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New Progress of T Cells in Oral Lichen Planus

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Abstract: *Oral lichen planus (OLP) is a relatively common chronic oral mucosal disease mediated by T cells, and its pathogenesis may include antigen-specific and non-specific. The etiology is unknown and the course of the disease is chronic and prolonged. The treatment has become a rather difficult clinical problem. There is no cure for OLP at present. Histologically, it is characterized by band-like infiltration of subepithelial T lymphocytes, rupture of the basement membrane, and liquefaction and degeneration of basal cells. Its etiology is not yet fully understood, its course is chronic, and its treatment has become a difficult clinical problem. Because of the malignant phenomenon of long-term erosion lesions, WHO lists it as a precancerous state. The main pathological changes of OLP are liquefaction and degeneration of basal cells and infiltration of subepithelial lymphocytes. The pathogenesis of OLP is not yet fully understood. OLP is an inflammatory disease mediated by T cells, which is related to autoimmune function. Various pathogenic factors lead to changes in the antigenicity of epithelial keratinocytes. The altered antigens are taken up by Langerhans cells and presented to* $CD4^+$ *T cells, these cells release and activate various cytokines to destroy the epithelium, and these cytokines activate* $CD8^+$ *T cells to initiate a series of immune responses, leading to the formation of OLP lesions. Studies have found that the pathogenesis of OLP is a process of immune damage mediated by T cells, which is related to the body's autoimmune function.*

Keywords: *T cells, Oral lichen planus, New developments*

1. Introduction

Lichen planus (LP) is a kind of skin. Chronic inflammatory disease characterized by abnormal mucosal keratinization. The skin and mucous membranes can develop independently or sequentially. Lesions that occur in the oral mucosa are called oral lichen planus. Oral lichen planus (OLP) is a T cell-mediated chronic oral mucosal disease of unknown etiology. The main histological changes are liquefaction and degeneration of the basal cell layer of the epithelium, destruction of the basement membrane, and band-like infiltration of lymphocytes in the lamina propria. At present, the etiology and pathogenesis of oral lichen planus (OLP) are still inconclusive, but a large amount of evidence shows that immune factors play a major role in the occurrence and development of the disease [1]. Statistics show that the subvariability of OLP is 0.4% to 3.2%, and the World Health Organization (WTO) lists it as possibly related to cancer. The typical pathological manifestations are incomplete keratinization of epithelial cells, liquefaction and degeneration of the basal layer, and a dense lymphocyte infiltration zone in the lamina propria [2]. Clinically, it can be divided into 6 types: reticular type, papule type, plaque type, blister type, atrophic type and erosive type. The course of disease is long, which can last for 20 years. The infiltrating cells in OLP lesion are mainly T lymphocytes [3]. What are the regular changes in the number, distribution, proportion of subgroups and products in the development of the local disease course of the lesion? How to stop or reverse these changes with medication? These issues have become the focus of research. The infiltration of T lymphocytes in the upper dermis suggests a close relationship between cell-mediated immune responses and the pathogenesis of OLP [4]. In recent years, various related studies at home and abroad have shown that both the peripheral blood and local lesions of OLP patients show a different distribution of T lymphocytes than normal people [5].

2. T cells in OLP

2.1. $CD8^+$ *Tcell*

Oral lichen planus (OLP) is a common mucosal disease second only to oral ulcers, and it occurs in

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middle-aged and elderly patients. Matthew et al observed that the lymphocytes in OLP were almost exclusively T cells [6]. The current research on its pathogenesis shows that immune factors play an important role in the pathogenesis of oral lichen planus [7]. $CD8^+$ represents T cytotoxic cells, $CD8^+$ can infiltrate the lesion area by chemotactic lymphocytes, monocytes and eosinophils by secreting various cytokines such as tumor necrosis factor and interferon, and eventually lead to liquefaction and degeneration of basal cells [8]. The majority of T cells within the LP and adjacent to damaged basal keratinocytes are activated $CD8^+$ lymphocytes. It is generally believed that oral lichen planus is an inflammatory disease mediated by T cells, which is related to autoimmune function, and various pathogenic factors lead to changes in the antigenicity of epithelial keratinocytes [9]. Studies have shown that $CD8^+$ cells and $CD8^+$ T cells play an important role in the occurrence and development of OLP. In the later stage of OLP development, the infiltration of $CD8^+$ T cells is more obvious, and the ratio of $CD4^+$ T/ $CD8^+$ decreases. The autoimmune response induced by OLP plays a major role in the pathogenesis of OLP [10]. Cells release and activate various cytokines to destroy the epithelium, and at the same time, these cytokines activate $CD8^+$ T cells to initiate a series of immune responses, leading to the formation of oral lichen planus lesions [11]. Compared with oral mucosa, the infiltration of $CD8^+$ T cells in OLP was significantly increased, and the distribution in the lamina propria was zonal, which was consistent with previous studies. In recent years, studies have suggested that apoptosis also plays a role in the pathogenesis of oral lichen planus. However, scholars at home and abroad have different opinions, and there is no unified conclusion, and the specific apoptosis mechanism is not very clear [12]. Statistical analysis of $CD8^+$ T cell infiltration found that there was no significant correlation between $CD8^+$ T cell infiltration and patient age, gender, location, and the presence or absence of erosion. In vitro, the cytotoxicity of diseased $CD8^+$ T cell clones can be blocked by anti-MHC-I (major histocompatabili-ty complex-I, MHC-I) monoclonal antibody [13]. A normal immune response depends on the mutual promotion or mutual restriction of various immune cells, especially T cell subsets [14]. The proper ratio of CD4 to CD8 is of great significance to maintain the immune balance and health of the body, and the ratio of CD4/CD8 has an important influence on the regulation of immune function in the body. Abnormal cD4/CD8 ratio can lead to cellular immune disorders.

