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Update on the Functionality of Thymic Stromal Lymphopoietin and its Interaction with Dendritic Cells, to Trigger a Pro or Anti-Inflammatory Status

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ABSTRACT

Thymic stromal lymphopoietin (TSLP) is a cytokine produced primarily by activated epithelial cells of the lung, skin and intestine. The foremost property of this cytokine is to condition dendritic cells (DC) to initiate type 2 responses, and consequently to develop a wide range of related disease, including asthma, atopic dermatitis, and allergic responses. However, TSLP is also associated with regulatory and homeostatic processes. The objective of this review is to provide a summary overview of the variety of functions found in this cytokine.

Keywords: Dendritic cells, Thymic stromal lymphopoietin

Abbreviations: DC: conventional dendritic cells; TSLP: thymic stromal lymphopoietin; sTSLP: short isoform TSLP, lTSLP: long isoform TSLP, TSLPR: TSLP receptor; TLR: Toll-like receptor; ACh: acetylcholine; Th: T helper; TFh: T follicular helper; Treg: T regulatory; NKT: Natural killer T; LPS: lipopolysaccharide; TEC: thymic epithelial cells; TECc: cortical thymic epithelial cells; TECm: medullar thymic epithelial cells; RSV: respiratory syncytial virus; HDM: house dust mite; KO: The knockout; HIV: human immunodeficiency virus; IBD: inflammatory bowel diseases; IEC: intestinal epithelial cells; MDC: macrophage-derived chemokine; TARC: thymus and activation-regulated chemokine; UC: ulcerative colitis; CD: Crohn´s disease; BCL- 2: B cell Leukemia/Lymphoma 2; STAT-5: signal transducer and activator of transcription 5; PPAR2: Peroxisome proliferator activated receptor; NF-kB: Nuclear Factor kappa B; TRPA1: transient receptor potential action channel subfamily-member 1/ transient receptor potential ankyrin; RIG-1: retinoic acid inducible gene 1

INTRODUCTION

It is widely recognized that the epithelial lining of several organs, such as skin, lungs and gut, has a fundamental role as a protective barrier against infection and physical or chemical injury [1]. However, the epithelium is no longer considered only as a physical barrier, but it is also the primary one that senses the external environment, working as a key sensor and modulator of the immune response [2]. The thymic stromal lymphopoietin (TSLP) is a cytokine produced by activated lung, skin and gut epithelial cells, inducing the activation of an extensive range of immune and non-immune cells [3,4]. Regarding the immune perspective, the main property of this cytokine is to condition the dendritic cells (DC) to initiate type 2 responses, and consequently a broad array for allergic responses [5,6].

Actually, TSLP is a pleiotropic cytokine belonging to the IL-2 family but it was identified in 1994 [7] as a secreted factor from a mouse thymic stromal cell line; which promote immature B cells [7] and T progenitors [8]. TSLP is a four-helix-bundle cytokine and was first cloned in humans in 2001 [4,9], interestingly close to the gene cluster encoding several Th2-related cytokines [4,10]. The human TSLP gene is located on chromosome 5q22.1 next to the atopic cytokine cluster such as IL-4, IL-5, IL-9, and IL-13 on 5q31

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[3,6,9,11,12]. The biological activity of TSLP, in both humans and mice, is mediated by binding to their complex composed by TSLP receptor α chain (RTSLP, chain specific of TSLP, also known as CRLF2; this chain is a member of the hematopoietic receptor family and binds with low affinity to TSLP) and the interleukin 7 receptor-α chain (IL-7Rα), both chains together induce a heteromeric complex of high-affinity [12-14].

There are many different stimuli including some allergens, cytokines, respiratory viruses [1,3,15,16], leading to the production of TSLP in epithelial cells, airway smooth muscle cells, human DCs, and mast cells, etc. [1,3,17,18]. Furthermore, different kind of cells and tissue can respond to TSLP including immune cells (e.g. DCs, ILC2, T and B lymphocytes, natural killer T (NKT), T regulatory cell (Treg.), monocytes, mast cells, macrophages, eosinophils, basophils) and non-immune cells (platelets and sensory neurons, heart, skeletal muscle, kidney and liver) [3,4,12,19], inducing different functions **(Table 1)**.

Table 1. Functional activities of TSLP.

