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The role of innate lymphoid cells in nasal inflammation and cancer

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Abstract. – OBJECTIVE: The innate lymphoid cells (ILCs) are a recently discovered type of innate immune cell. The functions of these cells resemble different T-cell subtypes. These cells play important roles in local injury, inflammation, pathogen infection, or tumours. However, there have been few studies focusing on the role of ILCs in nasal diseases.

MATERIALS AND METHODS: We reviewed the literature about the roles of ILCs in nasal inflammation, tissue remodeling, and cancer.

RESULTS: The ILCs represent a newly identified family of innate immune cells. These cells play important roles in inflammation, immune responses, tissue remodeling, and cancer immunity. The ILCs, especially ILC2s, play important roles in CRSwNP and AR. ILC2s may be involved in the pathogenesis of eosinophilic inflammation in non-allergic nasal diseases, such as non-allergic CRSwNP and non-allergic rhinitis. ILCs also play pro-tumor or anti-tumor roles in cancer immunity for head and neck cancer.

CONCLUSIONS: LC2s may be a useful therapeutic target for CRSwNP and AR. ILCs may also represent new therapeutic targets to activate anti-tumor immunity in head and neck cancer.

Key Words:
Innate lymphoid cells, T cells, Tissue remodelling, Chronic rhinosinusitis with nasal polyps, Allergic rhinitis.

Introduction

The innate lymphoid cells (ILCs) are a recently discovered type of innate immune cell. The functions of these cells resemble different T-cell subtypes[1]. In contrast to T and B cells, ILCs do not express antigen receptors but instead express a variety of activating and inhibitory receptors[2]. The ILCs can be divided into three subsets based on the expression of cytokines and transcription factors, i.e., ILC1s, ILC2s, and ILC3s, which are analogous to helper T cells[3]. The ILC1s consist of natural killer (NK) cells and T-bet$^+$ ILCs, which respond to IL-12, IL-15, and IL-18 to produce interferon γ (IFN-γ)[4]. The ILC2s express ST2 and CD25, which react to IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) to produce type 2 cytokines[5]. The ILC3s are composed of lymphoid tissue inducer (LTi) cells, natural cytotoxicity receptor (NCR)$^+$ ILC3s,, and NCR$^-$ ILC3s. They express Rorγt and are activated by IL-1 and IL-23 to produce IL-22 and/or IL-17[6].

The ILCs are located in the secondary lymphoid and 'non-lymphoid' tissues of epithelial barrier surfaces, such as the intestine, lung, skin, and nasal cavity[7,8]. The presence of ILC subsets has also been confirmed in the blood[9]. The ILCs are the 'first responders' of the immune system, protect epithelial barriers against pathogens, and maintain tissue homeostasis[10]. These cells can produce large amounts of pro-inflammatory and regulatory cytokines in response to local injury, inflammation, pathogen infection or tumours. However, there have been few studies focusing on the role of ILCs in nasal diseases. Here, we review the roles of ILCs in nasal inflammation, tissue remodelling, and cancer.

The Roles of ILCs in Fibrosis and Tissue Remodelling

Fibrosis is an important feature of most cases of chronic inflammation in epithelial organs, especially in the liver, lung, kidney, and heart[11]. Fibrosis and tissue remodelling involve excessive accumulation of the extracellular matrix (ECM), which is mainly composed of collagen deposits. This leads to structural changes of the tissue and functional impairment, ultimately resulting in organ failure[12]. Both the innate and adaptive immune systems play roles in the progression of fibrosis and tissue remodelling. Some studies[13] suggested that ILCs contribute to several fibrotic diseases and tissue remodelling. The ECM is mainly produced by fibroblasts, the major cells controlling ECM metabolism. The ILCs and their cytokines have been reported to directly regulate fibroblast function[14]. The IFN-γ, an ILC1s product, has been shown to suppress IL-4-induced collagen expression and synthesis in lung fibro-

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blasts[15]. The ILC2s can release cytokines, such as IL-4 and IL-13, which can directly regulate fibroblast function. In Crohn's disease, ILCs produces IL-13, which can inhibit fibroblast matrix metalloproteinase (MMP) synthesis and matrix degradation, leading to excessive collagen deposition[16]. The ILC2s can also express amphiregulin to repair intestinal injury and promote tissue remodelling[17]. IL-33 can activate liver resident ILC2s and promote hepatic tissue remodelling and fibrosis[18]. Additionally, cutaneous injury can promote an IL-33-ILC2s response, which promotes the restoration of skin integrity[19]. The ILC3s secrete IL-17A, which regulates synovial fibroblasts[20], cartilage catabolism[21], and lung connective tissue cells[22] to promote remodelling.

