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REVIEW

Thymic Stromal Lymphopoietin: To Cut a Long Story Short

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SUMMARY

TSLP is a cytokine involved in a plethora of physiologic and pathologic immune functions, including tolerance and allergy. The existence of two isoforms of the protein whose expression is driven by independent promoters can explain these contrasting activities.

Thymic stromal lymphopoietin (TSLP) was identified more than 20 years ago as a secreted factor of a mouse thymic stromal cell line; later, a human orthologue was also identified. The signaling pathway triggered by TSLP has been extensively studied, and upregulation of the cytokine itself is linked to the pathogenesis of numerous Th2-related diseases, including atopic dermatitis, asthma, allergic responses, as well as certain types of cancers. On the other hand, TSLP mediates several immune homeostatic functions in both the gut and the thymus. Thus, a paradox occurs; why is TSLP homeostatic in certain tissues and a hallmark of exacerbated Th2 responses in the aforementioned pathologies? We and others have recently shown that in humans a novel isoform exists; this is a shorter isoform of TSLP whose expression is constitutive and controlled by a separate promoter. Short TSLP isoform mediates the homeostatic functions, whereas the long isoform is expressed at low/undetectable level at steady state and upregulated during inflammation in several tissues. Here we review the most recent data concerning the differential expression of the 2 isoforms and provide a potential explanation to the paradox. TSLP is regarded as a promising target for treatment of relevant pathologies, with a number of clinical trials already underway. It is important to design new strategies aimed at leaving intact the homeostatic effects of the short isoform while targeting the inflammatory effects of the long isoform. *(Cell Mol Gastroenterol Hepatol 2017;3:174–182; http://dx.doi.org/10.1016/j.jcmgh.2017.01.005)*

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Cytokines (cyto, from Greek *κύτταρο kyttaro* "cell" + kines, from Greek *κίνηση kinisi* "movement") are a broad category of small proteins whose release has an effect on the behavior of cells around them. They can act in an autocrine, paracrine, and/or endocrine fashion and are important in a number of biological processes including developmental processes during embryogenesis; however, they are particularly important in the regulation of immune responses. Cytokine types include chemokines, interferons (IFNs), lymphokines, interleukins (ILs), and tumor necrosis factors (TNFs). Because cytokines are important in intercellular and intracellular communications, they are produced by a broad range of cells such as fibroblasts, stromal, endothelial, or immune cells. They can be part of a physiological, homeostatic response or act as danger signals initiating inflammation in response to the detection of pathogens. Indeed, different isoforms of the same cytokine have been observed to mediate different effects according to the context, cellular source, and targets. These isoforms can be the result of alternative splicing, as is the case for IL15,[1,2] or result from the expression of separate genes for each isoform, as is the case for the IFN, IL28[3] and IL17.[4]

Here we will examine how thymic stromal lymphopoietin (TSLP) belongs to the category of cytokines with more than 1 isoform, and we will review recent data that shed light on a paradox: despite the necessity for TSLP in the homeostatic development of certain immune cell subsets, the same cytokine seems to exert potent proinflammatory actions, and its upregulation underlies numerous allergic reactions and allergy-related pathologies.

Discovery and Initial Observations

TSLP is an IL7-like cytokine initially discovered in the culture supernatant of a mouse thymic stromal cell line and shown to act as a growth factor for T and B cells.[5] The existence of a human orthologue with similar functions was shown some years later by Quentmeier et al,[6] who observed constitutive TSLP expression in heart, lung, prostate, and testis human tissues. In the same study the authors cloned human TSLP and characterized the signaling pathway triggered by the TSLP–thymic stromal lymphopoietin protein receptor (TSLPR) interaction. In both human and mouse, the receptor for TSLP is a heterodimer composed of a chain specific for TSLP and the IL7R α-chain[6–8]; however, in

Abbreviations used in this paper: **DC, dendritic cell; IFN, interferon; IL, interleukin; ILC, innate lymphoid cells; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cells; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin protein receptor.**

