ORIGINAL ARTICLE

Interactions between Golli-MBP and Th1/Th2 cytokines in patients with oral lichen planus

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OBJECTIVE: Oral lichen planus (OLP) is a prevalent cell-mediated autoimmune disease of unknown etiology. Disruption in the Th1/Th2 equilibrium has been suspected to contribute to the pathogenesis of OLP. In this study, we aimed at exploring, in OLP, the interactions between Th1/Th2 cytokines and Golli-MBP, a regulator of autogenic T cells.Subjects and Methods: Thirty-six OLP patients aged 18–79 and nineteen control subjects aged 20–69 were enrolled in the dental clinics of Nanjing Medical University. OLP was diagnosed clinically and verified by histopathological examination. All subjects were free of other autoimmune diseases. Peripheral blood mononuclear cells (PBMC) and serum were collected from all subjects. Gene expression and protein levels of Golli-MBP, IFN-γ and IL-4 were measured, respectively, by semiquantitative reverse transcription polymerase chain reaction and enzyme-linked immunosorbent assay. Result: When compared with control, PBMC and serum from OLP patients exhibited a significantly higher expression and concentration of Golli-MBP and IL-4 and lower levels of IFN-γ. A strong negative correlation ($r = -0.838$, $P < 0.000$) was detected between the ratio of IFN-γ/IL-4 and Golli-MBP gene expression in PBMCs of OLP patients. Conclusion: These data support a potential link between Golli-MBP and the dysregulation of the Th1/Th2 equilibrium in OLP.

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Keywords: Golli-MBP; IFN-gamma; IL-4; Th1/Th2; oral lichen planus

Introduction

Oral lichen planus (OLP) is a mucosal disease with the appearance of chronic inflammation (Carrozzo and Thorpe, 2009; Farhi and Dupin, 2010). Approximately one to two percent of the general adult population is affected by OLP, and women are more susceptible than men (Axell and Rundquist, 1987). Clinically, six types of OLP lesions are classified individually or combined based on lesion appearance: These are papular, reticular, plaque-like, atrophic, erythematous/erosive, and bullous (Farhi and Dupin, 2010). While its etiology remains elusive, several factors have been linked to an increased risk of OLP. This includes genetic background, other autoimmune diseases, virus infection, and psychological stress and anxiety (Vallejo et al., 2001; Sugerman et al., 2002; Lodi et al., 2005; Lundqvist et al., 2006; Roopashree et al., 2010). Understanding the pathophysiological mechanism of OLP is an important area of research not only because of its elusive etiology but also because its chronicity, its potential for malignant transformation, and its occasional treatment refractory properties are unexplained.

Dysregulation of the immune system, specifically cell-mediated immunity, has been implicated in the etiology of OLP (Sugerman et al., 2002; Carrozzo and Thorpe, 2009; Farhi and Dupin, 2010). The accumulation of T cells in the superficial lamina propria and the migration of intraepithelial T cells is associated with the apoptosis of keratinocytes and the disruption of the basement membrane (Sugerman et al., 2002; Roopashree et al., 2010). CD4⁺ helper T cells likely play an important function during the initiation of OLP pathogenesis. Studies have shown that early lesion formation of OLP is induced by MHC class I antigen presentation to CD4⁺ helper T cells followed by CD8⁺ cytotoxic T-cell-triggered keratinocyte apoptosis (Sugerman et al., 2002). T helper (Th) cells are classified based on cytokine expression and helper function into two main subsets Th1, Th2. Th1 cells produce IL-2, IL-3, TNF-α, and most notably IFN-γ and regulate antigen presentation and immunity against intracellular pathogens; Th2 cells produce IL-4, IL-5, and IL-13 and mediate

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humoral responses and immunity against parasites (Yang et al., 2004; Gutcher and Becher, 2007; Nurieva et al., 2008). IFN-γ and IL-4 are not only key effector molecules which influence the secretion of other cytokines, but are also critical mediators of the differentiation of Th1 and Th2 cells, respectively (Kidd, 2003). The change of IFN-γ, or IL-4, or the ratio of IFN-γ/IL-4 may imply alteration of the immune response with potential pathological effect and has been reported in OLP patients (Rhodus et al., 2007; Kalogerakou et al., 2008).

