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An Examination of the Immunologic Features of Recurrent Aphthous Ulcers during Their Entire Course

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Abstract: Recurrent aphthous ulcer (RAU) is a frequent oral mucosal illness that can affect all areas of the oral mucosa. Its symptoms include erosion, ulcers, and localized oral mucosal congestion. Its pathogenesis and etiology, however, are convoluted and uncertain. As of right now, the prevailing opinion is that immunological factors, vitamin deficiencies, infections, genetic anomalies, and other factors may play a role in its development. The body's immune-related components, such as cytokines (interleukin gamma Interferons), humoral immunity (complement, immunoglobulin), and cellular immunity (T lymphocyte subpopulations), are now widely acknowledged as being key players in the pathophysiology of the condition. In patients with RAU, the alterations in the amounts of many immune-related components are extremely intricate. This paper outlines the roles of immune regulation and the alterations in immune factor levels throughout the onset and healing of RAU. This paper can be used as a reference to learn more about the process underlying mouth ulcers and to treat and lower the disease's recurrence rate.

Keywords: Recurrent Aphthous Ulcer; Immune Factors; Cytokine; Cellular Immunity; Humoral Immunity.

1. Introduction

Recurrent Aphthous ulcers (RAU) are a prevalent and frequent oral disease that significantly disrupts the patient's life and emotional well-being.

It is often characterized by burning pain at the site of attack, which affects eating, as well as multiple episodes of prolonged healing. The etiologies and pathogenesis of RAU are complex and have not yet been fully elucidated. Numerous investigations have revealed links between humoral immunity, inflammatory processes, and cellular immunity—such as the T-cell subpopulation—and the pathophysiology of RAU. This research reviews the evolution of oral ulcers during the pathogenesis and healing phase of RAU, as well as the roles and alterations of various immune function indicators (immune modalities, inflammatory agents, and healing factors). This research provides a reference for revealing the mechanism of oral ulcer development and for treating and reducing the recurrence of the disease.

2. Inflammatory Factor

2.1. Interleukin-1(IL-1)

IL-1 is a relatively potent pro-inflammatory cytokine that is mainly derived from monocyte-macrophages.IL-1 promotes T-cell activation, proliferation, and differentiation; activates B-cells in concert with cytokines such as IL-4; and also stimulates the synthesis and secretion of immunoglobulins. This may be achieved by IL-1-inducing IL-6 production by peripheral blood mononuclear cells. IL-1 enhances the killing activity of NK cells by increasing their sensitivity to cytokines such as IL-2. IL-1 stimulates the production of cytokinees such as IL-8 by monocytes and macrophages. It also play an important role in mediating neutrophil chemotaxis and regulating the migration of eosinophilic leukocytes.

It has been found that IL-1β plays an important role in the development of RAU, but its mechanism of action is not clear [1] . As a member of the IL-1 family, IL-1β has three main functions: 1） It inducing T cells to produce IL-2, promoting fibroblast proliferation, and facilitating tissue healing. 2） It promotes adhesion of endothelial cells and leukocytes eutrophil chemotaxis, and enhances TNF-a activity. 3）It increases the expression of granulocyte-macrophage clone-stimulating factor and enhances wound repair [2].

2.2. Interleukin-2 (IL-2)

Interleukin-2 (IL-2) is a cytokine-signaling molecule in the immune system that regulates the activity of lymphocytes. IL-2 binds to the IL-2 receptor on the surface of lymphocytes, and it is mainly derived from activated CD4+ T cells, activated CD8+ T cells, NK cells, dendritic cells, and macrophages.

Sun A, et al. [3] found that during the pathogenesis of RAU, the level of IL-2 in the saliva of patients gradually increased, and the increase in plasma level was more obvious during the active phase of RAU. IL-2 is able to activate NK cells, a non-specific cell in the body that is mainly used in the body's anti-tumor and viral functions. IL-2 activates NK cells, which are non-specific cells in the body, and plays a key role in the body's anti-tumor and anti-virus functions. In some cases, it is also involved in allergic reactions and autoimmunity. Jurgr S et al. [4] also showed that the level of NK cells increases during the onset of RAU and decreases during the remission period, i.e., during the onset of RAU, the increase in the level of IL-2 causes an increase in the level of NK cells, which, to a certain extent, may have an effect on the development of RAU disease.

