Cell Insight 1 (2022) 100042

Contents lists available at ScienceDirect

Cell Insight

journal homepage: www.journals.elsevier.com/cell-insight

Review

Signaling and functions of interleukin-33 in immune regulation and diseases

Xue-Mei Yi [a], Huan Lian [b], Shu Li [a,*]

[a] Department of Infectious Diseases, Zhongnan Hospital of Wuhan University, Medical Research Institute, Frontier Science Center for Immunology and Metabolism, Research Unit of Innate Immune and Inflammatory Diseases, Chinese Academy of Medical Sciences, Wuhan University, Wuhan, 430071, China
[b] Department of Microbial Pathogenesis, Yale University School of Medicine, New Haven, CT, 06536, USA

A B S T R A C T

Interleukin-33 (IL-33) which belongs to the interleukin-1 (IL-1) family is an alarmin cytokine with critical roles in tissue homeostasis, pathogenic infection, inflammation, allergy and type 2 immunity. IL-33 transmits signals through its receptor IL-33R (also called ST2) which is expressed on the surface of T helper 2 (Th2) cells and group 2 innate lymphoid cells (ILC2s), thus inducing transcription of Th2-associated cytokine genes and host defense against pathogens. Moreover, the IL-33/IL-33R axis is also involved in development of multiple types of immune-related diseases. In this review, we focus on current progress on IL-33-trigggered signaling events, the important functions of IL-33/IL-33R axis in health and diseases as well as the promising therapeutic implications of these findings.

1. Introduction

Interleukin-33 (IL-33) was originally described as DVS27 in 1999 and identified as a differentially expressed gene in vasospastic cerebral arteries after subarachnoid hemorrhage (Onda et al., 1999). It is also known as NF-HEV (nuclear factor from high endothelial venules) (Baekkevold et al., 2003). Being homologous with IL-1 family, DVS27 was designated as IL-33 (also known as IL-1F11), a ligand for IL-33 receptor (IL-33R) (also known as ST2, DER4, T1 and FIT-1 and IL-1RL1) in 2005 (Ohno et al., 2012). IL-33R is abundantly expressed by T helper 2 (Th2) cells, mast cells, activated leukocytes like regulatory T (Treg) cells, group 2 innate lymphoid cells (ILC2s), $CD8^+$ T cells as well as natural killer (NK) cells (Liew et al., 2016).

As a warning cytokine, IL-33 is released into the extracellular space when cells or tissues are damaged, alerting the immune cells expressing IL-33R (Cayrol and Girard, 2014; Bonilla et al., 2012). Binding of IL-33 to a heterodimer formed by IL-33R and IL-1 receptor accessory protein (IL-1RAcP) initiates the signaling transduction which leads to local immune responses. Recent studies have demonstrated that the IL-33/IL-33R axis plays indispensable roles in both innate and adaptive immunity, and it is also involved in the development of multiple types of immune-related diseases such as infection and respiratory diseases (Mantovani et al., 2019; Wu et al., 2020; Kaur et al., 2015). In this review, we summarize the molecular mechanisms of IL-33-triggered signaling, physiological and pathological functions of the IL-33/IL-33R axis and discuss the potential therapeutic strategies for IL-33-related diseases.

2. IL-33 and its receptor: properties and signaling

2.1. IL-33

Human IL-33 is a protein composed of 270 amino acid. It contains a homeodomain-like HTH domain, a central domain and a C-terminal IL-1-like cytokine domain (Fig. 1) (Carriere et al., 2007). There is a chromatin-binding motif and a nuclear localization signal in the HTH domain (Lefrancais et al., 2012, 2014). The nuclear localization is critical to avoid unwanted cytokine activity and spontaneous inflammatory responses. IL-33 is consistently expressed and associated with the acidic pockets of H2A-H2B at the surface of nucleosomes in the steady-state (Roussel et al., 2008). When Full-length IL-33 ($IL\text{-}33_{FL}$) is cleaved by inflammatory proteases from elastase, neutrophils and cathepsin G, it converts into mature forms with an intact IL-1-like cytokine domain. The activities of IL-33 mature forms are 10–30 times stronger than that of $IL\text{-}33_{FL}$ *in vitro* and *in vivo* (Lefrancais et al., 2012, 2014). As a protease sensor, $IL\text{-}33_{FL}$ can detect proteolytic activities associated with multiple environmental allergens, such as bacteria, fungi, pollens, and house dust mite. Incubation of low doses of $IL\text{-}33_{FL}$ with allergen proteases or allergen extracts results in robust production of IL-5, IL-13 and secretion of IL-6 by MC/9 mouse immune cells (Cayrol et al., 2018). Consistently, preventing cleavage of $IL\text{-}33_{FL}$ can inhibit allergic inflammation (Luthi et al., 2009).

