Role of thymic stromal lymphopoietin in allergy and beyond

Risa Ebina-Shibuya and Warren J. Leonard

Abstract | Thymic stromal lymphopoietin (TSLP) is a pleiotropic cytokine that acts on multiple cell lineages, including dendritic cells, T cells, B cells, neutrophils, mast cells, eosinophils and innate lymphoid cells, affecting their maturation, survival and recruitment. It is best known for its role in promoting type 2 immune responses such as in allergic diseases and, in 2021, a monoclonal antibody targeting TSLP was approved for the treatment of severe asthma. However, it is now clear that TSLP has many other important roles in a variety of settings. Indeed, several genetic variants for TSLP are linked to disease severity, and chromosomal alterations in TSLP are common in certain cancers, indicating important roles of TSLP in disease. In this Review, we discuss recent advances in TSLP biology, highlighting how it regulates the tissue environment not only in allergic disease but also in infectious diseases, inflammatory diseases and cancer. Encouragingly, therapies targeting the TSLP pathway are being actively pursued for several diseases.

The cytokine thymic stromal lymphopoietin (TSLP) was originally detected in the supernatant of a thymic stromal cell line and shown to support the long-term growth of a B cell line and to enhance the proliferation of unfraccionated thymocytes responding to stimulation with anti-CD3 antibody. It was later shown to be a critical mediator of type 2 immune responses and a promoter of T helper 2 (T(H2)) cell-mediated diseases, including asthma and atopic dermatitis (AD). However, work since this original definition now shows that TSLP has multiple functions, including in cell maturation, proliferation, survival and recruitment and is involved in various other diseases and host responses. Here, we review how TSLP broadly contributes to pathological conditions such as allergic disease, host defence, cancer and chronic inflammatory disease. Understanding the roles of TSLP has implications for new therapeutic strategies that target this cytokine signalling system.

Epithelial cells and stromal cells in the lungs, skin and gastrointestinal tract are the primary source of TSLP during both homeostatic and inflammatory conditions, although DCs, basophils and mast cells can also produce this cytokine. TSLP is also produced by hair follicles and, together with IL-7, TSLP contributes to the persistence within skin of ILCs, which tune the skin microbiota by controlling sebaceous gland function. TSLP production by epithelial cells can be induced by many stimuli, including mechanical injury, ligands for Toll-like receptor 3 (TLR3), TLR2 and NOD2, helminth infection, pro-inflammatory cytokines, and proteases, including trypsin and papain. TSLP production in the lungs is also triggered following infection with viruses, including respiratory syncytial virus (RSV), rhinovirus, influenza virus and lymphocytic choriomeningitis virus. TSLP acts as an alarmin, being released from cells rapidly and inciting further exogenous and endogenous danger signals and exacerbating inflammation.

TSLP production is positively regulated by the pro-inflammatory T(H)2-type cytokines IL-4 and IL-13 as well as by tumour necrosis factor (TNF), IL-1β and IL-25, with TNF synergizing with T(H)2-type cytokines to increase TSLP production. By contrast, interferon-γ (IFNγ) and IL-17 inhibit TSLP release. β2-Adrenoceptor agonists and glucocorticoids also inhibit TSLP release and synergize to inhibit poly(I:C)-induced release of TSLP. In the context of tissue injury, macrophage-derived progranulin induces TSLP production by mouse airway epithelial cells, leading to allergic inflammation. In addition, the cross-linking of IgE bound to its high-affinity...
Box 1 | Thymic stromal lymphopoietin versus IL-7

Thymic stromal lymphopoietin (TSLP) and IL-7 are paralogues, likely having arisen by a gene duplication event. They signal via a shared IL-7 receptor α-chain (IL-7Rα), which partners with the TSLP receptor (TSLPR) in the case of TSLP, or the common cytokine receptor γ-chain in the case of IL-7. Interestingly, whereas IL-7 binds more robustly to IL-7Rα, TSLP binds more robustly to TSLPR, a situation perhaps analogous to another cytokine pair, IL-4 and IL-13, which share IL-4Ra as a receptor component but where IL-4 dominantly binds to this protein and IL-13 primarily binds to IL-13Rα1 (REF.139). For IL-7 and TSLP, the question is why have both cytokine genes evolved and been retained, especially given that TSLP has a pathological role in several diseases. TSLP and IL-7 indeed share some functions related to lymphoid development but they also have unique functions, with IL-7 primarily contributing to T cell development and homeostasis, and TSLP having roles in allergic disease as well as a broad range of actions on T cells, B cells and other cells (as detailed in this Review and elsewhere140-144). The sharing of IL-7Rα suggests that these cytokinies might also compete for its recruitment and have competing actions. Both IL-7 and TSLP activate STAT5 but IL-7 does so more potently. Thus, what is the in vivo relationship between TSLP and IL-7? When do these cytokines cooperate and when do they potentially compete? Additionally, what is the physiological role of TSLP (that is, long-form TSLP) versus short-form TSLP? These are important questions for the better understanding of the overall biology of TSLP.

Receptor (FcεRI) induces mast cell production of TSLP. At the transcriptional level, nuclear factor-xB (NF-xB) and AP1 contribute to TSLP gene expression, and NF-xB binding sites have been identified in the TSLP promoter region145.

Two variants of human TSLP have been described: a long-form (IfTSLP) and a short-form (sfTSLP)146; the former is also known as TSLP and is the molecule that corresponds to mouse TSLP. Transcription of sfTSLP initiates from a promoter in intron 2 and is thus truncated at the amino-terminus but has the same carboxy-terminus as IfTSLP, having a total of 63 amino acids versus 159 amino acids for IfTSLP147. sfTSLP mRNA is constitutively expressed in keratinocytes, epithelial cells and lung fibroblasts148 and its expression is not upregulated by inflammation, whereas IfTSLP is induced by TLR ligands, including flagellin, and TNF-α149-151. The distinct regulation of sfTSLP and IfTSLP suggests different roles, with an anti-bacterial or anti-inflammatory function proposed for sfTSLP and a pro-inflammatory function for IfTSLP152-155. Accordingly, in a mouse asthma model, administration of sfTSLP ameliorated house dust mite-induced asthma, whereas administration of IfTSLP damaged airway barrier function, contributing to the pathogenesis of asthma151. Single nucleotide polymorphisms (SNPs) rs2289276 and rs2289278 in the TSLP promoter confer increased binding by AP1 and enhanced IfTSLP production, which may explain why these SNPs are associated with increased incidence of childhood atopic disease and adult asthma156. In ovarian and endometrial cancers, sfTSLP is predominantly expressed and promotes tumour growth through the activation of signalling pathways in cancer cells157. Further elucidating the different roles of these isoforms may provide new insights into TSLP biology.

