

# The Role of Thymic Stromal Lymphopoietin (TSLP) in Glomerulonephritis

Keum Hwa Lee, M.D.<sup>1,2</sup>

Jae Won Yang, M.D.<sup>3</sup>

Jin Young Cho<sup>4</sup>

Joo Yup Lee<sup>5</sup>

Eun Kyung Lim<sup>6</sup>

Michael Eisenhut, M.D., FRCPC, FRCP<sup>7</sup>

Dong Yeon Jeong, M.D.<sup>8</sup>

Johanna Steingroever<sup>9</sup>

Jae Il Shin, M.D., Ph.D.<sup>1,2,10</sup>

<sup>1</sup>Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea, <sup>2</sup>Department of Pediatric Nephrology, Severance Children's Hospital, Seoul, Korea, <sup>3</sup>Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea, <sup>4</sup>Konyang University College of Medicine, Daejeon, Korea, <sup>5</sup>Chonbuk National University College of Medicine, Jeonju, Korea, <sup>6</sup>Chonnam National University College of Medicine, Gwangju, Korea, <sup>7</sup>Luton&Dunstable University Hospital NHS Foundation Trust, Luton, United Kingdom, <sup>8</sup>Yonsei University College of Medicine, Seoul, Korea, <sup>9</sup>University of Hamburg, Medical Faculty, Hamburg, Germany, <sup>10</sup>Institute of Kidney Disease Research, Yonsei University College of Medicine, Seoul, Korea

## Corresponding author:

Jae Il Shin, M.D., Ph.D.

Department of Pediatrics, Yonsei University College of Medicine, Seoul 50 Yonsei-Ro, Seodaemun-gu, Seoul 03722, Korea

Tel: +82-2-2228-2050, Fax: +82-2-393-9118

E-mail: [shinji@yuhs.ac](mailto:shinji@yuhs.ac)

Received: 6 September 2017

Revised: 14 September 2017

Accepted: 18 September 2017

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2018 The Korean Society of Pediatric Nephrology

Thymic stromal lymphopoietin (TSLP) is an interleukin-7-like cytokine that is an important trigger and initiator of many allergic diseases. TSLP promotes a T-helper type 2 (Th2) cytokine response that can be pathological. A relationship is formed both at the induction phase of the Th2 response through polarization of dendritic cells to drive Th2 cell differentiation and at the effector phase of the response, by promoting the expansion of activated T cells and their secretion of Th2 cytokines and TSLP. In transgenic mice with TSLP overexpression, it has been reported that TSLP leads to the development of mixed cryoglobulinemic membranoproliferative glomerulonephritis. In addition, TSLP can play an important role in the pathogenesis of IgA nephropathy and systemic lupus erythematosus-related nephritis. From our knowledge of the role of TSLP in the kidney, further studies including the discovery of new therapies need to be considered based on the relationship between TSLP and glomerulonephritis.

**Key words:** Thymic stromal lymphopoietin (TSLP), glomerulonephritis, T-helper type 2 (Th2)-dominant immune response, TSLP transgenic mice

## Introduction

Thymic stromal lymphopoietin (TSLP), an interleukin (IL)-7-like cytokine, has been reported in several studies about multiple diseases such as allergic airway disease<sup>1</sup>, atopic skin disease<sup>2</sup>, inflammatory bowel disease (IBD)<sup>3,4</sup>, or even breast<sup>5</sup> and pancreatic cancer<sup>6</sup>. Even though glomerulonephritis including membranoproliferative glomerulonephritis (MPGN) remains an unsolved kidney disease for clinicians until now, however, there have been few reports of TSLP especially in the pathogenesis of glomerulonephritis.

In this review, we will focus on understanding the role of TSLP-related to unknown mechanism of glomerulonephritis and discuss the potential of TSLP in glomerulonephritis pathogenesis as a therapeutic manner.

## TSLP in relation to Th2 cytokines

TSLP can induce about dendritic cells (DCs)-mediated T-helper type 2 (Th2) inflammatory responses<sup>7</sup>. It is a trigger and initiator for many allergic diseases and it promotes Th2 cytokine responses that can be either host protective or

pathological<sup>8)</sup>. A relationship is shown both at the induction phase of the Th2 response through polarization of DCs to drive Th2 cell differentiation and at the effector phase of the response by promoting the expansion of activated T cells and their secretion of Th2 cytokines<sup>9)</sup>. TSLP can drive a Th2 cytokine response, potentially through effects on DCs, especially<sup>10)</sup>. After stimulated by TSLP, the dendritic cell activates CD 4+ T cells leading to T cell proliferation<sup>11)</sup>. In the absence of IL-12, dendritic cells induce expression of OX40L, the ligand for the cell survival factor OX40, OX40-OX40L interactions are critical for the ability of the DCs to drive Th2 cell differentiation<sup>12)</sup>.