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contrast to IL7, TSLP signaling results in JAK3-independent STAT5 phosphorylation.[6,7] Quentmeier et al observed that myeloid cells proliferate in response to human TSLP. These cell lines also upregulate granulocyte-macrophage colony-stimulating factor after conditioning; however, the authors demonstrate a direct effect of TSLP on the proliferation, independent from granulocyte-macrophage colony-stimulating factor and from the activity of mitogen-activated protein kinases (MAPKs).[6] TSLP also promotes the maturation of primary cells of myeloid origin, particularly $CD11c^+$ dendritic cells (DCs), one of the subsets on which expression of IL7R and TSLPR is highest.[9,10]

TSLP is primarily expressed by epithelial cells and keratinocytes in the skin, gut, lungs,[9] and ocular tissue[11] and seems to be involved in the regulation of inflammatory processes occurring at the barrier surfaces. It is also constitutively produced by the epithelial cells of Hassall corpuscles in the thymus, where it activates mature DCs and plasmacytoid dendritic cells to induce functionally different types of regulatory T (Treg) cells.[12,13] However, recent studies revealed that other types of cells, such as mast cells,[10,14] cancer cells,[15] basophils,[16] and DCs, produce TSLP.[17]

In particular, DCs can be robust producers of TSLP under certain conditions; on in vitro cultured DCs, activation of toll-like receptors (TLRs) by lipopolysaccharide and CpG oligodeoxynucleotides induces a significant upregulation of TSLP mRNA expression in a STAT6-dependent fashion. In vivo challenge with house dust mite, a well-known allergen for triggering asthmatic responses, induces TSLP production by both epithelial and dendritic cells in the lungs.[17] A more recent report confirms TSLP production by human DCs after challenge with β-glucans found on fungi. The authors show that IL1β, but not TNF-α, is necessary for TSLP production, and that this follows activation of both nuclear factor kappa B (NF-κB) and the p38 MAPK.[18]

Functions of Thymic Stromal Lymphopoietin in Barrier Surfaces and the Emergence of a Paradox

Innate and Adaptive Type 2 Immune Responses in Barrier Surfaces

As reports for epithelial cell–DC interactions and the consequent immunomodulatory effects became more numerous,[19–22] the effect of TSLP on adaptive immune responses through its action on DCs was also under investigation.

It was observed that TSLP-conditioned peripheral blood $CD11c^+$ DCs skew adaptive immune responses to a pathogenic and pro-allergic Th2 type. CD8 T cells expanded by TSLP-conditioned DCs produce the hallmark Tc2 cytokines IL5 and IL13, whereas concomitant activation of the DCs with CD40L induces potent cytotoxicity and IFN-γ secretion without dampening IL5 or IL13 secretion.[23] Of note, CD4 T cells co-cultured with similarly activated DCs also acquire a strong Th2 phenotype but only in the absence of IL12.[10,24]

Danger signals produced by the epithelia and secreted toward underlying tissues alert many cell subsets to the presence of pathogens/allergens. Thus DCs are not the only population of innate immune cells that responds to TSLP. Type 2 innate lymphoid cells (ILC2) robustly upregulate the hallmark Th2 cytokines IL4, IL5, and IL13 in response to TSLP alone or in synergy with other cytokines.[25] On the skin, TSLP acts on resident ILC2 to induce Th2 cytokine secretion by the latter and promote inflammation. This cell subset is more abundant in atopic dermatitis lesions from patients, and it is also critical for the development of inflammation in a mouse model of the disease.[26] In the lungs, it is the synergy between TSLP, IL33, and IL25 that promotes expansion of type 2 ILCs in response to allergens such as papain[27] and chitin as well as migratory helminths.[28]

Consistently, a marked upregulation of TSLP expression has been repeatedly observed in mouse models of atopic dermatitis, allergy, eosinophilic esophagitis, and asthma.[29–32] Elevated TSLP expression has been observed in eosinophilic esophagitis patients, in whom a gain-of-function polymorphism is associated with increased basophil responses in these patients.[31] Atopic dermatitis, asthma, psoriasis, and allergic rhinitis patients also show higher TSLP expression in inflamed tissues,[10,33–36] whereas expression of TSLPR is modulated in these diseases compared with the steady state.[37,38] In humans, the balance between TSLP secretion by the epithelia and TSLPR expression levels on target cells is pivotal.

