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The biology of thymic stromal lymphopoietin (TSLP)

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Abstract

Originally shown to promote the growth and activation of B cells, thymic stromal lymphopoietin (TSLP) is now known to have wide-ranging impacts on both hematopoietic and non-hematopoietic cell lineages, including dendritic cells (DCs), basophils, eosinophils, mast cells, $CD4^+$, $CD8^+$ and natural killer (NK) T cells, B cells and epithelial cells. While TSLP's role in the promotion of TH2 responses has been extensively studied in the context of lung- and skin-specific allergic disorders, it is becoming increasingly clear that TSLP may impact multiple disease states within multiple organ systems, including the blockade of TH1/TH17 responses and the promotion of cancer and autoimmunity. This review will highlight recent advances in the understanding of TSLP signal transduction, as well as the role of TSLP in allergy, autoimmunity and cancer. Importantly, these insights into TSLP's multifaceted roles could potentially allow for novel therapeutic manipulations of these disorders.

Keywords

allergy; atopy; cancer; cytokines; TSLP

I. Introduction

Thymic stromal lymphopoietin (TSLP) is a member of the IL-2 cytokine family, and a distant paralog of IL-7 (Leonard, 2002). Murine TSLP was discovered in thymic stromal cell line supernatants that supported B cell development (Friend et al., 1994). Like IL-7, TSLP can stimulate thymocytes and promote B cell lymphopoiesis. Accordingly, TSLP was initially studied as a B cell growth factor (Levin et al., 1999). A human homolog was subsequently identified, and further characterization of the cytokine revealed a four-helix bundle structure containing six conserved cysteine residues and multiple potential sites for N-linked carbohydrate addition. As discussed later, in spite of only 43% amino acid identity, human and murine TSLP share a significant degree of functional homology (Reche et al.,

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2001; Sims et al., 2000). During allergic inflammation, the primary producers of TSLP are epithelial cells, keratinocytes and stromal cells, although recent data have demonstrated that both dendritic cells (DCs) and mast cells are capable of TSLP production (Soumelis et al., 2002; Watanabe et al., 2004; Ying et al., 2005; Kashyap, Rochman, Spolski, Samsel, & Leonard, 2011; Moon, Choi, & Kim, 2011). Several groups identified a receptor capable of binding TSLP with low affinity (TSLPR subunit), which shares 24% identity to the common γ receptor chain (γ_c) (Pandey et al., 2000; Park et al., 2000). Upon further analyses, the functional receptor (TSLPR) was shown to include both the TSLPR subunit and the IL-7Rα chain in humans and mice (Quentmeier et al., 2001; Park et al., 2000). The functional TSLPR is expressed by a variety of hematopoietic cell populations, such as T cells, B cells, NK cells, monocytes, basophils, eosinophils and DCs, as well as some non-hematopoietic cell lineages such as epithelial cells (Ziegler, 2010; Reardon et al., 2011). While classified as a hematopoietin receptor based on structural homology, the TSLPR subunit contains notable differences from canonical hematopoietin receptors. The TSLPR subunit contains the conserved box1 sequence, which regulates Janus protein tyrosine kinase (JAK) binding in other cytokine receptors, but lacks the conserved box2, and contains only one tyrosine (Y) residue four amino acids from its carboxy terminus (Park et al., 2000). Additionally, it contains a modified WSXWS motif and multiple potential *N*-linked glycosylation sites (Tonozuka et al., 2001).

II. TSLP signaling

As a member of the hematopoietin receptor family, it was originally hypothesized that the TSLPR would utilize JAKs to activate STAT proteins downstream of the TSLPR. Indeed, TSLP stimulation of multiple cell lines leads to STAT5 phosphorylation. However, initial experiments in these cell lines showed that TSLPR signaling occurred in the absence of JAK activation, and dominant-negative forms of JAK-1 and -2 did not affect TSLP-mediated STAT5 activation (Isaksen et al., 1999; Levin et al., 1999). Several alternatives were implicated in TSLPR signaling, such as Src kinases and phosphinositol 3 kinase (Isaksen et al., 2002). However, two recent papers have demonstrated robust and sustained activation of JAK-1 and -2 following TSLP signaling in primary human dendritic cells and primary human and mouse $CD4^+$ T cells (Arima et al., 2010; Rochman et al., 2010). Surprisingly, unlike IL-7Rα and γ_c in IL-7 signaling, which utilize JAK-1 and -3, the TSLPR subunit bound and utilized JAK-2 in concert with IL-7Rα-associated JAK-1. These latest findings resolve a long-standing question about the mode of TSLP signaling, and show that TSLP-induced JAK activation precedes the activation of STAT proteins. In human peripheral blood-derived CD11c+ DCs TSLP stimulation activated STAT 1,3,4,5, and 6, as well as JAKs 1 and 2(Arima et al., 2010). Similar results have been seen using mouse DCs, with the exception that no phosphorylation of Stat6 was seen (B.D. Bell, M. Kitajima and S.F. Ziegler, manuscript submitted). These data suggest that TSLP is capable of activating multiple STAT proteins. Whether TSLP utilizes similar signaling pathways in other cell lineages and how each STAT molecule contributes has yet to be elucidated.

III. TSLP-Responsive Cells

A plethora of cell types have been shown to be capable of responding to TSLP in vivo and in vitro. These include DCs, CD4 and CD8 T cells, B cells, mast cells, basophils, eosinophils, and NKT cells. This long list of responding cell types suggests the important role of this cytokine in orchestrating the initial response to an epithelial insult. While the normal function of TSLP is likely the maintenance of Th2-type homeostasis at barrier surfaces(Ziegler & Artis, 2010), as will be discussed below, dysregulated TSLP expression can result in the development of type 2 inflammatory responses leading to allergic disease.