TSLP also seems to promote basophil responses. Influencing cytokine expression in DCs, the Th2 promoting properties of TSLP may be mediated through basophils<sup>13)</sup>. Basophils enhance the Th2 response and impair the Th1 response. Basophils can develop Th2 cells in vitro and in vivo by producing Th2 cytokines such as IL-4 and IL-13.

In this part of view, TSLP plays an important role in the pathogenesis of atopic dermatitis and asthma<sup>14)</sup>. TSLP induces upregulation of OX40L expression on DCs cells. Th2 cytokines released, including IL-4, IL-5, IL-9, IL-13, bind to their receptors and activate inflammatory and structural cells involved in the pathogenesis of asthma<sup>15)</sup>. TSLP is overtly expressed on skin lesions of atopic dermatitis. T cells from atopic dermatitis patients possess strong potential to directly interact with TSLP to promote a Th2 response<sup>16)</sup>. So, TSLP is a good therapeutic target in the treatment of allergic diseases, but its protective role in inflammatory bowel disease (IBD) is an important caution because neutralization of TSLP could potentially unmask or aggravate Th17 and or Th2 dominated inflammatory disease<sup>14)</sup>.

### TSLP transgenic mice and membranoproliferative glomerulonephritis (MPGN)

Membranoproliferative glomerulonephritis (MPGN) is an intractable kidney disease of unknown etiology which can be developed in children and young adults with features of nephrotic or nephritic syndrome<sup>17)</sup>. Renal dysfunction occurs frequently with rapid progression in MPGN<sup>17)</sup>. MPGN in children is mostly idiopathic, whereas MPGN in adults is commonly associated with cryoglobulinemia<sup>18)</sup>

or hepatitis C virus infection<sup>19)</sup> which can be shown as the glomerular injury of cryoglobulinemic MPGN. The mechanism of the deposition and the role of cryoglobulins in the kidney are unclear.

Mice transgenic for TSLP, under regulation of the lymphocyte-specific promotor lymphocyte protein tyrosine kinase (Lck), develop cryoglobulinemia and MPGN similar to the disease in patients. In 2001, Taneda et al. firstly presented transgenic mouse model of mixed cryoglobulinemia<sup>20)</sup>. This in vivo mouse model suggested that severe glomerular lesions were shown in pathologic findings, but the tubulointerstitium was intact compared to glomerular areas<sup>20)</sup>. They also found the pathologic findings such as capillary wall thickening, subendothelial immune-deposition, mesangium expansion, double contours of the basement membrane, which resemble MPGN findings in human kidney<sup>20)</sup>.

It is estimated that overexpression of TSLP in mice results in the development of mixed cryoglobulinemic MPGN. In TSLP transgenic mice with overexpression, cryoprecipitates are mixed type composed of IgG, IgM and light chains<sup>20)</sup>. In glomerular deposits, IgG, IgM, IgA and complement C3 are detected distinctively compared to C3 deposition that was detected in glomeruli from wild-type<sup>20)</sup>. These pathologic features closely resemble the pathologic features of human cryoglobulinemic MPGN<sup>20)</sup>. Therefore, TSLP-transgenic mice are a very attractive MPGN model and enable to study pathogenesis of human MPGN.

After development of TSLP transgenic mice, there were many studies using these animals to reveal the pathogenesis of MPGN. Segerer et al. tested oral interferon (IFN)-alpha (used as treatment in humans with cryoglobulinemic glomerulonephritis) in 41 TSLP transgenic mice<sup>21)</sup>. It was shown that IFN-alpha affected reducing influx of glomerular macrophage in contrast to little effect on the glomerular matrix deposition<sup>21)</sup>. They also suggest that IFN-alpha therapy can have some antiviral effects in TSLP transgenic mice<sup>21)</sup>. And transforming growth factor (TGF)-β1 protein increased when mesangial cells are stimulated with cryoglobulin in vitro<sup>21)</sup>. So it is concluded that cryoglobulins directly upregulate protease nexin (PN)-1, plasminogen activator inhibitor (PAI)-1 and TGF-β1 which are important mediators of glomerulonephritis<sup>21)</sup>.