Human Golli (for gene expressed in the oligodendrocyte lineage)-MBP (for myelin basic protein) was originally isolated from a human oligodendroglia cell line (Pribyl et al., 1993). The Golli-MBP gene contains 10 exons, whereas MBP only contains seven exons. MBP constitutes the myelin sheath of oligodendrocytes and Schwann cells in both central and peripheral nervous systems. MBP is expressed in the central and peripheral nervous system solely, Golli-MBP is also expressed in the hematopoietic system, especially in the immune system, including T lymphocytes, B lymphocytes, and macrophages (Pribyl et al., 1993; Marty et al., 2002). Golli-MBP is autoencephalitogenic (Marty et al., 2002). In animal models, intradermal injection of a Golli-MBP peptide results in paralysis. This effect is Th-1 cell mediated and is associated with increased expression of IFN-γ (Clark et al., 1999). In mouse models of experimental autoimmune encephalomyelitis (EAE), increased Golli-MBP expression was observed in the peripheral immune system in the relapsing phase of the disease. What is more, heterozygous Golli-MBP knockout mice demonstrated reduced relapse of EAE when compared with wild-type controls (Voskuhl et al., 2003). This suggests that immunization with Golli-MBP can induce activation of T cells and initiate autoimmune diseases and that Golli-MBP plays an essential role in the course of the autoimmune response.

Although animal models show that Golli-MBP induced Th-1-driven inflammation and is associated with the relapse of EAE, little is known about the molecular mechanism activated by Golli-MBP (Clark et al., 1999; Voskuhl et al., 2003). Recently, our laboratory reported that Golli-MBP was increased in OLP patients, and others reported a potentially pathogenic disruption of the Th1/Th2 equilibrium in OLP (Rhodus et al., 2007; Kalogerakou et al., 2008; Zeng et al., 2011). A link between Golli-MBP levels and Th1/Th2 cytokines ratio in OLP has yet to be established.

In this study, we investigated in OLP patients the potential link between Golli-MBP levels and the Th1 and Th2 cytokines, IFN-γ, and IL-4. We hypothesized that OLP patients had higher PBMCs’ gene expression and serum levels of Golli-MBP when compared with controls and that this correlated with the dysregulation in the Th1/Th2 cytokine ratio. Our results showed that the gene expression and protein levels of Golli-MBP and IL-4 in PBMCs and serum from OLP patients were significantly upregulated when compared with healthy controls. In contrast, IFN-γ was downregulated in PBMCs and lower in serum from OLP patients. Increased Golli-MBP correlated with a lower Th1/Th2 ratio (IFN-γ/IL-4) in OLP patients. These results suggest that Golli-MBP might play a role in the pathogenesis of OLP by affecting the equilibrium of Th1/Th2 cytokines.

Material and methods

Patients and controls

Thirty-six patients with OLP and nineteen healthy controls from the Outpatient Department of Jiangsu Province Stomatological Hospital (Nanjing, China) were enrolled in this study. This study was approved by the Ethics Committee of Nanjing Medical University, Nanjing, China. The diagnosis of OLP was first determined clinically by trained dentists and later confirmed by histopathological examination by a trained and licensed oral pathologist at the same medical center. Clinical and histopathological definition of OLP by the World Health Organization in 1978 was used for diagnosis of OLP (van der Meij and van der Waal, 2003). Patients were divided into erythematous/erosive (Group 1) and reticular (Group 2) subgroups based on the criteria of clinical manifestation (van der Meij and van der Waal, 2003). None of the subjects (OLP patients and healthy controls) reported taking prescription medication in the past 3 months, and all the subjects were free of other autoimmune diseases.