Regulatory Immune Responses in the Gastrointestinal Tract

Despite the aforementioned proinflammatory activity of TSLP in barrier surfaces such as skin and lung,[10,33] the cytokine is also known to be pivotal for the maintenance of homeostasis and the development of natural Treg in the gastrointestinal tract.

First, it appears that polarization of type 2 ILCs is independent of TSLP in the gut and is rather controlled by IL33[39] and the abundance of vitamins such as retinoic acid and vitamin D.[40] More specifically, retinoic acid synergizes with IL2, IL25, and IL33 but not TSLP to upregulate secretion of IL5 and IL13 as well as the gut homing integrins α4 and β7 on human ILC2 in vitro. This upregulation is inhibited by the addition of vitamin D in the culture medium in a dose-dependent fashion.[40]

Moreover, gut epithelial cell lines selectively upregulate TSLP on stimulation with bacteria in a strain-dependent fashion, and this upregulation synergizes with transforming growth factor-β to promote the differentiation of Treg cells through the induction of IL10 production by DCs.[41] After the first observations for the intestinal epithelial cells' pivotal contribution to the shaping of adaptive immune responses,[19,42,43] TSLP was identified as one of the key mediators produced by primary human intestinal epithelial cells for the conditioning of $CD103^+$ DCs to a tolerogenic phenotype.[44] In the latter study, we showed that supernatant from primary healthy intestinal epithelial cells boosts the capacity of $CD103^+$ DCs to induce Foxp3 expression in naive T cells. This regulatory interaction is not observed when intestinal epithelial cells from Crohn's

disease patients were used for DC conditioning, and this is mainly attributed to the complete absence of TSLP expression in Crohn's disease intestinal epithelial cells, when in contrast, healthy intestinal epithelial cells produce copious amounts of the cytokine. However, we also showed that in the mouse, expression of TSLPR in DCs is dispensable for Treg induction,[45] indicating either that TSLP is not involved in Treg development via DCs in the mouse or that signaling through the receptor is not required.

In the intestine, DC-derived TSLP has also been shown to favor Treg over Th17 responses acting directly on T cells,[46] whereas delivery of TSLP by using recombinant lactic acid bacteria exerts a protective effect in the mouse model of dextran sodium sulfate–induced colitis.[47] By using the same disease model, Reardon et al[48] observed impaired recovery and increased mortality of mice lacking TSLP, whereas ablation of the TSLP-TSLPR interaction in TSLPR knockout mice also leads to increased susceptibility to helminth infection, which in this case is attributed to the uncontrolled Th1/Th17 response due to the complete lack of Th2 responses.[49]

Mosconi et al[50] also showed that constitutive TSLP expression in the gut requires epithelial challenge by intestinal bacteria and has an important role in limiting the expansion of Th17 cells. The authors showed that in mice colonized with the benign altered Schadler flora, the TSLP-TSLPR interaction is key for the expansion of Helios-Foxp3+ Treg cells, and TSLPR−/− mice develop inappropriate Th17 responses in this model.

Emergence of a Paradox

Thus, we have so far seen that although expression of TSLP seems to be constitutive and homeostatic in certain tissues, an aberrant expression can lead to the development of a number of pathologies. Complete absence of the cytokine also seems to be an intriguing characteristic feature of autoimmune diseases such as Crohn's disease, where inflammation is mostly Th1 and Th17 related.[51]

The data available create a paradox in which the action of TSLP might be tissue specific (proinflammatory in skin and lungs but homeostatic in gut and thymus) or context specific; the cytokine could contribute to the maintenance of homeostasis by actively promoting Treg cell development or indirectly by dampening exacerbated Th1 responses by skewing T-cell phenotype to Th2.[49,52] Of note, the capacity of TSLP to inhibit IL12 secretion by human monocyte-derived DCs only occurs within a short "window" of concentrations, and it is absent in the high concentrations used in previous studies,[19,53] indicating the need for strict regulation of the cytokine expression for its homeostatic effects to be properly manifested.