In 2003, Mühlfeld et al. engaged immunoglobulin-binding

receptors (FcγRIIb) on leukocytes categorizing four mice groups: wild-type, FcγRIIb<sup>-/-</sup>, TSLP transgenic, and combined TSLP transgenic/ FcγRIIb<sup>-/-</sup> mice<sup>22</sup>. TSLP transgenic mice with knock out of FcγRIIb led to a significant aggravation of the immune complex-mediated renal disease and decreased renal function and increase in proteinuria. TSLP/ FcγRIIb<sup>-/-</sup> mice had significantly increased glomerular size due to an increase in glomerular extracellular matrix and glomerular cellularity<sup>22</sup>. Increased glomerular cellularity was due to an increase in proliferating glomerular cells and infiltration of monocytes/macrophage<sup>22</sup>. Also, FcγRIIb defect mice with TSLP overexpression showed upregulation of PN-1 and PAI-1<sup>22</sup>. The study showed that FcγRIIb<sup>-/-</sup> mice had no significant renal pathology whereas TSLP transgenic FcγRIIb<sup>-/-</sup> mice showed significantly impaired glomerular lesions with decreased kidney function and high mortality<sup>22</sup>. FcγRIIb was revealed to regulate immune responses and have possibilities as a useful therapeutic target for glomerular diseases<sup>22</sup>. PAI-1 was previously studied in various renal models, leading to renal fibrosis and renal failure<sup>23,24</sup>. PAI-1 and PN-1 expression was strong in mesangial matrix in TSLP transgenic mice and further increased in TSLP/FcγRIIb<sup>-/-</sup> mice<sup>25</sup>.

Banas et al. analyzed the level of toll-like receptors (TLR) in TSLP transgenic mice<sup>26</sup>. In TSLP transgenic mice, TLR subtype 1, 2, and 4 were increased and even higher in TSLP/ FcγRIIb<sup>-/-</sup> murine kidney<sup>26</sup>. Especially TLR4 was overexpressed in mature podocytes in vivo and in vitro<sup>26</sup>. In MPGN of TSLP/FcγRIIb<sup>-/-</sup> mice, TLR4 in podocytes may have a potential role in inflammatory reaction by responding to foreign bodies like pathogens or endogenous ligand like fibrinogens and recruiting inflammatory cells in glomerulonephritis<sup>26</sup>. In other words, TLR4 may act as a linkage of the innate immune system and glomerular injury triggered by elevated immune complexes<sup>26</sup>.

In another study, Mühlfeld et al. crossbred TSLP transgenic mice with overexpressing Crry (complement receptor-1 related gene/protein Y)<sup>27</sup>. There was no significant improvement of glomerulus in TSLP/Crry doubly transgenic mice suggesting that overexpressing Crry was not sufficient to suppress TSLP activation<sup>27</sup>. Iyoda et al. tested all-trans-retinoic acid (ATRA), a powerful anti-inflammatory agent, on TSLP transgenic mice<sup>28</sup>. Similar to Crry, ATRA does not protect aggravation of cryoglobulinaemic MPGN and

thus retinoid therapy has to be used with caution<sup>28</sup>.

Guo et al. developed TSLP transgenic mice expressing the human diphtheria toxin receptor (DTR) mice (Lck-TSLP; CD11b-DTR) to control and ablate the monocyte/macrophage-restricted CD11b promoter<sup>29</sup>. In this mouse model, suppression of macrophage showed protective effects on the disease progression in cryoglobulinemic MPGN<sup>29</sup>. Astrakhan et al. developed an in vivo K5-TSLP (doxycycline-inducible, keratin 5-driven transgene encoding TSLP) transgenic mouse model<sup>30</sup>. In this model, immature B cells were increased in periphery with expansion of follicular mature B cells meaning activation of systemic B cell development<sup>30</sup>. This finding suggests that expression of TSLP is closely related to systemic humoral autoimmunity<sup>30</sup>.

## TSLP and other glomerulonephritis

Although studies about TSLP are mainly dependent upon MPGN, there are two studies about IgA nephropathy and systemic lupus erythematosus (SLE)-related nephritis. Meng et al. found out that both the serum level of TSLP and the numbers of IgA-bearing cells were increased in IgA nephritis patients<sup>31</sup>. Overexpression of TSLP may enhance IgA class switching correlated with activation-induced cytidine deaminase (AID), TGF-β1, B cell-activating factor of the tumor necrosis factor family (BAFF), and a proliferation-inducing ligand (APRIL) in tonsillar follicular dendritic cells (FDC) and result in IgA deposition in the renal mesangium<sup>31</sup>. Ellison et al. used palifermin (recombinant human keratinocyte growth factor, also known as fibroblast growth factor-7) in acute or chronic GVHD mouse model which resembles pathologic findings of glomerular lesion in SLE<sup>32,33</sup>. Both palifermin-treated and untreated mice were shown pathological injuries in the kidney, but these changes in palifermin-treated recipients resemble those seen in TSLP transgenic mice<sup>32</sup>. They hypothesized that overexpression of TSLP was induced by treating palifermin and is closely related to GVHD or SLE nephritis<sup>32</sup>.

