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Immune Mechanisms and Emerging Therapeutic Strategies in the Management of Condyloma Acuminata

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ABSTRACT

This review summarizes current research on the relationship between human papillomavirus (HPV) infection and host immune responses in the development and persistence of condyloma acuminata (CA). It highlights how HPV evades immune surveillance and the implications for disease management and treatment.

Keywords: *Immune Mechanisms, Emerging Therapeutic Strategies, Management of Condyloma Acuminata*

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INTRODUCTION

Condyloma acuminata (CA) is caused by human papillomavirus (HPV) infection. So far, more than 100 HPV genotypes have been discovered, and more than 35 types can infect the genital epithelium. Among them, HPV6, 11, 16, and 18 are more common, and a small number of cases are closely related to the occurrence of cervical cancer [1]. Studies have shown that the persistence and intractability of CA are related to HPV escaping the body's immune surveillance. The body cannot establish an effective immune response and produce specific local anti-HPV cellular immunity, which may be one of the essential mechanisms for the occurrence and persistence of CA [2]. Therefore, studying the immune function of CA patients has gradually attracted the attention of scholars at home and abroad. This article reviews the research in this area as follows.

1. CHANGES IN CELLULAR IMMUNITY IN PATIENTS WITH CONDYLOMA ACUMINATA

1. Local cellular immunity: Due to the structure and characteristics of HPV, it is limited to infecting the local skin and has no systemic infection phase. Forming a specific immune response to the virus, especially local cellular immunity, is difficult. Therefore, the immune system does not easily clear the virus and is prone to repeated attacks in the local latent infection. Subclinical infection is an essential cause of CA recurrence.

1.1 Langerhans cells (LC) HPV antigens are mainly expressed in differentiated and mature keratinocytes but lack effective expression in basal cells, and their infection is non-cytolytic. LCs are the primary antigen-presenting cells in the epidermis, mainly distributed in the basal and middle layers of epidermal cells. They rarely have the opportunity to come into contact with viral antigens and present them to immune-competent cells in the dermis. Papillomavirus-like particles cannot activate LCs, cannot form specific humoral and cellular immunity against HPV, and cannot promote the migration of immune cells to the epidermal tissue [2]. In addition, studies have found that after HPV infection, the number of LCs in the lesions is significantly reduced, the morphology changes, and the cytoplasmic processes become shorter, reduced, or absent, which may be one of the critical factors leading to antigen presentation disorders. Using antigen-pulsed dendritic cells to treat CA patients, studies found that after treatment, many immune cells infiltrated the blood vessels in and around the lesions, the number of vacuolated cells decreased, and the symptoms of viral infection were relieved or disappeared [3]. This shows that activated dendritic cells not only have a strong antigen-presenting function locally, but also can induce the body's immunity, stimulate the body's immune cells to move to the infected site, improve the patient's damaged local cellular immune function, and thus help eliminate the virus and prevent further damage and recurrence of the body's cells. This suggests that enhancing the antigen-presenting function of local immune cells is the key to treating CA [3].

1.2 Keratinocytes (KC) After HPV infection, human leukocyte antigen-DR (HLA-DR) and intercellular adhesion molecule (ICAM-1) are diffusely expressed in keratinocytes, providing a structural basis for mutual contact and interaction with immune cells. It may play an important auxiliary role in strengthening the immune response as an antigen-presenting cell. Studies have shown that the host cells of HPV are mainly KCs, and their life cycle is closely related to the differentiation and maturation of KCs. The virus is often eliminated from the body with the apoptosis of mature KCs [4]. Many transcription factors, including the CCAAT/enhancer binding protein (C/BP) family, can regulate the differentiation of KCs. The E2 protein expressed by the virus has a synergistic effect with C/EBP-α and C/EBP-β, which can promote the differentiation of KCs. However, in HPV-infected skin, HPV capsid proteins E6 and E7 can inhibit the interaction between E2 and C/EBP, inhibiting the differentiation and maturation of KCs and allowing the virus to persist. It has also been reported that after HPV infection, specific antigens are expressed on the surface of keratinocytes, which allows infected keratinocytes to evade the cytolytic effect of cytotoxic T lymphocytes, making the infection difficult to eliminate [5].