Reverse transcription – polymerase chain reaction (RT-PCR)

Blood samples collected from OLP patients and normal healthy controls were drawn in sodium citrate tubes. Peripheral blood mononuclear cells (PBMC) were isolated by Ficoll–Hypaque density gradient centrifugation (Romeu et al., 1992). Total RNA was then extracted from PBMC using Trizol (Invitrogen, Carlsbad, CA, USA) and dissolved in diethyl pyrocarbonate (DEPC) treated water (Ambion Inc., Austin, TX, USA) according to the manufacturer’s instructions. After digestion with DNase I (Invitrogen, Carlsbad, CA, USA) at 37°C for 30 min, cDNA was synthesized from total RNA using TaKaRa PrimeScriptTM RT Reagent Kit (TaKaRa Bio, Otsu, Japan) following the manufacturer’s instructions. For semiquantitative measurement based on band intensity, PCR amplification was performed in 25 µl reaction mixture, which consists of 1 µl of cDNA, 12.5 µl of TakaRa Premix Ex Taq Version 2.0 (TaKaRa Bio, Otsu, Japan), 1 µl each of 20 µM forward/reverse primers, and 9.5 µl of sterile distilled water, and it was carried out in the Eppendorf Mastercycler 5333 thermal cycler (Eppendorf, Hinz GmbH, Hamburg, Germany) with 98°C for 10 s, annealing for 30 s, and 72°C for 1 min. The primers used for RT-PCR are listed in Table 1. A pilot PCR experiment was carried out to determine the number of cycles that amplified the target genes in exponential manner. PCR was performed twice at 27 and 30 cycles, respectively, for target genes and for the β-actin housekeeping gene, which was used as an internal control for the semiquantitative analysis. After 27 and 30 cycles of amplification, same volume of PCR products were loaded on a fresh 1.5% agarose gel that made at the same time and visualized under ultraviolet light. Both products of the target gene and β-actin were applied on the same agarose gel. Expression of Golli-MBP, IFN-γ and IL-4 genes was evaluated by band intensity analysis using...
Table 1 Primers designed for RT-PCR assessment

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward primer (5’-3’)</th>
<th>Reverse primer (5’-3’)</th>
<th>Amplicon (bp)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golli-MBP</td>
<td>GGCAGATGCGAACCAGA</td>
<td>GTCACCGCccAAAGGAGC</td>
<td>403</td>
<td>55</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>CATTCCAGTAGGCGGATGAA</td>
<td>TTTGGATGATCTCCTGTTTA</td>
<td>355</td>
<td>57</td>
</tr>
<tr>
<td>IL-4</td>
<td>TATGCTGAAACTTGTGATG</td>
<td>TTTGATGATCTCCTGTTA</td>
<td>401</td>
<td>50</td>
</tr>
<tr>
<td>β-Actin</td>
<td>CTCCATCCTGGCTCTGCTG</td>
<td>GCTGTACCCACTCGGTTCC</td>
<td>268</td>
<td>55</td>
</tr>
</tbody>
</table>

Enzyme-linked immunosorbent assay (ELISA)

Serum samples were collected in separator tubes, allowed to clot for 2 h at room temperature and centrifuged at 1000 g for 15 min. The supernatants were then transferred into new tubes. Concentration of Golli-MBP, IFN-γ and IL-4 was determined using human Golli-MBP ELISA kit (CUSABIO BIOTECH CO., Wu Han, Hubei, China) and the human IFN-γ and IL-4 ELISA kit (BioLegend, Inc., San Diego, CA, USA) according to the manufacturer’s instructions. Briefly, monoclonal antibodies specific for Golli-MBP, IFN-γ and IL-4 were pre-coated onto 96-well microtiter plates. Duplicate serial standards (0.1 ml), blank and samples (0.1 ml) were pipette into the wells and then sealed and incubated at 37°C for 2 h. After removing the liquid and washing with phosphate-buffered saline tween-20 (PBST) (Golli-MBP without washing), 0.1 ml/well of the diluted biotinylated detection antibody was added, and the plates were incubated at 37°C for 1 h for binding. Following a wash with PBST to remove any unbound antibody reagent, 0.1 ml of avidin conjugated Horseradish Peroxidase (HRP) was added into the wells and incubated at 37°C for 15–30 min. After washing with PBST three times, 0.1 ml of 3,3,5,5 tetramethylbenzidine (TMB) chromogenic solution was added into wells and incubated 37°C for 15–30 min. Color development was terminated by addition 0.1 ml of the stop solution. The intensity of the color was measured at 450-nm wavelength of their disease. A one-way ANOVA was used to analyze the overall level of significance between experimental groups. Pearson correlation coefficient was used to analyze the correlation between Golli-MBP and IFN-γ/IL-4 in OLP. 