A. Dendritic Cells

It has now become apparent that a major TSLP-responsive cellular subset in both humans and mice are myeloid-derived dendritic cells (mDCs)(Reche et al., 2001; Zhou et al., 2005). Co-culture of TSLP-activated DCs with naïve syngeneic CD4+ T cells led to T cell proliferation but no differentiation, suggesting a role for TSLP in CD4+ T cell homeostasis(Watanabe et al., 2004). However, when TSLP-stimulated DCs primed CD4+ T cells in an antigen-specific manner (e.g., in an allogeneic culture), the resulting T cells display characteristic features of Th2 differentiated cells (production of IL-4, IL-5, IL-13, and TNFα), with the exception that IL-10 production was not evident(Soumelis et al., 2002). These data suggest that TSLP-activated DCs primed for inflammatory Th2 cell differentiation. Interestingly, TSLP, in the absence of IL-12, induced OX40L expression on DCs, and OX40-OX40L interactions were critical for the ability of the DCs to drive Th2 cell differentiation(Ito et al., 2005). Consistent with a role in regulating Th2 cytokine responses, TSLP-activated DCs were also capable of supporting the maintenance and further polarization of CRTH2+ Th2 effector memory cells(Wang et al., 2006). In contrast, autologous TSLP-activated DCs supported the expansion and functions of $CRTH2^+$ $CD4^+$ TH2 memory cells (Wang et al., 2006), but led to T cell proliferation and elaboration of high levels of IL-2, but not IL-4, IL-5 or IL-13, when co-cultured with naïve T cells (Watanabe et al., 2004).

TSLP-conditioned DCs also augmented intestinal epithelial cell-mediated IgA2 class switching through the induction of APRIL (He et al., 2007). Finally, some in vitro studies have suggested a role for TSLP in the generation of tolerogenic DCs that can drive the differentiation of regulatory T cells (Tregs) (Watanabe et al., 2005; Besin et al., 2008; Iliev et al., 2009), although other studies have indicated that TSLP may hinder the production and/or maintenance of FOXP3+ Tregs in vivo in certain disease processes (Lei, Zhang, Yao, Kaplan, & Zhou, 2011; Duan et al., 2010).

B. T lymphocytes

Early work from the Leonard lab showed that TSLPR-deficient mice had normal lymphocyte numbers, but that γ_c/TSLPR double deficient mice had a more pronounced defect that γ_c-deficient mice along(Al Shami et al., 2004). The also showed that TSLP could drive the expansion of T and B cells when injected into γ_c-deficient mice, showing that TSLP can effect lymphoid homeostasis. Subsequent studies showed that TSLP can also act directly on CD4+T cells, and in the presence of TCR stimulation, promoted proliferation and

TH2 differentiation of naïve $CD4^+$ T cells through induction of IL-4 gene transcription (Omori & Ziegler, 2007; Rochman, Watanabe, Arima, Liu, & Leonard, 2007). IL-4 further upregulated TSLPR on $CD4^+$ T cells, resulting in a positive feedback loop. Although IL-4 maintained TSLPR expression on both *in vitro* differentiated TH2 and TH17 cells, higher TSLPR levels were present on TH2 than on TH1 and TH17 cells, which correlated with the ability of TSLP to drive the proliferation and survival of activated TH2 cells (Kitajima, Lee, Nakayama, & Ziegler, 2011). Naïve mouse $CD8^+$ T cells also express TSLPR, though TSLPR expression is low to absent on naïve human $CD8^+$ T cells; however, following activation, TSLPR expression is upregulated on both mouse and human $CD8^+$ T cells (Rochman & Leonard, 2008; Akamatsu et al., 2008). In both $CD4^+$ and $CD8^+$ T cells, TSLP stimulation upregulated the survival protein Bcl-2 in a STAT5-dependent manner (Rochman & Leonard, 2008; Rochman et al., 2010; Kitajima et al., 2011).

C. B lymphocytes

The initial studies describing TSLP demonstrated that TSLP can support B cell lymphopoiesis (Friend et al., 1994; Levin et al., 1999). In *in vitro* studies, pro-B cells derived from fetal liver, but not bone marrow, responded to TSLP, although pre-B cells from both origins could proliferate in response to TSLP (Vosshenrich, Cumano, Muller, Di Santo, & Vieira, 2003). The role of TSLP in normal B cell development or during inflammatory responses remains undefined. However, it is clear that aberrant TSLP signaling can have a significant impact on B cells, as has been demonstrated by the association of TSLPR mutations with a subtype of B cell leukemia(Chapiro et al., 2010; Roll & Reuther, 2010; Tasian & Loh, 2011). In addition, elevated systemic TSLP has been shown to lead to aberrant B cell development and function, with both direct effects on early B cell development and indirect effects leading to autoimmune hemolytic anemia(Astrakhan et al., 2007; Iseki et al., 2012).