The paradox of a dual role for TSLP is also evident in other pathologies such as cancer malignancies, with a number of studies showing opposite effects of TSLP overexpression on tumor growth and cell proliferation. Two independent studies report that TSLP expression by stromal or cancer cells contributes to tumor growth promoting a Th2-like environment in the tumor.[54,55] A role for TSLP in tumor growth through the regulation of the immune system is also supported by other studies in mouse models where an inhibition of tumor growth in TSLP-deficient hosts is observed.[56,57] However, more recently, different works in both the mouse and human system suggest a tumor-suppressing effect for TSLP for early pancreatic tumor,[58] skin cancer,[59,60] and colon cancer.[61] Di Piazza et al[60] and Demehri et al[58,59] demonstrate that the ablation of the TSLP-TSLPR signaling accelerates tumor growth in different murine models of skin carcinogenesis. TSLP levels are also negatively correlated with the clinical score of colon cancer patients. In this work, Yue et al[61] show that TSLP promotes the apoptosis of human colon cancer cells in a TSLPR-dependent manner.

Human Thymic Stromal Lymphopoietin: Two Isoforms to Explain the Paradox?

Two Isoforms Differentially Regulated

In 2009, Harada et al[62] described the existence of 2 different variants for TSLP in human bronchial epithelial cells. In this study, the authors observed that polyinosinic-polycytidylic acid, a TLR-3 ligand that was previously shown to upregulate TSLP,[63,64] actually only induces the significant upregulation of a long isoform of TSLP. A shorter isoform, composed of the last 63 amino acids of the longer one, is constitutively expressed in normal human lung fibroblasts, and its expression is not changed after challenge with lipopolysaccharide or polyinosinic-polycytidylic acid. It was initially thought that these 2 isoforms were the result of alternative splicing,[62] but, 1 year later, the same group reported the existence of 2 distinct 5′-untranslated regions resulting in 2 different open reading frames for TSLP in the human genome.[65] Of note, none of the studies published earlier had used tools to differentially analyze the expression or function of the 2 isoforms, and hence the observed effects of TSLP could have been attributed to either 1 of the 2 isoforms. Harada et al also examined 2 polymorphisms upstream the long isoform untranslated region that apparently increase transcription factor binding and, consequently, long TSLP expression. These 2 polymorphisms correlate positively with asthma susceptibility, whereas this is not true for the rs2289278 polymorphism, which is found in the second intron of the long form.[65]

After these studies on bronchial epithelial cells and because of the previously shown relevance of TSLP in the context of atopic skin diseases, Xie et al[66] went on to study the expression and differential modulation of the 2 isoforms in human keratinocytes. The strategy they followed was to use primers specific for the long isoform and compare the observed long TSLP expression with the total TSLP expression. The group confirmed that ligands for TLRs 2, 3, 5, and 6 only significantly upregulate long TSLP, an effect reproduced in the presence of an atopic cytokine milieu (IL4, IL5, and TNF-α). On the contrary, vitamin D and its analogues upregulate total but not long TSLP transcription, despite previous references to a vitamin D responsive element in the mouse TSLP gene promoter.[67] Of note, the authors noticed that in steady state, total TSLP transcripts are 2- to 3-log more abundant than long TSLP transcripts,

indicating that the main isoform expressed by human keratinocytes in steady state is the short one, although nothing was so far reported about the potential biologic activity of short TSLP.