In lung remodelling, ILCs can increase the expression of various genes, including genes encoding the ECM proteins decorin, asporin, dermatopontin, and amphiregulin[23]. This study showed that lung ILC2s were a primary source of amphiregulin, which promotes the restoration of airway epithelial integrity and tissue homoeostasis. Amphiregulin can regulate cell proliferation and differentiation by binding to the epidermal growth factor receptor. The ILCs can also interact with other non-immune cells to promote tissue remodelling[24]. Vannella et al[25] reported that the collective disruption of TSLP, IL-25, and IL-33 signalling reduced the levels of ILC2s and suppressed type 2 inflammation and fibrosis of the lung.

The roles of ILCs in Lower Airway Inflammation

The ILC2s play important roles in lower airway inflammation. Asthma is a serious condition involving obstructive inflammation, airway hyper-reactivity (AHR), and remodelling. Asthma usually presents with type 2 inflammation and is associated with the cytokines IL-5 and IL-13. Type 2 inflammation was previously regarded as mediated by Th2 cells. However, Kim et al[26] suggested that ILCs may mediate airway hyper-reactivity independent of adaptive immunity. The ILC2s have been considered another source of type 2 cytokines and were suggested to play a role in the onset of asthma. Klein et al[27] showed that ILC2s accounted for ~50% and ~80% of IL-5^+/IL-13^+ cells in the lung and broncho-alveolar lavage (BAL) fluid, after IL-25 and IL-33 administration[27]. The ILC2s were suggested to be the main source of eosinophilic airway inflammation in a chronic house dust mite-driven asthma model and to operate independently from B–T cell interaction[28]. The ILC2s may amplify the recruitment of eosinophils from the blood to the airways *via* the production of IL-5 and IL-13[29]. The prevalence of ILC2s in blood is also elevated in patients with asthma[30]. The ILC2s can cause epithelial barrier impairment by reducing transepithelial electrical resistance and increasing fluorescein isothiocyanate-dextran permeability in the cultures of human bronchial epithelial cells[31]. It has also been reported that influenza A virus can induce AHR and asthma through the IL-33-ILC2s axis independent of adaptive immunity[32]. The ILC3s also play a role in adult-onset severe asthma[33].

The ILC2s have also been shown to play roles in other types of airway inflammation. The activation of pulmonary ILC2s in murine models and human subjects can induce eosinophilia and allergic lung inflammation[34]. IL-33 was shown to activate ILC2s without exogenous stimuli in the neonatal lung and to promote type 2 inflammation[35]. The ILC2s in adult mouse lungs can be activated by inhaled allergens and produce large amounts of IL-13 and IL-5[36]. The ILC2s also respond to IL-33 and produce type 2 cytokines in mouse lungs[37]. Furthermore, the ILC2s interact with T cells and promote Th2 inflammation, adaptive immunity, and airway inflammation[38,39]. The ILC2s were shown to play roles in the early allergic response to aeroallergens in the airways, bridging the innate and adaptive immune responses[40]. Many factors, including viruses, tobacco smoke, and pollutants, can result in the activation of ILC2s in allergic disease[41]. It has been reported[42] that protein kinase C-theta (PKC-θ) could activate ILC2s in allergic lung inflammation. Other studies showed that the histone deacetylase inhibitor trichostatin A[43] and *H. polygyrus* excretory/secretory (HES)[44] could suppress murine allergic airway inflammation by blocking the activation of group ILC2s. Whereas the origin of eosinophilia in allergic asthma is largely understood, the triggers underlying eosinophilia in non-allergic eosinophilic airway inflammation remain to be elucidated. The ILC2s may be the main source of eosinophilic inflammation in non-allergic airway inflammation[45].

Although ILCs are known to be involved in pulmonary inflammation, the mechanisms underlying ILC activation, proliferation, and regulation in the lung are not yet clear.

