Expression profiles of toll-like receptor signaling pathway related genes in microscopic polyangiitis in Chinese people

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Abstract: Recent, emerging evidence indicates that inappropriate regulation of toll-like receptor (TLR) signaling pathway plays a fundamental role in the development of autoimmune diseases including microscopic polyangiitis (MPA). However, the role of TLR-related cytokines in microscopic polyangiitis remains unclear. To further investigate the role and imbalance of TLR-related cytokines in the pathogenesis of MPA, a quantitative reverse transcription polymerase chain reaction (RT-PCR) array (Human TLR for Autoimmunity & Inflammation PCR Array) analysis was performed to study TLR-related gene expression in peripheral blood mononuclear cells (PBMC) of 10 new-onset patients with MPA and 10 healthy volunteers. We then used quantitative real-time PCR to validate the array test. When gene expression for 84 target genes related to the TLR pathway in MPA patients was compared to the mean of normal controls, 13 genes (BCL3, CD14, CXCL11, CXCL9, FADD, IL10, IRAK3, IRF7, MUC1, TLR1, TLR4, TLR6, TOLLIP) were up-regulated and 10 genes (ATF3, CHUK, CIITA, CXCL10, IFNA7, JUN, RIPK2, SARM1, SOCS1, TLR10) were down-regulated. These genes encompassed a diverse group of proteins including toll-like receptors, negative regulation molecules, adaptors and TLR interacting proteins, effectors, downstream pathway and target genes, activating transcription factors and inflammatory cytokines. In conclusion, the expression profile of PBMCs in this study suggests that the TLR signaling pathway may be involved in the pathogenesis of MPA. This finding may provide new insights in understanding the pathogenesis of MPA as well as provide new therapeutic targets.

Keywords: Microscopic polyangiitis, toll-like receptor, gene expression, array, cytokine

Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) is a group of autoimmune disorders including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener’s) (GPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA). AAV predominantly affects small to medium-sized blood vessels and is characterized by a pauci-immune necrotizing vasculitis [8]. Since the first report of anti-neutrophil cytoplasmic antibodies in systemic vasculitis and segmental necrotizing glomerulonephritis of patients in 1982 [9], numerous studies have observed the pathogenicity of ANCA. In addition to ANCA, cytokines, immune cells and activation of complement system also participate in the development of the disease. Although the etiology of AAV remains unclear, genetic and environmental factors have been linked to AAV pathogenesis [17, 20, 21, 29]. Moreover, in a Japanese patients with MPO-ANCA-associated vasculitis (JMAAV) study, the research has indicated differential expression of several genes in MPA patients was compared to 1-week after the beginning of treatment [32].

Toll-like receptors (TLRs) are type I transmembrane proteins that bind to a variety of pathogenic microorganism ligands, and in turn, mediate the expression of immune effector molecules [43]. To date, at least 11 kinds of TLRs in humans and 13 in mice have been identified [18]. TLRs are widely expressed in various cells including mononuclear, B lymphocytes, granulocytes, as well as epithelial and endothelial cells [37, 53]. TLRs play a key role in regulating immune cell proliferation, differentiation and survival. TLRs also play an important role in autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)
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The ligand of TLR9 is unmethylated cytosine-phosphate-guanine oligodeoxynucleotide (CpG-ODN). CpG-ODN-mediated signaling results in the production of ANCA by activated B lymphocytes in vivo, contributing to AAV relapses [2, 28]. Furthermore, in vitro studies suggest that TLR2 and TLR9 ligands may be implicated in triggering disease activity during neutrophil infection by stimulating mPR3 up-regulation in GPA [47]. Moreover, in mice, it has been shown that TLR2 and TLR9 ligand initiates autoimmunity in AAV by inducing type 17 T helper cells (Th17) and Th1 autoimmunity respectively [27]. In addition, TLR9 activation-induced expression of membrane-bound B-cell activating factor (BAFF) on human B cells and resulted in the increased proliferation of both soluble and membrane-bound BAFF, and TLR9 activation on human B cells may play an important role in the pathogenesis of autoimmune diseases [46]. Moreover, on immunohistochemical examination, TLR2 and TLR4 expression is detected in the glomeruli of patients with AAV and absent in normal controls [22]. A recent study observed PR3-ANCA can increase expression of TLR2, TLR3, TLR4, TLR7, TLR9, NOD1 and NOD2 in human peripheral blood mononuclear cells (PBMCs), suggesting PR3-ANCA in GPA patients predominantly increases active human PBMCs by TLRs, NOD1 and NOD2 [5]. Overall, these findings suggest that TLR signaling may play an important role in the pathogenesis of MPA.