## Concluding remarks and future perspectives

We try to demonstrate that TSLP, a Th2-like cytokine,

could affect pathogenesis of MPGN by changing the podocytes in animal and human model. TSLP stimulates myeloid dendritic cells (mDC), which express the TSLP receptor. TSLP-activated mDC can promote naïve CD4+ T cells to differentiate into a Th2 phenotype and can trigger the expansion of CD4+ Th2 memory cells.

To summarize, TSLP can be an important cytokine to develop glomerulonephritis. Through previous studies, pathogenesis of glomerulonephritis has been clarified using TSLP-transgenic mice. It is also proposed that we could clarify whether TSLP is involved in the pathogenesis of glomerulonephritis by injecting TSLP to mice with gradually increasing concentration or if we can make an animal model which express podocyte-specific TSLP. Based on the results about the relationship between TSLP and glomerulonephritis, the new therapy could be invented based on the hypothesis that suppression of TSLP signaling improves glomerulonephritis in mice and in the human model by regulating dendritic cell-mediated T-helper type 2 inflammatory responses.

## Conflict of interest

The authors of the manuscript declare no conflict of interest.

## Acknowledgements

Jae Il Shin was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) and funded by the Ministry of Education, Science and Technology (2015R1C1A1A01052984).

## References

- Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002;3:673-80.
- Gao PS, Rafaels NM, Mu D, Hand T, Murray T, Boguniewicz M, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. *J Allergy Clin Immunol* 2010;125:1403-7.
- Noble CL, Abbas AR, Cornelius J, Lees CW, Ho GT, Toy K, et al. Regional variation in gene expression in the healthy colon is dysregulated in ulcerative colitis. *Gut* 2008;57:1398-405.
- Noble CL, Abbas AR, Lees CW, Cornelius J, Toy K, Modrusan Z, et al. Characterization of intestinal gene expression profiles in Crohn's disease by genome-wide microarray analysis. *Inflamm Bowel Dis* 2010;16:1717-28.
- Olkhanud PB, Rochman Y, Bodogai M, Malchinkhuu E, Wejksza K, Xu M, et al. Thymic stromal lymphopoietin is a key mediator of breast cancer progression. *J Immunol* 2011;186:5656-62.
- De Monte L, Reni M, Tassi E, Papa I, Recalde H, Braga M, et al. Intratumor T helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer. *J Exp Med* 2011;208:469-78.
- Wang WL, Li HY, Zhang MS, Gao PS, He SH, Zheng T, et al. Thymic stromal lymphopoietin: a promising therapeutic target for allergic diseases. *Int Arch Allergy Immunol* 2013;160:18-26.
- Ziegler SF, Artis D. Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol* 2010;11:289-93.
- Sokol CL, Barton GM, Farr AG, Medzhitov R. A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nat Immunol* 2000;9:310-18.
- He R, Geha RS. Thymic stromal lymphopoietin. *Ann NY Acad Sci* 2010;1183:13-24.
- Lu N, Wang YH, Wang YH, Arima K, Hanabuchi S, Liu YJ. TSLP and IL-7 use two different mechanisms to regulate human CD4+ T cell homeostasis. *J Exp Med* 2009;206:2111-9.
- Kitajima M, Lee HC, Nakayama T, Ziegler SF. TSLP enhances the function of helper T cells. *Eur J Immunol* 2011;41:1862-71.
- Ziegler SF, Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H. The biology of thymic stromal lymphopoietin (TSLP). *Adv Pharmacol* 2013;66:129-55.
- Miazgowiec MM, Headley MB, Larson RP, Ziegler SF. Thymic stromal lymphopoietin and the pathophysiology of atopic disease. *Expert Rev Clin Immunol* 2009;5:547-56.
- Harada M, Hirota T, Jodo AI, Hitomi Y, Sakashita M, Tsunoda T, et al. Thymic stromal lymphopoietin gene promoter polymorphisms are associated with susceptibility to bronchial asthma. *Am J Respir Cell Mol Biol* 2011;44:787-93.
- Indra AK. Epidermal TSLP: a trigger factor for pathogenesis of atopic dermatitis. *Expert Rev Proteomics* 2013;10:309-11.
- Cameron JS, Turner DR, Heaton J, Williams DG, Ogg CS, Chantler C, et al. Idiopathic mesangiocapillary glomerulonephritis. Comparison of types I and II in children and adults and long-term prognosis. *Am J Med* 1983;74:175-92.
- Alpers CE, Smith KD. Cryoglobulinemia and renal disease. *Curr Opin Nephrol Hypertens* 2008;17:243-9.
- D'Amico G, Fornasieri A. Cryoglobulinemic glomerulonephritis: a membranoproliferative glomerulonephritis induced by hepatitis C virus. *Am J Kidney Dis* 1995;25:361-9.