D. Innate immune cells

Multiple innate immune cells express the TSLPR and respond to TSLP. For example, TSLP can enhance cytokine production from mast cells, NKT cells and eosinophils (Nagata, Kamijuku, Taniguchi, Ziegler, & Seino, 2007; Allakhverdi et al., 2007; Wong, Hu, Cheung, & Lam, 2009). In addition, TSLP has very recently been shown to induce eosinophil extracellular traps (EETs), extrusions of mitochondrial DNA toxic granule molecules released in response to infection(Morshed, Yousefi, Stöckle, Simon, & Simon, 2012). Finally, TSLP has also been shown to be important for the development and function of a subset of basophils(Siracusa et al., 2011). This subset is IL-3-independent, and is recruited to site of type-2 inflammation where is it speculated that they play a role in promoting Th2-type responses(Siracusa et al., 2011; Sokol et al., 2009; Siracusa, Wojno, & Artis, 2012). Thus TSLP not only can directly promote type 2 responses through CD4 T cell differentiation, it can also influence responses through the recruitment and activation of innate immune cells capable of producing cytokines involved in type 2 inflammation.

IV. TSLP-associated diseases

The variety of TSLP-responsive cell types demonstrates that TSLP can impact type 2 inflammation through a myriad of different pathways. In addition, numerous studies in both humans and mice now implicate TSLP in a growing number of different disorders beyond allergic inflammation, including infection, cancer and autoimmunity. The following sections describe the disorders associated with TSLP and what is known about the mechanisms through which TSLP may act.

A. Skin disorders

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects an estimated 10 to 20 percent of infants and young children in the United States (Leung, Boguniewicz, Howell, Nomura, & Hamid, 2004; Boguniewicz & Leung, 2011). Interestingly, there is suggestive evidence of linkage between single nucleotide polymorphisms (SNPs) in the TSLP gene and AD(Gao et al., 2010). In addition, while TSLP protein was undetectable in non-lesional skin in AD patients, TSLP was highly expressed in acute and chronic AD lesions (Soumelis et al., 2002). TSLP was also over-expressed in the skin of individuals with Netherton syndrome (NS), a severe skin disease characterized by atopic dermatitis-like lesions as well as other allergic manifestations that result from mutations in the serine peptidase inhibitor Kazal-type 5 (SPINK5) gene, which encodes the serine protease inhibitor lymphoepithelial Kazal-type–related inhibitor (LEKTI) (Briot et al., 2009).

In mice, over-expression of TSLP specifically in the skin was sufficient to induce a disease phenotype characterized by all of the hallmark features of AD (Yoo et al., 2005). In the steady-state, TSLP expression in the skin appears to be negatively regulated by retinoid X receptors (RXR), since keratinocyte-specific ablation of the retinoid X receptor isotypes RXRα and RXRβ resulted in upregulation of TSLP and development of AD-like skin inflammation (Li et al., 2005). RXRs heterodimerize with many nuclear receptor partners, including the vitamin D receptor and peroxisome proliferator-activated receptors. Administration of vitamin D or its analogs upregulated TSLP and resulted in the development of dermatitis (Li et al., 2006; Li et al., 2009), suggesting that vitamin D administration may result in RXR derepression and recruitment of co-activators to promote transcription. Keratinocyte-specific deletion of Notch signaling, which causes severe epidermal differentiation defects, also resulted in high systemic levels of TSLP. However, TSLP expression in this model may be due to responses to the resulting skin barrier defect rather than directly from the loss of keratinocyte-specific Notch signaling itself, since wild-type and mutant keratinocytes produced similar amounts of TSLP in *in vitro* cultures (Demehri et al., 2008). In SPINK5 knockout (SPINK5 −/−) mice, which reproduce many of the key features of NS, the absence of LEKTI resulted in unrestrained activity of the serine protease kallikrein 5, which directly activated proteinase-activated receptor 2 (PAR-2) and induced nuclear factor κB (NF-κB)–mediated overexpression of TSLP without contribution of the adaptive immune system (Briot et al., 2009; Kouzaki, O'Grady, Lawrence, & Kita, 2009). Interestingly, in SPINK5/PAR-2 double knockout mice, TSLP expression was greatly diminished, although inflammation still occurred (Briot et al., 2010). Whether the cytokine milieu differs in the absence of TSLP remains to be determined.

TSLP may influence both the initiation and progression of allergic skin inflammation, but the relative contribution to these stages and the cellular requirements may differ depending on the context. Langerhans cell (LC) migration and activation was seen in human AD lesions *in situ* (Soumelis et al., 2002). Furthermore, TSLP has been shown to increase the number and maturation status of migratory LCs in human skin explants cultures and to condition LCs to prime co-cultured naïve $CD4^+$ T cells to adopt an inflammatory TH2 phenotype (Ebner et al., 2007). However, mouse models of AD implicate additional cell types in the initiation and promotion of AD by TSLP. A recent study by Oh *et al*. implicated TSLP in mediating skin fibrosis downstream of IL-13, in part through the stimulation of fibrocyte collagen production (Oh et al., 2011). In a model of allergic skin inflammation using epicutaneous (EC) sensitization to ovalbumin (OVA) on tape-stripped skin, TSLP acted directly on T cells during the challenge phase to potentiate TH2 cytokine production (He et al., 2008). T cells and eosinophils were also required for TSLP-mediated dermal inflammation induced through intradermal delivery of recombinant TSLP protein (Jessup et al., 2008). In contrast, TSLP was involved in both sensitization and challenge phases of FITC-mediated contact hypersensitivity, since ear swelling was minimal if blockade of TSLP occurred prior to sensitization, but was only modestly reduced when TSLP blockade occurred after sensitization but prior to challenge (Larson et al., 2010; Boehme et al., 2009). While DC migration was intact in the absence of TSLP in EC sensitization, loss of TSLP signaling in the FITC CHS model was associated with reduced migration and activation of skin-derived antigen-bearing DCs. In addition, TSLP-responsive $CD4^+$ T cells were not required to induce a TH2 response in the CHS model (R.P. Larson and S.F. Ziegler, unpublished observations). In the setting of chronic high TSLP expression, skin inflammation also occurred in the absence of T cells (Yoo et al., 2005), possibly due to the ongoing stimulation of innate immune cells by TSLP.