1.3 Lymphocytes: After HPV infection, patients experience a decrease in total T cell (CD3+) and helper T cell (CD4+) counts in their peripheral blood, while suppressor T cell (CD8+) counts increase. The CD4+/CD8+ ratio is significantly lower than normal individuals, suppressing the body's cellular immune function. This leads to an imbalance in the lymphocyte and its subsets within localized skin lesions. Studies have found that HPV-infected genital lesions are primarily infiltrated by CD4+ and CD8+ T lymphocytes. Still, most of these T cells are HLA-DR negative, and the CD4+/CD8+ ratio is decreased. In spontaneously resolving lesions, T cell numbers increase significantly, primarily CD4+ T cells, and the CD4+/CD8+ ratio is significantly higher than in lesions that show no signs of resolution, indicating that host cellular immune function is restored or enhanced during resolution.

1.4 Vascular Endothelial Cells: After HPV infection, endothelial cells (HLA-DR) and ICAM-1 show diffuse and strong expression in some veins with moderate to severe mononuclear cell infiltration. Applying HPV antigens to microvascular endothelial cells of the cervix has also revealed expression of selectin E, ICAM-1, and VCAM-1. Selectin E and VCAM-1 expression in endothelial cells is more prominent during wart resolution. The production of adhesion molecules facilitates the homing of antigen-specific lymphocytes to the site of inflammation and the continuous increase in immune cell numbers within the lesion.

2. SYSTEMIC IMMUNE RESPONSE:

The factors determining HPV clearance, persistence, or malignant transformation are unknown. Individuals with HLA-DQw3 and DR15 types are more susceptible to HPV-related malignancies, while those with HLA-DR13 have a lower risk.

2.1 T Lymphocytes: Cellular immunity plays a key role in viral clearance. Th1 cells mainly secrete IL-2 and IFN-γ. IFN-T is a decisive activating factor for monocytes and macrophages, while IL-2 and IFN-T are also potent activators of NK cells. Studies have found that CTL responses and Th1 cell response patterns can be detected in patients whose viruses have been cleared in the peripheral blood and local cervical tissues. CTL responses and Th2 cell response patterns are related to the subsequent clearance of HPV viruses. Patients with persistent HPV infection often show low levels of Th1 cell secretion factors, and the interaction between factors secreted by Th1 and Th2 cells is unbalanced [6]. The Th2 cell response pattern, which mainly expresses IL-4, 6, and 10, is closely related to the malignant transformation of cervical lesions.

2.2 Natural Killer Cells (NK Cells) are an important immune regulatory cell. A decrease in their activity can decrease the body's ability to clear tumor cells and viral infections. This is consistent with the results of studies on NK cells in the peripheral blood of patients with condyloma acuminata. The more obvious the decrease in NK cell activity, the more lesions there are in condyloma acuminata. Gauda reported that CA patients often have decreased IL-2 and IFN levels, speculated that decreased NK cell activity in CA patients may be secondary to these decreased levels. The increased risk of cancer in patients with chronic CA is not only related to the HPV subtype and long-term local irritation but may also be related to decreased NK cell activity [6].

2.3 Interleukin Family Studies by Gauda and other researchers have shown that serum IL-2 levels are decreased in CA patients. International studies have shown that soluble interleukin-2 receptor (sIL-2R) and membrane interleukin-2 receptor (mIL-2R) compete for IL-2 binding, neutralizing IL-2 surrounding activated T cells, thereby weakening the body's autocrine effect and acting like a blocking factor. They also have the effect of restoring activated cells to telogen, inhibiting T cell proliferation. Therefore, increased sIL-2R levels are believed to be a key factor in the suppressed immune function in CA patients [6-7]. Keratinocytes can spontaneously produce IL-1. When the epidermis is damaged, IL-1 is released into the extracellular fluid and participates in local and systemic immune responses in the skin. Arany's study found that patients with condyloma acuminata had reduced IL-1 levels. IL-10 is a cytokine that can produce bidirectional inhibition on Th1 and Th2 cells through different pathways. ELISA was used to detect the serum IL-10 and IL-2 levels in CA patients, and it was found that there was a negative correlation between IL-10 and IL-2. Patients had a series of cellular immune response inhibitory effects caused by cytokine imbalance. CA patients had low IL-6 and IL-8 levels. IL-12 can promote a Th1 cell response [7]. The ELISA method was used to measure the serum IL-12 level, which showed that its level was low and could not effectively enhance the activity of CTL and NK cells, nor could it selectively promote the proliferation and differentiation of Th1 cells, inhibiting the cellular immune response. It plays a vital role in the pathogenesis of condyloma acuminata. Studies have found that IL-15 and IL-12 can enhance the body's anti-tumor activity by up-regulating the expression of each other's receptors and synergizing the induction effect of IFN-γ. In addition, the low serum IFN-γ level in CA patients is related to IL-18, which leads to a series of cellular immune response inhibitory effects [7].