TSLP-induced signalling

TSLP signals through a heterodimeric receptor comprising TSLPR, a type 1 cytokine receptor encoded by Crlf2, and the IL-7 receptor α-chain (IL-7Rα; also known as CD127)41-43 (FIG. 2). This heterodimer is expressed on TSLP target cells such as DCs, mast cells, macrophages, basophils and T cells as well as epithelial cells and neurons158,159. Unlike its parologue IL-7, which activates JAK1 and JAK3 via a heterodimeric receptor comprising IL-7Ra and the common cytokine receptor γ-chain, TSLP activates JAK1 (via IL-7Ra) and JAK2 (via TSLPR). JAK1 and JAK2 then primarily activate signal transducer and activator of transcription 5A (STAT5A) and STAT5B and, to a lesser extent, STAT1 and STAT3 (REF.160), ultimately driving the production of IL-4, IL-5, IL-9 and IL-13 as well as pro-inflammatory effects. Unlike IfTSLP, it is unclear whether sfTSLP signals via the combination of TSLPR and IL-7Ra or potentially has an alternative mechanism of signalling given its truncated form.

TSLP in allergic disease

It is well established that TSLP, along with the other epithelial cell-derived cytokines IL-25 and IL-33, play pivotal roles in the development of allergic diseases, including asthma, AD and food hypersensitivity161. (FIG. 3), TSLP was initially shown to promote allergic responses by acting on DCs and inducing their expression of OX40 ligand (OX40L), CD80 and CD86, thereby promoting the differentiation of naive CD4+ T cells into pro-inflammatory Th2 cells that produce IL-4, IL-5, IL-13 and TNF-α. Subsequently, it was shown that TSLP-activated DCs also stimulate naive CD4+ T cells to differentiate into T follicular helper cells (defined by expression of CXCR5, IL-21, CXCL13 and BCL6), which can induce IgG and IgE secretion by memory B cells162, linking TSLP to IgE production in allergy. TSLP also promotes the release of T H2 cytokines and chemokines by eosinophils, mast cells and macrophages163,164. TSLP acting on basophils has been linked to the development of an IgE-independent mouse model of the food allergy-associated inflammatory disease eosinophilic oesophagitis165, although the importance of TSLP in basophil response remains unclear166,167. A DC–T cell–basophil cascade has been implicated in TSLP-driven type 2 immunity, whereby DCs activated by TSLP prime CD4+ T cells via OX40L to produce IL-3, which then leads to the recruitment of basophils and the production of IL-4 (REF.168). DCs themselves were reported to produce TSLP upon TLR stimulation, suggesting that TSLP might also act in an autocrine manner to amplify the T H2 cell response169.

Besides indirect effects of TSLP on CD4+ T cells, this cytokine also acts directly on CD4+ T cells148,155 and is required for their full proliferation in response to antigen as well as for the formation of memory T H2 cells and recall responses170,171. Mice lacking TSLPR (Grf2-/- mice) exhibit strong T H1 cell responses associated with high levels of IL-12, IFNγ and IgG2a, but low levels of IL-4, IL-5, IL-10, IL-13 and IgE. Grf2-/- CD4+ T cells proliferate only weakly to antigen172, and Grf2-/- mice do not develop ovalbumin (OVA)-induced lung inflammation unless supplemented with wild-type CD4+ T cells173. Interestingly, TSLP has different actions in models of airway inflammation depending on whether it is acting on innate or adaptive immune cells. A recent study used cell lineage-specific TSLPR-deficient mice to dissect the cell-intrinsic requirements for TSLP responsiveness in...
type 2 inflammation in the lungs. In a papain-induced model of airway inflammation, TSLP directly stimulated ILC2s but not basophils to enhance type 2 inflammation, whereas in OVA-induced airway inflammation, TSLP principally acted on DCs and CD4+ T cells, and not basophils or ILC2s, during the sensitization phase. Thus, TSLP has broad actions related to allergic diseases and, as discussed below, there is genetic predisposition related to TSLP in the development of AD and asthma, with key roles of this cytokine in skin and lung linked to pathogenesis in these diseases.

Atopic dermatitis. AD is a heterogeneous disease with multifactorial pathogenesis, including genetic predisposition and environmental and immunological factors. Genetic variants of TSLP affect the severity and persistence of this disease. For example, homozygosity of the TSLP variant rs1898671 is associated with a reduced risk of AD in children, whereas the variants rs2289278 and rs1837253 increase the risk for atopic diseases. TSLP is highly expressed in human AD lesions and its overexpression in mouse skin results in AD-like disease. DNA demethylation of a specific region of the TSLP promoter augments expression of TSLP in skin lesions of patients with AD and diminishes expression of filaggrin, a protein in which loss-of-function mutations are associated with epidermal barrier defects and more severe AD. TSLP expression in human keratinocytes and nasal epithelial cells may also be increased by histamine (a key mediator of allergic diseases) binding to histamine H4 receptor, suggesting a role for histamine in TSLP-dependent atopic disease.

Asthma. The prevalence of asthma varies among ethnic groups, and 35–80% of asthma may result from genetic variation, with childhood-onset asthma associated with TSLP SNP rs1837253. In mouse models, overexpression of TSLP in the lungs results in severe airway inflammation and airway hyper-responsiveness (AHR). Additionally, patients with asthma, especially those with severe asthma, have increased levels of TSLP and T_{H2} cytokines in the airways, with TSLP levels predictive of future asthma exacerbation. Biopsy sections from individuals with mild atopic asthma show that allergen challenge increases IL-25, IL-33 and TSLP levels in the bronchial epithelium and submucosa, and...
levels of these cytokines correlate with the extent of airway obstruction\(^1\). In addition, patients with eosinophilic asthma have raised levels of IL-4, which not only increases the permeability of airway epithelial cells by reducing expression of filaggrin and adhesion molecules, including E-cadherin, but also increases levels of IL-33 and TSLP, which further enhance the T\(_{H2}\) inflammatory response\(^1\).

Individuals with one atopic disease often have other atopic diseases and progress to allergic diseases, including asthma or rhinitis, which is known as the atopic march\(^2\). Early therapeutic intervention in individuals with AD who are at risk and a better understanding of the mechanisms triggering asthma may help to prevent asthma and the atopic march. TSLP is involved in both AD and asthma, and recent studies indicate its role in the atopic march\(^2\). Consistent with this idea, skin-derived TSLP promotes allergen-sensitive asthma in animal models. Interventions in animal models that induce the systemic release of TSLP, such as keratinocyte-specific deletion of the DNA-binding protein RBP-J (a mediator of Notch signalling important for epidermal differentiation) or topical application of the vitamin D analogue MC903, cause AHR upon allergen challenge in the lungs\(^3\). These studies are consistent with the hypothesis that skin barrier defects, associated with TSLP production, could trigger systemic atopy. Moreover, when mice are infected with RSV as neonates, upon reinfection, they exhibit enhanced AHR due to TSLP expression, with OX40L expression, lung DC migration and T\(_{H2}\) cell polarization, leading to allergic responses later in life\(^4\). Correspondingly, more than 40% of infants who have severe bronchitis or respiratory tract infections will develop asthma in childhood\(^5\). Persistence of an altered immune phenotype in male mice triggered by early infection of RSV and the associated production of TSLP is consistent with the fact that boys are more vulnerable to RSV infection and the onset of asthma\(^6\). Interestingly, TSLP induced by RSV infection alters chromatin structure in DCs and promotes the expression of epigenetic enzymes such as lysine-specific demethylase 6A, which regulates transcriptional programmes mediated by interferon-regulatory factor 4 and STAT3 and leads to a pathogenic gene programme\(^7\).