Consistently, Cultrone et al[68] showed that challenge of polarized intestinal epithelial cell lines with TLR agonists significantly upregulates long TSLP in an NF-κB–dependent fashion. After in silico analysis, the authors identified several putative binding sites for NF-κB and AP-1 within a 4-kilobase long region of the TSLP promoter (Figure 1). Targeted mutation of the more conserved proximal NF-κB binding site results in an abrogation of the IL1-dependent TSLP upregulation as observed in luciferase reporter assays. At the same time, another study confirmed the long isoform specific upregulation after challenge of primary human lung fibroblasts with TNF-α.[69] In agreement with the data by Cultrone et al, the 80-fold upregulation of the long isoform transcript was c-Jun dependent, whereas expression levels of the short isoform did not vary after TNF-α challenge. Conflicting data between the human and mouse system also emerged regarding the capacity of vitamin D to induce TSLP expression and cause Th2-dependent pathologies. In the article cited previously, Li et al[67] showed that when high concentrations of vitamin D are applied topically on the skin of mice (in which an open reading frame for the short isoform of TSLP is absent), subsequent TSLP upregulation results in the development of an atopic dermatitis–like phenotype.[67] However, these results were not confirmed in the human system in a more recent study that used primary human keratinocytes and skin biopsies.[70] Here the authors observe no TSLP production by healthy keratinocytes or healthy skin biopsies with or without challenge by the relevant vitamin D analogues, despite the efficient upregulation of other well-described vitamin D target genes in these biopsies. Upregulation of TSLP is only observed when vitamin D is used to treat psoriasis patients, but in that case the authors reported an amelioration of the phenotype, which they attributed to the concomitant downregulation of other proinflammatory mediators such as IL12/23p40, IL1α, IL1β, and TNF-α.[52] Whether this was a direct effect of vitamin D or upregulation of a non-specified TSLP isoform was necessary for the dampening of proinflammatory activity was not addressed.

In an effort to elucidate the relevance of TSLP isoforms in steady state and disease, we examined the differential expression and biologic activity of the 2 isoforms in vitro and in vivo.[71] After an in silico analysis of the human TSLP locus, we showed that the 2 isoforms are not the result of alternative splicing of the same transcript but are rather controlled by 2 different promoter regions. We examined the ENCODE track profiles showing active enhancers (H3K4me1 high, H3K4me3 low, and H3K27ac high) or promoters (H3K4me1 low, H3K4me3 high, and H3K27ac high) as well as the ENCODE DNaseI hypersensitive site clusters (indicating promoter accessibility to transcription factors) derived from ChIP-seq experiments of 125 different cell types. This analysis predicted a much higher transcription factor activity for the promoter region of the short isoform, whereas scarce, if any, activity in the long isoform promoter was observed. Consistently, we found that in healthy barrier surfaces such as gut and skin, short TSLP is the main transcript variant detected. We confirmed previous observations that vitamin D only upregulates the short isoform of the protein on primary epithelial cells. In

