

# Upregulation of Interleukin 21 and Interleukin 21 Receptor in Patients with Dermatomyositis and Polymyositis

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## Abstract

**Background:** The immunopathologic mechanism underlying dermatomyositis (DM) and polymyositis (PM) remains poorly understood. Many cytokines play a pathogenic role in DM and PM. Interleukin 21 (IL-21) has a pleiotropic effect on inflammation regulation. This study aimed to detect the serum IL-21 level and investigate the expression of IL-21 and IL-21 receptor (IL-21R) in muscle tissues of patients with DM and PM.

**Methods:** Biopsied muscle samples were obtained from 11 patients with DM, 12 with PM, and six controls; mRNA levels of IL-21 and IL-21R were analyzed by real-time quantitative reverse transcription-polymerase chain reaction; and immunohistochemical staining was used to evaluate the protein expression of IL-21 and IL-21R. Serum samples were obtained from 36 patients with DM, 19 with PM, and 20 healthy controls. The serum IL-21 level was detected by enzyme-linked immunosorbent assay.

**Results:** The expression of IL-21 was upregulated in patients with DM and PM. The IL-21 mRNA level was significantly increased in muscle tissues of patients with DM and PM (DM vs. control,  $P=0.001$ ; PM vs. control,  $P=0.001$ ), whereas IL-21R mRNA level in patients with DM/PM was not statistically different from that of healthy controls. Immunohistochemical staining showed both IL-21 and IL-21R were significantly expressed in the inflammatory cells in muscle tissues of patients with DM and PM. The serum IL-21 level was also significantly higher in patients with DM/PM than in controls (DM vs. control, 49.12 [45.28, 60.07] pg/ml vs. 42.54 [38.69, 48.85] pg/ml,  $P=0.001$ ; PM vs. control, 50.77 [44.19, 60.62] pg/ml vs. 42.54 [38.69, 48.85] pg/ml,  $P=0.005$ ).

**Conclusions:** IL-21 expression is upregulated in patients with DM and PM in both muscle tissue and serum. In addition, IL-21R protein is highly expressed in affected muscle tissues of patients with DM and PM. IL-21 may play a pathogenic role through IL-21R in patients with DM and PM.

**Key words:** Dermatomyositis; Interleukin 21; Interleukin 21 Receptor; Polymyositis

## INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous disorders that directly affect the muscle and usually have symmetrical muscle weakness, elevated serum level of muscle enzymes, and extramuscular manifestations such as fever, skin rash, arthralgia, and Raynaud's phenomenon; muscle biopsy usually shows muscle fiber necrosis and mononuclear cell infiltration.<sup>[1-3]</sup> According to different clinical and pathological characteristics, the IIMs can be classified into the following subtypes: dermatomyositis (DM), polymyositis (PM), necrotizing autoimmune myositis, inclusion body myositis, and overlap myositis.<sup>[3]</sup> DM and PM are the two major subtypes of IIMs.

Currently, the immunopathologic mechanism underlying DM and PM remains poorly understood; DM is usually considered to be a complement-mediated microangiopathy, whereas PM is a T-cell-mediated myopathy in which the muscle fibers are directly invaded by inflammatory cells;

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the common pathologic feature is infiltration of varieties of inflammatory cells in affected muscle tissues.<sup>[3,4]</sup> During recent years, it has become gradually accepted that cytokines are regulators of leukocyte activation and migration, which may play a pathogenic role in the occurrence of DM and PM.<sup>[5]</sup> Conventionally, T helper (Th) 1 linkage was considered to play a pivotal role in DM and PM, and the related cytokines are interferon (IFN)- $\gamma$ , tumor necrosis factor alpha, interleukin (IL)-18, and IFN- $\alpha$ ; within these cytokines, IFN- $\alpha$  is predominantly associated with DM.<sup>[5]</sup> Since the discovery of IL-17 as a T-cell-derived cytokine and the role of Th17 linkage in inducing chronic inflammation, several studies have demonstrated the expression and the pathogenic role of IL-17 in patients with DM and PM; another Th17-related cytokine, IL-22, has also been detected in muscle tissues of patients with PM and DM and found to correlate with disease severity.<sup>[6,7]</sup>

