The Contradictory Role of Interleukin-33 in Immune Cells and Tumor Immunity

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Abstract: Interleukin (IL)-33 is a member of the IL-1 superfamily and is a crucial cytokine playing the role of a dual-function molecule. IL-33 mediates its function by interacting with its receptor suppression of tumorigenicity 2 (ST2), which is constitutively expressed on T helper (Th)1 cells, Th2 cells, and other immune cells. Previously, we summarized findings on IL-33 and performed an intensive study of the correlation between IL-33 and tumor. IL-33 enables anti-tumor immune responses through Th1 cells and natural killer (NK) cells and plays a role in tumor immune escape in cancers via Th2 cells and regulatory T cells. Herein, we discuss the contradictory role of IL-33 in immune cells in different cancer, and our summaries may be helpful for better understanding of the development of research on IL-33 and tumor immunity.

Keywords: IL-33, cancer, immunity, immune cells

Introduction

Interleukin-33 (IL-33) is a cytokine that is part of the IL-1 family, which plays a key role in tumor immunity. Honda discovered IL-33 20 years ago, and IL-33 can be expressed as DVS27 in canine vasospastic cerebral cells.¹ A computational database study in 2015 yielded a compelling rationalization for the IL1R family, and IL-33 was identified as a tumorigenicity 2 receptor (ST2) ligand.² ST2 was first identified as an orphan receptor in 1989, and is encoded by the *IL1RL1* gene. IL-33 is likely a mediator of the factors in the T helper (Th)2 responses and the diseases associated with its receptor. The IL-33-ST2 axis is closely linked to several conditions, such as allergies,³ cancer and cardiovascular diseases.⁴ Given the inflammatory mechanisms in tumorigenesis, immunotherapy has become a current research trend and a novel method for tumor treatment.

In this review, we describe the characteristics and biological functions of IL-33. Importantly, we highlight recent studies on IL-33 in the immune mechanism, and summarizes the pivotal role of IL-33 in the pathogenesis of tumor immune in different cancers.

The Basic Function of IL-33

IL-33 is close to IL-1 α and high mobility group box 1 (HMGB1).^{5,6} IL-33 is located in the nucleus and functions as a cytokine.⁷ We summarize the most recent identification of the biological characteristics and functions of IL-33 (Figure 1), and explore its role in the inflammatory response in cancer.

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Figure 1 Source of IL-33 and the IL-33/ST2 signaling pathway. The biological activation of IL-33 could be released during necrosis and apoptosis from fibroblasts, epithelial cells and endothelial cells. IL-33 could bind the receptor complex and result in the activation and recruitment of MyD88, IRAK1/4 and TRAF6, cause the response of NF-κB, MAPK, causing inflammatory responses.

Molecular Characterization of IL-33

The human IL33 gene spans about 42 kb in genomic DNA, and contains eight exons.⁸ Human IL33 mRNA (2.7 kb) encodes 270 protein residues.^{2,8} The 12 β-strands are arranged in a β-trefoil fold, which is similar to that of the other family members, and contains a three-dimensional structure.^{9,10} IL-33 comprises a nuclear domain, central domain, and IL-1 like cytokine domain, which are considered functional domains.¹¹ Its gene is found in mice and humans, and has been delineated to human chromosome 9p24.1 and mouse chromosome 19qC1. A homeodomain-like helix-turn-helix in the N-terminus is a requirement for its nuclear translocation.⁸