Results

Basic information of the OLP and control subjects

36 subjects with OLP and 19 controls were enrolled. Description of the subjects’ age and gender and location of their OLP lesions is shown in Table 2. OLP subjects were divided into two groups based on the clinical appearance of their disease. A first group with erosive OLP consisted of eight men and twelve women aged between 18 and 79. A second group with reticular OLP included nine women and seven men aging between 19 and 62.

Golli-MBP levels

Golli-MBP mRNA level was evaluated by semiquantitative RT-PCR performed with two programs of either 27 or 30 cycles. The data shown here were collected from 30 cycles of PCR. In OLP patients, expression levels of Golli-MBP mRNA in reticular (0.790 ± 0.021) and erythematous/erosive (0.830 ± 0.019) groups were significantly upregulated when compared with that in control group (0.472 ± 0.023) (ANOVA for between group variables: F = 90.008, P < 0.001) (Figure 1b).

The concentration of Golli-MBP in serum was measured by ELISA. Golli-MBP levels were significantly higher in erythematous/erosive (8.574 ± 0.452) and reticular (7.820 ± 0.615) OLP patients as compared with healthy controls (5.019 ± 0.280) (ANOVA for between
group variables: \( F = 17.850, P < 0.001 \) (Figure 2). However, no significant difference was detected between two subtypes of OLP (\( P = 0.386 \) for mRNA expressions and \( P = 0.320 \) for serum concentration).

**IFN-\( \gamma \) and IL-4 levels**

Expression of IFN-\( \gamma \) and IL-4 mRNA levels were also measured using semiquantitative RT-PCR. The data shown here were collected from 30 cycles of RT-PCR. For IFN-\( \gamma \), OLP patients showed markedly downregulated expression in reticular (0.337 ± 0.021) and erythematous/erosive (0.282 ± 0.022) cases when compared with healthy controls (0.587 ± 0.026) (ANOVA for between group variables: \( F = 51.756, P < 0.001 \) (Figure 3b). Conversely, IL-4 mRNA expression was significantly upregulated in erythematous/erosive (0.621 ± 0.028) and reticular OLP patients (0.574 ± 0.018) when compared with healthy controls (0.277 ± 0.017) (ANOVA for between group variables: \( F = 70.456, P < 0.001 \) (Figure 3c).

The concentration of IFN-\( \gamma \) and IL-4 in the serum was assessed using ELISA. Consistently with the mRNA data, IFN-\( \gamma \) level was lower in both erythematous/erosive and reticular OLP than that in healthy controls (ANOVA between group variables: \( F = 19.021, P < 0.001 \), whereas IL-4 level was higher in erythematous/erosive and reticular
Table 3 Concentration of Interferon-gamma (IFN-γ) and IL-4 in serum (pg/ml)

<table>
<thead>
<tr>
<th></th>
<th>IFN-γ</th>
<th>IL-4</th>
<th>IFN-γ/IL-4</th>
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</thead>
<tbody>
<tr>
<td>Erythematous/</td>
<td>19.528 + 3.242</td>
<td>50.856 + 13.857</td>
<td>0.413 + 0.135</td>
</tr>
<tr>
<td>erosive (n = 20)</td>
<td></td>
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<tr>
<td>Reticular (n = 16)</td>
<td>19.396 + 4.003</td>
<td>52.602 + 13.668</td>
<td>0.394 + 0.134</td>
</tr>
<tr>
<td>Control (n = 19)</td>
<td>31.698 + 10.807</td>
<td>32.972 + 7.013</td>
<td>1.017 ± 0.481</td>
</tr>
<tr>
<td>Erythematous/</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>erosive vs</td>
<td></td>
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<tr>
<td>control (P value)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reticular vs</td>
<td>0.955</td>
<td>0.663</td>
<td>0.85</td>
</tr>
<tr>
<td>control (P value)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reticular</td>
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Table 4 Correlation of Golli-MBP and Th1/Th2 (IFN-γ/IL-4) in OLP

