Interaction of TIM4-TIM1 decreases the function of $CD4^+CD25^+$Treg in intestine in food allergic mice

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Abstract: Research in the area of food allergy has advanced rapidly in recent years, however, the mechanism of food allergy remains unclear. It has been shown that the T regulatory cells play an important role in preventing the allergic responses in the intestine. TIM1 (T cell immunoglobulin and mucin domain protein TIM 1 interacted with its endogenous ligand of TIM4 may attenuate the oral immune tolerance and lead to hypersensitivity reactions in the intestine. Forty male BALB/c mice fed on the OVA-free diet were randomly divided into five groups, and eight mice were used for each group: A group of mice were sensitized by intraperitoneal injection (ip) with Staphylococcal enterotoxin B (SEB) + Ovalbumin (OVA) and the other four groups of mice were separately treated with normal saline (NS), anti-TIM1 (2 μg/mouse) +SEB + OVA, anti-TIM1 (10 μg/mouse) +SEB + OVA, anti-TIM4 (10 μg/mouse) + SEB + OVA, on the 0, 3rd and 9th day; and all of the mice were challenged by means of lavage with SEB+ OVA (except NS) on the 7th and 14th day. Mice were treated intraperitoneally with the same doses anti-TIM4 or anti-TIM1 30 minutes before gavage. Twenty-four hours after the last gavage, the mice were killed and subjected to immunologic analyses. The expressions of Foxp3 mRNA in the jejunum and spleen decreased significantly in SEB+OVA group compared with those treated with NS, but the expressions of TIM4 mRNA increased significantly ($P<0.05$). The levels of TGF-β1 in serum and jejunum decreased significantly compared with those treated with NS. The expressions of Foxp3 mRNA in the jejunum and spleen and the levels of TGF-β1 in the serum and jejunum were significantly higher in anti-TIM1+SEB+OVA and anti-TIM4+SEB+OVA groups compared with SEB+OVA group (all $P<0.05$). The function of Treg cells can be suppressed in the intestine by sensitization that can be prevented by pretreatment with antibodies against TIM1 or TIM4.

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Key Words: Food allergy; $CD4^+CD25^+$Treg cells; Oral tolerance; TIM protein

1. Introduction

As many as 2% to 6% of the populations in the world have food allergy (FA) and food antigen-related disorders; its prevalence keeps increasing especially in last 20 years (Vierk KA, 2007; Sicherer SH,2009) Symptoms of food allergy vary from slight abdominal discomfort to life-threatening anaphylactic shock (Bahna- -SL, 2003) . However, the etiology and immune mechanisms of intestinal allergic diseases remain poorly understood. FA is generally regarded as a collapse of the balance between intestinal immune system and food antigens, resulting in a skewed Th2-dominant intestinal immune response. It is believed that under normal circumstances, the gut immune system is relatively hyporesponsive to food antigens and commensal bacteria, this state of hyporesponsiveness (tolerance) is maintained by a number of important mechanisms including the integrity of gut epithelium and the presence of tolerogenic dendritic cells (DCs) and regulatory T cells (Strobel- -S, 2006) . Thus, it is conceivable that any perturbation to the homeostasis between luminal antigens and the gut immune system might lead to gut inflammation and food allergy.

$CD4^+CD25^+$Treg cells were subset of regulatory T cells and they play an important role in maintaining the stabilization of internal homeostasis, anti-infection, oral tolerance, introduction of transplantation tolerance and autoimmune disorder. Reduction of Treg number and impairment of Treg function can breach the balance of oral tolerance (Wiest R, 2003). Recently the forkhead-winged helix family transcription factor, Foxp3, has been shown being specifically expressed in murine $CD4^+CD25^+$Treg cells, and appeared being a 'master gene' controlling the development and suppressive function of $CD4^+CD25^+$Treg cells, and previous studies reported that Foxp3 gene mutation or decreased expression could lead to Treg cell dysfunction (Powrie- -F, 2003; Coombes JL, 2005; Fantini MC,2006) .