IL-33 is constitutively expressed in a wide variety of cells, such as epithelial cells, endothelial cells, fibroblasts (Pichery et al., 2012;

* Corresponding author.
E-mail address: shuli@whu.edu.cn (S. Li).

https://doi.org/10.1016/j.cellin.2022.100042
Received 19 April 2022; Received in revised form 31 May 2022; Accepted 3 June 2022
Available online 11 June 2022

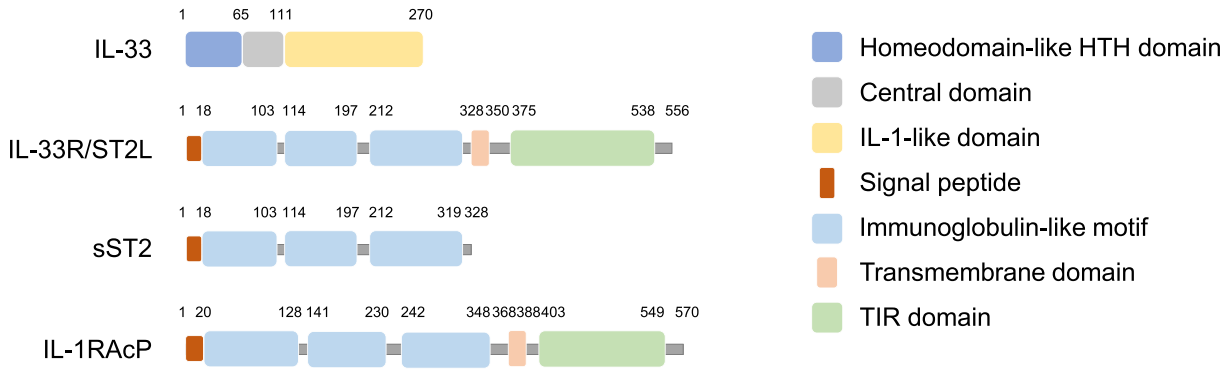

Fig. 1. Structures of IL-33 and its receptor. IL-33 consists of three domains: homeodomain-like HTH domain, central domain, and C-terminal IL-1-like domain. The IL-1-like domain of IL-33 binds to IL-33R, leading to activation of downstream components and production of cytokines. Three immunoglobulin-like motifs of IL-33R are responsible for specific binding to IL-33, and the TIR domain of IL-33R is critical for initiating intracellular signaling. sST2 is a decoy receptor that lacks the transmembrane and cytoplasmic domains and does not signal. IL-1RAcP, a co-receptor of IL-33R, consists of a transmembrane domain, three immunoglobulin-like motifs and a TIR domain.

Moussion et al., 2008), cardiomyocytes (Weinberg et al., 2002) and some immune cells including macrophages (Kurowska-Stolarska et al., 2009), mast cells (Moritz et al., 1998) and natural killer cells (Smithgall et al., 2008). It can be detected in multiple organs (Pichery et al., 2012; Moussion et al., 2008; Kearley et al., 2015), such as lymphoid organs, brain, lung, embryos, epithelial barrier tissues and inflamed tissues.

2.2. IL-33R

IL-33R, also known as suppression of tumorigenicity 2 (ST2), was first identified in mouse 3T3 fibroblasts in 1989 (Tominaga, 1989). Four isoforms of IL-33R have been identified, full-length IL-33R, sST2, ST2V and ST2LV. The full-length IL-33R is a transmembrane protein that consists of three immunoglobulin-like motif responsible for extracellular ligand-binding, an intracellular Toll/interleukin-1 receptor (TIR) domain and a transmembrane domain (Fig. 1). It is mostly expressed in cardiomyocytes (Weinberg et al., 2002), fibroblasts (Yanagisawa et al., 1993) and various immune cells, including macrophages (Kurowska-Stolarska et al., 2009), mast cells (Moritz et al., 1998), T helper 2 cells (Lohning et al., 1998), natural killer cells (Smithgall et al., 2008). Compared with full-length IL-33R, the soluble sST2 lacks intracellular and transmembrane domains but possesses a nine amino-acids

