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# Updated review on immune factors in the pathogenesis of Crohn's disease

Li N *et al*. Immune in the Pathogenesis of CD

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**Abstract**

Although the incidence of Crohn's disease (CD) in China is not as high as in European and American countries, there has been a clear increasing trend in recent years. Little is known about its pathogenesis, cause of deferment and the range of complications associated with the disease. Local and international scholars have presented many hypotheses of CD pathogenesis based on experimental and clinical studies, including genetic susceptibility, immune function defects, intestinal microflora disorders, delayed hypersensitivity and food antigen stimulation. But the specific mechanism leading to this immune imbalance, which causes persistent intestinal mucosal damage, and the source of the inflammatory cascade reaction are still unclear. So far, the results of research studies differ locally and internationally. The most current research in immune correlation is presented in this summary.

**Key words:** Crohn's disease; cytokines; immune; immunotherapy; intestinal inflammation; lymphocytes; pathogenesis; T lymphocytes

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**Core tip:** It is now clear that Crohn's disease (CD) is an autoimmune disease that involves at least the intestinal mucosal immune system, when mucosal immune system is invaded by food or bacterial antigens. But it is worth mentioning that the mechanism remains unclear. Whether activation of the immune system is the internal defects (constitutive activation or regulation mechanism disorder) or changes in the epithelial mucosal barrier leading to continuous stimulation, it is still not clear. The mechanism of CD is intensively studied by domestic and foreign scholars on the immune destruction. Now, the mechanisms about T cell immunity, innate cell immunity and cytokines are briefly summarized as the latest research status of immune correlation.

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**Introduction**

Crohn's disease (CD) is chronic granulomatous inflammation, involving any part of the gastrointestinal tract, predominantly the terminal ileum and adjacent colon, and appearing as a symptom with segmental, asymmetric distribution of granulomatous inflammation[1]. The main clinical symptoms are abdominal pain, diarrhea, fistula, anal lesions and systemic symptoms of different severity within the body. The incidence and prevalence rates of CD have been increasing rapidly. Zheng *et al*[2]collected data and analyzed the current status and prevalence changes of CD in mainland China in recent decades, and found that the CD incidence and prevalence rates of the last decade were 1.21 per 100000 persons/year and 2.29 per 100000 persons, respectively. These rates are higher than that during 1950-2002, 0.28 per 100000 persons/years and 1.38 per 100000 persons, respectively[2]. However, the pathogenesis, cause of deferment and variety of complications are not clear[3].

Scholars have presented many hypotheses about the pathogenesis of CD. Some have suggested that the environment is filled with intestinal pathogens or opportunistic pathogens, such as pathogenic *Escherichia coli*, which spreads through patients’ intestinal epithelial cells, and if innate immune cells such as monocytes, neutrophils and natural killer cell (NK) cannot kill these translocated bacteria, they function as antigens, and keep stimulating intestinal mucosal cells to cause immune responses[4], like Thl and Thl7 abnormal activation. Th17 activation results in the formation of granulomas[5]. Some antigens produced by bacteria can induce CD4+T cells to differentiate into targeted cytotoxic lymphocytes (CTL cells), and these cells can release IL-17 cell factor, which stimulates Th17 cells to produce transforming growth factor, interferon alpha (TNF-α), which causes persistent inflammation and fibrosis[6]. Another opinion presented by Papadakis is that after the early antigen enters the body, associated lymphoid tissues are stimulated. When this occurs, the body becomes sensitive to the antigen, creating a sensitive state and mucosal immunity for the antigen of normal intestinal bacteria, and from then, any secondary damage to the intestinal mucosa barrier results in the antigen contacting the lymphoid tissue again, stimulating a severe local immune response[7,8]. However, intestinal mucosa barrier damage occurs all the time, yet, most often, there is no immune response. This obviously means that this disease is also related to the body's genetic susceptibility,materials and environmental factors[9].