Importantly, the key pathogenic role for TSLP in asthma is supported by the finding that a human monoclonal antibody specific for TSLP, known as tezepelumab (Tezspire), which blocks its binding to TSLPR and its biological actions, reduces eosinophilic inflammation and AHR and lowers disease exacerbation in patients with asthma\(^8\). In a phase IIb trial (the PATHWAY trial; NCT02054130), tezepelumab reduced exacerbations by up to 71% and improved lung function, asthma control and health-related quality of life compared with placebo\(^9\). In a phase III multicentre, randomised, double-blind, placebo-controlled trial (the NAVIGATOR trial; NCT03347279), the rate of asthma exacerbations was significantly lower with tezepelumab than with placebo in patients with severe, uncontrolled asthma, including those with low blood eosinophil counts at baseline. Lung function was improved and exacerbations were reduced, with less hospitalization and emergency room visits for patients treated with tezepelumab\(^1\). Accordingly, in 2021, the US FDA approved tezepelumab for the treatment of severe asthma. Several clinical trials with tezepelumab for allergic diseases and chronic inflammatory diseases are ongoing (TABLE 1). Moreover, a humanized Fc-disabled IgG1 monoclonal antibody against IL-7Ra, which potentially blocks both TSLP and IL-7, is being evaluated for the treatment of autoimmune diseases\(^10\). However, in contrast to its effect on asthma, tezepelumab did not achieve a statistically significant improvement in AD in a phase IIa trial (NCT03809663).

**TSLP and host defence against infection**

**Staphylococcus aureus infection.** S. aureus can cause serious skin infections in healthy individuals, and these infections are becoming more problematic by the expansion of strains with antibiotic resistance, including methicillin-resistant S. aureus (MRSA). As mentioned, TSLP is highly expressed at barrier surfaces, including skin, and has been shown to enhance neutrophil-mediated killing of MRSA with direct actions of TSLP on neutrophils\(^1\). TSLP also enhances the killing of Streptococcus pyogenes, another important cause of skin infections. TSLP mediates its antibacterial effect by directly engaging the complement C5 system to modulate the production of reactive oxygen species by neutrophils and thereby increases MRSA killing in a neutrophil-dependent and complement-dependent manner\(^1\). **Helminth infection.** TSLP affects the function of immune cells, tissue inflammation and host protective immunity following helminth infection. Use of

---

**TABLE 1**

| TSLP and IL-7Ralpha-mediated signalling |
|-----------------------------------------|
| TSLP binds to a receptor comprising TSLP receptor (TSLPR) and IL-7 receptor α-chain (IL-7Ra), which are both type 1 membrane receptor proteins. TSLP binding activates JAK1, JAK2 and signal transducer and activator of transcription 5A and 5B (STAT5A and STAT5B) to promote the transcription of target genes, including the type 2 cytokines IL-4, IL-5 and IL-9. |
monoclonal antibody-mediated neutralization of TSLP or deletion of Crlf2 in normally resistant mice showed that TSLP is necessary for the development of protective T_h 2 cell responses after infection with the helminth Trichuris muris. The absence of TSLP signalling led to increased expression of IL-12p40, IFNγ and IL-17A, leading to severe intestinal inflammation. Treatment of Crlf2−/− mice with a neutralizing monoclonal antibody to IL-12p40 restored T_h 2 cytokine production and attenuated IFNγ production, rescuing host protective immunity. It has also been shown that excretory–secretory products from Heligmosomoides polygyrus and Nippostrongylus brasiliensis suppress the production of IL-12p40 by DCs, bypassing the need for TSLP.

ILC2s are also important in antihelminth immunity through their production of T_h 2 cytokines. Recent studies show that neurotransmitters and neuropeptides, including catecholamines, nicotine, acetylcholine, neuropepin U, vasoactive intestinal peptide and calcitonin gene-related peptide, can regulate ILC2 responses, highlighting an association between the nervous system and innate immunity at barrier surfaces. Activated ILC2s express increased levels of choline acetyltransferase, the enzyme responsible for the biosynthesis of acetylcholine, after infection with N. brasiliensis or after treatment with alarmins or cytokines, including IL-25, IL-33 and TSLP. Thus, TSLP can stimulate ILC2s to augment the production of choline acetyltransferase as a mechanism for promoting host defence to helminth infection.