The TIM (T-cell immunoglobulin domain and mucin domain) family was discovered (McIntire JJ, 2001) in 2001 and received much attention due to its location on mouse chromosome 11B1.1, a genetic region associated with multiple diseases including asthma, allergy and autoimmunity (Kuchroo, V. K,

2003). The TIM family consists of eight genes in mouse (TIM1–8) and three genes in human (TIM1, 3, and 4). Among these members, TIM1 is constitutively expressed on $CD4^+$ T cells; its ligand TIM4 is expressed in DCs. The interaction of TIM1 and TIM4 could promote Th2 cell polarization (Meyers JH, 2005; Umetsu SE, 2005). In addition, studies showed that TIM1-specific agonist antibody decreased the suppressive capacity of natural regulatory T cells, in line with a reduction in their expression of Foxp3, GITR (glucocorticoid-induced tumour-necrosis factor (TNF)-receptor-related protein), CTLA4 (cytotoxic T-lymphocyte antigen 4) and IL-10 (Degauque N, 2008) . However, the functional status of Treg cells and the impact of TIM1 on Treg cells have not been reported in FA, we speculated that Treg cells were dysfunctional and TIM4 interaction with TIM1 might attenuate the function of Treg cells and oral tolerance, which might be one of the important mechanisms leading to FA.

With the goal of elucidating the immunogenesis FA, we established a murine model of SEB+OVA allergy model and pretreatment with anti-TIM1 and anti-TIM4 to further study the functional status of Treg cells and the impact of TIM1 in food allergy mice.

2. Materials and Methods

2.1 Materials

Staphylococcal enterotoxin B (SEB; synthesized by Department of Biotechnology, Zhengzhou University, Zhengzhou, China). Ovalbumin (Sigma Aldrich, MO, USA). Monoclonal Anti-mouse TIM-1 Antibody(R&D, USA). Monoclonal Anti-mouse TIM-4 Antibody (BioLegend, USA). BALB/c mice were purchased from Experimental Animal Center of Henan Province. The experimental procedures were approved by the Animal Care Committee at Zhengzhou University.

2.2 Murine Model of Intestinal Allergy and anti-TIM1 anti-TIM4 intervention

Forty 6~8 wk male BALB/c mice fed on the OVA-free diet were randomly divided into five groups, and eight mice were used for each group: A group of mice were sensitized by ip injection with SEB (10 μg/mouse) + OVA(20 μg/mouse) and the other three groups of mice were separately treated with normal saline (NS), anti-TIM1(2 μg/mouse) +SEB + OVA, anti-TIM1 (10 μg/mouse) +SEB + OVA, anti-TIM4 (10 μg/mouse) + SEB + OVA, on the 0, 3rd and 9th day; and all of the mice were challenged by means of ig with SEB+ OVA (except NS) on the 7th and 14th day. Mice were treated intraperitoneally with the same doses anti-TIM4 or anti-TIM1 30 minutes before gavage. Twenty-four hours after the last gavage, the mice were killed and subjected to immunologic analyses.

2.3 RT-PCR

The total of RNA was isolated from mouse jejunum and spleen using TRIZOL Reagent (Invitrogen, USA). The primers and PCR conditions included TIM4, forward: 5'-AGGGTCCGCCTCACTAC-3'; reverse: 5'-TCCCGTCTTCATCATCCC-3' (55℃ 404 bp); β-actin: forward, 5'-GAGACCTTCAACACCCCGC-3'; reverse, 5'-CCACAGGATTCCATCCCAA-3'(59℃, 446 bp); Foxp3: forward: 5'-AGGAGAAAGCGGATACCA-3'; reverse: 5'-GAAGGACATACCCAGAAGC-3' (55℃ 349 bp). The normalized value for Foxp3 and TIM4 mRNA expression was calculated as the relative quantity of Foxp3 and TIM4 divided by the relative quantity of β-actin.

2.4 ELISA

Determination of OVA sIgE (ADL, USA), IL-4, TGF-β1, and IL-10(SHANGHAI WESTANG BIO-TECH INC, LTD) in the sera, the peripheral blood were kept standing at the temperature of 37℃ for 1 h, then centrifuged at a low temperature of 4℃. Levels of OVA sIgE, IL-4, TGF-β1 and IL-10 in the sera were quantified using enzyme-linked immunosorbent assay (ELISA) kits in accordance with the manufacturer's instructions.

2.5 Immunohistochemistry

Cryosections were prepared from jejunal segments and stained with anti-TGF-β1 monoclonal antibodies by SP (streptavidin-peroxidase). Some paraffin wax block were used for HE (hematoxylin-eosin) staining. The results were observed in the mucosa of all samples from different groups of mice.

2.6 Statistical analysis

Data were expressed as the means ± SD. All statistical analysis was performed using SPSS statistical version 13.0. Differences between groups were determined with one-way ANOVA; non-parametric data were compared by the Kruskal-Wallis. a P value of less than 0.05 was considered to be statistically significant.