There is limited data on TLR signaling pathway expression in peripheral blood mononuclear cells in the setting of MPA. PCR array has high specificity and sensitivity while requiring minimal RNA (as little as 1 ng of total RNA) [49, 57]. While TLRs are distributed in a variety of cell populations, its highest expression is in PBMCs. Therefore, to further investigate the role and imbalance of TLR cytokines in the pathogenesis of MPA, the current study was designed to characterize the expression of TLR signaling pathway members in PBMCs in new-onset MPA patients, in comparison to age-matched healthy individuals, and measure the mRNA levels of TLR-related cytokines using quantitative RT-PCR Array.

Materials and methods

Samples

The study protocol was approved by the local Ethics Committee.

Ten new-onset MPA patients (7 females and 3 males; mean age 51.05 ± 19.68 years, range from 18 to 73 years) were recruited at the Department of Nephrology, the First Affiliated Hospital of Guangxi Medical University, and ten healthy volunteers (7 females and 3 males, mean age 50.70 ± 14.30 years, ranging from 27 to 72 years). Diagnosis of MPA was established according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides criteria [8]. New-onset MPA was defined by the following criteria: (1) first time diagnosis of MPA; (2) no history of corticosteroids or immunosuppressive drugs use before registration. After obtaining informed written consent, peripheral blood samples were collected from patients and healthy volunteers.

Isolation of peripheral blood mononuclear cells and RNA extraction

Peripheral blood mononuclear cells were isolated from 6 ml of peripheral venous blood collected from each subject by Ficoll density gradient method (Ficoll-Paque PLUS, Tiangen, Beijing, China). Total RNA was extracted using Trizol reagent (Invitrogen, Rockville, MD, USA) according to manufacturer's instructions. Total RNA was quantified by Nanodrop ND-8000 Spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and integrity was confirmed by electrophoresis (2% agarose gel containing Gold View I SYBR Green).

cDNA preparation and qRT-PCR array

A final amount of 800 ng of RNA was used for cDNA synthesis. Samples were treated with a genomic DNA elimination buffer from the kit, and reverse transcription reactions were performed using the All-in-One™ First-Strand cDNA Synthesis Kit (GeneCopoeia, Rockville, MD, USA) according to the manufacturer’s protocol. Each cDNA was prepared for further use in qRT-PCR. Real-time polymerase chain reactions were performed using the RT² Profiler PCR Array (GeneCopoeia, Rockville, MD, USA) containing primers for 84 genes involved in the toll-like receptor pathway and 6 house-keeping genes. Amplification, data acquisition, and melting curve analysis were carried out in an iQ™5 Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA).
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Array data analysis

Values of cycle threshold (Ct) obtained in quantification were used for calculations of folds changes in mRNA abundance accordingly to $2^{-\Delta\Delta\text{Ct}}$ method [24]. Gene expression was considered up-regulated or down-regulated when the fold change was greater than 1.5. A two-tailed Student’s t test was used to analyze the data. P-values < 0.05 were considered statistically significant.

Real-time qPCR

Six genes (MUC1, BCL3, IRF7, IL10, TLR10, JUN) were selected from the array data analysis for validation. Total RNA was reverse transcribed to cDNA using Transcriptor First Strand cDNA Synthesis Kit (Roche, Mannheim, Germany). Quantitative PCR was performed with SYBR-Green (TaKaRa, Dalian, China) in the StepOne Plus real-time qPCR system (Life technologies, Rockville, MD, USA) according to the manufacturer’s instructions. The gene levels were normalized to GAPDH as an internal control. The relative abundance of each gene was calculated by $2^{-\Delta\Delta\text{Ct}}$ method and the results were assessed using t-test by SPSS version 17.0. The sequences of the primers for real-time qPCR are shown in Table 1.