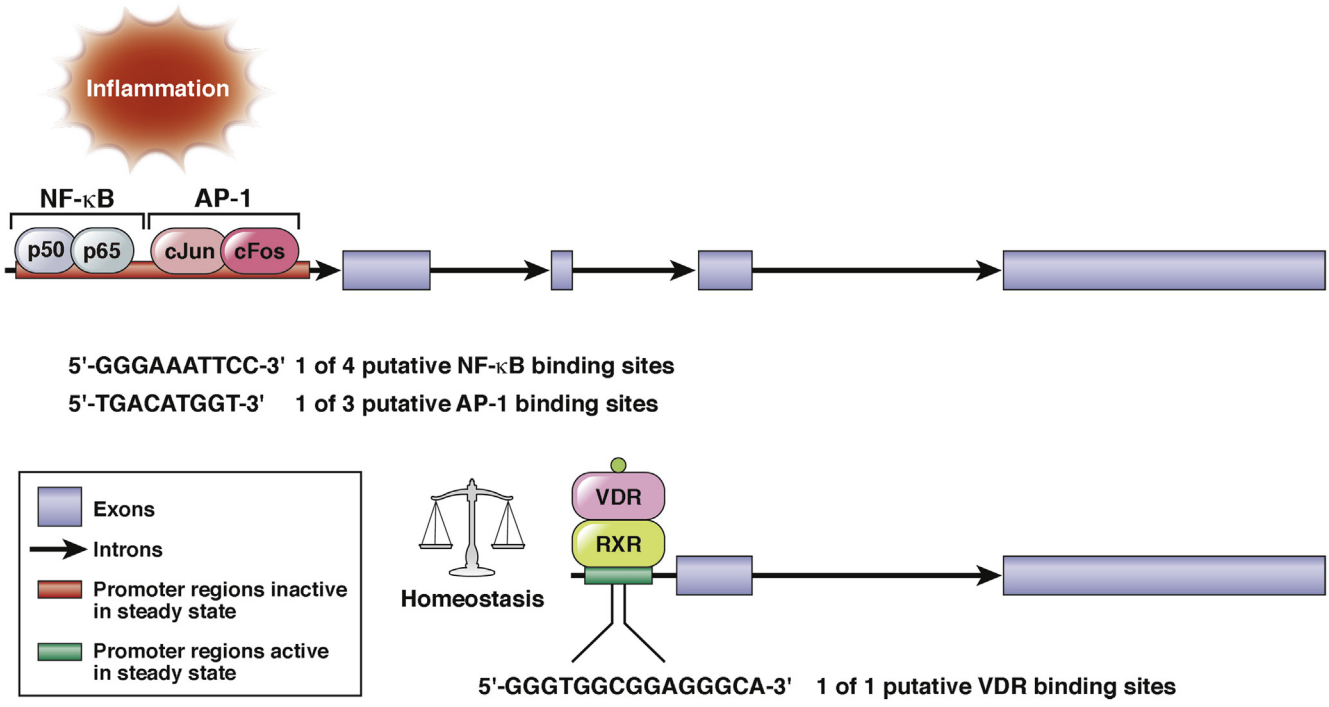

Figure 1. The human TSLP gene locus. Different transcription factors bind to different promoter regions, inducing expression of long or short TSLP, depending on the context, tissue, and stimulus. RXR, retinoic X receptor; VDR, vitamin D receptor.

agreement with these results, in silico analysis has identified 1 putative vitamin D receptor binding site in intron 3 of the TSLP gene just upstream of the short isoform open reading frame (Figure 1). We also reproduced previous observations for bacterial strain-specific effects on TSLP secretion by human intestinal epithelial cells. Highly immunogenic strains such as *Salmonella typhimurium* and adherent-invasive *Escherichia coli* (a gift from Dr Arlette Darfeuille-Michaud) upregulate the long isoform and downregulate the short isoform, whereas the opposite is true after challenge with a commensal *E coli* strain (Figure 2). This could mean that the dysbiosis observed in many barrier surface pathologies could impact the usually balanced, homeostatic expression of TSLP.

Short Thymic Stromal Lymphopoietin Function

Despite clear evidence of a dichotomy for the 2 isoforms of TSLP in humans, the role of the short isoform was poorly understood. Bjerkan et al[72] examined the expression and biologic activity of short TSLP on barrier surfaces such as the oral mucosa and the skin. Because the sequence of the 63 amino acids that make up short TSLP is completely homologous to the C-terminus of the long form, short form–specific antibodies are not available. Hence, we have seen that up to that point the differential expression of the 2 isoforms had only been studied by quantitative polymerase chain reaction analyses, with primer pairs specifically targeting one or the other transcript variant. In this work, the authors reproduced previous findings at the mRNA level, and they also used a clever indirect strategy to confirm the results at the protein level; commercially available polyclonal antibodies against total TSLP were incubated with synthetic short form TSLP coupled to CNBr-activated Sepharose 4B beads to remove antibody reactivity against the short isoform. By using this strategy, they showed that expression of TSLP on healthy barrier surfaces is limited to the short isoform, whereas long TSLP is only upregulated in oral mucosal lesions after challenge with smokeless tobacco. Because recombinant long TSLP had previously been observed to exert antimicrobial activities[73] and this effect had been pinpointed to the last 34 amino acids of the cytokine, the authors assessed the antimicrobial activity of synthetic short TSLP and found that the growth of all bacterial strains tested was potently inhibited.[72]