The Roles of ILCs in Cancer Immunity

Cellular stresses may disturb normal cellular processes, DNA proof-reading, and cell division,

which can lead to mutations in the cells and development of cancer[46]. Under normal conditions, the host immune system can recognise and clear cells harbouring mutations by apoptosis *via* immune effector cells[47]. The innate and adaptive immune cells can produce various cytokines to limit the growth of cancer. However, the immune surveillance of cancer is usually inhibited by surviving tumour clones. Cancer cells can proliferate and harness immune responses by destroying anti-tumor effector mechanisms and promote the accumulation of immunosuppressive immune cell subtypes in the tumour tissues[48]. Recently, immunotherapeutic strategies designed to adjust the immune system for the treatment of cancer were reported to show significant benefit in some patients with malignancies[49]. Common methods of cancer immunotherapy include cancer vaccination, adoptive cell therapy, and targeting of immune checkpoints. The development of successful cancer immunotherapeutic regimens will rely on clarification of the innate and adaptive immune systems in cancer.

The ILCs are innate lymphocytes involved in the adaptive immune system and may play a critical role in cancer immunity and immunotherapy[50]. However, few studies regarding the role of ILCs in this process have been performed. NK cells have been shown to directly kill tumour cells *via* natural cytotoxicity[51], and these cells are not discussed further in this review. Different subgroups of ILCs mainly produce different types of cytokines to promote cancer development, maintenance, or elimination[52,53].

The ILC1s secrete large amounts of TNF-α and IFN-γ in response to tumors[54,55]. IFN-γ can kill cancer cells by inhibiting cellular proliferation and promoting apoptosis. Additionally, IFN-γ can increase the expression levels of MHC class I and II molecules on tumor cells and of adhesion molecules on T cells that mediate the tumor-killing functions of these cells[56]. Previous studies[57,58] showed that IFN-γ increased the colonisation of melanoma cells in human and experimental animal models. Furthermore, TNF-α mediates the recruitment and activation of macrophages and dendritic cells (DCs), leading to anti-tumor responses[59]. However, TNF-α has dual roles in cancer, and TNF-α signalling can also promote tumor formation and growth[60].

The ILC2s can respond to IL-33 and release IL-5 and IL-13 to play roles in cancer immunity[61]. The ILC2s usually show pro-tumor activity by promoting tumor formation and progression[62]. This effect seems to rely on the recruitment of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs), Tregs, and M2 macrophages[63,64]. IL-13 promotes the recruitment and activation of MDSCs and inhibits anti-cancer immune responses[65]. IL-13 can also transmit signals through IL-13Rα2 in pancreatic cancer cells. IL-13Rα2 may serve as a prognostic biomarker of invasion and metastasis in pancreatic cancer[66]. The ILC2/IL-13 axis is also correlated with the level of monocytic MDSCs in bladder cancer, which is a predictor of tumor recurrence[67]. Trabanelli et al[68] indicated that ILC2s activated monocytic MDSCs *via* IL-13 secretion in acute promyelocytic leukaemia[68]. In breast cancer, IL-33-induced ILC2s can release IL-13 to increase MDSC numbers and reduce the numbers of NK cells[69]. IL-5 can activate and recruit eosinophils, which express cytotoxic activity and clear tumour cells. Hence, ILC2s also have effects in tumor surveillance through the production of IL-5.

The ILC3s may contribute to either pro-tumor or anti-tumor mechanisms, depending on the tumor microenvironment and stage. IL-23-induced ILC3s release IL-17 and IL-22 to maintain barrier homeostasis against cancer cells[70]. IL-23 signalling can promote tumor growth and progression, as well as the development of a tumoral IL-17 response[71]. IL-23 was also reported to activate ILC3s to promote gut tumorigenesis through IL-17 responses[72]. Kirchberger et al[73] reported that the numbers of IL-17$^+$IL-22$^+$ ILCs were increased in colon cancer. IL-22 had a unique role in the maintenance of cancer. IL-22 produced from ILC3s activates STAT3 signalling to promote colitis-associated cancer[74].