TSLP has also been implicated in the phenomenon referred to as the atopic march, which describes the increased likelihood of individuals with AD of developing allergic rhinitis (AR) and asthma later in life (Bieber, 2008). Several models of induced TSLP expression in mouse keratinocytes result in subsequent allergic airway inflammation following intranasal challenge, suggesting that TSLP may be an important factor contributing to this progression from AD to AR and asthma (Zhang et al., 2009; Demehri, Morimoto, Holtzman, & Kopan, 2009; Leyva-Castillo, Hener, Jiang, & Li, 2012; Jiang et al., 2012). While many of these methods used to induce TSLP expression result in artificially high systemic levels of TSLP that are not seen in AD patients, we have found that intradermal administration of TSLP triggers progression from atopic dermatitis to asthma in the absence of systemic TSLP(Han et al., 2012). In this study, TSLP was the airway response to antigen challenge was shown to be TSLP-independent. These models, as well as approaches that allow for more specific expression or deletion of TSLP, will be helpful in identifying the cellular targets of TSLP and the mechanisms involved in the progression from AD to AR and asthma.

B. Respiratory Diseases

The initial report demonstrating high TSLP expression in AD and potentiation of inflammatory TH2 responses by TSLP also suggested a potential role for TSLP in allergic airway disease(Soumelis et al., 2002). This hypothesis was supported by the demonstration

that TSLP mRNA was present in human lung fibroblasts and bronchial epithelial and smooth muscle cells (Soumelis et al., 2002), and that aberrant levels of TSLP were associated with certain human respiratory disorders (Ying et al., 2005; Zhang et al., 2007; Ying et al., 2008; Kamekura et al., 2009; Semlali, Jacques, Koussih, Gounni, & Chakir, 2010; Kimura et al., 2011; Shikotra et al., 2011; Xu et al., 2010). Lung epithelium and submucosa samples from asthmatics and chronic obstructive pulmonary disease (COPD) patients contained a greater number of TSLP mRNA positive cells, and bronchoalveolar lavage (BAL) samples from these patients had higher concentration of TSLP protein compared to healthy controls (Ying et al., 2005; Ying et al., 2008; Semlali et al., 2010; Shikotra et al., 2011). Although the level of TSLP expression can be variable in asthmatic patients, it has been shown to correlate directly with TH2 cytokine and chemokine expression and inversely with lung function (Shikotra et al., 2011; Ying et al., 2008). Increased expression of TSLP in the nasal epithelium has also been found in biopsies from allergic rhinitis patients and was associated with TH2 cytokine production and eosinophilic infiltration in epithelial-associated tissue (Mou et al., 2009; Kamekura et al., 2009; Kimura et al., 2011; Xu et al., 2010). Genetic studies also support a critical role for TSLP in allergic airway disease. Several SNPs at the TSLP genomic locus found across multiple ethnic backgrounds were associated with increased asthma susceptibility or protection (Harada et al., 2009; Hunninghake et al., 2010; Bunyavanich et al., 2011; Harada et al., 2010; Torgerson et al., 2011; Shamim et al., 2007). One such SNP present in the genomic TSLP locus creates a novel AP-1 transcription factor binding site that could potentially lead to increased TSLP transcription (Harada et al., 2009).

A role for TSLP in human asthma has been well supported by a variety of mouse models, such as the surfactant protein c (SPC)-TSLP mouse, in which TSLP is constitutively expressed by the lung epithelium under control of the SPC promoter (Zhou et al., 2005). With increasing age, these mice developed a progressive asthma-like disease characterized by lung infiltration of eosinophils and TH2 $CD4^+$ T cells, airway remodeling and airway hyperreactivity. Disease in these mice was largely dependent on IL-4, IL-13, $CD4^+$ T cells and antigen (Headley et al., 2009; Zhou et al., 2008). $CD4^+$ T cells and antigen were also required in an acute asthma model using intranasal administration of TSLP in conjunction with antigen (Seshasayee et al., 2007; Headley et al., 2009). In addition to driving allergic inflammation in the lung following direct TSLP administration, TSLP played a crucial role in the well-established ovalbumin (OVA)/alum allergic airway inflammation model. In this model, TSLP protein was found in the BAL and lung after intranasal OVA challenge, and disease symptoms were curtailed in the absence of TSLPR or when TSLP activity was blocked by antibody or recombinant TSLPR protein (Zhou et al., 2005; Al Shami, Spolski, Kelly, Keane-Myers, & Leonard, 2005; Shi et al., 2008; Li et al., 2010; Zhang, Huang, Hu, Song, & Shi, 2011). In an OVA-driven mouse model of allergic rhinitis, blocking TSLP also inhibited disease development (Miyata et al., 2008).

