Cellular Immunology 295 (2015) 144–149

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Review

Functions of thymic stromal lymphopoietin in non-allergic diseases

Guoqing Ying [a,b,1], Yanlu Zhang [a,1], Guoqiang Tang [a], Shuqing Chen [b,*]

[a] College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, China
[b] College of Pharmaceutical Science, Zhejiang University, Hangzhou 310028, China

ARTICLE INFO

Article history:
Received 13 January 2015
Revised 13 March 2015
Accepted 17 March 2015
Available online 23 March 2015

Keywords:
TSLP
Cancer
Metastasis
Tregs
Fibrosys

ABSTRACT

Thymic stromal lymphopoietin (TSLP) is an interleukin 7-like cytokine produced mainly by epithelial cells. Many studies indicate that TSLP contributes to promote T helper (Th) 2 immune responses which are associated with the pathogenesis of allergic inflammatory diseases. Base on the cross-talk between Th2 inflammation and cancers, we will highlight the role of TSLP in the progression of cancers in this review. TSLP is involved in the increasing prevalence of Tregs in the cancer microenvironment. Besides, TSLP has an important role in promoting the growth of vascular endothelial cells and angiogenesis, which could further promote the development and progression of cervical cancer. It gives the evidence that TSLP could induce EMT to promote cancer metastasis. In addition, TSLP could be detected in some fibroblasts and may play a role in the pathogenesis of non-allergic diseases characterized by a type 2 immune response and organ fibrosis.

1. Introduction

Thymic stromal lymphopoietin (TSLP) is currently a target of intense investigation due to its well-established role as a master regulator of allergic inflammation in humans and mice. Despite its well-known importance in allergic responses, the roles of TSLP in cancer have only recently been identified. It is known that inflammation plays critical roles at different stages of tumor development [1,2]. Considering proinflammatory and inflammatory cytokines induce TSLP in various tissues, it will not be surprising to find that TSLP has a more generalized function in cancer in addition to Th2-mediated diseases. In this review, we will first summarize the biology of TSLP, including the structure of TSLP and its receptor complex, as well as its signaling pathway. We will also focus on recent advances in our understanding of the effects of TSLP on the development of cancers, such as breast cancer [3], pancreatic cancer [4], cervical cancer [5] and lung cancer [6], and discuss the connections between TSLP and metastasis of cancer cells. These findings also indicate that TSLP is a promising therapeutic target in the treatment of cancer.

2. Introduction of TSLP

2.1. TSLP and TSLPR

Thymic stromal lymphopoietin is a interleukin 7-like cytokine, which is expressed in different types of cells, such as human epithelial cells in the thymus [7], lung, intestine [8], skin and tonsils [9] as well as stromal cells and mast cells [10]. TSLP was firstly discovered in the supernatants of conditioned medium of mouse thymic stromal cell clone, Z210R.1 [7]. The supernatants of this conditioned medium supported the growth of the NAG8/7 immature B cell line and enhanced the proliferation of unfractionated thymocytes cultured with suboptimal concentrations of anti-CD3 antibodies in vitro. In 2001, two research groups isolated cDNA clones encoding human TSLP based upon database research methods [8,11]. Although TSLP protein has some similarities with IL-7, it has distinct biological functions. For example, both cytokines can promote the maturation of B lymphocytes in long-term culture of fetal liver cells and bone marrow cells. However, TSLP apparently supports the progress of B lymphocytes to mature $B220^{+}IgM^{+}$ stages while IL-7 only promotes the development to an IgM^{-} stage [7,12,13]. Sequence prediction reveals that human TSLP and murine TSLP have a similar four-helix structure with two N-glycosylation sites and six cysteine residues. The mouse TSLP protein has 140 amino acids, while human TSLP protein has two isoforms which have 159 amino acids and 60 amino acids respectively [8,11]. Murine *Tslp* is located on chromosome 18, while human *TSLP* is mapped to chromosome 5q22.1 [11,14]. Although they have

* Corresponding author.
E-mail address: tgq1990414@163.com (S. Chen).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.cellimm.2015.03.006
0008-8749/

a poor homology with only 43% amino acid identity, they exert similar biological functions.

TSLP receptor (TSLPR) is a type I transmembrane protein which belongs to the hematopoietin receptor superfamily [15]. The functional TSLPR complex consists of TSLPR chain and IL-7Rα chain. TSLPR chain itself can bind to TSLP with low affinity. However, TSLPR binds with TSLP with high affinity leading to STAT5 activation and cell proliferation in response to TSLP stimulation when paired with the IL-7Rα chain [8,16,17]. Like TSLP, human and mouse TSLPR have a poor homology with only 39% identity at the amino acid level.

2.2. Expression of TSLP

TSLP is mainly expressed by epithelial cell in the thymus, lung, intestine, skin and stromal as well as tonsils cells and mast cells [10,11,18–20]. Initially, TSLP was thought to be a survival and maturation factor for B and T cells, but it has now been shown to act on a broad range of cell types including those implicated in the development of lung inflammation and asthma, such as dendritic cells (DCs), $CD4^+$ T cells, eosinophils, basophils, mast cells, innate type II cells, as well as on $CD8^+$ T cells, B cells, natural killer T cells and smooth muscle cells [21–24].