The Roles of ILCs in Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is a condition involving the chronic inflammation of the nasal cavity and sinuses, which can last for at least 3 months. CRS can be divided into two subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRSwNP has a more complex pathogenesis than CRSsNP. CRSwNP is usually associated with type 2 inflammation, which manifests as IgE elevation, IL-5, IL-13 secretion, and eosinophilic inflammation, especially in Caucasian patients. Therefore, CRSwNP has been linked with Th2 cells.

There is accumulating evidence that ILC2s, which are activated by TSLP, IL-25, or IL-33, play roles in the pathogenesis of CRSwNP. The

classic mechanism underlying the activation of naive T cells and the proposed mechanism of amplification by ILCs previously described are both bypassed in CRSwNP[75]. The ILCs may be closely related to environmental triggers, such as viruses and allergens. Poposki et al[76] reported that all ILCs subsets were present in nasal polyps (NP) but that ILC2s were dominant and significantly elevated compared with peripheral blood mononuclear cells, tonsil, CRSsNP, and normal sinus tissue. They suggested that ILC2s were activated in CRSwNP *in vivo* and may play important roles in the type 2 inflammation in CRSwNP. Ho et al[77] also reported higher levels of ILC2s in polyp tissue compared to sinus mucosa. Lee et al[78] reported that severe asthmatics with CRS had higher ILC2 counts in their nasal tissues. ILC2-induced type 2 inflammation may contribute to the decline of lung function and the recalcitrant status of asthma control. It has also been suggested that ILC2s are significantly enriched in CRSwNP and allergic CRS patients[79]. The ILC2s may represent early events in the pathogenesis of CRSwNP[80]. However, there have been very few studies[81] regarding the roles of ILC1s and ILC3s in CRS.

Tissue damage may lead to IL-33 expression in NP, which can activate the ILC2s responsible for perpetuating eosinophilic inflammation in CRSwNP[82]. An increased percentage of ILC2s is also observed in inflamed sinonasal mucosa from CRSwNP compared with CRSsNP. These ILCs secrete IL-13 in response to IL-33 stimulation[83]. TSLP, a protein that can activate ILC2s, is involved in many inflammatory processes, including asthma and allergic rhinitis (AR). The activity of TSLP is increased in NP tissue[84] and is involved in the pathogenesis of polyposis[85]. The number of $TSLP^+$ cells in nasal polyps from patients with atopy was also significantly greater than that in the non-atopic patients[86]. TSLP regulates the function of human ILC2s by enhancing expression of the transcription factor GATA3 in the NP of patients with CRSwNP[87]. IL-25, a member of the IL-17 family, plays roles in the pathogenesis of CRSwNP *via* modulation of ILC2s[88]. IL-25 expression was increased at both mRNA and protein levels in NP tissues compared with the control uncinate process tissues. Exposure to IL-25 simultaneously activated ILC2s and Th2 cells in NP, which further increased Th2 cytokine production *in vitro*[89]. The ILC2s were enriched in NP and responsive to IL-25 and IL-33[90]. Additionally, TSLP, IL-25 and IL-33, which were shown to act on ILC2s and Th2 cells, can induce IL-4, IL-5, and IL-13 in CRS[91,92].

The ILC2s are closely related to other immune cells, such as B cells and eosinophils. The ILC2s may play an important role in B cell responses or in their local class switch recombination in CRSwNP[93]. The numbers of ILC2s are elevated in patients with CRSwNP. These cells may play a role in the activation and survival of eosinophils[94]. Scholars[45,95-98] also suggested that ILC2s were elevated in polyps in eosinophilic CRSwNP compared with non-eosinophilic CRSwNP, CRSsNP, and controls. However, some studies[98,99] did not show increased proportions of ILC2s in peripheral blood. This happens because ILC2s are recruited from the peripheral blood circulation and enter the nasal mucosa. In CRSwNP, there is a synergistic effect among ILC2s, eosinophils, and Th2 cells. The ILC2s can activate the eosinophils and prolong their survival. In return, pre-activated eosinophils can enhance IL-5 production of ILC2s in an IL-4-dependent manner[100]. The ILC2s also promote the proliferation of Th2 cells[97]. In CRSwNP, systemic corticosteroid treatment can reduce ILC2s and increase ILC2 apoptosis[80,95].

