Review article

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The Role of Thymic Stromal Lymphopoietin (TSLP) in Glomerulonephritis

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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[1)], atopic skin disease[2)], inflammatory bowel disease (IBD)[3,4)], or even breast[5)] and pancreatic cancer[6)]. 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[7)]. It is a trigger and initiator for many allergic diseases and it promotes Th2 cytokine responses that can be either host protective or

pathological[8]. 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[9]. TSLP can drive a Th2 cytokine response, potentially through effects on DCs, especially[10]. After stimulated by TSLP, the dendritic cell activates CD 4+ T cells leading to T cell proliferation[11]. 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[12].

TSLP also seems to promote basophil responses. Influencing cytokine expression in DCs, the Th2 promoting properties of TSLP may be mediated through basophils[13]. 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[14]. 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[15]. 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[16]. 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[14].

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[17]. Renal dysfunction occurs frequently with rapid progression in MPGN[17]. MPGN in children is mostly idiopathic, whereas MPGN in adults is commonly associated with cryoglobulinemia[18] or hepatitis C virus infection[19] 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[20]. This in vivo mouse model suggested that severe glomerular lesions were shown in pathologic findings, but the tubulointerstitium was intact compared to glomerular areas[20]. 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[20].

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[20]. In glomerular deposits, IgG, IgM, IgA and complement C3 are detected distinctively compared to C3 deposition that was detected in glomeruli from wild-type[20]. These pathologic features closely resemble the pathologic features of human cryoglobulinemic MPGN[20]. Therefore, TSLP-transgenic mice are a very attractive MPGN model and enable to study pathogenesis of human MPGN.

After development of TSLP transgemic 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[21]. It was shown that IFN-alpha affected reducing influx of glomerular macrophage in contrast to little effect on the glomerular matrix deposition[21]. They also suggest that IFN-alpha therapy can have some antiviral effects in TSLP transgenic mice[21]. And transforming growth factor (TGF)-β1 protein increased when mesangial cells are stimulated with cryoglobulin in vitro[21]. 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[21].

In 2003, Mühlfeld et al. engaged immunoglobulin-binding

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

Banas et al. analyzed the level of toll-like receptors (TLR) in TLSP transgenic mice[26]. In TSLP transgenic mice, TLR subtype 1, 2, and 4 were increased and even higher in TSLP/FcγRIIb -/- murine kidney[26]. Especially TLR4 was overexpressed in mature podocytes in vivo and in vitro[26]. In MPGN of TSLP/FcγRIIb -/- 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[26]. In other words, TLR4 may act as a linkage of the innate immune system and glomerular injury triggered by elevated immune complexes[26].

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

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[29]. In this mouse model, suppression of macrophage showed protective effects on the disease progression in cryoglobulinemic MPGN [29]. Astrakhan et al. developed an in vivo K5-TSLP (doxycycline-inducible, keratin 5–driven transgene encoding TSLP) transgenic mouse model[30]. In this model, immature B cells were increased in periphery with expansion of follicular mature B cells meaning activation of systemic B cell development[30]. This finding suggests that expression of TSLP is closely related to systemic humoral autoimmunity[30].

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[31]. 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 ligan (APRIL) in tonsillar follicular dendritic cells (FDC) and result in IgA deposition in the renal mesangium[31]. 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[32,33]. 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[32]. They hypothesized that overexpression of TSLP was induced by treating palifermin and is closely related to GVHD or SLE nephritis[32].

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.

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