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Original Article

Tuft cells contribute to the pathogenesis of human primary and experimental murine Sjögren's disease

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Tuft cells;
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IL-25,Type II immunity

Abstract *Background/purpose:* Tuft cells (TCs) activate type II immunity by interleukin-25 (IL-25) and stimulate proliferation and mucus secretion of goblet cells to defense worms. TCs have been identified in the striated ducts of submandibular glands. Sjögren's disease (SjD) has been linked to type II immunity, with increased IL-25 expression, yet the role of TCs in this context remains and their association with SjD and contribution to IL-25 production are unknown.

Materials and methods: Labial gland biopsies from SjD patients and patients with labial gland cysts were collected for histological staining. Immunofluorescence was employed to detect the expression and localization of DCLK1, KRT19, and IL-25. C57BL/10 mice and NOD.B10 mice were selected to measure salivary flow rate. RT-qPCR was used to detect the gene expression of POU2F3, DCLK1, and IL-25 in the submandibular glands.

Results: DCLK1-positive TCs were detected in labial gland from SjD patients and the submandibular glands of NOD.B10 mice. DCLK1 and IL-25 proteins were strongly expressed in striated ducts adjacent to lymphoid foci in both SjD patient and NOD.B10 mice, showing a positive correlation with the degree of lymphoid infiltration and ductal dilation with colocalization. TC markers, including DCLK1 and POU2F3 were significantly upregulated, concomitant with reduced salivary flow and increased lymphoid infiltration.

Conclusion: TCs are closely associated with salivary gland pathology and lymphoid infiltration in SjD. TCs-derived IL-25 implies their involvement in the pathological process of SjD. This work underscores the promise of TCs as a promising target for both understanding and treating SjD pathogenesis.

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Introduction

Rhodin and Dalhamn first identified tuft cells (TCs) in the tracheal epithelium sixty years ago. Morphologically, TCs are bottle-shaped and characterized by brush-like microvilli arranged in clusters at their apical surface.[1,2] Subsequent studies revealed that TCs are primarily distributed within epithelial cell subpopulations of the digestive and respiratory tracts, where they serve a vital role in mucosal defense. POU class 2 homeobox 3(POU2F3) is indispensable for TC differentiation. The absence of this transcription factor leads to a complete loss of intestinal TCs in mice.[3,4] Doublecortin-like kinase 1 (DCLK1) also exhibits highly specific expression in TCs[5] and serves as a reliable TC marker.[6,7] DCLK1 also plays an indispensable role in epithelial repair,[8] likely through its regulation of microtubule polymerization.[7]

Within the intestinal epithelium, the canonical function of TCs is to serve as sentinel cells during helminth infection. By detecting succinate and releasing IL-25, TCs trigger a type II immune response that activates ILC2s and Th2-like cells, ultimately driving the expansion of TCs and goblet cells.[3,9,10] This response is orchestrated by ILC2s and Th2 cells-derived type II cytokines (IL-4, IL-5, and IL-13), among which. IL-4 and IL-13 mediate structural remodeling of the intestinal epithelium by driving the proliferation of TCs and goblet cells with aberrant resist in-like molecule β (Retnlb) expression.[3,11,12] Retnlb directly disrupts helminth physiology[12–14] and facilitates parasite expulsion by enhancing mucus secretion and smooth muscle contraction.[15]

TCs also function in organs beyond the intestine. Those in the respiratory tract are also termed brush cells or solitary chemosensory cells-release acetylcholine (ACh) to promote mucociliary clearance.[16] In the nasal cavity, TCs contribute to the regulation of respiratory rhythm and inflammatory responses upon stimulation.[16] Tracheal TCs modulate respiratory reflexes[17] and regulate ciliary clearance by sensing bacterial metabolites.[18] In the urethra, TCs detect exogenous bitter compounds via cholinergic signaling, thereby influencing urination reflexes through modulation of visceral sensory nerves.[19] Initial evidence for salivary gland TCs came from a 1998 study that detected their presence in the rat submandibular gland using transmission electron microscopy.[20] More recently, multiple species, including humans, mice, and pigs, possess TCs within the striated ducts of their submandibular glands.[21] Despite these findings, the physiological role of TCs in salivary glands remains poorly understood.