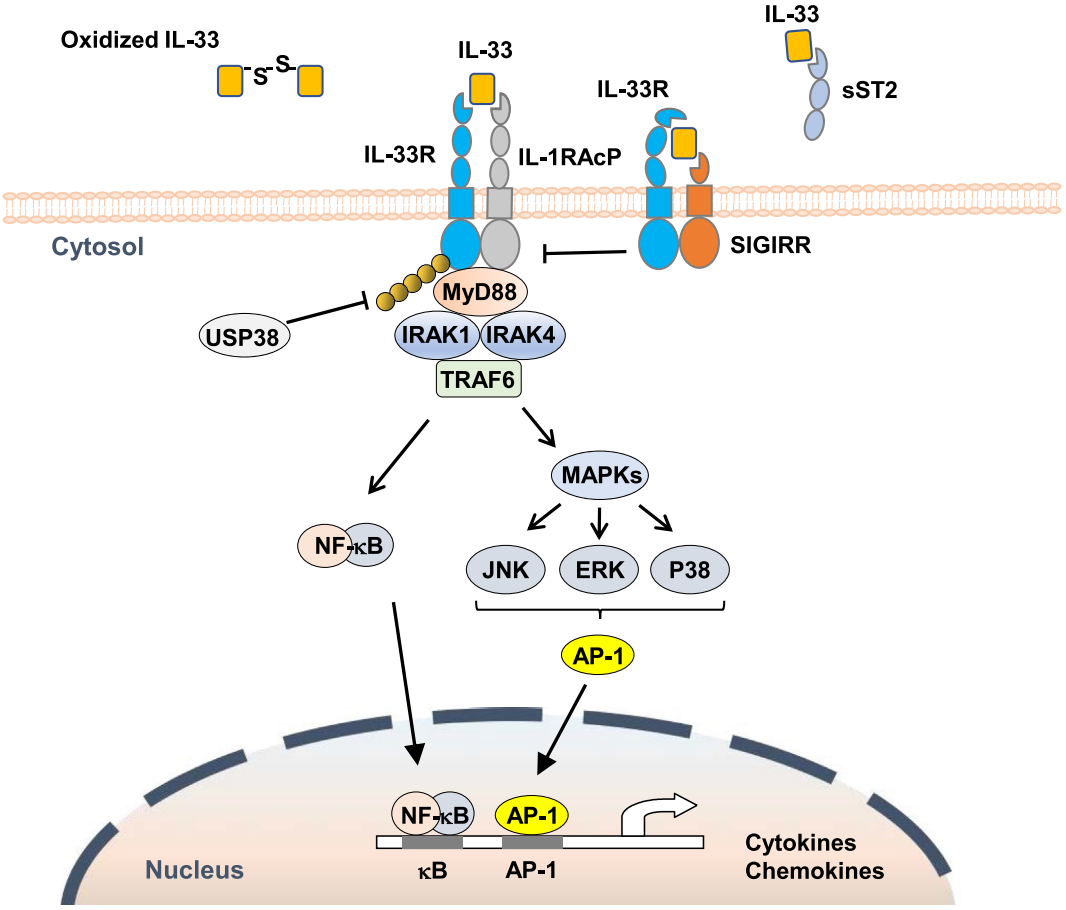

Fig. 2. IL-33/IL-33R signaling pathways. See text for details.

C-terminal sequence (Fig. 1) (Gachter et al., 1996). As a decoy receptor, sST2 prevents IL-33-induced signal transduction by competing with IL-33R for ligand binding. Under physiological conditions, sST2 exists mostly in glycosylated form. ST2V is expressed on the cell surface of human stomach, small intestine and colon. It lacks the third extracellular immunoglobulin-like motif (Tominaga et al., 1999; Tago et al., 2001). ST2LV which lacks transmembrane domain has been found in chicken solely so far (Iwahana et al., 2004).

2.3. IL-1RAcP

IL-1 receptor accessory protein (IL-1RAcP) is a co-receptor of IL-1Rα, IL-33R and IL-36R respectively (Boraschi and Tagliabue, 2013). IL-1RAcP consists of a transmembrane domain, an extracellular ligand-binding domain and a TIR domain (Fig. 1). IL-1RAcP does not directly associated with IL-33. It is recruited to IL-33R to form an activated heterodimer receptor complex after IL-33 stimulation. The receptor complex then recruits downstream signaling components through their TIR domain (Schmitz et al., 2005; Lott et al., 2015). sIL-1RAcP, a soluble isoform of IL-1RAcP, lacks the transmembrane and intracellular domain which inhibits IL-1-mediated signaling (Jensen et al., 2000).

2.4. IL-33-triggered signaling pathways

As an alarmin (Cayrol and Girard, 2014), IL-33 is rapidly secreted outside cells after cell injury or infection (Zhao and Hu, 2010; Cayrol and Girard, 2009). The first step in the cytokine-induced signaling is IL-33-triggered conformational change of IL-33R, followed by recruitment of IL-1RAcP. The activated receptor complex then recruits downstream signaling proteins such as myeloid differentiation primary response protein 88 (MyD88), tumor necrosis factor acceptor associated factor 6 (TRAF6) and subsequently induces activation of IL-1R-associated kinases, such as IRAK-1/4, which activate mitogen-activated protein kinases (MAPKs), ERK, p38, JNK and downstream IKK complex, leading to activation of the transcription factors AP-1 and nuclear factor-κB (NF-κB). The activated AP-1 and NF-κB collaboratively induce transcription of a series of cytokines and chemokines (Schmitz et al., 2005; Lott et al., 2015; De Boeck et al., 2020).