Results

Up-regulated and down-regulated TLR-related genes in microscopic polyangiitis

As show in Table 2, the expression profiles of 23 of the 84 genes showed significant change; thirteen genes were up-regulated, and ten genes were down-regulated. Up-regulated genes encompassed toll-like receptors (TLR1, TLR4, TLR6), negative regulation molecules (IRAK3, TOLLIP), adaptors and TLR interacting proteins (CD14), effectors (FADD), downstream pathway and target genes mainly include NF-kB pathway (BCL3, IL10, MUC1) and interferon regulatory factor (IRF7, CXCL9, CXCL11). Down-regulated genes included toll-like receptor (TLR10), negative regulation molecules (SOCS1), adaptors and TLR interacting proteins (SARM1, RIPK2), and downstream pathway and target genes including NF-kB pathway (CHUK), C-Jun N-terminal Kinase (JNK/p38) pathway (JUN), and interferon regulatory factor (CXCL10), activating transcription factors (ATF3, CIITA) and inflammatory cytokine (IFNA7). The gene expression heat map comparing MPA patients and normal control is shown in Figure 1.

Discussion

TLRs can identify a variety of pathogenic microorganism ligands via pathogen associated molecular patterns (PAMPs) [6]. Studies indicate that TLRs play a crucial role in autoimmune diseases such as microscopic polyangiitis through the activation and regulation of innate and adaptive immune responses [3]. However, data on TLR-related cytokines expression in MPA remains unclear. In the present study, genes with modified cytokines expression in MPA was analyzed.
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Table 2. Comparison of mRNA expression of TLR related genes between MPA patients and normal control patients

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene name</th>
<th>Fold change</th>
<th>t test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCL10</td>
<td>Chemokine (C-X-C motif) ligand 10</td>
<td>-1.51</td>
<td>4.04E-02</td>
<td></td>
</tr>
<tr>
<td>SARM1</td>
<td>Sterile alpha and TIR motif containing 1</td>
<td>-1.56</td>
<td>1.21E-02</td>
<td></td>
</tr>
<tr>
<td>TLR10</td>
<td>Toll-like receptor 10</td>
<td>-1.57</td>
<td>4.99E-02</td>
<td></td>
</tr>
<tr>
<td>ATF3</td>
<td>Activating transcription factor 3</td>
<td>-1.58</td>
<td>3.39E-03</td>
<td></td>
</tr>
<tr>
<td>CIITA</td>
<td>Class II, major histocompatibility complex, transactivator</td>
<td>-1.69</td>
<td>2.37E-02</td>
<td></td>
</tr>
<tr>
<td>JUN</td>
<td>Jun oncogene</td>
<td>-1.86</td>
<td>1.27E-02</td>
<td></td>
</tr>
<tr>
<td>RIPK2</td>
<td>Receptor-interacting serine-threonine kinase 2</td>
<td>-1.91</td>
<td>1.31E-02</td>
<td></td>
</tr>
<tr>
<td>CHUK</td>
<td>Conserved helix-loop-helix ubiquitious kinase</td>
<td>-15.26</td>
<td>4.51E-13</td>
<td></td>
</tr>
<tr>
<td>IFNA7</td>
<td>Interferon, alpha 7</td>
<td>-16.13</td>
<td>6.65E-08</td>
<td></td>
</tr>
<tr>
<td>SOCS1</td>
<td>Suppressor of cytokine signaling 1</td>
<td>-22.35</td>
<td>4.43E-12</td>
<td></td>
</tr>
<tr>
<td>IRAK3</td>
<td>Interleukin-1 receptor-associated kinase 3</td>
<td>1.50</td>
<td>2.05E-02</td>
<td></td>
</tr>
<tr>
<td>TLR4</td>
<td>Toll-like receptor 4</td>
<td>1.57</td>
<td>1.65E-02</td>
<td></td>
</tr>
<tr>
<td>TOLLIP</td>
<td>Toll interacting protein</td>
<td>1.65</td>
<td>1.91E-02</td>
<td></td>
</tr>
<tr>
<td>CXCL11</td>
<td>Chemokine (C-X-C motif) ligand 11</td>
<td>1.67</td>
<td>4.61E-02</td>
<td></td>
</tr>
<tr>
<td>FADD</td>
<td>Fas (TNFRSF6)-associated via death domain</td>
<td>1.83</td>
<td>2.39E-02</td>
<td></td>
</tr>
<tr>
<td>TLR6</td>
<td>Toll-like receptor 6</td>
<td>1.93</td>
<td>2.13E-02</td>
<td></td>
</tr>
<tr>
<td>IRF7</td>
<td>Interferon regulatory factor 7</td>
<td>1.97</td>
<td>4.98E-02</td>
<td></td>
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<tr>
<td>CD14</td>
<td>CD14 molecule</td>
<td>2.02</td>
<td>4.54E-02</td>
<td></td>
</tr>
<tr>
<td>BCL3</td>
<td>B-cell CLL/lymphoma 3</td>
<td>2.02</td>
<td>3.12E-02</td>
<td></td>
</tr>
<tr>
<td>TLR1</td>
<td>Toll-like receptor 1</td>
<td>2.42</td>
<td>2.80E-02</td>
<td></td>
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<tr>
<td>CXCL9</td>
<td>Chemokine (C-X-C motif) ligand 9</td>
<td>2.51</td>
<td>4.98E-02</td>
<td></td>
</tr>
<tr>
<td>MUC1</td>
<td>Mucin 1, cell surface associated</td>
<td>3.11</td>
<td>1.32E-02</td>
<td></td>
</tr>
<tr>
<td>IL10</td>
<td>Interleukin 10</td>
<td>10.17</td>
<td>3.67E-02</td>
<td></td>
</tr>
</tbody>
</table>