**Viral infection.** As discussed above, the role of TSLP in T_h 2-type responses has been extensively studied, but its role in CD8+ T cell responses is less well characterized. Influenza virus infection is a major cause of respiratory disease, with substantial morbidity and mortality, accounting for approximately 500,000 deaths per year. During influenza virus infection or administration of poly(I:C), which mimics viral double-stranded RNA, pulmonary epithelial cells produce pro-inflammatory cytokines, including TSLP, that alter the immune response in the lungs. TSLP supports the survival of cytotoxic T cells both directly and indirectly through the activation of DCs. However, there are conflicting reports about the effect of TSLP on CD8+ T cells.
| Trial                                                                 | Status           | Trial participants                                    | Interventions                                      | Result                                                                 | Clinical trials identifier and Refs |
|----------------------------------------------------------------------|------------------|-------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------|-----------------------------------|
| Healthy individuals                                                   |                  |                                                      |                                                    |                                                                      |                                   |
| Pharmacokinetics of tezepelumab delivered by APFS, AI, or vial and syringe, phase I | Completed Dec. 2019 | Healthy adult individuals | Tezepelumab | NA | NCT03989544 |
| Tezepelumab pharmacokinetics, phase I                                 | Completed Oct. 2020 | Healthy Chinese individuals | Tezepelumab versus placebo | NA | NCT04362410 |
| Asthma                                                               |                  |                                                      |                                                    |                                                                      |                                   |
| Tezepelumab home use, phase III                                      | Completed Jun. 2020 | Adolescents and adults with severe asthma | Tezepelumab administered by APFS versus AI | APFS and AI were functional and reliable, and performed equally well at home and in the clinic | NCT03968978 (REF.185) |
| Efficacy and safety of tezepelumab in reducing oral corticosteroid use, phase III (SOURCE) | Completed Sep. 2020 | Adults with oral corticosteroid-dependent asthma | Tezepelumab versus placebo | NA | NCT03406078 (REF.186) |
| Efficacy and safety of tezepelumab, phase III (NAVIGATOR)            | Completed Nov. 2020 | Adults and adolescents with severe uncontrolled asthma | Tezepelumab versus placebo | Tezepelumab associated with fewer exacerbations and better lung function, asthma control, and health-related quality of life than placebo | NCT03347279 (REF.187) |
| Effects of tezepelumab on airway inflammation, phase II (CASCADE)    | Completed Nov. 2020 | Adults with uncontrolled asthma and other hypersensitivity airway diseases | Tezepelumab versus placebo | Tezepelumab improved clinical outcomes in patients with asthma, with reduction of eosinophilic airway inflammation; it also reduced hyperresponsiveness to mannitol | NCT03688074 (REFS.188,189) |
| Long-term safety of tezepelumab, phase III                           | Completed Mar. 2021 | Japanese adults and adolescents with inadequately controlled severe asthma | Tezepelumab | NA | NCT04048343 |
| Pharmacokinetics of tezepelumab, phase I                             | Recruiting       | Children with asthma | Tezepelumab | NA | NCT04673630 |
| Efficacy and safety of tezepelumab, phase III                        | Recruiting       | Adults with severe uncontrolled asthma | Tezepelumab versus placebo | NA | NCT03927157 |
| Extension study on safety and tolerability of tezepelumab, phase III (DESTINATION) | Active, not recruiting | Adults and adolescents with severe, uncontrolled asthma | Tezepelumab versus placebo | NA | NCT03706079 |
| Effect of tezepelumab on the immune response to influenza vaccination, phase III (VECTOR) | Active, not recruiting | Adolescents and young adults with moderate to severe asthma | Tezepelumab versus placebo | NA | NCT05062759 |
| Effect of tezepelumab on airway structure and function, phase III (WAYFINDER) | Not yet recruiting | Adults with uncontrolled moderate-to-severe asthma | Tezepelumab versus placebo | NA | NCT05280418 |
| Efficacy and safety of tezepelumab in reducing oral corticosteroid use, phase III | Not yet recruiting | Adults with severe asthma on high-dose corticosteroids | Tezepelumab | NA | NCT05274815 |
| Other allergic and chronic inflammatory diseases                      |                  |                                                      |                                                    |                                                                      |                                   |
| Safety and efficacy of tezepelumab, phase II                          | Terminated       | Patients with moderate-to-severe atopic dermatitis | Tezepelumab versus placebo | Tezepelumab did not reach the targeted efficacy level pre-established for this patient population | NCT03809663 |
| Effect of tezepelumab in COPD exacerbation, phase II                 | Recruiting       | Patients with moderate-to-very-severe COPD | Tezepelumab versus placebo | NA | NCT04039113 |
T cells during primary influenza virus infection\(^9,10\). One study found that IL-7 is necessary for generating robust influenza A virus-specific CD4\(^+\) and CD8\(^+\) T cell responses but TSLP did not affect the control of primary infection nor viral-specific CD8\(^+\) T cell responses\(^9\). Another study concluded that TSLP is required for the expansion and activation of virus-specific effector CD8\(^+\) T cells in the lungs during primary infection but that this results from TSLP-induced IL-15 production by CD11b\(^+\) inflammatory DCs\(^9\) rather than from direct effects on CD8\(^+\) T cells. Other studies used an adoptive co-transfer model of wild-type and Crlf2\(^{-/-}\) T cell receptor-transgenic cells. After infection with influenza virus, selective loss of TSLPR signalling in the antiviral CD8\(^+\) T cells decreased their proliferation and accumulation in the respiratory tract, indicating that TSLP enhances primary CD8\(^+\) T cell responses\(^8\). However, TSLP was also reported to act directly on CD8\(^+\) T cells to limit their responses during primary infection, with more virus-specific Crlf2\(^{-/-}\) cells than virus-specific wild-type cells\(^9\). Conflicting reports on the roles of TSLP in CD8\(^+\) T cell responses during primary influenza virus infection may, in part, be owing to differences in experimental models (that is, direct studies in Crlf2\(^{-/-}\) mice versus co-transfer models) and different influenza virus strains (that is, X31 versus PR8). Recently, the role of TSLP in memory CD8\(^+\) T cells was studied using a competitive adoptive co-transfer model of wild-type and Crlf2\(^{-/-}\) P14 T cells (T cell receptor-transgenic CD8\(^+\) T cells specific for lymphocytic choriomeningitis virus gp33)\(^3\). TSLP did not affect the development or maintenance of memory CD8\(^+\) T cells after primary influenza virus infection but it limited memory CD8\(^+\) T cell recall responses, with higher responses by Crlf2\(^{-/-}\) CD8\(^+\) T cells following secondary influenza virus infection.

A recent study revealed a previously unknown pathway in antiviral defence involving TSLP. Influenza virus-induced release of IFN\(\lambda\) can trigger the synthesis of TSLP by airway microfold cells in the upper airway overlying bronchus-associated lymphoid tissue, which stimulates CD103\(^+\) migratory DCs and promotes antigen-dependent germinal centre reactions in draining lymph nodes\(^11\). The IFN\(\lambda\)–TSLP axis mediated the production of virus-specific IgG1 and IgA after immunization with influenza virus vaccines, leading to enhanced resistance against influenza virus infection. TSLP also suppressed the expression of influenza virus-induced genes related to cell cycle, apoptosis or protection from virus; thus, modulating TSLP might affect the control of influenza virus infection and have therapeutic potential.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), is associated with cytokine release syndrome, which is characterized by T\(_{h}1\) and T\(_{h}2\) cell-associated inflammation. TSLP production is also induced in patients with COVID-19, with high TSLP levels associated with greater severity of disease\(^12,13\). Thus, TSLP seems to feed into pathological pathways and may be a useful target for therapeutic strategies to inhibit T\(_{h}2\) cell responses in patients with COVID-19.

Besides respiratory viruses, several other viral infections have been reported to induce TSLP production by epithelial cells, including vesicular stomatitis virus\(^10\), hepatitis C virus\(^11\), immunodefiency viruses (HIV and SIV)\(^10\) and human papillomavirus (HPV)\(^17\), highlighting the role of TSLP as an alarmin. Certain strains of HPV cause cervical cancer, the progression of which is associated with a marked increase of serum IgE levels\(^14\). Infection with these high-risk HPV's correlated with increased production of TSLP by epithelial cells in cervical cancer, leading to a T\(_{h}2\) cell response and immunosuppressive microenvironme\(\text{nt}^1\). More recently, it was shown that expression of HPV oncoprotein in skin drove the onset of AD-like pathology that was associated with the secretion of high levels of TSLP and increased numbers of ILC2s\(^19\).

In summary, TSLP functions in a wide range of infectious diseases other than helminth infections, including both bacterial and viral infections. The reported roles of TSLP in viral infection are still controversial given differing results depending on the specific model system used. The roles of TSLP induced by microbial infection may potentially contribute to the exacerbation of allergic diseases, such as asthma, in these settings.

**TSLP and cancer**

Over the past decade, roles of TSLP in the control and onset of a variety of cancers, both solid tumours and leukaemias, have been elucidated, revealing that TSLP has both pro-tumour and antitumour effects, depending on the context and type of tumour [Fig. 4].

**Acute lymphocytic leukaemia.** Philadelphia chromosome-like acute lymphoblastic leukaemia (ALL) is commonly associated with genetic alterations affecting CRLF2, which encodes TSLPR\(^12\). In a large cohort of patients with T cell ALL, overexpression of CRLF2, causing
activation of the JAK–STAT pathway, was associated with poor prognosis. Indeed, targeting of JAKs, for example, by proteolysis-targeting chimeras (PROTACs) directed against JAKs, has been shown to be a potent treatment for CRLF2-rearranged ALL. In Down syndrome-associated ALL, in which there is a high rate of rearrangement of CRLF2, TSLP increases binding of the tyrosine phosphatase PTPN11 to RAS, resulting in RAS protein activation, which promotes ALL cell growth.