While IL-33-triggered signaling plays critical roles in immunity, deregulation of the signaling causes numerous diseases. Thus, the IL-33/IL-33R axis is precisely regulated under physiological conditions. There are diverse mechanisms by which the IL-33/IL-33R signaling pathway is negatively regulated to inhibit sustained inflammatory responses. Extracellular IL-33 is rapidly inactivated because of the formation of two disulfide bridges in its IL-1-like cytokine domain caused by oxidation of cysteine residues which leads to disruption of IL-33R binding (Cohen et al., 2015). sST2 inhibits IL-33-triggered signaling by competing with IL-33R for ligand binding (Hayakawa et al., 2007). The IL-33/IL-33R axis is also inhibited by the single immunoglobulin domain IL-1R-associated molecule (SIGIRR; also called TIR8), which disrupts the binding of IL-33R and IL-1RAcP (Kumar et al., 1997). Moreover, previous studies have demonstrated that USP38 functions as a negative regulator of IL-33 signaling through down-regulating IL-33R by removing its K27-linked polyubiquitination (Yi et al., 2022). Finally, exosomes from nematode parasites inhibit type 2 responses by targeting IL-33R through transferring small RNAs to mammalian cells (Buck et al., 2014). The signaling mechanisms of the IL-33/IL-33R axis are summarized in Fig. 2.

3. Physiological functions of IL-33

IL-33 plays crucial roles in immunity and tissue homeostasis. The physiological functions of IL-33 has been well characterized in immune responses mediated by ILC2s and $CD4^+$/$CD8^+$ T cells as well as in tissue repair mediated by Tregs (Bonilla et al., 2012; Baumann et al., 2015; Schiering et al., 2014; Guo et al., 2009).

Previous studies have shown that IL-33 participates in Th2 immune response and regulates inflammatory responses by directly inducing expansion of ILC2 in multiple anatomic sites (Schmitz et al., 2005; Rak et al., 2016; Monticelli et al., 2015). IL-33 deficiency leads to diminished ILC2 response and tardive cutaneous wound healing. And overexpression of IL-33 enhances ILC2 response and accelerates cutaneous wound healing (Rak et al., 2016). Blocking IL-33-induced signaling by anti-IL-33R antibody significantly reduces both total cell number and frequency of ILCs expressed $CD90^+$ and $CD25^+$ in the lungs of mice (Monticelli et al., 2011). Additionally, IL-33-activated ILC2s are involved in differentiation and proliferation of $CD4^+$ T cells and promote functions of $CD4^+$ T cells by presenting antigen to T cells and production of Th2 cytokines (Drake et al., 2014; Halim et al., 2014). IL-33-activated $CD4^+$ T cells recruit activated eosinophils and participate in a cross-mucosal immune mechanism that intestinal helminths may protect their hosts from co-infection (Filbey et al., 2019).

IL-33 is essential for cytotoxic $CD8^+$ T cell (CTL) responses and antiviral immunity. After infection with lymphocytic choriomeningitis virus (LCMV), proliferation of virus-specific $CD8^+$ T cells is 90% lower in IL-33-deficient mice. CTL responses in mice treated with IL-33 decoy receptors is deficient compared with in the controls. IL-33 enhances clonal expansion in a CTL-intrinsic fashion, determines plurifunctional effector cell replication and differentiation, and is necessary for virus control (Bonilla et al., 2012).

IL-33 has been reported to promote repair of skeletal muscle by inducing accumulation of Treg cells (Kuswanto et al., 2016). Punctual depletion of Treg cells in the process of repair prolongs proinflammatory infiltration and impairs muscle repair, while treatments that increase or decrease activities of Treg cells diminish or enhance muscle damage respectively in a dystrophy model (Burzyn et al., 2013). Tregs from mice treated with IL-33 show much stronger activities in inhibiting the expression of inflammatory cytokines, chemokines and macrophage matrix metalloproteinases of smooth muscle cells, and in enhancing polarization of M2 macrophage than those from vehicle-treated mice. Consistently, IL-33R-deficiency mutes these activities of Tregs (Li et al., 2019).

4. Roles of the IL-33/IL-33R axis in diseases

4.1. Infection

Studies have demonstrated that IL-33 plays critical roles in host defense. In a mouse model of keratitis induced by *Pseudomonas aeruginosa*, the mRNA and protein levels of IL-33 and IL-33R are increased in local inflammatory lesions. IL-33 treatment leads to a less severe disease while sST2 treatment increases corneal infection (Huang et al., 2007; Hazlett et al., 2010). IL-33 is also significantly elevated in skin lesions of *Staphylococcus aureus* (*S. aureus*)-infected patients compared with the controls. IL-33 enhances antibacterial defense against skin bacterial infection by promoting the antibacterial ability of dermal macrophages (Li et al., 2014a). In addition, studies have shown that enhancement of neutrophil extracellular trap production induced by IL-33 contributes to trapping *S. aureus* and enhancing bactericidal activity *in vitro* and *in vivo,* thus strengthening the host's ability to resist *S. aureus* infections (Wang et al., 2020). Over the past decade, the incidence rate caused by *C. difficile* tripled due to the emergence of highly virulent strains, which is known to cause devastating colon inflammation. IL-33 is up-regulated during *C. difficile* infection and prevents *C. difficile*-related death and epithelial cell destruction by driving colonic lymphocyte-like cell activation. sST2 is a poor prognosis factor in human *C. difficile* infection. Higher sST2 expression is accompanied by higher patient mortality (Frisbee et al., 2019). Furthermore, expression levels of IL-33 and IL-33R are obviously increased in *Helicobacter pylori* (*H. pylori)*-infected cells. IL-33R is recruited to the lipid rafts to exacerbate inflammation (Kuo et al., 2019). IL-33 attenuates sepsis by increasing the transfer of neutrophils to the infected site (Alves-Filho et al., 2010) and promotes wound healing associated with *Staphylococcus aureus* infection by promoting the

proliferation and chemotaxis of neutrophils (Yin et al., 2013). However, high level of IL-33, which leads to immunosuppression, is often observed in septic survivors. Thus, there may be multiple negative feedback regulations for maintaining homeostasis of IL-33 (Boomer et al., 2011).

