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Research Progress on Helicobacter Pylori Infection and Autoimmune Thyroid Disease

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Abstract: In recent years, more and more studies have focused on the extra-digestive manifestations of Helicobacter pylori, and thyroid disease is a current hot spot. It has been confirmed that changes in the structure and composition of intestinal flora are related to the occurrence and development of autoimmune thyroid disease (AITD). When the intestinal flora is unbalanced, Helicobacter pylori colonizes the body through the damaged gut and releases special proteins that have similar amino acid sequences to thyroid antibodies. These proteins also destroy the metabolism of the body through molecular simulation and other mechanisms, attack the autoimmune system, especially the thyroid system, and ultimately lead to AITD. Therefore, Helicobacter pylori may play an important role in the pathogenesis of autoimmune thyroid disease, and this evidence may provide new ways to treat autoimmune thyroid disease.

1. Introduction

Autoimmune thyroid diseases (AITDs) are autoimmune diseases that target the thyroid gland and have a prevalence of approximately 5 percent, more in women than in men[1]. Clinically, Graves' disease (GD) and autoimmune throiditis (AIT) are the most common. Hashimoto thyroiditis (HT) is a common type of AIT, characterized by thyroid dysfunction and lymphocyte infiltration of thyroid tissue, characterized by hyperthyroidism and hypothyroidism, respectively, and often elevated thyroid autoantibodies, such as thyroid-stimulating hormone receptor antibodies (TRAb), thyroglobulin antibodies (TGAb), and thyroid peroxidase antibodies (TPOAb)[2].

The aetiology of AITDs is unknown and may be related to factors such as genetics, sex, infection, iodine intake, cytokines, and stress response. Studies have found that exposure to excessive iodine promotes disease in people with specific genetic backgrounds. Recent bacterial and viral infections

are the focus of discussion, possibly by molecular mimicry mechanisms, cross-immune responses of antibodies to antigen structures, or chronic inflammatory responses[3]. As the largest endocrine organ, the gut has a rich flora that plays an irreplaceable role in the progression of autoimmune thyroid diseases (AITDs) but is often overlooked[4]. Helicobacter pylori (HP) is a spirochete-like bacterium that colonizes the gastric mucosa as a microanaerobic gram-negative bacterium, and humans are its sole host and source of infection. Helicobacter pylori was recognized as a class I carcinogen by the World Health Organization in 1994[5]. At present, Helicobacter pylori is one of the most common bacteria in the world, which is associated with many digestive diseases, such as chronic gastritis, Helicobacter pylori-related peptic ulcer, gastric cancer, gastric mucosa-associated lymphoid tissue lymphoma, etc.[6]. In recent years, the relationship between Hp infection and TN and AITDs has also been revealed, and studies have found that the rate of Hp infection in patients with AITDs is increased, so the pathogenesis of AITDs may be related to Hp infection, so eradication of Hp infection is expected to reduce autoimmune antibodies in patients with AITDs[7].

2. Helicobacter pylori pathogenesis

Helicobacter pylori (Hp) was developed in 1979 by Australian scholar J. Robin Warren and Barry J. Marshall successfully isolated and cultured curved bacteria from gastric antral mucosal biopsy specimens from patients with chronic gastritis, a spiral-shaped, flagella-negative gram-stained pathogenic bacilli parasitic on the surface of the gastric mucosal epithelium, and since then, worldwide interest in this bacterium has increased[8][9][10]. Hp infects approximately half of the world's population, and rates of Hp infection vary by age, ethnicity, geographic region, and socioeconomic status, in fact, with higher prevalence in developing and less socioeconomic countries[11].

As early as 1988, Penhale and Young found that in conventionally raised rats, the composition of normal gastrointestinal flora is prone to cross-reactivity with thyroid tissue antigens, and the regulation of gut microbiota has a significant effect on thyroid autoimmune susceptibility[12]. At present, it has been found from histoculture that both the stomach and thyroid are derived from the foregut[13], and the foregut is the anterior part of the liver formation part, which can be divided into the oral cavity, pharynx, esophagus, stomach, and duodenal beginning. Gastric mucosa-associated lymphoid tissue (MALT) can be observed in the gastric mucosa of patients infected with Helicobacter pylori[14], as can lymphoid tissue formation by lymphocytes infiltrating the thyroid gland in thyroid tissue in patients with autoimmune thyroiditis[15]. Molecular simulation theory suggests that dozens of bacterial proteins have local amino acid sequence similarities to TSHR, and one is similar to TPO, while fragments of TSHR, TPO, and NIS all partially or completely contain at least one of their own epitopes containing Helicobacter pylori protein[16]. Due to the structural similarity of Helicobacter pylori antigen and thyroid autoantigen, cross-immune reaction occurs between them, which eventually leads to the occurrence of thyroiditis. This confirms the reactive hyperplasia caused by Helicobacter pylori infection. Most of the patients with autoimmune thyroid disease are positive for cytotoxin associated gene A antigen (CagA). CagA can increase the level of systemic inflammatory factors in patients, including the inflammatory of stomach and thyroid [17][18][19]. Then, the blood cell count of neutrophils and basophils will also increase [20]. Autoantibodies cause cytokine storms and chain reactions aggravate the inflammatory invasion of thyroid gland.