These theories have some differences related to gene mutations causing immune dysfunction, delayed hypersensitivity, alterations of intestinal flora, and activation induced by some special food[10] or bacterial antigen. However, each mechanism ultimately involves the immune response and broken immune tolerance. At present, the specific process of disrupting the immune tolerance, and its sequence of genetic variation is still unclear. Although immunity is now a universally acknowledged cause of CD, hormone therapy can cause remissions, which demonstrates that CD is an immune-related disease. However, the specific mechanisms leading to immune imbalance, the source of the inflammatory cascade reaction and other aspects of the process are still unclear. Furthermore, so far, the results from the available literature are not the same locally and internationally. The latest research status of immune correlation is summarized as follows: At present, the specific processes involved in the breakdown of immune tolerance, and the associated sequence of genetic changes are still unclear[11-13] Also, the specific mechanisms leading to this immune imbalance, which causes persistent intestinal mucosal damage, and the source of the inflammatory cascade reaction are still unclear. So far, the results of research studies differ locally and internationally. The most current research in immune correlation is presented in this summary.

**Cell immunity and Inflammatory Factors**

## *T lymphocytes*

## CD4 / CD8T lymphocytes and cytokines: Some studies have found that CD results mainly from chronic inflammation of T lymphocytes, especially CD4+ T cells. As cells that mediate in humoral-immunity, B lymphocytes do not participate in CD’s occurrence and development. CD4+ T cells are the main effector lymphocytes in intestinal inflammatory tissue. Eventually, despite the differences in the development of the inflammatory process, the process of inflammation is induced by Th1 or Th2 cells. The two subgroups of cytokines produced by Th1 or Th2 cells are mutual antagonists, once a group of cytokines are produced earlier or more than the other, it will inhibit the other group of cytokines. Therefore, for the same inflammation, two kinds of CD4 + T cells can lead to different consequences, presenting two different types of immune response, CD and ulcerative colitis (UC). Lymphocytes play a dominant role in CD patients，mainly secreting IL-12, IFN-α, TNF-γ, IL-1, interferon gamma (IFN-γ), IL-2 and other cytokines[14-16] But for patients with UC in the intestinal mucosa, the characteristics of Th2 lymphocytes are atypical infiltration and production of IL-4, IL-5, 1L-13, TGF- beta cytokines. So, more autoantibodies are present in UC patients than in CD patients, mainly Th2 type immune response related antibody. In CD animal models, intestinal bacteria and some specific antigens, such as certain pathogenic *Escherichia coli*, can induce intestinal mucosal Th1, which induces a cellular immune response. However, cellular immunity can be induced in a specific susceptible gene animal model such as in *IL-10* gene knockout mice, whereas cellular immunity cannot be induced in wild type mice[17-19]. This also suggests that gene deletion and mutation cause the natural immunity defects that induce CD, and not just the adaptive immune response control. However, there is growing evidence that the Th1-Th2 classification is too simple; the two paths of mutual exclusion hypothesis has been questioned, and increasing evidence shows that IL-4 and IL-13 from the Th2s take part in ileal CD. In CD, there are two simultaneous changes in the initial stage of inflammation: the induction phase and the effector phase. Both Th1 and Th2 may participate in each phase simultaneously or sequentially.

Studies have found that CD8+ cells also exist in the intestinal mucosa. For example, many cytotoxic T cells are observed in CD models, indicating a greater effect than in other diseases. When a CD8 gene is deleted, there is no influence on CD inflammation, whereas when CD4+ genes are deleted, there is an improvement in intestinal mucosal inflammation, so the inflammatory response appears to be related to CD4+T lymph cells, and the CD8+ cell’s effect in CD remains unclear. However, the pathological effect of CD8+ should not be ruled out completely[19,20]. So far, cytotoxic T-lymphocytes (CTLS) in the pathogenesis of CD, and in the study of CD8+ cell subsets and T lymphocytes (CTLS, CD8, CD28+), are believed to play a key role in the recognition and elimination of cells, and their variation caused by graft-versus-host reactions. Compared with healthy subjects, CTLS in CD patients releases enzymes, such as perforin and telomerase, and increases cytotoxic protein activity. Studies have compared the CD8+ chromosomal changes in patients with CD to that of normal patients. Early activation of CD8+ may determine subsequent proliferation, cytokine production, and antigen recognition capability, so an intervention causing early activation of CD8 is a potential therapeutic option[21]. It has been found that the K+ pathway plays an important role in the activation of T cells in the early stage of CD, and in the expression of Kv1.3 and IKCa1. Additionally, many scholars have reported two kinds of potassium ion channel that play an important role in mouse and human inflammatory bowel disease development. The basic function of these ion channels is to maintain intracellular negative potential, so that the influx of calcium in the body fluids activates the immune function[22]. These studies have shown that the effects of CD8+ toxicity and T cell depletion on CD inflammation are different, but different Th1 mediated inflammatory responses play a major role in the pathogenesis of CD. So, the immune balance is deranged, and persistent inflammatory response is seen. Further detailed research is needed.

