively prevent and control the occurrence and development of acne. At present, there is no successful acne vaccine in the world. With the rapid development of modern medicine, biotechnology and artificial intelligence, the development and application prospect of acne vaccine are worth looking forward to.

4. Conclusion

This article briefly reviews the prevalence of acne, pathogenic factors, treatment options and existing problems, acne is a chronic skin disease, serious acne will not only bring pathological harm to patients, but will leave facial scars, discomfort, emotional stress, damage, and even permanent skin scars, lead to bad self-esteem, anxiety, social

fear and depression, largely reduce the physical health and quality of life, bring huge economic costs and psychological burden to individuals and society. Among the pathogenic factors of acne, four known acne physiopathological factors are included, including increased sebum secretion influenced by androgen, abnormal keratosis of sebaceous glands, excessive microbial proliferation of acne, inflammatory reactions caused by bacterial antigens and cytokines; moreover, genetic, environmental changes, diet, stress and hormonal factors may also cause or aggravate acne. In focus on the current mainstream acne treatment plan, focus on the development of acne vaccine, present situation, challenges and future trends, aims to further promote acne vaccine research and development to provide certain theoretical basis and reference value, and provide new ideas and methods of acne prevention and treatment, may help to solve the chronic skin disease of many teenagers. However, this paper still has some limitations, such as the pathogenesis of this review is not complete, only summarizes the main four, some potential pathogenic mechanism is not analyzed, and the vaccine treatment did not cover all, the scheme is only based on theory or only in mice, in the subsequent experiment is still insufficient, used for human body will have the same effect and whether unpredicted side effects are still unknown. Although there is no successful acne vaccine in the world, with the rapid development of modern medicine, biotechnology, artificial intelligence, the development and application prospects of acne vaccine are worth looking forward to.

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