Allergic fungal sinusitis (AFRS) is a special type of CRS, which manifests as characteristic CT imaging findings, nasal polyps, allergy to fungi, and eosinophilic mucin. Padro et al[101] reported equivalent levels of ILC2s and a small trend towards increased Th2 cell numbers in AFRS. AFRS may result from defects in the innate immune system reflected by the inability to clear fungi from the sinuses.

Taken together, the results outlined above indicate that ILC2s play important roles in CRS and represent novel therapeutic targets.

The Roles of ILCs in AR

AR is a type of chronic rhinitis, which is caused by evident allergens. AR is a type 1 hypersensitivity reaction in the nasal mucosa mainly mediated by IgE, which shows Th2 and eosinophilic inflammation. Patients with AR usually show nasal obstruction, sneezing, rhinorrhoea, and nasal itching. As mentioned above, ILCs (especially ILC2s) play important roles in allergic lower airway inflammation. However, the roles of ILCs in AR are still unclear.

Peripheral blood ILC2s were reported to rapidly increase in patients with AR after a cat allergen challenge. The mechanisms underlying the increase of ILC2s in the peripheral blood may trigger by both humoral and cellular mechanisms[102]. Kato et al[103] reported that ILC2s resided in the nose and produced IL-5 and IL-13 in $Rag2^{-/-}$ mice

sensitised with ragweed pollen. They suggested that ILC2s alone could not induce strong nasal responses. Kumagai et al[104] suggested that ozone induced eosinophilic rhinitis, nasal epithelial remodelling, and type 2 inflammation dependent on ILCs[104]. Lin et al[105] reported that ILC2s played a pro-inflammatory role in a murine AR model. They considered ILC2s a potential new target for future AR therapy. Prostaglandin D2 and leukotriene D4 induced by mast cells and basophils can activate ILC2s in patients with AR or local allergic rhinitis (LAR), thus promoting immediate-phase[106] and late-phase responses[107]. Some studies also suggested that allergen subcutaneous immunotherapy could suppress ILC2s in patients with AR[108,109]. However, the effects of immunotherapy on ILCs are still uncertain[110]. Additionally, the activation of ILC2s in a mouse model of AR may induce resistance to corticosteroid treatment[111]. Zhu et al[112] found that miR-155 played critical effects on Th2 factor expression and allergic inflammatory response in ILC2s in AR.

There have been few studies[113,114] regarding the roles of ILCs in AR. Several reports have presented details regarding the production of pro-inflammatory cytokines by ILCs, such as IL-25, IL-33, and TSLP. The IL-33 levels in the sera of patients with AR were significantly higher than those of the controls. Expression of IL-33 and its receptor ST2 were significantly increased in the epithelium from patients with AR[115]. The level of TSLP was also increased in AR patients[86]. Xu et al[116] reported that the levels of both TSLP and IL-25 were significantly elevated in patients with AR. Furthermore, IL-25 enhanced dsRNA-induced TSLP production in human nasal epithelial cells (Figure 1).

As ILC2s induce type 2 inflammation independent of allergen stimulation, further studies are required to determine the roles of these cells in non-allergic rhinitis.

The Roles of ILCs in Cancer of the Head and Neck

There have been few papers regarding ILCs in cancer of the head and neck and in the primary stages. Several studies regarding the cytokines, such as TNF-α, IFN-γ, IL-5, IL-13, IL-33, IL-23, and IL-17, associated with ILCs in cancer of the head and neck, have been published. However, the results are still controversial.