TLRs are the most important receptors of the innate immune system and are expressed by a variety of immune cells. Studies have indicated a positive association between TLR1 R80T and ulcerative colitis (UC) with pancolitis, and a negative association between TLR6 S249P and UC with proctitis [10]. However, data on expression of TLR1, TLR6 and TLR10 in MPA is lacking. Interestingly, TLR4 has increased expression by monocytes in AAV [53], a finding consistent with our current study.

Even though TLRs play an important role in inflammatory defense mechanisms, TLR excessive signaling can result in chronic inflammatory and autoimmune diseases. Therefore, given the immune system requires a delicate balance between activation and inhibition, TLR signaling must be strictly regulated especially with respect to its negative regulatory mechanism. In our study, we observed that Interleukin-1 Receptor-Associated Kinase 3 (IRAK3), Suppressor of Cytokine Signaling 1 (SOCS1), Toll Interacting Protein (TOLLIP) are differentially expressed in PBMCs of MPA patients compared to control patients, and serve as intracellular negative regulators. IRAK3, also known as IRAKM, may regulate TLR4 and TLR9 by inhibiting phosphorylation of IRAKI [13]. IRAKM, encoding a member of the interleukin-1 receptor-associated kinase protein family, is primarily expressed in monocytes and functions as a negative regulator of toll-like receptor signaling. SOCS1 is a member of the STAT-induced STAT inhibitor (SSI) family that acts as a cytokine-inducible negative regulator of cytokine signaling. SOCS1 may negatively regulate TLR4 and...
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TLR9 by suppressing IRAK [33, 35]. TOLLIP encodes an ubiquitin-binding protein that interacts with several TLR signaling cascade components. It specifically regulates inflammatory signaling and is involved in interleukin-1 receptor trafficking as well as turnover of IL1R-associated kinase (provided by RefSeq, Aug 2011). Additionally, TOLLIP negatively regulates TLR4 and TLR2 by inhibiting autophosphorylation of IRAK1 [54]. Over-expression of TOLLIP results in inhibition of TLR2 and TLR4-mediated NF-κB activation [40]. Therefore, our findings suggest down-regulation of SOCS1 and up-regulation of TOLLIP and IRAK3 lead to an imbalance of negative regulation of the TLR signaling pathway.