IMMUNE CELL	FUNCTION
DC	Th2 differentiation/maintenance memory Th2 [20]
LT CD4+	IL-4 secretion, induction Th2. Enhance BCL-2/ STAT-5 Survival [21]
ILC2	drive Th2 and inflammation [22]
LB	Increase proliferation [23]
Regulatory T Cells	Short isotype modulates homeostasis in gut and skin [24]
TFh	Differentiation [25]
NKT	Increase IL-13[17]
Eosinophils	Increase recruitment [26]
Basophils	Increase IL-13 [27]
Mast cells	Not complete degranulation. Secretion of cytokines and chemokines that promote Th2 polarization [28]
LT CD8+	Increase cytotoxicity and BCL-2/STAT-5 survival [29]
NON INMUNE CELL	**FUNCTION**
Sensory neurons	Itch in atopic dermatitis [**30**]
Keratinocytes	PPAR2 activation
Fibroblast	PPAR2 Activation [31]

One particularly pertinent reason to develop this topic is that the up regulation of the cytokine itself is closely linked up to the pathogenesis of numerous Th2 related diseases, including asthma, atopic dermatitis and allergic responses [32]. It is reported that the cytokine not only promote Th2 response but also can be associated, with autoimmune disorders [33,34] and finally in recent times has been linked the TSLP to the pathogenesis with different tumors, like breast cancer [35], leukemia lymphocytic acute (ALL) [36], cutaneous T cell lymphomas [37], enhances lung metastasis

[38]. Moreover, intratumor Th2-type cell infiltrate correlates with cancer-associated fibroblast TSLP production and reduced survival in pancreatic cancer [39]. On the contrary, TSLP also mediates several immune homeostatic functions in thymic [40], intestinal [41] and trophoblastic cells [42,43].

The objective of this review is to describe the recent advances in the homeostatic and inflammatory mechanisms carried out by the TSLP as modulate of physiology of immune cell mainly DCs.

DC PRIMING BY TSLP: IS RESPONSIBLE FOR PROINFLAMMATORY OR REGULATORY STATUS?

Inflammatory function

Conventional DCs are specialized antigen-presenting cells with a unique ability to activate resting T cells and to direct their differentiation into several effector profiles [5,44-46]. Human TSLP markedly activates and maintains the survival of DCs and Langerhans cells [6,47,48]. In addition, TSLP-conditioned DC up regulated the costimulatory molecules CD40, CD80, CD86 and OX40L, and produces high levels of IL-8 IL-15, Eotaxin2, thymus and activation-regulated chemokine (TARC/CCL17) and macrophage-derived chemokine (MDC/CCL22) [6,49]. Moreover, naive allogeneic T cells that were cocultured with TSLP-conditioned DC acquired an inflammatory Th2-like phenotype with production of IL-4, IL-5, IL-13, and TNF-α but not IL-10 [50,51]. Likewise, it seems that TSLP induces human myeloid DC to express OX40L (the TNF superfamily protein) [49], which induce the generation of inflammatory Th2 cells. The relevance of the OX40L molecule is clearly reflected in the initiation of the Th2 response which, independently of IL-4, depends on the interaction of OX40 with OX40L expressed in activated naïve T and DC cells respectively [20,52,53] **(Figure 1)**. As a matter of fact, Ito et al. observed that, anti-OX40L or anti-IL-4 monoclonal antibody strongly inhibited the production of IL-4, IL-5 and IL-13 [53,54]. Respectively, there is clear evidence which support that TSLP, even in the absence of IL-4, could directly promote Th2 differentiation and type 2 cytokine from naive T cells *in vitro* [55].