2.4 Interferon: A TH1-type cytokine, it primarily stimulates macrophages to kill intracellular bacteria.

2.5 Tumor Necrosis Factor (TNF): Excessive TNF can inhibit the differentiation of specific T cell clones and have direct cytotoxic effects, such as on CD4+ cells, leading to immune suppression. TRAIL, also known as apoptin-2 ligand, belongs to the TNF receptor superfamily and is the third apoptotic molecule discovered in the tumor necrosis factor family, following tumor necrosis factor (TNF) and FasL. The development, persistence, resolution, and recurrence of CA are associated with abnormal expressions of TRAIL and its receptor.

2.6 Pathogenesis of the Th1/Th2 Pattern: An overview of the cytokine network in patients with condyloma acuminata reveals that an imbalance in the interaction between Th1 and Th2 cell-secreted factors is one of the primary reasons for the patient's inability to exert immune responses. Liblau proposed the clonal drift theory, which posits that Th1 and Th2 cell activity is in a dynamic equilibrium under normal circumstances. However, when foreign antigens invade, the function of one Th1 or Th2 cell subset increases, while the other decreases. In CA patients, Th1 cytokine levels are low, making them weaker, while Th2 cytokine levels are elevated, making their activity stronger. This causes an imbalance between Th1 and Th2 cell subsets, shifting toward the Th2 direction. Consequently, Th1 and Th2 cell subsets become less effective in cellular immunity, allowing HPV to escape the immune system. Based on the Th cell drift pattern, efforts can be made to shift the immune response from Th2 to Th1, adjusting the Th1/Th2 balance. This can then be used to design appropriate treatment plans, potentially aiding the clinical treatment of genital warts.

II. Changes in humoral immunity in patients with condyloma acuminata

1. Antibody-mediated immune effects: Studies have shown that in an athymic mouse xenotransplantation model, antibodies against HPV capsid surface antigenic determinants can neutralize HPV infection, and the HPV-specific antibody level in the serum of the affected mice decreases. Clinically, condyloma acuminata can partially disappear, suggesting that the body's humoral immune response to HPV-related proteins plays a specific role in preventing infection and promoting the disappearance of skin lesions.

2. Antibody levels in patient serum: The IgA and IgG antibody responses of patients with cervical neoplasms were significantly higher than those of HPV-6 and HPV-18. The IgA and IgG responses were specific to HPV-16 and had cross-reactions among different types [5].

3. Antibody responses in CA patients: (1) The detected antibodies seemed to be type-specific and had no cross-reactions; (2) HPV16E7 antibodies were closely related to the presence of cervical cancer; (3) Anti-HPV16E7 antibodies were also a marker for the occurrence of cervical cancer, recurrence, or recent HPV infection.

III. Certain populations are genetically susceptible to HPV

Current studies on the HLA system of CA patients have shown that some people have a particular genetic susceptibility to HPV [8]. CA patients are significantly associated with HLA-A3, B60, and DQ2[9]. Qian Henglin et al. found that CA was associated considerably with HLA-A10 in Han Chinese [10]. This suggests that HLA-A3, B60, and DQ2 may be susceptibility genes for CA or linked to CA susceptibility genes. A study found that the presence of HLA-I type DQ3 antigen increases the risk of cervical cancer by 7 times [11]. At the same time, studies have shown that: ICAM-1 and HLA-DR antigens on the surface of KC in CA patients' lesions change the local cellular immune state, inducing T cells to gather and activate in the lesions, which is the key to effectively start and participate in local immunity and promote the regression of CA; there are abnormalities in the expression of HLA and DR antigens on peripheral blood lymphocytes in CA patients;