In our study, Sterile Alpha and TIR Motif Containing (SARM1), CD14 molecule (CD14) and serine-threonine kinase 2 (RIPK2) expressions are altered in MPA patients. TLR signal transduction is mediated by adaptor proteins; to date, five adaptor proteins have been identified of which four have been assigned distinct functions [42]. SARM is the fifth member of this adaptor family, and its function remains unknown. SARM is a negative regulator of the TLR signaling pathway and is involved in inducing apoptosis [55]. Studies suggest that SARM may play an important role beyond that of a TLR adaptor as a mediator of innate immune function [51].

CD14 is a TLR coreceptor and an effective pattern recognition receptor. Recent studies show that CD14 is involved in the innate immune response to microbial infection [7, 31]. Notably, in vitro experiments document increased CD14 on monocytes in response to c-ANCA or p-ANCA IgG [52]. Moreover, increased CD14 expression has been documented on monocytes in AAV patients [12].

RIPK2, also known as RIP2, RICK or CARDAK, plays important roles in regulating innate and adaptive immune responses and inducing inflammatory cytokines [34]. Studies indicate that RIPK2 may play an important role in the pathogenesis of autoimmune diseases, such as inflammatory bowel disease [30, 50, 59] and multiple sclerosis [11]. Our study reveals up-regulation of RIPK2 mRNA expression levels in PBMCs of MPA patients. Research has shown...
that RIPK2 participates in TLR signal transduction. Macrophages of Rip2-deficient mice stimulated with peptidoglycan (PGN), lipopolysaccharide (LPS) and double-stranded RNA (dsRNA) results in significantly decreased cytokine production. Furthermore, RIPK2 plays an important role in regulating the downstream molecules of TLR2, TLR3 and TLR4 [61], further indicating that RIPK2 may play an important role in the pathogenesis of MPA.

**Effectors**

Fas-associated via death domain (FADD) is a fas-associated protein containing a death domain (DD) in the cytoplasm. FADD mediates cell apoptosis by inducing the Fas-Fasl apoptotic pathway. Increased expression of Fas has been shown on mononuclear cells from ANCA-positive vasculitis patients after treatment (Christensson et al., 2002). Furthermore, patients with vasculitis show increased expression of Fas and Fasl in renal biopsy specimens irrespective of disease phase. In turn, we suggest from our findings that FADD may play a key role in the disease process of MPA patients.

**Downstream pathways and target genes**

Downstream pathway and target genes of TLR signaling pathway mainly include NF-kB pathway (BCL3, IL10, MUC1, CHUK), C-Jun N-terminal Kinase (JNK/p38) pathway (JUN), and interferon regulatory factor (IRF7, CXCL9, CXCL10, CXCL11). To activate transcription of cytokines effecting cell growth and apoptosis, the TLR signaling pathway first activates the expression of target genes through nuclear factor Kappa B (NF-kB). B-cell CLL/lymphoma 3 (BCL3) is an anti-apoptotic gene that contributes to the regulation of cell proliferation and the transcriptional activation of NF-kB target genes. In the cytoplasm, it inhibits the nuclear translocation of the NF-kB p50 subunit. In the nucleus, it acts as a transcriptional activator that promotes transcription of NF-kB target genes. Differential expression of BCL3 is documented in the PBMCs of patients with autoimmune diseases, including SLE, Crohn’s disease (CD) and ulcerative colitis (UC) [15]. However, BCL3 mRNA levels are decreased in PBMCs of multiple sclerosis (MS) patients [60]. Interleukin 10 (IL-10), a pleiotropic cytokine with complex and multiple effects in immune modulation, can be produced by monocytes. Studies have found the level of IL10 is increased in EGPA, but not in GPA [26, 48]. Genetic polymorphisms at the IL10 3575/1082/592 TAC haplotype, part of the haplotype IL10.2, have been correlated reproducibly with increased IL10 expression in ANCA-negative EGPA [44]. We suggest that the expression of IL10 may be involved in the pathogenesis of MPA. Mucin 1 (MUC1) encodes a membrane-bound protein that is a member of the mucin family. MUC1, via the C-terminal domain of its beta subunit, modulates signaling in NF-kappa-B pathways, and is involved in both innate and adaptive immunity [14, 25]. Studies suggest inflammatory mediators can increase expression of MUC1 [19, 39]. Conserved helix-loop-helix ubiquituous kinase (CHUK) belongs to the canonical IKK complex, and its role remains unclear. It has been shown that CHUK has anti-inflammatory activity and inhibits innate immunity. A recent study has shown that CHUK activity is required for functional maturation of dendritic cells [41]. However, there is a paucity of data on the role of CHUK on PBMCs in MPA.