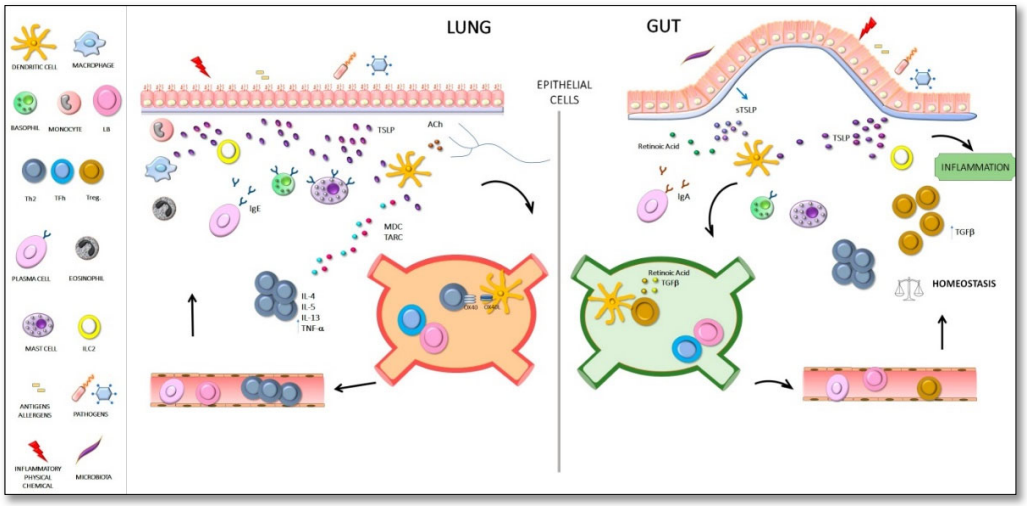

Figure 1. Different immune response by TSLP-conditioned DC

Lung: *TSLP-conditioned DC up regulates the costimulatory molecules mainly OX40L, and produces chemokine's like TARC and MDC, inducing the activation chemo taxis of Th2 profile. The inflammatory Th2-like phenotype produces of IL-4, IL-5, IL-13, and TNF-α but not IL-10. The increase of IL-4 induces a switch isotype to IgE in the LB inducing the asthmatic response.* ***Gut:*** *Pathogenic bacteria induce long isoform TSLP (conventional TSLP) and down-regulate the short isoform and commensal bacteria increased the sTSLP expression on the mucosa. IEC-conditioned DC induces Treg profile in homeostatic condition. The increased of TGFβ induce a switch isotype to IgA in the LB*

Taking into account all the information mentioned before, the Th2 profile is induced and the recruitment of Th2 cells favors them to migrate towards inflammatory sites and reflects the disease activity in pathologies like dermatitis, asthma, allergic responses, [32,51].

Interestingly, our group observed that DC cultured with Acetylcholine (ACh); the most important parasympathetic neurotransmitter in the airways [56]; in presence of TSLP showed higher levels of OX40L expression than cells cultured with individual stimuli. A similar effect was observed with the expression of maturation markers and the TNF-α and IL-8 cytokine production. Moreover, when DC were cultured with both TSLP and ACh, a higher stimulation of IL-4, IL-5, and IL13 production was observed, all of that, suggesting that a neurotransmitter like ACh combined with TSLP-stimulated DC could enhance the Th2 profile polarization facilitating, in consequence, the development of asthma [57].

Homeostatic function

At the beginning of this review, we describe several factors capable of inducing TSLP secretion by epithelial cells, especially during the inflammatory response, but this is also critical for the generation and maintenance of the homeostatic microenvironment, in which DC again is one of the main protagonists [41,58,59].

FUNCTIONAL ROLE OF TSLP IN THE GUT

For a few years, attempts have been made to deepen its action on the intestinal mucosa and the pathologies associated with its immune dysregulation. The gastrointestinal tract is the largest surface of the body and the most exposed to potentially pathogenic microorganisms. It has a role of allowing the uptake of micronutrients and preventing the entry of microorganisms while maintaining homeostasis [60]. Multiple mechanisms of both innate and adaptive immunity participate in maintaining mucosal homeostasis [61]. Indeed, it is the epithelial cells that play an essential role. This physical barrier that separates the lumen from immune cells includes tight junctions, produces antimicrobial peptides and mucins that prevent the adherence and subsequent colonization of microorganisms but it also secretes constitutive factors and cytokines such as TGFβ and IL-10 that maintain the mucosa tolerance not only to microbial challenge but also to dietary antigens [62,63]. In fact, the breakdown of this barrier leads to the development of inflammatory diseases as allergies, diabetes and inflammatory bowel diseases (IBD). In recent years, intestinal epithelial cells (IEC) have acquired central importance in sensing the environment and instructing dendritic cells in intimate contact to act accordingly [64,65]. Thus, CD103+ dendritic cells in the presence of a non-activated line of human IEC acquire an anti-inflammatory phenotype. The gastrointestinal tract expresses TSLP constitutively, with low levels in the small intestine and higher in the colon [24]. The TSLP was established as one of the main factors secreted by the IEC when sensing the flora; modulate the basal levels of this hematopoietic factor for instructing DC towards a non-inflammatory profile [58]. EIC-conditioned mucosal DC increase the expression of the OX40L molecule inducing a Th2 profiles while decreasing the expression of IL-12/23 p40 subunit, effects mediated by TSLP and limiting Th1/Th17 polarization reducing the production of IFN-γ and IL- 17 [48,66,67]. In the same way, conditioned DC acquires a non-inflammatory phenotype activating the differentiation of Foxp3 Treg cells suppressing immune response and inducing tolerance [68]. In vitro assays with naive CD4+ CD25- cells showed that TSLP per se is not capable of inducing CD4+CD25+ Foxp3+ Treg cells [6, 69]. This only occurs when TSLP previously interacted with DC of mesenteric lymph node or lamina propria. The regulatory phenotype acquisition is not induced when conditioned DC are co-cultured with peripheral naive lymphocytes [70]. The knockout (KO) of the RTSLP in DC was shown to prevent the induction of Foxp3 Treg lymphocytes in a murine model [71]. Facts which reinforce the essential TSLP role in the homeostasis control of the gastrointestinal tract.