3. Results

3.1 SEB+OVA sensitization increased the levels of IgE and promotes Th2 responsiveness

Antigen-specific antibodies and Th2 cytokines play a critical role in intestinal allergic reactions (Owen CE, 2007) and are important diagnostic parameters in diagnosing and evaluating

therapeutic efficiency in patients with allergic diseases (Venarske D, 2003). Therefore, we assessed OVA-specific antibodies of IgE and IL-4 in the serum. The results showed that OVA-specific IgE and IL-4 increased significantly in mice sensitized to SEB+OVA (Table 1). Eosinophils are the major effector cells in hypersensitivity reactions, to further strengthen our observation, we examined the numbers of these cell types in the intestine. The results showed that the numbers of eosinophil increased significantly in mice sensitized to SEB+OVA (Figure 1). These results might indicate the successful establishment of murine food allergy model.

Table 1. Levels of IgE and IL-4 in serum in different groups (n=8, mean±SD)

group	IgE (ng/L)	IL-4 (ng/L)
Normal saline control group	0	41±7[a]
SEB + OVA group	197±58[c]	66±6[c]
anti-TIM1 group (10 μg/mouse)	87±8[a]	50±9[a]
anti-TIM1 group (50 μg/mouse)	48±16[a]	40±7[a]
anti-TIM4 group (50 μg/mouse)	50±18[a]	44±6[a]

[a]P<0.05 vs SEB + OVA group, [c]P<0.05 vs normal saline control group

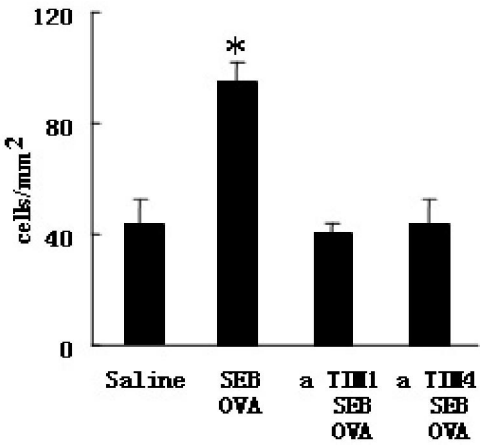

Figure 1. Pretreated with anti-TIM1 (or TIM4) antibody reduces the number of eosinophils. The jejunal segments were processed for the hematoxylin-eosin staining. Positively stained cells were counted under a light microscope. Bars indicate the numbers of eosinophils per mm2 jejunal tissue in different groups. Data were expressed as mean ± SD. *P<0.05, compared with saline group. aTIM1 (or aTIM4): Pretreated with anti-TIM1 (or TIM4) antibody.

3.2 SEB+OVA sensitization decreased the expressions of Foxp3 mRNA in the jejunum and spleen

Since Foxp3 plays an important role in the lineage commitment of Treg cells and deficiency of Foxp3 results in severe intestinal inflammation (Barnes MJ, 2009), we postulated that the expression of Foxp3 in the intestine might be compromised in food allergy mice. By the approach of RT-PCR, we found that expressions of Foxp3 mRNA in the jejunum and spleen decreased significantly in SEB+OVA group compared with those treated with NS (0.401±0.145 vs 0.732±0.162, P<0.05; 0.407±0.082 vs 0.691±0.145, P<0.05). Of interest, the results indicate that pretreatment with anti-TIM1 and anti-TIM4 effectively could restore the expressions of Foxp3 mRNA in jejunum and spleen (P = 0.000, P = 0.000) (Figure 2), that was prevented by pretreatment with different doses of anti-TIM1 in a dose-dependent manner (Figure 3). These results indicate that allergic responses interfere with the expression of Foxp3 in the intestine; the interaction of TIM1/TIM4 plays a role in the regulation of expression of the Foxp3 gene.