Activation of C-Jun N-terminal Kinase (JNK), also called stress-activated kinase, pathway leads to upregulation of multiple proteins including various cytokines and growth factors. The JNK signaling pathway is an important regulator of cells in both normal as well as disease states, and plays important roles in cell proliferation, apoptosis, stress response, and inflammatory diseases. Our study revealed JUN mRNA expression levels were significantly abnormal on PBMCs of MPA patients. Therefore, we suggest that the JNK signaling pathway may be
involved in the pathogenesis of MPA, and plays a role in its pathogenesis. However, elucidation of mechanism requires further study.

Chemokine (C-X-C motif) ligand 9 (CXCL9), CXCL10, CXCL11 are small cytokines belonging to the CXC chemokine family. A study has demonstrated that CXCL9 and CXCL11 play a key role in the pathogenesis of SLE. Furthermore, CXCL10 and CXCL11 are associated with neutrophil accumulation in the alveolar space of SLE patients with pulmonary fibrosis and may contribute to SLE-associated interstitial fibrosis [4]. CXCL10 plays a key role in autoimmune diseases such as SLE, psoriatic arthritis, and rheumatoid arthritis [16]. Therefore, we suggest that CXCL9, CXCL10 and CXCL11 may play an important role in the pathogenesis of MPA.

Interferon regulatory factor (IRF) is a family of transcription factors that [45] participates in a variety of biological processes, including innate immunity and adaptive immunity regulation. IRF7 is an important regulator of IFN induced expression [62]. We suggest that the expression of IRF7 may be associated with the development of MPA.

Activating transcription factors and inflammatory cytokines

Activating transcription factor 3 (ATF3) is a novel downstream target of JunB that mediates the survival mechanism of β-cells under inflammatory stress [58]. Class II transactivator (CIITA) plays a key role in regulating the expression of major histocompatibility complex class II (MHC-II), an important player in adaptive immune response and activation of T cells. Mutations in CIITA have been associated with bare lymphocyte syndrome type II (also known as hereditary MHC class II deficiency or HLA class II-deficient combined immunodeficiency) as well as increased susceptibility to rheumatoid arthritis (provided by RefSeq, Nov 2013). By stimulation of inflammation factors, including LPS and TNF-α, CIITA mRNA synthesis and protein expression are remarkably and rapidly suppressed [23]. Misregulation of the CIITA gene promoter can modulate the expression of MHC-II, leading to autoimmune disease. In our study, we found interferon alpha 7 (IFNA7) is significantly decreased in MPA patients. However, a study has observed significantly higher levels of IFN-α in AAV patients [38]. Therefore, the role of IFNA7 in MPA requires further study.

In this study, several limitations should be noted. As only 20 subjects were enrolled for this study, which may not have enough to convince an entire group analysis. Moreover, we studied the gene expression of PBMCs in MPA patients, and did not study relative gene expression in CD4 cells or other cells. Despite the above limitations, we showed that PBMCs from MPA patients presented significant changes in gene expression, exhibiting 23 differentially expressed genes compared to PBMCs from normal control. Moreover, this is the first study to analyze the expression profiles of TLR signaling pathway related genes in MPA in Chinese people. Further strengthening this study, patients were enrolled prior to initiation of corticosteroids or immunosuppressive therapy which excluded the confounding effects of treatment.

In summary, this study showed that MPA patients have a distinct TLR pathway gene expression profile, indicating that the TLR pathway may be implicated in the pathogenesis of MPA.

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Disclosure of conflict of interest

None.

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