Variations in TSLP levels in the intestinal mucosa are essential to define the degree of activation of the DC and the bias of the concomitant effector response. Low concentrations maintain low IL-2 secretion and favor non-inflammatory Th2 polarization. The bacterial ligands of toll like receptors (TLR) such as lipopolysaccharide (LPS), peptidoglycan and flagellin when interacting with IEC increase TSLP levels in the mucosa, mediated effect via the activation of the NFk-β pathway [72-74]. Also, viral components of rotavirus and human immunodeficiency virus (HIV) increase TSLP levels when sensed by the IEC [75]. Minimal variations in these basal concentrations instruct DC into an inflammatory profile capable of producing IL-12 and induce inflammatory Th1 response profiles [24].

FUNCTIONAL ROLE OF TSLP IN THE THYMUS

The thymic stroma is mainly made up of a heterogeneous population of epithelial cells, thymic epithelial cells, (TEC) present in both the cortex and the medulla, which are called cortical thymic epithelium (TECc) and medullary (TECm) cells, respectively. It is known that TECc are involved in the process of positive selection, while TECm and thymic DC are involved in the process of negative selection [76] . As regards, TSLP, it is expressed in Hassall's corpuscle where also in the medulla localized activated DC, and CD4+ CD25+ Treg. Due to its expression by Hassal´s corpuscles in the thymus, TSLP has homeostatic activities like regulation on the capacity of DC and plasmacytoid DC to drive development of Treg [58,77,78]. Interestingly, the number of Foxp3+ Treg in the tumor microenvironment correlated with the increase expression of TSLP protein in some tumor, like lung cancer [79].

FUNCTIONAL ROLE OF TSLP IN TROPHOBLASTIC AND PREGNANCY

Physiologically, pregnancy can be considered a successful embryo allograft. Guo et al. [42] described that human trophoblast, cells secreted soluble TSLP in maternal-fetal interface of early placentas. They described that the functional RTSLP is highly expressed in human decidual CD1c DC (dDC) and, besides, TSLP or supernatants from human trophoblasts culture specifically stimulate dDC to highly produce interleukin-10 and Th2-attracting chemokine TARC/CCL-17. The TSLP-conditioned dDC prepare decidual CD4+ T cells for Th2 cell differentiation, involved in maternal-fetal immunotolerance. Moreover, the combination of hormones like progesterone or estradiol at physiological levels in early human pregnancy also induces TSLP mRNA and protein expression [43,80], too deep in this theme, Lin et al. [80,81] discover that, in a murine model, TSLP-conditioned DC can boost the production of

TARC/CCL17, which can afterwards, attract Th2-type cells to immigrate into the uterus. In addition, Du et al. [82] proposed a crosstalk model between embryo trophoblasts and decidual leukocyte subsets of the maternal–fetal interface in human first-trimester pregnancy, they confirmed, trophoblast-derived TSLP actives the DC to induce CD4+ CD25+ FOXP3+ T cells profile in early pregnancy via TGF-β1. In summary the TSLP is critical for a successful pregnancy, mainly in the beginning of the maternal-fetal interface.