IL-33 Expression and Release

IL-33 mRNA is expressed in a variety of organs and cell types in human and mice.² IL-33 protein can be detected in fibroblasts, epithelial cells, and endothelial cells, particularly in high endothelial venules.^{5,12-15} Due to its blood vessels expression in endothelial cells,^{5,16} IL-33 protein is expressed in nearly all organs. Biologically activated IL-33 is released during necrosis and apoptosis. IL-33 is cleaved by caspases-3/7, which inactivates its pro-inflammatory characteristic. The full-

length IL-33 may act as an endogenous danger signal.¹⁷

The pro-inflammatory IL-33 is found in necrosis, and responses to viruses result in the release of IL-33.¹⁸ There have been numerous studies on IL-33 release and secretion. Infection and autoimmune diseases are tightly connected with the immune system. For this reason, IL-33 plays an extracellular role and functions in a merocrine manner at all times.¹⁹ Living cells release IL-33 when the human bronchial epithelium is exposed to *Alternaria*,²⁰ fibroblasts release it upon experiencing stress.²¹ In addition, extracellular ATP can stimulate IL-33 production or secretion in models of allergic inflammation.^{20,22,23}

IL-33-Induced Tumor Immune Regulation

Considerable expression data support the interaction between IL-33 and tumors. However, the immunological mechanism is largely unknown.²⁴⁻²⁷ It has been revealed that the tumor microenvironment is primarily orchestrated via inflammatory cells, and plays a key part in fostering the proliferation, survival and migration of tumor progression. Recently, many studies have emphasized the important role of IL-33 in tumor immunity.

The IL-33 receptor is a heterodimer, which is termed IL-1RL1, also known as ST2, IL-1RAcP and T1. ST2 mRNA is from serum-stimulated fibroblasts and has two major forms: transmembrane (ST2L) and soluble ST2 (sST2). ST2 is abundantly expressed on the surface of Th2 and mast cells, instead of Th1 cells. IL-33 promotes ST2 expression, which can occur in Th2 lymphocytes when applied together with a STAT5 (signal transducer and activator of transcription 5) activator. However, ST2 is dependent on the transcription factors T-bet and STAT4. In mice, lymphocytic choriomeningitis virus induces transient upregulation of Th1 cells via ST2. The unique biological effects of IL-33 likely depend on ST2 expression. Nuclear factor kappa-B (NF- κ B) and mitogen-activated protein kinases (MAPK) are activated in cells activated by links between IL-33 and ST2. In addition, ST2 can be expressed in various immune cells, such as group 2 innate lymphoid cells (ILC2s), Th2 cells, dendritic cells (DC), basophils, eosinophils, mast cells (MC), myeloid-derived suppressor cells (MDSC), and regulatory T (Treg) cells.¹¹ In fact, the most recent studies have reported that ST2 is also expressed in immune cells of type1 immunity, such as Th1 cells, natural killer (NK) cells, CD8⁺ T cells, neutrophils, macrophages, B cells, and NKT cells.^{28–30} IL-33

appears to be a double-edged sword, often combining with different immune cells to play different roles across different identities and methods. Our in-depth understanding and summary of tumor immunity studies based on the characteristics of IL-33 will aid exploration of the pathogenesis of IL-33 in tumors (Figure 2).

IL-33 Affecting Anti-Tumor Immune Responses Through Th1 and NK Cells

Virchow et al first³¹ found inflammatory cells in tumor tissue in 1853. Inflammation is believed to be the body's mechanism for resisting pathogen invasion. Inflammatory factors, such as IL-33, exert anti-tumor effects in many ways. The role of IL-33-ST2 in adaptive type 1 immune and innate immune responses mainly depend on the expression of ST2 by CD8⁺ T cells, Th1 cells, and NKT cells.^{28,30,32,33}

CD8⁺ T cells are a part of the polarized type 1 cytotoxic (Tc1) cells, which can express ST2. ST2 expression in Tc1 cells is determined by T-bet, a Th1/Tc1 transcription factor. Most T-bet is expressed in the effector CD8⁺ T cells, and has a prominent effect on their performance.^{34,35} Previous studies discovered the function of T-bet for IL-33, where it

Figure 2 ST2⁺ immune cells play the contradictory role in tumor with the influences of IL-33. The IL-33 affecting anti-tumor-immune responses through Th1 cells and NK cells in anti-tumor. It could promote the expression of IFN- γ or CD107a in Melanoma. However, IL-33 also accelerate tumor immune escape through Th2 cells and regulatory T cells with the secretion of IL-5 or IL-13. The contradictory role of IL-33 in tumor would be explored in future.