Most data currently point to a primary role for TSLP in the sensitization/priming stage of allergic airway disease. TSLP produced by activated human-derived lung cells stimulated human DCs to prime $CD4^+$ TH2 cell development and mast cell production of TH2-associated cytokines (Soumelis et al., 2002; Allakhverdi et al., 2007; Bleck, Tse, Gordon, Ahsan, & Reibman, 2010). Furthermore, multiple studies have shown that TSLP-mediated

DC activation was responsible for the disease phenotype observed in mouse models of asthma (Zhou et al., 2005; Seshasayee et al., 2007; Shi et al., 2008; Li et al., 2010; Zhang et al., 2011). TSLP-induced DC expression of costimulatory molecules, in particular OX40L, and DC production of TH2 chemokines, such as CCL17 and CCL21, are likely the predominant mechanisms of action (Zhou et al., 2005; Seshasayee et al., 2007). However, TSLP may also influence the challenge stage of allergic airway disease by supporting TH2 $CD4^+$ T cell cytokine production (Shi et al., 2008; Miyata et al., 2008; Li et al., 2010; Zhang et al., 2011; Al Shami et al., 2005; He et al., 2008). As mentioned above, TSLP may also influence the regulatory T cell compartment. Several reports have shown the ability of TSLP to promote the development of thymic regulatory T cells (Tregs) *in vitro* (Mazzucchelli et al., 2008; Hanabuchi et al., 2010); however, *in vivo*, its role is less clear. In allergic airway disease, TSLP inhibited IL-10 mediated Treg function and the formation of inducible Tregs to exogenous antigen (Nguyen, Vanichsarn, & Nadeau, 2010). Importantly, the BAL fluid from asthmatics inhibited pulmonary Treg function in a TSLP-dependent manner (Nguyen et al., 2010). In the OVA allergen model, TSLP was shown to interfere with tolerance by inhibiting the generation of allergen-specific Tregs(Lei et al., 2011). In the same model, nucleotide-binding oligomerization domain-containing protein 2 (Nod2), and to a lesser extent Nod1 stimulation blocked tolerance to OVA intranasal challenge in a TSLP- and OX40L-dependent manner (Duan et al., 2010). In this model, loss of TSLP signaling correlated with increased antigen-specific $FOXP3^+$ T cells following Nod2 stimulation.

A variety of stimuli, such as IL-4, IL-13, TNF-α, IL-1, bacterial peptidoglycan, lipoteichoic acid, double-stranded RNA (dsRNA), respiratory viruses, air pollutants and allergens have been shown to induce TSLP expression by lung-derived parenchymal cells and immune cells (Soumelis et al., 2002; Allakhverdi et al., 2007; Lee & Ziegler, 2007; Zhang et al., 2007; Bleck et al., 2010; Kouzaki et al., 2009; Smelter et al., 2010; Kashyap et al., 2011; Kato & Schleimer, 2007). In particular, stimulation of Nod1 and Nod2 in non-hematopoietic cells were potent inducers of TH2 immunity via TSLP (Magalhaes et al., 2011). These stimuli likely all drive NF-κB-dependent expression of TSLP, as was shown to occur in human lung epithelial cells (Lee & Ziegler, 2007). Furthermore, TSLP transcription was negatively regulated by 9-cis-retinoic acid via retinoid X receptors in lung cells (Lee, Headley, Iseki, Ikuta, & Ziegler, 2008). Exposure to certain infectious agents or repeated environmental irritants may prime production of TSLP, leading to TH2-mediated human disease. For example, even in the absence of known lung disease, lung samples from smokers contained increased TSLP levels as compared to nonsmokers (Ying et al., 2008). In addition, lung epithelial cells from asthmatics produced more TSLP in response to dsRNA (viral analog) stimulation in culture (Uller et al., 2010; Brandelius et al., 2011), which may explain, at least in part, why patients with asthma tend to suffer more airway dysfunction after respiratory infections compared to healthy individuals (Jackson & Johnston, 2010). This aberrant TSLP production in response to lung insults may thus influence both the susceptibility of certain individuals to develop allergic respiratory diseases such as asthma, as well as the clinical complications that arise after environmental insults to the lungs of these individuals.

Collectively, these data illustrate that aberrant lung expression of TSLP is associated with human allergic airway disease and can mimic asthma-like disease in mice. According to genetic studies and *in vitro* analyses, lung samples from individuals with asthma or COPD produce more TSLP in response to lung insult as compared to samples from healthy individuals. Clinical trials targeting TSLP in these conditions are currently underway. According to mouse asthma models, TSLP appears to influence the sensitization stage of allergic airway responses, but a more in depth examination of TSLP's influence on the allergic effector response is required. Where and when TSLP acts during allergic airway disease will likely explain any trial results and dictate future therapeutic design.

C. Intestinal Inflammation

TSLP is constitutively expressed in both the mouse and human gastrointestinal tract, but can be further induced by a variety of cytokines, microbes and microbial products (Rimoldi et al., 2005; Zaph et al., 2007; Taylor et al., 2009; He et al., 2007; Tanaka et al., 2010; Zeuthen, Fink, & Frokiaer, 2008; Humphreys, Xu, Hepworth, Liew, & Grencis, 2008). Mice carrying gene deletions specifically affecting the gut mucosa provide additional clues into the regulation of TSLP expression within the gut. TSLP mRNA levels were significantly decreased in mice with intestinal epithelial-specific deletion of Dicer (Biton et al., 2011), an enzyme involved in microRNA biosynthesis, or IκB kinase-β (Zaph et al., 2007). Both of these knockout mice showed increased susceptibility to infection with the mouse whipworm *Trichuris muris*. TSLP expression was also decreased in mice carrying a missense mutation in the *Muc2* mucin gene that resulted in an epithelial defect and spontaneous colitis (Eri et al., 2011). In *in vitro* analyses of TSLP intestinal function, human colonic or gastric epithelial-derived TSLP has been implicated in conditioning DCs to drive development of inflammatory TH2 cells (Kido et al., 2010), regulatory T cells (Iliev, Mileti, Matteoli, Chieppa, & Rescigno, 2009) or T cell-independent IgA(2) class switching (He et al., 2007). While supernatants from both human and mouse intestinal epithelial cells (IECs) can condition DCs to drive Treg differentiation, the requirements for TSLP may differ in humans and mice, since the presence of TSLP was required in mouse but not human IEC supernatants to drive a tolerigenic DC phenotype (Iliev et al., 2009; Iliev et al., 2009). Additional studies are just beginning to define whether and under what conditions TSLP may function in these pathways *in vivo*.