TSLP and a new paradigm

The difference between the activation of DC with the induction of homeostatic in certain tissues and the hallmark of exacerbated Th2 profile on the microenvironment where the DC were found, is an issue that generates the beginning of the paradigm of the function of TSLP. Recently, different groups have shown that exists in humans a novel isoform, that is to say, a shorter isoform of TSLP who is constitutively expressed in a variety of tissues, including bronchial and colonic epithelial cell, keratinocytes and lung fibroblasts [42,83]. Furthermore, short TSLP isoform (sTSLP) is involved in homeostatic functions, whereas the long TSLP isoform (lTSLP, conventional isoform) is expressed constantly at a very low level and up regulated during inflammation in different tissues [24]. Fornasa et al. [84] described the two coding transcripts code for the lTSLP of 159 amino acids and for sTSLP which has the last 63 residues of lTSLP and is identical to its C-terminal portion. They describe that sTSLP is the homeostatic isoform of TSLP present under steady-state conditions in the gut and skin. They described whether sTSLP had anti-inflammatory properties on DC. However, only lTSLP significantly up regulated TARC/CCL17 and MDC/CCL22 expression and the secretion of TNF alfa, but was not affected, in none of the 3 cytokines, by the presence of sTSLP. Finally, Tsilingiri et al. [24] reported that the 2 isoforms were not the result of alternative splicing of the same transcript; they are controlled by two different promoter regions.

Interestingly, a dual tissue-dependent role is assigned to TSLP. In general, its role is inflammatory in the skin and lung and anti-inflammatory in the intestine and thymus. In the intestine they contribute to maintain homeostasis through the induction of regulatory response profiles. In part, the immunomodulatory effect was attributed to the sTSLP whose transcript is most expressed in the epithelial barrier. The lack of animal models, which do not express the short isoform and the fact that TSLPR-IL7Rα heterodimeric receptor, is for the long form makes a functional study difficult. However, the fact that IEC in contact with pathogenic bacteria up- regulates the long isoform and down-regulates the short one while the contrary is observed with commensal bacteria supports the theory of homeostatic action of the short form on the mucosa [24,85,86].

TSLP IN PATHOLOGIES

Asthma

Asthma is a chronic inflammatory disease of the conducting airways that involving a series of events with the participation of epithelial cells and the activation of immune cell effector mechanisms It is known that this series of events involving the airways is associated with the development of a Th2 profile, airway inflammation, bronchial hyper reactivity, the excessive production of mucous secretion and the structural remodeling of the airway. Th2 lymphocytes with the consequent production of IL-4, IL-5 and IL-13 cytokines; lead to chronic inflammation characterized by infiltration of the mucosa of eosinophil's, mast cells, and Th2 lymphocytes [46,87,88]. As the DC are the orchestral conductors of the immune response, imposing a specific Th lymphocyte profile, their ability to sense the surrounding microenvironment is of utmost importance for the initiation of allergic processes.

As described previously the TSLP secreted by epithelial cell is the cytokine responsible for conditioning DC to a Th2 inflammatory profile that produce the classical Th2 cytokines IL-4, IL- 5, and IL-13, and a high concentration of TNF-α promoting development to asthma pathogenesis [20,32]. Furthermore, an experiment made in TSLPR KO mice failed to develop an inflammatory lung response, underlining the importance for this cytokine in the development in allergic response [11]. The TSLP overexpressed in airway epithelia lung biopsies of asthmatic patients [89,90] and in asthmatic mice, [2,91] which is associated to the pathogenesis of airway disease, correlated with the severity of asthma. Moreover, a polymorphism in the TSLP locus was associated with an increased risk or more susceptibility in development of asthma [92,93].

Studies carried out in serum samples of 65 pediatric patients, newly diagnosed for allergic asthma, showed an increased production of the TSLP that correlated negatively with asthma control test samples and Treg cells [94]. Different groups proposed the TSLP as a biomarker for inflammation asthma patients and also as a biomarker of severe asthma [94,95]. As described previously the TSLP may have dual immunoregulatory roles. Dong et al. [96] found that house dust mite (HDM) and lTSLP impaired barrier function and the treatment with sTSLP and 1,25D3 prevented HDM-induced airway epithelial barrier disruption. Moreover, sTSLP and 1,25D3 treatment ameliorated HDM-induced asthma in mice.