Sun Lifei et al [5] concluded that the defective immune system of T-lymphocytes is an important reason for the occurrence and development of RAU and wound repair, and low concentration of IL-2 can regulate the immune system in vivo, which has a better therapeutic effect on RAU. However, Yang M et al. [6] observed that the plasma levels of IL-2 in RAU patients also decreased compared to normal values prior to the administration of the drug, whereas after one course of the drug, their plasma levels of IL-2 increased, and at the same time, the immune response in the body and the tissue healing

ability of oral ulcers also improved, and there was a significant improvement in the clinical manifestations of RAU. There are different views on the function of IL-2 in the development of RAU, which is still inconclusive, and its specific pathogenic mechanism and function need to be explored in depth.

2.3. Interleukin-6 (IL-6)

IL-6 belongs to a kind of cytokine possessing multiple functions, which can regulate the growth and differentiation of various cells, and its major role lies in immune regulation, which plays a key role in maintaining the stability of human physiological and biochemical functions when the human body is subjected to pathogens. Meanwhile, IL-6 also plays a very crucial role in the chronic inflammatory response. ShenC, YeW, GongL et al. [7] showed that the level of IL-6 was significantly increased in RAU patients.

In the early stage of RAU disease, a variety of etiological factors cause changes in the oral mucosal microenvironment, and pattern recognition receptors for example Toll-like receptor 4 are activated, which stimulates the body to secrete pro-inflammatory cytokines such as IL-1 and IL-6, and promotes the activation and proliferation of T-cells, which initiates cellular immunity, resulting in an intensification of the inflammatory response and dysfunction of T-cells. The excessive inflammatory response damages the integrity of the gingival epithelium and causes tissue defects, which leads to the development of RAU and severely limits wound repair. Karakus [8] et al. utilized a study on the association between IL-6 gene polymorphisms and RAU, and the results showed that there was a significant positive correlation between IL-6 and the development of RAU and that high levels of IL-6 in the body played a significant role in the development of RAU.

During the pathogenesis of oral ulcers, the epithelial cells of the oral mucosa will gradually apoptoze, and the apoptotic cells will be stripped, producing a great deal of inflammatory factors, which in turn accelerate the progression of the ulcers. When the ulcer area gradually expands and the disease gradually aggravates, its pro-inflammatory effect is also enhanced, inflammatory factors are continuously secreted, and the level of IL-6 is also gradually increased and expressed at a high level.

Jia Yanmin et al. [1] found in their work that RAU formation is due to an imbalance of inflammatory factors such as IL-6, whose levels increase abnormally under normal conditions; therefore, reducing the level of inflammatory factors is beneficial to the repair of oral ulcers, and during the period from the beginning of the oral ulcers to the healing of the oral ulcers, the level of IL-6 first increase and then decreases; therefore, the decrease in the level of inflammatory factors also indicates that the mouth ulcers are gradually recovering.

2.4. Tumor Necrosis Factor-α (TNF-α)

An important source of TNF-α is monocyte-macrophage cells, and its concentration in the body is very small, while its concentration in the body increases significantly when the body has an inflammatory response and, in a sense, promotes the production of pro-inflammatory factors such as IL-2, which exacerbates the inflammatory response and causes the formation of ulcers [9]. It is hypothesized that TNF-α may be a key link in the pathogenesis of RAU.

Several national and international studies have shown that TNF-α concentrations are significantly higher in patients with recurrent aphthous ulcers compared to healthy individuals. It is suggested that the level of TNF-α is closely related to the development of RAU, and in the treatment of recurrent ulcers, the plasma TNF-α concentration of patients gradually decreases until it tends to normalize.