Sjögren's disease (SjD), formerly known as Sjögren's syndrome, is an irreversible autoimmune disorder marked by impaired exocrine gland function, resulting in pronounced mucosal dryness.[22] The underlying pathogenesis reflects a complex interplay between the epithelial barrier and immune responses.[23] Within the labial glands' germinal centers from SjD patients, Th2 cells are selectively recruited, accompanied by increased IL-4 and IL-33 levels.[24] Recent evidence has highlighted that IL-25 (IL-17E) acts as a key mediator in type II immune responses.[25] IL-25 exerts diverse effects by binding to interleukin-17 receptor B (IL-17RB).[26] Notably, IL-25 modulates autoimmune response driven by IL-17 secreting T cells.[27] In the context of SjD, IL-25 is strongly expressed in salivary glands, where it contributes to disease pathology. Indeed, administration of IL-25 neutralizing antibodies in experimental SjD mouse models reduces lymphocytic infiltration.[28] However, it remains unclear whether TCs represent the main source of IL-25 in this context.

This study demonstrated that TC numbers were elevated within salivary gland lymphocytic infiltration foci and positively correlated with the degree of lymphoid infiltration in SjD patients and NOD mice. Immunofluorescence colocalization further revealed that IL-25 is predominantly produced by TCs. These findings establish a foundation for clarifying the contribution of TCs and type II immunity to SjD pathogenesis.

Materials and methods

Animals study

Female C57BL/10 and NOD.B10 mice aged 6 or 12 weeks (weighing approximately 20–26 g, 5 mice per group) were obtained from the Animal Experimental Center of Dalian Medical University All animal procedures were approved by the Animal Care and Use Committee of Dalian Medical University (Approval No.: AEE22006) and adhered to ARRIVE guidelines.

Salivary flow rate assay

Saliva was collected from mice. Briefly, a pilocarpine (5 mg/kg, BoShiLun, JiNan, China) was administered intraperitoneally after mice were anesthetized. Stimulated saliva was then collected for 10 min using a capillary tube.

Histological sections of human labial gland biopsies

All paraffin-embedded sections of human lip gland biopsies for SjD were a gift from B Sun. The use of sections was approved by the Ethics Committee of the Stomatological Hospital of Dalian Medical University (Approval No.: 2024001).

Immunohistochemical staining

For hematoxylin-eosin (HE) staining, tissue sections were stained following manufactory protocol. For immunofluorescence (IF) staining, sections were incubated with primary antibodies (anti-DCLK1, BS49504, Bioworld, NanJing, China and anti-IL-25, 31486, SAB, WuHan, China) overnight, then incubated with fluorescent secondary antibodies (Abcam, Cambridge, UK). Sections were mounted with DAPI containing antifade mounting medium.

Real-time reverse transcription polymerase chain reaction (RT-qPCR)

Total RNA from the glands were extracted using RNAKey reagent (SM139-02, SEVEN, BeiJing, China), reverse-transcribed into cDNA via the SevenFast two-step method, and the experiment was performed with an RT-qPCR kit. RT-qPCR was performed using the Bio-Rad Real-Time PCR System, and data were analyzed using the $2^{-\Delta\Delta}$Ct method. (The primer sequences used were listed in Table 1).

Statistical analysis

Mean $\pm$ SEM is used to present data. Statistical differences between two groups were calculated by Two-tailed test, whereas for more than two groups, One-way ANOVA combined with Bonferroni multiple comparisons test was applied in GraphPad Prism 9.5.0 (San Diego, CA, USA), and $P < 0.05$ was considered to indicate statistical significance.

Results

Tuft cells marker doublecortin-like kinase 1 is markedly increased around the striated ducts within lymphocytic infiltrates in NOD.B10 mice

Relative to BL/10 controls, NOD.B10 mice exhibited a progressive reduction in salivary flow (Fig. 1A). HE staining demonstrated focal lymphocytic sialadenitis (FLS) and lymphoepithelial lesion (LEL) pathology in the submandibular glands (SMGs) of NOD.B10 mice, accompanied by dilated striated ducts within lymphocytic infiltrates (Fig. 1B). To characterize TC expression, immunohistochemistry (IHC) using a DCLK1 antibody revealed that DCLK1 was primarily localized to the striated ducts. DCLK1 expression was increased in the SMGs of NOD.B10 mice, with the highest levels observed in dilated striated ducts adjacent to lymphocytic foci (Fig. 1C). RT-qPCR analysis further confirmed significant upregulation of the TC markers POU2F3 and DCLK1 in 12-week-old NOD.B10 mice (Fig. 1D). Moreover, immunofluorescence (IF) co-staining revealed that DCLK1 was predominantly localized to KRT19^{+} ductal epithelial cells, particularly in the striated ducts within lymphocytic infiltration zones (Fig. 1E).

