

## Study on the Role of Th17 Cells in Idiopathic Dermatomyositis Induced Myocardial Damage

Feng Chen<sup>1</sup>, Zhen Tian<sup>2</sup>

<sup>1</sup> Dermatology Department, China-Japan Union Hospital of Jilin University, Changchun, Jilin, 130033, China

<sup>2</sup> Cardiology Department, China-Japan Union Hospital of Jilin University, Changchun, Jilin, 130033, China

**Keywords:** Th17 Cells, Idiopathic Dermatomyositis, Induced Myocardial Damage

**Abstract:** In recent years, an important reason for little knowledge about the pathogenesis of PM is the lack of suitable animal models. This paper has successfully induced experimental autoimmune myositis models by immunizing animals with sarcoplasmic globulin extracted from skeletal muscle of increased doses of skeletal muscle and inoculation with PT. The model has the advantages of short time consumption and high repetition rate. This provides a good experimental tool for studying idiopathic inflammatory myopathy and exploring new treatments.

### 1. Introduction

Human idiopathic inflammatory myopathy (IIM) is a group of skeletal myositis diseases characterized by symmetric proximal muscle weakness and lymphocytic infiltration of non-necrotic striated muscle fibers. It is heterogeneous, acquired, and often involved. Organs, serious people are life-threatening. Polymyositis (PM) is one of the subtypes. PM has a slow onset. It is mainly characterized by progressive aggravation of symmetrical limb muscles, neck muscles and pharyngeal muscle weakness. It is a non-suppurative inflammatory disease of striated muscle. Involved in multiple organ lesions, may be associated with tumors and other connective tissue diseases. More common in women, myositis combined with other connective tissue disease patients, male to female ratio can be as high as 1:10. At present, the drugs for treating PM can alleviate the development of patients' disease to a certain extent, but due to the long treatment period, the side effects are large and the curative effect is limited. Therefore, it is urgent to clarify the exact pathogenesis of PM. In recent years, an important reason for the poor understanding of the pathogenesis of IIM is the lack of suitable animal models. We have successfully induced experimental autoimmune myositis models by immunizing animals with sarcoplasmic globulin extracted from skeletal muscle of increased doses of skeletal muscle and inoculation with PT. The model has the advantages of short time consumption and high repetition rate. This provides a good experimental tool for studying idiopathic inflammatory myopathy and exploring new treatments. Previous studies have suggested that PM is a T lymphocyte-mediated autoimmune disease. The presence of the MHC-I/CD8 complex has a definite diagnostic value for PM. Th17 cells are a third type of effector CD4<sup>+</sup> T cell subset found in 2005 different from Th1 and Th2 cells, and play an important role in the process of tissue inflammation and autoimmune diseases. ROR $\gamma$ t is a major but non-specific transcription factor of Th17 cells and plays an important role in the differentiation of Th17 cells. But is Th17 cell involved in the pathogenesis of PM and EAM? There are no relevant reports yet.

### 2. Overview of idiopathic inflammatory myopathy

Human idiopathic inflammatory myopathy (IIM) is a group of skeletal myositis diseases characterized by symmetric proximal muscle weakness and lymphocytic infiltration of non-necrotic striated muscle fibers. It is heterogeneous, acquired, and often involved. Organ disease, severely life-threatening. According to clinical characteristics and immunopathology, it can be divided into the following six types: 1 primary polymyositis (PM); 2 primary dermatomyositis (DM); 3

non-specific myositis; 4 inclusion body myositis (IBM); 5 immune-mediated necrotizing myopathy; 6 overlapping myositis. IBM is the most common acquired myopathy in adults after age 50. Overlapping myositis is sometimes referred to as PM or myositis associated with specific autoantibodies (such as anti-synthetase enzymes or anti-signal recognition particle antibodies). And PM is a rare and easily misdiagnosed disease.