Subsequently, our own studies deepened knowledge on the functional properties of the 2 isoforms, revealed immunomodulatory activity for short TSLP, and partly explained the apparently contradictory results that had been obtained in different model systems and disease conditions in the previous years.[71] We first addressed the biologic activity of the short isoform in vitro by conditioning with short TSLP monocyte-derived DCs, which do not express TSLPR if not activated. We found that in presence of short TSLP, DCs

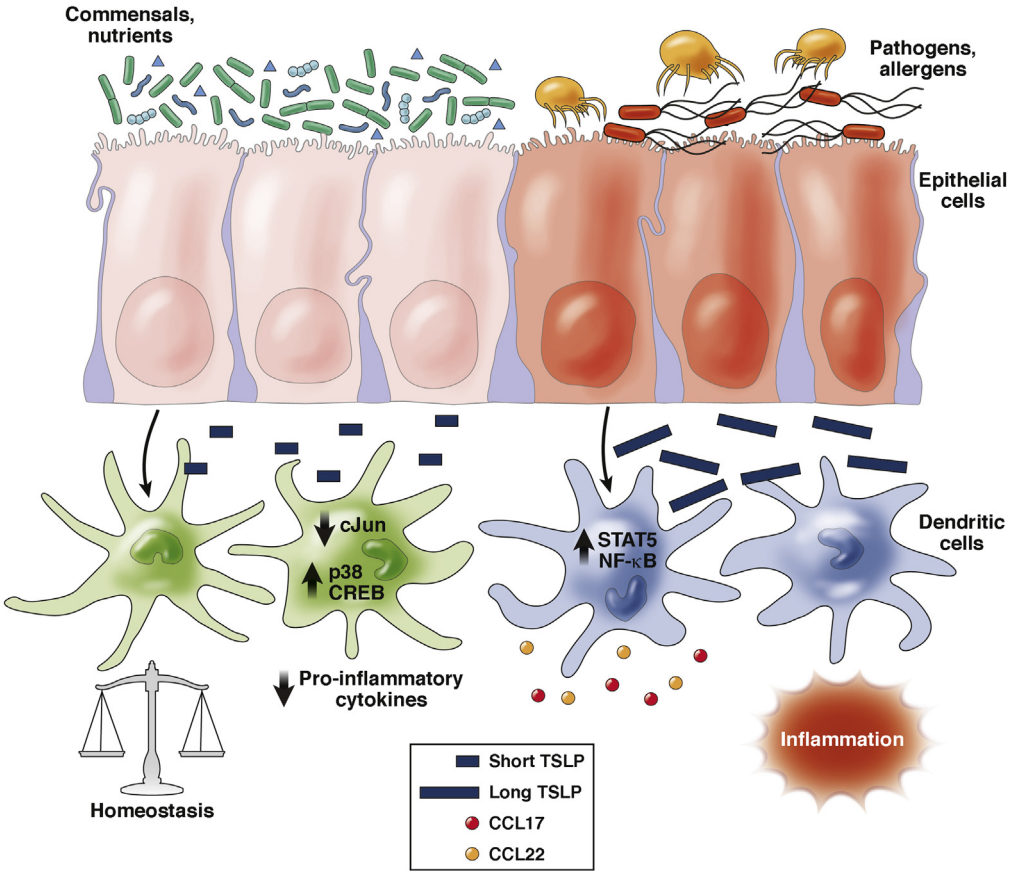

Figure 2. Induction of TSLP expression by endothelial cells and DC conditioning. In microbe-inhabited barrier surfaces, commensal bacteria such as *E coli* and nutrients such as vitamin D enhance short TSLP expression. Pathogens such as *S typhimurium* and allergens such as house dust mite upregulate the long isoform.

respond more mildly to bacterial infection. Moreover, IFN-γ production in allogenic bidirectional mixed lymphocyte reactions from healthy donors is dampened after short TSLP conditioning and increased in the presence of the long isoform. We also showed that the anti-inflammatory effect of short TSLP on human monocyte-derived DCs is mediated via an as yet undescribed molecular mechanism involving p38 phosphorylation rather than STAT5 phosphorylation through which the long isoform signals.[71]