2.2. $CD4^+$ *Tcell*

T lymphocytes are derived from lymphoid stem cells in the bone marrow, develop and mature in the thymus, and differentiate into $CD4^+$ T cells and $CD8^+$ T cells, of which $CD4^+$ cells are helper T cells (Th), which play a major role in cellular immunity. $CD8^+$ T cells are cytotoxic T cells (Tc/CTL), which are a kind of effector cells with killing activity. The main pathological changes of OLP are the band-like infiltration of a large number of inflammatory cells in the lamina propria and the liquefaction and degeneration of the basal cell layer, suggesting that cell-mediated autoimmunity damages the basal cells [15]. Although most lymphocytes in OLP intraepithelial and superficial lamina propria are $CD8^+$ cytotoxic T cells, Junge found by immunoelectron microscopy that most lymphocytes in the lamina propria are $CD4^+$ helper T cells [16]. The lesions of patients often have symptoms such as roughness, woodiness, burning, pain and discomfort. Since the etiology and pathogenesis of OLP are still unclear, the course of the disease is prolonged, the treatment is difficult, there is a risk of cancer, and it causes great harm to the body and mind of the patient, so it is reasonable [17]. Treatment has important implications for patients with OLP. Sugerman et al. isolated non-cytotoxic $CD4^+$ T cell clones from in vitro skin pit lesions [18]. In recent years, with the progress of research on the correlation between OLP and T lymphocyte subsets, it is generally believed that immune imbalance plays an important role in the occurrence and development of diseases. Under the stimulation of various antigens, $CD4^+$ T lymphocytes can abnormally activate and proliferate, differentiate into different types of cell subsets, secrete various cytokines, and participate in OLP in the form of a network [19]. $CD8^+$ T cells can up-regulate the secretion of Th1 cytokines from $CD4^+$ T' cells, suggesting that there is a large number of interactions between $CD8^+$ T cells and $CD4^+$ T cells in OLP. The search for key regulatory factors has always been a Hot spots and difficulties in the field of OLP research [20].

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3. New progress of T cells in oral lichen planus

3.1. Establishment of human oral lichen planus keratinocyte cell line

The culture technology of normal oral keratinocytes is becoming more and more mature, and the related finished culture medium has also been successfully developed, and a relatively perfect culture system has been established. We need to establish an in vitro cell model of human OLP. The in vitro culture of human OLP keratinocytes is an important basis for the establishment of the OLP cell model. In the process of epithelial cells moving from the basal layer to the surface, the cells continuously synthesize proteins, among which a very important one is the intermediate filament keratin, which is a tension filament under the electron microscope, and its chemical composition is cytokeratin, which is the main cytoskeleton. Proteins are important for maintaining cell shape. The cultured human OLP keratinocytes are scattered and arranged, the cells are polygonal or round, and the microvilli around the cells are radiating with different lengths; the central bulge of the cells is the nucleus, and the surface shows a white high-density area, this area is microscopic. The villi are abundantly aggregated. Vacuole-like cells were seen in passages 5 and 6. The whole cell growth period is a single keratinocyte, the cell is polygonal, and when it grows to a certain density, it presents a typical paving stone shape, which is in line with the growth morphological characteristics of epithelial cells, and the cells can be passed down for 5 to 6 generations. In the process of epithelial cells moving from the basal layer to the surface, the cells continuously synthesize proteins, among which a very important one is the intermediate filament keratin, which is a tension filament under the electron microscope, and its chemical composition is cytokeratin, which is the main cytoskeleton. Proteins are important for maintaining cell shape. To establish a cell line, first of all, it is necessary to identify the tissue source of the cell line, that is, whether the cultured cells are epithelial cells or fibroblasts. In keratinocyte cultures, fibroblasts are most likely to be mixed. To demonstrate that the cultured cells were single keratinocytes, vimentin immunohistochemical analysis was performed. The experimental results can clearly show that the cultured cells are not mixed with fibroblasts, but are single keratinocytes.