IL-21 is a four-helix bundle cytokine and a member of the Type 1 cytokines, which also include IL-2, IL-4, IL-7, IL-9, and IL-15. IL-21 can be produced by a variety of immune cells such as cluster of differentiation (CD) 4+ T-cells, natural killer T-cells, neutrophils, and CD8+ T-cells (under certain conditions); T follicular helper and Th17 cells, which belong to the subsets of CD4+ T-cells, were reported to secrete the highest level of IL-21.<sup>[8]</sup> Biological activities of IL-21 are mediated by a heterodimeric receptor, which consists of a common  $\gamma$  chain subunit shared with other Type 1 cytokines and a private subunit (named IL-21 receptor [IL-21R]). The interaction between IL-21 and its receptor can induce activation of Janus kinase (JAK)-1 and JAK3 and then activate signal transducers and activators of transcription (STAT) 1 and STAT3.<sup>[9]</sup> IL-21R is highly expressed on a variety of lymphocytes such as B lymphocytes, natural killer cells, and naïve and activated T-cells.<sup>[8]</sup> Thus, IL-21 has pleiotropic effects on the regulation of inflammation by affecting these cells.

Several studies have revealed that IL-21 plays a pathogenic role in many autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis.<sup>[8]</sup> It remains unclear that whether IL-21 and IL-21R are also expressed in patients with DM and PM. In this study, we demonstrate the expression of IL-21 and IL-21R in patients with DM and PM for the first time, indicating that IL-21 may play a pathogenic role in patients with DM and PM.

## METHODS

### Ethical approval

This study was approved by the Human Ethics Board of Qilu Hospital Affiliated to Shandong University, and written informed consent was obtained from all the patients and controls.

### Subjects

Muscle specimens were retrospectively obtained from 11 patients with DM, 12 patients with PM, and six controls; all patients with DM and PM fulfilled the Bohan and Peter

criteria.<sup>[10,11]</sup> The six controls were initially suspected of having muscle diseases; however, muscle biopsies revealed normal histologic findings, and no neuromuscular disease was present after long-term follow-up. Serum specimens were retrospectively obtained from 36 patients with DM, 19 with PM, and 20 healthy age- and sex-matched controls. All patients with DM and PM in either muscle specimen group or serum specimen group did not undergo immunosuppressive therapy before obtaining of specimens. Patients with infectious, malignancy, and other autoimmune diseases were excluded. The muscle weakness in patients with DM and PM was measured by the manual muscle test (MMT) according to a previous report,<sup>[7]</sup> and the creatine kinase (CK) level of patients at the time of specimen collection was also obtained. Muscle specimens from patients and controls were frozen in isopentane that had already been precooled in liquid nitrogen and stored at  $-80^{\circ}\text{C}$  until use. Venous blood samples were collected from patients and healthy controls, and then centrifuged at  $3000 \times g$  for 15 min. Serum was collected and stored at  $-80^{\circ}\text{C}$  until use.

### Real-time quantitative reverse transcription-polymerase chain reaction

Total RNA was extracted from the frozen muscle tissue using TRIzol reagent (Sigma, St. Louis, Missouri, USA) according to the manufacturer's protocol. The quality of RNA was verified using bioanalyzer (Thermo scientific, Wilmington, Delaware, USA), and  $2 \mu\text{g}$  total RNA was reverse transcribed to complementary DNA using PrimeScript<sup>TM</sup> RT reagent Kit with genomic DNA eraser (Takara, Dalian, China) according to the manufacturer's protocol. TaqMan gene expression assays including primers and probes for target gene human IL-21, IL-21R, and the endogenous control gene  $\beta$ -actin were obtained from Applied Biosystems (Applied Biosystems, Foster City, California, USA; assay ID: IL-21: Hs00222327\_m1, IL-21R: Hs00222310\_m1,  $\beta$ -actin: Hs99999903\_m1). Quantitative real-time polymerase chain reaction (qRT-PCR) was performed using the ABI Prism 7900 HT system (Applied Biosystems, Foster City, California, USA) according to the manufacturer's instructions; each sample was tested in triplicate. Relative gene expression value of IL-21 and IL-21R in patients and controls was calculated using the  $2^{-\Delta\Delta\text{CT}}$  method.

