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Review

Insight into the role of TSLP in inflammatory bowel diseases

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ABSTRACT

Proinflammatory cytokines are thought to modulate pathogeneses of various inflammatory bowel diseases (IBDs). Thymic stromal lymphopoietin (TSLP), which has been studied in various allergic diseases such as asthma, atopic dermatitis (AD) and eosinophilic esophagitis (EoE), has been less considered to be involved in IBDs. However, mucosal dendritic cells (DCs) induced by various cytokines including TSLP were reported to cause polarization of T cell toward Th2 response, the differentiation of regulatory T-cell (Treg), and secretion of IgA by B cells. In this review, we discuss the concept that decreased TSLP has the potential to accelerate the development of Th1 response dominant diseases such as the Crohn's disease (CD) while increased TSLP has the potential to lead to a development of Th2 cell dominant diseases such the ulcerative colitis (UC). To examine TSLP's role as a potential determining factor for differentiating UC and CD, we analyzed the effects of other genes regulated by TSLP in regards to the UC and CD pathogeneses using data from online open access resources such as NetPath, GeneMania, and the String database. Our findings indicate that TSLP is a key mediator in the pathogenesis of IBDs and that further studies are needed to evaluate its role.

Abbreviations: AD, atopic dermatitis; AHR, aryl hydrocarbon receptor; AI, autoimmune; AIEC, adherent invasive *E. Coli*; ANCA, anti-neutrophil cytoplasmic antibody; APC, antigen-presenting cell; APRIL, a proliferation inducing ligand; ATG16L1, autophagy-related 16 like 1 gene; BAFF, B-cell activating factor; BAX2, BCL-2-associated X-protein; BCL-2, B-cell lymphoma 2; CCL #, C-C chemokine ligand #; CCL 4, C-C chemokine ligand 4; CCL 5, C-C chemokine ligand 5; CCL 11, C-C chemokine ligand 11; CCL 24, C-C chemokine ligand 24; CCR #, C-C motif receptor #; CCR 1, C-C motif receptor 1; CCR 2, C-C motif receptor 2; CCR 3, C-C motif receptor 3; CCR 4, C-C motif receptor 4; CCR 5, C-C motif receptor 5; CCR 6, C-C motif receptor 6; CCR 7, C-C motif receptor 7; CCR 8, C-C motif receptor 8; CCR 9, C-C motif receptor 9; CCR 10, C-C motif receptor 10; CD, Crohn's disease; CD11c, cluster of differentiation 11c; CD14, cluster of differentiation 14; CD33, cluster of differentiation 33; CD40, cluster of differentiation 40; CD56, cluster of differentiation 56; CD68, cluster of differentiation 68; CD80, cluster of differentiation 80; CD103, cluster of differentiation 103; CD127, cluster of differentiation 127; CD161, cluster of differentiation 161; CD205, cluster of differentiation 205; CD209, cluster of differentiation 209; CLDN-1, claudin-1; CRH, corticotropin releasing hormone; CSF-1, colony stimulation factor 1; CX3CR1, CX3C chemokine receptor 1; CXCL #, C-X-C motif ligand #; CXCL 1, C-X-C motif ligand 1; CXCL 2, C-X-C motif ligand 2; CXCL 3, C-X-C motif ligand 3; CXCL 5, C-X-C motif ligand 5; CXCL 9, C-X-C motif ligand 9; CXCL 10, C-X-C motif ligand 10; CXCR #, C-X-C motif receptor #; CXCR 1, C-X-C motif receptor 1; CXCR 2, C-X-C motif receptor 2; CXCR 3, C-X-C motif receptor 3; CXCR 4, C-X-C motif receptor 4; CXCR 5, C-X-C motif receptor 5; CXCR 9, C-X-C motif receptor 9; DC, dendritic cell; DSS, dextran sodium sulfate; EC, epithelial-cell; EoE, eosinophilic esophagitis; FOXP3, forkhead box p3; GATA3, GATA binding protein 3; HASM, human airway smooth muscle; HMGB1, high mobility group box 1 protein; HSP90, heat shock protein 90; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; IFN-α, interferon-α; IFN-β, interferon-β; IFN-γ, interferon-γ; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgλC, immunoglobulin