Sjögren's disease labial salivary gland biopsies show increased striated duct tuft cells in lymphocytic infiltration zones

We next examined labial salivary gland biopsies from patients with SjD. The lesions displayed characteristic FLS with prominent lymphocytic infiltration (Fig. 2A). DCLK1 expression was enriched in dilated striated ducts located within lymphocytic infiltration zones (Fig. 2B). Immunofluorescence(IF)co-staining demonstrated that DCLK1 was predominantly expressed in KRT19^{+} ductal epithelial cells, with a marked increase in dilated striated ducts (Fig. 2C). Together, these findings demonstrate an expansion of the TC population in the salivary glands of individuals with SjD and specifically accumulate in dilated striated ducts within regions of lymphocytic infiltration.

Interleukin-25 is primarily derived from tuft cells and correlates with the extent of lymphoid infiltration

In the intestine, TCs contribute to anti-helminth immunity by secreting IL-25, which has also been implicated in SjD. We next assessed IL-25 expression. Immunofluorescence (IF) analysis of SMGs from NOD.B10 mice revealed colocalization of DCLK1 and IL-25. Within dilated striated ducts in lymphocytic infiltration zones, IL-25 expression was highly enriched in DCLK1^{+} cells, in contrast to controls and non-infiltrated regions, and showed a positive correlation with the severity of lymphoid infiltration (Fig. 3A). RT-qPCR confirmed a significant upregulation of IL-25 in NOD affected mice (Fig. 3B). These findings were replicated in labial salivary gland from SjD patients (Fig. 3C). Together, these findings indicate that IL-25 is derived from TCs and suggest that TCs may contribute to SjD pathogenesis by producing IL-25.

Discussion

TCs are chemosensory epithelial cells with distinct morphological and molecular features that play essential

Table 1 Primer sequences for RT-qPCR.

Genes	Forward	Reverse
Dclk1	CAGCCTGGACGAGCTGGTGG	TGACCAGTTGGGGTTCACAT
Il-25	TCTTGGCAATGATCGTGGGA	TGTGGTAAAGTGGGACGGAG
Pou2f3	AGAGAATCAACTGCCCCGTG	GGAAGGCACGACTCTCTTCC
Gapdh	GGACTTCGAGCAGGAGATGG	AGGAAGGAGGGCTGGAAGAG

Dclk1: Doublecortin-like kinase 1, Il-25: Interleukin-25, Pou2f3: Pou class 2 homeobox 3.