### Immunohistochemistry

Six-micrometer unfixed cryostat sections of muscle tissue were collected and air-dried at room temperature, then fixed at  $4^{\circ}\text{C}$  acetone for 10 min, and rinsed using phosphate buffered saline (PBS). The PV-9000 polymer detection system (ZsBio Ltd., Beijing, China) was then used. Sections were blocked in 10% normal goat serum (ZsBio Ltd., China) for 30 min at room temperature. After draining the goat serum, the sections were then incubated with rabbit anti-IL-21 antibody (1:100 dilution, ab5978, Abcam, Cambridge, UK) or rabbit anti-IL-21R antibody (1:50 dilution, sc32902, Santa Cruz, California, USA) at  $4^{\circ}\text{C}$  overnight. After washing the primary antibody with PBS, the sections were incubated with polymer helper (ZsBio Ltd.,

China) for 20 min, again washed by PBS, then incubated with polymerized horseradish-peroxidase-conjugated anti-mouse/rabbit immunoglobulin G (IgG) (ZsBio Ltd., China) for 30 min at 37°C. Peroxidase activity was visualized using diaminobenzidine. The slides were counterstained with hematoxylin, dehydrated, and mounted with neutral balsam. An isotope IgG (ZsBio Ltd., China) was used as a negative control for the primary antibodies.

### Enzyme-linked immunosorbent assay

Serum IL-21 level of the patients and controls was measured using a commercial human IL-21 enzyme-linked immunosorbent assay kit (BioLegend, No. 433807, San Diego, California, USA) according to the manufacturer's protocol; each sample was measured in duplicate, a standard curve was generated, and serum IL-21 concentration was calculated.

### Statistical analysis

Data were presented as mean  $\pm$  standard deviation (SD) or median (interquartile range) when appropriate; the normality test was assessed using the Kolmogorov–Smirnov test and the Mann–Whitney *U*-test or unpaired *t*-test was used to compare the differences between groups. Pearson's correlation or Spearman's rank correlation test was used to determine the associations between serum IL-21 level or muscle IL-21 mRNA level and CK level or MMT score. All the data were analyzed using SPSS software (version 19.0, IBM SPSS, Chicago, Illinois, USA), and figures were created by GraphPad Prism software (version 5.0, GraphPad Software, La Jolla, California, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Characteristics of patients

In this study, muscle samples were obtained from 11 patients with DM and 12 with PM. Patients with DM included 7 females and 4 males; mean age was  $45.73 \pm 21.58$  years. Patients with PM included 9 females and 3 males; mean age was  $53.58 \pm 14.98$  years. Serum samples were collected from 36 patients with DM and 19 with PM. Patients with DM included 24 females and 12 males, and mean age was  $35.61 \pm 22.07$  years. Patients with PM included 13 females and 6 males, and mean age was  $45.37 \pm 14.38$  years. Table 1 summarizes the baseline clinical and laboratory characteristics of the patients around the time of collection of muscle or serum samples.