is used to promote the production of interferon (IFN)- γ together with IL-12.³² In tumor tissues, IL-33 strengthens the function of CD8⁺T cells, thereby enriching IFN- γ production, inducing a tumor microenvironment that supports the complete recovery of the tumor.³⁶ Recombinant IL-33 plays a significant role in prolonging the survival of mice with acute myeloid leukemia (AML) in a CD8⁺T cell-dependent manner.³⁷ This study suggested the key function of exogenous IL-33 in enhancing the rapid growth of the effector memory CD8⁺ T cells and the anti-tumor effect.

Several lines of evidence indicate that NK and NKT cells play an anti-tumor role. IL-33 acts directly on both human²⁸ and mouse³⁰ immune cells, which is consistent with the function of CD8⁺T cells. Regarding IL-12 function, NKT and NK cells promote IFN- γ production which leads to the establishment of Th-1 immunity.³⁶ Several other studies have revealed the function of IL-33 in the anti-inflammatory effect through NK and NKT cells. IL-33^{-/-} mice in particular have modulated CD25⁺ NK cells and other large numbers of immune cells. Undoubtedly, IL-33 acts as a potent immune cell modulator.³⁸ IL-33 exerts its anti-tumor effects through NK cells, IFN- γ , and perforin effector molecules. Compared with mice with injected with control monoclonal antibodies (m-Abs), mice injected with anti-NK or anti-CD8 mAbs had shorter survival. Similarly, another study injected recombinant IL-33 protein into the spleen of mice bearing subcutaneous B16 cells, and enhanced the rates of CD107a⁺IFN- γ ⁺ NK cells.³⁹ The compared analyses all suggested that IL-33 may mainly play a contrary role in the tumor microenvironment via NK cells.

IL-33 expression, such as by DC and Th17 cells, is involved in preventing tumor development. IL-33 can also induce Th9 cell differentiation and enhance anti-tumor efficacy with the aid of dectin-1-activated DC.⁴⁰ Recombinant IL-33 (RIL-33) was used for treating chronic colitis in mice of the colonic proper, where it promoted Th17 cell numbers.⁴¹ MC are effective tissue-resident immune cells that highly express ST2 activation induces and regulates the tissue environment.⁴² Given its intricate dual role in cancer, IL-33, which is targeted in cancer immunotherapies should be considered with caution.

IL-33 Accelerate Tumor Immune Escape Through Th2 and Treg Cells

The inflammatory response is a double-edged sword, and the response process also has a key function in promoting cancer cell proliferation, invasion, and metastasis. Cancer cells develop and proliferate in the tumor microenvironment via

combating the immune system. Inhibition, tolerance, and escape are recognized as the key pathogenesis in tumor evasion of immune surveillance. IL-33 regulates the viability and survival of myeloid and lymphoid cells, playing a key role in the production of type 2 immune mediators.^{43,44} The lymphoid cells with ST2 include Th2 cells, Treg cells, and ILC2. ST2 is expressed first by Th2 cells. Anti-tumor immunity is dominated by the Th1 response. When the body mainly exhibits a Th2 phenomenon, it indicates that anti-tumor immunity is in a state of inhibition.