**Solid tumours.** Immune responses in the tumour microenvironment are affected by factors produced by tumour cells and tumour-associated cells, including cancer-associated fibroblasts (CAFs). TSLP secretion by CAFs or tumour cells promotes predominantly type 2 inflammation in the tumour microenvironment, mostly via DC activation and upregulation of OX40L, CD80 and CD86 expression following TSLPR-induced phosphorylation of STAT5. A detrimental role for TSLP in cancer was first demonstrated in pancreatic cancer and breast cancer. Patients with pancreatic cancer in which GATA3+ TH2 cells were dominant had a worse prognosis than patients with T-bet+ T,8, cell infiltrates. TSLP was secreted by CAFs when activated with tumour-derived pro-inflammatory cytokines, including TNF and IL-1β, and these TSLP-containing supernatants upregulated the expression of TSLPR on myeloid DCs, which secreted TH2 cell-attracting chemokines and promoted TH2 cell polarization of CD4+ T cells. Interestingly, tumour-released IL-1α, IL-1β and apoptosis-associated speck-like protein containing a CARD (ASC) augment the secretion of TSLP by CAFs, suggesting that targeting these cells might decrease type 2 inflammation and tumour growth. Moreover, basophil recruitment into draining lymph nodes was associated with TH2 cell polarization in patients with pancreatic cancer, and this was associated with a worse prognosis.

In breast cancer, cancer cells can produce TSLP, and this is associated with the presence of OX40L+ DCs in primary breast tumour infiltrates. These DCs promote the development of TH2 cells producing IL-13 and TNF in vitro, and blocking the actions of TSLP or OX40L lowered IL-13 production and reduced tumour growth in a xenograft model. Interestingly, the release of IL-1β by DCs is necessary for TSLP production by breast cancer cells. The role of TSLP in the growth and metastasis of tumours is illustrated in Fig. 4.
of breast cancer was also studied in an orthotopic mouse model using 4T1 cells, which are derived from a BALB/c breast ductal carcinoma. 4T1 cells produce TSLP, and the level of TSLP production correlated with the metastatic potential of different 4T1 clones. Transplantation of 4T1 cells into C57BL/6 mice was associated with reduced T<sub>1</sub>,2 cytokines and decreased tumour growth. Thus, the delayed tumour development in C57BL/6 mice was due to defective CD4<sup>+</sup> T cell responses, consistent with TSLP promoting a T<sub>1</sub>,2-type tumour microenvironment that supports the development and growth of metastatic breast cancer.

Conversely, other studies have suggested that TSLP can have tumour-suppressive activity. One study found that genetic or chemical induction of TSLP at a distant site led to robust antitumour immunity against spontaneous breast carcinogenesis in mice, mediated by T<sub>1</sub>,2 cells. However, in this study, breast cancer-prone PyMT<sup>+</sup> mice, in which cancer is driven by mammary-specific polyomavirus middle T antigen overexpression, were crossed with mice that overexpress TSLP in their skin, which not only induced TSLP production but also caused systemic inflammation, making it possible that either TSLP or the inflammatory process or both could contribute to the antitumour effect. Another report found that TSLP was produced in fewer than 10% of breast cancers, with undetectable TSLPR expression on haematopoietic cells or stromal cells within the primary tumour microenvironment, and another study demonstrated that the expression of TSLP was higher in normal tissue than in breast cancer tissue and that TSLP expression was associated with the increased survival of patients with breast cancer. Thus, the role of TSLP may be context and/or tumour specific.

Reports regarding the role of TSLP in skin cancer have also differed. Groups have reported an antitumour role for TSLP in skin carcinogenesis in mice with clonal loss of Notch signalling in skin. In this model, high levels of TSLP released by barrier-defective skin caused severe inflammation, resulting in gradual elimination of Notch-deficient epidermal clones and resistance to skin tumorigenesis. CD4<sup>+</sup> T cells are required to mediate these effects of TSLP, analogous to the breast cancer models reported above. Another group reported that cutaneous T cell lymphoma lesions in advanced stages exhibited mainly T<sub>1</sub>,2 cytokines and chemokines. In vitro and ex vivo cell lines and peripheral blood mononuclear cells from patients with cutaneous T cell lymphoma expressed TSLPR and produced higher levels of IL-4 and IL-13 in response to TSLP. High TSLP expression is a poor prognostic marker for gastric cancer and oropharyngeal squamous cell carcinoma, indicating that TSLP and inflammation can exert pro-tumour activity in these settings.

In addition to the T<sub>1</sub>,2-dependent roles of TSLP in cancer discussed above, T<sub>1</sub>,2 cell-independent effects of TSLP have been reported. Depending on the context, TSLP-induced signalling in tumour cells can lead to apoptosis, proliferation and remodelling of pro-angiogenic gene signatures. In breast cancer, tumour-derived IL-1α can induce expression of TSLP by tumour-infiltrating myeloid cells, which can induce expression of the anti-apoptotic molecules BCL-2 and BCL-XL and promote tumour cell survival. Consistent with this, TSLP could promote metastasis. Moreover, in another study, tumour cell-derived TSLP increased the invasive and angiogenic gene expression profile of alveolar macrophages, whereas depleting these cells significantly reduced the growth of TSLP-expressing tumour cells. TSLP could downregulate expression of the bone marrow-retention receptors CXCR4 and VLA4 in B cell precursors, increasing cellular motility, survival and proliferation. These pre-B cells were induced by tumour cells to differentiate into regulatory B cells, which down-modulated antitumour immunity and promoted lung metastases. Thus, lower TSLP production by cancer cells or lower TSLPR expression by B cells could decrease the accumulation of peripheral pre-B cells and potentially diminish cancer metastasis, suggesting that targeting TSLP might have therapeutic benefit.

A tumour-promoting function for TSLP was also described in lung cancer. Expression of TSLP protein in tumours was significantly higher than in benign lesions and non-cancer lung tissue, and the prevalence of regulatory T cells in the tumour microenvironment correlated with the expression of TSLP in lung cancer. Furthermore, TSLP and TSLPR are expressed in macrophages purified from the lungs of patients with lung cancer, with a presumed pro-tumorigenic role for TSLP.

T<sub>1</sub>,2 cell-independent pro-tumour roles of TSLP in cervical cancer, gastric cancer and ovarian cancer have also been reported. TSLP was secreted from cervical cancer cells by hypoxia, inducing the release of chemokine CCL17, which then recruits eosinophils, leading to increased proliferation and diminished apoptosis of tumour cells through the upregulation of Ki-67 and BCL-2, respectively, and indirectly stimulates angiogenesis by inducing the production of IL-8 and vascular endothelial growth factor. TSLP also promoted the proliferation and invasion of cervical cancer cells by downregulating microRNA-132, the expression of which was lower in cervical cancer than in non-cancerous tissues. Human gastric cancer cells also produce TSLP, and its expression correlated with metastasis. Moreover, in ovarian cancer, higher TSLP expression was associated with worse prognosis.

Increased expression of TSLP and TSLPR has also been reported in colorectal cancer, and the TSLP SNP rs10043985 was shown to be a biomarker for an increased risk of colorectal cancer in the Saudi population. Nevertheless, antitumour effects of TSLP in colorectal cancer have also been reported, with decreased TSLP levels in tumour than in adjacent tissue and TSLP levels negatively correlated with the clinical staging score. In this disease, TSLP was shown to activate INK and MAPKp38 and promote apoptosis mainly through the extrinsic pathway. Analogous to this antitumour effect in colon carcinoma, TSLP can also prevent skin carcinogenesis through a T<sub>1</sub>,2 cell-independent mechanism. Using loss-of-function and gain-of-function mouse models for Notch and WNT signalling, it was shown that TSLP-mediated inflammation protects against cutaneous carcinogenesis, and this was mainly mediated by...
actions of TSLP on T cells. Deleting TSLPR resulted in the accumulation of CD11b+ GR1+ myeloid cells that promoted tumour growth by secreting WNT ligands and activating the WNT–β-catenin pathway in the neighbouring epithelium, whereas deleting β-catenin prevented the recruitment of CD11b+ GR1+ myeloid cells and carcinogenesis in skin, suggesting that the epithelial population initiates tumour development.

