IL-33 and kidney disease (Review)

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Received December 11, 2014; Accepted October 6, 2015

DOI: 10.3892/mmr.2015.4516

Abstract. Interleukin (IL)-33, is a novel member of the IL-1 superfamily, and act as a dual-function molecule as a nuclear factor and cytokine. The expression of IL-33 can be detected in several tissues and cells in humans and in mice. In addition to the conventional secretion approach for cytokines, full-length IL-33 can also be released into the extracellular space following cell damage or mechanical injury. IL-33 mediates its biological effects by interacting with the receptors, suppression of tumorigenicity 2 (ST2) and IL-1 receptor accessory protein, activating intracellular molecules in the nuclear factor-κB and mitogen-activated protein kinase signaling pathways, which drive the production of type 2 cytokines, including IL-4, IL-5 and IL-13, from polarized T helper 2 cells. Increasing evidence indicates that IL-33 is important in chronic kidney disease, and may be involved in the progression of renal fibrosis associated with systemic lupus erythematosus and renal graft damage. In addition, IL-33 contributes to acute kidney injury. In the present review, the biology of IL-33, and the association of IL-33 with kidney diseases are discussed.

Contents

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Key words: interleukin-33, suppression of tumorigenicity 2, kidney disease, chronic kidney disease, acute kidney injury

1. Introduction

Interleukin (IL-33) is a cytokine, which belongs to the IL-1 superfamily, and induces T helper (Th) cells to produce type 2 cytokines (1). In 1999, Onda *et al* identified the Dvs27 gene in canine vasospastic cerebral arteries following subarachnoid hemorrhage (2). Nuclear factor from high endothelial venule (NF-HEV) was cloned in 2003 (3), and 2 years later, Schmitz *et al* determined the Dvs27 and NF-HEV definitions as the same type of molecule, which was termed IL-33 (4). IL-33 mediates its biological effects by interacting with the receptors suppression of tumorigenicity 2 (ST2) and IL-1 receptor accessory protein (IL-1RAcP), activating intracellular molecules in the NF-κB and mitogen-activated protein kinase signaling pathways, which drive the production of type 2 cytokines , including IL-4, IL-5 and IL-13 from polarized Th2 cells (5). The induction of type 2 cytokines by IL-33 *in vivo* is considered to induce severe pathological changes in mucosal organs (6).

The focus of the present review is on the properties of this cytokine in kidney diseases, as well as in renal graft damage associated with renal transplantation. Understanding the involvement of IL-33 in the pathogenesis of kidney diseases may assist in identifying novel therapeutic strategies to mitigate or prevent kidney diseases.

2. Structure of IL-33

IL-33, also termed IL-F11, is a novel member of the IL-1 superfamily. The human IL-33 gene is located on chromosome 9p24.1, comprises 270 amino acids and the relative molecular mass of full-length proteins is ~30 kDa. The mouse IL-33 gene can be found on the chromosome 19qC1 region and encodes 266 amino acid polypeptides, corresponding to full-length proteins with a calculated mass of 29.9 kDa (4). IL-33 has, in its amino-terminal portion, a helix-corner-helix structural pattern, which involves a chromatin binding motif and nuclear localization signal. In its carboxy-terminal portion is an IL-1-like β-trefoil domain, which binds with the orphan receptor, ST2 (7). Roussel *et al* showed that IL-33 combines to chromatin by an acidic pocket area of histone H2A-H2B (8).

3. Distribution of IL-33

In humans, the constitutive and widespread expression of IL-33 can be detected in several normal tissues. For example, IL-33 is

constitutively expressed in human secondary lymphoid tissues, including the lymph nodes and appendix (9), and widespread expression is observed along the vascular tree, including large and small blood vessels from normal tissues, including the liver, skeletal muscle, kidney and prostate, despite the microcirculation of the brain and kidney glomeruli (9). In certain tissues exposed to the external environment, high levels of IL-33 have also been found, including the skin, mucosal surfaces and gastric glands in the stomach, as well as in tonsillar crypts and salivary glands (9). Furthermore, the accumulation of IL-33 has been reported in adenocarcinoma of the kidney, stomach, liver, pancreas, lung, breast and colon (9). In addition, IL-33 is substantially elevated in lymphoid tissues, the synovium in chronically inflamed rheumatoid arthritis and the intestines in Crohn's disease (10). Together, these results indicate that IL-33 is broadly expressed in normal, tumor and chronically inflamed human tissues. High mRNA expression levels of IL-33 have been found in stomach, lung, spinal cord, brain and skin in the mouse, whereas low mRNA expression levels of IL-33 have been detected in mouse lymph tissue, the spleen, pancreas, kidney and heart (3).