### Expression of interleukin 21 and interleukin 21 receptor in muscle tissues of patients with dermatomyositis and polymyositis

The mRNA level of IL-21 was significantly increased in inflamed muscle tissues of patients with DM and PM compared with normal controls ([Figure 1a], DM vs. control,  $P = 0.001$ , PM vs. control,  $P = 0.001$ ); there was no significant difference between patients with DM and PM ( $P = 0.065$ ). The mRNA level of IL-21R is shown in Figure 1b; in

**Table 1: Clinical and laboratory characteristics of patients with DM and PM**

Characteristic	DM	PM	<i>P</i>
Patients with muscle sample			
Gender (female/male)	7/4	9/3	0.667
Age (year)	$45.73 \pm 21.58$	$53.58 \pm 14.98$	0.319
Disease duration (month)	$5.55 \pm 3.05$	$5.08 \pm 3.18$	0.726
CK (U/L)	$2219.45 \pm 1986.15$	$2732.25 \pm 1753.26$	0.518
MMT score	$35.09 \pm 11.64$	$41.67 \pm 6.00$	0.099
Patients with serum sample			
Gender (female/male)	24/12	13/6	0.895
Age (year)	$35.61 \pm 22.07$	$45.37 \pm 14.38$	0.054
Disease duration (month)	4 (1.63, 9)	5 (3, 8)	0.433
CK (U/L)	2194 (297, 6050)	2852 (1668, 6175)	0.236
MMT score	43.5 (40, 46)	42 (39, 46)	0.625

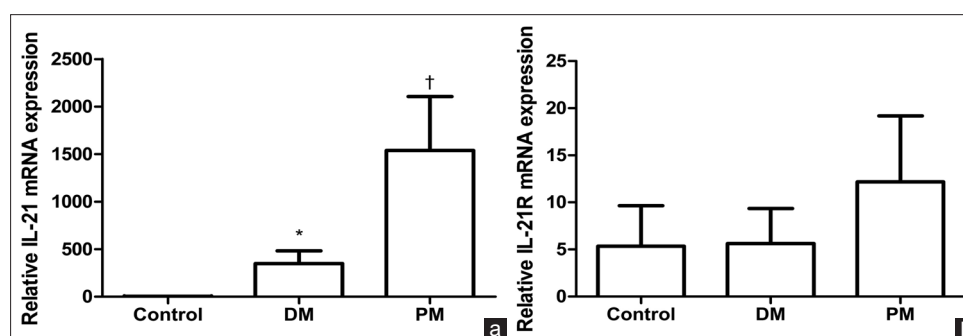
Data are presented as mean  $\pm$  SD or median (interquartile range). DM: Dermatomyositis; PM: Polymyositis; CK: Creatine kinase; MMT: Manual muscle test; SD: Standard deviation.

contrast to IL-21, IL-21R mRNA in inflamed muscle tissue of patients with DM and PM was not significantly upregulated compared with that in normal controls (DM vs. control,  $P = 0.269$ , PM vs. control,  $P = 0.134$ , and DM vs. PM,  $P = 0.085$ ). Although IL-21 mRNA was significantly higher in inflamed muscles of patients with DM and PM, it did not correlate with the CK level or MMT score in either patient group (DM IL-21 mRNA and CK,  $P = 0.133$ ; PM IL-21 mRNA and CK,  $P = 0.966$ ; DM IL-21 mRNA and MMT,  $P = 0.543$ ; and PM IL-21 mRNA and MMT,  $P = 0.469$ ).

In accordance with the high expression in mRNA level, IL-21 was obviously detected in the inflammatory mononuclear cells in inflamed muscle tissue of patients with DM and PM [Figure 2]. In patients with DM, IL-21 was mainly detected in the perivascular inflammatory cells; in patients with PM, it was detected in inflammatory cells surrounding the muscle fibers. IL-21 was not detected in the muscle fibers of either patient group. IL-21 was also not detected in the muscle tissues of normal controls. Although IL-21R mRNA was not highly expressed in patients with DM and PM compared with normal controls, IL-21R can still be obviously detected in inflammatory cells in patients with both DM and PM; its expression pattern was identical to that of IL-21 and cannot be detected in normal controls [Figure 2].

