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Review

Signaling cascades initiated by TSLP-mediated signals in different cell types

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ABSTRACT

Thymic stromal lymphopoietin (TSLP) has been well characterized as a consequence of its ability to modulate allergic and neoplastic diseases. However, downstream signaling mediated by TSLP varies significantly between the cell type and species examined. Since this observation is often overlooked and in some cases ignored, this review aims to consolidate the molecular pathways activated by TSLP receptors expressed by various human and mouse cell types.

1. Introduction

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine widely expressed by a variety of cell types that can have effects on a broad spectrum of cell types including B cells, T cells, dendritic cells (DCs), eosinophils, macrophages, basophils, mast cells, natural killer (NK) cells, smooth muscle cells, and even tumor cells. As a result there has been an increase in research examining TSLP mechanisms of action. These heterogeneous effects have resulted in studies examining the role of TSLP in the context of allergic diseases, such as atopic dermatitis and asthma [1–5]. In addition, since TSLP can be produced by various tumor cells, the role of TSLP in the induction of tolerance and promotion of polarized Th2 responses resulting in tumor progression has also been examined [6–10]. The mechanisms associated with TSLP-mediated tolerance induction remain to be identified.

The TSLP receptor (TSLP-R) and the complex downstream-associated signals following ligation with TSLP define the effects of TSLP on respective cell types. As a consequence, the significant differences these signals have on different cell types (and species) has resulted in controversy regarding the function of TSLP since different molecules are up-regulated in different cell types and species. These differing reports regarding the effects of TSLP-mediated signals are partially due to the different species (i.e., mouse vs. human) tested, and ambiguity regarding the nature of the cell lines tested in previous studies [1]. This review aims to define the molecular mechanism associated with signals transmitted via the TSLP-R in various cells from both humans and mice since the effects of TSLP vary between species and cell type (Table 1).

1.1. TSLP and the TSLP-R

Although TSLP is an IL-7-like cytokine, the downstream signaling and biological activities mediated by this molecule are quite different from those of IL-7. TSLP requires a heterodimeric receptor complex consisting of the IL-17 receptor α subunit and a unique TSLP receptor subunit that transmits signals into the cell [11–13]. Even though mouse and human TSLP are 43% identical (39% identity between receptors) cross-reactivity between human and mouse TSLP receptors following ligation with TSLP from respective species has been rarely reported [14–16]. Although the TSLP proteins are structurally and sequentially divergent between species, the biologic functions remain similar.

Abbreviations: TSLP, thymic stromal lymphopeietin; JAK/STAT, Janus kinase/signal transducers and activators of transcription; JNK, Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; mDCs, myeloid DCs; DEP, diesel exhaust particles; MAPK, Mitogen-activated protein kinase.

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Table 1
TSLP-initiated signaling in various cell types.

Cell type	Function	Human	Mouse
B cells	Activate	STAT1[a], STAT3[a], STAT5, JAK2, JAK1[a]	STAT5, Tec family[a]
	Inactivate		JAK1, JAK2
$CD4^+$ T cells	Activate	STAT1, STAT5, JAK1, JAK2	STAT5, STAT6, Bcl-2, JAK1, JAK2
	Inactivate		JAK3, TYK2, Tec, Itk, Rlk
$CD8^+$ T cells	Activate	STAT5, Bcl-2	STAT5, Bcl-2, Akt
	Inactivate		
DCs	Activate	Jagged-1, JAK1, JAK2, Akt, ERK, JNK, NF-κB (p50, RelB), STAT1, STAT3, STAT4, STAT5, STAT6	NF-κB
	Inactivate		
Eosinophils	Activate	ERK, p38, NF-κB	
	Inactivate	STAT3, STAT5, Akt	
Smooth muscle cells	Activate	STAT3, ERK1/2, p38, JNK	
	Inactivate	STAT5	
Intervertebral disc cells	Activate		PI3-kinase/Akt
	Inactivate		
Cytotropho-blasts	Activate	STAT3-c-myc	
	Inactivate		

[a] Possibly activate/inactivate.

1.2. JAK/STAT

Janus kinase/signal transducers and activators of transcription signal (JAK/STAT) are responsible for numerous cellular activities. JAKs contain a catalytic domain and a second kinase-like region functionally associated with STATs and IFN [17,18]. In humans, four JAK and seven STAT molecules have been described. Although activation of JAKs can result in phosphorylation of STATs under some circumstances, STATs can be activated via JAK family-independent mechanisms [19].