Compared with its expression in tissue, IL-33 mRNA is more restricted at the cellular level. Activated dendritic cells and macrophages are the only hematopoietic cells to exhibit low mRNA expression levels of human IL-33. By contrast, IL-33 mRNA has been found in resting dendritic cells and activated macrophages in mice (11). Human smooth muscle cells (SMCs) of various tissues, as well as epithelial cells forming the bronchus or small airways exhibit constitutive expression of IL-33 mRNA (11). In addition, high expression levels of IL-33 have been confirmed in activated dermal fibroblasts, activated and resting bronchial SMCs, resting pulmonary artery SMCs, resting coronary artery SMCs and bronchial epithelial cells (4). The distributions of IL-33 in humans in mice are presented in Table I.

4. Cleavage of IL-33

It has been suggested that IL-33 is produced as a pro-form IL-33 (pro-IL-33), and is digested into a mature form with a lower molecular weight when it is secreted from the cells (12). Mature IL-33 was initially considered to be the active form, however, subsequent reports have shown that the active pro-form of IL-33 is digested into an inactive mature form (4,13). The initial investigation of IL-33 suggested that it is activated via caspase-1-dependent proteolysis, similar to the proinflammatory cytokines, IL-1β and IL-18 (14). By contrast, Cayrol and Girard reported that full-length IL-33 (1-270) is active, and that processing by caspase-1 results in IL-33 inactivation, rather than activation (13). Another previous report independently arrived at the conclusion that the executioner caspase-3 and caspase-7 inactivate IL-33 by cleaving the carboxy-terminal IL-1-like structure to prevent an inappropriate immune response during apoptosis, but not in necrosis (15).

5. Secretion of IL-33

In addition to the conventional secretion approaches for cytokines, including autocrine, paracrine, intracrine, juxtacrine and retrocrine pathways, full-length IL-33, as with high mobility group protein-1, can also be released into the extracellular space following cell damage or mechanical injury (13). The release of IL-33 by necrotic cells is another recognized mechanism for a cytokine to exert its function, termed a 'necrocrine' pathway (16). The necrocrine pathway can be deleted by endogenous apoptotic caspases in cells undergoing apoptosis (15,17). Therefore, IL-33 functions as an extracellular 'danger signal' in a necrocrine manner, to alert the immune system during infectious and autoimmune diseases.

6. Receptors of IL-33

IL-33R is a heterodimer comprised of IL-1RL1, also ST2, and IL-1RAcP (18). ST2, which exhibits marked homology to the ligand-binding subunits of the IL-1 and IL-18 receptor complexes, was identified in 1989, prior the identification of IL-33, and has been termed an 'orphan receptor' (19). The human ST2 gene is located on chromosome 2, and its germline sequence is conserved (20). IL-33 mediates signal transduction through ST2, which is expressed on mast cells and Th2 cella, but not Th1 cells (21,22). Enhancing the expression of ST2 is associated with an increased risk of developing atopic dermatitis (23).

ST2 has two major forms: soluble (s)ST2 and membrane-bound ST2 (ST2 L), which are produced from the IL-1RL1 gene as a result of alternative splicing under the control of two distinct promoters (24-26). sST2 is a soluble ST2, which has no transmembrane sequence, therefore, it can be excreted outside cells. Increased levels of soluble ST2 have been associated with several human diseases, including acute myocardial infarction, asthma with acute exacerbation, eosinophilic pneumonia, sepsis and trauma, and exacerbated idiopathic pulmonary fibrosis (27-32). ST2L is the transmembrane ST2, possessing a transmembrane sequence, and is considered to be a functional component of IL-33R, whereas sST2 is regarded as a decoy receptor for IL-33 (33). T cell-associated ST2L augments Th2 immune responses, however, macrophage-associated ST2L has been reported to exhibit anti-inflammatory activity (34). There are two splice variants of ST2: ST2V and ST2LV, produced via loss of the third immunoglobulin motif and alternative splicing in the C-terminal portion of ST2 (35).