2.5. Interferon-γ (Interferon-γ, IFN-γ)

Currently, the view that "immune dysfunction may be one of the pathogenic mechanisms" has been unanimously recognized by many scholars at home and abroad. Lewkowicz et al. [10] believe that the Th1 cell-mediated inflammatory response plays a key role in the process of ulcer formation in RAU patients. However, T-lymphocytes such as Th0, Th1, and Th2 play a crucial role in the differentiation process in the body. These two diseases not only produce different levels of inflammatory responses in the body but also have different effects on the function of Th1/Th2.Dysregulation of Th1/Th2 balance is an important cause of oral ulcers. However, IFN-γ is predominantly a Th1 cell, which can induce the conversion of static CD+4 T lymphocytes to Th1 and inhibit the proliferation of Th2 cells [11], thus causing an imbalance of cellular immunity in patients with RAU, which contributes to the occurrence of oral ulcers to some extent. Meanwhile, along with the gradual restoration of the lesion to health, the IFN-γ concentration then gradually decreases until it tends to normalize.

3. Humoral Immunity

Immunoglobulins and complement are important components of humoral immunity. Their changes during the onset and healing stages of oral ulcers influence lesion regression.

3.1. Immunoglobulins

Wu Wei et al [12] found that the levels of serum immunoglobulins IgG, IgM and IgA in the venous blood of patients with RAU were higher than those in the general population. Li Haibo et al [13] also showed that the levels of IgG and IgA in RAU patients were higher than those in normal subjects, but the levels of IgM didn't change significantly. This is similar to the study of Zou Lilin et al [14], who also found that the levels of IgE were higher in RAU patients than in healthy subjects. The experimental results of Lelia et al [15] also showed that the level of IgE levels in saliva of RAU patients were significantly higher than those of the normal group, suggesting that IgE can be used as an early assessment indicator for patients with oral ulcers. Huan-Huan Ruanet al [16] found that IgG, IgA, and IgE levels were elevated in refractory RAU compared with the healthy group. Wang Xiang et al [17] found that in the study of RAU, the serum immunoglobulin levels of gender group had no significant difference in serum immunoglobulins, while the results of the age group showed that Serum IgA levels were higher in RAU patients over 50 years of age than in those under 50 years of age, while there was no significant difference in other serum immunoglobulin parameters between age groups.

However, the results of other scholars are not in line with the above-mentioned results. Yan Yagen et al [18] showed that serum immunoglobulin levels were not associated with the development of RAU. Du Yijun et al [19] found that serum IgA, IgM and IgG levels were normal in RAU patients. Wu Huihua et al. [20] found the results of salivary.

SlgA samples in RAU patients were lower than that of

normal control group, and serum immunoglobulin samples did not show any significant changes compared to the normal group. Another scientist [21] suggested that IgA samples in the RAU group were lower than those in the normal group, and this result suggests that the protective effect of immunoglobulins on the local mucosa is weakened in the early stages of ulceration, which leads to an increased risk of pathogen invasion and increased damage to the local mucosal barrier by metabolic cytotoxins.. Currently, various studies on the role of immunoglobulins in the RAU may be closely related to the period of sample collection, and elevated serum immunoglobulin levels are often indicative of the body's humoral immune function.

3.2. Complement

The levels of C3 and C4 are good indicators of humoral immunity [22].The results of Mai Xi et al [23] showed that serum complement C3 and C4 levels in RAU patients were significantly higher after healing.Wu Wei et al [12] found that C3 and C4 levels were higher than those in the control group, and Li Haibo et al [13] found that C3 and C4 levels were higher in the ulcer group than those in the normal group,which was closely related to the enhancement of humoral immunity.Wang Xiang et al [17] found that serum C3 levels in the severe RAU group were significantly higher than those in the mild RAU group.The C3 level in the group with larger ulcer area was significantly higher than that in the group with smaller ulcer area.

They concluded that elevated serum complement levels would lead to increased hemolytic activity, resulting in increased hemoglobin, vitamin B12, and folate deficiencies, which remain to be investigated. Huan-HuanRuan et al [16] found that the C3 and C3 levels in patients with refractory RAU and generalized RAU were higher than those in the other groups. Complement activation releases mediators of inflammation, amplifying the immune effect and exacerbating the disease response. About Complement levels in patients with RAU have been documented differently, and Zou Li lin et al [14] showed that serum C3 and C4 levels in patients with refractory RAU were not significantly different from those in healthy controls. Chen Zhi jie [10] found that C3 and C4 levels in RAU patients were significantly different from those in healthy controls.They suggested that C3 and C4 were involved in the inflammatory response of RAU, causing a sharp decrease in C3 and C4 levels and mediating the development of disease. Therefore, the complement pathway plays an extremely important role in the immunization process of RAU.