IL-33 expanded Treg cells expressing ST2 can be found in immune or non-immune tissues, with potent suppressor function in anti-tumor immunology. In the presence of IL-33, Treg cells are unable to inhibit effector T cells. For example, CD4⁺FOXP3⁺ Treg cells in the lungs express ST2. IL-33 induces the activation of type 2 cytokines manipulation and Treg cells by increasing the canonical Th2 transcription factor GATA-binding protein 3 (GATA3) and ST2.⁴⁵ IL-33 not only enables Treg cell proliferation, but also favors their immunosuppressive properties. Treg cell can enhance the reduction of IFN- γ , and upregulates GATA3 and ST2 production in IL-33-treated mice.⁴⁶

ILC in damaged epithelium releases IL-33 during type-2 innate immune responses; IL-5 production or increases IL-13.⁴⁷ The anti-tumor responses of IL-33 are largely dependent on NK cell expansion and activation. ILC2s lead to the promotion of tumor growth via NK cell expansion and activity.⁴⁸ The expansion of the ILC2 population modifies adjust of IL-33 and Arg1 (arginase 1).⁴⁹ ILC2 may play a negative role in anti-tumor responses.

Alternative activated macrophages (AAM) also have a crucial role in type 2 immunity. IL-33 with (AAM) accelerates the healing of cutaneous wounds. IL-33 plays a key role in magnifying AAM location and chemokine production.⁵⁰ IL-33 mediates eosinophilia and plays a significant role in Th2 immunity in chronic intestinal inflammation, which is dependent on the gut microbiome.⁵¹ In short, aided by Treg, AAM and the regulation of IL-33 prevent allograft rejection and tissue injury during infection.⁵²⁻⁵⁴

The Role of IL-33 in Cancer by Immune Surveillance

Tumor development is inextricably linked to immune surveillance. The immune system can identify the immunogenic

cellular components of tumor cells. IL-33 has varied effects on the different stages of different cancers (Table 1).

Colorectal Cancer

Colorectal cancer (CRC) is one of the leading causes of cancer death around the world.⁵⁵ IL-33 is associated with CRC development. It was firstly reported in 2014 that the IL-33-ST2 interaction would be more gainful in metastasis of human CRC.⁵⁶ The expression level of ST2, but not IL-33, in CRC tissues is associated with tumor-node-metastasis (TNM) stage, and the clinical stage of patients was closely related to ST2 levels.⁵⁷

O'Donnell et al found that compared with non-tumor tissue ST2L expression was lower in CRC tissues.⁵⁸ However, the functions may be connected with the cell type, tissue, and organ examined; therefore, further research on the role of IL-33 and ST2 in CRC is required.

The tumor microenvironment and intestinal microecology are the main key pathogenesis in the current cancer research. A larger amount of sST2 in the tumor

microenvironment causes altered tumor angiogenesis by IL-33.⁵⁹ Similar research has also revealed that IL-33 promotes polyposis through the formation of a pro-tumorigenic microenvironment. The extracellular matrix components, remodeling proteins, growth factors, angiogenesis regulators, and activated stoma are indispensable components for tumor growth.⁶⁰ These substances expressed by subepithelial myofibroblasts and MC can respond to IL-33.⁶⁰ In inflammatory bowel disease (IBD) in humans, the increase IL-33 and the associated accumulation of Treg cells is prone to inducing cancer. IL-33-Treg axis blockade can regulate chronic inflammation through a tumor-promoting immune environment.⁶¹ Moreover, increased IL-33 could recruit tumor-infiltrating ST2⁺Treg cells in mouse colon cancer model,^{51,62} and Treg ST2KO (St2 knockout) mice had significantly increased CD8⁺ T cells.⁶¹ Charlotte et al found an anti-tumorigenic role for IL-33 in colon cancer. IL-33 stimulation induced the migration of colon cancer cells, which was connected with the decrease in macrophage in vitro.⁵⁸ In a colon-26 tumor