Thus, TSLP has been associated with promoting or reducing cancer in a range of malignancies, suggesting context-dependent effects for this cytokine in malignant disease.

**TSLP in fat metabolism**

Obesity increases the risk of numerous diseases, including hyperlipidaemia, diabetes mellitus, certain cancers, fatty liver and cardiovascular diseases. It has been shown that chronic, low-grade inflammation of adipose tissue increases type 2 immune cells, including ILC2s and eosinophils133–135. These cells increase the metabolic rate by promoting adipose tissue beiging and upregulating thermogenic energy consumption156–160. Regulatory T cells suppress the inflammatory state of adipose tissue, resulting in improved insulin resistance151,162. Recently, TSLP was reported to play a role in fat metabolism, selectively promoting the loss of white adipose tissue, which protected against obesity both in genetic models and diet-induced obesity as well as in insulin resistance and non-alcoholic steatohepatitis134. Mice with augmented levels of TSLP had greasy hair owing to the excessive loss of lipids through skin as sebum as well as elevated triglycerides, free fatty acids, cholesterol esters, free cholesterol and wax esters, which resulted from the TSLP-mediated induction of sebum and sebum-associated antimicrobial peptide release by skin CD4+ or CD8+ T cells. Ablating TSLPR signalling or deleting T cells diminished the secretion of sebum and antimicrobial peptides with altered skin homeostasis, thus identifying a previously unappreciated role for TSLP in adaptive immunity. Given that ILCs exposed to TSLP in skin negatively regulate sebaceous gland size and lipid content14, it is possible that ILCs and T cells regulated by TSLP might have opposing roles in controlling sebum secretion.

TSLP is also expressed in human adipose tissue and is produced by differentiated adipocytes in response to thyroid-stimulating hormone, IL-1β and TNFα. In humans, the level of TSLP in the serum was related to the basal metabolic index165. Obesity increases the risk of asthma by increasing bronchial hyperreactivity, leading to worse control of asthma, and obese patients with metabolic dysfunction have to face more severe asthma166. Thus, TSLP produced from more than one source, such as either adipocytes or epithelial cells, can potentially affect the severity of asthma by regulating immune cells, as discussed above.

**TSLP in chronic inflammatory diseases**

Emerging evidence indicates that TSLP has roles in chronic inflammation and autoimmune diseases that are independent of Th2 cells, highlighting its role beyond the Th2-type response. These findings indicate a wide range of effects for TSLP, potentially in a wide range of human diseases.

**Chronic obstructive pulmonary disease.** Chronic obstructive pulmonary disease (COPD) is generally associated with Th1 cells, macrophages and neutrophils, whereas asthma is primarily associated with Th2 cells, eosinophils and/or mast cells. Despite being a predominantly Th1-cell-associated disease, TSLP mRNA and protein levels were increased in the bronchial epithelium of COPD compared with controls167. Factors known to exacerbate COPD, including respiratory viruses22, double-stranded RNA19,167, cigarette smoke extracts168,169 and pro-inflammatory cytokines that activate NF-kB16,170, stimulate the production of TSLP in patients with COPD, suggesting involvement of TSLP in the development and/or exacerbation of COPD, and thus that TSLP can affect lung pathophysiology in situations beyond Th2-related asthma.

**Idiopathic pulmonary fibrosis.** Idiopathic pulmonary fibrosis (IPF) is a severe, progressive and ultimately fatal disorder, characterized by interstitial fibrosis of the lungs of unknown aetiology. TSLP and TSLPR are overexpressed in the lungs of patients with IPF171, and TSLP is increased in bronchoalveolar lavage and serum from patients with IPF171,172. The observation that TSLP levels decreased in the lungs of patients treated with anti-fibrotic therapy but not in individuals with progressive disease, supports a possible contribution of TSLP to pro-fibrotic type 2 immune responses in IPF172. However, more studies are required to fully understand the role of TSLP in the aetiology and progression of this disease.

**Rheumatoid arthritis.** Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder that affects the joints, which are characterized by chronic synovitis — predominantly associated with Th17-type and Th17-type inflammation. Recently, the relationship between TSLP gene polymorphisms and RA susceptibility risk was demonstrated, with SNPs at rs11466749, rs11466750 and rs10073816 of TSLP leading to increased levels of TSLP associated with susceptibility to RA173. TSLP and TNF levels in the synovial fluid and plasma from patients with RA are significantly higher than in control patients173–175. Interestingly, TNF can induce TSLP production by synovial fibroblasts not only from patients with RA but also from control patients, suggesting that TSLP production by synovial fibroblasts is not specific to RA and is augmented by TNFα16,174. Correspondingly, blockade of TSLP activity by anti-TSLP neutralizing antibodies ameliorated TNF-dependent experimental arthritis injury in mice induced by anti-type II collagen antibodies, suggesting a role for TSLP in the pathogenesis of RA. Moreover, in collagen-induced arthritis in mice, TSLP injection significantly exacerbated the severity of arthritis with activation of T cells leading to joint destruction176. Mast cells and macrophages in the RA synovium have been suggested to contribute to TSLP levels in the RA joint172–175. In the collagen-induced arthritis model, which is not a classic Th2 cell-associated disease, the effector inflammatory phase of arthritis depends on
Conclusions

TSLP is a pleiotropic cytokine with pleiotropic actions. Although the original role for TSLP as an initiator of type 2 inflammatory responses is well established, the biology and actions of this cytokine extend much further as described in this Review. TSLP is now implicated in viral infections, including influenza virus and SARS-CoV-2 infections, cancer, chronic inflammation and fat metabolism. TSLP appears to often be deleterious (for example, in allergic disease) but, in host defence, it may be protective (for example, in S. aureus or helminth infections) and, in cancer, there are a range of studies that indicate that TSLP can be beneficial or deleterious, depending on the malignancy and biological context. It is possible that TSLP has more than a single effect. Obviously, more studies are needed to rigorously define when the beneficial versus deleterious actions of TSLP occur, including studies and, eventually, clinical trials testing the effect of blocking TSLP. Indeed, the application of anti-TSLP-based therapy may hold promise beyond allergic diseases, an area of ongoing investigation. Moreover, there may be clinical settings in which augmenting, rather than blocking, TSLP might be desirable. Since the discovery of TSLP as a factor that could stimulate B cells, there have been huge advances, but the full significance of this cytokine and the range of therapeutic manipulations are still evolving. Collectively, the roles of TSLP in a range of diseases and in cellular homeostasis indicate its potential as a predictive marker of disease severity and as a therapeutic target.