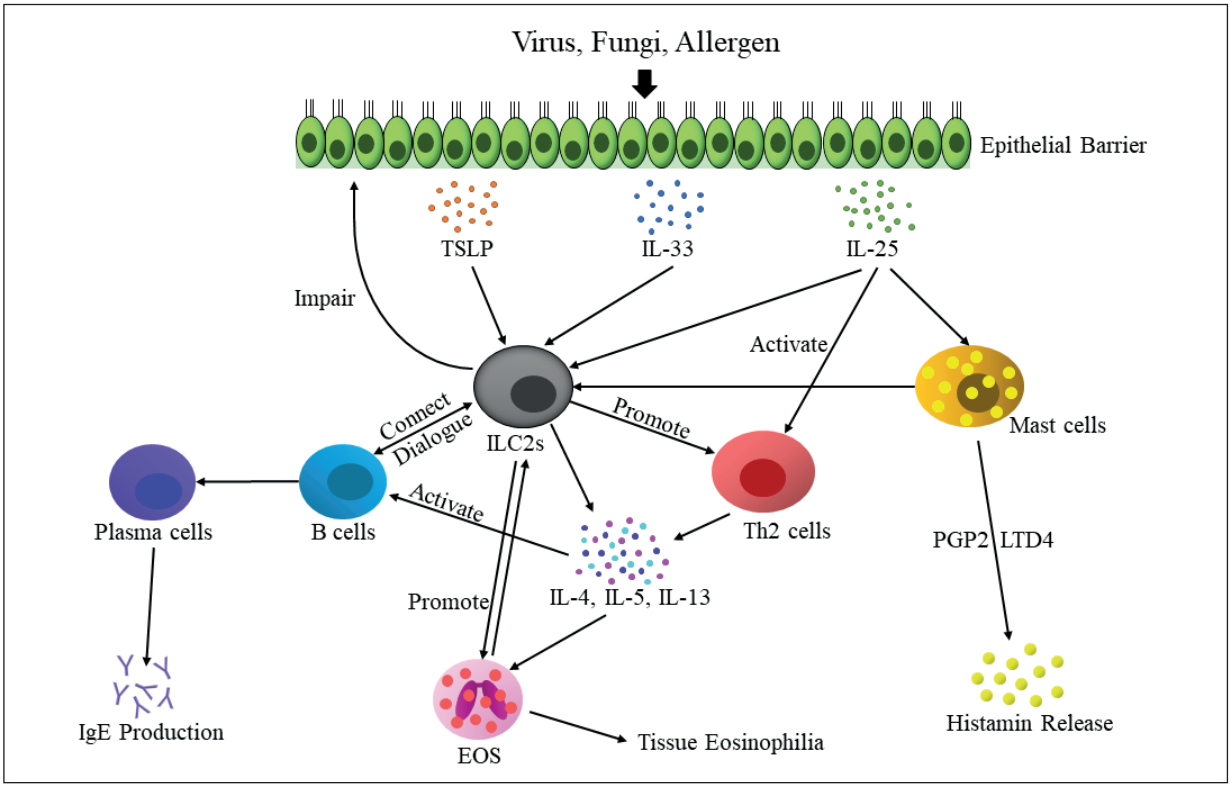

Figure 1. The roles of ILC2s in CRS and AR.

The role of TNF-α in head and neck cancer is unclear[117]. Arthur et al[118] suggested that TNF-α and IFN-γ play roles in head and neck squamous cell carcinoma (HNSCC). Sánchez-Rodríguez et al[119] reported that TNF-α and IFN-γ played anti-tumor roles in HNSCC. A pilot study[120] demonstrated significant decreases in the serum levels of IFN-γ and IL-13 in patients with HNSCC. In contrast, Hoffmann et al[121] reported that the levels of TNF-α and IFN-γ were altered in the serum of patients with HNSCC compared with healthy individuals. Si et al[122] suggested that TNF-α promoted tumor formation in HNSCC by mediating the genome-wide redistribution of the cREL/p63/p73 and AP-1 interactome, to diminish the TAp73 tumor suppressor function. Other studies[123,124] also indicated that TNF-α in the plasma of HNSCC patients was upregulated and significantly related to shorter survival. By contrast, Eyigor et al[125] did not detect TNF-α and IFN-γ in peripheral venous blood samples from patients with HNSCC. Serous levels of TNF-α were found to be quite high in cases of squamous cell tonsil carcinoma. After radiotherapy, the TNF-α levels returned to normal limits[126]. Yuan et al[127] suggested that there was no significant association between TNF-α-308G/A polymorphism and the risk of head and neck cancer.