The relevance of TSLP towards the induction of a Th2 profile and the development of the asthmatic process is not limited to its effect on DC, other cell types favor this profile such as mast cells, basophils [1,32] and Innate lymphoid cells 2 (ILC2), in the last one mainly his survival [97]. ILCs are a recently identified family of heterogeneous immune cells that can be divided into three groups based on their

differential developmental requirements and expression of effector cytokines. The ILC2s produce the type 2 cytokines interleukin-5 (IL-5) and IL-13 and promote type 2 inflammation in the lung and intestine. Kabata et al. [98] suggest that the ILC2 priming by TSLP may play a critical role in the resistance to steroid in allergic airway inflammation.

TSLP and viral infection

Respiratory virus infections, such as respiratory syncytial virus (RSV) and rhinovirus infections have been associated, in children and adults, with the development of persistent or exacerbations asthma. Indeed, rhinovirus infection in the first 3 years of life is associated with increase in risk for asthma [99,100]. Viral infection may development of the Th2 immune response, be part of leading to reduced IFN-γ and IL-12, and inefficient antiviral immunity asthmatic individuals [101], by activation of different TLR [102].

Tanaka et al. [103] evaluated how the relationship between TSLP and TLR3 ligand stimulation influences DC activation. They suggested that through DC activation, human TSLP and TLR3 ligands promote differentiation of Th17 cells with the central memory T cell phenotype under Th2- polarizing conditions. This result is relevant to patients with severe asthmatic disease who have a neutrophil infiltrate and inflammation, probably induced by the Th17 profile.

Lee et al. [104] reported RIG-I as a novel pathway that leads to TSLP expression after respiratory virus infection of airway epithelial cell, confirming that airway epithelial cells from asthmatic children produce significantly greater levels of TSLP after RSV infection than cells from healthy children. On the other hand, they confirm that RSV-induced TSLP expression was found to be critical for the development of immunopathology, in a murine model.

Conversely to the previously mentioned works, there would seem not to be a beneficial role of TSLP in antiviral immunity, in fact, studies realized with TSLPR-deficient mice, show that TSLP was required for the expansion and activation of virus-specific effector CD8 +T cells in the lung, but not in the lymph node. The mechanism involved TSLPR signaling on newly recruited CD11b+ inflammatory DC [105]. TSLP may be the connections between virus infection and persistent or exacerbations asthma.

Atopic dermatitis

Atopic dermatitis (AD) is a common chronic skin disorder, with relapsing eczematous skin inflammation often accompanying severe pruritus [106].

Soumelis et al. [50] determined in the 2002, the expression of TSLP protein in of skin lesions, atopic dermatitis, nickel-induced contact dermatitis and cutaneous lupus erythematous samples. High expression of TSLP was found in the keratinocytes of acute and chronic atopic dermatitis, a clear Th2 profile of allergic disease. This group determined also that the expression of TSLP was associated with the activation of Langerhans cells. Murine models confirmed that DC migrate to lymph nodes and activate to Th2 profile [107].

Moreover, like in asthma patients, important concentration of the TSLP detected in serum of patients both children and adults with AD [108-110]. Polymorphisms in the TSLP gene are associated with an increased risk of development and progression of AD. In this pathology the polymorphisms can involve both TSLP and its RTSLP or RIL-7 [110,111].

Perinatal supplementation with probiotics has been shown to reduce the incidence of AD in infancy [112]; as one of the cytokines found in breast milk is TSLP [113] it was postulated that the mechanism that reduces the AD involved this cytokine, but neither TSLP nor TGFβ would seem to be involved [114].

One of the most interesting research of the last years, described a directly communication between epithelial cells to cutaneous sensory neurons via TSLP to promote itch. TSLP acts directly on a subset of TRPA1-positive sensory neurons to trigger robust itch behaviors, giving other clear evidence of the influence of the nervous system on allergic pathologies [30].

Both Basophils [115] and ILC2 have a significant relevance in TSLP activation in AD. In fact, a population of skin resident ILC2s present in healthy human skin was identified by Kim et al. [116] besides this is enriched of these cells in lesioned human skin from AD patients. ILC2 is mainly regulated by IL-25 and IL-33 in gut and lung, but Kim et al. [116] described that the ILC2 in skin and skin-draining lymph nodes responds critically to TSLP. Finally, TSLP interacts directly with skin-homing Th2 cells in AD patients which have enhanced TSLPR expression [117].