### Serum level of interleukin 21 in patients with dermatomyositis and polymyositis

Serum level of IL-21 was tested in 75 subjects (36 patients with DM, 19 with PM, and 20 healthy controls); statistical analysis was performed between these three groups. Serum level of IL-21 was higher in patients with DM and PM than in healthy controls (DM  $49.12 [45.28, 60.07]$  pg/ml, PM  $50.77 [44.19, 60.62]$  pg/ml, and control  $42.54 [38.69, 48.85]$  pg/ml, DM



**Figure 1:** mRNA level of IL-21 (a) and IL-21R (b) in muscle tissue of patients with DM/PM and controls. The data showed that mRNA level of IL-21 was higher in patients with DM/PM than in controls (a). Comparison of IL-21 mRNA expression between groups: DM versus control, \* $P = 0.001$ ; PM versus control, † $P = 0.001$ . The mRNA level of IL-21R was not higher in patients with DM/PM than in controls; (b). IL-21: Interleukin 21; IL-21R: Interleukin 21 receptor; DM: Dermatomyositis; PM: Polymyositis.

vs. control  $P = 0.001$ , PM vs. control  $P = 0.005$ ), and there was no statistically significant difference between patients with DM and PM ( $P = 0.88$ ) [Figure 3]. We also performed the correlation test between serum IL-21 level and CK level or MMT score, and there was no statistically significant correlation in patients with DM or PM (DM serum IL-21 level and CK,  $P = 0.393$ ; PM serum IL-21 level and CK,  $P = 0.138$ ; DM serum IL-21 level and MMT,  $P = 0.29$ ; and PM serum IL-21 level and MMT,  $P = 0.69$ ).

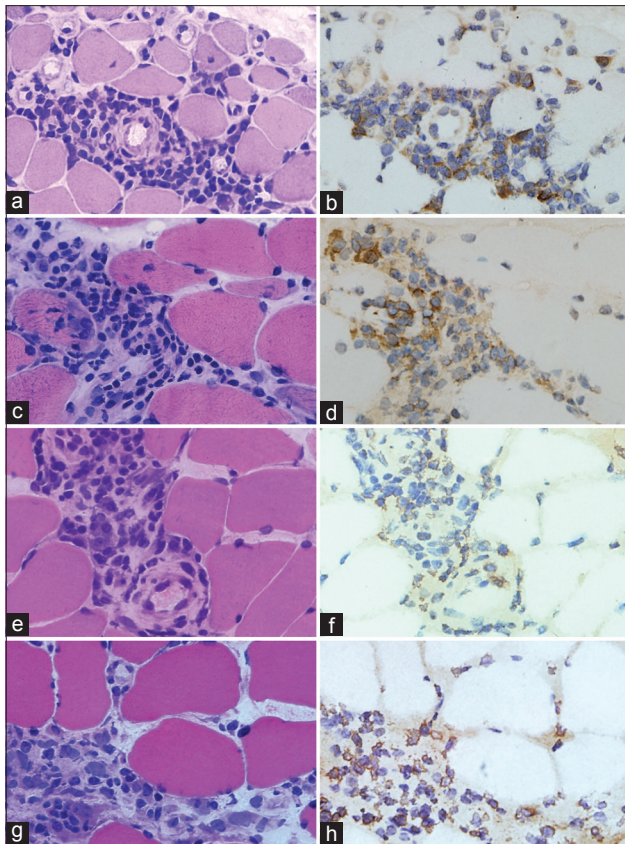
## DISCUSSION

In this study, we demonstrate the high expression of IL-21 and IL-21R in inflamed muscle tissues of patients with both DM and PM at the protein level and higher IL-21 mRNA expression in above inflamed muscle tissues compared to controls for the first time; elevated serum level of IL-21 was also first detected in both DM and PM patients. IL-21 has pleiotropic actions in controlling a complex range of immune components through IL-21R; loss of function of IL-21R can induce immunodeficiency syndrome.<sup>[8]</sup> These data indicate that the IL-21/IL-21R pathway may participate in the inflammatory process of patients with DM and PM.