Table 1 Summary of IL-33 Has Varied Effects on the Different Cancers

Cancer Type	Role of IL-33			
	Tumor Suppressor	Ref.	Tumor-Promoting	Ref.
Colorectal cancer (CRC)	Macrophage IgA-microbiota axis CD8 ⁺ T Cell -	[58] [64] [63] -	promotes polyposis IL-33/Treg axis MMP9, MMP2 Recruit of tumor-infiltrating ST2 ⁺ regulatory T cells	[60] [61] [53] [51,62]
Breast cancer	CD8 ⁺ T, NK Cells breast cancer stem cell	[21] [72]	MDSC NK cells, Th1/Th17 cytokines	[51,69] [71]
Gastric cancer	ILC2s Arginase-I, Treg Tristetraprolin	[79] [72] [78]	the activation of JNK pathway macrophage polarisation -	[77] [80] -
Lung cancer	Eosinophils -	[85] -	the tumor-associated M2 macrophages and regulatory T cells NF- κ B signaling	[83] [84]
Head and neck cancer	-	-	Treg	[87]
Melanoma	CD8 ⁺ T cells and NK cells Th9 Cells eosinophils	[70,81] [40] [39]	ILC2s Treg -	[45] [94] -
Pancreatic tumor	ILC2s	[95]	-	-
Acute myeloid leukemia	CD8 ⁺ T cells	[36]	-	-
Esophageal squamous cell carcinoma (ESCC)			Treg	[94]

model, the balance between CD8⁺T cells and Treg cells in the tumor microenvironment plays a key role in IL-33 mediated antitumor responses.⁶³

In this context, comprehensive consideration of intestinal microecology and tumor immunity is important. IL-33 plays different roles in intestinal microecology. IL-33^{-/-} mice treated with dextran sulfate sodium (DSS) had increased IL-1 α release in the form of colitis closely related to overexpression of the mucolytic bacterium *Akkermansia*.⁶⁴ On the contrary, there was no difference in the number of tumors between *Apc Min*^{+/+} mice (transgenic mice expressing IL-33 in the intestinal epithelial cells) injected with V33 and *Apc Min*^{+/+} mice injected with antibiotics.⁶⁵

To conclude this section, further studies are required to explore the present accumulation of findings for the role of IL-33 in CRC immunology.

Breast Cancer

Breast cancer was among the 10 predominant cancers in women in 2017.³⁷ To our knowledge, the first report to show that IL-33 can accelerate 4T1 breast cancer progression is related to cancer immune escape. A large sample experiment showed that patients with breast cancer had notably higher serum IL-33 (sIL-33) levels than healthy controls.^{24,66,67} sST2 levels in patients with estrogen receptor (ER)-positive breast cancer is associated with poor prognosis.⁶⁸ The IL-33-ST2 axis promotes breast cancer growth and metastases by suppressing anti-tumor immunity and enhancing neoangiogenic. IL-33 treatment might amplify the immunosuppressive activities of positive MDSC. The administration of IL-33 accelerates breast cancer progression, which is associated with increased intratumorally accumulation of MDSC.^{51,69} The subsequent induction of Treg cells may lead to suppressed NK cell cytotoxicity the tumor growth and metastases.²¹ However, it has been proved that IL-33 inhibits tumor growth and metastasis in breast cancer through CD8⁺T and NK cells in tumor tissue.⁷⁰ Jovanovic et al found that mice with mammary carcinoma had reduced tumor growth and metastasis due to the deletion of St2 and the increased NK cell cytotoxic activity. They further discovered that St2 deletion increased the balance of Th1/Th17 cytokines in tumor-bearing ST2^{-/-} mice.⁷¹ Kim et al found that IL-33-induced COT phosphorylation to enhance ERK1/2 (MAPK3/1), JNK1/2 (MAPK8/9) and STAT3 activity. In the breast, IL-33 also plays a facilitating role during epithelial cell proliferation and

tumorigenesis.³⁹ In breast cancer, IL-33 can also give rise to endocrine resistance via cancer stem cell-like properties in breast cancer.⁷² In summary, IL-33 might be a suitable biomarker for predicting the malignant potential and immunosuppression of breast cancer.

Gastric Cancer

Gastric cancer (GC) also has a high mortality rate.⁷³ As far as we know, sIL-33 levels are related to GC status. IL-33 levels in patients with GC are significantly higher than that in healthy volunteers, and are factors of poor prognosis factors.^{74,75} The most recent report evaluated the connection between sIL-33 levels in patients with GC and progression-free survival (PFS).