IL-13 showed cytotoxin anti-tumor effects on head and neck cancer cells[128,129]. However, the role of IL-13 in cancer of the head and neck is still controversial. Aziz et al[130] reported that the salivary IL-13 level was upregulated in patients with oral squamous cell carcinoma. It was also suggested that there are no differences in IL-13 gene polymorphisms between patients with HNSCC and healthy subjects[131]. Chen et al[132] identified IL-33 as a critical mediator in the carcinoma-associated fibroblast-induced invasiveness of HNSCC. Recent studies[133,134] showed that the serum concentrations of IL-17 were significantly elevated in patients with laryngeal squamous cell carcinoma and oral epithelial squamous cell carcinoma. Upregulation of the IL-17 level is also associated with poor prognosis in squamous cervical cancer and oropharyngeal squamous cell carcinoma[135,136]. IL-23 can induce IL-17 secretion in HNSCC[137] (Figure 2).

Conclusions

The ILCs represent a newly identified family of innate immune cells. These cells play important roles in inflammation, immune responses, tissue remodelling, and cancer immunity. The ILCs,

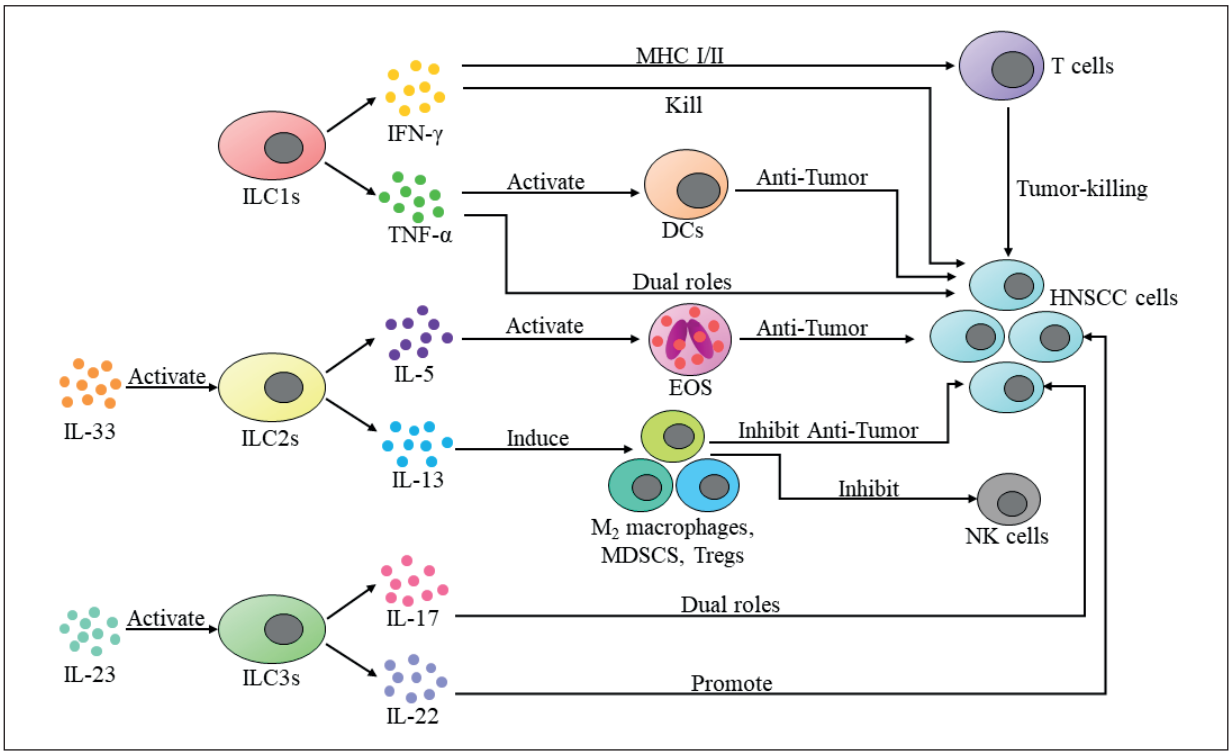

Figure 2. The roles of ILCs and its cytokines in cancer immunity of the head and neck.

especially ILC2s, play important roles in CRS and chronic rhinitis, especially in CRSwNP and AR. The ILC2s may be involved in the pathogenesis of eosinophilic inflammation in non-allergic nasal diseases, such as non-allergic CRSwNP and non-allergic rhinitis. The ILC2s may be a useful therapeutic target for these diseases. The ILCs also play pro-tumor or anti-tumor roles in cancer immunity. These cells may represent new therapeutic targets to activate anti-tumor immunity in head and neck cancer.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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