Conventionally, DM and PM were considered to have distinct clinical and pathologic characteristics, and the underlying pathogenesis was also thought to be different. DM is usually regarded as a CD4+ T-cell-related disease, whereas PM may have a CD8+ T-cell-mediated autoimmune process.<sup>[12]</sup> During recent years, IL-17-producing Th17 cells have been found in the inflamed muscle tissues of myositis patients, and IL-17 was thought to play a key role in these diseases.<sup>[13]</sup> Increased expression of IL-17 mRNA has been detected in muscle tissues of patients with DM and PM, and immunohistochemical studies have demonstrated the expression of IL-17 in the lymphocytic infiltrates.<sup>[14-16]</sup> Several studies have reported increased levels of IL-17 in the serum of patients with DM and PM; the level positively correlated with disease activity.<sup>[13]</sup> In this study, we observed the overexpression of IL-21 and IL-21R in muscle tissue of patients with PM and DM. In addition, an elevated serum level of IL-21 was detected in these patients. As IL-21 can

be produced by Th17 cells and stimulate the differentiation of Th17 cells to produce IL-17 in an autocrine manner,<sup>[17,18]</sup> it can also affect the differentiation, proliferation, and function of CD4+ and CD8+ T-cells and B-cells, which are the main inflammatory cells in patients with DM and PM.<sup>[8,12]</sup> We inferred that IL-21 may play a role similar to that of IL-17 in myositis patients. Although the level of IL-21R mRNA was not significantly higher in myositis muscle tissues than in controls in our study, immunohistochemical staining showed that IL-21R was upregulated at the protein level. Thus, IL-21 may actively participate in the pathogenesis of DM and PM through actions on these aforementioned inflammatory cells by IL-21R.

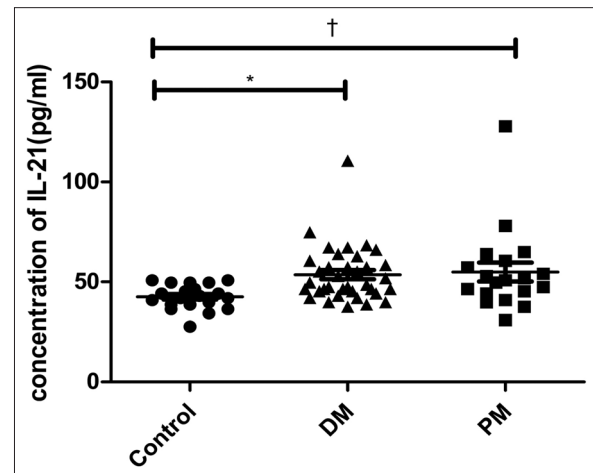
Currently, several studies have revealed that IL-21 plays an important role in the development of many autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, and multiple sclerosis.<sup>[19-23]</sup> Among these diseases, IL-21R can not only be expressed by a variety of lymphocytes but also by disease target cells such as fibroblast-like synoviocytes in patients with rheumatoid arthritis, neurons in patients with multiple sclerosis, and keratinocytes in patients with systemic sclerosis.<sup>[22-24]</sup> In rheumatoid arthritis, IL-21R is upregulated in fibroblast-like synoviocytes. Blockade of the IL-21/21R pathway can attenuate the proliferation of fibroblast-like synoviocytes, which play an important role in the pathogenesis of rheumatoid arthritis. In multiple sclerosis, IL-21R is expressed on the neurons, and IL-21 may directly damage the neuron and reduce the size and density of neurons through IL-21R. Similar phenomena can also be found in patients with systemic sclerosis. IL-21R is upregulated in the keratinocytes and participates in the pathogenesis of systemic sclerosis by inducing production of vascular endothelial growth factor, which can induce angiogenesis and adhesion of leukocytes in the dermis of patients.<sup>[22-24]</sup> Thus, in the aforementioned three diseases, IL-21 can not only act on the inflammatory cells but also directly act on the disease target cells; in the current study, we found only the expression of IL-21R on the lymphocytes, and no IL-21R was expressed on the muscle cells. This phenomenon indicated that the detailed pathologic role that