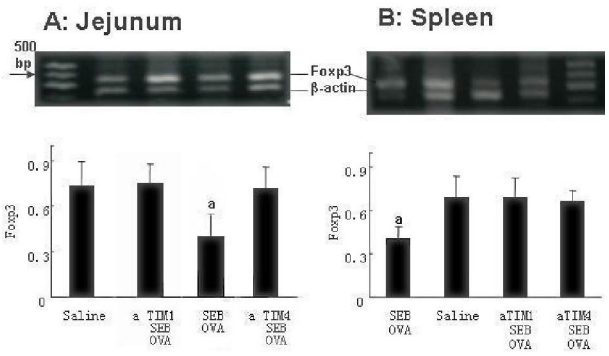

Figure 2. Expressions of Foxp3 mRNA in jejunum and spleen in different groups The average optic density of the electrophoresis bands were obtained by Bandscan. Bars indicate the ratio of the average optic density of Foxp3 mRNA divided by the average optic density of β-actin mRNA in different groups. Data were expressed as mean ± SD. [a]P <0.05 vs normal saline control group.

3.3SEB+OVA sensitization increased the expressions of TIM4 mRNA in jejunum

TIM4 is the natural ligand of TIM1. Interaction of TIM1/TIM4 promotes Th2 polarization (Meyers JH, 2005; Yang PC, 2007). Based on these previous studies, we postulated that the expression of TIM4 in the intestine might be increased. Indeed, expressions of TIM4 mRNA in jejunum increased significantly in SEB+OVA, anti-TIM1+SEB+OVA and anti-TIM4+SEB+OVA group compared with those treated with NS (P=0.004, P=0.007, P=0.033) (Figure 4). There was no significant difference between anti-TIM1+SEB+OVA and

anti-TIM4+SEB+OVA group. The results indicate that sensitization can markedly increase the expression of TIM4 gene in the intestine and disruption of TIM4-TIM1 pathway may not impact it.

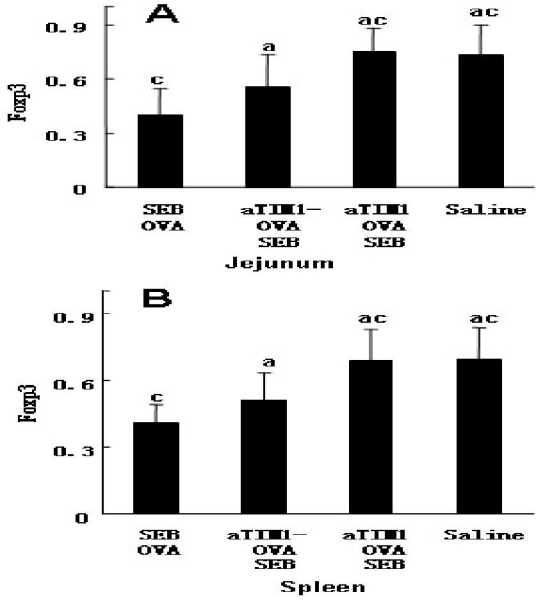

Figure 3. Expressions of Foxp3 mRNA in jejunum and spleen in different doses of anti-TIM1 groups. aTIM1-: Pretreated with anti-TIM1 antibody (10μg/mouse). aTIM1: Pretreated with anti-TIM1 antibody(50μg/mouse). The average optic density of the electrophoresis bands were obtained by Bandscan. Bars indicate the ratio of the average optic density of Foxp3 mRNA divided by the average optic density of β-actin mRNA in different groups. Data were expressed as mean ± SD. ^{a}P <0.05 vs SEB+OVA group, ^{c}P <0.05 vs aTIM1- group.

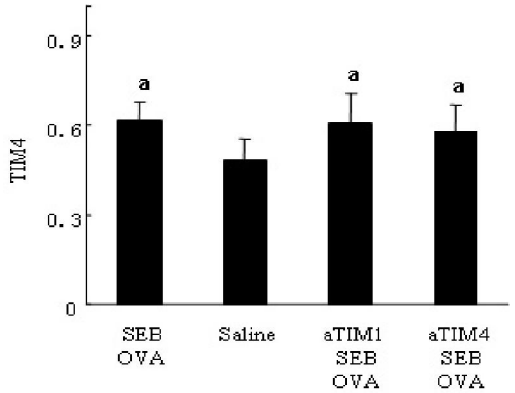

Figure 4 Expressions of TIM4 mRNA in jejunum in different groups The average optic density of the electrophoresis bands were obtained by Bandscan. Bars indicate the ratio of the average optic density of TIM4 mRNA divided by the average optic density of β-actin mRNA in different groups. Data were expressed as mean ± SD. ^{a}P <0.05 vs normal saline control group.