## *The new type of T lymphocytes and cytokines*

In recent years, researchers have found a new T cell, called the Treg cell. Human or mice CD4+T cells were put into IL-10 *in vitro* to repeat stimulation, and the secretion of high levels of IL-10 and low level of IL-2 subsets of T cells was induced. Treg cells have weak proliferation ability[23], but their cytokine secretion pattern is quite stable, so they can secrete a small amount of transforming growth factor-β (TGF-β), inhibit antigen-specific immune responses, and they can restrict intestinal inflammation through down-regulation of IL-10[24]. Treg cells are a group of T cell subsets with immunosuppressive effects. They can negatively regulate the immune system by inhibiting the proliferation and activation of CD4+ and CD8+T cells. Th17 cells are a newly discovered helper T cell subset, named after its secreted cytokine IL-17. Th17 cells play important functions in innate immunity and acquired immunity by the secretion of IL-17A/F, IL-22 and IL-21. TNF- α is an inflammatory cytokine in host defense in extracellular bacterial infection, and in anti-parasite immunity mediated by chronic inflammation and organ transplant rejection. Th17 cells have received extensive attention in many important physiological or pathological processes in immune disease and cancer, especially in the study of the pathogenesis of autoimmune diseases[25]. Researchers have found that Th17 and Treg are subsets of CD4+T cells. Th17 promotes intestinal inflammation induced by autoimmune diseases, while Treg inhibits intestinal mucosal inflammation, which means they have opposing functions. A recent study found that TGF- beta can induce naive T cells into Treg immunosuppression. In the presence of IL-6, TGF- β promotes naive T lymphocyte differentiation to Th17 cells; secretes proinflammatory cytokines IL-17, and promotes the occurrence of autoimmunity and inflammation[26]. Treg can repair mucosal inflammation in patients with inflammatory bowel disease (IBD), but under the influence of IL-6 and /or IL-23, Treg differentiate into Th17, then Th17 secrete large amounts of IL-17[27]. Kinugasa pointed out that IL-17 participates in the regulation of intestinal epithelial barrier function through the extracellular signal regulated (ERK) - mitogen activated protein kinase (MAPK), a pathway which may be a potential cause of intestinal inflammation[28].

Carrier *et al*[29] reported another kind of T cell that mediated oral tolerance by TGF-β called Th3 cells. The difference between Th3 and Tr is mainly that the former secretes high levels of TGF-β, inhibiting immune responses. Due to the lack of an immunomodulatory effect, IL-10 or TGF-α gene knockout mice easily suffer from autoimmune colitis. So, it is speculated that Treg and Th3 cell function disorders are involved in the pathogenesis of IBD, especially CD. Because previous studies of Th1 lymphocytes cannot fully explain the pathogenesis of CD, new T cells such as Th17, Treg and Th3 have become the mainstream of the inflammatory bowel disease system, which provides a new direction for the treatment for our in-depth study of CD.