Recent evidence shows that IL-33-mediated worm elimination mainly relies on $CD4^+$ T cells and ILC2s. In order to ensure their survival, worms manipulate the host's immune system to affect other pathogen infections. Co-infection experiments show that the lung migrating *Nippostrongylus brasiliensis* larvae are killed in the lungs of *Heligmosomoides polygyrus*-infected mice. The lung pathological changes related to larval migration is also reduced. This process is closely associated with $CD4^+$ T cells activated by IL-33, which release IL-5 and recruit activated eosinophils (Filbey et al., 2019). These studies suggest that IL-33-induced Th2 immune response plays important roles in transmucosal immune processes. There are two different subsets of ILC2s: steady-state natural type and inflammatory type ($ILC2^{INFLAM}$). Upon infection by worms, ILC2s change from a steady-state natural type to an inflammatory type to exert anti-worm infection functions. Recent studies have shown that IL-33 promotes the production of $ILC2^{INFLAM}$ through tryptophan hydroxylase 1 (Tph1). IL-33, Tph1and inducible T-cell co-stimulator (Icos) play critical roles in promoting the production of $ILC2^{INFLAM}$ and the mucosal type 2 immune response (Flamar et al., 2020). Tph1 expression in ILC2s is upregulated after infection with helminth in an IL-33-dependent manner. Moreover, conditional deletion of Tph1 in lymphocytes results in impaired $ILC2^{INFLAM}$ response, tardive recruitment of $ILC2^{INFLAM}$ to immune organs, increased susceptibility to helminth and alters gene expression in Tph1-deficient ILC2s (Flamar et al., 2020).

4.2. Respiratory diseases

Airway hyper responsiveness, mucus secretion, bronchoconstriction and chronic inflammation are the main features of asthma (Olin and Wechsler, 2014). High levels of IL-33 mRNA and protein are detected in airway specimens of asthmatic patients, including lung epithelial cells (Kurowska-Stolarska et al., 2009; Prefontaine et al., 2010), induced sputum (Hamzaoui et al., 2013), submucosal inflammatory cells (Saglani et al., 2013), and bronchoalveolar lavage (BAL) fluids (Prefontaine et al., 2010; Christianson et al., 2015). IL-33 levels are correlated with disease severity (Christianson et al., 2015). Numerous studies have shown that IL-33 responds quickly to allergen exposed in the airway. IL-33 treatment induces goblet cell hyperplasia and airway hyperresponsiveness through activation of ILC2s in mice (Kondo et al., 2008). In IL-33R-difficient mice, airway hyperresponsiveness and eosinophilic airway inflammation induced by IL-33 and OVA are thoroughly eliminated compared with wild type mice, which indicates that IL-33R-mediated signaling plays a critical role in inducing asthma-like phenotypes (Magat et al., 2020). Salidroside, which has been reported to inhibit allergic asthma in OVA-induced mouse models, is a potential therapeutic strategy for allergic asthma by targeting the IL-33/IL-33R axis (Cai et al., 2020).

Pulmonary fibrosis is a terminal change of pulmonary diseases. Its symptoms include fibroblast proliferation and massive accumulation of extracellular matrix, accompanied by inflammatory damage and structural destruction. Elevated IL-33 levels in BAL and lung tissues have been observed in patients with idiopathic pulmonary fibrosis compared with healthy controls (Luzina et al., 2012). Overexpression of sST2 obviously improves survival rate and attenuates pulmonary inflammatory cell infiltration and fibrosis (Gao et al., 2016). Bleomycin is a broad-spectrum chemotherapeutic agent for cancer with serious side effects including pulmonary fibrosis which are caused by the cytotoxic activity of bleomycin related to DNA splicing and induction of reactive oxygen species. Interestingly, IL-33 positive cells are accumulated in the lungs of mice stimulated by bleomycin. IL-33 treatment or adoptive transfer of ILC2s enhances lung inflammation and fibrosis induced by bleomycin, while deficiency of IL-33R, anti-IL-33 antibody treatment or depletion of alveolar macrophage attenuates bleomycin-induced pulmonary fibrosis (Li et al., 2014b).