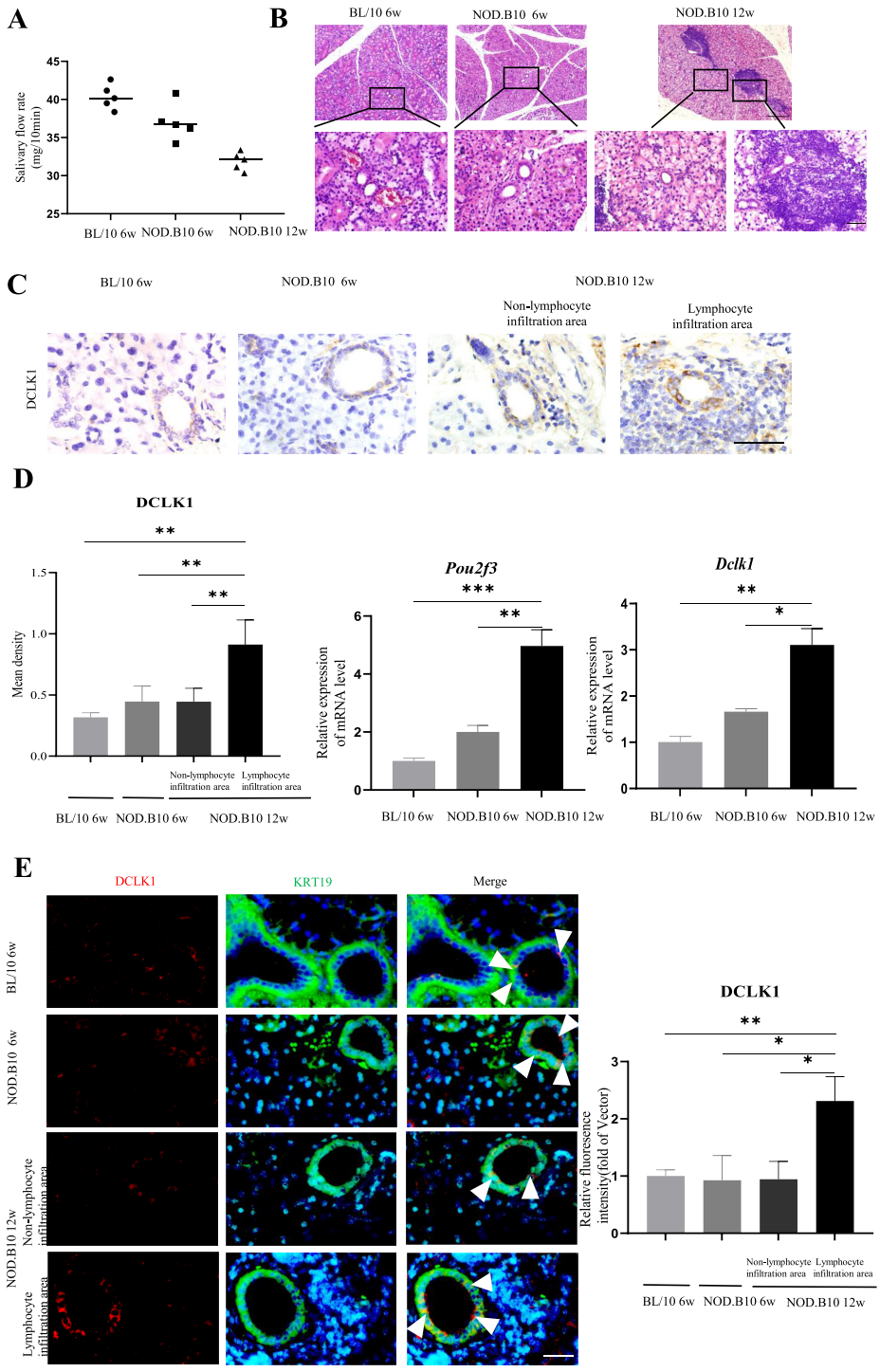

Figure 1 Distribution of tuft cells (TCs) in the salivary glands of NOD.B10 mice. (A) Salivary flow rate. (B) HE staining of the submandibular glands of mice. The upper scale bar measures 200 μm and the lower one measures 50 μm. The regions shown in magnification are indicated by dashed boxes. (C) Detection of TCs in submandibular glands using an anti-DCLK1 antibody (brown) with corresponding intensity analysis. Scale bar: 50 μm. (D) Assessing tuft cell marker genes *Pou2f3*, *Dclk1* in submandibular glands via RT-qPCR analysis (E) Immunofluorescence staining and fluorescence intensity of Keratin19 (KRT19) (green) and DCLK1 (red) in submandibular gland sections of mice. Arrows denote tuft cells. Scale bar: 50 μm *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. TCs, tuft cells. DCLK1, Doublecortin-like kinase 1. Pou2f3, Pou class 2 homeobox 3. KRT19, Keratin19.

roles in immune regulation. These cells are present not only in various mucosal surfaces but also in non-mucosal sites such as the thymus and pancreas. Their presence has further been documented in the salivary glands of humans, rats, and pigs. In this study, we used specific markers to identify salivary gland TCs and demonstrated their