## *Intestinal lamina innate lymphocyte and cytokines*

Natural killer cells (NK cells) are considered a part of the natural immune system of the lymphoid cell lineage. Innate immunity is a natural immune defense function formed through the body’s process of evolution and development. However, since the discovery of lymphoid tissue induction cell (LTi cell) in 1997, the lymphocyte populations in the innate immune system have been continuously expanded[30]. The loss of LTi cells lead to ROR γt expression defects, and the mice could not form lymph nodes and isolated lymphoid follicles, which means LTi cells are crucial for lymphatic tissues and organs, and the latter is the basis of the intestinal mucosal immune barrier and intestinal immune steady-state. In recent years, researchers have found some new immune cells in the mucosa of mice and human mucosal tissue. These cells belong to the lymph cell lineage in the form and development degree, but do not express specific antigen recognition receptors on the surface of the mature lymphocytes and they are similar to NK cells. Due to the characteristics of LTi cells, they are called innate lymphoid cells (ILC)[31]. Numerous studies have shown that ILC participates in the regulation of intestinal mucosa homeostasis, and plays an important role in the pathogenesis of inflammatory bowel disease through multiple pathways. Based on secretion factors and the transcription factor expression of the different cells, the family of ILC is divided into three categories: (1) ILC1; including classic NK cell, tissue residing in NK cells and mucous membrane ILC1; expressing T box transcription factor (T bet) and (or) Eomes. Under the stimulus of IL-12 and IL-18, ILC1 produce IFN-γ (interferon - gamma), which is mainly responsible for antiviral, bacterial and toxoplasma infection, and also plays a role in the immune memory. (2) ILC2; including NH cells (natural helper cell), producing Th2 sample cytokines, such as IL-5 and IL-13, that play an important role in parasite infection, allergy and asthma. (3) ILC3; including all the produced ILC subsets of LTi, IL-17 or IL-22, with LTi being the earliest reported ILC subset, can induce intestinal lamina propria isolated lymphoid follicles and the formation of lymphoid tissue by expressing the ROR-γ transcription factor[32,33]. A study[34] using model mice infected with *Citrobacter* and *Candida albicans* showed that ILC3 secretes IL17 and IL22, which can promote Paneth cells to secrete antimicrobial peptides (such as Reg IIIβ, Reg IIIγ). These peptides can block the contact between bacteria and epithelial cells, and inhibit intestinal inflammation. Some studies have shown that the reduction of IL-22 + ILC3 in intestinal mucosa is associated with the occurrence of IBD[35]. IL-22 promotes epithelial cell proliferation through the JAK-STAT pathway, thereby preserving the integrity of the epithelial barrier and hindering intestinal microbial invasion[36]. The deficiency of IL-22 causes damage to the intestinal mucosal barrier, which leads to the exposure of intestinal tissue to many antigens, and induces an abnormal immune response in the genetic susceptible host, which causes the occurrence of IBD[37]. Meanwhile, the macrophages and the intestinal secretion of IL-1β can stimulate ILC3 to produce granulocyte macrophage colony stimulating factor (GM-CSF): the latter in the gut of regulatory T cells plays a role in the proliferation[38]. Inhibition of GM-CSF can lead to a decrease in the number of regulatory T cells and immune tolerance defect, which also plays a role in the occurrence and development of IBD.

Studies have found that increased ILC3 can overexpress major histocompatibility complex (MHC) II[39,40]. ILC3 as antigen-presenting cells can pass through the surface of the MHCII, and induce CD4 + T cell apoptosis, and thus avoid the T cell response to produce intolerance to intestinal symbiotic bacteria. Further studies of IBD patients compared with non-IBD patients with intestinal mucosa biopsy pathology found that the expression of MHCII by ILC3 were significantly reduced and limited to CD4+ T cell apoptosis in IBD patients, and caused an immune reaction in its flora, damaging intestinal mucosa. Thus, the intestinal mucosa barrier damage and immune tolerance defects cause a disorder in intestinal homeostasis, which plays an important role in the pathogenesis of IBD, maintenance of homeostasis of the body and the coordination among the different subtypes that work together. Regarding CD, an increasing number of studies have confirmed that the imbalance in the regulation of ILC breaks down the intestinal tolerance for food and bacterial antigens in the gut leading to CD, with ILC3 being the most important[29,34,36,41]. A study found that the deletion of IL-22 + ILC3 caused the spread of *Alcaligenes sp.* in the intestinal lymph tissue and caused a systemic immune response, which may be deeply related to the occurrence of CD[42]. Mast cells stimulate fibroblast proliferation and collagen synthesis, and promote collagen protein aggregation activity and expression of c- kit receptor at the same time. Mast cells also stimulate chemotaxis through stem cell receptors (c-kit), and stimulate interstitial cell proliferation[43], using the *Salmonella typhi* aroA strain, induced C57/B16 mice to produce a severe and persistent bowel wall fibrosis in an animal model. In this animal model, chronic infection was caused by intestinal flora; large extracellular matrix (ECM) accumulation was seen in the ileocecal region and colon, fibrosis and extensive transmural inflammation extended to the colon[44], but the most serious and extensive fibrosis was found in the ileocecal valve[45] A study showed that ILC3 caused overexpression of IL-22, which activates monocytes, macrophages and mast cells during inflammatory mucosal repair. Finally, the innate lymphocytes in the tissue result in fibrosis. Many studies on inflammatory factors have reveal that IL-22 arguably secreted by ILC3s can promote Paneth cells to secrete antimicrobial peptides (*e.g*., Reg IIIβ, Reg IIIγ). These peptides can restrict bacterial contact with epithelial cells, and inhibit intestinal inflammation at the same time, and IL-22 promotes epithelial cell proliferation by passing through the JAK-STAT pathway to maintain the integrity of the epithelial barrier, and to prevent intestinal microbial invasion. Moreover, a lack of IL-22 causes intestinal mucosa barrier damage, and the intestinal tissue to be exposed to many antigens, inducing abnormal genetic susceptibility to host immune response, leading to CD[34,36,37]. Scholars believe that Th17 cells through inflammatory cytokines such as IL-17, IL-22, IL-21, and TNF-α, are involved in the body's defense of extracellular bacterial infection, parasitic immune resistance and mediated chronic inflammation, but excessive expressions of inflammatory markers lead to CD[25], and the results of the study were inconsistent. Further studies examining the role of IL-22 in the pathogenesis of CD are needed.