7. IL-33/ST2 signaling pathway

IL-33 can transfer extracellular information through binding of a receptor complex comprised of ST2 and IL-1RAcP as a cytokine-alarmin (9). ST2L and IL-1RAcP are necessary for IL-33 action (36,37). Extracellular IL-33 signals results in recruitment of myeloid differentiation primary response gene 88, IL-1 receptor-associated kinase 1 and tumor necrosis factor (TNF) receptor-associated factor 6, leading to activation of the transcription factor NF-kB, c-Jun N-terminal kinase1/2 and extracellular regulated protein kinase 1/2, and finally causing inflammatory responses (4,36-38). IL-33-mediated signalling can be inhibited by single Ig IL-1-related molecule, also known as Toll IL-1R8, through interactions with the IL-33 receptor complex (39) (Fig. 1).

Table I. Distribution of interleukin-33 in humans and mice.

Site	Human	Mouse	Reference
Tissue			(3,9,10)
Appendix	+	NA	
Brain	–	+	
Colon	+	–	
Kidney	+	+	
Liver	+	+	
Lung	+	+	
Lymph nodes	+	+	
Pancreas	+	+	
Prostate	+	NA	
Salivary glands	+	NA	
Skeletal muscle	+	NA	
Skin	+	+	
Spinal cord	NA	+	
Stomach	+	+	
Tonsillar crypts	+	NA	
Cells			(4,8-11)
Activated dermal fibroblasts	+	NA	
Activated macrophages	+	+	
Epithelial cells	+	+	
Resting dendritic cells	–	+	
Smooth muscle cells	+	NA	

+, positive; -, negative; NA, not available.

8. Function of IL-33

Similar to the chromatin-associated cytokine, high-mobility group box 1 (HMGB1), IL-33 acts as a dual-function molecule, as a nuclear factor and cytokine. As a nuclear factor, the transcriptional repressor function of IL-33 may be involved in the nucleus. Küchler *et al* showed that nuclear IL-33 is rapidly downregulated during wound healing and is lost in tumor endothelium. In addition, activation of endothelial cell cultures with either TNF-α or vascular endothelial growth factor and subcutaneous injection of these cytokines also leads to a downregulation in vascular IL-33 (40). The above evidence supports the hypothesis that the transcriptional repressor function of IL-33 may be involved in the control of endothelial cell activation.

As a cytokine, IL-33 promotes the polarization of T cells towards a Th2 cell phenotype and is involved in Th2-type responses through stimulating the production of IL-5, IL-6, IL-13 and granulocyte-macrophage colony-stimulating factor *in vivo* (41). In addition, IL-33 has been referred to as an 'endogenous danger signal' or 'alarmin', similar to HMGB1, in order to alert the immune system of tissue damage and infection, and to promote the initiation of a healing responses (42).

9. IL-33 and kidney disease

IL-33 and chronic kidney disease (CKD). A study by Bao *et al* (43) on CKD aimed to examine the association between serum levels of IL-33 and sST2, and disease severity. This involved comparing the serum concentrations of IL-33 and sST2 between patients with CKD and healthy individuals. The results showed no difference in the serum concentration of IL-33 between the patients with CKD and healthy individuals, whereas a higher serum level of sST2 was found in the patients with CKD. Therefore, the results revealed a significant correlation between the serum level of sST2 and disease severity. In addition, higher levels of sST2 correlated with elevated parathyroid hormone, serum phosphorus and serum calcium (43). However, the expression of IL-33 was observed to be increased in aortic endothelial cells from a mouse model of CKD (44). Additionally, higher concentrations of sST2 appeared to be associated with impaired kidney function in a study involving participants with cardiovascular disease (45). Together, these findings indicate that the levels of IL-33 and sST2 are relevant to the progressive deterioration of kidney function.