Pre-chemotherapy patients have significantly higher sIL-33 levels than post-chemotherapy patients and healthy people. IL-33 can be used to as a predictive biomarker of PFS in patients with GC and has been⁷⁶ considered a good marker for clinical use. It has been suggested that sIL-33 levels should be detected before drug medication during the genetic therapy of GC. The emphasis on IL-33 results from activation of the JNK pathway and the ST2 expression caused by IL-33. Therefore, IL-33 and ST2 adverse to platinum therapy in GC.⁷⁷ Suppressing IL-33 expression led to the effect of GC process during the inhibition of triste-trapoxin.⁷⁸ We were able to combine the two as a target for cancer treatment. IL-33 in the tumor micro-environment and the increased of sIL-33 in GC affects the immunosuppressive microenvironment and the ILC2 effector cells.⁷⁹ IL-33, which contained inILC2s can influence the immunosuppressive microenvironment in GC. The significant upregulation of IL-33 in macrophages is associated with the expression of SPEM (spasmolytic polypeptide-expressing metaplasia). The progress of SPEM is derived from IL-33 through acceleration of the Th2 inflammatory response, and leads to the recruitment of M2a-polarized macrophages.⁸⁰ Moreover, an evaluation of 126 patients with GC reported that IL-33 represents the immune characteristics associated with Treg cells in GC.⁸¹ IL-33 can also be considered an effective biomarker for predicting GC progression.

Lung Cancer

One study found, for the first time that the bronchoalveolar lavage fluid (BALF) of patients with non-small cell lung cancer (NSCLC, n=45) had markedly lower IL-33 levels than that of patients with Bardet-Biedl syndrome (BBS). However, receiver operator characteristic (ROC)

curve analysis showed that the effectiveness of IL-33 in the serum and in BALF for lung cancer diagnosis was uncertain.⁸² Wang et al established a patient-derived NSCLC tumor xenograft model, and treated it with recombinant IL-33 protein and IL-33 neutralizing antibody or ST2 neutralizing antibody. They discovered that inhibiting IL-33 could slow the growth of xenograft and limit the proliferative viability of NSCLC cells by enhancing the accumulation of tumor-associated M2 macrophages and Treg cells.⁸³ As IL-33 promotes the activation of NF- κ B signaling, which is related to CD8⁺ T cells and NK cell proliferation, activation, and infiltration, they found that it is a useful therapeutic strategy for restricting NSCLC glycolysis and tumor progression by blocking IL-33 in clinical practice.⁸⁴ Another study reported that IL-5 and IL-33 may have a joint direct effect on eosinophils that creates an antitumorigenic environment.⁸⁵ To sum up, considering both aspects of IL-33 may be a useful approach for the clinical treatment of lung cancer.

Other Cancers

IL-33 has also been investigated in other kinds of tumor. The Th1/Th17 immune response can induce disease progression, while higher IL-33 is associated with the advance of inflammatory autoreactive T cells in a receptor-independent manner. The IL-33-ST2 axis has a protective effect in Con A-hepatitis (concanavalin A-induced hepatitis). ST2-deficient mice with dominant Th1/Th17 systemic response developed more severe hepatitis, with higher inflammatory cell invasion in the liver.⁷⁹ A study of head and neck cancer, a paracrine effect of IL-33, in the carcinoma-associated fibroblast (CAF)-related promotion of cancer aggressiveness. High IL-33 expression in the CAF was tightly related to poor clinical outcome.⁸⁶ Immunohistochemistry of 68 patients with laryngeal squamous cell cancer showed a clear association between IL-33 and Tregs in neck squamous cell carcinoma (HNSCC).⁸⁷ IL-33 might be a prospective biomarker in the clinical diagnosis of glioma, where IL-33 expression can be used for predicting disease development based on the expression of its mRNA and protein.^{88–90} In melanoma, CD8⁺ T and NK cell promulgation, activation and infiltration through the NF- κ B signaling way, and IL-33, could inhibit pulmonary metastasis in B16 melanoma and LLC (Lewis lung cancer) mouse models.⁹¹ Advanced research found that IL-33 can activate eosinophils to promote the efficient killing of target melanoma cells, suggesting that IL-33 treatment leads to immediate anti-tumor