Polymyositis (PM) is a slow onset, mainly characterized by progressive aggravation of symmetrical limb muscles, neck muscles and pharyngeal muscle weakness. It is a non-suppurative inflammatory disease of striated muscle, often involving multiple organ lesions. Concomitant with tumors and other connective tissue diseases, severe cases of crisis. The main pathological changes of PM are inflammatory cell infiltration and degeneration and necrosis of muscle fibers. Immunohistochemical studies have found that a large number of CD4 and CD8 lymphocytes infiltrate in muscle inflammatory tissues. It is generally considered that PM is a T lymphocyte-mediated autoimmune disease. Sexual diseases. Since the pathogenesis of this disease is still unclear, there is no effective treatment. The clinical treatment of polymyositis is: Glucocorticoid is the standard treatment for idiopathic inflammatory myopathy (IIM), and its efficacy has not been confirmed by randomized, placebo-controlled trials. The consensus is that glucocorticoids are relatively safe and can improve the course of the disease and are often used as the drug of choice to determine if a stronger immunosuppressant treatment is needed in the future. Although the drug can relieve the disease to some extent in clinical practice, its treatment time is long and the side effects are large.

In principle, immunosuppressants are drugs that are followed by hormones. Commonly selected drugs are: methotrexate, azathioprine, cyclophosphamide and tacrolimus. The ideal treatment regimen is to reduce prednisone and maintain it in small doses of methotrexate for several months to a year. These drugs have large side effects and are less effective. The side effects of related drugs are methotrexate pneumonia, and other side effects include gastrointestinal symptoms, leukopenia, and hepatotoxicity. Intravenous immunoglobulins have shown satisfactory results for PM, but are only suitable for short-term impact treatments, which are expensive and have a risk of transmitting the virus. There are also plasmapheresis and leukocyte replacement, treatment of biological agents, etc. These treatments are ineffective and costly. In short, the current clinical use of drugs for the treatment of PM can alleviate the development of the disease to a certain extent, but due to its large side effects, limited efficacy and long treatment time, it is urgent to clarify the exact pathogenesis of PM.

### **3. Th17 cells and autoimmune diseases**

A large number of studies have shown that IL-17 secreted by Th17 cells can activate downstream leukocytes to secrete various pro-inflammatory factors, chemokines, and activate cytotoxic effects (CTL) of CD8<sup>+</sup> T lymphocytes, leading to inflammatory reactions. Although there are a large number of studies on the relationship between Th17 cells and multiple autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus and inflammatory bowel disease, the research report on the relationship between Th17 cells and polymyositis is limited. Th17 cells are newly discovered effector helper T cells, which are involved in multiple autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus as an important pro-inflammatory cell. Previous studies have suggested that PM is an autoimmune disease dominated by cellular immunity, and Th17 cells are important participants in many autoimmune diseases. We have reason to believe that it may also be involved in the pathogenesis of polymyositis. . But how does T lymphocytes work during the onset of PM, which ultimately causes damage to muscle tissue? Little is known about it.

The differentiation process of Th17 cells requires three stages, including induction, amplification, and stabilization/maintenance. First, in the induction phase, Th17 cells initiate differentiation by the interaction of TGF- $\beta$  and IL-6; differentiated Th17 cells secrete IL-21, which promotes the expansion of Th17 cells by self-activation; finally, through IL-23. The signal achieves stability and maintenance of Th17 cell characteristics. IL-6 is a pro-inflammatory factor that produces large

amounts of IL-6 in infections, trauma, and localized inflammatory foci, and TGF- $\beta$  is considered to be an anti-inflammatory cytokine. In mice, a combination of TGF- $\beta$  and IL-6 is required for the induction of Th17 cell differentiation in vitro. The differentiation of human Th17 cells is very different from that of mice, and the current research is still not deep. The mainstream view in 2007 was that in vitro culture, IL-1 and IL-6 cytokines were sufficient to induce Th17 differentiation without the need for additional TGF- $\beta$ . However, further studies have shown that TGF- $\beta$  is an indispensable cytokine. Lower doses of TGF- $\beta$  are sufficient to induce Th17 cell differentiation. Various studies have shown that the concentration of TGF- $\beta$  is elevated, although the level of IL-17 produced by Th17 cells also increases, but this Th17 is highly expressed IL-10, low expression of T-bet and IFN- $\gamma$ . The induction of autoimmune diseases is significantly weakened and even inhibited. This suggests that TGF- $\beta$  can exert immunostimulatory or immunosuppressive effects, respectively, depending on the dose.