4.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) mediated by Th17 cells is an autoimmune disorder. IL-33 mRNA and/or protein are increased in the serum, synovial fluid or inflamed lesions of the RA patients, and higher IL-33 levels are correlated with more severe diseases (Tang et al., 2013). IL-33 in chronic inflamed tissues of RA patients is mainly secreted from endothelial cells (Carriere et al., 2007). In mouse models of RA, inhibiting the IL-33/IL-33R axis through neutralizing IL-33 by sST2 (Leung et al., 2004), IL-33R-specific antibody (Palmer et al., 2009) or deleting IL-33R gene (Xu et al., 2008) reduces the severity of RA. IL-33 injection exacerbates development of inflammatory arthritis in a mouse model of RA (Xu et al., 2010). These studies demonstrate that IL-33/IL-33R signaling plays critical roles in rheumatoid arthritis.

4.4. Inflammatory bowel diseases

IL-33 has been considered as a critical regulator in inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, which are characterized by intestinal tissue damage and destruction caused by abnormal immunological responses (Sedhom et al., 2013; Rosen et al., 2015). There are high levels of IL-33 in the inflamed mucosa of IBD patients. IL-33 might be a potential biomarker of IBD since its levels are associated with disease severity (Sedhom et al., 2013; Pastorelli et al., 2010). Mechanistical studies indicate that the roles of IL-33 in colitis are probably complicated and dependent on different pathological processes. At onset of a dextran sodium sulfate (DSS)-induced colitis animal model, treatment with recombinant IL-33 exacerbates disease severity, while ameliorates DSS-induced colitis during recovery or chronic phases (Grobeta et al., 2012). Therefore, further investigations into the roles of IL-33 in IBD are of great significance for exploration of better therapeutic approaches.

4.5. Skin diseases

Psoriasis is a common, chronic autoimmune skin disease characterized by hyperplasia of epidermal keratinocytes and chronic plaque. IL-33R knockout mice exhibit reduced skin inflammation compared with wild-type mice in a model of skin inflammation induced by phorbol ester. Consistently, injection of IL-33 into the ears of mice induces inflammatory skin lesion (Hueber et al., 2011).

Atopic dermatitis (AD) is also known as Besnier constitutional prurigo, atopic eczema. Patients or their families show obvious “atopic” characteristics, such as familial asthma, allergic, rhinitis eczema, allergy to heterologous proteins, elevated eosinophils in blood. The mediators distorting the immune microenvironment of epithelium such as topical application of chemicals, proteins, histamines, inflammatory cytokines induce AD. Th2-type inflammation is critical for the pathogenesis of AD (Dainichi et al., 2018). Overexpression or application of IL-33 in the skin results in an AD-like phenotype such as infiltration of eosinophil, ILC2 and mast cell (Imai et al., 2013). In addition, IL-33 also drives neutrophils to the infected sites and promotes their activation (Alves-Filho et al., 2010; Lan et al., 2016; Yazdani et al., 2017; Xu et al., 2017). Recent studies have shown that sustained expression of IL-33 in mouse keratinocytes is sufficient to induce AD-like inflammation which is mediated by basophils and ILC2s. ILC2s participate in early skin allergic reactions and T helper type 2 cellular responses (Ryffel and Alves-Filho, 2019). Using IL-33 antibody to block IL-33, or deletion of IL-33 or IL-33R gene, reduces the severity of AD in mouse models (Peng et al., 2018; Li et al., 2017).

4.6. Cancer

Chronic inflammatory diseases account for about 20% of all cancer-related deaths around the world (Mantovani et al., 2008). For example, IBD is one of the major risk factors for colon and rectal cancer (CRC)

(Triantafillidis et al., 2009). Tumor-promoting immune environment plays critical roles in regulating tumor progression (Mantovani et al., 2008) and is often referred to as type 2 immune environment, which is mainly composed of cytokines including tumor necrosis factor (TNF)-α, IL-6, chemokines, transforming growth factor (TGF)-β and tumorigenic immune cells including Tregs, Th2 cells, mast cells, M2 macrophages and eosinophils (Shalapour and Karin, 2015).

The IL-33/IL-33R axis has been shown to regulate tumor microenvironment by recruiting a series of immune cells, and ultimately plays a role in promoting or suppressing tumors. Upregulation of IL-33 has been detected in established invasive cancers. In chronic inflammation, IL-33/Tregs axis is indispensable in promoting development of tumor-promoting immune environment (Ameri et al., 2019). Of note, significantly increased IL-33-expressing cells and Tregs are observed in patients prone to cancer, or with colon and skin chronic inflammatory diseases. Deletion of IL-33R specifically on Tregs prevents chronic allergic contact dermatitis (ACD)-induced skin tumorigenesis and suppresses colitis-induced CRC in mice (Ameri et al., 2019). As IL-33 targets a wide variety of cells, a thorough understanding of IL-33-triggered signaling and the unique and potential functions of IL-33 on Tregs and other immune cell types are critical.