IL-33 and systemic lupus erythematosus (SLE) nephropathy (LN). Renal fibrosis is the common pathway of chronic kidney disease eventually lead to kidney failure, which is one of the most serious complications of SLE (46). Fibrotic disease is characterized by the excess accumulation of extracellular matrix components, including collagen, and requires eosinophils and RAG-dependent lymphocytes (47). Of note, IL-33 mediates the regulation of several extracellular matrix-associated genes, including collagen VI, collagen III

Table II. Role of IL-33 in kidney diseases.

Kidney disease	Role of IL-33	Reference
CKD	Serum levels of IL-33 not correlated with disease severity in CKD. Serum levels of sST2 are significantly correlated with disease severity in CKD.	(44,45)
Systemic lupus erythematosus nephropathy	Mediates regulation of several extracellular matrix-associated genes, resulting in IL-33R-dependent accumulation of eosinophils, RAG-dependent lymphocytes and $CD3^+$ lymphocytes.	(47-49)
Diabetic nephropathy	Expression of IL-33 is not associated with kidney injury, but the increase may be a result of diabetes.	(50,51)
Renal transplantation	Immune mediator following transplantation during kidney IRI in humans; correlated with cold ischemia duration; activates invariant natural killer T cells in kidney transplant recipients.	(53-55)
Acute kidney injury	Stimulates $CD4^+$ T cell infiltration in the kidney, induces higher levels of serum creatinine, acute tubular necrosis and apoptosis.	(57-59)

IL-33, interleukin-33; CKD, chronic kidney disease; IRI, ischemia reperfusion injury.

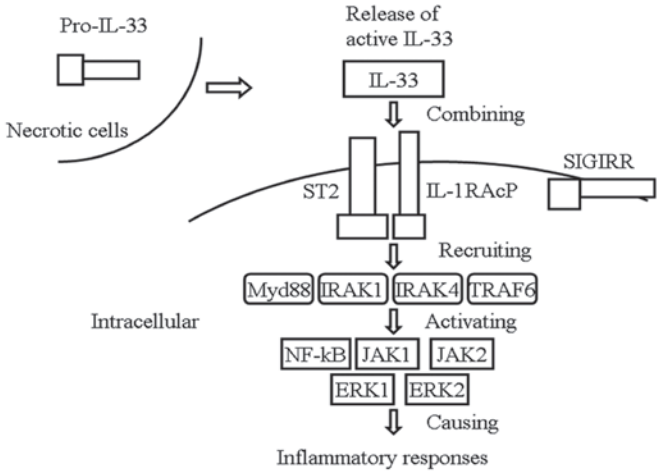

Figure 1. IL-33/ST2 signaling pathway. IL-33 can transfer extracellular information through the binding of the receptor complex. comprised of ST2 and IL-1RAcP, following release into the extracellular space during cell damage or mechanical injury. Extracellular IL-33 signals result in the recruitment of Myd88, IRAK1/4 and TRAF6, leading to the activation of transcription factor NF-kB, JNK1/2 and ERK1/2, causing inflammatory responses. IL-33-mediated signaling can be inhibited by SIGIRR through interactions with the IL-33 receptor complex. IL, interleukin; ST2, suppression of tumorigenicity 2; IL-1RAcP, IL-1 receptor accessory protein; Myd88, myeloid differentiation primary response gene 88; IRAK1/4, interleukin-1 receptor-associated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; JNK1/2, c-Jun N-terminal kinase1/2; ERK1/2, extracellular regulated protein kinase 1/2; SIGIRR, single IgIL-1-related molecule.

and tissue inhibitor of metalloproteases-1. In addition, the administration of IL-33 resultes in IL-33R-dependent accumulation of eosinophils, RAG-dependent lymphocytes and $CD3^+$ lymphocytes (48). The levels of IL-33 in patients with SLE have been found to be greater than those in a healthy control group, and were correlated with elevated erythrocyte sedimentation rate and C-reactive protein, suggesting that the abnormal increase in serum IL-33 is closely associated with the development of SLE and may be involved in the acute phase reaction of SLE (49). Shui-Lian *et al* indicated that the IL-33/ST2 axis has a detrimental effect in the pathogenesis of renal fibrosis associated with LN (46). Therefore, IL-33 may involved in renal fibrosis associated with SLE. Further mechanistic investigations examining the precise physiological and pathophysiological roles of IL-33 in SLE are required.