As is seen in atopic diseases of the skin and lung, aberrant expression of TSLP was also seen in allergic diseases of the gut. Polymorphisms in TSLP and the TSLPR were associated with the food allergy-related disorder eosinophilic esophagitis (EoE), and this association persisted when comparing EoE patients with allergic individuals without EoE (Rothenberg et al., 2010; Sherrill et al., 2010). Additionally, TSLP mRNA expression was higher in the esophagus of pediatric patients with EoE compared to controls, and was decreased in homozygotes of the protective GG minor allele for the rs3806932 SNP. Some studies suggest, however, that TSLP not only plays an important role in the promotion of TH2 responses, but is also a key player in maintaining intestinal homeostasis and modulation of TH1/TH17 inflammation. In contrast to the increased TSLP expression seen in EoE, decreased TSLP expression was seen in non-inflamed colonic tissue in Crohn's disease (CD) and ulcerative colitis (UC), the two types of inflammatory bowel disease (IBD) (Noble et al.,

2010; Noble et al., 2008; Rimoldi et al., 2005; Iliev et al., 2009). However, studies of UC have indicated that in inflamed tissue, TSLP expression is upregulated compared with non-inflamed tissue from either UC patients or controls (Noble et al., 2008; Tanaka et al., 2010).

Mouse models of TH2- and TH1-type inflammation also suggest important roles for TSLP in TH2-mediated immunity, maintenance of homeostasis and modulation of TH1/TH17 responses within the gut. TSLP was required to induce diarrheal disease in a mouse model of food allergy (Blazquez, Mayer, & Berin, 2010) and protective TH2 responses to infection with *Trichuris muris* (Zaph et al., 2007). However, TSLP was not required for oral tolerance to OVA, or for anaphylaxis and IL-4, IL-13 and IgE production following intragastric OVA/cholera toxin sensitization and challenge (Blazquez et al., 2010). Additionally, other helminths such as *Heligmosomoides polygyrus*, *Nippostrongylus brasiliensis* and *Schistosoma mansoni* still induced TH2 responses in TSLPR knockout mice, although in some cases, these responses were modified or slightly attenuated (Massacand et al., 2009; Ramalingam et al., 2009). Thus, while TSLP may promote TH2 responses in the gut, it is not absolutely required for TH2-type inflammation. In contrast to *T. muris*, both *H. polygyrus* and *N. brasiliensis* produce excretory/secretory (ES) products that acted on DCs to attenuate IL-12/23p40 production. Of note, protective TH2 responses can be induced in *T. muris* infections in the absence of TSLP following the blockade of either IFN-γ or IL-12/23p40 (Taylor et al., 2009; Massacand et al., 2009), suggesting that TSLP may play a prominent role in attenuating TH1 and TH17 responses.

Studies using mouse models of colitis have demonstrated important effects of TSLP in modulating the disease phenotype in intestinal inflammation, although there have been some conflicting results. In a chemical colitis model using dextran sulfate sodium (DSS), Taylor *et al*. showed that mice lacking the TSLPR developed more acute weight loss and increased colonic inflammation that correlated with higher levels of IFN-γ and IL-17A within the mesenteric lymph nodes (Taylor et al., 2009). In contrast, Reardon *et al*. reported comparable disease onset and severity in the DSS colitis model between mice that lack TSLP signaling versus controls. However, while wild-type mice recovered after DSS withdrawal, mice lacking either TSLP or its receptor had progressive disease and weight loss (Reardon et al., 2011). Reardon *et al.* showed that secretory leukocyte peptidase inhibitor (SLPI) was induced in DSS colitis in wild-type mice and that this induction was lost in TSLP knockout (TSLP KO) mice. Neutrophil elastase (NE) is a target of SLPI, and functions to degrade a number of substrates, including progranulin, a protein important in wound healing. Consistent with a role for TSLP in the inhibition of NE, TSLP KO mice displayed increased NE activity after treatment with DSS, and inhibition of NE reduced mortality in TSLP KO mice in this colitis model. While methodological differences may account for some of the discrepancies between these studies, a growing body of evidence demonstrates that differences in microbiota among various facilities can have profound effects on the development and function of the intestinal as well as systemic immune system (Gill & Finlay, 2011). Thus, further exploration of how the gut microbiota affects TSLP expression and function may be warranted.

These studies support a role for TSLP in the promotion of TH2 responses in the gastrointestinal system, but also provide important evidence that TSLP plays a key role in

the maintenance of immune homeostasis within the gut. Not only does TSLP function to attenuate TH1/TH17 responses, but also acts directly on the intestinal epithelium to support wound healing in colitis. Whether TSLP also contributes to wound healing and blockade of TH1/TH17 responses at other sites remains to be determined.