Fornasa et al. [84] found an up regulation of the lTSLP isoform in lesioned as opposed to nonlesional biopsy specimens but they found that sTSLP was significantly down regulated in lesioned biopsy, indicating an imbalance of the 2 isoforms in patients with AD because they showed down regulation of sTSLP and up regulation of lTSLP.

GUT PATHOLOGIES

Epithelial cells of the mucosa and dysbiosis of the micro biota are pillars in the development of inflammatory bowel diseases. IBD refers to two entities defined as ulcerative colitis (UC) and Crohn disease (CD) [62,118]. These diseases have a high prevalence of 396 per 100,000 individuals, values that increase year by year. Because of the symptoms with which they occur such as diarrhea, abdominal pain, and weight loss, they are considered disabling diseases. Due to the homeostatic function of TSLP in the intestine plus the fact that it is produced in a constitutive homeostatic way, it is assumed that alterations

in these levels are associated with pathology. The expression of TSLP was demonstrated in the colon lesions of patients with UC whose effector mechanism is the induction of Th2 lymphocytes. In contrast, in colon biopsies of patients with Crohn's disease, characterized by Th1/Th17 response profiles, down regulation of the TSLP gene was described [70], strikingly when their CDs when stimulated by bacterial ligands they secrete IL-12, which is consistent with the inability in these patients to induce tolerogenic or non-inflammatory DC [85,119]. Likewise, in vitro tests with DC derived from human monocytes are only observed at low concentrations of TSLP, not when the concentrations are high. Indicating the existence of a concentration window outside of which the inflammatory response is triggered.

Gene association studies found a correlation of TSLP with genes associated with the development of IBD. The most notable is that the CCR5 and CLCX10 chemokine receptors that govern the migration of T lymphocytes to the epithelium are up regulated by TSLP, which is essential in the development of necessary Th2 letters associated with UC [120,121]. Another Th2 chemo attractant is CCL11, which is increased in biopsies of UC patients and CCR2 that allows homing of intraepithelial lymphocytes that express the αEβ7 molecule up regulated by TSLP in UC [70]. In contrast, the decrease of CCL11 in CD was not associated with TSLP [122]. IL-4 and Il-13 cytokines are increased by TSLP in the colon of UC patients. It was demonstrated that IL-13 induces an increase of the permeability in the IECs mediated by the activation of cellular apoptosis and the decrease of the ocludin 2 leading to the damage associated with this pathology [123, 124]. Genes are also up regulated in DCs that have to do with the induction of the Th2, CCL24/eotaxin profile that induce eosinophil recruitment in UC patients [125].

It should be noted that an association was also found between the levels of TSLP and genes associated with the junctions of epithelial cells. In this sense, a decrease in Zo-1 and ocludin, a protein that is part of tight junctions in UC patients, was found. Disruption of barrier permeability is known to be one of the first mechanisms in inducing inflammatory response associated with damage to the mucosa and pathology, on the contrary, the CLN1 gene is increased, which produces ocludin-1, a mechanism associated with compensating for damage [70,126,127].

An attempt has been made to define the association of isoforms with each pathology. The most relevant results show that in the biopsies of patients with CD the short isoform is down- regulated; while there would be no alteration in the long isoform [127], the opposite effect occurs in biopsies of patients with UC. Tsilingiri et al. [84] using specific-isoform antibodies demonstrated a down-regulation of short isoform in the biopsies of untreated celiac patients. These results encourage future therapies to restore the homeostatic levels of this isoform [128]. The results are generally consistent in that the long isoform would be responsible for the induction of disease-associated damage. All this allows us to think that blocking TSLPR-TSLP signaling would be encouraging in the development of therapies that improve the quality of life of patients with IBD interfering with the activation of the inflammatory response through the restoration of homeostatic conditions.

Conclusion and therapeutic target

In conclusion, the TSLP is a key modulator of the responses through its impact mainly on DC. Due to the relevance of TSLP in the pathophysiology of diseases such as asthma and atopic dermatitis, the blocking of this cytokine has been the target of important research, leading to development of a numerous of clinical trials with very promising results to the treatment of this pathologies [1,21,110,129].

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