IL-33 and diabetic nephropathy. The principle of the pathogeny of type 2 diabetes and its complications, including diabetic nephropathy, remain to be fully elucidated, however predicting the potential complications of diabetic patients can assist in early treatment. Whether IL-33 can be used for predicting the early stage of kidney injury in diabetic patients remains to be elucidated. In a study by Caner *et al* identified three groups: Healthy group; diabetes mellitus (DM) group without any known kidney disease; and DM+microalbuminuria (MA) group, assumed to have nephropathy. Following assessment of the concentrations of IL-33 in the three groups, it was found that the level of IL-33 in the DM group was greater than that in the healthy group; and the level of IL-33 in the DM+MA group was greater than that in the healthy group; although no difference was observed between the DM and DM+MA group. Therefore, IL-33 cannot be used in the early recognition of diabetic nephropathy (50). A study by Miller *et al* showed that the levels of sST2 in individuals largely without vascular disease, are associated principally with markers associated with diabetes, and support a role for sST2 in diabetes (51). These findings support the hypothesis that the increase in IL-33 levels in diabetic nephropathy is not associated with kidney injury, but that the increase may be a result of diabetes. Further investigations are required to clarify the value of IL-33 in DM and the early stage of kidney injury.

IL-33 and renal transplantation. Ischemia-reperfusion injury (IRI) contributes to the development of renal graft damage

associated with renal transplantation (52). Inflammatory and immune responses are involved in kidney IRI (52). IL-33 has been identified as an alarmin, capable of mediating danger signals during tissue damage (53). Thierry *et al* addressed the role of IL-33 in IRI following human kidney transplantation (54). This involved analysis of the levels of IL-33 in a cohort of 26 deceased renal transplant recipients, and revealed that the level of IL-33 was significantly increased as soon as 30 min post-reperfusion, which supported the potential role of IL-33 as an immune mediator following transplantation during kidney IRI in humans (54). Consistent with this, invariant natural killer T cells, which have been suggested to be crucial in IRI and targeted by IL-33, exhibited a state of early activation in kidney transplant recipients (54). In addition, a significant correlation was found between serum and urinary levels of IL-33 levels and cold ischemia duration, between 30 min and 3 days post-tranplantation (55). In conclusion, these results emphasize the possible role of IL-33 as an innate-immune mediator during IRI in humans.

IL-33 and acute kidney injury (AKI). AKI contributes to significant morbidity and mortality rates in intensive care units (56). Alterations in renal hemodynamics, inflammation, endothelial dysfunction, tubular obstruction and glomerular thrombosis are involved in the pathogenesis of AKI (57). To determine whether IL-33 promotes AKI, a study by Akcay *et al* examined the protein expression of IL-33 in the kidney using an AKI mouse model. Following neutralizing IL-33 activity with sST2, these mice had fewer CD4 T cells infiltrating the kidney, lower levels of serum creatinine, and reduced acute tubular necrosis and apoptosis, compared with cisplatin-induced AKI in the untreated mice. By contrast, the administration of recombinant IL-33 exacerbated cisplatin-induced AKI (58). Of note, IL-33 mediates cisplatin-induced AKI by acting as an proinflammatory cytokine, whereas IL-10 protects against cisplatin-induced AKI by acting as an anti-inflammatory cytokine (59). In addition, high expression levels of IL-33 have been observed in lipopolysaccharide-induced acute glomerular injury (57). The inhibition of IL-33 may provide a novel strategy in the treatment of AKI (Table II).

10. Conclusion

In conclusion, increasing evidence indicates that the IL-33/ST2 axis has a significant effect in the pathogenesis of kidney disease. Although the mechanism underlying the effects of IL-33 in kidney disease remains to be fully elucidated, accumulating evidence links IL-33 to the nephropathies, indicating that the antagonism of IL-33 may be a novel strategy for the treatment of kidney disease. Further detailed investigations of the association between IL-33 and kidney disease are required in the future.

Acknowledgements

This study was supported by the Natural Science Foundation of Hubei province (grant. no. 2012FFB03708) and the Natural Science Foundation of Yichang City (grant. no. A13301-020).

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