D. Cancer

A series of recent studies have implicated TSLP in the growth and metastasis of breast and pancreatic cancer, especially those which display an increased infiltration of TH2 cells (De Monte et al., 2011; Olkhanud et al., 2011; Pedroza-Gonzalez et al., 2011). Breast and pancreatic cancer cells and cancer-associated fibroblasts have been shown to produce TSLP in response to tumor-derived inflammatory cytokines and possibly other unidentified stimuli (De Monte et al., 2011; Olkhanud et al., 2011; Pedroza-Gonzalez et al., 2011). Furthermore, treatment of DCs with supernatants from these cells induced theTH2-attracting chemokines CCL17 and CCL22, as well as upregulation of DC costimulatory molecules CD80, CD86, OX40L and TSLPR, in a TSLP-dependent manner. Additionally, these primed DCs were able to promote TH2-polarizition of $CD4^+$ T cells *in vitro*. In support of these *in vitro* data, activated DCs and CCL17 and CCL22 were detected in the tumor and draining lymph nodes, but not non-draining lymph nodes of human patients (De Monte et al., 2011). Importantly, a decreased ratio of TH1/TH2 cells in human pancreatic cancer cases was associated with disease progression and was an independent prognostic marker of reduced survival (De Monte et al., 2011). While breast cancer cells with intact TSLP expression were able to induce tumor growth and metastasis in mice, shRNA knockdown of TSLP in these cells resulted in clones with minimal growth or metastasis (Olkhanud et al., 2011). Tumor progression and metastasis of an injected breast cancer or melanoma cell line was also decreased in TSLPR-deficient mice compared to wild-type mice (Olkhanud et al., 2011).

Previous work has shown that TH2 cytokines promote disease progression through increased survival of cancer cells, M2 macrophage differentiation, and fibrosis (collagen degradation and synthesis) (Wynn, 2004; Aspord et al., 2007; Mantovani, Romero, Palucka, & Marincola, 2008; Joyce & Pollard, 2009). TSLP may be linked to these phenomena in some human cancers, possibly based on its ability to drive TH2 differentiation and M2 macrophage differentiation ((Ziegler, 2010) and Han, H. and Ziegler, S.F., manuscript submitted). Alternatively, TSLP may promote tumor progression by controlling Treg migration. CCL22 production in human breast cancer is involved in the influx of tumor Tregs that may then alter the immunoregulatory environment (Gobert et al., 2009; Ménétrier-Caux, Gobert, & Caux, 2009). Further investigation is needed to identify the important sources and targets of TSLP within the tumor environment.

In addition to the association of TSLP with certain solid tumors, the TSLPR has been shown to be over-expressed in 5 to 10 percent of childhood B cell progenitor acute lymphoblastic leukemia (ALL) cases and approximately 60 percent of acute lymphoblastic leukemia cases in children with Down's Syndrome (Roll & Reuther, 2010; Tasian & Loh, 2011; Mullighan et al., 2009; Russell et al., 2009; Ensor et al., 2011). Approximately 15 percent of adult and high-risk pediatric B-ALL that lack characteristic rearrangements demonstrated TSLPR over-expression (Yoda et al., 2010). In addition, some cases of activating TSLPR mutations

were found(Chapiro et al., 2010). In almost all cases, TSLPR over-expression was associated with intra-chromosomal deletion or rearrangement of the TSLPR/CRLF2 locus with the immunoglobulin heavy chain (IGH) locus, placing TSLPR/CRLF2 under alternate transcriptional control downstream of the P2YR8 promoter (Russell et al., 2009; Mullighan et al., 2009; Yoda et al., 2010). These rearrangements were highly correlated with the presence of JAK2 mutations and were associated with a poor prognosis (Roll & Reuther, 2010; Mullighan et al., 2009; Russell et al., 2009; Cario et al., 2010; Harvey et al., 2010; Yoda et al., 2010; Ensor et al., 2011). In murine Ba/F3 cells, expression of TSLPR and JAK2 mutant alleles promoted growth factor-independent growth (Mullighan et al., 2009; Yoda et al., 2010). Mice with systemic over-expression of TSLP may provide a model for understanding the signaling mechanisms involved. In particular, loss of keratinocyte-specific Notch signaling resulted in high systemic levels of TSLP which correlated with a rapid expansion of pre-B cells in the early postnatal period that contributed to early mortality in these animals (Demehri et al., 2008). Interestingly, over-expression of TSLP early in the postnatal period was sufficient to drive a B cell lymphoproliferative disorder, but administration or induction of TSLP after postnatal day 14 was not, although other studies have shown expansion of B cell compartments following TSLP expression in adult mice (Astrakhan et al., 2007).

The association of TSLP and TSLP signaling pathways with hematologic malignancies as well as solid tumors implicates TSLP/TSLPR in numerous regulatory pathways that support cell growth and survival in cancer. In B-ALL, activation of signaling pathways downstream of TSLP directly promotes the growth and survival of malignant cells, whereas in breast and pancreatic cancer, TSLP likely contributes to multiple components of the tumor environment that affect growth and metastasis as well as immune evasion. Several reports suggest that TSLP/TSLPR may be useful as a prognostic marker and may present a novel target for therapeutic intervention in cancer.

E. Other Autoimmune Diseases and Issues of Tolerance

Mouse models with constitutive or inducible over-expression of TSLP have demonstrated that TSLP can be associated with autoimmune phenomena. TSLP over-expression in these mice was associated with the development of cryoglobulinemic glomerulonephritis due to increased production and kidney deposition of systemic polyclonal IgM and IgG via a monocyte/macrophage dependent mechanism (Taneda et al., 2001; Astrakhan et al., 2007). In addition, these mice developed red blood cell-specific auto-antibodies and autoimmune hemolytic anemia in a $CD4^+$ T cell and IL-4-dependent manner (Iseki et al., 2012). Whether TSLP is involved in human mixed cryoglobulinemia or autoimmune hemolytic anemia is unknown.