**Figure 2:** Immunohistochemistry analysis of IL-21 and IL-21R expression in muscle tissues of patients with DM/PM. (a, b, e, and f) The expression of IL-21 and IL-21R in a patient with DM. (a and e) H and E staining. (b) IL-21 staining. (f) IL-21R staining. IL-21 and IL-21R were expressed in the perivascular lymphocytes (original magnification  $\times 400$ ). (c, d, g and h) The expression of IL-21 and IL-21R in a patient with PM. (c and g) H and E staining, (d) IL-21 staining, (h) IL-21R staining. IL-21 and IL-21R were mainly detected in the lymphocytes surrounding the muscle fibers (original magnification  $\times 400$ ). IL-21: Interleukin 21; IL-21R: Interleukin 21 receptor; DM: Dermatomyositis; PM: Polymyositis.

IL-21 played in patients with DM or PM may be different from that of rheumatoid arthritis, multiple sclerosis, and systemic sclerosis.

Our study also found increased levels of IL-21 in the serum of patients with both DM and PM; however, unlike the significant correlation between serum level of IL-17 and disease severity, the serum level of IL-21 in our study did not correlate with CK level or MMT score, which reflected the severity of the disease. The IL-21 mRNA level in inflamed muscle also did not correlate with the CK level or MMT score. It has been reported that IL-17 can induce the production of cell adhesion molecules and cytokine/chemokine by human myoblasts or muscle tissues such as IL-6.<sup>[14]</sup> It also can inhibit the migration and myogenic differentiation of myoblast,<sup>[25]</sup> which means that IL-17 can directly act on the muscle cells. In our study, we did not find the expression of IL-21R on muscle cells, and serum level of IL-21 and IL-21 mRNA in muscle tissue did not correlate with disease severity. Therefore, we infer that



**Figure 3:** Serum level of IL-21 in patients with DM/PM and controls. The concentration of serum IL-21 was higher in patients with DM/PM than in healthy controls (comparison of serum IL-21 level, DM vs. control,  $*P = 0.001$ ; PM vs. control,  $†P = 0.005$ ). IL-21: Interleukin 21; DM: Dermatomyositis; PM: Polymyositis.

IL-21 may only participate in the inflammation initiating process of DM and PM, and it could not directly act on the muscle cell and did not participate in the process of muscle damage, unlike the role that IL-17 plays on muscle cells. During the inflammation initiating period, IL-21 may induce the differentiation and proliferation of CD4+ T- and B-cells in DM patients; while in PM patients, IL-21 may enhance the cytotoxic function and induce the proliferation of CD8+ T-cells.<sup>[8]</sup> A common pathway is that IL-21 can induce the differentiation and proliferation of Th17 cells to produce IL-17 which play a similar role in both DM and PM patients.<sup>[6,8]</sup>

It should be noted that our study has some limitations. First, this study is a single-center study and the number of cases included is relatively small. Further study with more patients is still needed. Second, because we did not obtain the data or serum of the patients after treatment, we could not compare the changes in serum IL-21 level in patients before and after treatment. Third, this study only demonstrated the expression of IL-21 and IL-21R in patients with DM and PM. Further study is still needed to clarify the detailed mechanism of IL-21 in patients with DM and PM.

In conclusion, this study demonstrated the expression of IL-21 and IL-21R in DM and PM patients' muscle tissue and serum. Our findings indicate that IL-21 may participate in the pathogenesis of DM and PM through IL-21R. Further studies with larger numbers of patients are needed to clarify the exact role that IL-21 plays in patients with DM and PM, and whether the role that IL-21 plays between patients with DM and PM is the same needs to be studied.

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## Conflicts of interest

There are no conflicts of interest.

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