20. Taneda S, Segerer S, Hudkins KL, Cui Y, Wen M, Segerer M, et al. Cryoglobulinemic glomerulonephritis in thymic stromal lymphopoietin transgenic mice. *Am J Pathol* 2001;159:2355-69.
21. Segerer S, Hudkins KL, Taneda S, Wen M, Cui Y, Segerer M, et al. Oral interferon-alpha treatment of mice with cryoglobulinemic glomerulonephritis. *Am J Kidney Dis* 2002;39:876-88.
22. Mühlfeld AS, Segerer S, Hudkins K, Carling MD, Wen M, Farr AG, et al. Deletion of the Fc $\gamma$  receptor IIb in thymic stromal lymphopoietin transgenic mice aggravates membranoproliferative glomerulonephritis. *Am J Pathol* 2003;163:1127-36.
23. Huang Y, Nobel N. An unexpected role of plasminogen activator inhibitor-type1 (PAI-1) in renal fibrosis. *Kidney Int* 2005;67:2502-3.
24. Matsuo S, Lopez-Guisa JM. Multifunctionality of PAI-1 in fibrogenesis: Evidence from obstructive nephropathy in PAI-1-overexpressing mice. *Kidney Int* 2005;67:2221-38.
25. Taneda S, Hudkins KL, Mühlfeld AS, Kowalewska J, Pippin JW, Shankland SJ, et al. Protease nexin-1, tPA, and PAI-1 are upregulated in cryoglobulinemic membranoproliferative glomerulonephritis. *J Am Soc Nephrol* 2008;19:243-51.
26. Banas MC, Banas B, Hudkins KL, Wietecha TA, Iyoda M, Bock E, et al. TLR4 links podocytes with the innate immune system to mediate glomerular injury. *J Am Soc Nephrol* 2008;19:704-13.
27. Mühlfeld AS, Segerer S, Hudkins K, Farr AG, Bao L, Kraus D, et al. Overexpression of complement inhibitor Crry does not prevent cryoglobulin-associated membranoproliferative glomerulonephritis. *Kidney Int* 2004;65:1214-23.
28. Iyoda M, Hudkins KL, Wietecha TA, Banas MC, Guo S, Liu G, et al. All-trans-retinoic acid aggravates cryoglobulin-associated membranoproliferative glomerulonephritis in mice. *Nephrol Dial Transplant* 2007;22:3451-61.
29. Guo S, Wietecha TA, Hudkins KL, Kida Y, Spencer MW, Pichaiwong W, et al. Macrophages are essential contributors to kidney injury in murine cryoglobulinemic membranoproliferative glomerulonephritis. *Kidney Int* 2011;80:946-58.
30. Astrakhan A, Omori M, Nguyen T, Becker-Herman S, Iseki M, Aye T, et al. Local increase in thymic stromal lymphopoietin induces systemic alterations in B cell development. *Nat Immunol* 2007;8:522-31.
31. Meng H, Li H, Ohe R, Naing YA, Yang S, Kabasawa T, et al. Thymic stromal lymphopoietin in tonsillar follicular dendritic cells correlates with elevated serum immunoglobulin A titer by promoting tonsillar immunoglobulin A class switching in immunoglobulin A nephropathy. *Transl Res* 2016;176:1-17.
32. Ellison CA, Lissitsyn YV, Gheorghiu I, Gartner JG. Immunomodulatory effects of palifermin (recombinant human keratinocyte growth factor) in an SLE-like model of chronic graft-versus-host disease. *Scand J Immunol* 2012;75:69-76.
33. Chu YW, Gress RE. Murine models of chronic graft-versus-host disease: insights and unresolved issues. *Biol Blood Marrow Transplant* 2008;14:365-78.