Published online 1 June 2022
Siracusa, M. C. et al. TSLP promotes interleukin-3
Fornasa, G. et al. Dichotomy of short and long thymic
Mann Mem, E. et al. Expression of the short isoform of
Cavene, M. C. et al. TSLP signaling in CD4+ T cells programs a pathogenic T helper 2 cell state.
Van Dyken, S. J. et al. A hericogon regulatates type 2 immunity. Nat. Immunol. 17, 1581–1586 (2016).
Ochiai, S. et al. Thymic stromal lymphopoietin drives the development of IL-17 Th2 cells. Proc. Natl Acad. Sci. USA 115, 9438–9443 (2018).
Dong, H. et al. Distinct roles of short and long thymic stromal lymphopoietin in house dust mite-induced asthmatic airway epithelial barrier disruption. Sci. Rep. 6, 39559 (2016).
Varricchi, G. et al. Thymic stromal lymphopoietin isoforms, inflammatory disorders, and cancer. Front. Immunol. 9, 1775–1781 (2018).
Engelbert, M. G., Thijssen, P., de Jong, A. A. et al. Thymic stromal lymphopoietin and IL-7 use two different mechanisms for the induction of CD4+ Th2 cytokine profile through thymic stromal lymphopoietin in allergic asthma. J. Allergy Clin. Immunol. 129, 191–199 (2012).
Corren, J. et al. Tzeepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma in PATHWNAV. Allergy Asthma Immunol. 126, 187–193 (2021).
Corren, J. et al. Tzeepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma. N. Engl. J. Med. 377, 956–964 (2017).
Menozzi-Gonzalez, A. et al. TSLP-driven chromatin remodeling and latent systemic immunity after neonatal respiratory viral infection. J. Immunol. 206, 1315–1328 (2021).
Diver, S. et al. Effect of tezepelumab on airway inflammatory cells, remodeling, and hyperresponsiveness in subjects with moderate-to-severe uncontrolled asthma (CASCADA): a double-blind, randomized, placebo-controlled, phase 2b trial. Lancet Respir. Med. 9, 1295–1312 (2021).
Corren, J. et al. Tzeepelumab in adults with uncontrolled asthma. Nature Rev. Immunol. 129, 1005–1013 (2013).
Murrison, L. B. et al. Genome-wide association study of asthma and atopy in British twins. Nature Genet. 45, 1038–1044 (2013).
Rochman, Y. et al. Thymic stromal lymphopoietin (TSLP)-mediated dermal inflammation aggravates experimental asthma. Mucosal Immunol. 5, 342–351 (2012).
Demeini, S., Morimoto, M., Holtzman, M. J. & Kopian, R. Skin-derived TSLP triggers progression from epithelial barrier defects to asthma. PLoS Biol. 7, e1000607 (2009).
Zhang, Z. et al. Thymic stromal lymphopoietin overproduced by keratinocytes in mouse skin aggravates experimental asthma. Proc. Natl Acad. Sci. USA 106, 1536–1541 (2009).
Tsurud, S. et al. Respiratory viral infection virus provokes airway remodelling in allergen-exposed mice in absence of prior allergen sensitization. Clin. Exp. Allergy 38, 1016–1029 (2008).
Barnier, I. et al. Distinct finding of asthma after severe respiratory syncytial virus bronchiolitis. J. Allergy Clin. Immunol. 130, 91–100 e3 (2012).
Malinca, C. A. et al. Salbutamol treatment induced immune alterations following early-life RSV infection leads to enhanced allergic disease. Mucosal Immunol. 13, 1193–1279 (2020).
Malinca, C. A. et al. TSLP-driven chromatin remodeling and latent systemic immunity after neonatal respiratory viral infection. J. Immunol. 206, 1315–1328 (2021).
Diver, S. et al. Effect of tezepelumab on airway inflammatory cells, remodeling, and hyperresponsiveness in subjects with moderate-to-severe uncontrolled asthma (CASCADA): a double-blind, randomized, placebo-controlled, phase 2b trial. Lancet Respir. Med. 9, 1295–1312 (2021).
Corren, J. et al. Tzeepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma in PATHWNAV. Allergy Asthma Immunol. 126, 187–193 (2021).
Corren, J. et al. Tzeepelumab in adults with uncontrolled asthma. N. Engl. J. Med. 377, 956–964 (2017).
Menozzi-Gonzalez, A. et al. TSLP-driven chromatin remodeling and latent systemic immunity after neonatal respiratory viral infection. J. Immunol. 206, 1315–1328 (2021).
Diver, S. et al. Effect of tezepelumab on airway inflammatory cells, remodeling, and hyperresponsiveness in subjects with moderate-to-severe uncontrolled asthma (CASCADA): a double-blind, randomized, placebo-controlled, phase 2 trial. Lancet Respir. Med. 9, 1295–1312 (2021).
Corren, J. et al. Tzeepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma. N. Engl. J. Med. 384, 1800–1809 (2021).
This study shows that tezepelumab lowered exacerbation frequency and led to improved lung function, asthma control and quality of life.
Ellis, J. et al. Anti-IgE receptor alpha monoclonal antibody (GSK2618960) in chronic, randomized, double-blind, placebo-controlled study. Br. J. Clin. Pharmacol. 85, 304–315 (2019).
Taylor, B. C. et al. TSLP and IL-25 in skin lesions of patients with atopic dermatitis. J. Allergy Clin. Immunol. 136, 1005–1013.e3 (2015).
Van Dyken, S. J. et al. A tissue checkpoint regulates TSLP polymorphisms, allergen exposures, and the risk for asthma in Australian twins. Proc. Natl Acad. Sci. USA 106, 2093–2098 (2009).
Ashley, D. L., Martin, N. G., Battistutta, D., Hopper, J. L. & Du, J. et al. National surveillance of asthma: 1997–2011. J. Allergy Clin. Immunol. 130, 1005–1013 (2012).
Corren, J. et al. Tzeepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma. N. Engl. J. Med. 377, 956–964 (2017).
Menozzi-Gonzalez, A. et al. TSLP-driven chromatin remodeling and latent systemic immunity after neonatal respiratory viral infection. J. Immunol. 206, 1315–1328 (2021).
Diver, S. et al. Effect of tezepelumab on airway inflammatory cells, remodeling, and hyperresponsiveness in subjects with moderate-to-severe uncontrolled asthma (CASCADA): a double-blind, randomized, placebo-controlled, phase 2 trial. Lancet Respir. Med. 9, 1295–1312 (2021).
This study shows that elevated levels of epidermal thymic stromal lymphopoietin expression by chronic cough exacerbations in patients with idiopathic pulmonary fibrosis and the expression of Th2 cytokine production in human airway smooth muscle epithelial cells leads to Th2-like inflammatory responses, Th2 type of immune responses, and TSLP-dependent macrophage recruitment in macrophage-derived cell lineages.

This study shows that TSLP induces the loss of Th cells and the expression of Th2 cytokine production in human airway smooth muscle epithelial cells, leading to Th2-like inflammatory responses, Th2 type of immune responses, and TSLP-dependent macrophage recruitment in macrophage-derived cell lineages.

TSLP induces the proliferation and invasion of cervical cancer cells by downregulating microRNA-132 expression. Oncol. Lett. 14, 7910–7916 (2017).

Baroese, R., Mahmoudian, R. A., Abbaszadeh, M. R., Mansouri, A. & Gholamin, M. Evaluation of thymic stromal lymphopoietin expression in epithelial uterine cervical carcinoma. Med. Oncol. 32, 217 (2015).