3. Helicobacter pylori infection and Graves disease

Graves' disease (GD) is a multisystem syndrome that includes hypermetabolic syndrome, diffuse goiter, eye signs, skin lesions, and thyroid acral disease. Because most patients have both

hypermetabolism and goiter, it is also called toxic diffuse goiter. It is an autoimmune disease caused by antibodies (TRAb) produced by thyroid-stimulating hormone receptor (TSHR) on the membrane of thyroid follicular cells, which is the most common cause of hyperthyroidism, with an annual incidence of about 20~30/1 000,000, about 3% of women and 0.5% of men, generally concentrated in the 30~60 age group[21]. At present, the pathogenesis of GD has not been fully elucidated, and the occurrence of hyperthyroidism is significantly related to human leukocyte antigen (HLA class II antigen), and its detection rate varies according to race. Immune response is the core pathogenic mechanism of GD occurrence and development, T cell subset imbalance is the main factor, B and T cells are activated by antigen-presenting cells (APCs) and cytokine pathways, resulting in directed differentiation of helper T cells (Th) and regulatory T cells (Treg)[22]. CD4 T cells then recognize thyroid autoantigens and bind to their receptors and are activated, resulting in the production of various adhesion molecules and cytokines, and activate CD8 T lymphocytes or B cells, eventually producing autoantibodies[23], leading to the development of GD. Choi YM et al. found that H. pilory infection may increase serum TPO-Ab[24].

Studies have found that there is local structural homology between thyroid peroxidase and thyroglobulin and some Helicobacter pylori antigens, so after the human body is infected by Helicobacter pylori, it induces the body's immune response and forms antibodies against Helicobacter pylori, which have functional and structural similarities between this antibody and thyroid autoantibodies, and have a countervailing effect on thyroglobulin and thyroid peroxidase, thereby attacking the thyroid gland itself [25]. According to the experimental results, Zonulin is upregulated by about 8 times in toxic diffuse goiter and 5 times in Graves' ophthalmopathy [26][27], leaky gut induces the release of inflammatory cytokines, which themselves promote increased permeability, which is a vicious cycle that facilitates the entry of antigens derived from diet and gut microorganisms, thereby inducing the activation of intestinal immunity. Su X et al. demonstrated other evidence that the gut causes GD immune disorders, and the intestinal flora leads to an imbalance of Treg/Th17 through propionic acid-regulated pathways, which causes the occurrence of GD, in addition to elevated inflammatory cytokines such as IL-6 and IL-2, the researchers also verified that elevated IL-18 is a key factor in intestinal inflammation [28]. Studies in patients with autoimmune thyroid disease reported a significant 2.24-fold increased risk of AITDs with serum CagA positivity [29]. Bassi et al. also found that the number of IL-6, TNF-α, and thyroid autoantibodies in CagA-infected patients was significantly higher than in CagA-negative uninfected patients, suggesting that Helicobacter pylori leads to GD by increasing the chance of inflammatory infection and molecular mimicry mechanisms [30]. This was confirmed in a study of Chinese populations, with H. pylori CagA-positive strains associated with GD (P=0.015, OR=1.811), and patients with HLA-DQA1*0201 negative or HLA-DQA1*0501 positive were more exposed to GD [31]. A foreign case reported the first case of gastric mixed gonadal neuroendocrine carcinoma originating from Hp-related atrophic gastritis, and the histopathological results of the patient's lesions showed multiple atrophy of the gastric mucosa, positive Hp and neuroendocrine cell nests, and the patient contained higher titers of TPO-Ab and TgAb, indicating that Hp and the endocrine system have a common molecular pathway or mechanism [32].

In addition, the gut microbiota can affect thyroid hormone concentrations through enterohepatic circulation to control uptake and degradation of iodine and hormones, as well as the bioavailability of levothyroxine (L-thyroxine), while minerals also interact with the gut microbiota, mainly zinc content affects the gut microbiota. Furthermore, the microbiota may play a role in thyroid disease by influencing the nervous system, regulating the endocrine axis, and thus influencing TSH secretion [33].