4. Cellular Immunity

Studies have shown that T-lymphocytes play a crucial role in the onset of RAU. The imbalance of T-lymphocyte subsets in the peripheral blood and locally in the ulcers of patients with RAU leads to impaired cellular immunoregulation, in which CD4+ T-cells are the key pivotal cells of the body's immunoregulation, while CD8+ T-cells act as suppressive T-lymphocytes, which are capable of effectively preventing the over-activity of the immune cells, and the two are coordinated by mutual constraints, thus maintaining the balance of the CD4+/CD8+ ratio in the body [24]. Many of the results on the specific change trends of each subpopulation are not uniform, and the differences in these findings may be related to the development of the disease course of the observed subjects, the timing of sample collection, and the testing process.

Studies on peripheral blood T-lymphoid subpopulations in RAU patients have mostly concluded that RAU patients have decreased CD4+ and CD4+/CD8+, suggesting that recurrent aphthous ulcers are associated with cellular immune dysfunction [25-26]. Mei Haili, Zhang Jing, Zou Yuhong, Chen Ying, He Wei, Ren Xiangying, Luo Zhixiao, and Ruan Huanhuan [27-34] found that RAU patients had elevated CD8+ along with decreased CD4+ and CD4+/CD8+, and some scholars [34] studied the experiments in which peripheral blood CD4+ cell levels and CD4+/CD8+ ratios were significantly lower in the attack group compared with the healing group, and CD8+ levels, on the other hand, were significantly elevated, which was especially evident during the onset period.

The episodes of RAU have a certain regularity, and some scholars have categorized the episodes into the prodromal, ulcerative, interval, and healing phases. The clinical recognition of this regularity is based on the experience summarized from the results of a large number of studies. Some scholars [35-39] compared the different attack periods of RAU and found that there were fewer CD4+ T cells in the pre-exacerbation period of RAU when there was a significant increase in CD8+ T cells, causing a decrease in the ratio of CD4+ to CD8+. While the ulcer stage [39] had elevated CD8+ T cell content and abnormal cellular immune regulation, the decrease in CD4+ cells and increase in CD8+ cells in RAU patients were able to increase the cytotoxic effect of B cells and damage normal epithelial cells. In the presence of immunodeficiency, the reduction of CD4+/CD8+ makes the cells more susceptible to various pathogenic factors, resulting in localized destruction, ulceration, and necrosis of the oral mucosa. Therefore, some scholars [31] speculated that the cause of RAU may be related to the infection caused by immune dysfunction, and this conclusion may provide useful guidance for clinical treatment.

In addition, some studies [40–41] have found a decrease in CD4+ cells in the peripheral blood of RAU patients, while the CD8+ cell content remained within the normal range. Another study [24] found that the number of CD4+ and CD8+ cells in the T lymphocyte subpopulations of RAU patients was significantly decreased, which was significantly different from that of the normal population. It has been hypothesized that the pathogenesis of RAU may be related to a decrease in the number of immune cells in the body, which leads to a decrease in cellular immune function; at the same time, a decrease in the ability of the immune system to produce specific adsorption of antigenic substances leads to humoral immune suppression. The increase in persistent inflammatory response at the RAU lesion is due to the decrease in the content of cytokines that have anti-inflammatory effects because of the increase in the level of inflammatory cytokines [24].

5. Conclusion

Up to now, the reasons and mechanisms for the occurrence of RAU remain unclear. Nonetheless, the aforementioned findings suggest that immunological variables are crucial in the development of RAU. In order to keep the body in a dynamic equilibrium, inflammatory factors, humoral immunity, cellular immunity, healing factors, and other multi-factors both encourage and inhibit one another. Once the expression of each of these factors is imbalanced, it will cause an immune imbalance in the body, which will lead to inflammation, ulceration and other tissue damage. Therefore,

in order to deeply explore the causes of RAU and the immune factors affecting its development, it is necessary to test the immune factors related to it and analyze its immune function status. In addition to immune factors, there are genetic, systemic diseases, environmental and other factors that can lead to the development of recurrent ulcers. There is currently a consensus among academic community regarding the etiology and pathogenesis of RAU, which indicate that a variety of circumstances contribute to the disease's emergence.

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