Xu, J. et al. Overexpression of thymic stromal lymphopoietin is correlated with poor prognosis in epithelial ovarian carcinoma. Breast Cancer Res. 39, BSR20190161 (2019).

Senechal, A. et al. Expression and polymorphism of TSLP/TSLP receptors as potential diagnostic markers of colorectal cancer progression. Genes 12, 1586 (2021).

Yue, W. et al. Thymic stromal lymphopoietin (TSLP) inhibits human colon tumor growth by suppressing apoptosis of tumor cells. Oncotarget 7, 16860–16854 (2016).

Sun, K., Kusminski, C. M. & Scherer, P. E. Adipose tissue remodeling and obesity. J Clin Investig. 121, 2094–2101 (2011).

Cildir, C., Akinçilar, S. C. & Tergaonkar, V. Chronic adipose tissue inflammation: all immune cells on the stage. Trends Mol. Med. 19, 487–500 (2013).

Cox, A. J., West, N. P. & Crisps, A. W. Obesity, inflammation, and the gut microbiota. Cancer Diabetes Endocrinol. 5, 108122 (2021).

Lee, M. W. et al. Activated type 2 innate lymphoid cells regulate beige fat biogenesis. Cell 170, 74–85 (2017).

Qiu, Y. et al. Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. Cell 174, 511–523 (2018).

Brestoff, J. R. et al. Group 2 innate lymphoid cells promote beige white adipose tissue and obesity. Nature 519, 242–246 (2015).

Moorthy, A. B. et al. Innate lymphoid cell type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. J. Exp. Med. 210, 525–549 (2012).

Wu, D. et al. Eosinophil sustained adipose alternately activated macrophages associated with glucose homeostasis. Science 332, 243–247 (2011).

Kolodin, D. et al. Antigen- and cytokine-driven accumulation of regulatory T cells in visceral adipose tissue of lean mice. Cell Metab. 26, 157–15 (2017).

Feurer, M. et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat. Metab. 15, 930–939 (2020).

Chen, R. et al. Thymic stromal lymphopoietin induces adipose loss through sebum hypersecretion. Science 373, eabv2855 (2021).

This study shows that TSLP induces the loss of white adipose tissue and protects against obesity by promoting sebum hypersecretion. Science 351, 155284 (2020).

Gluck, J. & Gluck, M. R. NKT cell-mediated repression of tumor-driven evolution of immunosuppressive type 2 inflammation. J. Immunother. Cancer 7, 56 (2019).

Gluck, J. & Gluck, M. R. NKT cell-mediated repression of tumor-driven evolution of immunosuppressive type 2 inflammation. J. Immunother. Cancer 7, 56 (2019).

Ding, S. et al. Identification of a novel immune-related prognostic signature associated with thymic stromal lymphopoietin expression by chronic cough exacerbations in patients with idiopathic pulmonary fibrosis and the expression of Th2 cytokine production in human airway smooth muscle epithelial cells leads to Th2-like inflammatory responses, Th2 type of immune responses, and TSLP-dependent macrophage recruitment in macrophage-derived cell lineages.

This study shows that TSLP induces the loss of Th cells and the expression of Th2 cytokine production in human airway smooth muscle epithelial cells, leading to Th2-like inflammatory responses, Th2 type of immune responses, and TSLP-dependent macrophage recruitment in macrophage-derived cell lineages.

This study shows that IFN-γ induced by virus triggers cytokine production by TSLP-expressing macrophages in macrophages and other cell types, leading to enhanced adaptive mucosal immunity.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.

This study shows that TSLP, but not interleukin-7, plays an adjuvant role in BCG-mediated CD8+ T cell immunity by boosting release of thymic stromal lymphopoietin.
fibrosis: a prospective one-year follow-up cohort study. J. Clin. Med. 8, 1590 (2019).

175. Wang, W. et al. The level of thymic stromal lymphopoietin and its gene polymorphism are associated with rheumatoid arthritis. Immunobiology 226, 152055 (2021).

176. Kokama, K. et al. A possible role for TSLP in inflammatory arthritis. Biochem. Biophys. Res. Commun. 557, 99–104 (2007).

177. Moret, F. M. et al. Thymic stromal lymphopoietin, a novel proinflammatory mediator in rheumatoid arthritis that potently activates CD1c+ myeloid dendritic cells to attract and stimulate T cells. Arthritis Rheumatol. 66, 1176–1184 (2014).

178. Hartgring, S. A. et al. Critical proinflammatory role of thymic stromal lymphopoietin and its receptor in experimental autoimmune arthritis. Arthritis Rheum. 63, 1878–1887 (2011).

179. Okayama, Y. et al. FcepsilonRI-mediated thymic stromal lymphopoietin production by interleukin-4-primed human mast cells. Eur. Respir. J. 34, 425–435 (2009).

180. Jeong, H. J. et al. Interleukin-52-induced thymic stromal lymphopoietin plays a critical role in macrophage differentiation through the activation of caspase-1 in vitro. Arthritis Res. Ther. 14, R259 (2012).

181. Rivellese, F. et al. Mast cells in early rheumatoid arthritis associate with disease severity and support B cell autoantibody production. Ann. Rheum. Dis. 77, 1773–1781 (2018).

182. Peterson, L. W & Arts, D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. Nat. Rev. Immunol. 14, 141–153 (2014).

183. Abraham, C. & Medzhitov, R. Interactions between the host innate immune system and microbes in inflammatory bowel disease. Gastroenterology 140, 1729–1737 (2011).

184. Ordogez, F. et al. Pediatric ulcerative colitis associated with autoimmune diseases: a distinct form of inflammatory bowel disease? Inflamm. Bowel Dis. 18, 1809–1817 (2012).

185. Ziegler, S. F. et al. The biology of thymic stromal lymphopoietin (TSLP). Adv. Pharmacol. 66, 129–155 (2013).

186. Tahaghoghi-Hajghorbani, S. et al. Protective effect of TSLP and IL-33 cytokines in ulcerative colitis. Auto. Immun. Highlights 10, 1 (2019).

187. Alpizar, S. et al. Functionality and performance of an accessorized pre-filled syringe and an autoinjector for at-home administration of tezepelumab in patients with severe, uncontrolled asthma. J. Asthma Allergy 14, 381–392 (2021).

188. Pham, T. H. et al. Tezepelumab normalizes serum interleukin-5 and -13 levels in patients with severe, uncontrolled asthma. Ann. Allergy Asthma Immunol. 127, 689–691 (2021).

189. Keegan, A. D. & Leonard, W. J. In Paul Fundamental Immunology 8th edn Ch. 9 (ed. Flajnik, M.) (Wolter Kluwer, 2022).

Acknowledgements
We thank R. Spolski and J.-X. Lin for critical comments on the manuscript. We acknowledge funding by Division of Intramural Research National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
W.J.L. is an inventor on NIH patents related to thymic stromal lymphopoietin (TSLP). R.E-S. declares no competing interests.

Peer review information
Nature Reviews Immunology thanks O. Lamiable, F. Ronchese and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher’s note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This is a U.S. Government work and not under copyright protection in the US; foreign copyright protection may apply 2022.