TSLP can be induced by a variety of factors including the proinflammatory and inflammatory cytokines, gut commensals, bacterial and viral infections, Toll-like receptors (TLR) and Nod2 agonists, and allergens [25]. Accompanied with Th2 cytokines IL-1α and TNF-α can induce sufficient TSLP to promote the maturation of blood $CD11c^+$ DCs. However, TNF-α or IL-1α alone cannot stimulate significant amounts of TSLP in human skin explant [26]. NF-κB has been shown to be important in TSLP activation. There are NF-κB binding sites in the promoter of both mouse and human *TSLP* gene [27]. In human airway epithelial cells, the expression of TSLP is regulated by IL-1β and TNF-α in a NF-κB-dependent manner [27]. Because of all TLR signaling pathways culminate in activation of NF-κB which controls the expression of an array of inflammatory cytokine genes, various TLR agonists, as well as infections, can stimulated TSLP expression in epithelial cells [27–38].

2.3. TSLP signaling pathway

Although TSLP is a member of the IL-2 family of cytokines and shares homology with IL-7, its receptor does not contain the common cytokine receptor γ chain which is shared by the IL-2 family of cytokines [39,40]. Instead, the high affinity TSLP receptor complex is composed of the IL-7Rα chain paired with the TSLP-specific receptor component, TSLPR. Initial studies using mouse TSLP and IL-7 receptors revealed that both receptors activated the transcription factor STAT5 and induced the expression of common STAT5 target genes [41]. Likewise, human TSLP induces phosphorylation of STAT5 and STAT3 in Ba/F3 cells expressing human IL-7Rα and human TSLPR [8]. Although initial research demonstrate that TSLP, which bind to TSLPR, could complex activated STAT5 without detectable JAK activation [41], recent results demonstrated that, in primary mouse and human $CD4^+$ T cells, JAK1 and JAK2 could bind to IL-7Rα and TSLPR chain, respectively, could activated TSLP-mediated STAT5 [42].

Human TSLP activated many STATs in DC by inducing broad and robust JAK-dependent signaling pathway. In particular, TSLP directly activated STAT6, which explained the unique ability of mDCs to produce the TH2-attracting chemokine CCL17. Besides, it increased the abundance at the cell surface of OX40L, which is a key molecule for polarizing naïve $CD4^+$ T cell differentiation into inflammatory TH2 cells through the activation of the NF-κB pathway. Also TSLP did not increase the abundance of IRF-8 or STAT4 which were the two critical transcription factors required for the production of IL-12 in mDCs [43]. Unlike IL-7 signaling which utilizes JAK1 and JAK3 to activate STAT proteins. Upon TSLP binding to its high affinity receptor TSLPR recruits JAK2 and IL-7Rα recruits JAK1 resulting in the activation of primarily STAT5A, STAT5B and STAT1, STAT3, and other STAT proteins to a lesser extent depending on the cell type [42,44]. In the $CD4^+$ T cells of mouse activation of Stat5 by TSLP could direct the initial IL-4 production independent of IL-2 [45].

3. The Role of TSLP in primary cancers

It is known that inflammation plays critical roles at different stages of tumor development [1,46]. The cytokines, especially IFN-γ, can trigger cancer cell destruction as illustrated by regressions of bladder cancer after treatment with microbial preparations, for the presence of the effector cells [47]. It reports that early neoplastic events would drive an M1 toward M2 switch of TAM functions [48] and are probably connected to the profound changes occurring in the tumor microphysiology (e.g., hypoxia, glucose levels, pH) [49]. Couple of researches demonstrate chronic inflammation could promote cancer cells survival and metastasis because of the presence of Th2 cytokine-, IL-4-, and IL-13-activated macrophages (M2) [46,50–52].

Recently, many articles point out the evidences that TSLP plays an essential role in tumor microenvironment which initiates a cross-talk between Th2 inflammation and cancer [1]. TSLP produced by human breast cancer cells can activate DCs to migrate to the draining lymph nodes. TSLP activated $OX40L^+$ mDCs induce $CD4^+$ T cells to secrete IL-13 as well as TNF, and these inflammatory $CD4^+$ T cells contribute to tumor development through an IL-13-dependent pathway [53–55].

Based on data both in vitro and in vivo, a model of a complex cross-talk among tumor cells cancer-associate fibroblasts (CAFs), Th2 cells, and possibly other immune cells is proposed favoring tumor progression. Proinflammatory cytokines IL-1α plays a pivotal role in triggering proinflammatory responses in fibroblasts [56]. Pancreatic tumor cells release TNF-α and IL-1β which induces the release of TSLP by CAFs [4,57]. TSLP released by activated CAFs can induce the activation/maturation of tumor antigen-loaded resident DCs. The activated DCs then migrate to the draining lymph nodes and activate tumor antigen–specific Th2 cells. At the same time, tumor derived Th2 chemoattractants (TARC/CCL17 and MDC/CCL22) induce the Th2 cells to home to the tumor. $CD4^+$ $GATA3^+$ Th2 cells recruited to tumor thus exert tumor promoting effector functions [4]. Furthermore, Th2 responses have been shown to be strongly linked with fibrogenesis with Th1 and Th2 cytokines exert opposing roles in promoting collagen degradation and synthesis, respectively [58]. Therefore, the change of the balance between Th1 and Th2 cytokines in the tumor microenvironment might further contribute to fibrosis.

$CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells (Tregs) which could suppress the activity of lymphocytes and help tumor cells to escape the host immune surveillance [59–61] were increased in the peripheral blood or tumor microenvironment in patients with breast cancer [62], non-small cell lung cancer [63], gastrointestinal malignancies [64], and head–neck carcinoma [65]. TSLP was involved in the increasing prevalence of Tregs in the cancer microenvironment. One study indicated that the expression of TSLP was significantly increased in tumor tissue compared with that in benign lesion and non-cancer lung tissue. Furthermore, the number of $FOXP3^+$ Tregs in the tumor microenvironment correlated with the expression of TSLP protein in tumor tissue. First, DCs derived from PBMC collected from