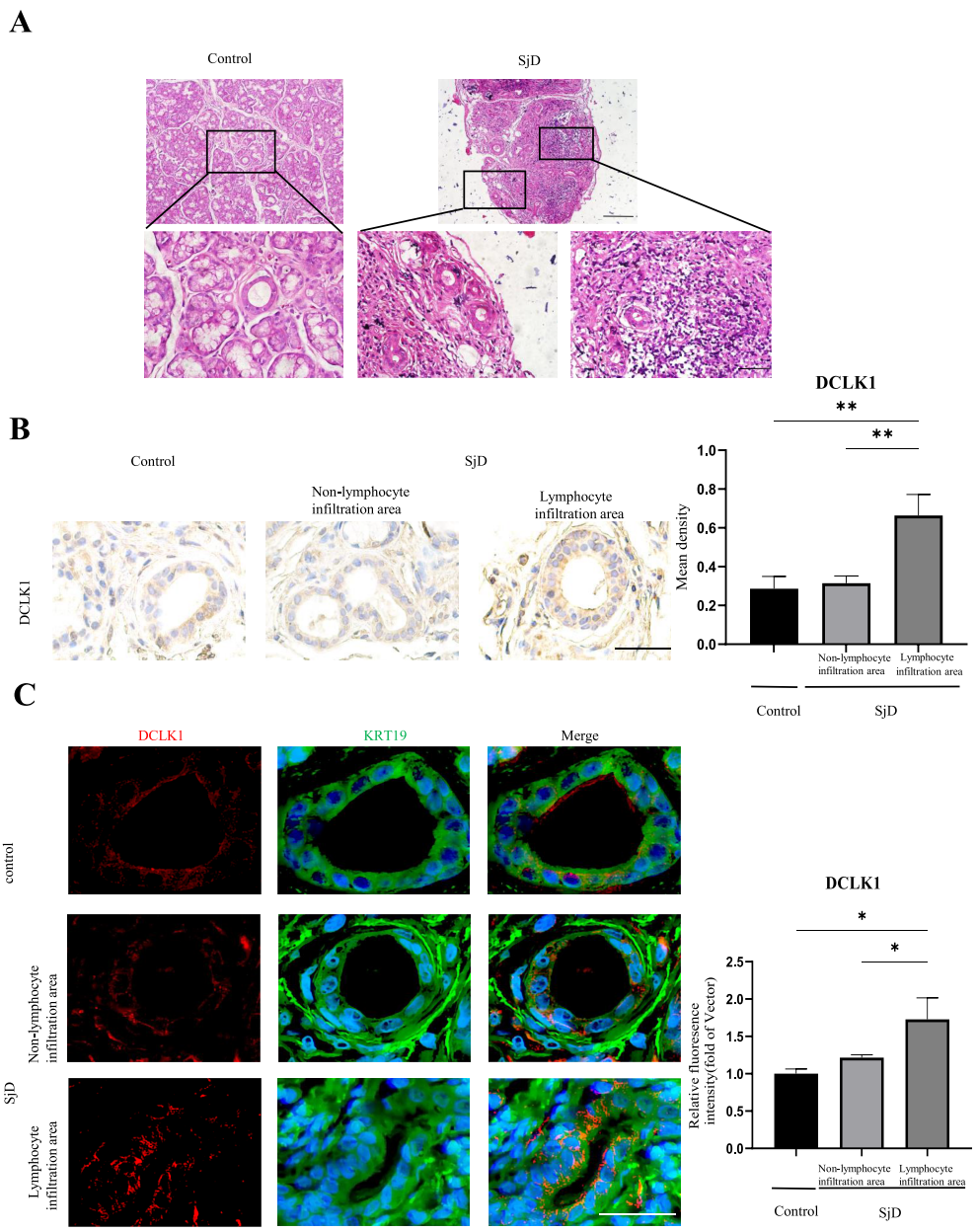

Figure 2 Distribution of tuft cells in the salivary glands of patients with SjD. (A) HE staining of labial gland tissue sections. The upper scale bar measures 200 μm and the lower one measures 50 μm. The regions shown in magnification are indicated by dashed boxes. (B) Detection of TCs in labial glands using an anti-DCLK1 antibody (brown) with corresponding intensity analysis. Nuclei of adjacent epithelial cells were counterstained with hematoxylin. Scale bar: 50 μm. (C) Immunofluorescence staining and fluorescence intensity of KRT19 (green) and DCLK1 (red) in labial gland sections. Scale bar: 50 μm $^{*}P < 0.05$; $^{**}P < 0.01$. SjD, Sjögren's disease. TCs, tuft cells. DCLK1, Doublecortin-like kinase 1. KRT19, Keratin19.

association with SjD. TC numbers increased in parallel with lymphocytic infiltration, suggesting their potential contribution to SjD pathogenesis.