λC; IL-1, interleukin-1; IL-1β, interleukin-1β; IL-2R, interleukin-2 receptor; IL-3, interleukin-3; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-7, interleukin-7; IL-7R, interleukin-7 receptor; IL-8, interleukin-8; IL-9, interleukin-9; IL-10, interleukin-10; IL-12, interleukin-12; IL-12A, interleukin-12A; IL-12B, interleukin-12B; IL-12p35, interleukin-12p35; IL-12R, interleukin-12 receptor; IL-13, interleukin-13; IL-15, interleukin-15; IL-17, interleukin-17; IL-17A, interleukin-17A; IL-17F, interleukin-17F; IL-18, interleukin-18; IL-21, interleukin-21; IL-22, interleukin-22; IL-23, interleukin-23; IL-23A, interleukin-23A; IL-23p19, interleukin-23p19; IL-23R, interleukin-23 receptor; IL-26, interleukin-26; IL-27, interleukin-27; IL-33, interleukin-33; IL-35, interleukin-35; IL-37, interleukin-37; ILC #, innate lymphoid cell #; ILC1, innate lymphoid cell subset 1; ILC2, innate lymphoid cell subset 2; ILC3, innate lymphoid cell subset 3; IRF3, interferon regulatory factor 3; IRF4, interferon regulatory factor 4; JAK1, Janus tyrosine-kinase 1; JAK2, Janus tyrosine-kinase 2; LP, lamina propria; M-CSF, macrophage colony stimulating factor; MAMP, microbe-associated molecular pattern; MHC, major histocompatibility complex; miR #, microRNA #; MMP, matrix metalloproteinase; MUC-1, mucin-1; MUC-13, mucin-13; MUC-4, mucin-4; MUC-5B, mucin-5B; MUC, mucin; NE, neutrophil elastase; NFkB, nuclear factor-kappa light chain enhancer of activated B cells; NKT, natural killer T cell; NOD2, nucleotide binding oligomerization domain 2; OmpC, outer membrane protein C of (*E. coli*); P2X7R, purinoreceptor P2X7 receptor; PAMP, pathogen-associated molecular pattern; PDGF-Rβ, platelet-derived growth factor receptor-β; PPAR-γ, peroxisome proliferation activated receptor-γ; RORγt, retinoic acid receptor related orphan receptor γt; SLP1, secretory leukocyte peptidase inhibitor; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transduction and activation of transcription 3; STAT4, signal transduction and activation of transcription 4; STAT5, signal transduction and activation of transcription 5; T-bet, T-box transcription factor; TER, trans-epithelial resistance; Tfh cell, follicular B helper T cell; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinase 1; TJ protein, tight junction protein; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TNF, tumor necrosis factor; TNFSF4, tumor necrosis factor superfamily 4; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoetin receptor; UC, ulcerative colitis; VEGF-A, vascular endothelial growth factor A; VEGF-R2, vascular endothelial growth factor R2; XCR1, XC motif chemokine receptor 1.

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Contents

1. Introduction

Inflammatory bowel disease (IBD) is a highly prevalent chronically relapsing immunologic disease and two major types of IBDs are most widely diagnosed due to high prevalence: Crohn's disease (CD) and ulcerative colitis (UC). These IBDs are often characterized pathologically by an epithelial injury from aberrant inflammatory responses [1,2]. From an immunological standpoint, important evidence in recent years suggested that these two diseases may be triggered by opposing immune responses. While the Th1 immune response is considered to greatly contribute to the pathogenesis of Crohn's disease, the Th2 immune response is considered more likely to lead to ulcerative colitis, suggesting that these two diseases may be in fact separate clinical entities. To explain the differences in pathology between these two diseases from an immunologic point of view, cytokines have lately received much attention as key factors in regulating the intestinal immune responses.