In recent years, IL-33/IL-33R axis is thought to play vital roles in many types of cancer including gastric cancer (GC), liver cancer, breast cancer and colon cancer (Zhou et al., 2020; Heinrich, 2022; Shani et al., 2020; Akimoto et al., 2016). Studies have shown that IL-33 and IL-33R are increased in GC and served as biomarkers for the low survival of GC patients (Zhou et al., 2020). IL-33 induces epithelial-mesenchymal transition in IL-33R-dependent manner, thus enhancing the migration and invasion capacity of GC cells. In nude mice, knockdown of IL-33 in cancer-associated fibroblasts or knockout of IL-33R in GC cells leads to less peritoneal nodules and prevents metastatic potential of GC cells (Zhou et al., 2020). Patients with metastatic liver cancer have higher levels of IL-33, IFN-α, and IFN-γ in their sera compared with those with non-metastatic liver cancer (Zhang et al., 2012), which suggests that the IL-33/IL-33R axis is involved in the occurrence and development of hepatocellular carcinoma. The IL-33/IL-33R is also associated with breast cancer. IL-33 treatment enhances the growth and invasiveness of breast cancer cells and promotes angiogenesis. Deletion of IL-33R in mice bearing mammary carcinoma attenuates tumor growth and metastasis. And the levels of IL-17, TNF-α and IFN-γ are increased while the level of IL-4 is decreased in serum. IL-33R-deficient mice have a higher percentage of active, cytotoxic NK cells with faster turnover. Injection of IL-33 promotes proliferation of tumor cell and angiogenesis in wild type mice (Jovanovic et al., 2011, 2012).

However, the roles of IL-33/IL-33R axis in the development of some tumors such as colon cancer, lung cancer and pancreatic cancer remains controversial. Take a brief analysis of colon cancer as an example. Compared with non-cancer tissues, IL-33 levels in CRC tissues are significantly increased (Cui et al., 2015). Overexpression of IL-33 in CRC cells enhances their growth, metastasis and reduces the survival time in nude mice (Liu et al., 2014). Knockout of IL-33 (Maywald et al., 2015) or IL-33R (Mertz et al., 2016) inhibits proliferation, angiogenesis and induces apoptosis, leading to the decrease of tumor number and size. Unlike the promoting functions of IL-33/IL-33R axis in CRC, much higher levels of IL-33R is detected in early stage of CRC compared with higher grade or more advanced tumors, which indicate that IL-33/IL-33R axis may have a protective function in colon carcinogenesis. Moreover, knockdown of ST2 in murine colon cancer cells leads to increased tumor growth *in vivo* and gradually decreased level of ST2L in tumor cells with increasing tumor stage (O'Donnell et al., 2016). Therefore, the specific mechanism in colon cancer needs to be further studied.

4.7. Alzheimer's disease

Alzheimer's disease (AD), a neurological disease, is characterized by cognitive impairment, memory loss, personality changes, and rapid loss and deterioration of neurons. Pathophysiologically, AD is caused by excessive accumulation of extracellular β-amyloid plaque and intracellular neurofibrillary tangles in the brain (Xiong et al., 2014). Previous studies have shown that IL-33, IL-33R and IL-1RAcP are highly expressed in brain tissues (Schmitz et al., 2005; Allan et al., 2016; Yasuoka et al., 2011). IL-33 injection reverses cognitive deficits and synaptic plasticity damage in mice with Alzheimer's disease. Exogenous IL-33 promotes microglial recruitment and β-amyloid phagocytic activity which leads to the decrease of soluble β-amyloid and amyloid plaque accumulation. Additionally, exogenous IL-33 polarizes microglia toward anti-inflammatory phenotypes and inhibits the transcription of pro-inflammatory genes such as NLRP3, IL-1β, and IL-6 to regulate the innate immune responses (Fu et al., 2016).

4.8. Cardiovascular diseases

Cardiovascular diseases are a series of diseases involving the circulatory system, and it is generally related to arteriosclerosis. IL-33 injection reduces hypertrophy and fibrosis and improves survival of wild type mice with transverse aortic constriction (TAC). Compared with wild type littermates, *IL-33R*$^{-/-}$ mice have more fibrosis, more chamber dilation, more left ventricular hypertrophy, less fractional shortening, and impaired survival after TAC (Sanada et al., 2007). Exogenous IL-33 reduces development of atherosclerosis and increases type 2 cytokines levels in the serum in a high-fat diet model (Miller et al., 2008). IL-33-treated mice produce much more specific antibodies against atheroprotective oxidized low-density lipoprotein in an IL-5 dependent manner. On the contrary, treating mice with sST2 aggravates atherosclerosis development (Miller et al., 2008). These studies together indicated that IL-33 plays an essential role in prevention of atherosclerosis and provide a potential therapeutic strategy for prevention and treatment of atherosclerotic vascular diseases. sST2 levels are immediately elevated after myocardial infarction in humans. Moreover, the concentration of sST2 is associated with impaired left ventricular function as well as poor prognosis, which suggest that sST2 is a marker to predict subsequent death or heart failure (Weinberg et al., 2003; Shimpo et al., 2004).

4.9. Obesity

Obesity is closely associated with the onset of type 2 diabetes. At present, obesity is considered to be a major risk factor for diabetes. Studies have demonstrated that the IL-33/IL-33R axis is associated with type 2 diabetes and obesity. IL-33 is associated with protective lipid profiles in non-diabetic subjects and is negatively correlated with body mass index and body weight in lean and overweight but not obese subjects (Hasan et al., 2014). IL-33 induces Th2 cytokines in white adipose tissues (WATs) and the polarization of WAT macrophages towards an M2 alternatively activates phenotypes with reduced adipose mass and fasting glucose (Miller et al., 2010).