3.4SEB+OVA sensitization decreased the levels of TGF-β1 in serum

TGF-β and IL-10 are the major effector molecules with which Tregs suppress other effector T cell's activities. Since the gene expression of Foxp3 was decreased as shown above, we postulated that the serum levels of TGF-β and IL-10 might be suppressed under an allergic environment. As shown by ELISA, the levels of TGF-β1 in the serum decreased significantly in SEB+OVA group compared with those treated with NS, anti-TIM1 and anti-TIM4 (P=0.012, 0.010, 0.000). And the levels of TGF-β1 in the serum increased in response to different doses of anti-TIM1 stimulation in a dose-dependent manner. The levels of IL-10 was significantly higher in SEB+OVA group compared with those treated with NS (P = 0.001), but there's no statistical significance in other groups (Table 2).

Table 2. Levels of TGF-β1 and IL-10 in serum in different groups (*n*=8, mean±SD)

group	TGF-β1(ng/L)	IL-10(ng/L)
Normal saline control group	8342±488^{ae}	40±6
SEB + OVA group	7859±126^{e}	46±5^{c}
anti-TIM1 group (10 μg/mouse)	8058±97^{a}	42±2
anti-TIM1 group (50 μg/mouse)	8356±222^{ae}	43±5
anti-TIM4 group (50 μg/mouse)	8628±455^{ae}	43±3

^{a}P<0.05*vs* SEB + OVA group, ^{e}P<0.05 *vs* anti-TIM1 group (10 μg/mouse), ^{c}P<0.05 *vs* normal saline control group

3.5Number of TGF-β1-expressing cells is reduced in the intestine

TGF-β1 plays an important role in the immune regulation in the intestine. Since the serum level of TGF-β1 was decreased in sensitized mice, we speculated that the number of TGF-β1 expressing cells might be decreased as well. To this end, jejunal segments were processed and examined by immunohistochemistry. A number of TGF-β1^{+} cells were localized in the jejunum of mice treated with saline that were scarcely seen in mice sensitized to SEB+OVA. Pretreatment with antibodies against TIM1 or TIM4 could prevent the suppression of TGF-β1^{+} cells in the jejunum by sensitization (Fig.5).

3.6 Pretreated with anti-TIM1 (or TIM4) antibody reduced allergic responses

Above of these results demonstrate that pretreated with anti-TIM1 (or TIM4) antibody might

restore the function of Tregs. Indeed, the sensitized mice have profuse liquid stool, and the symptom was recovered by pretreating with anti-TIM1 (or TIM4) antibody. Importantly, we found that pretreatment with antibodies against TIM1 or TIM4 diminished the levels of IgE and OVA-specific Th2 cytokine responses in the serum (Table 1). As expected, the numbers of eosinophils were reduced in anti-TIM1 and anti-TIM4 group compare with that of sensitized mice (Figure 1). These results showed that blocking the interaction of TIM1/TIM4 is effective to abolish allergic responses.

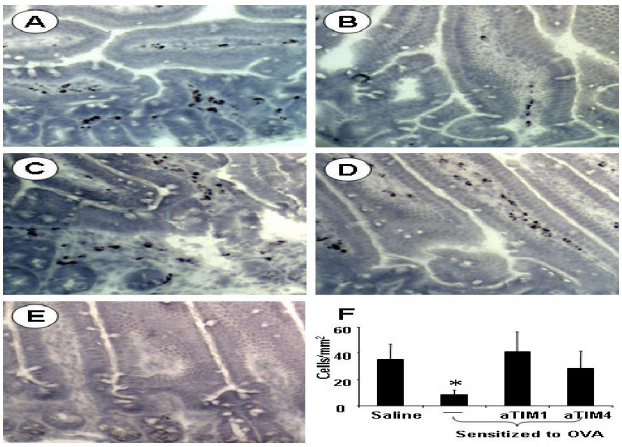

Figure 5 Sensitization reduces the number of TGF-β1-expressing cells in the intestine. Representative immunohistochemistry images from mice treated with (A) saline, (B) both SEB and OVA, (C) both SEB and OVA and pretreated with anti-TIM1 antibody, (D) both SEB and OVA and pretreated with anti-TIM4 antibody. The dark stained cells are TGF-β 1-expressing cells in panel A-D. Positively stained cells (dark staining) were counted under a light microscope. Panel E is isotype IgG staining. F, bars indicate the numbers of TGF-β1 cells per mm2 jejunal tissue in different groups. Data were expressed as mean ± SD. *P<0.05, compared with saline group. aTIM1 (or aTIM4): Pretreated with anti-TIM1 (or TIM4) antibody.