<table>
<thead>
<tr>
<th></th>
<th>Correlations</th>
<th>Golli-MBP mRNA</th>
<th>IFN-γ mRNA/IL-4 mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golli-MBP mRNA</td>
<td>Pearson correlation</td>
<td>1.000</td>
<td>–0.838*</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant (two-tailed)</td>
<td></td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>IFN-γ mRNA/IL-4 mRNA</td>
<td>Pearson correlation</td>
<td>–0.838*</td>
<td>1.000</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant (two-tailed)</td>
<td></td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>IFN-γ/IL-4 mRNA</td>
<td>Pearson correlation</td>
<td>–</td>
<td>0.000</td>
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<tr>
<td>n</td>
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<tr>
<td>IFN-γ/IL-4 mRNA</td>
<td>Pearson correlation</td>
<td>–</td>
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<td>n</td>
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*Correlation is significant at the 0.05 level (two-tailed).

OBL patients (ANOVA between group variables: F = 15.444, P < 0.001) (Table 3). Moreover, IFN-γ/IL-4 ratio was attenuated in erythematous/erosive and reticular OLP patients when compared with healthy controls (ANOVA between group variables: F = 25.382, P < 0.001). There were no significant differences of IFN-γ, IL-4 concentrations, or IFN-γ/IL-4 ratio between two different subtypes of OLP (Table 3).

The ratio of IFN-γ/IL-4 mRNA expression mimicked that of serum concentrations shown in Table 3. IFN-γ/IL-4 mRNA was significantly lower in erythematous/erosive (0.469 ± 0.041) and reticular (0.593 ± 0.038) OLP when compared with healthy controls (2.233 ± 0.148) (ANOVA between group variables: F = 112.088, P < 0.001). However, no significant difference was detected between two subtypes of OLP (P = 0.224 for IFN-γ; P = 0.313 for IL-4; P = 0.634 for IFN-γ/IL-4).

Correlation of Golli-MBP and Th1/Th2 balance in OLP

The relationship between Golli-MBP and Th1/Th2 cytokine gene expression in OLP patients was analyzed using SPSS statistical software. Pearson’s correlation analysis revealed a strong negative correlation between Golli-MBP and the ratio of Th1/Th2 (IFN-γ/IL-4) mRNA expression in OLP patients (r = -0.838, P < 0.001) (Table 4). No significant correlation was found between the serum concentrations of Golli-MBP and the ratio of IFN-γ/IL-4 (Pearson correlation coefficient: r = -0.066, P = 0.701) (Table 5).

Table 5 Correlation of Golli-MBP and Th1/Th2 (IFN-γ/IL-4) in OLP

<table>
<thead>
<tr>
<th></th>
<th>Correlations</th>
<th>Golli-MBP</th>
<th>IFN-γ IL-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golli-MBP Pearson correlation</td>
<td>1.000</td>
<td>0.066</td>
<td></td>
</tr>
<tr>
<td>Significant (two-tailed)</td>
<td>–</td>
<td>0.701</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>IFN-γ/IL-4 Pearson correlation</td>
<td>0.066</td>
<td>1.000</td>
<td></td>
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<tr>
<td>Significant (two-tailed)</td>
<td>–</td>
<td>0.701</td>
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<td>n</td>
<td>36</td>
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</table>

Correlation between serum concentrations of Golli-MBP and the ratio of IFN-γ/IL-4 was analyzed in OLP patients using SPSS statistical software.

Discussion

Oral lichen planus is a chronic inflammatory disease of unknown etiology characterized by the accumulation of T lymphocytes in the superficial lamina propria (Sugerman et al, 2002). In this study, we measured and compared the mRNA expression and protein levels of Golli-MBP and cytokines, IFN-γ and IL-4, in PBMCs and serum of OLP patients and healthy controls. The results indicated that both mRNA expression and protein levels of Golli-MBP and IL-4 were upregulated, while IFN-γ was downregulated in OLP patients when compared with healthy controls. No significant differences were detected between two subtypes OLP: reticular and erythematous/erosive. The gene expression of Golli-MBP and the ratio of the mRNA levels of the Th1/Th2 cytokines IFN-γ/IL-4 exhibited a strong and significant negative correlation.