4.10. Kidney injury

IL-33 plays a strong protective role on renal ischemia-reperfusion injury (IRI), which mainly depends on the expansion of IL-33-elicited-ILC2s. The beneficial functions of the IL-33-ILC2 pathways have been demonstrated in mouse models as well as in human kidney injury. Recombinant mouse IL-33 treatment significantly prevents damage of renal structure and function and reduces mortality of IRI mice. Compared with the control group, IRI mice treated with IL-33 have more ILC2s, Tregs and M2 macrophages and elevated IL-4 and IL-13 levels in serum and kidney. Transfer of *ex vivo*-expanded human ILC2s or human IL-33 treatment effectively improves kidney injury in humanized mice with IRI (Cao et al., 2018), which provide a potential therapeutic strategy for human IRI.

5. Therapeutic intervention targeting the IL-33/IL-33R axis

The roles of IL-33/IL-33R axis in diseases are probably complicated

and depend on different pathological processes. IL-33 plays a protective role in cardiovascular diseases and type 2 diabetes, while a pathological role in respiratory diseases and rheumatoid arthritis. Therefore, uncovering the mechanisms of the IL-33/IL-33R axis in specific inflammatory diseases is of clinical value.

Significant progress on developing IL-33/IL-33R blocking tools have been made in the past twenty years. There are three major approaches for blocking the binding between IL-33 and IL-33R: (1) Soluble IL-33 antagonists, sST2 and IL-33 Trap; (2) IL-33 neutralizing antibodies; (3) anti-IL-33R antibodies. At least two decoy receptors of IL-33 have been developed to block the function of free IL-33, including sST2 and IL-33 Trap. IL-33 Trap is a fusion protein that consists of the extracellular domain of IL-33R and IL-1RAcP, which is produced using knob technology. IL-33 Trap has been reported to reduce the release of inflammatory mediators from Müller cells, inhibit mononuclear phagocytes accumulation in outer layer of retina, and protect cones and photoreceptor rods after a retina damage (Xi et al., 2016). As a novel IL-33 antagonist, IL-33 Trap is superior to natural IL-33 decoy receptors for IL-33 blocking and shows anti-inflammatory activities in allergen-induced acute allergic airway inflammation mouse model (Holgado et al., 2019). Several groups have developed anti-IL-33 neutralizing antibodies, which are in the stage of clinical research evaluation (Corren, 2019). Anti-IL-33R antibodies are also in clinical evaluation for chronic obstructive pulmonary diseases treatment (Yousuf et al., 2022). In addition to the above therapeutic advantages of blocking IL-33/IL-33R signaling, using recombinant IL-33 to activate the signaling is also effective in certain disease models. IL-33 deficiency promote mice mortality induced by cecal ligation and puncture, while IL-33 treatment improves the survival rate (Lv et al., 2017). Therefore, IL-33 injection may be beneficial for patients with related diseases.

6. Conclusions and perspectives

IL-33 as an alarming factor is usually released by barrier cells such as epithelial cells and endothelial cells under conditions of necrosis, injury and exposure to pathogens or allergens. IL-33-induced activation of receptor complex triggers a cascade of signaling events that ultimately lead to local immune responses.

IL-33 has pleiotropic functions in immune responses, which is consistent with the fact that the IL-33/IL-33R axis exhibits different immune-regulatory functions in different diseases and pathological processes. IL-33 plays an important protective role in type 2 diabetes, obesity, cardiovascular diseases and certain pathogen infections. IL-33 mediates tissue protection through tissue repair during the recovery phase of tissue damage, which involves the activation and participation of ILC2s and Tregs. Furthermore, IL-33 also plays a pathological role in respiratory diseases, rheumatoid arthritis and certain other diseases. Thus, targeting the IL-33/IL-33R axis by different ways is vitally important for the treatment of distinct IL-33-related diseases.

Although considerable progress has been achieved on the signaling and functions of the IL-33/IL-33R in health and diseases, many questions remain unanswered. For examples, (1) How is the expression of IL-33R in specific cells determined? (2) How is the expression and secretion of IL-33 and sST2 regulated? (3) How is the balance between IL-33 and sST2 maintained under physiological condition? (4) In addition to ubiquitination, are IL-33R regulated by phosphorylation or other post-translational modifications? (5) Are there other components in the IL-33/IL-33R axis that can be targeted for therapeutic intervention? Of note, many pharmaceutical preparations targeting the IL-33/IL-33R axis are currently in clinical trials and more potential therapeutic strategies are also expected. The selection of the best treatment strategy requires more scientific evidence and a comparative analysis of the effects of clinical trials.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (31830024, 31871415 and 32070775), the CAMS Innovation Fund for Medical Sciences (2019-I2M-5-071), and the Fundamental Research Funds for the Central Universities.

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