Moreover, recently, various linkages and genome-wide association studies identified over a total of 163 independent loci associated with IBD, a large of portion of which consisted of multiple susceptibility loci that are implicated in other immune-mediated diseases [3,4]. However, the results of Cleynen and colleagues' strongly powered study focusing mainly on genetic factors detected not a single genetic predictor for the disease progression and extent of CD and UC, respectively, suggesting that important loci or genetic factors influencing either disease remain to be investigated and that a development of a new research roadmap that systematically integrates various genetic factors is in demand [4,5].

The role of thymic stromal lymphopoietin (TSLP) which has been extensively studied in numerous other allergic diseases such as asthma, atopic dermatitis (AD) or eosinophilic esophagitis (EoE) has not been analyzed in the pathogenesis of IBD. In this review, we first discuss TSLP's role as an important cytokine in both the development of an IBD and the differentiation of CD and UC. Using gene-to-gene and protein-to-protein networks from online open access database, we also evaluate the importance TSLP in IBD pathogenesis and stress the need to direct future studies to evaluate its potential as a therapeutic target for the development of a novel immune-based therapy.

2. Structure and functions of TSLP

2.1. Structure and receptor

TSLP, which belongs to an IL-7 like cytokine family and consists of four helix bundles, is mainly expressed by epithelial cells, especially those located in the gut, lung, and skin [6–8]. However, TSLP was first extracted from a thymic stromal cell line from which its current name was derived [9,10]. Subsequent studies have found that TSLP signals through a heterodimeric receptor complex consisting of an IL-7 receptor-α chain and a unique TSLP receptor (TSLPR) which is similar to the γ chain of common receptor in IL-2, 4, 9 and -15 [10–12].

TSLPs are often activated through various danger signals, more concretely, by infection related agents, allergens, and cytokines such as IL-4, IL-13, IL-1 and TNF-α [13–21]. Normally, TSLPR has a low binding affinity for the ligand TSLP. However, when TSLPR is coupled together with IL-7 receptor-α, the affinity for TSLP by the binding site in TSLPR is markedly increased. After TSLPR is stimulated by the above-mentioned factors, the heterodimeric receptor complex transmits the signal by means of activating a variety of transcription factors such as the signal transducer and activator of transcription1 (STAT1), STAT3, STAT5, Janus kinase1 (JAK1) and JAK2 [22,23]. Activation of STAT5 by TSLP in particular was found to promote development of B and T cells while activating DCs to secrete more chemokines involved in Th2 cell differentiation via upregulation of MHC class I and II molecules in addition to activating mast cells and NKT cells [6,24,25].

2.2. Role of TSLP in educating DCs in normal healthy individuals

Considering their ability to induce Th2 differentiation in *in vitro* T cell priming assays and stimulate B-cells to secrete immunoglobulin A (IgA), mucosal DCs have long been considered to function as a crucial factor in creating a non-inflammatory environment in the gut [26–28]. More importantly, studies have found that various factors such as TSLP, IL-25 and those expressed by the epithelial cells are key mediators of this process [29].

TSLP is crucial for maintaining the immune responses of the human intestine in a variety of ways. Foremost, colonic epithelial cells from normal healthy donors were reported to constitutively express TSLP, resulting in the induction of 'non-inflammatory' DCs in concert with the other EC derived factors such as the transforming growth factor-β (TGFβ) and retinoic acid, which are known for promoting the polarization of T cells toward a 'classic' non-inflammatory Th2 response even after being exposed to a Th1-inducing pathogens such as *Salmonella* [30]. The type of TSLP produced constitutively in this context has been demonstrated to be the short isoform [31].

However in addition to contributing to the Th2-adaptive immunity, both TSLP and IL-25 were found to be involved in constructing the immunosuppressive state of the human intestine [32]. In general, the