Cytokines, which are produced by T helper cells, play an important role in the immune system by mediating and regulating immune and inflammatory reactions. Type I proinflammatory cytokines primarily promote cell-mediated immunity, whereas type II anti-inflammatory cytokines mediate humoral immunity (Gutcher and Becher, 2007). Our data demonstrated a lower level of IFN-γ (type I cytokine) and a higher level of IL-4 (type II cytokine) in PBMC and serum specimen of OLP patients. Thus, the equilibrium of Th1/Th2 was disrupted, leading to a lower ratio of IFN-γ/IL-4 and a shift to a Th2 predominant immune response in OLP patients. This is consistent with the data published by others with peripheral blood lymphocytes, PBMC, serum, or saliva (Yamamoto et al, 1990; Karagouni et al, 1994; Liu et al, 2009; Ghallab et al, 2010). The lower ratio of IFN-γ/IL-4 in OLP patients was also consistent with similar finding in saliva collected from OLP subjects (Liu et al, 2009). Together, this suggests that OLP features a relative cellular immunosuppression and a Th2 predominant immune response similar to allergy, asthma, and systemic lupus erythematosus (Kidd, 2003).

To further understand the mechanism of Th1/Th2 disturbance and pathogenesis of OLP, we explored the correlation between the expression of Golli-MBP, which has been suspected to play a role in the etiology of autoimmune disease and the ratio of IFN-γ/IL-4 gene expression. In our study, Golli-MBP expression was increased in OLP patients compared with healthy controls, suggesting Golli-MBP could influence cytokine productions and development of the disease. It raises the possibility that enhanced Golli-MBP could activate...
MBP-specific T lymphocytes and stimulates cytokine secretion, including IFN-γ, IL-4, and interleukin 10 (IL-10), in OLP patients. Indeed, elevated IL-10 has been detected in tissue-infiltrated mononuclear cells (TIMC), saliva and serum of OLP patients, although it was not measured in our study (Yamamoto and Osaki, 1995; Dan et al., 2011; Pekiner et al., 2012). IL-10 is the cytokine produced by Th1, Th2 as well as B cell (Del et al., 1993; Burdin et al., 1997; O’Garra and Vieira, 2007). It plays a complex role in the control of immune response by suppressing the expression of proinflammatory cytokines and modulating T-cell proliferation and cytokine synthesis. IL-10 seems to exert stronger effects on Th1 cells than Th2 (Del et al., 1993; Moore et al., 2001; Asadullah et al., 2003; Groux and Cottrez, 2003). Hence, it is expected that Golli-MBP stimulated the secretion of Th1 and Th2 cytokines in OLP patients, especially IL-10; in turn, IL-10 suppressed IFN-γ (Th1) production (Kidd, 2003). As result, IFN-γ failed to increase and showed lower levels in PBMC of OLP patients while IL-4 was higher than healthy controls. It has been demonstrated that imbalance of Th1/Th2 with impaired Th1 function was involved in the pathogenesis of OLP (Karakoumi et al., 1994) (Yamamoto et al., 1990; Liu et al., 2009). A strong and negative correlation between Golli-MBP and Th1/Th2 gene expression was observed in PBMCs but not in serum levels of OLP patients. This implies that Golli-MBP may influence cytokine gene expression in PBMCs but that this effect is not strong enough to be reflected in serum levels.

Altogether, we propose that an upregulation of Golli-MBP expression may initiate disruption of equilibrium of Th1/Th2 by reducing the IFN-γ production and elevating the IL-4 production, consequently contributing to the pathogenesis and/or the chronicity of OLP. Mechanisms that control upregulation of Golli-MBP in pathological condition, such as OLP, and potentially influence other cytokines need further investigation. Our study therefore provides new clues for future therapeutics of OLP.

Acknowledgements

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Author contributions

Ming Ding: experiment consulting, data analysis and manuscript writing; Juan Zeng: experiment conduct and data collection; Jinhua Yu: experiment consulting and design; Juanyong Xu: histopathological diagnosis; Xinlong Cheng: graphic work and critical reading; Herve Sroussi: critically revising; Yuan Fan: research design and mentoring.

References