3.2. Mast cells and basement membrane destruction

Oral lichen planus is characterized by liquefaction and degeneration of basal cells, subepithelial lymphocytic infiltrates, and increased numbers of intraepithelial T cells (TCs) [21]. Some scholars believe that OLP is a T cell-mediated immune response, the specific mechanism is not clear. JungeLL et al. used immunohistochemical methods to observe widespread changes in the OLP epithelial basement membrane, such as breaks, bifurcations, and overlaps [22]. Zhou et al found that the density of mast cells at OLP basement membrane rupture was significantly higher than that in normal mucosa, speculated that the accumulation of mast cells and the media from which they originate may be related to basement membrane rupture [23]. It has been more than a century since Nobel laureate Ehrlich first described MC. Studies have found that MC is derived from hematopoietic stem cells and derived from CD34+ bone marrow stem cells. It enters the bloodstream and settles in different organs, including the digestive tract, lungs and skin [24]. Urogenital tract. Zhao et al. showed that mast cell density was increased in OLP compared to normal, with approximately 60% of mast cells degranulated, compared with only 20% in normal mucosa [25]. MCTs are mainly distributed in the respiratory tract and the mucosal layer of the small intestine, while MCTCs are mainly distributed in the skin and lower layers of the small intestine. Degranulated mast cells release pro-inflammatory mediators such as TNF-a, chymase, trypsin, and histamine. In rodents, they are divided into mucosal MC (MMC) and connective tissue MC (CTMC) according to the characteristics of their colonization in the body [26]. The two are distinguished by the difference in Alcian blue staining and particle composition [27]. The former is distributed in the mucosal layer of the respiratory tract and small intestine, which is distributed in the skin connective tissue, abdominal mucosa, muscle blood vessels and peripheral nerve tissue [28]. Recently, it was found that CK has a significant effect on the function of MC. IL-12 induces the production of IFN-r in mouse peritoneal MC, but does not produce IFN-r under the stimulation of anti-IgE antibody or lipopolysaccharide (LPS), and psoriatic skin MC can produce IFN-r. r. The significance of these findings is to suggest that MC can lead to Th1 or Th2 type immune responses depending on the stimuli.

3.3. Mast cells and T cell activation

Morphological studies have shown that degranulated mast cells are in close proximity to T cells, speculating that there may be substantial interactions between the two cells [29]. Direct contact between MC and TC is the basic condition for antigen presentation, and electron microscope observation of MC

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and TC in the human nasal mucosa does have this heterotypic contact. Mast cells secrete and synthesize various factors that can activate T cells, including TNF-d, IL-3, 4, 5, 6, 8, 10, 13, 16, monocyte chemoattractant protein-1, macrophage inflammatory Protein la, 1B and regulators of normal T cell expression and secretion activity, etc [30]. The reason for the interaction between MC and TC is that CK and chemokines secreted by MC and TC can activate MC and release mediators, and the role of chemokines and chemokine receptors can regulate the dynamic balance of cell migration, colonization and other factors [31]. The progression of inflammation. Mast cells express both MHC-I-related antigens and MHC-II-related antigens, both of which are necessary for presenting antigens to $CD8^+$ or $CD4^+$ T cells, and mast cells also express B71, B72, and CD54 adhesion molecules [32]. These molecules are secondary signals for T cell activation in antigen presentation. MC affects TC migration, and it has been reported that MC can release chemokines by releasing chemokines. MC expresses CD54, also known as intercellular adhesion molecule, which can bind to CD11α and integrin on activated TC, TNF-α can strengthen the structural interaction between MC and TC, and TNF-α can be expressed outside the cells in the inflammatory zone [33]. At the stromal TC binding site, TNF-α binds to the TNF-α receptor on TC, activates TC to release active regulatory protein expressed and secreted by normal T cells, and causes TC aggregation [34]. Recent studies have found that the supernatant of OLP lesioned T cell culture can trigger degranulation of mast cells, resulting in the release of histamine and TNF-a, and TNF-a can activate the lesioned T cells to produce RANTES [35]. RANTES is the most potential mast cell activator, which stimulates mast cell degranulation through RANTES receptors on mast cells, and this cycle may be one of the reasons for the chronic characteristics of OLP.

4. Conclusions

The etiology of OLP is not yet clear, but it may be related to genetic factors, autoimmunity, infection, and mental factors. The pathogenesis is currently believed to be caused by apoptosis of epithelial basal cells mediated by autotoxic $CD8^+$ T cells. At present, drug therapy is still the main treatment method. The diagnosis and treatment guidelines recommend the use of glucocorticoids and immunosuppressive drugs, such as systemic use of prednisone, hydroxychloroquine, thalidomide, transfer factor, and tretinoin. The study found that most of the cells infiltrated by inflammation in OLP were $CD4^+$ T and $CD8^+$ T cells, and the CD4/CD8 ratio decreased. Khan et al also found that most lymphocytes in the superficial lamina propria in the epithelium and subepithelial are $CD8^+$ T cells, and $CD8^+$ T cells are adjacent to apoptotic keratinocytes. The acetylation modification of $CD4^+$ T lymphocytes in OLP peripheral blood includes abnormal changes, and the activity changes of HDACs in peripheral blood are closely related to the acetylation modification. However, due to the numerous classifications of HDACs and the involvement of many different kinds of proteases, the specific mechanism of action of different kinds of HDACs in oral lichen planus remains to be further explored in future studies.

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