IL-21 belongs to the IL-2 family and is produced by NKT cells and activated T cells, while Th17 cells also secrete large amounts of IL-21. Studies have found that IL-21 produced by newly differentiated Th17 cells can promote the differentiation of other Th17 cells by self-activation. IL-23 is a member of the IL-12 family, which consists of two subunits p19 and p40. An innovative research, Cua and coworkers studies have shown that IL-23 deficient animals can not induce EAE onset, whereas IL-12p35 deficient animals (i.e. deletion of IL-12 and Th1 response, IL-23 Still alive) EAE is more likely to occur, and these data suggest that IL-23, but not IL-12, is important for the development of autoimmune diseases. Later studies have found that IL-23 can induce the production of IL-17-secreting cells (ie, Th17 cells). In addition, IL-23 can increase the proliferative capacity of pathogenic Th17 cells in vitro. These data show that IL-23 plays a very important role in the production of pathogenic Th17 cells. However, it should be emphasized that the initial differentiation of Th17 cells not involved in the IL-23, IL-23 only complete differentiation of Th17 cells play a role. Studies have shown that only Th17 cells induced by the combination of TGF- $\beta$  and IL-6 can not cause an inflammatory reaction, but if IL-23 is added when culturing Th17 cells, the cells can cause tissue inflammation. It indicated that IL-23 acts on differentiated Th17 cells and plays an important role in the stability and maintenance of Th17 cell characteristics.

#### **4. Th17 cells and Treg**

We usually call Treg CD4<sup>+</sup>CD25<sup>+</sup> Foxp3<sup>+</sup>Treg cells, and there is a lot of evidence that this group of cells plays an important role in peripheral immune tolerance and immune system homeostasis. A 2003 study found that Foxp3 is a hallmark of Treg-specific expression, but the cause of autoimmune disease caused by Foxp3 mutations has been unclear. Differentiation and function of Treg cells with TGF- $\beta$  has close relationship, studies have shown that TGF- $\beta$ 1-deficient mice derived from the CD4 + CD25 + Treg cells in SCID mice model fails treating autoimmune diseases in colitis Show any therapeutic effect.

Since the differentiation of Th17 cells and Treg cells shares the cytokine of TGF- $\beta$ , it suggests that they have some association during differentiation. The differentiation of Th17 cells and Treg cells is antagonistic. Initial studies have found that naive Th cells tend to express Foxp3 in the presence of only TGF- $\beta$  stimulation, thus becoming Treg cells. When inflammatory is caused by IL-6 (infection, injury, and local inflammatory foci can be produced in large amounts) or IL-21, it can inhibit TGF- $\beta$ -induced Foxp3 expression, thereby preventing the differentiation of Treg cells, making naive Th cells to Th17. Cell Differentiation.

#### **5. Conclusion**

Immunohistochemical results in patients with polymyositis suggest that there is more IL-17 in the inflammatory tissue of the muscle. This result suggests that Th17 cells may be involved in the inflammatory pathogenesis of PM. In the myositis animal model, the increase of Th17 cells and the up-regulation of ROR $\gamma$ t mRNA in EAM muscle inflammatory tissues were also observed, suggesting that Th17 cells may be involved in the pathogenesis of EAM.

## References

- [1] Cai Xiaoping, Wu Guanling. Effects of chemokines on Th1/Th2 immune balance[J]. Foreign Medical Sciences: Parasitic Diseases, 2004, 31(4): 154-157.
- [2] Yang Xiaomeng. Study on the shift of Th1/Th2, Tc1/Tc2 subgroups in children with idiopathic thrombocytopenic purpura [J]. Chinese Journal of Immunology, 2005, 21(1): 76-79.
- [3] Wu Weiquan, Sun Yanhua, Qiu Shaoling. Study and significance of Th1/Th2, Tc1/Tc2 subpopulation in peripheral blood of patients with AIHA[J]. Journal of Practical Medical Techniques, 2006, 13(7): 1044-1046.
- [4] Fan Yanying, Wu Changyou. IL-4, IL-10 and anti-IL-12 receptor  $\beta$ 1 mAb inhibit IL-23-induced IFN- $\gamma$  production in normal human memory T cells [J]. Journal of Immunology, 2006, 22 (4): 353-357.
- [5] Liu Wuyi, LU Aiyun. Effects of overtraining on glycogen content, AMPK activity and GLUT4 in skeletal muscle of rats[J]. Chinese Journal of Sports Medicine, 2006, 25(6): 668-673.