TCs contribute to immunity through multiple pathways. Studies have demonstrated that TCs express key components of the taste transduction pathway which mediate immune regulation via chemosensory signals. In addition, TCs can modulate neuronal and inflammatory pathways, such as acetylcholine,[10] signaling and the release of allergy related eicosanoid signaling molecules, including cysteinyl leukotrienes and prostaglandin D2 (PGD2).[29] By activating taste receptors and the signaling molecules downstream of them, TCs respond to stimuli and stimulate adjacent epithelial cells as well as both immune and non-immune cells.[30,31] Current research has primarily focused on intestinal TCs, where DCLK1, a canonical TC marker, serves an important function in regulating tissue repair and regeneration.[32]

In studies of intestinal diseases, compelling evidence indicates that TCs serve as the main producers of IL-25.[33] TCs actively secrete IL-25, a key cytokine that stimulates ILC2s and Th2 to generate IL-13 and IL-4, thereby inducing

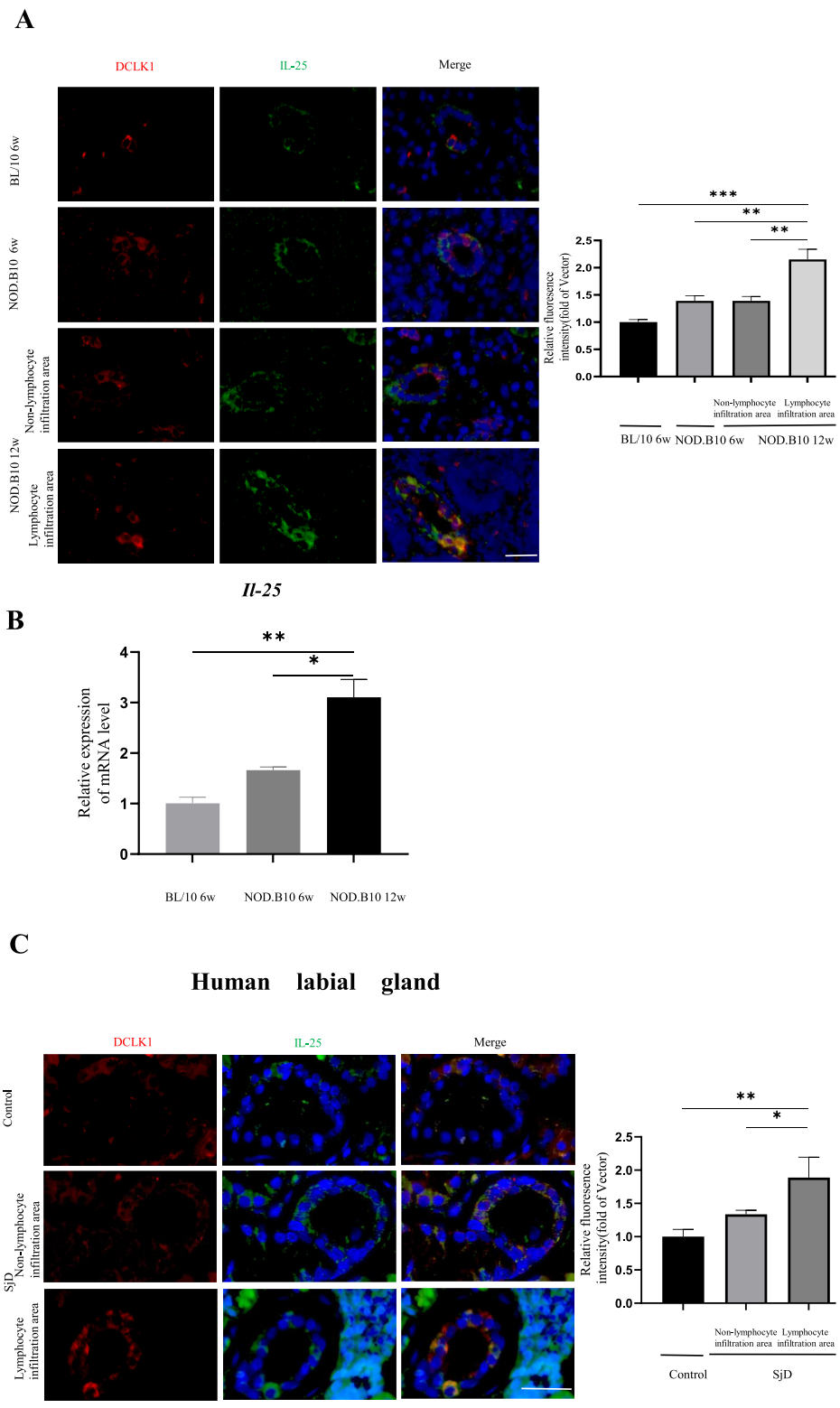

Figure 3 IL-25 is predominantly produced by tuft cells. (A) Immunofluorescence staining and fluorescence intensity of IL-25 (green) and DCLK1 (red) in submandibular gland sections of mice. Scale bar: 50 μm. (B) Assessing *IL-25* expression levels in submandibular glands using RT-qPCR. (C) Immunofluorescence staining and fluorescence intensity of IL-25 (green) and DCLK1 (red) in labial gland sections from with SjD patients. Scale bar: 50 μm *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. IL-25, Interleukin-25. DCLK1, Doublecortin-like kinase 1. SjD, Sjögren's disease.

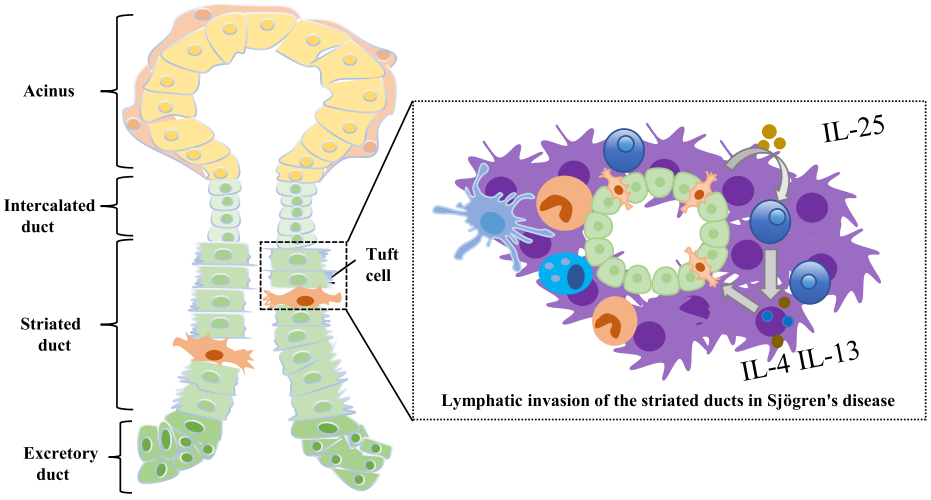