the expression and activation of CD69 and HLA-DR molecules on T cells in peripheral blood, and the number of HIL-CD8+ cells are significantly reduced, which is negatively correlated with the course of CA patients [12]. Since Siege [13] proposed the new concept of red blood cell immunity in 1981, studies have shown that changes in red blood cell immune function also play a specific role in the pathogenesis of condyloma acuminata. In recent years, studies have found that some apoptosis-related genes (such as Fas, Fasl, and TRAIL) are abnormally expressed, suggesting that CA may have abnormal cell apoptosis. 8. Research on HPV-related issues in patients with condyloma acuminata. HPV E6 and E7 proteins have multiple essential functions closely related to the pathogenic mechanism of the virus, including binding and degradation of the P53 protein and the pRb protein, thereby leading to cell cycle disorders. Suppressor of cytokine signaling 1 (socs1/JAB) plays a vital role in regulating E7 protein levels and transforming potential, and can be used as a new therapeutic tool for HPV-induced tumors [14-15].

From the current research on CA, it can be seen that the onset and recurrence of CA are related to a series of cellular immune response inhibitory effects caused by the body's local cellular immune function deficiency and cytokine imbalance, suggesting that in the future, CA treatment can seek more effective drugs by regulating the body's immune function [16]. In terms of local immunity, further research is needed on activating and enhancing LC processing and antigen recognition to develop effective vaccines and activate effective local immunity. How to block the expression of E6/E7 to promote cell differentiation, and how infected cells evade T cell mechanisms, all need to be further explored [17].

IV. Emerging Treatments and Immunotherapies for Condyloma Acuminata

Recent developments in immunotherapy offer promising therapeutic strategies for CA. One of the most compelling areas of exploration is the inhibition of immune checkpoints, such as the PD-1/PD-L1 axis [18-20]. This pathway is frequently exploited by HPV to evade immune surveillance, thus enabling the persistence of viral infections and the recurrence of CA lesions. Blocking the PD-1/PD-L1 pathway has been shown to enhance the immune response by preventing the suppression of cytotoxic T cells, which are crucial for targeting HPV-infected cells. Early-phase studies have demonstrated that immune checkpoint inhibitors, when used alone or combined with conventional treatments like cryotherapy or laser ablation, may significantly improve outcomes in patients with persistent HPV infections [18-20]. This approach is particularly beneficial for individuals who are immunocompromised or have undergone unsuccessful treatments for CA, as it may restore the body's ability to clear the infection and prevent the recurrence of warts [21]. While further clinical trials are necessary to confirm the efficacy of these therapies, initial results suggest that immune checkpoint inhibition holds promise as a valuable adjunct to traditional treatment regimens. Moreover, advances in mRNA vaccine technology show promise in treating HPV-related cancers, which traditional vaccines cannot cure. Unlike preventive vaccines, mRNA vaccines stimulate the immune system to target specific proteins on tumor cells. Early studies in mice and clinical trials for HPV-related head and neck cancers have shown encouraging results, particularly when combined with immune checkpoint inhibitors. Despite challenges like immunogenicity and instability, ongoing research suggests that mRNA vaccines could be crucial in developing effective therapies for HPV-associated malignancies [22-23].

In addition to immune checkpoint inhibition, the development of therapeutic vaccines targeting HPV-specific antigens represents another promising avenue for CA management. Unlike preventive vaccines such as Gardasil and Cervarix, which aim to prevent HPV infection, therapeutic vaccines stimulate the immune system to target and eradicate existing HPV-infected cells [22-24]. These vaccines primarily focus on eliciting an immune response against the HPV oncoproteins E6 and E7, critical to the development and persistence of CA and related malignancies [23]. Initial studies evaluating therapeutic HPV vaccines have shown encouraging results, particularly in their ability to induce potent T cell-mediated immunity and reduce viral load in patients with persistent infection [23]. When combined with cytokine-based therapies, which further activate and enhance immune cell function, these novel therapeutic vaccines could significantly alter the treatment paradigm for HPV-related diseases, offering a new line of defense against CA and reducing the risk of progression to cervical cancer [22-24].

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