4. Discussion

In recent years, rapid progress has been made in the understanding of pathogenesis of food allergy. Researches have focused on the imbalance of Th1/Th2 cell, hygiene hypothesis, combined effect of bacterial toxins and food protein and oral tolerance (Yazdanbakhsh M, 2002; Liu T, 2006; Faria AM, 2005). However, the pathogenesis and mechanisms leading to food allergy still remain to be further understood. The discovery of TIMs and their bioactivities on immune regulation in food allergy has brought about new ideas. Each of TIM genes is predicted to encode a type of membrane protein with a similar structure, consisting of a signal sequence followed by an immunoglobulin variable region (IgV)-like domain, a mucin-like domain, a transmembraner region and an intracellular tail (McIntire JJ, 2001). TIM proteins have played a significant role in autoimmune disease, hypersensitivity diseases and transplantation tolerance. Mouse $CD4^+$ T cells expressed TIM1, TIM4 is its endogenous ligand, expressed in dendritic cells, and the pathway of TIM1-TIM4 play a crucial role in the differentiation of $CD4^+$ T cells (Liu T, 2007), but its influence on Treg cells was little understood. Treg cells have played an important role in the maintenance of oral tolerance. Dysfunctional Treg cells could impair oral tolerance and promote FA (Ganeshan K, 2009). Therefore, it's necessary to elucidate the function of Treg cells and the impact of TIM1on Treg cells in FA.

Degauque et al. have confirmed that the activation of TIM1 can reduce the function and quantity of $CD4^+CD25^+$Treg cells *in vitro* experiments, resulting in destruction of transplantation tolerance (Degauque N, 2008). We speculated that the similar mechanism existed in FA. Co-stimulation with SEB and OVA could promote the expression of TIM4 on DC (Venarske D, 2003), we have also confirmed it in the present experiment, and TIM4 interaction with TIM1 might abolish the function of Treg cells in FA. After pretreatment with anti-TIM1 or anti-TIM4 in SEB + OVA allergic mice, we found the expressions of Foxp3 and TGF-β1 was significantly restored in a dose-dependent manner, these results suggesting that the activation of TIM1 could down-regulate the function of Treg cells in FA. Antigen-specific antibodies and Th2 cytokines are important diagnostic parameters in diagnosing and evaluating therapeutic efficiency in patients with allergic diseases (Yang PC, 2007), the results showed that pretreatment with antibodies against TIM1 or TIM4 diminish the levels of IgE and OVA-specific Th2 cytokine responses in FA mice. Pathologic diagnosis is a valid indicator of FA, mast cells and eosinophils are the major effector cells in hypersensitivity reactions, in the present studies showed that there were a large amount of eosinophils in the allergic mice jejunum segments, while these cells were reduced significantly in anti-TIM1 and anti-TIM4 groups. These results demonstrated that pretreatment with anti-TIM1 or anti-TIM4 is effective and the disruption of TIM4-TIM1 pathway might be an optimal target for the treatment of FA.

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In the previous study we found that SEB play an important role in the pathogenesis of allergy (Liu T, 2007), and SEB could enhance the TIM4 expression in DC and had a dose-dependent manner, and SEB-conditioned DCs could induce Th2 cell polarization, application with anti-TIM1 or anti-TIM4 could block the induced Th2 cell polarization (Khattri R, 2003). We previously found co-exposure to both SEB and OVA significantly promote the expression of TIM4 in DCs. In addition, we detected other bacterial products such as Staphylococcus peptidoglycan and pertussis toxin could also promote the expression of TIM4 in DCs (Liu T, 2006) . Another study showed that concurrent *in vivo* exposure to both cholera toxin and peanut extract can induce the development of FA (Feng BS, 2008), the previous studies and our findings together suggested that concurrent *in vivo* exposure to both pathogenic microbial toxin and food antigen are crucial in the development of intestinal allergy. However, the complex pathogenesis of FA keeps unknown and further research is needed.

Our experiments confirmed that the function of Treg cells was decreased in food allergic mice. Pretreatment with anti-TIM1 or anti-TIM4 can restore Treg cells' function and abolish the intestinal allergy, suggesting that the pathway of TIM4 - TIM1 may cause dysfunction of Treg cells. In summary, the activation of TIM1 plays a key role in $CD4^+$ T cell polarization in FA, not only can it promote Th2 cells polarization, but also reduce the function of Treg cells, while block the pathway of TIM1 and TIM4 can effectively restore the balance of oral tolerance and dampen allergic responses.

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