# Immunotherapy

The traditional view is that CD is due to acquired immune system disorders, and Th1 cytokines are the main factors in the development of CD. But only some of them can be used in the treatment of CD, including: IL-1, 2, 6, 12, 18, IFN-α and TNF-γ. They can invade intestinal epithelial cells and cause epithelial cell apoptosis by activating lymphocytes. So far, the most successful example is the use of anti TNF-α antibodies for the treatment of refractory CD with fistula. Mannon *et al*[46] reported the safety of subcutaneous anti IL-12 monoclonal antibody for 7 wk, and despite the small number of cases studied, the clinical response was significant when a higher dose of IL-12 monoclonal antibody therapy (3 mg/kg body weight) was given. Long-term safety is a particularly important problem because the Th1 cytokines are important factors as anti-infectives. For example, long term inhibition of the host response to TB caused by the treatment of anti TNF-alpha antibodies may lead to the recurrence of latent TB in the patient; anti IL-12 treatment should be considered for the possibility of recurrent asthma. Moreover, the etiology of CD is complex, especially in multiple stage disease. In some cases, the cytokines are likely to be harmful rather than beneficial. In some patients, anti TNF- α antibody (infliximab) treatment does not reduce CD progression, which shows that it is not only due to the Th1 pathway but also due to different mechanisms in the different periods of the disease progression. However, the innate immune system is also important, especially in the stage of disease induction; the congenital immune system cells is an important generator of cytokines, such as IL-1, TNF-α and alpha IL-6 and other cytokines, and these factors play an important role in intestinal mucosal inflammation. The CD susceptibility genes encoding intracellular proteins (such as NOD2/CARD15) were found first in the innate immune system, which can activate certain cytokines dependent on NF-kappa B to cause intestinal bacteria to break the immune tolerance of the intestinal mucosa[47]. By using monoclonal antibodies against cell factor, fusion protein, and receptor antagonists for cytokine blocking, immunomodulation of CD can be done effectively.

# Conclusion

Research on the relationship between the immune regulation and the pathogenesis of CD has greatly improved awareness in the development of CD. Since the discovery of the Th1 immune cells of new types of T cells such as Treg, Th3 and Th17, the application of inflammatory factor TNF- α antibodies to IL-12, IL-22, and other new cytokines, it is clear that the CD is a complex disease, not only due to the Th1 pathway, but also due to different mechanisms in different periods of disease progression, which is why the use of IL-12, TNF-α antibody treatment in many patients with CD is not so effective. Hereditary susceptibility, the surrounding environment, the intestinal flora and other factors may also be involved. Although there are a variety of cytokine antagonists in clinical application, the results are not satisfactory. So far, we have not found the main immune response pathway induced by CD. So, it is necessary to carry out a large-scale screening of important inflammatory cytokines and inflammatory cells in Asian populations, to find the main cause of the CD immune response pathway.

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**Figure 1 The main immune process of Crohn's disease.**



**Figure 2 The main immune mechanism of Crohn's disease.**