activity of eosinophils. These findings support the premise that IL-33 regulates tumor growth and pulmonary metastasis.³⁹ The dual role of IL-33 indicates that IL-33based cancer immunotherapies must discuss this possibility.

Concluding Remarks

Cytokine regulation is an essential process in tumor immunity because of the direct link to tumor oncogenesis and treatment. The most recent findings show that it is apparent that IL-33 is a broadly active co-stimulator of immune cell responses. Integrated research has found that IL-33 is highly expressed in normal epithelial cells in many lining tissues, suggesting a role in immune surveillance of tissue damage. Accordingly IL-33 is also referred to as alarmin, as it may function as a damage-associated molecular pattern (DAMP) molecule⁵ whose expression is increased after damage.

IL-33 also acts as a central mediator to drive Th2 differentiation to induce IL-5 and IL-13 production.^{92,93} Studies have reported primarily on Th1 immune responses with respect to IL-33. IL-33 function is connected to the tumor microenvironment. In our understanding, IL-33 is related to tumor immunity and develops from infection to inflammation and metabolic disease. However, its presence and function in tumors are uncertain. Here, we summarize the connection between IL-33 and immune cells. We have focused the effect of IL-33 on various types of cancer and especially where related to immune cells. IL-33 has contradictory roles in tumor, and it would be worthwhile to focus on its value, as understanding of IL-33 remains largely unclear, for example, its main role in tumor pathogenesis, and its presence in ILC2, Treg cells, DC, M2 macrophages, and non-hematopoietic cells. Much current interest in IL-33 has been prompted by its role in the activation and expansion of ILC2 and Treg cell populations, or together with their marked effect in modulating infection and autoimmune diseases. Treg accumulation in tumor, which suppresses anti-tumor immune responses, has been well documented. IL-33 plays a central role in Treg cell proliferation and function. Gene expression analysis indicates that in esophageal squamous cell carcinoma (ESCC). IL-33 expression is normalized to FOXP3⁺ Treg cells within the tumor microenvironment.⁹⁴ A more recent study shows that knockout of IL-33 in Treg cells resulted in the loss of immune response suppression in vivo in a melanoma model.⁹⁵ Therefore,

further study is warranted to identify the specific mechanisms and effects of IL-33 and Treg cells, which would be advantageous for in-depth investigation of immune-suppressive function; IL-33 and Treg expression may be essential for staging the tumor and predicting its prognosis. ILC2 are identified by the constitutive expression of ST2. Recently, ILC2 have been widely studied in cancer immunotherapy. In 2020, ILC2-based adoptive immunotherapy for pancreatic ductal adenocarcinoma (PDAC) was demonstrated.⁹⁶ Upon stimulation, IL-33 played a key role in activating ILC2. Further investigation of ILC2 in tumor pathogenesis has enabled continual exploration of the role of IL-33 in tumors, which would be an attractive target for immunotherapy. In the field of tumor immunotherapy, IL-33 would be a new prospect for prevention. From an immune mechanism viewpoint, it is worth exploring to clarify the clinical role of IL-33 in tumor.

Immunotherapy in new immune cell therapy and targeted immune control points has become the next stage of cancer treatment breakthrough. So far, IL-33 is known for its function in tumors, and is critical for immune function and the tumor immune microenvironment. IL-33 expression in both the tumor epithelial and stromal compartments warrants further study. Therefore, further exploration of the mechanism may reveal that IL-33 is a valuable indicator for clinical application.

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