As discussed earlier, TSLP expression was decreased in IBD, a disorder that is thought to arise due to inappropriate immune activation against normally harmless microflora. Additionally, loss of TSLP signaling in a mouse model of autoimmune gastritis resulted in more severe disease (Nishiura et al., 2012). Although the impact of TSLP on colitis in mice appears more complex (Taylor et al., 2009; Reardon et al., 2011), this supports a model in which loss of TLSP, which can block TH1/TH17 responses, leads to increased

inflammation. However, data from humans and mouse models suggest that TSLP may actively promote inflammation in TH1/TH17-associated autoimmune diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS). In a proteoglycan-induced arthritis mouse model of RA, TSLPR-deficient mice had reduced immunopathology associated with decreased levels of production of IL-17, IL-1β, and IL-6, but increased IFNγ and IL-10 (Hartgring et al., 2011). Furthermore, blocking TSLP in a collagen-induced arthritis model ameliorated disease, while administering recombinant TSLP protein exacerbated disease (Koyama et al., 2007; Hartgring et al., 2011). Increased synovial concentrations of TSLP, as well as TNFα, have also been seen in synovial fluid from RA patients compared to samples from patients with osteoarthritis. In *in vitro* studies, TSLP-primed human myeloid DCs induced proliferation of self-reactive $CD4^+$ T cells capable of TH1 or TH2 differentiation, and TSLP priming of DCs, in conjunction with TLR3 ligand, supported TH17 differentiation (Watanabe et al., 2004; Tanaka et al., 2009; Koyama et al., 2007). Thus, although the role of TSLP in RA is largely undefined, these data provide intriguing evidence of its possible involvement.

SNPs in the IL-7Rα gene locus have been associated with multiple sclerosis (MS) and altered Treg numbers or function (Gregory et al., 2007; Lundmark et al., 2007). While TSLPR pairs with IL-7Rα and TSLP can affect Treg development, neither disease has yet been directly linked to TSLP. However, administration of TSLP or TSLP-treated bone marrow-derived DCs into nonobese diabetic mice prevented the development of diabetes in these mice (Besin et al., 2008), suggesting a possible role for TSLP in disease therapy. Although the mechanisms involved in protection from diabetes have not been determined, protection was associated with an increased number of Tregs. One final link that has been made between TSLP and immune tolerance is in maternal-fetal tolerance during pregnancy(Li & Guo, 2009). TSLP was produced and secreted by first semester trophoblasts, and tissue from normal pregnancies demonstrated a TH2 bias and higher levels of TSLP expression than samples from miscarriages (Guo et al., 2010; Pu et al., 2012; Wu, Guo, Jin, Liang, & Li, 2010). Thus, while TSLP expression and a TH2 bias may lead to disease progression in cancer, TSLP may contribute to tolerance at the maternal-fetal interface.

V. Conclusion

Much progress has been made in the understanding of TSLP biology and its role during TH2-type inflammation. Multiple cell lineages express the functional TSLPR that helps drive the immune response. More recent data has illustrated that TSLP is also involved in numerous disorders beyond just allergy, and may play a role in maintaining homeostasis in diseases such as IBD or in disease progression in cancer and autoimmunity. In order to utilize the knowledge gained about TSLP's biological effects, a better understanding of cell-specific signaling pathways must be delineated. Of utmost importance is deciphering whether TSLP invokes similar signaling pathways within different cells. Knowledge of the key targets and sources of TSLP in different disease states will also be important in furthering our comprehension of the pathophysiology of TSLP-associated disorders. Tools that can address these questions, such as approaches that use conditional deletion of the

TSLPR and cytokine, will be important in the continued investigation of the role of TSLP during both atopic and non-atopic conditions.

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Abbreviations

TSLP	thymic stromal lymphopoietin
TSLPR	thymic stromal lymphopoietin receptor
IL-7Rα	interleukin-7 receptor alpha
JAK	Janus kinase
STAT	Signal Transducers and Activators of Transcription
γ_c	common γ receptor chain
AD	atopic dermatitis
NK	natural killer
SNP	single nucleotide polymorphism
NS	Netherton's syndrome
SPINK5	serine peptidase inhibitor Kazal-type 5
LEKTI	lymphoepithelial Kazal-type–related inhibitor
RXR	retinoid X receptor
PAR-2	protease-activated receptor 2
LC	Langerhans cell
EC	epicutaneous
FITC	fluorescein isothiocyanate
CHS	contact hypersensitivity
AR	allergic rhinitis
COPD	chronic obstructive pulmonary disease
BAL	bronchoalveolar lavage
SPC	surfactant protein C
FOXP3	forkhead box P3
EoE	eosinophilic esophagitis
CD	Crohn's disease
UC	ulcerative colitis

IBD	inflammatory bowel disease
DSS	dextran sulfate sodium
SLPI	secretory leukocyte peptidase inhibitor
NE	neutrophil elastase
ALL	acute lymphoblastic leukemia
B-ALL	B cell ALL
CRLF2	cytokine receptor-like factor 2
TNF	tumor necrosis factor
OX40L	OX40 ligand (CD134)
TLR	toll-like receptor
APRIL	a proliferation inducing ligand
IEC	intestinal epithelial cell

VIII. Reference List

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