Thymic Stromal Lymphopoietin Isoform Expression in Pathologies

The expression of both TSLP isoforms in pathologies with a well-documented long TSLP contribution changes dramatically compared with the steady state. Interestingly, the pattern of expression is pathology-dependent (Table 1). By using long form–specific antibodies produced in our laboratory, we confirmed the specific upregulation of long but not short TSLP in biopsies from atopic dermatitis and ulcerative colitis patients.[71] Interestingly, we also observed a significant downregulation of the short TSLP transcript in untreated celiac disease patients, which is in line with our group's previous observations for reduced total TSLP expression in another intestinal pathology, Crohn's disease.[44] The scarce expression of short TSLP and its potential relevance in refractory celiac disease are confirmed by Biancheri et al,[74] who argue that restoring said expression could be a valid therapeutic strategy.

Volpe et al[36] also detected a potential implication for TSLP in the IL23/IL17 proinflammatory axis, because they found the cytokine is significantly upregulated in psoriatic lesions but not normal skin from patients. They showed that in vitro, TSLP is capable of inducing the production of copious amounts of IL23 by primary human blood DCs in synergy with CD40L and TNF-α. Although in this study the authors did not distinguish between the 2 isoforms, data produced in our laboratory indicate long but not short TSLP upregulation with high statistical significance for this pathology (Table 1 and unpublished data).

It is now recognized that in pathologic conditions, TSLP expression can also be controlled by endogenous proteases important to regulate its activity. Bianchieri et al demonstrated that the protease furin, which was upregulated in biopsies from untreated celiac disease patients, could degrade the long isoform producing fragments of 10 and 4 kDa that show different activity on human peripheral blood mononuclear cells compared with the mature TSLP.[35] Similarly, another group demonstrate, in 2 distinct publications, that TSLP is truncated in 2 fragments (aa29-124 and aa131-159) by furin-like and carboxypeptidase N proteases in inflamed tissue. These fragments showed enhanced pro-Th2 activity on mast cells and ILC2 compared with the full mature long TSLP.[35,75]

We have seen how in recent years, the dual role of TSLP and the dichotomy of the 2 isoforms' expression in homeostasis and disease have been dissected by us and others. Despite the existence of a plethora of mouse models to study inflammatory bowel disease,[76] as well as other diseases, in which TSLP has a proven contribution and because the short isoform is absent in the mouse, these models are not indicated for the elucidation of the 2 isoforms' potential role in these pathologies. Thus, it would be of great interest to examine the differential expression of the 2 isoforms in tissues from patients with diseases such as airway inflammation due to allergy, asthma, or chronic obstructive pulmonary disease, eosinophilic esophagitis, allergic rhinitis, chronic rhinosinusitis, etc.

Because of the physiological relevance of long TSLP expression in all these diseases, the cytokine has been repeatedly suggested as a valid target for immunotherapy with antibodies that would target TSLP and/or prevent its binding to TSLPR. However, because it is now conclusively shown that the short isoform of TSLP has important homeostatic functions, this should be taken into account when designing adequate therapeutic strategies. Monoclonal antibodies used to neutralize long TSLP should ideally not interact or hamper in any way the homeostatic effects of short TSLP, whereas exogenous administration of short TSLP could mediate important regulatory effects and dampen proinflammatory activity, leading to the amelioration of pathologies such as celiac disease, Crohn's disease, and psoriasis.

Table 1. Differential Expression of TSLP Isoforms in Barrier Surface Diseases

Pathology	Short TSLP	Long TSLP
Asthma	-	↑↑
Crohn's disease	↓↓	-
Ulcerative colitis	-	↑
Celiac disease	↓↓	↓↓
Atopic dermatitis	↓↓	↑
Psoriasis	-	↑↑

-, unchanged; ↑↑, upregulated; ↓↓, downregulated.

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Conflicts of interest
The authors disclose no conflicts.