Figure 4 Proposed mechanism of TCs in SjD. Within the salivary glands of individuals diagnosed with SjD, TCs within striated ducts near lymphocytic infiltrates produce IL-25. This cytokine stimulates immune cells to secrete IL-4 and IL-13, which further stimulate tuft cell proliferation, thereby contributing to disease pathogenesis. TCs, tuft cells. SjD, Sjögren's disease. IL-25, Interleukin-25. IL-4, Interleukin-4. IL-13, Interleukin-13.

intestinal epithelial remodeling.[3] This process drives intestinal stem cells to differentiate into TCs, facilitating parasite expulsion.[34] Although the role of TCs in intestinal immune regulation is well established,[35] their function within the salivary glands remains largely unexplored. In particular, the molecular mechanisms by which TC derived IL-25 contributes to SjD pathogenesis are not yet fully understood. Here, we observed similar cytokine features in SjD. TCs represent the main source of IL-25 which is elevated in SjD and neutralizing IL-25 with specific antibodies attenuates disease pathology. Based on these findings, we hypothesize that TCs contribute to the pathological progression of SjD by secreting IL-25. We propose that IL-25, released by TCs within striated ducts adjacent to lymphocytic infiltrates, activates ILC2s and Th2 which triggers the secretion of IL-4 and IL-13, ultimately driving disease progression (Fig. 4).

Future research should investigate the mechanisms underlying the increased presence of TCs in SjD, the relationship between TCs and type II immune response, and the upstream regulators of TC derived IL-25 secretion. Additionally, studies should elucidate the signaling pathways through which IL-25 and other potential effector molecules influence target cell function. Such work will provide a critical theoretical foundation for understanding SjD pathogenesis and for the development of targeted therapeutic strategies.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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