4. Helicobacter pylori infection and Hashimoto thyroiditis

Hashimoto thyroiditis (HT) was first discovered and named by Dr. Hashimoto Hakaru (1881-1934) of Kyushu University in Japan in 1912, also known as chronic lymphocytic thyroiditis, Hashimoto's thyroiditis is a common disease in autoimmune diseases and has become a global public health problem, accounting for about 5% of the general population [34], with a global prevalence of 10-12%, and women are more susceptible to infection. The peak age of incidence is between 30 and 50 years[35][36]. Hashimoto's thyroiditis is a chronic, autoimmune, aseptic inflammatory disease that uses its own thyroid tissue as an antigen. HT is characterized by diffuse inflammatory changes accompanied by thyroid lymphocyte infiltration, leading to the destruction of thyroid epithelial cells and subsequent fibrosis, local production, release, and diffusion of inflammatory factors, and as blood circulation to various parts of the body acts on distant tissues and organs, causing damage to distant organs, thereby participating in the pathogenesis of Hashimoto's thyroiditis, which can be manifested as an increase in the number of thyroid-related antibodies[37].

There is substantial evidence that both deregulation of the intestinal flora and increased intestinal permeability increase the incidence of HT, and the endocrine axis associated with the thyroid gland and the gut has been proposed, which is closely related to the overall metabolism of the body[38]. Single nucleotide polymorphisms of TSH receptor and thyroglobulin molecules have been found to be significantly associated with HT, they may increase their autoantigen potential and alter their expression changes at the thymus level, thereby reducing central tolerance to HT[39][40], while presenting antigens for specific HLA II recognized by CD4 T helper cells and presenting them to TCR (T cell receptor) cells on T lymphocytes while binding to HLA molecules[41][42]. Lauritano et al. revealed that apparent hypothyroidism is associated with bacterial overgrowth[43]. Several studies have shown that the presence of H. pylori is positively correlated with HT[44][45][46][47], and studies have found that patients with certain genes infected with Helicobacter pylori are more likely to develop Hashimoto's thyroiditis[48]. Lanza et al. reported that an autoimmune marker associated with H. pylori infection in patients with Hashimoto's thyroiditis and not present in the control group, an allele DRBI-0301 associated with autocellular antibodies, is more likely to develop Hp infection in patients with this allele[49].

A study by Benvenga S et al. on the role of the gut microbiota in AITD found cross-immune responses between certain microbial antigens and autoantigens [50][51]. Hp infection may induce the proliferation of CD4 T lymphocytes, which can also recognize the epitope of H.pylori, and the structure of these lymphocytes resembles the proton pump of parietal cells H+/K+ adenosine triphosphatase (H+/K+ ATPase), an enzyme found on the parietal cell apical membrane[52]. The interaction between genetic and environmental factors allows antigens to be presented to T lymphocyte receptors by specific (monocytes, etc.) or non-specific antigen-presenting cells (thyroid cells), which bind to autoantigens and T cell receptors, jointly stimulating the inflammatory factor storm and activating the proliferation and polarization of autoreactive effector lymphocytes [53][55][56]. Dendritic cells present these common epitopes to naïve T cells, and Th1-driven autoreactive clones are activated in the absence of peripheral interference[54][55][56]. The cellular immune mechanisms of autoimmune thyroiditis have some similarities to those of CAG, in which inflammatory stimulation leads to the secretion of IFN-γ, a cytokine that converts thyroid cells into antigen-presenting cells[57]. Due to Th17 cell polarization, the inflammatory state and subsequent fibrosis dominate in the early stages of thyroiditis[58]. In later stages, when lymphocyte infiltration and parenchymal destruction are common, the Th1 profile changes accordingly[40], and Th1 lymphocytes help cytotoxic T lymphocytes to produce TNF-α and IFN-γ in thyroid cells, ultimately causing apoptosis, and gastric autoimmune-related diseases have been found to increase changes in

Th2 cytokine profiles[58]. However, the exact mechanism leading to the death of thyroid cells and parietal cells remains unknown, however, due to IL-1 produced by activated macrophages, Fas in thyroid cells will be upregulated, which is accompanied by expression and induces autocrine interactions, which may be the main mechanism for inducing apoptosis[55][59].

5. Conclusion

With the rapid development of society, people's work, economy, mental pressure increased, resulting in the decline of human autoimmunity, Helicobacter pylori has become one of the most common chronic infection bacteria in the clinic, Hp is chronic gastritis, Helicobacter pylori related peptic ulcer and other important pathogenic factors of gastrointestinal diseases, Hp infection rate in the population is extremely high, the world's total infection rate has exceeded half of the world's population, Hp is also one of the causes of a variety of human autoimmune diseases, can affect human immune function. In recent years, autoimmune diseases such as autoimmune thyroiditis have also gradually increased, and their pathogenesis and etiology are still not very clear, and it is generally believed that it may be the result of a combination of factors such as environment, immune response, genetic susceptibility and so on. Many researchers believe that gut bacteria can mimic the antigenic phenotype of the outer surface of thyroid cell membranes and play a pathogenic role in the development of autoimmune thyroid diseases. At present, the research on the correlation between Hp and AITDs infection has attracted the attention of relevant scholars at home and abroad, which points out a new direction in the clinical treatment of autoimmune thyroid diseases, and brings new breakthroughs to the study of etiology.

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