Even though it has been widely reported that various cell types are susceptible to TSLP-mediated signals resulting in the activation of STATs little is known regarding these signaling pathways in the context of activation of JAK kinases. As a result, the debate regarding how TSLP regulates phosphorylation of STATs remains undefined. Initial work attempted to define JAK activation mechanisms associated with TSLP-mediated signals based on the knowledge that IL-7 induced JAK/STAT activation [20,21], but these studies failed to detect JAK/STAT activation in B cells [13]. More specifically, subtypes of JAKs or STATs eactivated in response to TSLP-mediated signals vary between cell types and species studied.

1.2.1. $CD4^+$ and $CD8^+$ T cells

The effects on DCs by TSLP-mediated signals has been studied extensively in the context of allergic inflammation and with respect to T cell function. Together with T cell activation via the TCR, signals delivered following ligation of TSLP are similar in that these signals influence the development of naive $CD4^+$ T cells into Th2 cells following the induction of IL-4 transcription [22–24]. In addition to eliciting the proliferation of naive $CD4^+$ T cells, TSLP also induced the activation and differentiation of naïve human $CD8^+$ T cells into cytotoxic T cells that promote allergy [25]. However, the underlying mechanisms and cell signaling pathways mediating these effects on T cells remain unclear.

Tyrosine-phosphorylation of STAT5 in $CD4^+$ T cells from both humans and mice [22,23] and STAT6 activation in murine $CD4^+$ T cells [22] occurs following TSLP stimulation. In murine $CD4^+$ T cells, since progression towards Th2 polarization following TSLP stimulation also requires IL-4, TSLP-mediated STAT6 activation contributes to IL-4 expression thus facilitating Th2 differentiation. However, TSLP-mediated activation resulting in these downstream effects is complex [22,26] and includes the activation of STAT5 that lowers the IL-2 signaling threshold of $CD4^+$ T cells resulting indirectly in increased $CD4^+$ T cell proliferation [23]. In addition to the indirect effects of STAT5, Rochman et al. described a critical role for STAT5 following TSLP signaling in mouse $CD4^+$ T cells. via direct regulation of target genes such as CISH and Bcl2 it was shown that STAT5 stimulated $CD4^+$ T cell proliferation following TSLP-mediated signals (in contrast to IL-7-mediated signals) [27]. The effect of TSLP on activation of other STATs is significantly less, for example, only low levels of STAT1 activation in human $CD4^+$ T cells was observed and easily inhibited in the presence of an anti-TSLP neutralizing mAb [28].

During the early search for intermediate signaling molecules associated with STATs and TSLP-mediated signals studies examined paradigms associated with its biological analogue IL-7. This approach focused on determining whether JAK1 and JAK3 were also activated following TSLP-mediated signals similar to signals observed following stimulation with IL-7. These studies demonstrated that signaling mediated by TSLP and IL-7 were not homologous. Subsequent studies also failed to demonstrate an involvement for JAK1 or JAK2 regarding signaling pathways resulting in STAT5 phosphorylation following signaling via TSLP although not all experiments were carried out using T cells [13]. Later studies focused on examining roles for Tec family kinases (such as Tec, Itk, and Rlk) as potential signaling molecules associated with TSLP signaling pathways, however, to date it has not been shown that these molecules are involved in TSLP-mediated signaling. In both human and mouse primary $CD4^+$ T cells, JAK1 that associates with IL-7Rα and JAK2 that links to the TSLP-R, are dependent on TSLP-mediated STAT5 phosphorylation [27]. By contrast, JAK3 and TYK2 are not involved in this process in mice as shown in studies using knockout mice [27].

As with $CD4^+$ T cells, TSLP maintains sustained phosphorylation of STAT5 in murine naive and pre-activated $CD8^+$ T cells, but less potent STAT5 activation is observed in pre-activated human cells compared to phosphorylation observed following stimulation with IL-2 and IL-7 [29].

1.2.2. Regulatory T cells

A subset of $CD4^+$ T cells described as regulatory T cells (Tregs) play a critical role in mediating immunologic tolerance [30–32]. For many years it was believed that TSLP played a role in mediating Treg proliferation and differentiation via DCs [33,34]. However, recent studies have indicated that TSLP can directly impact naive Tregs, however, some of the data are contradictory. For example, one study demonstrated that TSLP promoted Treg differentiation from $CD4^+CD8^-CD25^-$ naive cells independently of DCs [35] via undefined molecular mechanisms. Conversely, low TSLP levels exert direct inhibitory effects on the development of either human or